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# Editorial Board InaJEMD

ORIGINAL ARTICLE

# Isolation, In Vitro Expansion, and Cryopreservation of Primary Cells Derived from Human Thyroid Carcinoma

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**ABSTRACT**
Thyroid carcinoma is a malignant neoplasm arising from thyroid parenchymal cells and currently ranks as the fourth most diagnosed cancer in Indonesia. This study aimed to isolate thyroid carcinoma cells for in vitro expansion and long-term preservation as a reliable cell culture stock, including cryopreservation for future research applications. In addition, we sought to identify and characterize cells derived from papillary thyroid carcinoma (PTC) tissue to evaluate the presence of mutations with potential prognostic significance. Primary cell isolation was performed via enzymatic digestion using collagenase, enabling effective separation of tumor cells from adjacent non-malignant thyroid tissue. Cell proliferation was supported using Dulbecco's Modified Eagle Medium (DMEM) supplemented with 5% fetal bovine serum (FBS), selected for its high concentration of growth-promoting factors that enhance proliferation rates. For biobanking purposes, cryopreservation of the thyroid carcinoma-derived cells was conducted using a standard slow-freezing protocol. Molecular characterization was carried out through PCR amplification, gel electrophoresis, and Sanger sequencing of key oncogenic drivers, specifically the BRAF gene and five RAS gene targets: HRAS exon 2, NRAS exons 2 and 3, and KRAS exons 2 and 3. No pathogenic mutations were identified in the analyzed BRAF or RAS gene regions.

**Keywords**: Papillary thyroid carcinoma, primary cell culture, and BRAF and RAS mutations

## INTRODUCTION

Thyroid carcinoma is a malignant tumor arising from follicular thyroid cells.[1] Its incidence has risen markedly over the past four decades in the United States.[2] Globally, it ranks as the 13th most common cancer and the sixth most prevalent among women aged 20-45.[3] In Indonesia, according to 2015 data from the Ministry of Health, thyroid carcinoma is the fourth most frequently diagnosed cancer and the tenth leading cause of cancer-related death at Dharmais Cancer Hospital.

As the most common endocrine malignancy, thyroid cancer is categorized by differentiation, histology, and genetic mutations. Major histological types include differentiated thyroid carcinoma (papillary, follicular, and Hürthle cell subtypes), medullary thyroid carcinoma, poorly differentiated carcinoma, and anaplastic thyroid carcinoma.[4] Papillary thyroid carcinoma (PTC) accounts for about 85% of cases, while anaplastic thyroid carcinoma, though rare (1%), causes 15-40% of thyroid cancer deaths.[5,6]

The rising incidence of thyroid cancer has prompted the development of in vitro models using tumor-derived cells. These models are widely used to study tumor behavior, compare malignant and normal thyroid cells, and conduct drug testing.[7] Isolating primary cells from thyroid tumors is essential for accurate identification and further analysis. In vitro models have helped explore genetic and epigenetic drivers of thyroid tumorigenesis, assess drug response, and identify cancer stem cells.[8]

This study investigates the in vitro behavior of papillary thyroid carcinoma cells compared to normal thyroid cells, including isolation, culture, cryopreservation, identification, and mutation analysis with potential prognostic significance.

## MATERIALS AND METHODS

### Primary Cell Isolation from Human Thyroid Carcinoma Tissue

This in vitro study utilized cell samples obtained from human thyroid carcinoma tissues during thyroidectomy procedures. Primary cell isolation was performed on both malignant and adjacent non-malignant thyroid tissues. The culture medium consisted of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 5% fetal bovine serum (FBS), 2 mM glutamine, 2.6 g/L sodium bicarbonate ($NaHCO_3$), 5 µg/mL gentamicin, 1% non-essential amino acids (NEAA), and six growth-supporting supplements: 10 mIU/mL thyrotropin (TSH), 10 mIU/mL insulin, 1 nM hydrocortisone, 2 ng/mL glycyl-histidyl-L-lysine acetate, 5 µg/mL transferrin, and 10 ng/mL somatostatin. The excised thyroid tissue (13.66 g) was decontaminated and finely minced into small fragments under sterile conditions using a surgical blade. These fragments were rinsed with Dulbecco's Phosphate-Buffered Saline (DPBS), then immersed in a 0.25% trypsin solution and stored overnight at 4°C.

On the following day, tissue fragments from both carcinoma and normal thyroid regions were transferred into 50 mL conical tubes and incubated with type I collagenase in 0.25% trypsin at 37°C for approximately 3 hours, with gentle agitation every 30 minutes. The resulting cell suspensions were filtered through a cell strainer and centrifuged at 1500 rpm for 7 minutes at 4°C to collect the cell pellets. After discarding the supernatant, the pellets were resuspended and homogenized. Due to remaining turbidity, a portion of the suspension was transferred into 15 mL tubes and re-centrifuged at 2000 rpm for 7 minutes at 4°C. Meanwhile, cells in the 50 mL tubes were resuspended in complete DMEM and plated into separate T-75 flasks designated for healthy and carcinoma-derived cells. Following re-centrifugation, visible cell pellets in the 15 mL tubes were recovered, resuspended in complete medium, and added to their respective primary cultures in the T-75 flasks.[7]

### Primary Cell Culture

Primary thyroid cells were cultured and expanded under standard conditions, with medium replacement every two days. Once the cells reached confluency in T-75 flasks, subculturing was carried out. When the total cell count exceeded $5 \times 10^6$, harvesting was performed. Cells were centrifuged at 500 × g for

2 minutes, the supernatant was discarded, and the resulting pellet was retained. The cell pellet was resuspended in 100-200 µL of phosphate-buffered saline (PBS) for subsequent analysis or experimental use.[8,9]

**Cryopreservation of Thyroid Carcinoma Cells**
Cryopreservation was carried out using a cryoprotectant solution composed of 700 µL thyroid carcinoma cell suspension, 200 µL fetal bovine serum (FBS), and 100 µL dimethyl sulfoxide (DMSO). The cell mixture was initially frozen at -80°C overnight in a deep freezer, then transferred to a liquid nitrogen cryogenic storage system for long-term preservation.[10]

**Identification and Characterization of Cells Derived from Thyroid Carcinoma Tissue** The primary cells utilized in this study were isolated from histopathologically confirmed papillary thyroid carcinoma tissue.

**DNA Extraction and PCR Amplification of BRAF-RAS Mutation Regions**
Genomic DNA was extracted from over one million cultured cell isolates derived from patient-derived papillary thyroid carcinoma (PTC) tissue, in addition to normal human dermal fibroblasts (HDF) and the HSC-3 human tongue squamous cell carcinoma line. DNA isolation was performed using the Quick-DNA™ Miniprep Plus Kit (Zymo Research), in accordance with the manufacturer's protocol. The concentration of the extracted nucleic acids was measured using a Tecan fluorometric system. Approximately 100-200 ng of DNA was utilized for polymerase chain reaction (PCR) amplification targeting BRAF and RAS gene mutation regions. DNA samples were either used immediately for PCR analysis or stored at -20°C for future application.[11]

**PCR Amplification of Six BRAF-RAS Gene Mutation Regions**
Subsequent PCR amplification targeted six known mutation regions within the BRAF-RAS gene family, enabling molecular analysis relevant to thyroid carcinogenesis. The amplification of six mutation regions within the BRAF-RAS gene family was conducted using the MyTaq HS Red Mix PCR Kit (Bioline), following the manufacturer's protocol. The six targeted regions included BRAF, HRAS exon 2, NRAS exon 2, NRAS exon 3, KRAS exon 2 and KRAS exon 3.[12]

**Detection of BRAF-RAS Mutations by Sanger Sequencing**
DNA sequencing was conducted using an automated 96-capillary ABI 3730xl DNA Sequencer (Applied Biosystems) at Apical Scientific Sdn. Bhd., Malaysia, through PT. Genetika Science Indonesia. The resulting sequences were analyzed using the BLASTN platform to confirm alignment with the respective BRAF-RAS gene regions. Mutation screening was subsequently performed by aligning the sequence data with the corresponding reference sequences from the GenBank database. Multiple sequence alignment was carried out using ClustalW to detect nucleotide variations indicative of potential mutations.[13]

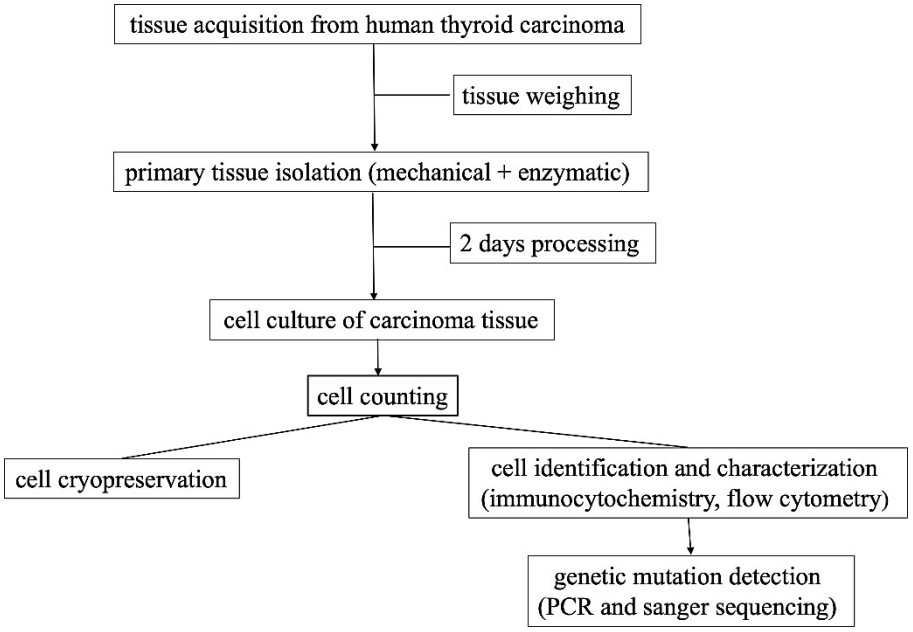


Figure 1. Research Flow

## RESULTS

### Primary Cell Isolation from Normal and Carcinoma Thyroid Tissue

Primary cells isolated from both normal and carcinoma thyroid tissues, previously incubated in 0.25% trypsin solution, were transferred into 50 mL conical tubes and treated with collagenase type I to promote further tissue dissociation.

Figure 2. Tissue separation process using a cell strainer

Following centrifugation, each cell suspension was resuspended in culture medium and transferred into T-75 flasks, yielding two separate cultures: one containing normal thyroid cells and the other containing carcinoma-derived thyroid cells.

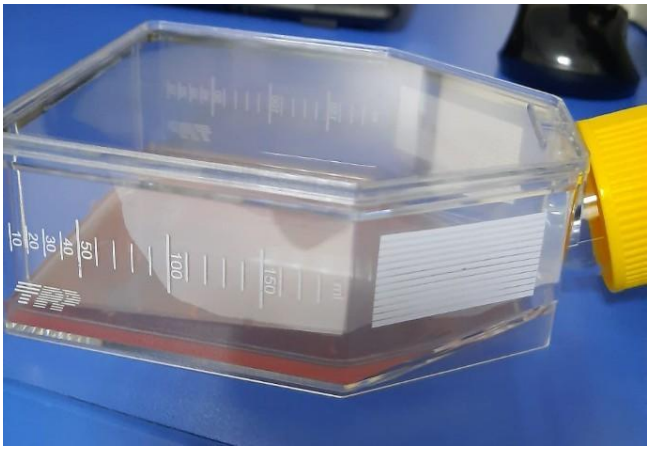

**Figure 3. T-75 flask containing cells in complete DMEM medium**

Observations were conducted on both thyroid-derived cell types. On day 5 of cultivation, cell growth was observed in both T75 flasks.

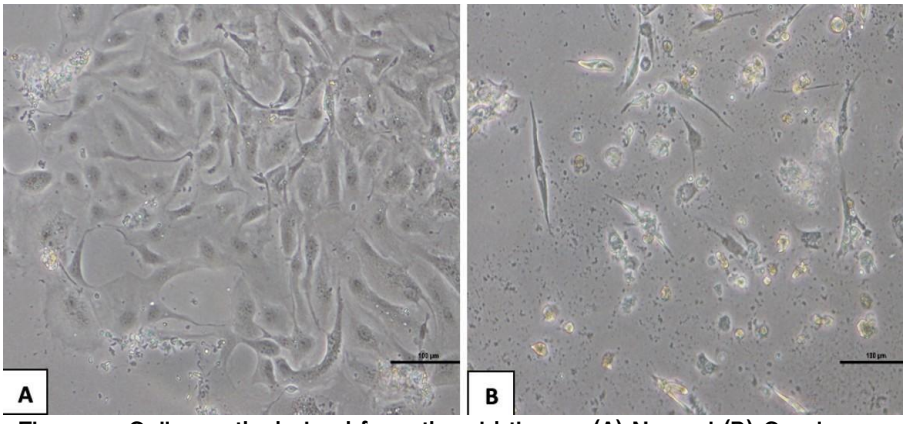


**Figure 4. Cell growth derived from thyroid tissue. (A) Normal (B) Carcinoma**

The above images illustrate cells derived from both normal thyroid tissue (A) and thyroid carcinoma tissue (B), exhibiting a flattened spindle or fusiform shape, with fine granular cytoplasm and elongated nuclei. In image (A), cell proliferation appears more extensive compared to image (B).

**Cell Culture and Expansion of Normal and Papillary Thyroid Carcinoma Tissues**

Cell observation and proliferation were carried out until day 12, by which time the cells had reached 80% confluence in the T75 flask, with cellular morphology as shown below.

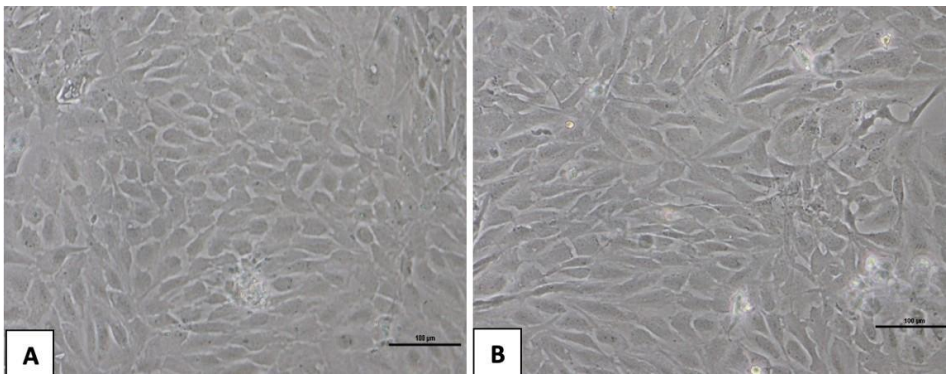


**Figure 5. Proliferation of thyroid-derived cells on day 12: (A) Normal, (B) Cancerous**

Figure 5 shows cells with a spindle-shaped or fusiform morphology, consistent with fibroblast-like appearance, observed in both normal and cancerous thyroid-derived cells. Once the cells reached confluence in the T75 flask, they were harvested using 0.25% trypsin, and counted with a hemocytometer. The total cell counts obtained were 1,562,500 cells from normal thyroid tissue and 3,525,000 cells from thyroid carcinoma tissue. These results indicate a higher and faster proliferation rate in cancer-derived thyroid cells.

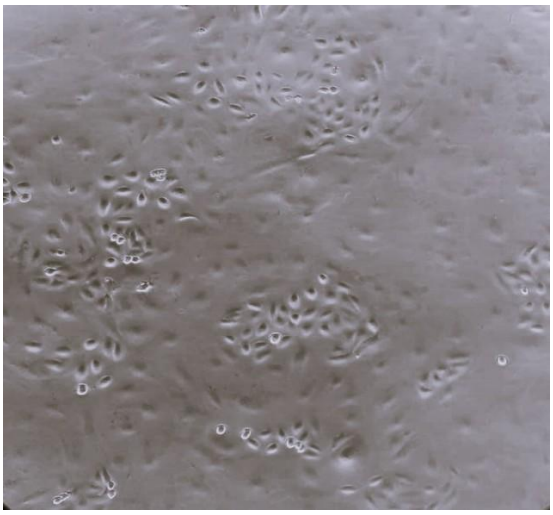

**Figure 6. Morphology of thyroid carcinoma-derived cells after administration of 20% FBS**
The subsequent process involved subculturing using complete DMEM supplemented with 20% FBS until the cells were ready for experimentation. The proliferation phase lasted for 10 days and resulted in cells with predominantly round morphology, some slightly flattened, forming clusters surrounded by spindle-shaped cells. This morphological appearance is suggestive of epithelial-like cells (Fig 6).

**Cell Cryopreservation**

Cryopreservation of thyroid tissue-derived cells requires an appropriate method to maintain cell viability and functionality after thawing. The primary methods used include (1) Slow freezing, which is the most commonly employed technique for thyroid tissue cryopreservation, as it gradually reduces ice crystal formation; (2) Vitrification, which involves ultra-rapid freezing using high concentrations of cryoprotectants, preventing ice crystal formation by converting the solution into a glass-like state; (3) Controlled-rate freezing (CRF) using a programmable freezer, similar to slow freezing but offering more precise temperature control due to specialized equipment.

Cryopreservation relies on cryoprotective agents (CPAs) to protect cells from damage caused by ice crystal formation during freezing. CPAs are generally divided into two categories (1) Penetrating (permeable) cryoprotectants, which enter the cell and protect intracellular structures by minimizing ice formation, such as dimethyl sulfoxide (DMSO), glycerol, ethylene glycol, and propylene glycol; (2) Non-penetrating (non-permeable) cryoprotectants, such as sucrose, trehalose, polyvinylpyrrolidone (PVP), and albumin. These agents are often used in combination to enhance cryopreservation efficiency and maintain cell viability post-thaw.

In this study, the cryopreservation process employed the slow freezing method and DMSO as the cryoprotectant, commonly used for stem cells and hematopoietic cells. The protocol consisted of mixing 700 µL of thyroid carcinoma cells, 200 µL of FBS, and 100 µL of DMSO. The mixture was initially stored in a deep freezer at -80°C and transferred the

following day to a cryo-freezer containing liquid nitrogen.

### Identification and Characterization of Thyroid Carcinoma-Derived Cells

PCR was performed with slight modifications to accommodate the concentration of extracted DNA and the melting temperatures (Tm) of each primer used. The table below presents the primer sequences for the BRAF-RAS genes (Table 1).

**Table 1.** Primer Sequences of the BRAF-RAS Genes

| No | Primer | Gene | Exon | Sequence 5'--> 3' | Size (bp) |
|---|---|---|---|---|---|
| 1 | BRAF_F<br>BRAF_R | BRAF | 15 | TCATAATGCTTGCTCTGATAGGA<br>GGCCAAAAATTTAATCAGTGGA | 224 |
| 2 | HRAS_ex2_F<br>HRAS_ex2_R | HRAS | 2 | GACGGAATATAAGCTGGTGGTG<br>CCTATCCTGGCTGTGTCCT | 178 |
| 3 | NRAS_ex2_F<br>NRAS_ex2_R | NRAS | 2 | CAATTAACCCTGATTACTGG<br>GGTGGGATCATATTCATCTACA | 152 |
| 4 | NRAS_ex3_F<br>NRAS_ex3_R | | 3 | TCCCTGCCCCCTTACCCT<br>TTGATGGCAAATACACAGA | 173 |
| 5 | KRAS_ex2_F<br>KRAS_ex2_R | KRAS | 2 | GTATTTGATAGTGTATTAAC<br>CTCTATTGTTGGATCATATTCG | 195 |
| 6 | KRAS_ex3_F<br>KRAS_ex3_R | | 3 | CAGACTGTGTTTCTCCCTTCTC<br>ATGATTTAGTATTATTTATGG | 181 |

PCR process was carried out in the following sequence: initial denaturation at 95°C for 1 minute, followed by 35 amplification cycles at 95°C for 15 seconds. This was followed by annealing and polymerization steps at specific temperatures and durations depending on the primer used. A final extension was performed at 72°C for 3 minutes. The table below shows the modified PCR conditions for each BRAF-RAS gene.

**Table 2.** Modified PCR Conditions for Each BRAF-RAS Gene

| No. | Mutation Region | Pre-denaturation | Denaturation/Annealing/ Polymerization (°C) | Post-polymerization | Cycles |
|---|---|---|---|---|---|
| 1 | BRAF | 95°C 1 min | 95 (15sec)/55 (15sec)/72 (10sec) | 72°C 3 min | 35 cycle |
| 2 | HRAS_ex2 | | 95 (15sec)/64 (15sec)/72 (10sec) | | |
| 3 | NRAS_ex2 | | 95 (15sec)/55 (15sec)/72 (10sec) | | |
| 4 | NRAS_ex3 | | 95 (15sec)/60 (10sec)/72 (20sec) | | |
| 5 | KRAS_ex2 | | 95 (15sec)/54 (15sec)/72 (10sec) | | |
| 6 | KRAS_ex3 | | 95 (15sec)/50 (10sec)/72 (10sec) | | |

**PCR-Electrophoresis Results of BRAF-RAS Genes**

PCR results were visualized on 2% agarose gel using a 100 bp ladder marker. This PCR method successfully detected six mutation regions of the BRAF-RAS genes, as indicated by the presence of distinct white DNA bands. The DNA band lengths were as follows: BRAF gene - 224 bp, HRAS exon 2 - 178 bp, NRAS exon 2 - 152 bp, NRAS exon 3 - 173 bp, KRAS exon 2 - 195 bp, and KRAS exon 3 - 181 bp.

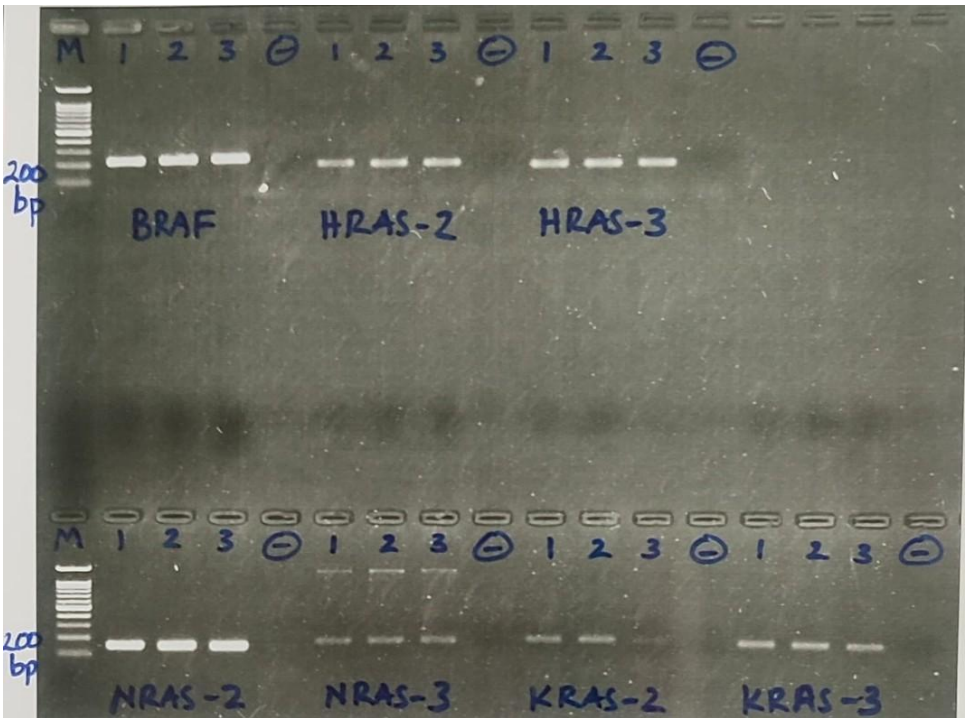


**Figure 7. PCR-Electrophoresis Results of the BRAF-RAS Genes**

**Legend:**

1 = Normal Human Dermal Fibroblast cells (HDF cells)
2 = Papillary Thyroid Cancer cells (PTC cells)
3 = Human Tongue Squamous Cell Carcinoma cells (HSC-3 cells) (-) = Negative control for the PCR reaction

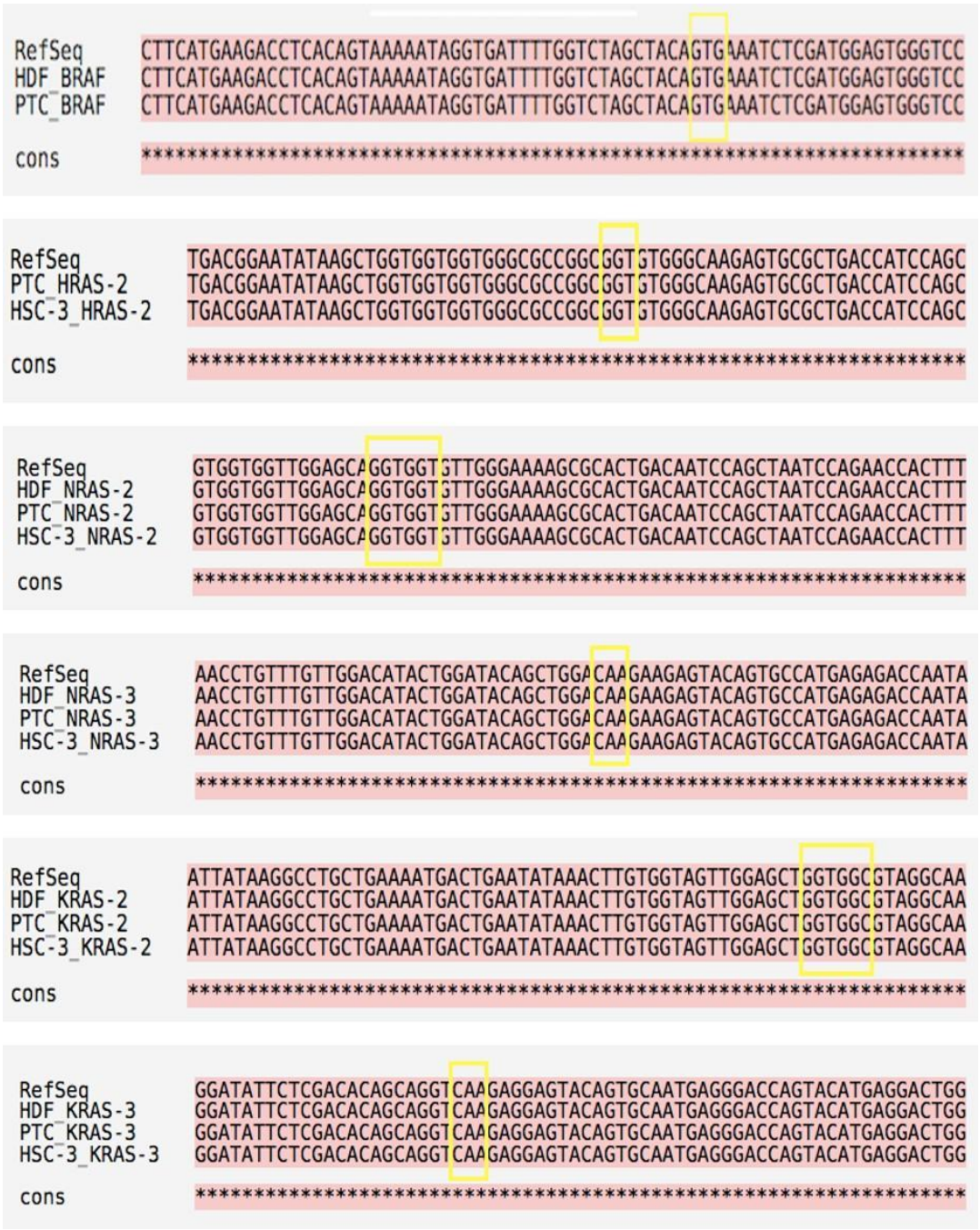


**Figure 8. Sequence Alignment of the BRAF-RAS Genes in Papillary Thyroid Cancer Cell**

Based on the sequencing results obtained from PTC cancer cells of the patient, no mutations were identified in the six analyzed genes, namely BRAF, HRAS exon 2, NRAS exon 2, NRAS exon 3, KRAS exon 2, and KRAS exon 3. This was indicated by the absence of amino acid changes at known mutation sites when compared to the corresponding amino acids in HDF cells, which represent normal or healthy individual cells.

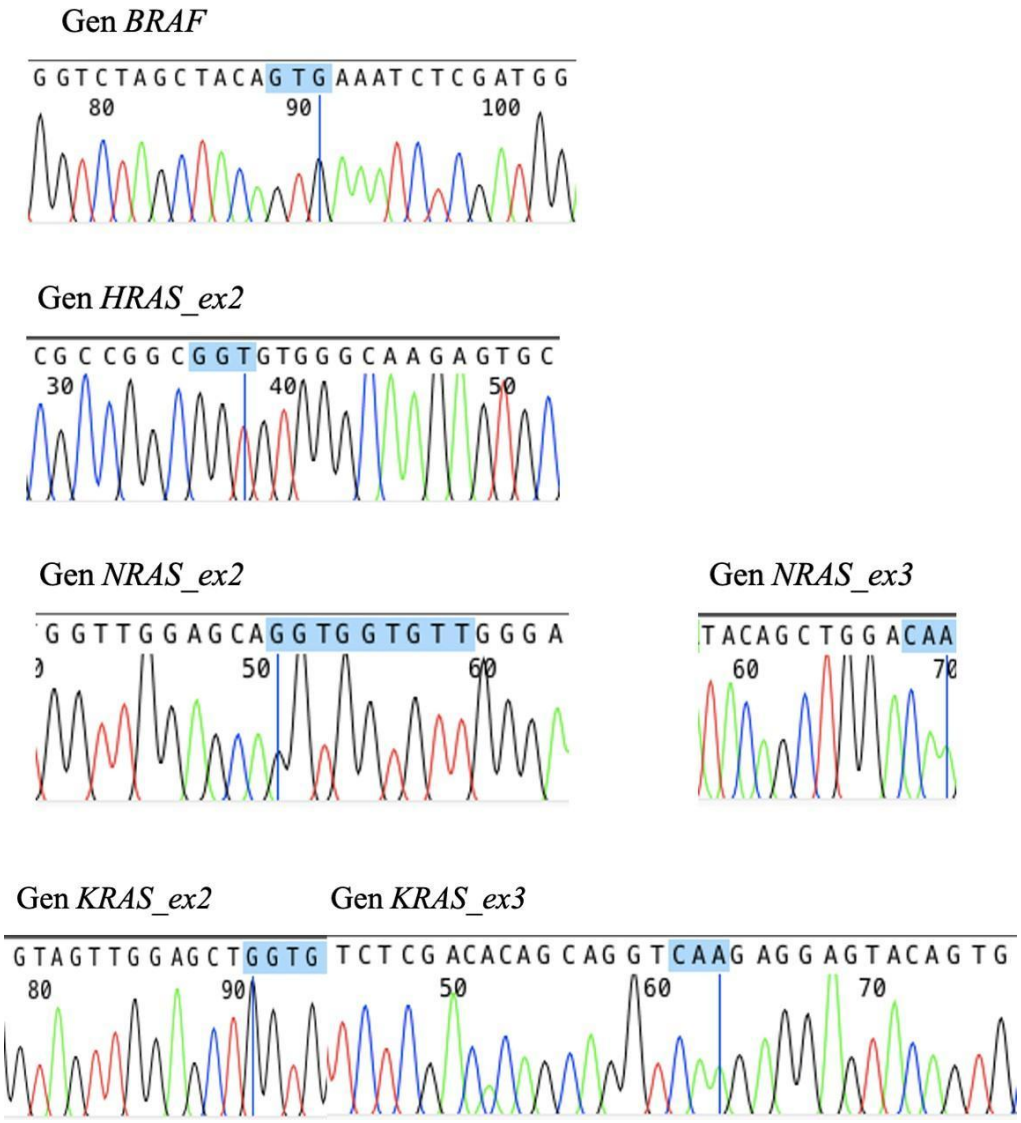


Figure 9. Sequencing Results of the BRAF-RAS Genes in Papillary Thyroid Cancer Cell

## DISCUSSION

### Primary Cell Isolation from Normal and Carcinoma Thyroid Tissue

The method used in this study was the enzymatic method. Enzymatic cell isolation is a technique used to dissociate cells from tissues or cultures with the aid of enzymes that digest extracellular components, such as the extracellular matrix or cell-cell adhesions. The basic principle of the enzymatic method involves using specific enzymes to break the bonds between cells in tissue, allowing individual cells to be released without compromising their structural integrity. In this study, the enzymatic method was used to culture primary cells derived from thyroid carcinoma tissue. The choice of enzyme depends on the type of tissue to be isolated. Common enzymes used in enzymatic cell isolation include collagenase—as used in this study—which digests collagen in the extracellular matrix, particularly in connective and muscle tissues. Other frequently used enzymes include trypsin, which cleaves proteins between cells in culture; hyaluronidase, which breaks down hyaluronic acid in connective tissue to release cells; dispase, which helps release cells from epithelial tissue or culture surfaces; and DNase, which prevents cell aggregation by digesting DNA released from lysed cells.[6,7]

### Cell Culture from Normal and Carcinoma Thyroid Tissue

Cell culture using DMEM (Dulbecco's Modified Eagle Medium) and 10% FBS (Fetal Bovine Serum) is a commonly applied technique in cell biology laboratories to maintain and propagate cells in vitro. DMEM is characterized by its content of glucose, amino acids, vitamins, and mineral salts essential for cell growth. FBS, derived from fetal bovine blood, is frequently used as a supplement in culture media due to its rich content. The concentration of FBS can be adjusted depending on the cell type. In this study, a 20% FBS concentration was used due to its higher growth factor content, which accelerates the proliferation rate, albeit at a higher cost.[8,9]

The figure below compares the results of thyroid tissue-derived cell cultures using complete DMEM supplemented with 10% and 20% FBS on day 3 of cultivation. The cells exhibit a slightly flattened, fusiform shape with fine granular cytoplasm and oval nuclei. Cultures using complete DMEM with 10% FBS showed slower cell growth and a less epithelial-like morphology compared to cultures with 20% FBS.

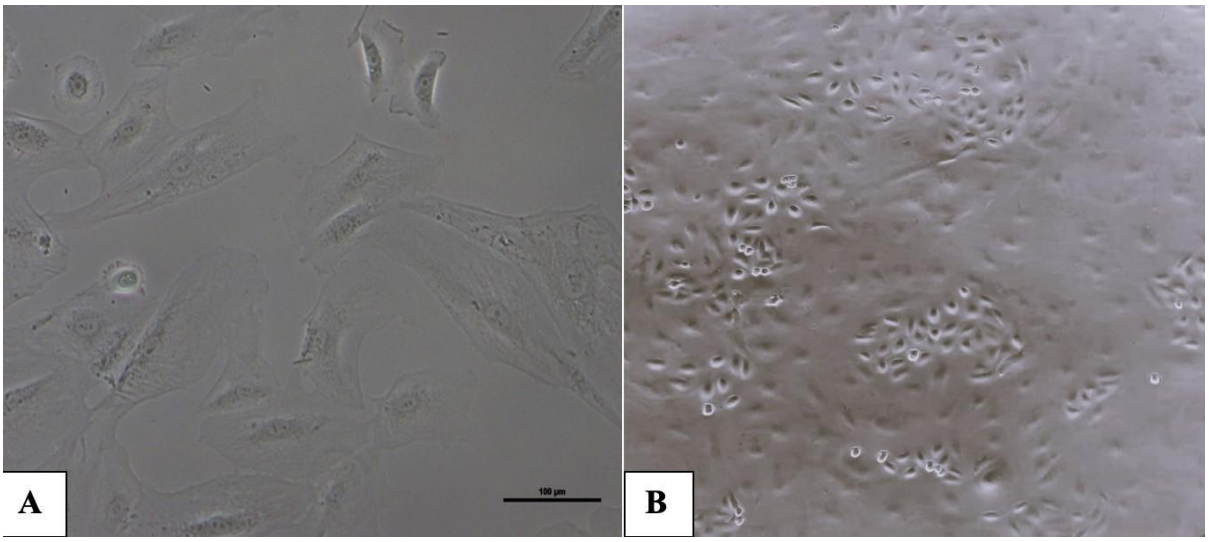


**Figure 10.** Growth of thyroid carcinoma-derived cells in complete DMEM on day 3 of culture with the addition of (A) 10% FBS and (B) 20% FBS.

### Cryopreservation of Thyroid Carcinoma-Derived Cells

In this study, the storage of cells for subsequent experiments was conducted using the cryopreservation method. Cryopreservation aims to preserve cell viability without causing damage and is commonly used for storing embryos, sperm, oocytes, stem cells, and biological tissues for medical or research purposes. It is also applied in in vitro fertilization (IVF) programs, regenerative therapies, tissue transplantation, and the conservation of endangered species. Cryopreservation is a technique used to store cells, tissues, or organs at ultra-low temperatures to maintain their viability over extended periods. The temperature typically reaches as low as -196°C, utilizing liquid nitrogen as the freezing medium. The method of cryopreservation in this study was performed using the slow freezing method. The preservation medium consisted of 700 µL of thyroid carcinoma cell suspension, 200 µL of FBS, and 100 µL of DMSO. The mixture was first stored in a deep freezer at -80°C. On the following day, the samples were transferred to a cryofreezer containing liquid nitrogen.[14]

In this study, cryopreservation was performed using the slow freezing method. The preservation medium consisted of 700 µL

of thyroid carcinoma cell suspension, 200 µL of FBS, and 100 µL of DMSO. The samples were stored in a deep freezer at -80°C, and on the following day, transferred to a cryofreezer containing liquid nitrogen.

An alternative cryopreservation method is the controlled-rate freezer (CRF) technique, which uses specialized equipment to gradually control the cooling rate of samples. This method is standardized and widely used to preserve the viability of cells, tissues, or embryos during freezing. CRF operates by reducing the temperature in a controlled and documented manner using computer programming to ensure gradual cooling. It prevents the formation of large ice crystals that can damage cells and allows for higher post-thaw survival rates compared to rapid freezing methods. In the CRF method, the temperature typically decreases at a rate of 1°C per minute, so reaching -80°C requires only about 2 hours, after which the sample can be directly transferred to a cryofreezer. This method is highly suitable and commonly applied in biomedical fields, in vitro fertilization (IVF), and stem cell storage.[15] Identification and Characterization of Thyroid Carcinoma-Derived Cell

Thyroid carcinoma is a malignant neoplasm originating in the thyroid gland, located in the anterior region of the neck.[16] Histopathologically, thyroid cancer is classified into four main subtypes. The most common is papillary thyroid carcinoma (PTC), accounting for approximately 75-85% of all cases. PTC typically presents in women and is characterized by slow progression. Microscopically, it demonstrates papillary structures alongside enlarged nuclei, intranuclear cytoplasmic inclusions, and psammoma bodies. The second most common subtype is follicular thyroid carcinoma (FTC), comprising around 15% of cases. FTC generally affects older individuals than PTC and displays a follicular growth pattern with microfollicular or trabecular architecture. Diagnosis of FTC relies on identifying capsular and/or vascular invasion. Notably, it lacks the hallmark nuclear features of PTC.

Medullary thyroid carcinoma (MTC) arises from parafollicular or C cells responsible for calcitonin production and represents approximately 5% of thyroid cancers. Histologically, MTC consists of polygonal to spindle-shaped cells, typically arranged in solid, trabecular, or insular formations, with the presence of amyloid stroma. The least common but most aggressive subtype is anaplastic thyroid carcinoma (ATC). ATC is characterized by pleomorphic giant and spindle cells, high mitotic rates, undifferentiated growth, and extensive necrosis. Due to its rapid local invasion and metastatic potential, ATC is associated with a poor prognosis.[16,17]

In this study, histopathological analysis confirmed the presence of multifocal papillary thyroid carcinoma, including oncocytic, classic, follicular, and tall cell variants. Molecular characterization of the carcinoma was performed using PCR electrophoresis targeting the BRAF and RAS gene families. These genetic markers play an important diagnostic and prognostic role in thyroid cancer. Detection of driver mutations guides personalized therapeutic approaches, including the use of BRAF inhibitors (e.g., vemurafenib, dabrafenib) or radioactive iodine (RAI) therapy.[18]

The BRAF gene encodes a serine/threonine protein kinase involved in the MAPK/ERK signaling cascade, which controls cell growth, proliferation, and differentiation. Activating mutations in BRAF, particularly the BRAF V600E mutation—caused by a substitution of valine with glutamic acid at codon 600—result in constitutive activation of the signaling pathway, promoting tumorigenesis. Found in approximately 40-80% of PTC cases, the BRAF V600E mutation is associated with aggressive tumor behavior, increased risk of metastasis, reduced sensitivity to RAI therapy, and potential resistance to BRAF-targeted treatments.[18] In the current study, no BRAF V600E mutation was detected,

suggesting a more favorable biological behavior and treatment response.

The RAS gene family—comprising HRAS, KRAS, and NRAS—encodes small GTPases involved in key cell signaling pathways, particularly RAS-RAF-MEK-ERK and PI3K-AKT, which regulate proliferation, survival, differentiation, and apoptosis. RAS proteins function as molecular switches, transitioning between an active GTP-bound state and an inactive GDP-bound state. Mutations in RAS genes lead to constitutive activation of downstream signaling, promoting unregulated cell proliferation, angiogenesis, apoptosis resistance, and metastatic spread. In thyroid cancer, specifically FTC and ATC, mutations in NRAS and KRAS are most frequently observed.[19,20]

Detection of RAS mutations can be achieved through PCR-electrophoresis, real-time PCR (qPCR), Sanger sequencing, next-generation sequencing (NGS), or immunohistochemistry (IHC) targeting mutant RAS protein expression. In this study, PCR-electrophoresis was employed for RAS mutation screening in primary thyroid carcinoma cells. The presence of RAS mutations often correlates with more aggressive clinical features and resistance to standard therapies, including BRAF inhibitors and radioactive iodine.

To further define the molecular profile, sequencing analysis was conducted to evaluate one BRAF gene region and five RAS gene exons: HRAS exon 2, NRAS exons 2 and 3, and KRAS exons 2 and 3. No pathogenic mutations were identified in either the BRAF or RAS loci analyzed, indicating a mutation-negative molecular profile. This finding supports a favorable clinical prognosis. In such cases, conventional treatments—including thyroidectomy, radioactive iodine therapy, and levothyroxine suppression—remain standard and effective.

Although targeted therapies specifically for RAS mutations are currently under clinical investigation, MEK inhibitors, such-as trametinib and selumetinib, have shown promise in the treatment of RAS-mutant cancers and may offer benefit in select cases of RAS-positive thyroid carcinoma in the future.

## CONCLUSION

Primary isolation of thyroid carcinoma-derived cells in this study was achieved through enzymatic digestion using collagenase, effectively separating malignant cells from adjacent normal thyroid tissue. Subsequent cell proliferation was supported using Dulbecco's Modified Eagle Medium (DMEM) supplemented with 20% fetal bovine serum (FBS), chosen for its elevated growth factor content, which facilitated enhanced cellular expansion. For long-term storage, cryopreservation was performed employing the standard slow-freezing protocol. Molecular characterization of the isolated cells was conducted via PCR-based electrophoresis followed by Sanger sequencing of key oncogenic targets: the BRAF gene and five RAS gene exons, including HRAS exon 2, NRAS exons 2 and 3, and KRAS exons 2 and 3. No pathogenic mutations were detected in the BRAF or RAS gene families (HRAS, NRAS, KRAS) in the samples analyzed.

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ORIGINAL ARTICLE

# Clinical Inertia on Glycemic Control in Patients with Type 2 Diabetes Mellitus: a Study in Primary Healthcare Facilities

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**ABSTRACT**

The prevalence of type 2 diabetes mellitus (T2DM) in Indonesia continues to rise, with projections estimating 28.6 million cases by 2045. This increase poses significant health and economic burdens, especially due to complications resulting from poor glycemic control. This study aimed to evaluate the proportion of T2DM patients achieving optimal glycemic control (HbA1c ≤7%) and to identify factors related to clinical inertia in primary healthcare facilities in Malang, Indonesia. A cross-sectional study design was used, incorporating secondary data from 2256 PROLANIS patients' medical records (2020) and primary data from 580 questionnaires administered to doctors, healthcare providers, and patients. Only 32% of patients achieved HbA1c ≤7%, with higher levels of HbA1c observed among male patients and those with abnormal lipid profiles and microalbuminuria. Metformin alone was associated with the highest rate of glycemic control, while combination regimens such as metformin + sulfonylurea were linked to lower control. Logistic regression identified age, sex, lipid profile, and microalbuminuria as significant factors affecting glycemic control. From the provider side, good clinical practices were associated with adherence to guidelines, moderate workloads, and sufficient patient education. However, variability in guideline availability and lack of standardized protocols in Prolanis facilities posed barriers. Patient knowledge did not correlate significantly with treatment adherence, although most patients had moderate understanding of their condition. These findings underscore the need for standardized care guidelines and targeted interventions at the patient, provider, and system levels to improve glycemic outcomes and reduce diabetes-related complications in primary care settings.

**Keywords:** Type 2 diabetes mellitus, glycemic control, HbA1c, clinical inertia, primary healthcare

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) patients are increasing from year to year globally. Data from the International Diabetes Federation (IDF) 2021 the number of people with diabetes in the world reaches 537 million people.[1] In Southeast Asia alone, people with diabetes reach 75 million people.[2] While in Indonesia in 2021, there will be 19.5 million people with diabetes, and it is predicted that in 2045 there will be an increasing number of patients around 28.6 million people with diabetes in Indonesia. The high number of people with diabetes in Indonesia can have an impact on the economic sector[1,2] The National Healthcare BPJS (Social Insurance Administration Organization) database involving 812,204 diabetes patients in Indonesia shows that the average annual direct medical cost is $708/person (US ±$1247/person). People with complications (US $ 930/person/year ± US $1480/person/year) incur higher costs than those without complications (US $ 421/person/year ± US $ 745/person/year). The total cost of treating T2DM and its complications was US$576 million in 2016, with 74% of the cost being spent on the management of patients with diabetes-related complications.[3]

The risk of diabetic complications in T2DM patients is strongly related to the blood glycemic level. Tighter glycemic control has been shown to reduce the risk of microvascular and macrovascular complications of diabetes.[4] Glycated hemoglobin A1c (HbA1c) has been used by physicians as the gold standard for measuring patients' glycemic control for the previous 2-3 months.[5] This makes it possible to make treatment decisions to achieve favorable diabetes control with the aim of reducing or avoiding complications associated with hyperglycemia.

The achievement of HbA1c in the population is also an obstacle in the management of T2DM. Diabcare 2012 research data involving 1967 participants, showed an average HbA1c of 8.3% in the population and only 30.8% of participants achieved HbA1c <7%.[6] Another similar study conducted by Soetedjo et al.,(2018) on 785 participants also found the same result with an average HbA1c of 8.3% with subjects who achieved HbA1c <7% as much as 29.2%.[7] In a community context, optimal glycemic control is difficult to achieve because long-term blood glucose monitoring is required for diabetic patients. In addition, the complexity of the problem among patients becomes one of the obstacles, followed by patient and healthcare provider factors related to difficulties in achieving optimal glycemic control. As a result, primary healthcare facilities in Indonesia reported that most type 2 DM patients developed poor glycemic control. There are many factors that can affect the achievement of optimal glycemic control. Factors from patients, doctors, and the healthcare system in primary healthcare facilities can also be the cause.[8] Clinical inertia defined as a discrepancy between clinical guidelines and the reality of a clinical practice that occurs in the management of T2DM.[9] In clinical inertia, there is also a failure to initiate and intensify therapy according to indications in T2DM patients.[10]

From the statement above, we want to know how the proportion of patients who achieve optimal blood glycemic control, especially in Malang and which clinical inertia affects the achievement of HbA1c in the patient population in primary healthcare facilities. The results of this study are expected to be a reference for other researchers to see the prevalence of successful T2DM therapy, especially in the context of health services at the primary level and can be used as a basis for evaluation of the next program.

## MATERIALS AND METHODS

This cross-sectional observational study uses medical record data as a secondary source of data obtained from BPJS Malang City and primary data from questionnaires given to doctors, patients, and the health care system. The data taken includes PROLANIS patient data at primary health facilities in Malang City in January-December 2020. This study was declared ethically feasible based on the ethical license number 136/EC/KEPK/05/2022 approved by the Ethical Committee of the Faculty of

Medicine, Universitas Brawijaya. Participants who joined the study were patients with type 2 DM with data that included patient profile data (age and gender), HbA1c, lipid profile, creatinine, microalbuminuria, urea, and drug regimen. shows the electronic medical record data by BPJS and the number of participants is 2256 patients.

The primary endpoint in this study was the proportion of patients who succeeded in achieving blood glycemic control, characterized by HbA1c <7%. Secondary endpoints in this study included demographic data (age and gender), lipid profile, creatinine, urea, microalbuminuria, and the drug regimen given to the patient. In addition, to determine the most dominant factor in clinical inertia that affects the achievement of glycemic control in T2DM patients.

Statistical analysis of the data that has been collected will be carried out with descriptive analysis and bivariate analysis and multivariate analysisi (e.g logistic regresion). Missing data will be immediately excluded from the data pool. Descriptive analysis will be displayed in the form of mean and standard deviation for numerical data, and frequency for categorical data. Then for the bivariate test, a chi-square test will be carried out on non-parametric data. Meanwhile, the parametric data will be tested by independent T-test.

## RESULTS

Table 1. Patient Characteristics of Primary Healthcare Facilities in Malang

| Characteristic | Public health center (n=774) | Private clinic (n=982) | Independent practicing doctor (n=500) | Total (n = 2256) | *p-value* |
|---|---|---|---|---|---|
| Age (mean ± SD) | 61,03 ± 9,37 | 60,25 ± 9,60 | 62,56 ± 9,33 | 61,03 ± 7,82 | 0,00* |
| Gender | | | | | |
| • Male | 235 (30%) | 397 (40%) | 199 (40%) | 831 (37%) | 0,00* |
| • Female | 539 (70%) | 585 (60%) | 301 (60%) | 1425 (63%) | |
| HbA1c (mean ± SD) | 7,91 ± 2,27 | 7,75 ± 2,19 | 7,81 ± 2,08 | 7,82 ± 2,19 | - |
| Therapeutic Target (HbA1c) | | | | | |
| • Achieved (HbA1c ≤ 7,0) | 253 (33%) | 301 (31%) | 157 (31%) | 711 (32%) | - |
| • Not achieved (HbA1c > 7,0) | 521 (67%) | 681 (69%) | 343 (69%) | 1545 (68%) | |
| Lipid profile (mean ± SD) | | | | | |
| • Total | 211,27 ± 47,56 | 208,43 ± 46,89 | 208,87 ± 44,80 | 209,50 ± 46,66 | 0,00* |
| • TG | 190,11±118,57 | 172,87±118,33 | 182,12±126,90 | 180,83±120,55 | 0,00* |
| • HDL | 51,66 ± 13,45 | 48,99 ± 12,19 | 51,11 ± 13,27 | 50,37 ± 12,93 | 0,00* |
| • LDL | 132,68 ± 43,22 | 132,42 ± 42,29 | 133,44 ± 42,88 | 132,76 ± 42,73 | 0,00* |
| Creatinine (mean ± SD) | 1,23 ± 2,92 | 1,32 ± 5,27 | 1,18 ± 0,55 | 1,26 ± 3,88 | 0,74 |
| Microalbuminuria(mean ± SD) | 98,73 ± 145,28 | 84,08 ± 131,97 | 93,13 ± 144,16 | 91,10 ± 139,46 | 0,00* |
| Ureum (mean ± SD) | 32,48 ± 23,81 | 32,52 ± 18,78 | 33,56 ± 15,54 | 32,74 ± 20,03 | 0,41 |

In this analysis, we looked at several parameters including age, gender, HbA1c, HbA1c target achievement, lipid profile, creatinine, microalbuminuria, and urea which will be divided into the population of public health center, private clinics, private practice doctors, and the total of the three health facilities. The total population reached 2256 patients consist of 774 patients from public health center, 982 patients from private clinics, and 500 patients from private practice doctors. Each population of health facilities have the

same characteristics, where the average age of participant is over 60 years. The older population was found in the private practice doctors, while the younger population was found in the private clinics. The proportion of sexes in each health facility has the same characteristics, but at the public health center it has a higher proportion of women.

Based on the total proportion, only 32% of patients achieved the optimal HbA1c target. The highest proportion of non-optimal achievement of the HbA1c target was in the private clinics and private practice doctors. The lipid profile was good in the entire population and each health facility also has similar characteristics with values that are not far apart. The highest total cholesterol, HDL, and TG were found in the public health center population. Meanwhile, LDL cholesterol was slightly higher in the private practice doctors population. Related to kidney function where the highest creatinine is found in the private clinics population, high microalbuminuria in the public health center population, and the highest urea in the private practice doctors population. However, each population has the same statistical result and does not differ much in value. It was found that the bivariate test on all parameters had a significant difference in the achievement of glycemic control in T2DM patients except for the urea and creatinine parameters ($p<0.05$).

Table 2. Distribution of Drug Regimen

| Regimen | Total | Optimal target | Non optimal target |
|---|---|---|---|
| Metformin | 205 (9,6%) | 112 (54,6%) | 93 (45,4%) |
| Sulfonilurea + Metformin | 1245 (58,3%) | 356 (28,6%) | 889(71,4%) |
| Sulfonilurea + Acarbose | 130 (6,1%) | 38 (29,2%) | 92 (70,8%) |
| Acarbose | 61 (2,9%) | 20 (32,8%) | 41 (67,2%) |
| Sulfonilurea | 113 (5,3%) | 37 (32,7%) | 76 (67,3%) |
| Metformin + TZD | 1 (0,05%) | 0 (0%) | 1 (100%) |
| Metformin + Acarbose | 7 (0,3%) | 3 (42,9%) | 4 (57,1%) |
| Metformin + Sulfonilurea + TZD | 2 (0,1%) | 0 (0%) | 2 (100%) |
| Metformin + Sulfonilurea + Acarbose | 239 (11,2%) | 68 (28,5%) | 171(71,5%) |
| Insulin/ Insulin + OAD | 132 (6,2%) | 20 (15,2%) | 112(84,8%) |

*Optimal target : HbA1c $\leq$ 7%, Non Optimal target : HbA1c > 7%

The most frequently used drug regimens in primary healthcare facilities are sulfonylnurea + metformin, metformin + sulfonylurea + Acarbose, and metformin alone. Metformin drug regimen has the highest percentage of achieving blood glycemic control compared to other regimens. The sulfonylurea + metformin regimen had the highest percentage of unattainable blood glycemic control compared to other regimens.

Table 3. Logistic Regression of Factors Affecting the Failure of Glycemic Control in Patients with Type 2 DM

| Parameter | Odds Ratio | CI 95% | p-value |
|---|---|---|---|
| Age | 0,977 | 0,967-0,987 | 0,00* |
| Sex | | | |
| • Female | Ref | Ref | Ref |
| • Male | 1,369 | 1,121-1,672 | 0,002* |
| Primary healthcare facilities | | | |
| • Public health center | Ref | Ref | Ref |
| • Private clinics | 0,834 | 0,648 – 1,073 | 0,158 |
| • Independent practicing doctors | 1,015 | 0,796 – 1,295 | 0,903 |
| Total Cholesterol | 1,000 | 0,996 - 1,004 | 0,887 |
| HDL | 0,988 | 0,979 – 0,996 | 0,004* |
| LDL | 1,004 | 1,000 – 1,008 | 0,030* |
| Trigliserida | 1,003 | 1,002 – 1,005 | 0,00* |
| Creatinine | 1,002 | 0,980 – 1,025 | 0,836 |
| Microalbuminuria | 1,002 | 1,002 – 1,003 | 0,00* |
| Ureum | 0,998 | 0,992 – 1,004 | 0,469 |

After the bivariate test has been carried out, the secondary data will then be processed using multivariate analysis in the form of a binomial logistic regression test to determine the factors that influence the inability to achieve glycemic control. The reference value used lies in the first data, so the interpretation of the odds ratio refers to the factors that cause glycemic control not to be achieved. There are several factors that influence the failure to achieve optimal blood glycemic control in T2DM patients including age, gender, total cholesterol, HDL, LDL, TG, and microalbuminuria.

### Participant Characteristic of Primary Data

This data consists of 3 population groups, consist of doctors, the health care system (BPJS), and patients. Each of these groups will be analyzed using a questionnaire that will determine the merits of practice, knowledge, and compliance. The number of samples of doctors reached 123 participants, the healthcare system reached 99 participants, and patients were 358 participants. The sampled doctors were general practitioners working at each primary health facility. The health service system referred to the existence of clinical practice guidelines, availability of drugs and laboratory tests at each primary healthcare facility. Patients indicators are the level of knowledge and patient compliance in diabetes treatment.

### Analysis of Factors Affecting Clinical Inertia at Primary Healthcare Facilities in Malang

This analysis is a test conducted to assess the factors that influence the occurrence of clinical inertia in primary healthcare facilities in Malang which focuses on 3 populations, namely doctors, systems, and patients. In the population of doctors, there are 3 factors that we examine including the use of guidelines, workload as a doctor, and education to patients. Here are the results we got in the doctor population.

Table 4. Frequency of Guideline Utilization Score, Workload, Patient Education, and Doctor's Total Clinical Practice Score Based on Primary Healthcare Facilities Types

| Parameter | | Primary Healthcare Facilities Types | | | |
|---|---|---|---|---|---|
| | | Public Health Center (%) | Private Clinic (%) | Independent Practicing Doctor (%) | Total (%) |
| Guideline Utilization | Good | 96,9 | 95.6 | 82.6 | 93 |
| | Bad | 3,1 | 4.4 | 17.4 | 6.5 |
| Workload | Heavy | 25 | 33.8 | 21.7 | 29.3 |
| | Moderate | 50 | 44.1 | 39.1 | 44.7 |
| | Mild | 25 | 22.1 | 39.1 | 26 |
| Education to patient | Good | 87.5 | 97.1 | 87 | 92.7 |
| | Bad | 12.5 | 2.9 | 13 | 7.3 |
| Total Score | Good | 87.5 | 86.8 | 78.3 | 85.4 |
| | Bad | 12.5% | 13.2 | 21.7 | 14.6 |

Table 5. Parameter Description

| Parameter | | Scoring from Questionnaire |
|---|---|---|
| Guideline Utilization | Good | 6-11 |
| | Bad | 12-18 |
| Workload | Heavy | 4-7.33 |
| | Moderate | 7.33-10.66 |
| | Mild | 10.66-14 |
| Education to patient | Good | 6-8 |
| | Bad | 3-5 |
| Total Score | Good | 26.6-40 |
| | Bad | 13-26.5 |

Table 6. Logistics Regression of Unattainable Doctor's Clinical Practice

| Characteristic | Odds Ratio | CI 95% | p-value |
|---|---|---|---|
| **Guideline Utilization** | | | |
| Bad | Ref | Ref | Ref |
| Good | 0,04 | 0,00-0,62 | 0,02* |
| **Workload** | | | |
| Heavy | Ref | Ref | Ref |
| Moderate | 0,001 | 0,00-0,21 | 0,01* |
| Mild | 0,09 | 0,01-5,91 | 0,34 |
| **Education to Patient** | | | |
| Bad | Ref | Ref | Ref |
| Good | 0,15 | 0,00-0,32 | 0,01* |

It was found that the use of good guidelines had the highest percentage in public health centers and the lowest in independent practicing doctors. Then for heavy workloads, the highest number of workloads was obtained at Primary Clinics and the most light workloads were independent practicing doctors. Among the three types of primary healthcare facilities, the

most are moderate workloads. In education scores for patients, the most good scores were obtained at the Primary Clinic. The use of a good guideline for type 2 DM has a 96% probability of achieving good clinical practice in the management of DM. The moderate workload has a 99% probability of achieving good clinical practice in the management of DM. Good patient education has a 98% probability of achieving a good doctor's clinical practice in the management of DM.

Table 7. Frequency of Healthcare System Score Based on Primary Healthcare Facilities Types

| Parameter | Primary Healthcare Facilities Types | | | |
|---|---|---|---|---|
| | Public Health Center | Private Clinic | Independent Practicing Doctor | Total |
| **Guideline procurement** | | | | |
| - **Yes** | 12 (54,5%) | 40 (66,7%) | 15 (88,2%) | 67 (67,7%) |
| - **No** | 10 (45,5%) | 20 (33,3%) | 2 (11,8%) | 32 (32,3%) |
| **Durg Availability** | | | | |
| - **Good** | 18 (81,8%) | 49 (81,7%) | 15 (88,2%) | 82 (82,8%) |
| - **Bad** | 4 (18,2%) | 11 (18,3%) | 2 (11,8%) | 17 (17,2%) |
| **Laboratory Examination** | | | | |
| - **Good** | 12 (54,5%) | 58 (96,7%) | 17 (100%) | 87 (87,9%) |
| - **Bad** | 10 (45,5%) | 2 (3,3%) | 0 (0%) | 12 (12,1%) |
| **Total Score** | | | | |
| - **Good** | 19 (86,4%) | 57 (95%) | 17 (100%) | 93 (93,9%) |
| - **Bad** | 3 (13,6%) | 3 (5%) | 0 (0%) | 6 (6,1%) |

Table 8. Logistics Regression of Unattainable Healthcare System Score

| Characteristic | Odds Ratio | CI 95% | p-value |
|---|---|---|---|
| **Guideline Procurement** | | | |
| No | Ref | Ref | Ref |
| Yes | 0,22 | 0,04-1,25 | 0,09 |
| **Drug Availability** | | | |
| Bad | Ref | Ref | Ref |
| Good | 0,00 | 0,00-1,00 | 0,45 |
| **Laboratory Examination** | | | |
| Bad | Ref | Ref | Ref |
| Good | 0,02 | 0,001-0,300 | 0,00* |

For the healthcare system, we assess 3 parameters which include procurement guidelines, drug availability, and laboratory tests. The total of respondents who got a good PROLANIS system achievement reached 93.9% of the 93 respondents. Independent practicing doctors have the highest proportion in achieving a good PROLANIS system (100%), followed by private clinics (95%), then public health centres (86.4%). A good laboratory examination has a 98% probability of achieving a good PROLANIS system. The use of type 2 DM guidelines and drug availability are not dominant factors in achieving a good PROLANIS system.

Table 9. Frequency of Patient Knowledge and Treatment Adherence Based on Primary Healthcare Facilities Types

| Parameter | Primary Healthcare Facilities Types | | | |
|---|---|---|---|---|
| | Public Health Center | Private Clinic | Independent Practicing Doctor | Total |
| **Knowledge** | | | | |
| Low | 4 (6,3%) | 13 (5,5%) | 2 (3,3%) | 19 (5,3%) |
| Moderate | 54 (85,7%) | 163 (69,4%) | 44 (73,3%) | 261(72,9%) |
| High | 5 (7,9%) | 59 (25,1%) | 14 (23,3%) | 78 (21,8%) |
| **Treatment Adherence** | | | | |
| Good | 44 (69,8%) | 190 (80,9%) | 46 (76,7%) | 280(78,2%) |
| Bad | 19 (30,2%) | 45 (19,1%) | 14 (23,3%) | 78 (21,8%) |

Table 10. Spearman Correlation Test of Knowledge Score & Patient Treatment Adherence Score

| | | Knowledge Score | Adherence Score |
|---|---|---|---|
| **Knowledge Score** | Coefficient | | 0,18 |
| | *p-value* | | 0,00 |
| **Adherence Score** | Coefficient | 0,18 | |
| | *p-value* | 0,00 | |

The highest percentage of knowledge scores was obtained in patients at the Private Clinic and the lowest knowledge score was the highest percentage at the public health center. Then, for treatment adherence, the most routine medication adherence was found in the private clinic group and the least obedient in the public health center group. The data shows a significant weak positive correlation on the knowledge score on the compliance score. The knowledge score is interpreted if the higher the score, the patient will have a good tendency. In contrast to the adherence score, where the higher the score, the patient will tend to be disobedient in treatment. So it can be concluded that the higher the knowledge score, the patient has a tendency to be disobedient in treatment.

## DISCUSSION

The mean value of HbA1c (%) in all type 2 DM patients was 7.82 ± 2.19. Where the higher HbA1c value was obtained at the public health care, namely 7.91 ± 2.27 and the lower average value was obtained at the private clinics, namely 7.75 ± 2.19. Overall, out of 2256 subjects only about 32% of patients achieved the HbA1c target (≤7%). This data is not much different from the research in primary health care in Indonesia conducted by Cholil et al (2012), where the achievement of HbA1c control in the range of 30.8% of the type 2 DM population.[6] Research conducted by Soetedjo et al., (2018), the achievement of HbA1c ( <7%) in 783 patients in Indonesia is only 29.2% of the population.[7] What distinguishes this study is that although both were unable to achieve HbA1c control, the average HbA1c in the population of Prolanis type 2 DM patients in Malang was better than Soetedjo's study, which was 8.3%, this is possible because Prolanis patients have received long-term disease management. and good monitoring, while Soetedjo's study used a population sample of diabetic patients with varied glycemic control management and monitoring.

This result is slightly better than the data in America and Japan. Data from the National Health and Nutrition Examination Survey shows that in America only 50% of type 2 DM patients can achieve control of HbA1c <7% and that number has been decreasing since 2003-2006 and 2011-2014.[11] The achievement of HbA1c control in Japan is also not much different from the data from America. In a study involving 9956 subjects with type 2 DM at primary health

facilities, there were 52.9% subjects who achieved HbA1c <7%.[12]

There are several things related to not achieving optimal blood glycemic control in type 2 DM patients which include age, sex, total cholesterol, HDL, LDL, TG, and microalbuminuria. With increasing age, patients had better glycemic control (HbA1c 7%) by 3%. This is the same as research Cambra et al. (2016) who stated that type 2 DM patients with age < 65 had an average HbA1c of > 10. Male sex had a 1.36-fold probability of not achieving glycemic control compared to women. This is different from the results of research by Cambra et al. (2016) which stated that more males (61.2%) achieved HbA1c 7% compared to females (58.8%).[13] Research conducted by G Duarte et al (2019) also states that women have the possibility of worse glycemic control than men. Possible factors that cause poorer glycemic control in women include differences in glucose homeostasis, response to therapy and psychological factors.[14] In addition, hormonal factors, differences in the distribution of body fat and obesity levels, which are more prone to occur in women, may be factors that influence the achievement of glycemic control. From the fat profile data, it is known that the mean total cholesterol of type 2 DM patients is 209.5 ± 46.6 (mg/dl). Meanwhile, the mean LDL level was 132.76 ± 42.73 (mg/dl). This mean LDL is higher than the study in Spain by Cambra et al. (2016), the mean LDL in type 2 DM patients was lower at 109.1 mg/dl where about 40% of patients had LDL levels < 100 mg/dl.

There are 3 things that are evaluated from the doctors' perspective, including the use of type 2 DM guidelines, workload and education provided by doctors to patients. From the data, it was found that the use of type 2 DM guidelines has the possibility of achieving good clinical practice of doctors by 96% with a confidence level of p = 0.02. If it is associated with the achievement of HbA1c values in all subjects, the use of type 2 DM guidelines by doctors has been carried out so that statistically it is not a factor that affects the failure to achieve HbA1c in type 2 DM patients. According to Tunceli et al (2015), the implementation of the use of diabetes clinical guidelines will improve diabetes care. In addition, the use of the American Diabetes Association guidelines will increase the understanding of primary care providers for diabetes management, reduce the number of treatments due to diabetes emergencies, reduce diabetes care costs and improve glycemic control. Baptista et al (2016) and Al Harbi et al (2015) also concluded that the use of diabetes clinical guidelines will improve several problems in diabetes management and improve glycemic control.

Regarding the doctors' workload on primary healthcare facilities, it was found that mostly the participant had a moderate workload. From the statistical test a moderate workload will support good clinical practice, so it is not a factor that affects the failure to achieve HbA1c control in type 2 DM patients. According to Guan et al (2020) a doctor in outpatient services should ideally only work a maximum of 4 hours continuously. It was also stated that the longer the doctor worked, the less the clinical service provided to the patient would be, which in turn could have an impact on the failure to achieve HbA1c in type 2 DM patients.

Education from doctors to patients is needed in the management of type 2 DM. Understanding the patient about his condition will increase awareness in the management of type 2 DM which will be carried out in the long term. From the data obtained, good education will have an 85% effect on good clinical practice, so it is not a factor that affects the failure to achieve HbA1c control in type 2 DM patients. Judging from several indicators, namely doctors who have used guidelines in the care of type 2 DM patients besides that; they have also done quite good education for patients. The workload, which is mostly light and moderate, also supports the achievement of good clinical practice by doctors at primary healthcare facilities.

There are 3 factors analyzed in this study, namely the use of guidelines, drug procurement and laboratory tests. From the data on the use of the type 2 DM guideline, it was found that the

distribution of the use of the type 2 DM guideline varied. A total of 32.3% of the subjects stated that there was no guideline used for patient care. A total of 16.2% stated that there was a guideline in the form of an official letter, 25.3% in the form of a soft file guide, and 26.3% in the form of a guidebook. From the distribution of these data, it can be concluded that currently there is no standard guideline used in the service of type 2 DM patients at the primary healthcare facilities BPJS Kesehatan Malang City.

In multivariate statistical analysis, it was found that the use and application of guidelines in patient care will support 89.9% of good clinical practice, which indirectly affects the achievement of HbA1c in type 2 dm patients. clinic, but because there is no standard guideline from the Prolanis service provider in primary healthcare facilities, this becomes a problem that can lead to non-standard clinical practice in all types of primary healthcare facilities managers of Prolanis BPJS.

The availability of good drugs and laboratory support in the Prolanis service system will support good clinical practice. The ideal availability of drugs is when there is a standard guideline in which there is a choice of drugs according to the condition of each patient and indications for treatment. From the system factor, it can be seen the fact that clinical practice services have been running well in terms of medicines and laboratory support, but because there is no standard guideline issued by Prolanis service providers, good clinical practice cannot be implemented because there are no standard in management of type 2 DM patients at primary healthcare facilities BPJS in Malang city.

We analyzed the patient population from 2 different aspects consisting of patient knowledge and patient treatment adherence. A total of 72.9% with moderate knowledge, 21.8% with high knowledge, and 5.3% with low knowledge. A total of 78.2% of subjects were adherent to treatment and 21.8% did not adhere to treatment. From the relationship of knowledge and compliance, there was no significant correlation between the two. So, from statistical data, it can be concluded that the high score of knowledge has no effect on patient compliance in treatment. This is different from the research conducted by Boyoh et al (2015), which concluded that there is a relationship between knowledge and compliance. The difference in the results is possible from the number of research samples which are only 58 respondents, besides the operational definition of knowledge is not explained in detail in the study.

The limitations of our study are limited to data and sample size. The HbA1c data that we got from the database did not contain specific information regarding each health facility. Then, research that includes primary data only takes a few representative samples where a total sampling needs to be carried out on a daily basis with data related to secondary data, so that there is a direct relationship between the two.

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CASE REPORT

# Two-Year Follow-Up of Parathyroid Hormone, Calcium, and Vitamin D Serum Levels in a Patient after Parathyroidectomy

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**ABSTRACT**

Parathyroidectomy is the definitive treatment for primary hyperparathyroidism. Because of the hungry bone syndrome and prolonged hypocalcemia risk, we must follow up on a patient's parathyroid hormone, calcium, and vitamin D serum levels after parathyroidectomy. In this case report, we reported on a parathyroidectomy patient whom we followed for two years and who, interestingly, had elevated parathyroid hormone levels. A 35-year-old male patient diagnosed with a left parathyroid tumor underwent parathyroidectomy and isthmolobectomy. The patient was treated with calcium, vitamin D, and levothyroxine supplementation. We diagnosed the patient with hungry bone syndrome on the fourth day of post-parathyroidectomy. Then, we documented calcium, vitamin D, and PTH levels in the next two years. The calcium levels are 7.2 (June 2022), 8.2 (July 2022), 8.5 (September 2022), 7.8 (October 2022), 8.1 (June 2023), and 9.7 (June 2024). The PTH levels are 244.2 (June 2022), 328.3 (July 2022), 306.5 (September 2022), 457.2 (October 2022), 163.3 (June 2023), and 34.4 (June 2024). The Vitamin D levels are 34.4 (July 2022), 13.4 (March 2023), 35.2 (September 2023), and 50.4 (April 2024). We increased the dose of calcium and vitamin D supplementation. The patient is in good condition and has reached a normal level of these laboratory parameters in the second year post-parathyroidectomy. PTH, calcium, and vitamin D serum are needed for follow-up in patients after parathyroidectomy. Normalizing calcium and vitamin D serum is essential to maintaining a normal PTH level. Normal PTH, calcium, and vitamin D serum levels are the cure indications in this patient.

**Keywords**: Parathyroidectomy, parathyroid hormone, calcium, vitamin D

## INTRODUCTION

Parathyroidectomy is the definitive treatment for primary hyperparathyroidism. Parathyroidectomy is the preferred choice of treatment and indicated for all patients with symptomatic primary hyperparathyroidism, along with recommendations with other considerations. However, parathyroidectomy is not without possible flaws. Hungry bone syndrome may occur postoperatively. This condition is most defined as a profound hypocalcemia of less than 8.4 mg/dL which persists for more than four days postoperatively, presenting along with hypophosphatemia, hypomagnesemia, and normal parathyroid hormone (PTH) levels.[1-7] Because of the hungry bone syndrome and prolonged hypocalcemia risk, we need to follow up on a patient's parathyroid hormone, calcium, and vitamin D serum after parathyroidectomy. PTH is integral in the regulation and homeostasis of serum calcium and phosphate. A reduction in serum calcium levels stimulates the release of PTH from the parathyroid glands which subsequently enhances calcium reabsorption through the kidney, inhibits phosphate reabsorption, and induces phosphaturia. PTH also stimulates conversion of the inactive 25-hydroxyvitamin D (25[OH]D) to the active metabolite 1,25(OH)2D through transcriptional activation of the gene which codes for the 25-hydroxyvitamin D-1a hydroxylase (CYP27B1) enzyme. This active metabolite could increase intestinal absorption of calcium and, less significantly, phosphate. These PTH responses to hypocalcemia aim to restore serum calcium levels towards the normal range.[8]

In this case, parathyroidectomy patient that we followed for two years and interestingly had elevated parathyroid hormone levels. Postoperative increase of PTH may be associated with persistent or recurrent hyperparathyroidism, vitamin D insufficiency, mild renal failure, hyperfunction of previously suppressed parathyroid glands, unrecognized familial hypercalciuric hypocalcemia, and increased bone redistribution of calcium.[9-11]

## CASE ILLUSTRATION

A 35-year-old male patient diagnosed with left parathyroid tumor by laboratory and radiologic examination underwent parathyroidectomy and isthmolobectomy. The patient was treated with calcium, vitamin D, and levothyroxine supplementation. We diagnosed the patient with hungry bone syndrome on 4$^{th}$ day of post parathyroidectomy.

Then, we documented calcium, vitamin D, and PTH levels in the next two years. The calcium levels are 7.2 mg/dl (June 2022), 8.2 mg/dl (July 2022), 8.5 mg/dl (September 2022), 7.8 mg/dl (October 2022), 8.1 mg/dl (June 2023), 9.7 mg/dl (June 2024). The PTH levels are 244.2 pg/ml (June 2022), 328.3 pg/ml (July 2022), 306.5 pg/ml (September 2022), 457.2 pg/ml (October 2022), 163.3 pg/ml (June 2023), 34.4 pg/ml (June 2024). The Vitamin D levels are 34.4 ng/ml (July 2022), 13.4 ng/ml (March 2023), 35.2 ng/ml (September 2023), 50.4 ng/ml (April 2024). We found an increase in PTH levels in the six months; then, we increased the dose of calcium supplementation and vitamin D. The patient is now in good condition and has reached a normal level of these laboratory parameters in the second year post-parathyroidectomy. We suggested an increased PTH level in this patient because of vitamin D deficiency.

## DISCUSSION

Parathyroid hormone (PTH) is secreted by the chief cells of the parathyroid glands. Calcium, ionized in the extracellular fluid as $Ca^{++}$, acts as a predominant regulator of PTH production. $Ca^{++}$ which binds to the calcium sensing receptor (CaSR) results in signaling in the parathyroid gland, which inhibits PTH gene expression and PTH secretion or even enhance PTH degradation. On the contrary, lower $Ca^{++}$ may increase PTH gene expression, promoting synthesis of PreproPTH which is then converted to ProPTH and to PTH to be secreted. Vitamin D in the active form of 1,25(OH)2D could bind to the vitamin D receptor (VDR) and also inhibit PTH gene transcription and subsequent expression.[8]

Parathyroid hormone (PTH) enhances calcium reabsorption and inhibits phosphate

reabsorption through the renal tubules, promotes renal synthesis of 1,25-dihydroxyvitamin D which subsequently increases intestinal calcium absorption, and may also increase bone resorption through stimulation of osteoclasts and release of $Ca^{++}$ and inorganic phosphate from the skeleton. Pathological overproduction of PTH may cause inappropriate increases of calcium and decrease of phosphate, with hypercalcemia cited as a complication to incorrectly treated parathyroid adenoma, possibly aggravating into a clinical phenomenon of parathyroid crisis which is characterized by extremely high calcium levels of more than 15 mg/dL.[8,12] The American Association of Endocrine Surgeons have established guidelines for definitive management of hyperparathyroidism which includes recommendations on the indications of parathyroidectomy. Parathyroidectomy is indicated for all patients with symptomatic primary hyperparathyroidism.[1]

Postoperative failure to reestablish normal calcium homeostasis within 6 months remains the most common complication of parathyroidectomy. This may be associated with persistent primary hyperthyroidism with failure to achieve normocalcemia within 6 months of surgery or recurrent primary hyperthyroidism with recurrence of hypercalcemia after a normocalcemic interval at more than 6 months after surgery. Several studies have found the incidence of permanent postoperative hypocalcemia in 0.5% to 3.8% cases, and persistent/recurrent hyperparathyroidism in 2% to 5% cases.[1,13–17]

Hungry bone syndrome is defined by profound hypocalcemia of less than 8.4 mg/dL which persists beyond four days postoperatively and often presents with hypophosphatemia, hypomagnesemia, and normal PTH level. It often occurs in the post-operative period in patients who have undergone parathyroidectomy or thyroidectomy, or even in patients with osteoblastic metastases. Several risk factors postulated to be correlated with hungry bone syndrome are elevated PTH, elevated alkaline phosphatase, radiological evidence of bone disease, higher BMI, higher blood urea nitrogen levels, larger volume of gland removal, and higher number of osteoclasts found through biopsy. Hungry bone syndrome in primary hyperparathyroidism is found to be associated with older age and higher preoperative calcium levels; meanwhile, it is found to be associated with younger age and lower preoperative calcium levels in secondary hyperparathyroidism.[5-8]

Hungry bone syndrome is treated with calcium supplementation, intravenous and oral or oral alone; vitamin D supplementation, possible magnesium supplementation to prevent calcium replacement hindrance due to hypomagnesemia and its alteration of PTH's ability to exert its effects, with monitoring to these associated levels.[5–8,18–22] Previous studies have cited causes of postsurgical persistent or recurrent hyperparathyroidism to be adenoma (68%), parathyroid hyperplasia (28%), parathyroid carcinoma (3%), and other causes such as parathyromatosis and autograft relapse (1%). Double adenomas or four-gland hyperplasia increases the likelihood of persistent or recurrent hyperparathyroidism. Other states associated with postsurgical increase in PTH include vitamin D insufficiency, mild renal failure, parathyroid hyperfunction, unrecognized familial hypercalciuric hypocalcemia, and increased bone redistribution of calcium.[9,11]

Vitamin D has specific receptors at the level of PTH production in parathyroid cells and displays direct inhibitory effect towards the hormone secretion. Through the feedback mechanism, vitamin D deficiency stimulates the cells to secrete PTH. Thus, elevated PTH value may be found following surgery and may not necessarily indicate surgical failure but instead may point to an uncorrected vitamin D deficiency. Lower levels of vitamin D before surgery has also been associated with larger parathyroid adenomas with more severe phenotype of hyperparathyroidism. PTH kinetics after parathyroidectomy have been found to remain unchanged due to lack of vitamin D deficiency correction, even as PTH is displayed

at higher values. On the contrary, achieving and maintaining normal vitamin D levels postoperatively will help absorption of calcium, normalization of PTH levels, and may improve bone mineral density.[1,20]

Short-term vitamin D and calcium supplementation should be considered to prevent hypocalcemia following parathyroidectomy. Patients known to be vitamin D deficient are also strongly recommended to receive vitamin D supplementation after parathyroidectomy. Intravenous calcium administration with either calcium chloride or calcium gluconate is indicated for treatment of hungry bone syndrome in cases with a serum calcium level of less than 7.6 mg/dl, symptomatic cases, or cases with ECG changes such as QTc prolongation. The recommended regimen begins with a bolus of 10% calcium gluconate, 10 to 20 mL in 50 to 100 mL of D5%, given over 5 to 10 minutes, which provides an equivalent of approximately 100 to 200 mg of elemental calcium. It is followed by a continuous infusion with a dose of 100 mL of 10% calcium gluconate in 1 L of D5%, equivalent to approximately 1 mg/mL of elemental calcium, starting at 50 mL/hour and titrated every 4 to 6 hours according to calcium, phosphorus, and magnesium levels. The aim of administration is a rate of 0.5 to 1.5 mg elemental calcium/kg/hour. Oral supplementation of calcium using calcium citrate (211 mg elemental calcium per 1 g) or calcium carbonate (400 mg elemental calcium per 1 g) should also be given with vastly varying recommendations of dosage among different underlying etiologies, with case reports citing doses as low as 800 mg of elemental calcium in cases with parathyroid adenoma to doses of 36 g elemental calcium per day in cases with hungry bone syndrome after parathyroidectomy for secondary hyperparathyroidism. Vitamin D supplementation is also recommended using calcitriol 0.25 to 1 mcg per day, with consideration that the effects of vitamin D may take days to manifest in correlation to calcium levels.[1,20–23]

Several complications may occur after parathyroidectomy for parathyroid hormone, calcium, and vitamin D. Permanent hypoparathyroidism may occur after parathyroidectomy (0%-3.6%). Assessment of prolonged hypoparathyroidism requires evaluation for at least 6 months. Assessment should include calcium, PTH, and 25-hydroxyvitamin D levels. Intraoperative parathyroid hormone (PTH) monitoring can predict outcomes. PTH ≤40 pg/mL or a decrease of ≥50% from baseline minimizes the possibility of persistence. Intraoperative PTH measurement can reduce the risk of recurrence rate to 2.5%-5%. Risk factors for persistence are hyperplasia and normal parathyroid tissue on histopathology. Risk factors for recurrence are cardiac history, obesity, endoscopic approach, and low-volume center (minimum 31 cases/year). Cases with multiple adenomas or quadruple hyperplasia have a greater chance of persistence/recurrence.[1,10,24]

Surgery is considered successful if postoperative eucalcemia persists beyond the first six months. Hypercalcemia that persists during this period is defined as persistence, and recurrence is defined as hypercalcemia after 6 months of normocalcemia. Moderate postoperative hypocalcemia has been reported in 5% to 47%. Patients may experience transient paresthesias after surgery related to low or normal calcium levels, but hypocalcemia can also be asymptomatic. Calcium levels > 9.7 mg/dL for 6 months and eucalcemic parathyroid hormone elevations at 6 months may be associated with recurrence requiring long-term follow-up. Serum calcium ≥ 9.8 mg/dL for 6 months and parathyroid hormone ≥ 80 pg/mL indicate a risk of recurrence. Prophylaxis of hypocalcemia after parathyroidectomy should be considered with short-term calcium and/or vitamin D supplementation. Supplementation may be based on parameters such as preoperative calcium levels, adenoma weight, rate of hormone decline index (HDI) decline, or immediate or 24-hour calcium levels. Severe and prolonged postoperative hypocalcemia may occur and require intravenous calcium administration after parathyroidectomy, which

may complicate reoperation.[1,10]

Vitamin D is an important factor for good outcomes. Normal postoperative vitamin D levels facilitate calcium absorption and normalization of PTH levels and may increase bone mineral density (BMD). Vitamin D deficiency can worsen a variety of medical problems, ranging from decreased BMD to cardiovascular disease. Up to 40% of patients after parathyroidectomy may have elevated postoperative PTH levels, which have been associated with vitamin D deficiency. The combination of elevated PTH levels and low 25-OH vitamin D levels has been associated with higher fracture rates in normocalcemic postmenopausal women. Normal postoperative vitamin D levels may help increase BMD, calcium absorption, and normalize PTH levels. In patients undergoing surgery for calcium absorption and maintenance of skeletal health, patients with 25-OH vitamin D deficiency should ideally receive vitamin D supplementation until adequate 25-OH vitamin D levels are achieved (>30 ng/mL). Once patients achieve normal 25-OH vitamin D levels, they should receive the recommended daily intake of vitamin D. [1,10,24]

In this case report, laboratory parameters of parathyroid hormone, calcium, and vitamin D were monitored, aiming to prevent persistence or recurrence hyperparathyroidism. The patient was also given calcium and vitamin D supplements, to maintain eucalcemia as a therapeutic goal in the patient.

## CONCLUSION

The PTH, calcium, and vitamin D serum are needed for follow-up in patients after parathyroidectomy. Normalizing calcium and vitamin D serum are essential to maintain normal PTH levels. Normal PTH, calcium, and vitamin D serum are the cure indications in this patient.

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CASE REPORT

# Hyperemesis Gravidarum with Gestational Transient Thyrotoxicosis Inducing Thyrotoxic Periodic Paralysis in Diabetes Mellitus and Hypertension: A Case Report

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**ABSTRACT**

Hyperemesis gravidarum (HG) is often associated with gestational transient thyrotoxicosis (GTT) due to elevated human chorionic gonadotropin (hCG) levels, affecting approximately 60% of HG patients. GTT is generally self-limiting, resolving by the first or early second trimester without requiring pharmacological treatment. We present the case of a 38-year-old pregnant woman, in her third pregnancy, who experienced severe nausea and vomiting at 6 weeks of gestation, with a Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) score of 12. Laboratory findings indicated low thyroid-stimulating hormone (TSH) and high free thyroxine (FT4), consistent with GTT, while thyroid ultrasound showed no abnormalities. The patient had a history of chronic hypertension since her first pregnancy and diabetes mellitus diagnosed a year earlier. Three weeks later, she was readmitted and diagnosed with thyrotoxic periodic paralysis (TPP) secondary to GTT. Treatment included intravenous fluids, potassium supplementation, antiemetics, vitamins, antithyroid drugs, and continued management of her diabetes and hypertension. HG, which is most common in the first trimester, is often linked to thyroid dysfunction due to hCG stimulation. While GTT is typically self-limiting, complications like TPP can arise, adding complexity to patient management, especially with coexisting conditions like diabetes and hypertension. Treatment strategies focused on symptom control, fluid rehydration, and careful adjustments of medications for thyroid, glycemic, and blood pressure management. Unfortunately, the patient did not return for follow-up, limiting further evaluation of her thyroid function in the second trimester. This case highlights the need for accurate diagnosis and timely intervention to prevent severe maternal and fetal outcomes, particularly in complex cases with multiple comorbidities.

**Keywords**: Hyperemesis gravidarum, hyperthyroidism, gestational transient thyrotoxicosis, thyrotoxic periodic paralysis

## INTRODUCTION

Hyperemesis Gravidarum (HG) is a condition characterized by severe nausea and vomiting during pregnancy, associated with fluid and weight loss, ketonemia, ketonuria, electrolyte and acid-base imbalance, dehydration, and weight loss ≥5%.[1-3] HG typically develops between the 4th and the 10th weeks of pregnancy and resolves by the 20th week.[1] HG can lead to serious metabolic complications including malnutrition, vitamin K deficiency, Wernicke encephalopathy, acute liver and kidney failure, esophageal rupture, pneumothorax, pre-eclampsia, placental abruption, neuro-developmental delay of the fetus, preterm birth, and maternal death.[3]

HG occurred due to higher levels of pregnancy hormones, especially human chorionic gonadotropin (hCG). hCG can stimulate either the upper gastrointestinal tract or thyroid gland function activity due to its structural similarity to thyroid-stimulating hormone (TSH), potentially allowing hCG to exhibit TSH-like effects.[1,4] About 5% of women may have a serum TSH level below 0.1 mIU/L by 11 weeks of pregnancy.[5]

During pregnancy, thyroid function changes, and hormone levels shift from their normal ranges. The concentrations of total triiodothyronine (T3) and thyroxine (T4) increase, leading to gestational transient thyrotoxicosis (GTT). GTT is characterized by hyperthyroidism that develops for the first time in early pregnancy, without signs of thyroid autoimmunity or evidence of Graves' disease, and typically resolves by the end of the first trimester or early in the second trimester.[1] GTT induced by hCG can be distinguished from Graves disease by the absence of any history of thyroid disease, negative TSH receptor antibodies, and normal thyroid ultrasound findings.[5-7] Approximately 60% of patients with HG experience transient hyperthyroidism.[1] GTT is a self-limiting condition and will resolve spontaneously and rarely requires drug treatment.[2,6,8]

The primary mechanism of thyroid stimulation during pregnancy leading increased total T3 and T4 levels as a result of elevated estrogen levels, which leads to increased production of thyroid-binding globulin (TBG) and reduced T4 metabolism.[1,4,9] This mechanisms results in elevated free T4 levels. Thyrotoxic periodic paralysis (TPP) is also associated with hyperthyroidism with characterized by acute paralytic episodes and hypokalemia.[10]

## CASE ILLUSTRATION

A 38-year-old pregnant woman (G3P2L2A0) presented to the emergency department with complaints of severe nausea and vomiting exceeding 10 episodes since that morning. She also reported generalized weakness, fatigue, and epigastric pain but denied diarrhea, fever, vaginal discharge, or bleeding. She did not experience palpitations, nervousness, hand tremors, heat intolerance, or anterior neck swelling. She denied blurred vision, headache, or pedal edema. Over the past year, she experienced unintentional weight loss of 7 kg. The first day of her last menstrual period was April 3, 2024. Her menarche occurred at age 15, with a history of regular monthly cycles. She had two prior full-term vaginal deliveries. Upon admission, her Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) score was 12, indicating moderate HG. She had a history of diabetes mellitus managed with metformin 500 mg BID and glibenclamide 5 mg OD and hypertension diagnosed during her first pregnancy, however she does not take any drugs routinely.

On examination, the general condition was poor. Her blood pressure was 169/90 mmHg, heart rate 110 bpm, respiratory rate 22 breaths per minute, temperature 36.8°C, and oxygen saturation 98% on room air. She weighed 35 kg (pre-pregnancy weight: 34 kg) with a height of 143 cm, resulting in a BMI of 16.67 kg/m$^2$, categorized as underweight. Her mid-upper arm circumference was 23 cm, indicating chronic energy deficiency. There were no signs of exophthalmos or thyroid enlargement. Abdominal examination revealed epigastric tenderness. Laboratory results are

summarized in table 1 ECG showed normal sinus rhythm.

Transabdominal ultrasound confirmed a single live intrauterine pregnancy with a crown-rump length (CRL) of 0.82 cm, corresponding to 6 weeks and 3 days of gestation, with a positive fetal heartbeat. Thyroid ultrasound revealed a normal-sized gland without increased vascularity or nodules (figure 1). She was clinically diagnosed with hyperemesis gravidarum complicated by gestational transient thyrotoxicosis (GTT), diabetes mellitus, chronic hypertension, and chronic energy deficiency.

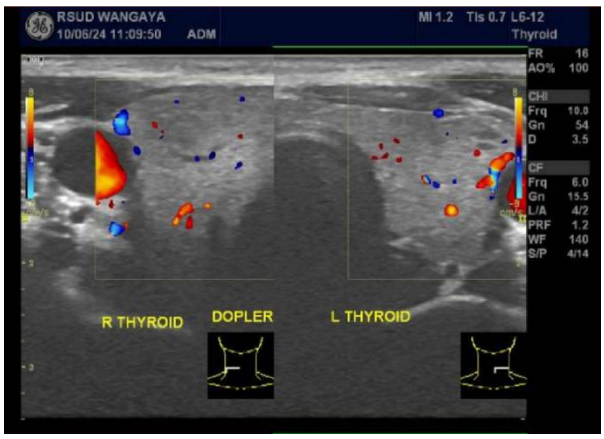


**Figure 1. Thyroid ultrasound of the Patient**

The patient was treated with intravenous fluids (5% dextrose and Ringer's lactate, 2000 mL/day), ranitidine 50 mg BID, ondansetron 8 mg TID, vitamin B6 10 mg OD, multivitamin infusion (B1, B6, B12), folic acid 400 mcg OD, insulin aspart 3 units TID, methyldopa 250 mg BID, and amlodipine 5 mg OD. She tolerated oral intake and was discharged after six days with a PUQE score of 7. She was prescribed ranitidine 150 mg BID, ondansetron 8 mg TID, folic acid 400 mcg OD, propylthiouracil (PTU) 100 mg OD, methyldopa 250 mg BID, amlodipine 5 mg OD, and was temporarily taken off insulin. However, she did not return for follow-up or medication monitoring.

Three weeks later, she returned with fatigue, weakness, and bilateral lower extremity paralysis (motor strength 4/5) lasting two days, accompanied by nausea and vomiting five times daily. Blood pressure was 140/90 mmHg, and heart rate 90 bpm. Ultrasound revealed a single live intrauterine pregnancy at 9 weeks 6 days (CRL 2.90 cm) with a positive fetal heartbeat. Laboratory results showed hypokalemia and elevated liver enzymes (Table 1). She was treated with intravenous potassium replacement (25 mEq potassium chloride), ranitidine 50 mg BID, ondansetron 8 mg TID, multivitamin infusion, folic acid 400 mcg OD, PTU 100 mg OD, curcuma tablets TID, and insulin aspart 6 units TID. On day three, she experienced hypoglycemia (blood glucose 50 mg/dL), prompting discontinuation of insulin.

Potassium levels normalized by day six. She was started on propranolol 10 mg BID and methyldopa 500 mg BID. Echocardiography revealed a left ventricular ejection fraction of 60%, concentric hypertrophy with mild mitral regurgitation, for which digoxin 0.25 mg BID was added. She was discharged after 21 days with improved symptoms, stabilized glucose levels, and better nutritional intake. She was discharged with the following medications: ranitidine 150 mg BID, ondansetron 8 mg TID, vitamin B6 10 mg OD, folic acid 400 mcg OD, PTU 100 mg BID, methyldopa 250 mg BID, amlodipine 5 mg OD, and potassium slow release (KSR) 1200 mg TID.

Preventing GTT can be challenging, as it is often related to the physiological changes that occur during early pregnancy. In this case, it is important to treat the precipitating factors of HG that exacerbate thyroid dysfunction, maintain adequate hydration and nutrition, and evaluate and address any preexisting thyroid disorders.

Table 1. Patient's Laboratory Results

| Gestational Age | 6w3d | 9w6d | | |
|---|---|---|---|---|
| Parameter | | | Units | Reference Values |
| | 7th June | 30th June | | |
| Haemoglobin | 15.1 | 12.9 | g/dL | 12.0 - 16.0 |
| Haematocrit | 43.4 | 36.4 | % | 37.0 - 47.0 |
| Leucocyte | 13.040 | 13.720 | /µL | 4.0 - 10.0 |
| Platelet | 297 | 314 | $10^3$/µL | 150 - 400 |
| AST | 27 | **100** | U/L | 0 - 37 |
| ALT | **52** | **149** | U/L | 0 - 42 |
| Urea | 25 | 15 | mg/dL | 10 - 50 |
| Creatinine | 0.4 | 0.3 | mg/dL | 0.3 - 1.2 |
| Sodium | 139 | 131 | mmol/L | 130 - 145 |
| Potassium | 4.3 | **2.9** | mmol/L | 3.5 - 5.5 |
| Chloride | 102 | 100 | mmol/L | 95 - 108 |
| Random Blood Sugar | 201 | 224 | mg/dL | 80 - 200 |
| HbA1c | 5.5 | 7.0 | % | |
| TSH | **0.17** | **0.06** | mIU/L | 0.35 - 5.10 |
| fT4 | **1.79** | **4.63** | ng/dL | 0.5 - 1.4 |
| Urinalysis | | | | |
| Ketone | **+4** | **+4** | | Negative |
| Glucose | **+4** | **+3** | | Negative |
| Protein | Negative | Negative | | Negative |

## DISCUSSION

HG incidence is more higher occurred during the first trimester, especially in multiple pregnancies compared to single pregnancy.[3] A systematic review and meta-analysis by Farshbaf-Khalili et al.[1] found a significant association between HG and thyroid function markers such as free triiodothyronine (fT3), TSH, TTG, free thyroxine (fT4), TSH, TT4, and hCG. Women with HG showed significantlyttg elevated serum levels of fT3, fT4, and TT4, while TSH levels reduced compared to women without HG, indicating a strong link between HG and GTT.[1] From Nijsten et al.[11] study findings TSH and FT4 levels are not predictive of HG severity, while Zheng et al.[12] study findings β-hCG levels correlate with the degree of HG severity and associated hyperthyroidism. Although GTT is typically self-limiting and resolves spontaneously, atypical presentations may occur, such as delayed onset, and severe symptoms requiring interventions, or prolonged duration.[13]

During pregnancy, the thyroid gland volume increases by 10-40% and occurs due to iodine deficiency caused by active iodine transport to the fetus through the placenta, increased renal excretion, and increased iodine consumption by the maternal thyroid.[4,9] Despite the elevation in total thyroid hormone levels, the free-form remains steady, maintaining a euthyroid state in pregnant woman.[9] Reference ranges for thyroid function tests during pregnancy is different due to physiological changes such as increase of TBG levels and the peak of hCG levels (see Figure 1)[14] and normal references ranges for thyroid hormones among non-pregnant and pregnancy are outlined in Table 2.

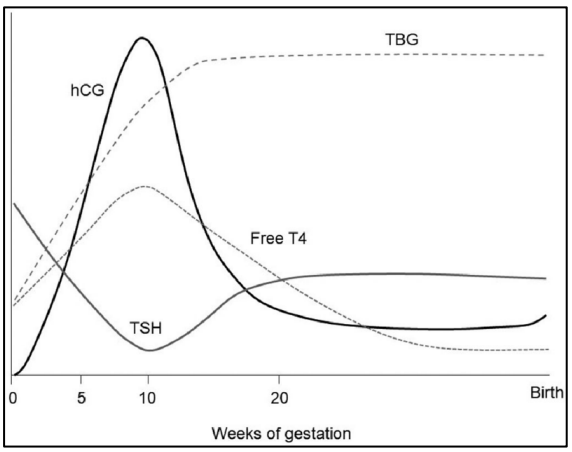

Figure 2. Alteration of thyroid function tests during pregnanc

Table 2. Normal References Range for Thyroid Hormones[4]

| | Non-pregnant (fertile period) | 1st trimester | 2nd trimester | 3rd trimester |
|---|---|---|---|---|
| TSH (mU/l) | 0.5 - 4.1 | 0.6 - 3.4 | 0.37 - 3.6 | 0.38 - 4.0 |
| Free T3 (pmol/l) | 2.0 - 7.0 | 1.54 - 5.22 | 1.78 - 5.29 | |
| Free T4 | 0.9 - 1.7 ng/dl | 0.95 - 1.53 pmol/l | 0.87 - 1.45 pmol/l | |
| TBG (µg/ml) | 16 - 24 | 10 - 40 | 23 - 46 | 19 - 49 |

There are many overlapping symptoms of HG and hyperthyroidism such as vomiting, dehydration, and weight loss, which can also complicate preexisting with diabetes melitus. In this patient, tachycardia initially appeared to result from dehydration due to HG. However, the persistence of tachycardia post-rehydration prompted evaluation for GTT and through TSH and fT4 testing. HG complicated by GTT often presents with abnormal laboratory result such as hyponatremia, hypokalemia, mild hyperbilirubinemia, and mild-to-moderate liver enzyme elevations, which correlated with the severity of liver dysfunction.[13,15] Furthermore, GTT can also lead to severe complications, such as thyroid storm. To differentiate it, we must calculate the Burch-Wartofsky score, which in this patient was 30, indicating an impending storm. Therefore, more aggressive treatment with loading doses is required. Additionally, thyroid ultrasound was performed to ruled out with other thyroid disease and obstetric ultrasound also performed to exclude secondary causes of HG, such as gestational trophoblastic disease or multiple pregnancies.[8,16] It's essential to make an accurate diagnosis to determine the appropriate treatment, monitoring, and prognosis of the patient.

There are also reports of higher fT4-to-fT3 ratio in pregnancy involved with gestational diabetes melitus.[12] However, in this case, the patient had preexisting diabetes melitus, managed with antidiabetic medications for the past year. For HG management, the antiemetics approved for pregnancy is ondansetron with selective 5-HT3 receptor antagonist, pyridoxine (vitamin B6) 10 mg with or without doxylamine 10 mg and promethazine are recommended.[3,17] For fluid rehydration intravenous recommended for patients with HG with severe dehydration or ketonuria preferred with 10% glucose to help nutritional supplement in moderate to severe cases.[3] Given 2 liter daily of 0.9% sodium chloride solution with 20 mmol of potassium chloride intravenously over 4 h also proven effectiveness resolving of dehydration.[17] To reduce risk of refeeding syndrome and Wernicke's encephalopathy should be given thiamine (100 ml of 0.9% sodium chloride contains 100 mg).[3]

Despite thyroid dysfunction during pregnancy, universal screening is not recommended by the American Congress of Obstetrics and Gynecology (ACOG) along with the American Thyroid Association (ATA) and European Thyroid Association.[4,9] However, thyroid dysfunction should be aware because associated with fetal and maternal complications such as pregnancy loss, preterm delivery, pre-eclampsia, and increased neonatal morbidity.[4] In pregnancy, hyperthyroidism can be managed with medication antithyroid drugs namely PTU or methimazole, but PTU is commonly preferred and can be used from the first trimester.[4] The medication should be evaluated carefully because it can crosses the placenta and acts on the fetal thyroid.[4] GTT treatment must be considered initiated before 18 weeks of pregnancy due to hCG influence and possibility of normalized T4 levels in this period. In the second half trimester, the symptoms typically improve, and the medical treatment needs to be adjusted accordingly. The goal in these cases is to maintain fT4 levels at the upper normal range to minimize the dosage of anti-thyroid medication.

In this patient, the risk factors for her pre-existing diabetes remain unclear, as she has no history of gestational diabetes in previous pregnancies, no history of delivering an infant with weight ≥4000 g, and no known family history of diabetes. The management in this patient was stop oral antidiabetic medication and initiated insulin therapy as recommended that approved during pregnancy with the glycaemic targets are: (1) ≤ 95 mg/dl in the fasting state, (2) ≤ 140 mg/dl at one-hour postprandial, and (3) ≤ 120 mg/dl at two-hour postprandial glucose.[18]

The patient has a history of hypertension diagnosed prior to first pregnancy so she was diagnosed with chronic hypertension. ACOG recommended for pregnant women with severe hypertension (≥160/105-110 mmHg) should be treating with antihypertensive medications with first line nifedipine 30-120 mg/day PO or second line with methyldopa 250-3000 mg/day PO in divided doses every 6-12 hours.[19] The main goal managing chronic hypertension during pregnancy to achieve ACOG blood pressure targets with minimal medications at the lowest effective doses.[19]

Hypokalemia in this patient likely resulted from inadequate potassium intake and persistent vomiting of HG. The pathogenesis of TPP because of hyperthyroidism of serum T4 level being increased of adrenergic response made activation of NaK/ATPase channel leading to intracellular potassium shifting result of hypokalemia (Figure 3).[10,20,21] The patients also given propanolol by cardiologist to reduced the heart rate. Beta blockers can be used during pregnancy to manage the adrenergic symptoms of thyrotoxicosis like tachycardia but should be limited to short durations. They have not shown teratogenicity but can lead to neonatal bradycardia and hypoglycemia if administered late in pregnancy.[22]

Unfortunately, the patient did not return for follow-up, limiting our ability to reassess TSH and fT4 levels at the beginning of the second trimester, as hCG levels would have decreased, potentially confirming GTT resolution.

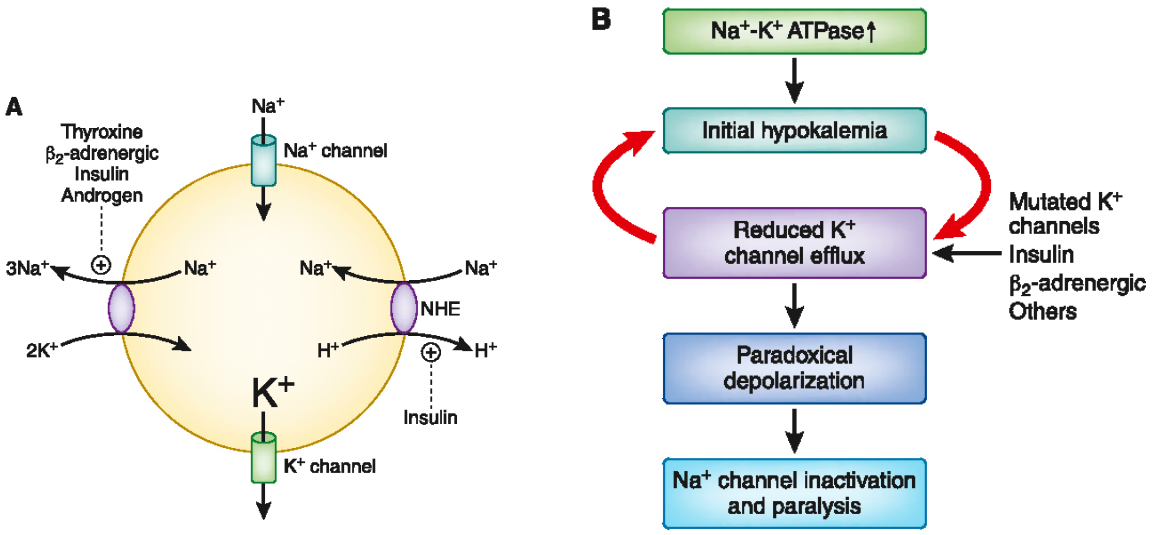


Figure 3. (A) Mechanism of TPP (B) Mechanism of hypokalemia to paralysis[21]

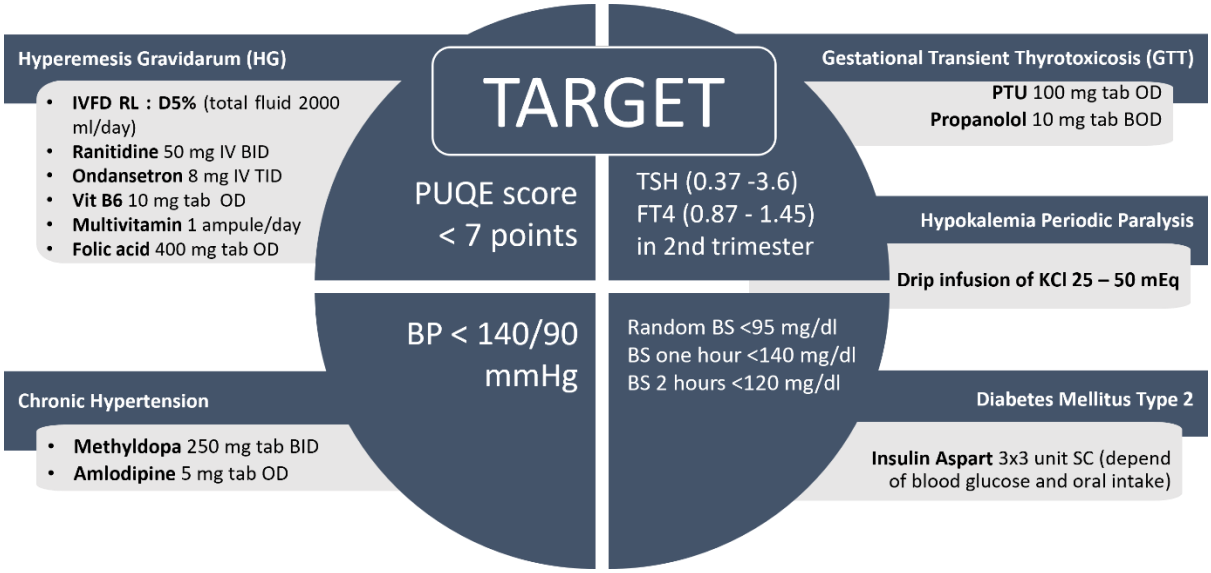


**Figure 4. Patient's clinical diagnosis with the therapy given and the expected target outcome**

## CONCLUSION

This case highlights the importance of accurately diagnosing hyperemesis gravidarum (HG) and identifying its underlying causes, such as gestational transient thyrotoxicosis (GTT), particularly in early pregnancy. The patient presented with complications including periodic hypokalemia and elevated liver enzymes, alongside preexisting chronic hypertension and diabetes mellitus. Managing complex, coexisting conditions in the first trimester requires careful observation and a multidisciplinary approach. Early intervention and appropriate treatment are crucial to minimizing maternal and fetal complications and improving pregnancy outcomes.

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CASE REPORT

# Tertiary Hyperparathyroidism in Patient with End-Stage Chronic Renal Disease

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**ABSTRACT**

Mineral and bone disorder is frequently associated with chronic kidney disease (CKD) which starts early and worsens with renal progression. This condition depends on calcium and phosphate metabolism which will change parathyroid hormone (PTH) release. Understanding the pathophysiology of both secondary and tertiary hyperparathyroidism can reduce the development of its complications, such as renal osteodystrophy and cardiovascular disease. To describe a case of hypercalcemia patient caused by tertiary hyperparathyroidism with end-stage renal disease (ESRD) who underwent continuous ambulatory peritoneal dialysis (CAPD). A 34-years old patient was consulted for treatment of hyperparathyroidism due to mineral bone disease-related CKD. The patient has high levels of serum calcium, phosphate, and parathyroid hormone levels. She has already taken a phosphate binder and does CAPD 4 times daily. She underwent several radiology tests and knew that there was enlargement of her parathyroid glands. Based on that, she underwent parathyroidectomy with implantation. Until now, we still need to evaluate the changes in serum calcium, phosphate, and PTH level after the surgery. Hyperparathyroidism is a condition related to disturbance in calcium and phosphate homeostasis in CKD patients. Many factors contribute to the development of its progression. Early recognition and holistic treatment will be the most important thing to reduce the complication of hyperparathyroidism in CKD patients.

**Keywords:** Renal disease, hyperparathyroidism, calcium homeostasis

## INTRODUCTION

Hyperparathyroidism (HPT) is a common complication of chronic kidney disease (CKD) characterized with disturbance in calcium, phosphate, and vitamin D homeostasis. It is a condition that is frequently met in patients with chronic kidney disease and the progression depends on patients' renal condition. Renal HPT (rHPT) is classically divided into secondary and tertiary hyperparathyroidism. In secondary HPT, the parathyroid gland will be enlarged caused by hyperplasia of the parathyroid gland. Tertiary HPT develops because of long-standing untreated secondary parathyroid hormone (PTH) and will induce autonomous PTH secretion and hypercalcemia. Serum calcium concentration is the main determinant of PTH release. Patients with CKD have defects in vitamin D activation and will lead to hypocalcemia and hyperphosphatemia. Underlying patho-physiology of HPT becomes more complex, with the activation of several factors, such as fibroblast growth factor (FGF) 23 and Klotho. Several treatments have been established to treat HPT in CKD patients, such as the use of vitamin D analogs, phosphate-binders, calcimimetic drugs, and parathyroidectomy.

## METHODS

In this manuscript, we present a case report of a hypercalcemia patient caused by tertiary hyperparathyroidism with end-stage renal disease (ESRD) who underwent continuous ambulatory peritoneal dialysis (CAPD).

## CASE ILLUSTRATION

A 34-years old male patient was consulted by the nephrology division for further work-up of high serum calcium and phosphate level. He has undergone haemodialysis since 2013, 2 times weekly. In 2019 and 2020, he felt pain in his left and right hip. He was diagnosed with bilateral hip fractures. He underwent total hip replacement at his left hip and before he underwent total hip replacement for his right hip, he was consulted to evaluate his parathyroid hormone status. From the nephrology department, he has already done laboratory examinations with increased levels of serum calcium and PTH hormone. He has already consumed sevelamer and vitamin D supplementation. There was no history of diabetes and allergy. He has hypertension and already took some medications.

From the physical examination, we found the patient in good condition. He was fully alert, blood pressure 143/70 mmHg, heart rate and respiratory rates in normal value. He was pale. From the palpation of the neck, we found no thyroid nodules. Other physical examinations were normal.

Table 1. Laboratory results of peri-parathyroidectomy surgery

| | 4/6/21 | 27/7/21 | 17/11/21 | 25/2/22 | 10/6/22 | 6/9/22 | 25/10/22 | 7/2/23 | 10/3/23 | Normal value |
|---|---|---|---|---|---|---|---|---|---|---|
| Hb/Ht/ Leu/Tr | | | | | | 10,4/32/60 90/258.000 | | | 11/32/646 0/164.000 | |
| Alb | 4,1 | | 3,9 | 4 | 4,1 | 4,2 | | 4,3 | 4,1 | |
| Ur/Cr | | | 119/9,3 (6,7) | 98/10 | 115/7,4 (8,8) | 100,6/5,6 (10,7) | | 64/9 (69,2) | 70,6/- | |
| Fosfat inorganic | 7,1 | | 4,8 | 4,2 | 5,7 | 2,2 | 3,8 | 4,3 | 4,3 | 2,3-4,7 mg/dl |
| Ca darah | 11,1 | | | 6,6 | 7,69 | 15 | 11,6 | | 10,7 | 8,4-10,2 mg/dL |
| Ca ion | | | | 0,85 | 1,07 | 1,55 | 1,5 | 1,39 | | 1,01-1,31 mmol/l |
| Na/K/Cl | | | | | | 133/4,8/96 | | | 136/4/101 | |
| Mg | 2,4 | | 2,21 | 2,39 | 2,5 | 2,6 | 2,77 | | | 1,67-2,6 |
| iPTH | 2308 | 1480 | | 1878 | 652,4 | 10,95 | 17,25 | | | 15-65 pg/ml |
| Vit D 25(OH) | 21,2 | | | | | | 17,1 | | | 30-100 ng/ml |
| Alk fosfatase | | | | 500 | 708 | | | | 67 | 40-150 U/L |

Purple circles showed the time of first and secondary parathyroidectomy surgery. From the parathyroid scintigraphy with MIBI-scan between the second parathyroid surgery showed left inferior parathyroid adenoma with differential diagnosis was parathyroid hyperplasia. Hip x-ray showed there were complete fracture of bilateral hip. Bone mineral densitometry showed low bone density for age (z-score of left wrists joint -2.4).

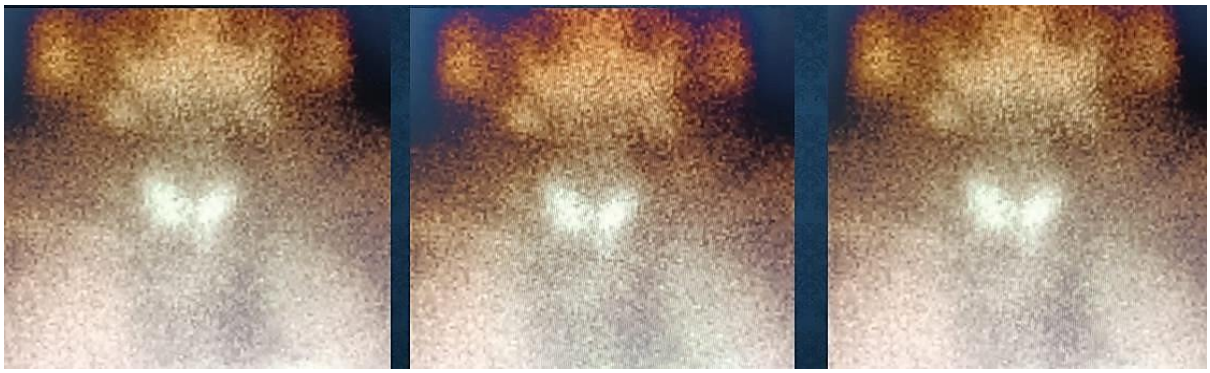

**Figure 1. MIBI Scan of the patient before secondary parathyroidectomy**

From the laboratory and radiology findings, he was diagnosed with hypercalcemia due to tertiary hyperparathyroidism, CKD stage V on dialysis with renal anemia, hypertension, secondary osteopenia, and closed fracture of bilateral femoral neck. He regularly consumed kolkatriol 2x0.5 mcg, calcium supplementation 3x500 mg, Actonel 35 mg/week and with 3 times HD for every week.

**Table 2. Laboratory iPTH Level Perioperatively**


## DISCUSSION

Chronic kidney disease affects a large amount of the world-wide population with impact based on its complications. One of the complications that commonly meet is altered bone metabolism. These biochemical and clinical abnormalities include mineral and bone disorder (CKD-MBD) and renal osteodystrophy (ROD). Mineral and bone disorder refers to the clinical syndrome with mineral, bone, and vascular calcification abnormalities; whereas ROD refers to the bone pathology of CKD which are found in bone biopsy, such as bone turnover, mineralization, and volume of the bone. The

biochemical abnormalities of CKD-MBD begin in CKD stage 3 but have variability in rate and severity. Based on these underlying mechanisms, it is recommended to monitor serum level of calcium, phosphorus, and PTH level in CKD patients.

Parathyroid hormone is a polypeptide protein released by the parathyroid gland and has an essential role in bone mineralization and calcium homeostasis. Free serum calcium concentration is the main determinant of PTH release. Calcium and phosphate homeostasis is maintained through a complex relationship between the bones, intestine, kidneys, and parathyroid gland. Parathyroid hormone plays important roles in calcium metabolism through 3 mechanisms, such as: (1). PTH will stimulate PTH receptors on osteoblasts then stimulate osteoclasts through multiple cell-to-cell mechanisms leading to bone resorption and increased serum calcium and phosphate; (2). PTH activates 1-α-hydroxylase in the kidney which catalyzes the conversion of inactive 25-hydroxy (25-OH) vitamin D to activated 1,25 dihydroxy-(1,25-OH) vitamin D and leads to increased absorption of calcium and phosphate in the gut; (3). PTH increases reabsorption of calcium and decreases reabsorption of phosphate in the kidney.

The development of secondary and tertiary HPT results from many factors, including deficiency of calcitriol, retention of phosphorus, decrease in activation of the calcium-sensing receptor (CaR) in the parathyroid gland, and skeletal resistance to the calcemic effect of PTH. Disturbance in the activation of vitamin D in the kidney can affect serum calcium and phosphate level and result in compensatory increase in parathyroid gland cellularity and PTH production. This is the pathomechanism of secondary hyperparathyroidism in CKD patients. More recently, the underlying pathophysiology has become more complex, with the progressive awareness that fibroblast growth factor 23 (FGF23), a-Klotho (subsequently called "Klotho") as well as the Wnt B-catenin signalling pathway also play an important role in hyperparathyroidism in CKD. FGF-23 stimulates phosphate excretion in the kidney and decreases 1-α- hydroxylase activity and leads to reduced 1,25-OH vitamin D levels.

Renal HPT, both secondary and tertiary HPT, manifests as one of two types of renal osteodystrophy; either a high turnover state known as osteitis fibrosa, or, in combination with low bone turnover, known as mixed uremic osteodystrophy. Severe secondary HPT is associated with morbidity and mortality in patients with CKD, especially CKD stage 3-5.

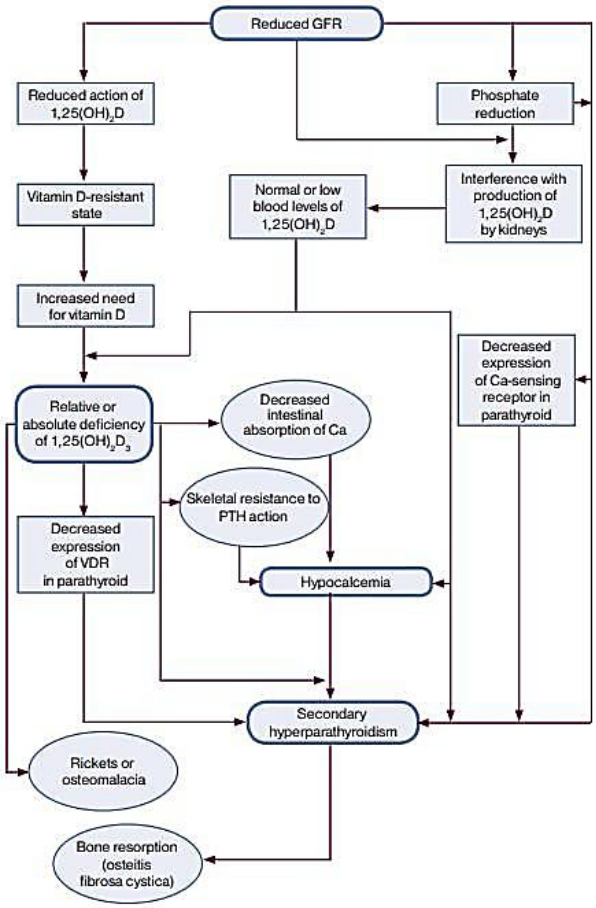


**Figure 2. Pathogenesis of mineral metabolism and bone disease in CKD patients**

In CKD patients, as the GFR declines, serum phosphate levels start to rise and induce hypocalcemia by binding bioavailable calcium as calcium hydrogen phosphate (CaHPO) and leads to a further rise in PTH production. Chronic stimulation of the parathyroid gland triggers diffuses polyclonal hyperplasia that leads to development of nodules with loss of negative feedback seen in tertiary HPT.

The other important complication of HPT besides renal osteodystrophy in CKD patients is cardiovascular disease. The abnormalities in calcium and phosphate metabolism may accelerate vascular, including coronary artery calcification. This can affect myocardium, atrial-ventricular conduction, and valvular function. Some studies have suggested that FGF-23 may induce arterial smooth muscle myocytes to change into osteoblast-like cells that lead to vascular calcification. Based on these underlying mechanisms and other atherosclerotic mechanisms, the morbidity and mortality caused by cardiovascular risk are seen higher in CKD patients.

The management of rHPT follows a stepwise approach with the goal of normal serum phosphate and calcium level. These managements include low phosphate diet, phosphate binders, vitamin D derivatives, calcimimetic medications, and surgery.

### Low phosphate diet

Low phosphate diet is recommended in CKD patients with rHPT with hyperphosphatemia. Dietary phosphorus comes from 2 sources, such as protein-rich food groups such as meat and milk and phosphorus additives used to process meat and cheese. Patients with CKD must restrict dietary phosphorus to 800-1000 mg/day.

### Phosphate binders

Phosphate binders are an essential part of medical therapy for CKD patients. It is shown to decrease serum phosphate and PTH levels. Several phosphate binders are aluminium hydroxide, calciumsalts, sevelamer hydrochloride, sevelamer carbonate, and lanthanum carbonate. In patients who remain hyperphosphatemic despite initiation of a single phosphate binder, combination therapy can be used.

### Vitamin D analogs

Replacement of vitamin D has been shown to be effective in suppressing PTH secretion. Several vitamin D analogs are ergocalciferol (requires activation in the kidney to 1,25-OH vitamin D), active forms of vitamin D such as calcitriol, paricalcitol, and doxercalciferol. If PTH remains elevated or is progressively rising, treatment with calcitriol or vitamin D analogs is suggested. Patients with CKD stage 5 on dialysis, it is suggested to get active vitamin D sterols such as calcitriol to control HPT.

### Calcimimetics

Cinacalcet HCL is a calcimimetic agent that exhibits allosteric modulation of the calcium receptor on the parathyroid gland, increasing sensitivity to extracellular calcium and thereby suppressing PTH secretion. Cinacalcet is shown to lower the rates of fractures and parathyroidectomy.

### Surgery

Indication for consideration for parathyroidectomy are: (1) medical management of rHPT > 6 months with hypercalcemia or hyperphosphatemia, PTH > 800 pg/ml, (2) calciphylaxis with documented elevated PTH levels, (3) osteoporosis (T-score >2,5 SD below mean), pathologic bone fracture, (4) symptoms/signs: pruritus, bone pain, severe vascular calcifications, myopathy. There are three most common surgical procedures used in the treatment of rHPT are total parathyroidectomy (TPX) alone, TPX with auto-transplantation, and subtotal parathyroidectomy. In TPX with auto transplantation, all 4 glands are removed followed by autologous reimplantation of 20 mg to 70 mg of the most normal-appearing gland into the sternocleidomastoid muscle, pectoralis major muscle, or forearm brachioradialis muscle. The implantation needs 3 to 4 weeks to revascularize and resume function. Based on long-term prognosis, successful parathyroidectomy can improve symptoms, like bone pain, arthralgia, muscle weakness, and psychological disturbances. Long-term relative risks of death are reduced by 10-15%.

## CONCLUSION

Renal hyperparathyroidism is one of the common complications in CKD patients. Morbidity and mortality associates with disturbance in serum calcium and phosphate level which correlates with osteodystrophy renal and cardiovascular risk in CKD patients. Early recognition and treatment to normalize calcium, phosphate, and PTH level will reduce the risk of hyperparathyroidism, both secondary and tertiary.

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CASE REPORT

# Detection of Small Lesion Insulinoma with $^{68}$Ga-DOTATATE PET/CT scan: A Case Report

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**ABSTRACT**

Endogenous hyperinsulinemia is a rare condition characterized by inappropriate insulin secretion, with insulinoma accounting for approximately 55% of cases. A 36-year-old woman presented with recurrent hypoglycemic episodes for 4.5 years, particularly in the morning, relieved by glucose intake. Laboratory findings during a supervised fasting test revealed a blood glucose of 44 mg/dL, elevated insulin (15 µIU/mL), C-peptide (2.27 ng/mL), proinsulin (53.1 pmol/L), and suppressed beta-hydroxybutyrate (0.1 mmol/L), indicating endogenous hyperinsulinemia. Initial imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) failed to localize the lesion. The patient discontinued investigation but resumed a year later with nuclear imaging studies. A 99mTc-HYNIC-TOC scan was inconclusive, but subsequent ^68Ga-DOTATATE PET/CT at Hasan Sadikin Hospital revealed a somatostatin receptor-expressing nodule at the pancreatic head, consistent with insulinoma. Given the lesion's location and imaging findings, treatment options were discussed, including Whipple's procedure versus radiofrequency ablation. Insulinomas are typically small, with 80% under 2 cm and 40% under 1 cm, often making localization challenging. While CT and MRI have detection rates of 70% and 86% respectively, the combination of CT and EUS may reach 100% sensitivity. In cases where conventional imaging is inconclusive, ^68Ga-DOTATATE PET/CT provides a valuable alternative, capable of detecting neuroendocrine tumors as small as 6 mm. This case highlights the critical role of nuclear medicine in localizing elusive insulinomas and guiding definitive treatment.

**Keywords**: hypoglycemia, insulinoma, $^{68}$Ga-DOTATATE PET/CT scan

## INTRODUCTION

Insulinoma is the most common pancreatic functional pancreatic neuroendocrine tumor (F-NET), arising from beta islet cells that secrete insulin and is associated with hypoglycemia neuroglycopenia and sympathetic overstimulation. Most are benign and well differentiated NETs. Insulinomas are rare functional neuroendocrine tumours (NETs) of the pancreas. The majority of insulinomas are small, measuring less than 2 cm. Despite their small size, insulinomas are the most common functional neuroendocrine tumours. Although mostly sporadic, up to 10% may be associated with hereditary multiple endocrine neoplasia type I (MEN-1).[1] The challenges of insulinoma diagnosis, localisation and surgical management have changed over the last few decades. Once the biochemical diagnosis of an insulinoma is established, localisation procedures are performed. Due to their small size (82% <2 cm and 47% <1 cm), insulinomas are difficult to localise with current imaging techniques.[2,3] Accurate preoperative localization of an insulinoma is desirable because some tumors may not be palpable at the time of surgery. Several studies have shown that when $^{68}$Ga-labelled somatostatin analogue positron emission tomography (PET) is combined with computed tomography (CT), the sensitivity for detecting neuroendocrine tumors is higher than with SSTR scintigraphy. A meta-analysis study suggested that $^{68}$Ga-DOTATATE is the most accurate for detecting neuroendocrine tumours.[3] Although the importance of this examination is for finding especially for small lesion insulinoma, but this modalities not yet available in every nuclear medicine facilities in Indonesia.

## CASE REPORT

A 36-year-old woman has had recurrent episodes of hypoglycemia for 4.5 years. The first symptoms are recognized when the patient hardly gets out of bed in the morning, accompanied by heavy sweating. After a glass of sweet tea, the patient regains consciousness. No seizure is reported. The patient often eats every 4-6 hours to overcome the symptoms of hypoglycemia, resulting in an increase in her body weight of about 25 kilos in 4.5 years. There is no history of taking herbs or other routine medications that could potentially cause hypoglycemia. A laboratory test shows an fasting blood glucose (FBG) of 45 mg/dL. The patient then goes to the endocrinologist and a prolonged fasting test concludes that the patient has endogenous hyperinsulinemia, where are at BG 44 mg/dL, the C-Peptide 2.27 ng/mL, insulin level at 15 µIU/mL, proinsulin level at 53.1 pmol/L and beta-hydroxybutyrate 0.1 mmol/L. The patient has undergone several imaging studies, from abdominal ultrasound to abdominal magnetic resonance imaging (MRI), but without satisfactory results. endoscopic ultrasound (EUS) has also been performed but shows no specific findings. Patient feels disappointed and does not seek further opinion.

Figure 1. Prolonged fasting test result[4]

| Examination | Patient result | Diagnosis criteria for Endogenous Hyperinsulinemia | | Normal lab reference |
|---|---|---|---|---|
| | | Western | Chinnesse large cohort study | |
| End of fast glucose | 44 mg/dL | < 3 mmol/L (< 54 mg/dL) | < 2,8mmol/L ( < 50mg/dL) | 60 -140 mg/dL |
| Insulin | 15 µIU/mL | > 3 µIU/mL | > 5.5 | 2 – 25 µIU/mL |
| β-hydroxybutyrate | 0,1 mmol/L | | | < 0,6 mmol/L |
| C-peptide | 2,27 ng/mL | > 0.6 ng/mL | > 0,9 ng/mL | 0,78 – 5,19 ng/mL |
| Proinsulin | 53,1 pmol/L | >= 5 | >= 12 | <= 18,8 pmol/L |

After 1 year, the patient decided to restart the investigation and a nuclear medicine scan was scheduled. At first a $^{99}$mTc HYNIC TOC examination is performed but shows no typical neuroendocrine tumour in pancreas or other organ, and then after waiting for several months

a $^{68}$Ga-DOTATATE PET/CT was performed in Hasan Sadikin Hospital and result shows a nodule at head of pancreas surrounding pancreaticoduodenal junction that expresses somatostatin receptor, suggesting an insulinoma. A meeting was done and the definitive treatment option are between Whipple's procedure or radiofrequency ablation (RFA). An RFA was chosen after family meeting held with team.

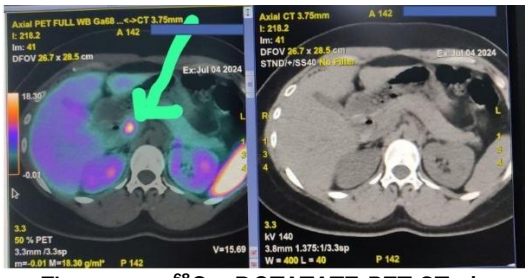

Figure 2. a $^{68}$Ga-DOTATATE PET/CT shows suggestive a insulinoma at head of pancreas

## DISCUSSION

Although insulinoma is a rare endocrine disorder, it is the most common cause of hypoglycemia in apparently healthy adults when factitious hypoglycemia is excluded. As insulinomas occur in the pancreas in the majority of patients, the pancreas is the first site to be investigated. A variety of symptoms have been described in patients presenting with this tumour.[5] Unfortunately, only 53% of patients are diagnosed within 5 years of their first symptom.[1] Spontaneous hypoglycemia from insulinoma can cause neuroglycopenic symptoms. Patients typically present with neurological symptoms such as confusion, dizziness, behavioral changes and may be accompanied by weight gain with normal thyroid function.[1]

Table 1. Frequent symptoms of insulinoma[1]

| Neuroglycopenic symptoms | Adrenergic symptoms |
|---|---|
| Confusion (80%) | Diaphoresis (69%) |
| Visual disturbances (59%) | Tremors (24%) |
| Amnesia or coma (47%) | Palpitations (12%) |
| Abnormal behavior (36%) | Hyperphagia/weight gain (50%) |
| Seizures (17%) | |

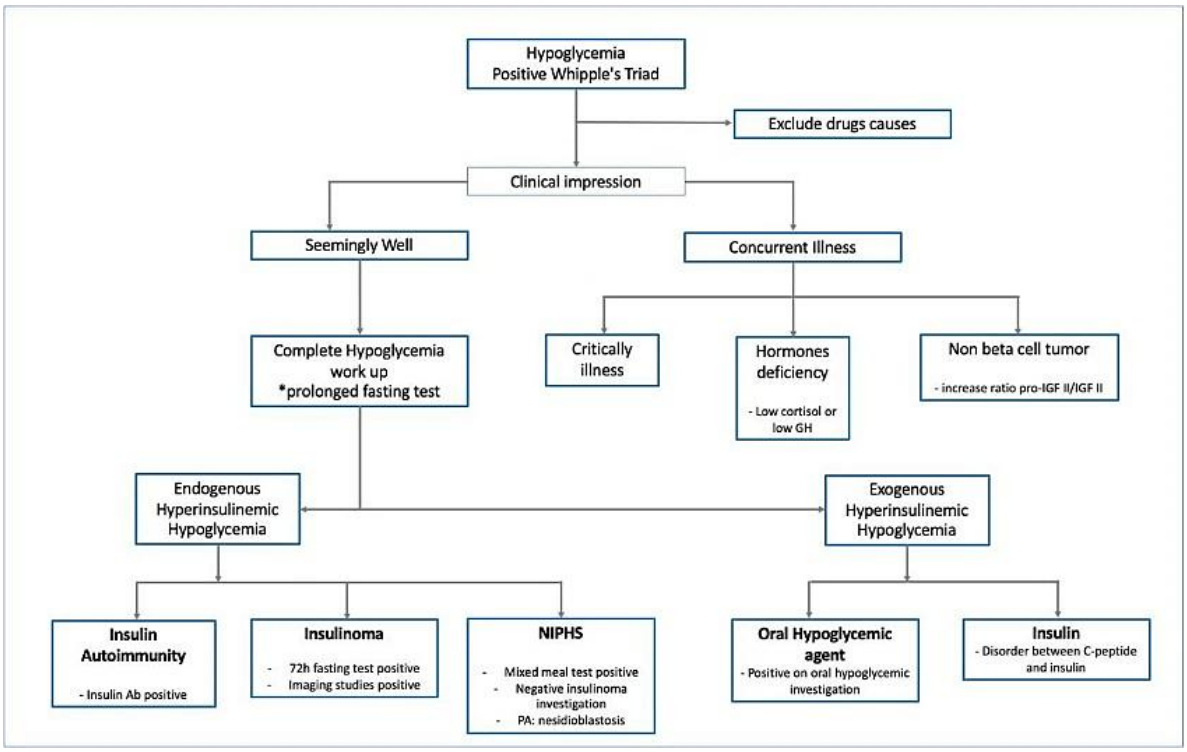


Figure 3. Algorithm for evaluating hypoglycemia in adult (modified from Marten et al)[6]

Once a high clinical suspicion for an insulinoma is confirmed, biochemical tests based on prolonged monitored fasting are performed to confirm the diagnosis. The 72-

hour monitored fast has been the gold standard for the diagnosis of this tumor for over 80 years. The protocol involves measuring the levels of plasma glucose, insulin, C-peptide and proinsulin in the same sample and repeating the measurements every 6 hours until the plasma glucose level is 58 mg/dL; the fast is terminated either when the plasma glucose level is 45 mg/dL or the patient has signs and symptoms of hypoglycaemia.[1] Biochemical abnormalities of insulinoma may be seen in other conditions associated with fasting hypoglycemia or postprandial hypoglycemia, so other causes should be ruled out first.[7]

**Table 2. Differential diagnosis of hypoglycemia[7]**

| | |
|---|---|
| 1. | Oral hypoglycemics (sulfonylureas, meglitinides) |
| 2. | Exogenous insulin administration |
| 3. | Systemic conditions (renal failure, liver failure, sepsis, non-pancreatic malignancies, adrenal insufficiency) |
| 4. | Autoimmune disease (SLE) |
| 5. | Multiple myeloma |
| 6. | Post-gastric bypass hypoglycemia |
| 7. | Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome (NIPHS) |

When the biochemical diagnosis of an insulinoma is confirmed, the next step is preoperative localization. The most effective method of locating insulinomas is still controversial, as both preoperative and intraoperative approaches have been advocated. Preoperative localization of insulinomas can be non-invasive or invasive. Non-invasive imaging modalities include abdominal ultrasonography, bolus enhanced helical computed tomography (CT), magnetic resonance imaging (MRI) and somatostatin receptor scintigraphy. Invasive studies include selective angiography, transhepatic portal vein sampling, endoscopic ultrasound (EUS) and selective arterial calcium stimulation (SACS). Some suggest that the combination of surgical exploration and intraoperative ultrasound (IOUS) can identify more than 90% of insulinomas.[1] These are stepwise suggestion in diagnosing insulinoma.

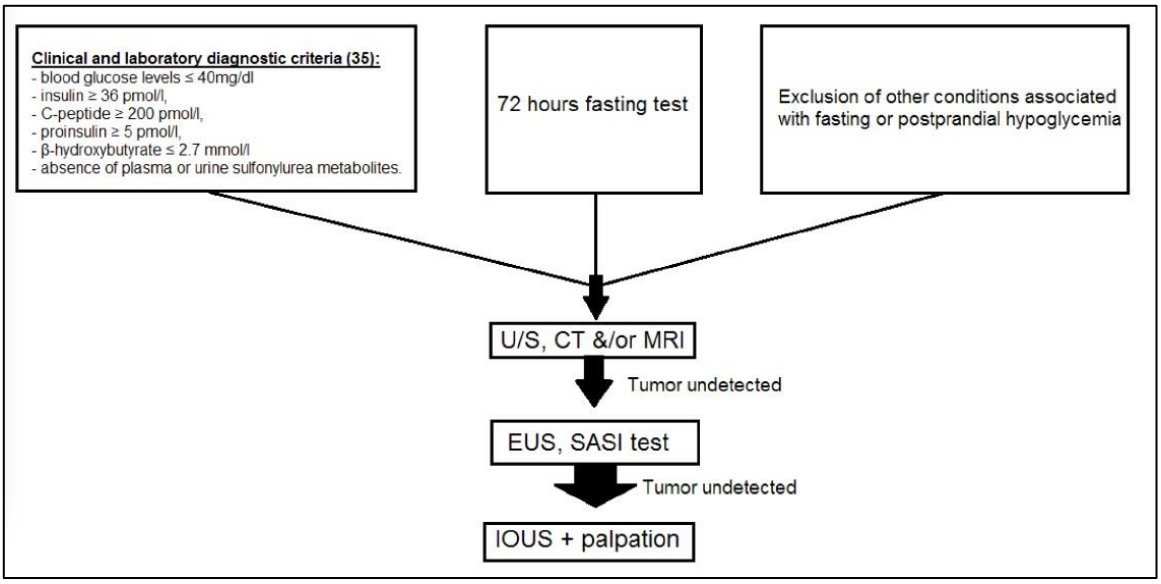


**Figure 4. Algorithm for the diagnosis and localization of insulinomas[7]**

In this case, a series of stepwise imaging procedures were conducted after biochemical diagnoses were confirmed, including abdominal ultrasound, CT scan, MRI and EUS, but these did not yield a satisfactory result for locating the lesion. After the patient underwent a $^{68}$Ga-DOTATATE PET/CT scan, this examination enabled the location of the lesion to be determined, which was found in the head of the pancreas in the vicinity of the pancreatico-

duodenal junction. The diameter of the lesion was measured at 11 mm.

It has previously been reported that $^{68}$Gallium DOTATATE PET/CT scan can detect NETs as small as 6 mm.[8] In a study comparing different imaging modalities for the localitation of insulinomas, the accuracy of $^{68}$Gallium DOTATATE PET/CT scan was around 90% compared to CT (55%), MRI (61%) and US (21%).[8] The $^{68}$Gallium DOTATATE PET/CT scan has a high affinity for somatostatin receptor 2 (SSTR2), which is commonly expressed in NETs. This SSTR2 expression in insulinomas is present in up to 80% of cases.[9] Although Selective Arterial Secretagogue Injection (SASI) is more accurate for regionalizing insulinomas, it's a costly and invasive test that requires a skilled interventional radiologist, who may not be readily available, and it can be associated with complications. A $^{68}$Ga-DOTATATE has been shown to be safe with a lower total radiation exposure than $^{18}$F-FDG.[8]

## CONCLUSION

Due to their small size, the localization of insulinomas is challenging. Imaging with $^{68}$GaDOTATATE PET/CT may be an alternative imaging modality for patients with negative results from other non-invasive radiological localization studies. Availability of this modality in Indonesia would be another issue.

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CASE REPORT

# Diagnostic Challenges of Primary Thyroid Lymphoma: A Case Report

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**ABSTRACT**

Primary Thyroid Lymphoma (PTL) requires a pathology confirmatory test to conclude the definitive diagnosis. Concerns arise when insufficient pathology specimen collection results in nonspecific pathological conclusion, in spite of the fact that the patient's clinical and radiological presentation strongly suggests a diagnosis of PTL. Patient 69-year-old male with complaint of a painless lump in the neck that has been progressively getting bigger since a month ago. He also reported shortness of breath, intermittent fever, decreased appetite, weight loss of 5 kilograms, and general weakness. Physical examination showed a single and immobile palpated mass measuring ± 10x10x10 centimeters in the neck with hard consistency. Imaging concluded that the patient had a suspected malignant tumor with bilateral lymphadenopathy and cervical thoracic spondyloarthritis. Rapidly growing neck mass leads to heterogeneous diagnosis. PTL is suggested prominently in progressive thyroid mass expansion. The presented case was a male patient 69-year-old male with clinical presentation showing a rapidly growing neck mass with an airway compression. While working on confirmatory testing of pathology examination (to define the type and immunohistochemistry characteristic of the tumor), the patient was treated adequately with supportive treatments. Supportive treatments for suspected PTL patients are important in securing airway patency, adequate fluid and nutritional intake, and prevent aspiration while working on confirmatory test. Diagnostic challenges of PTL not only limited to insufficient sample collection leading to unspecified pathologic results. Repetitive testing may result in delayed treatment and increase risk of complications.

**Keywords**: Neck mass, primary thyroid lymphoma, diagnostic challenge, supportive treatment

## INTRODUCTION

Rapidly growing neck mass leads to heterogeneous diagnosis. Primary Thyroid Lymphoma (PTL) is suggested prominently in progressive thyroid mass expansion along with Anaplastic Thyroid Cancer (ATC). Both diseases have differences in treatment responsiveness and clinical outcomes. Primary Thyroid Lymphoma (PTL) shows a higher treatment response and better outcome compared to ATC. In common, patients with rapidly growing neck mass may report neck discomfort, decreased range of movement, hoarseness, dysphagia, shortness of breath, or even recurrent bleeding. Those clinical presentation makes it a dilemma for clinicians to provide precise treatment without knowing the definitive diagnosis.[1,2]

The path towards the definitive diagnosis is a true challenge to overcome. Despite a well-developed algorithm for establishing a diagnosis, clinicians remain hard to implement the common bias found in specimen collections to get the pathology reports, the ultimate diagnostic gold standard.[1,2,3] This case report was conducted to describe the challenges faced by internal medicine professionals at Dr. Zainoel Abidin General Hospital, Banda Aceh, in assessing the diagnosis of suspected Primary Thyroid Lymphoma (PTL). The challenges are mainly related to the progressiveness of the disease and the uncertainty result of the pathology tests.

## CASE ILLUSTRATION

A 69-year-old male was admitted to the emergency room with chief complaint of a painless lump in the neck that has been progressively getting bigger since a month ago. He also reported shortness of breath, intermittent fever, and decreased appetite. Patient had 5 kg weight loss during the last month. Patient also experienced asthenia (complete weakness, no energy). Patient had a history of long-standing hypertension and dyspepsia.

Vital signs examination showed that blood pressure 176/94 mmHg, heart rate 42 rates per minute, respiratory rate 29 times per minute, oxygen saturation 87%, axillary temperature 36.6° Celsius. Oropharyngeal inspection showed that no significant findings on the oropharyngeal lumen, retropharyngeal walls, uvula, tonsils, and its surrounding tissues. However, there are multiple mouth ulcers with leukoplakic areas and erythematous lesions suspecting for oral candidiasis in the whole oral cavity. Neck examination showed a single immobile palpable mass measuring ± 10x10x10 centimeters with hard consistency. We then conducted an ultrasonography on the neck which found bilateral thyroid nodules and lymph nodes enlargements. Further imaging studies were needed to determine the anatomical abnormality related to the mass. Below are photograph and imaging reports showing the clinical condition of the patient's neck (See **Figure 1**).

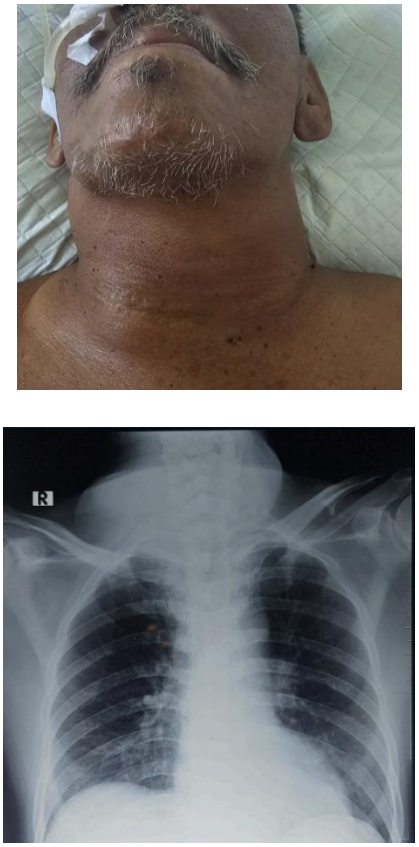


**Figure 1**. (Left) Clinical presentation of a patient showing a lump in his neck. No signs of inflammation were observed. (Right) Chest X-ray showing soft tissue mass in the right and left side of the neck (VC4-VT 2).

CT scan of the nasopharynx revealed a lobulated solid mass 40 hounsfield unit (HU) with a partially indistinct margin, measuring ± 11.15 x 13.06 x 9.9 centimeters in the right thyroid with contrast enhancement 84 HU. The mass affected the right thyroid muscle, hypopharynx, inferior constrictor muscle of the pharynx, longus muscle of the right-left neck, and right sternocleidomastoid muscle. Below are the CT scan findings in this patient (figure 2).

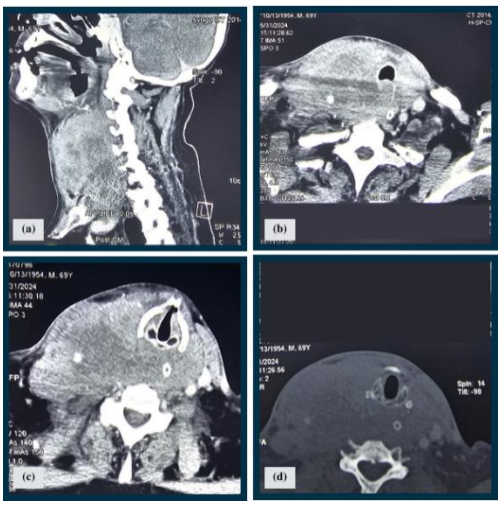

Figure 2. CT scan of the nasopharynx

Figure 2 CT scan of the nasopharynx revealed a lobulated solid mass 40 HU with a partially indistinct margin (±11.15 x 13.06 x 9.9 centimeters) with contrast enhancement 84 HU. The mass in the isthmus shifted the airway lumen to the left side and narrowed the lumen (narrowest width was ± 0.63 centimeters) at the level of the VT 1.

Mass in the isthmus shifted the airway lumen to the left side and narrowed the lumen with the narrowest width of ± 0.63 centimeters at the level of the thoracic vertebrae 1. Multiple lymph node enlargements were obtained in the right-left neck and submandibular region with the largest diameter of ± 1.08 centimeters. Cervicothoracic osteophytes were also obtained with narrowing of the intervertebral space of cervical 6-7, cervical 7 - thoracic 1, thoracic 1-2, and thoracic 2-3. Based on the imaging findings it was concluded that the patient had a suspected malignant tumor with bilateral lymphadenopathy and cervical thoracic spondyloarthritis. Table is shows the result of a blood test on the 1$^{st}$ and 7$^{th}$ days of hospitalization. Blood test also included thyroid function test.

**Table 1. Result Blood Test Parameter**

| Blood test parameter | Result (Day 1) | Result (Day 7) |
|---|---|---|
| Hemoglobin | 13,4 g/dL | 12,8 g/dL |
| Hematocrit | 40% | N/A |
| Leucocyte | 7,57 $10^3$mcL | 10,62 $10^3$mcL |
| - Eosinophil | 2 | 1 |
| - Basophil | 1 | 0 |
| - Banded neutrophil | 0 | 0 |
| - Segmented neutrophil | 71 | 81 |
| - Lymphocyte | 20 | 9 |
| - Monocyte | 5 | 9 |
| Thrombocyte | 233 $10^3$mcL | 324 $10^3$mcL |
| Erythrocyte | 5. $10^6$mcL | 6. $10^6$mcL |
| - Mean corpuscular volume (MCV) | 91 fL | 91 fL |
| - Mean corpuscular hemoglobin (MCH) | 31 pg | 31 pg |
| - Mean corpuscular hemoglobin concentration (MCHC) | 34 g/dL | 34 g/dL |
| Lactate dehydrogenase (LDH) | N/A | 693 U/L |
| Erythrocyte sedimentation rate (ESR) | N/A | 130 mmpH |

| Blood test parameter | Result (Day 1) | Result (Day 7) |
|---|---|---|
| Prothrombin time (PT) | N/A | 0,86 second |
| Activated Partial Thromboplastin Time (aPTT) | N/A | 1,03 second |
| D-dimer | N/A | 3390 ng/mL |
| Electrolyte | | |
| - Natrium (Na) | 145 mmol/L | 137 mmol/L |
| - Kalium (K) | 4,1 mmol/L | 3,3 mmol/L |
| - Chloride (Cl) | 102 mmol/L | 94 mmol/L |
| Calcium (Ca) | N/A | 8,5 mg/dL |
| Blood Glucose | 90 mg/dL | N/A |
| - Ureum | 38 mg | N/A |
| - Creatinine | 1,25 mg/dL | N/A |
| Thyroid-Stimulating Hormone (TSH) | 85,4 uIU/mL | N/A |
| Thyroxine (T4) | 5,4 ng/dL | N/A |

Abbreviation:
g: gram; dL: desiliter; N/A: not applicable; mcl: microliter; fl: femtoliters/cubic microns; pg: picogram; U: unit; mmpH: milliliter per liter; ng: nanogram; mmol: millimole/one-thousandth of a mole; mg: milligram; uIU: micro-international units; mL: milliliter.

The first pathological tissue examination of the neck mass concluded an unspecified metastasis from undifferentiated carcinoma and tuberculous lymphadenitis. The sample was collected by fine needle aspiration biopsy (FNAB). We suggested another pathological examination conducted in the future. We also planned to perform ultrasonography (US) and thoracic CT scan with and without contrast. While working on a confirmatory test for definitive diagnosis, the patient was treated adequately with supportive treatments. Patient laid down in a semi fowler position, given 8 to 10 liters of oxygen per minute using a simple mask, 200 mL ketogenic enteral nutrition every four hours using a nasogastric tube. Patient also received infusions of 500 mL isotonic sodium chloride (0,9%) every eight hours. Patient received 10 milligrams amlodipine and 80 milligrams valsartan to reduce hypertension, both given orally once daily.

## DISCUSSION

The presented case was a male patient with clinical presentation showing a rapidly growing neck mass causing airway compression. Imaging studies confirmed respiratory tract complications with a suspected malignant tumor, bilateral lymphadenopathy, and cervical thoracic spondyloarthritis. Further testing was required to define the type and immunohistochemistry characteristic of the tumor. Core and fine Needle Aspiration Biopsy (FNAB) with US or CT scan guided procedure may be feasible options to collect the specimen.[1,2,3] However, due to inconclusive findings of the pathological examination, the patient was then planned for further testing and received supportive treatments. The blood test including thyroid function test showed a non-specific finding of strongly suggested ongoing systemic inflammation with alteration in thyroid functions (hypothyroidism). The blood test cannot rule out the possibility of other diagnoses such as tuberculosis and metastatic processes. Thus, we planned to conduct further tests such

as ultrasonography and thoracic CT scan with and without contrast.[1,2,3]

The above-mentioned supportive treatments were to ensure airway patency, adequate fluid and nutritional intake, and to prevent aspiration during hospitalization. Patient also received anti-hypertensive drugs to lower his stage II hypertension. The confirmatory testing was undergone and took several days to complete. The repetition of specimen collection and testing should not become a reason to postpone any emergency treatment.[1,2,3] Additionally, the abnormal thyroid function should also be a priority in treating this patient. For instance, patient may be admitted to the hospital with contrary thyroid functions. Some may present with hypothyroid profile, while others present with hyperthyroid. These profiles are beneficial in determining the most possible cause.[1,2,3]

In this report, patient was admitted with hypothyroidism. It is commonly caused by Hashimoto Thyroiditis. The clinical presentations of the patient in this report were not fully linear to the findings of hypothyroid profile. Patient experienced intermittent fever, decreased appetite, weight loss, and complete weakness. The unreported findings were hoarseness, dry skin, and bradycardia. Patient was unaware of the latest symptoms. On the other hand, a patient may present with hyperthyroidism. But this is less likely to occur and reported only in a small number of cases.[3,4] The team was working on defining the definitive diagnosis, as it was highly suspected to be a Thyroid Lymphoma. Thyroid lymphoma may present either primarily or secondarily. Primary Thyroid Lymphoma (PTL) is diagnosed when thyroid glands are firstly impacted and then spread to loco-regional lymph nodes and/or other organs. On the other hand, Secondary Thyroid Lymphoma (STL) is lymphoma originated from outside of the thyroid glands, which later affect the thyroid glands.[3]

The diagnosis of PTL is established by an integrative approach of comprehensive examination. A-well conducted history taking, detailed physical examination, and further confirmatory tests, including blood tests, imaging, and pathology should be done. Our team found it was challenging to establish the definitive diagnosis due to unspecified findings in the pathology test from FNAB.[5] To confirm the diagnosis of Primary Thyroid Lymphoma (PTL), immunohistochemical testing is essential. Key findings include a solid proliferation of lymphoid cells expressing the B-cell marker CD20 and for lymphomas with plasma cell differentiation demonstrating light chain restriction with kappa and lambda antibodies is helpful. Cytokeratins are used to highlight lymphoepithelial lesions, while follicular dendritic cell markers (CD21 or CD23) indicate follicular colonization. Additionally, Hans' classification markers like BCL6 and MUM1 are utilized by some institutions. Therefore, the minimum immunohistochemical panel for diagnosing PTL should include B-cell markers, T-cell markers, light chains, cytokeratins, and follicular dendritic cell markers.[5,7]

In general, Primary Thyroid Lymphoma (PTL) belongs to the category of B-cell non-Hodgkin lymphomas. It accounts for up to 98% of all cases of PTL.[6] The subtype of PTL in the most prevalent order are Diffuse Large B-cell Lymphoma (DLBCL), Mucosa-associated Lymphoid Tissue (MALT) Lymphoma / Extranodal Marginal Zone Lymphoma, Follicular Lymphoma, Small Lymphocytic Lymphoma, Chronic Lymphocytic Lymphoma, and Mantle Cell Lymphoma. The prevalence of the subtype may be different in studies conducted widespread. A well-defined diagnosis of PTL may direct the future treatment of the patient. A DLBCL patient may receive a combination of chemotherapy and radiotherapy, as it is beneficial for the clinical improvement, especially in early stages of DLBCL.[7] Chemoimmunotherapy is suggested in patient with advanced stages (IIIE or IV) of DLBCL in conjunction with chemotherapy.

On other pathological findings such as MALT and follicular lymphoma, patients in early stages are treated by radiotherapy with or without chemoimmunotherapy. In late stages (IIIE or IV) patients are treated by chemoimmunotherapy with or without chemotherapy. The selective monoclonal

antibody of rituximab is the first line therapy in patients undergoing chemoimmunotherapy treatment in DLBCL, MALT, and follicular lymphoma. This agent is selectively binding the CD20 and the pre-mature to mature B cell lymphocytes.[7,8]

## CONCLUSION

Supportive treatments for suspected PTL patients are important in securing airway patency, adequate fluid and nutritional intake, and prevent respiratory aspiration while working on confirmatory tests. Diagnostic challenges of PTL mostly due to inconclusive pathologic results. Repetitive sampling and testing may result in delayed definitive treatment and increase risk of further complications.

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CASE REPORT

# Gynecomastia and Galactorrhea in Male Older Patients: Distinguish Between Drug Induced or Prolactinomas?

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**ABSTRACT**

Finding the cause of gynecomastia and galactorrhoea can be challenging, hence one of the most important cornerstones is detailed case history. Gynecomastia is an enlargement of the breast in males due to hyperplasia of the glandular tissue. Gynecomastia can be caused by physiological (20%), pathological (30%), drugs (10-20%), and idiopathic (25%). We report a case of gynecomastia with prolactin disorder and previous use of antihypertensive medication. A 68 year old man, with hypertensive heart disease, controlled on medication (low dose spironolactone 25mg/day, digoxin 0.25mg/day and diltiazem 30 mg three times a day), for the last 12 months; presented with painful swelling and discharge of bilateral breasts for the last 14 days; on examination of both breasts a firm, mobile lump was palpated under the right nipple; blood tests: blood urea nitrogen (BUN) 12 mg/dL; creatinine 1.1 mg/dL; thyroid stimulating hormone (TSH) 0.57 µIU/ml; luteinizing hormone (LH) 12,0 IU/mL; testosteron 6,41 ng/mL; estradiol 111,8 pmol/L; prolactin 87.5 ng/mL. Head magnetic resonance imaging (MRI) was performed; multiple chronic lacunar infarcts, intrasellar and suprasellar were normal and no mass or infection was visible. The probable cause was attributed to spironolactone and digoxin, the medications were stopped; the patient's pain and swelling improved and returned to normal after 2 months of discontinuation, prolactin was assessed at 0.193 ng/mL. Gynecomastia due to spironolactone has many mechanisms: blockade of androgen receptors, prevent binding of testosterone and dihydrotestosterone; decrease testosterone production from testes, increase estrogens by enhancing peripheral conversion of testosterone to estradiol. It has been suggested that digoxin binds to the estrogens receptor and may directly stimulate breast tissue proliferation, inducing gynecomastia. Spironolactone is known to cause gynecomastia, but there are very few case reports of digoxin-induced gynecomastia. No other evidence of prolactinoma in this case. It is important for the clinician to keep this in mind; although low doses combination between spironolactone and digoxin may cause gynecomastia.

**Keywords:** Gynecomastia, galactorrhoea, spironolactone, prolactin, digoxin

## INTRODUCTION

Finding the cause of gynecomastia and galactorrhoea can be challenging, hence one of the most important cornerstones is detailed case history. Gynecomastia is very common. Up to 70% of all boys develop pubertal gynecomastia and up to two-thirds of all adult men might have palpable breast tissue on examination.[1] Gynecomastia can be caused by physiological (20%), pathological (30%), drugs (10-20%), and idiopathic (25%).[2] It is a clinically significant phenomenon commonly observed in males during adolescence. While physiological or pubertal gynecomastia is the most frequently encountered cause during this period, other potential etiologies are uncommon but may arise from various pathological conditions, such as obesity, aromatase excess syndrome (AES), primary or secondary hypogonadism, congenital adrenal hyperplasia, Klinefelter syndrome (KS), testicular feminization syndrome, adrenal and testicular tumor, hyperthyroidism, liver and renal diseases, and malnutrition. Additionally, certain medications have been shown to induce proliferation of male breast tissue.[3] Drugs are causative in approximately 20% of men presenting with gynecomastia.[4] Spironolactone, an aldosterone antagonist, is associated with gynecomastia. Digoxin, which can also cause gynecomastia.[5] Prolactinomas represent the most common secretory tumor of the pituitary gland. Clinical presentation may be due to prolactin over-secretion, localized mass effect, or a combination of both.[6] In men, the main complaint is usually associated with hypogonadism, namely decreased libido, erectile dysfunction, and gynecomastia.[7] The challenge facing endocrinologists lies in their ability to distinguish between drug induced and prolactinoma causes of gynecomastia and galactorrhoea.

## CASE ILLUSTRATION

We present a case of a 68 year old man with gynecomastia and galactorrhoea. He also had symptoms suggesting hypertensive heart disease and the diagnosis was confirmed by physical examination, chest X ray and electrocardiogram in the previous hospital. Therapy with spironolactone 25 mg/day, digoxin 0.25mg/ day and diltiazem 30 mg three times a day (tid) was prescribed earlier by his internist already in 1 year.

He was admitted with bilateral breast tenderness with discharges, pain and symmetrical enlargement, occurring 2 weeks before the present hospital admission. He also noted decreased sexual desire and became impotent during spironolactone administration. No complaints about vision and other conditions. Physical examination of his breasts was consistent with the diagnosis of bilateral gynecomastia and galactorrhea. On examination, there was no ulceration, nipple retraction or skin color changed and discharge was expressed from the nipple. The size was about 3 cm on both breasts. Normal scrotal on examination. Imaging by breast ultrasound was not performed. Routine biochemical test included blood urea nitrogen (BUN) 12 mg/dL; creatinine 1.1 mg/dL; thyroid-stimulating hormone (TSH) 0.57 µIU/ml; luteinizing hormone (LH) 12.0 IU/mL; testosterone 6.41 ng/mL; estradiol 111.8 pmol/L; levels of serum prolactin; 87.5 ng/mL and we conducted a head magnetic resonance imaging (MRI) without contrast. The result was multiple chronic lacunar infarcts, intrasellar and suprasellar were normal and no mass or infection was visible. The probable cause was attributed to spironolactone and digoxin. The medications were stopped; and replaced with candesartan 16 mg/ day, diltiazem 100 mg/day and initiated bromocriptine 2.5 mg/ day. The patient's pain and swelling improved and returned to normal after 2 months of discontinuation bromocriptine stopped while known prolactin level was at 0.193 ng/mL, and dual therapy antihypertensives still continuing to control hypertensive heart disease.

## PATHOGENESIS

Receptors for androgens, estrogens, progesterone, and prolactin are found in the male breast. It has been shown that estrogens stimulate breast tissue proliferation, whereas androgens inhibit this process. It is believed that

most cases of gynecomastia are caused by an imbalance of these two influences, with estrogens induced stimulation predominating. Such an imbalance may occur with increased estrogens action on the breast, decreased androgen action, or a combination of the two. This may be due to an increase in circulating or tissue levels of estrogens, a decrease in circulating or tissue levels of androgen, increased responsiveness of the breast to estrogens (e.g. increased numbers of estrogens receptors), or decreased breast responsiveness to androgens (e.g. androgen insensitivity due to receptor mutations or drugs).[8]

Other hormones might also be involved in the development of gynecomastia; prolactin, progesterone, insulin-like growth factor (IGF) 1, IGF 2 and luteinizing hormone (LH and/or human chorionic gonadotropin (hCG) have been found in male breast tissue.[1] Hyperprolactinemia has been associated with gynecomastia, but it probably plays an indirect role by causing hypogonadism although prolactin receptors are expressed in gynecomastia. Only some men with hyperprolactinemia develop gynecomastia, and many men with gynecomastia do not have hyperprolactinemia. It is not clear how prolactin and progesterone might regulate each other in men.[4] Aging is often accompanied by increased adiposity, leading to increased aromatization of androgens to estrogens. Also, serum sex hormone binding globulin (SHBG) levels rise with increasing age, further decreasing the free and bioavailable testosterone. Additionally, older men often have multiple medical problems and require multiple medications, some of which may contribute to gynecomastia.[1]

## DISCUSSION

Various medications and conditions are associated with gynecomastia.[9] It is well known that spironolactone can cause gynecomastia and was described several times in the literature.[10] Spironolactone may increase peripheral conversion of testosterone to estradiol and displace testosterone from SHBG. it is also suggested to bind to peripheral androgen receptors to competitively inhibit testosterone and dihydrotestosterone.[4] Deepender and Braunstein wrote some expert opinion about spironolactone association with gynecomastia, this medicine level is good quality evidence for gynecomastia. Among 1663 heart failure patients receiving 25mg/day of spironolactone develop gynecomastia in 10% population follow up in 24 months.[11] Digoxin has been suggested to binds to the estrogen receptor and may directly stimulate breast tissue proliferation, inducing gynecomastia[4]. Deepinder and Braunstein also wrote that one of the drugs that can cause gynaecomastia is digoxin, although it is not know if it is dose dependent or not. The time of occurrence after taking this medicine is around 2 months with low quality evidence of associations.[11] The most frequent cause of non tumoral hyperprolactinemia is medications. Neuroleptics or antipsychotic agents are the ones most commonly causing hyperprolactinemia. Medication induced hyperprolactinemia is usually associated with prolactin levels ranging from 25 to 100 µg/L. In this case result levels of serum prolactin of 87.5 ng/mL. Some patients with medication induced hyperprolactinemia remain asymptomatic, and men may present with low libido and erectile dysfunction.[12] Although patients came to the polyclinic with bilateral breast tenderness, pain and symmetrical enlargement, occurring in 2 weeks before. We obtained a pituitary magnetic resonance imaging (MRI) to differentiate between medication induced gynecomastia and symptomatic gynecomastia with hyper-prolactinemia due to a pituitary or hypothalamic mass (prolactinoma). The head MRI without contrast imaged was multiple chronic lacunar infarcts, intrasellar and suprasellar were normal and no mass or infection was visible. It is thought that gynecomastia is caused by a medication or recreational drug. Withdrawal from this agent should result in at least some improvement over a period of a few months.[8] The patient was no longer taking spironolactone and digoxin, as at the preferred hospital, only diltiazem 30 mg tid was being administered. At the endocrinology polyclinic, the medication

was replaced to candesartan 16 mg/day and diltiazem CD 100 mg/day.

## CONCLUSION

In conclusion, no causal factors other than the administration of medication could be identified in the present case; these changes regressed upon the discontinuation of spironolactone and digoxin. In patients presenting with symptomatic gynecomastia and galactorrhoea, careful history and physical examination are essential. Appropriate screening laboratory tests must be conducted to identify underlying disorders and inform the subsequent therapeutic approach. The underlying causes of the condition should be addressed and corrected. Further follow-up is required to rule out other potential causes. Further examination and laboratory testing are required to ascertain whether an additional causative disorder or disease is present in this case, to gain a fuller understanding of the underlying pathology.

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CASE REPORT

# Successful Management of Antithyroid Drug-Induced Agranulocytosis Using Granulocyte Colony-Stimulating Factor: A Case Report

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**ABSTRACT**

Agranulocytosis is a rare condition and occurs in all age groups. Incidence ranges from 6 to 8 cases per million population per year. About 70% of the cases are found to be involved with medication usage. The use of granulocyte colony-stimulating factor (G-CSF) is effective for antithyroid drug (ATD)-induced agranulocytosis, though some patients do not respond. A 22-year-old female was diagnosed with Grave's disease (GD) three months ago and began using Methimazole (MMI) at an initial dose of 20 mg/day. She was taken to the emergency room after complaining of a fever and stomachache for a week. Laboratories: The patient had leucopenia (white blood cell count 2040/mm3) and severe neutropenia, with an absolute neutrophil count (ANC) of 122.4/μL, thyroid stimulating hormone (TSH) of 0.005 IU/mL, and free thyroxine (FT4) of 46.81 pmol/L. The patient received G-CSF, which normalized her neutrophil counts after the first injection and resolved her fever. She was recommended to quit methimazole therapy. MMI is thionamide used as a first-line treatment for GD. The most severe side effect is agranulocytosis. Agranulocytosis can have various presentations; it most frequently occurs between 2 weeks and 3 months after the initiation of treatment. If the patient recovers, granulocytes begin to reappear in the periphery within a few days to 3 weeks. This drug-induced agranulocytosis is a lethal condition but reversible if recognized early and treated accordingly. G-CSF may shorten the recovery period.

**Keywords:** Agranulocytosis, grave's disease, antithyroid drug, granulocyte colony-stimulating factor

## INTRODUCTION

Agranulocytosis occurs when the absolute neutrophil count (ANC) is fewer than 100 neutrophils per microliter of blood. It is possible to inherit or acquire agranulocytosis. Agranulocytosis is a hazardous illness that can have lethal effects. To prevent mortality from septicemia, early detection and treatment are necessary.[1] The reported incidence of agranulocytosis, a rare disorder that affects people of all ages, ranges from 6 to 8 instances per million population annually. Medication use is shown to be linked in almost 70% of the instances. It also happens more often in women than in men, possibly because women use medications more often or because autoimmune illnesses are more common in women. Agranulocytosis is not racially biased.[2]

The early symptoms include malaise, fever, and chills, or infections that commonly occur in the form of ulcers, necrotizing lesions of the gingiva, the floor of the mouth, buccal mucosa, throat, or other locations within the oral cavity.[1] When clinicians encounter patients with agranulocytosis, the first response is typically to employ granulocyte colony-stimulating factor (G-CSF) as an emergency intervention; G-CSF is beneficial for (antithyroid drug) ATD-induced agranulocytosis, while some patients do not respond.[3]

Hematopoietic growth factors stimulate neutrophil production, maturation, migration, and cytotoxicity. Agents used to treat agranulocytosis include filgrastim, a granulocyte colony-stimulating factor (G-CSF), sargramostim, a granulocyte-macrophage colony-stimulating factor, and pegfilgrastim (a long-acting filgrastim).[1] Over the last 20 years, granulocyte colony-stimulating factors (G-CSFs) have been the main therapeutic choice for treating patients with neutropenia.[4] Malcolm Moore and Karl Welte discovered granulocyte colony-stimulating factor (G-CSF) from human cells in 1984. It was the foundation for filgrastim, one of the most important cancer treatments. In the hierarchical development of hematopoiesis, G-CSF primarily drives the myeloid cell series from committed progenitor cells to mature neutrophil granulocytes.[5]

## CASE ILLUSTRATION

A 22-year-old female was admitted to the Emergency Room complaining of fever and abdominal pain for a week. Fever complaints all day long, a febrifuge reduces fever. She also complains of nausea, vomiting three or more times each day, and decrease in appetite so that could only complete half of a plate of regular meals, but not accompanied by weight loss. There are no complaints of urination and defecation. Patient with ongoing fatigue, palpitations, and tremors since three months ago. Previously, she was diagnosed with Grave's Disease the last three months ago and started Methimazole at an initial dose of 20 mg/day and a beta-blocker for symptom control.

Were Upon first admission, the vital sign BP 152/96 mmHg, HR: 128 bpm regular, RR 22 tpm, T 38,5$^{o}$C, On physical examination we found exophthalmos and a diffuse enlargement of the thyroid gland. Examination of the abdomen found tenderness in the epigastric. On the thorax, we found a dilated. The left heart border was obtained, Left boundary of the heart in Intercostalis V was 2 cm from linea midclavicularis sinistra. Laboratories found (table 1) leucopenia (white blood cell count 2040/mm$^3$) and severe Neutropenia, absolute neutrophil count (ANC) 122,4/µL with multinational association of supportive care in cancer (MASCC) score 24 (low risk) clinical index of stable febrile neutropenia (CISNE) score 3 or high risk. Differential counting showed: 6% neutrophils, 81% lymphocytes, 9% monocytes, 3% eosinophils, and 1% basophils. Thyroid stimulating hormone (TSH): 0.005 ulU/mL and free thyroxine (FT4) 46.81 pmol/L, confirmed the diagnosis of hyperthyroid.

This patient was diagnosed with ATD-induced agranulocytosis and impending thyroid stom (Burch wartofsky score: 40). Because of serious concern about ATD, she was advised to discontinue methimazole treatment promptly. A granulocyte colony-stimulating factor and

antibiotics were provided after a week. The WBC and granulocyte counts were evaluated 3 days during hospitalization.

Table 1. Laboratory Examination of Patient in Day 1,3, and 6

| Inspection | Day 1st | Day 3rd | Day 6th | Normal Range |
|---|---|---|---|---|
| Hemoglobin | 10,0 | 9,8 | 9,9 | 14,0 - 17,0 |
| Hematocrit | 29 | 29 | 30 | 45 - 55 |
| Erythrocytes | 4,0 | 3,9 | 3,9 | 4,7 - 6,1 |
| Thrombocytes | 330 | 381 | 454 | 150 - 450 |
| Leukocytes | 2,04 | 2,01 | 12,75 | 4,5 - 10,5 |
| MCV | 73 | 74 | 78 | 80 - 100 |
| MCH | 25 | 25 | 25 | 27 - 31 |
| MCHC | 35 | 33 | 33 | 32 - 36 |
| Eosinophils | 3 | 0 | 0 | 0 - 6 |
| Basophils | 1 | 2 | 1 | 0 - 2 |
| Stem Neutrophils | 0 | 0 | 0 | 2 - 6 |
| Segmented Neutrophils | 6 | 50 | 80 | 50 -70 |
| Lymphocytes | 81 | 39 | 13 | 20 - 40 |
| Monocytes | 9 | 9 | 6 | 2 - 8 |
| FT4 | 46,81 | | | 9 - 20 |
| TSHs | 0,005 | | | 0,25 - 5 |
| ANC | 122,4 | 1.005 | 10.200 | 1.500 – 8.000 |

Three Days after the injection of GCSF, it was found that ANC started to increase by 1.005 /µL, Day 6th after the third injection 10.200/µL. We decided to stop injecting G-CSF. The methimazole treatment was terminated on admission due to concern for drug-induced agranulocytosis. Subsequently, her infectious workup was negative and antibiotics were stopped. The patient received granulocyte stimulating colony factor with normalization of her neutrophil counts and resolution of her fever.

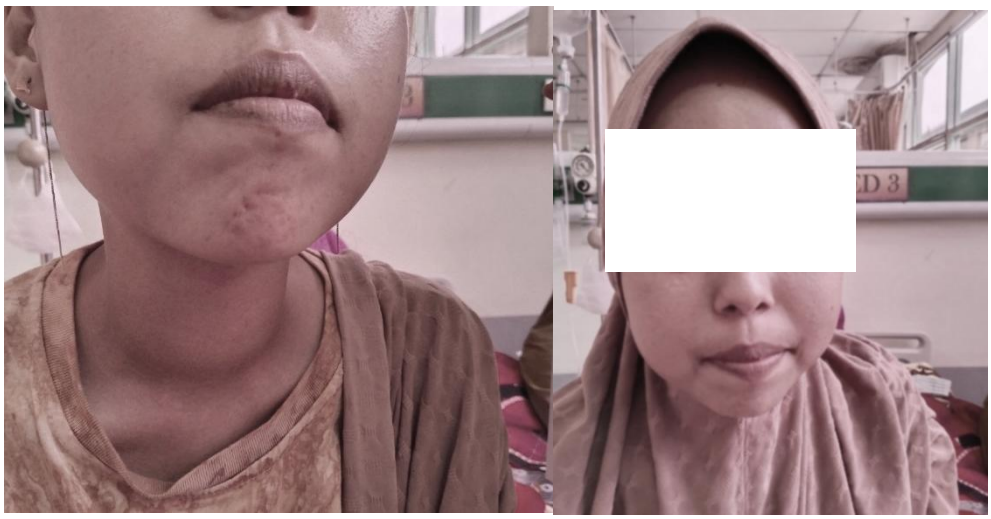

Figure 1. Clinical picture of the patient showed diffuse thyroid enlargement and exophthalmos

## DISCUSSION

Methimazole (MMI) is a thionamide used as the first-line therapy for Graves' disease (GD). MMI has mild adverse effects such as skin rash and liver problems, with agranulocytosis being the most serious. Agranulocytosis often appears within 2-3 months of starting medication. Treatment with thioamide propylthiouracil (PTU) is more likely to cause serious adverse effects such as hepatotoxicity, vasculitis, and polyarthritis compared to MMI.[6]

Agranulocytosis can cause a variety of symptoms, including fever, chills, and sore throat. It can be a life-threatening illness that demands immediate diagnosis and treatment.[1] Agranulocytosis is a potentially fatal side effect of antithyroid drug (ATD) treatment. Its incidence is 0.2% to 0.5%, and its mechanism is unknown. Antithyroid drugs are commonly used to control hyperthyroidism, especially when patients refuse other therapies such as radioiodine and surgery. Despite their acceptability, especially in Eastern countries, antithyroid drugs are associated with many complications. Of the known complications, antithyroid drug-induced agranulocytosis, although rare, is the most severe and life-threatening.[7]

Agranulocytosis can be roughly categorized into two types: hereditary and acquired. The hereditary condition is caused by genetic abnormalities in the gene that codes for neutrophil elastase, or ELA2. The most prevalent alterations are intronic substitutions, which deactivate a splicing site in intron 4. Diseases can be acquired as a result of numerous drugs, toxins, autoimmune problems, or infections.[8]

The following are the medications commonly involved with agranulocytosis:[9]

1. Cancer chemotherapies
2. Analgesic and anti-inflammatory (gold, naproxen, and penicillamine)
3. Anti-thyroid (carbimazole, propylthiouracil)
4. Anti-arrhythmics (quinidine, procainamide)
5. Anti-hypertensives (captopril, enalapril, nifedipine)
6. Antidepressants/psychotropics (clozapine, amitriptyline, dosulepin, mianserin)
7. antimalarials (pyrimethamine, dapsone, sulfadoxine, chloroquine)
8. Anticonvulsants (phenytoin, sodium valproate, carbamazepine)
9. Antibiotics (sulphonamides, penicillin, cephalosporins)
10. Miscellaneous (cimetidine, ranitidine, chlorpropamide, zidovudine)

Infections that can cause agranulocytosis include:

1. Bacterial (typhoid fever, shigella enteritis, brucellosis, tularemia, tuberculosis)
2. Rickettsial (rickettsialpox, human granulocytic anaplasmosis, Rocky Mountain spotted fever)
3. Parasitic (kala-azar, malaria)
4. Viral (human immune deficiency, Epstein-Barr virus, cytomegalovirus, hepatitis viruses, human herpesvirus

Agranulocytosis is thought to occur according to the following mechanisms:

1. when the drug attaches to the granulocyte, antibody production begins to destroy granulocytes;
2. antibodies may target the drug metabolites complex absorbed on the neutrophil granulocyte in the presence of plasma component; and
3. the drug may cause the production of autoantibodies.[10]

If agranulocytosis is identified, the medication should be stopped, the patient should be watched for infection symptoms, and antibiotics should be started if needed. Factors that stimulate granulocyte colonies may reduce the healing time. Within a few days to three weeks, granulocytes start to return to the periphery if the patient recovers; a normal granulocyte count soon follows.[10] It has been observed that G-CSF treatment of ATD-induced agranulocytosis reduces the mortality rate from 21.5 to 5%.[11] Infection is the primary agranulocytosis consequence. The frequency of infection is closely correlated with the length and intensity of agranulocytosis. The incidence of infection reaches 100% when the ANC stays below 100 cells per microliter of blood for more than three to four weeks.[1]

Another serious side effect of agranulocytosis is sepsis. The clinical state known as sepsis is brought on by the body's dysregulated reaction to an infection. Sepsis, bacteremia, and septic shock result from the body's inability to combat the offending pathogens due to a significant reduction in the number of mature granulocytes caused by agranulocytosis. A distributive or vasodilatory shock that causes circulatory and metabolic problems and is linked to a greater death risk is septic shock.[1]

Since agranulocytosis is a dangerous illness, therapy should be started right once. Regardless of whether the patient exhibits symptoms or not, any suspected offending drugs or agents should be stopped as soon as agranulocytosis is confirmed. It normally goes away one to three weeks after the offending agent is ceased if it is caused by drugs or another substance. In the meanwhile, general care measures like gargles, anesthetic gel for oral and gingival lesion discomfort, and good oral hygiene to avoid infection of the teeth and mucosa are beneficial. Constipation can be treated with stool softeners. Abrasions and skin infections need to be treated right away.[1]

Before and after the introduction of G-CSF, the beginning patterns of agranulocytosis caused by antithyroid drugs were divided into the following two categories: The asymptomatic group had no signs or symptoms of infection throughout the disease, while the symptomatic group had signs and symptoms of infection as the initial clinical features of agranulocytosis or, when agranulocytosis was identified by routine WBC count monitoring, symptoms were absent and infection only developed a few days later despite stopping antithyroid medication therapy. G-CSF has been used to treat all individuals with agranulocytosis brought on by antithyroid medications since July 1990. Until the granulocyte count exceeded 109/L, a subcutaneous dosage of 75 g G-CSF was given every day. Bone marrow punctures were sometimes done once at the development of agranulocytosis or granulocytopenia and again during the recuperation phase.[12]

G-CSF is the mainstay of therapy since it dramatically speeds up granulopoiesis regeneration. Due to higher rates of bacterial resistance, G-CSF prophylaxis is suggested by the ASCO recommendations as a better way to avoid infections than antibiotic prophylaxis. G-CSF promotes neutrophil regeneration following allogeneic stem cell transplantation. Increased rates of both acute and chronic graft-versus-host disease (GvHD) have been reported in certain investigations. Meta-analyses, however, revealed a one-day advantage in neutrophil regeneration but no discernible rise in the risk of GvHD. Hospital stay duration and survival were unaffected.[5]

## CONCLUSION

Agranulocytosis occurs generally within a few weeks or months of taking the anti-thyroid medication but onset may be delayed by one year. This drug-induced agranulocytosis is a lethal condition but reversible if recognized early and treated accordingly. In patients with ATD-induced agranulocytosis, the recovery duration can be substantially reduced by G-CSF.

## ACKNOWLEDGMENTS

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CASE REPORT

# Hashitoxicosis: A Case Report

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**ABSTRACT**

Hashimoto Thyroiditis with Grave's disease/Hashitixicosis is found in some cases, and this case report describes a case of a woman with Hashitoxicosis. A 27-year-old woman came to polyclinic on 18th March 2024 with complain of a lump felt, fatique, constipation and weight loss two month before she had weight gain later without any treatment. She was compomentis, BP 149/90 mmHg, HR 87x/i, Wayne index 0, Billewicz score -22. TSH 93.40 mcIU/mL and FT4 0.39 ng/dL, anti-TPO >1000 Iau/mL, TRAb 2.46 IU/L. Thyroid ultrasound showed toxic diffuse struma, thyroid scintigraphy revealed enlarge lobes with high and even distribution and capture of radioactivity with conclusion of toxic diffuse struma, and cytologic examination showed colloid goiter. Patient was diagnosed as Hashitoxicosis and has been treated with levothyroxine 100 mg once daily. This woman was diagnosed as Hashitoxicosis based on clinical features of hypothyroidism at admission to polyclinic following clinical features of hyperthyroidism initially without any treatment, with laboratory results showed hypothyroidism with the increased of antibody for Hashimoto Thyroiditis and Grave's disease. Treatment with levothyroxine 100 mg once daily showed the decrease of TSH and normal FT4 level. We report a case of Hashitoxicosis based on clinical features of hypothyroid following hyperthyroidism initially, laboratory, thyroid ultrasound, thyroid scintigraphy, and cytologic examination result. Treatment with levothyroxine showed improvement.

**Keywords**: Hashimoto's thyroiditis, graves' disease, hashitoxicosis

## INTRODUCTION

Hashimoto's thyroiditis (HT), also known as an autoimmune disease of the thyroid gland, is often characterized by an enlarged thyroid gland, hypothyroidism, which damage to the thyroid gland occurs due to lymphocytic infiltration and elevated serum autoimmune antibody levels[1,2]. Based on a worldwide meta-analysis study of 48 studies in 20 Europe, 16 Asia, 5 South America, 3 North America, and 3 Africa, the prevalence of HT was 7.5%. The prevalence of HT varies according to geography, namely Africa 14.2%, Oceania 11%, South America and Europe 8.0%, North America 7.8%, and Asia 5.8%.[3] HT was diagnosed with anti-thyroid antibodies against peroxidase (TPOAb) and anti-thyroid antibodies against thyroglobulin (TGAb), and it was confirmed using thyroid ultrasonography. In a study, 24 patients had hypothyroidism, and they were followed up during the period 2000–2016.

Following HT diagnosis, patients developed GD after a mean time of 38 ± 45 months, and levels of free triiodothyronine (fT3), free thyroxine (fT4), and thyrotropin receptor antibody (TRAb) were significantly higher, and TSH levels were significantly lower at the hyperthyroid state.[4] 61-year-old woman who was diagnosed with hypothyroidism 30 years ago and then, the patient returned to the hospital in 2015 with a hypothyroid blood result with anti-TPO 83 IU/mL, elevated TRAb, and a hyperthyroid picture. In 2017, it was found that her TSH was completely suppressed, FT4 elevated, and then called this condition hypothyroidism conversion to hyperthyroidism.[5] This case report describes a case of a woman, 27th years old with HT.

## CASE ILLUSTRATION

A woman, 27 years old, came to the internal medicine specialist with complaints of a palpable neck lump for two months. Complaints of pain and fever are not found. Complaints of palpitations were not found, complaints of a 2 kg weight loss were found, but then the weight rose again. Fast fatigue is found, thumping is not found, and sweating is not found. A family history of the same disease was found that the patient's mother experienced the same thing but was only suctioned, and there was no routine medication. The patient stated constipation and urination were normal. The examination revealed cpmpos mentis (CM) sensorium, blood presure (BP) 149/90 mmHg, heart rate (HR) 87x/i, Wayne's Index 0, Billewicz score -22, thyroid ultrasound result (18/3/24) was diffuse toxic struma. The patient was advised to check TSH and FT4 at the next visit. On March 25, 2024, the results of TSH 93.40 mcIU/mL and FT4 0.39 ng/dL were obtained, then referred to radionuclear for thyroid print examination. On April 5, 2024, a thyroid scintigraphy examination revealed enlarged lobes with high and even distribution and capture of radioactivity, which was concluded to be diffusa toxic struma.

On cytologic examination of aspirate samples, cystic colloid goiter was found. Based on the results of history and examination, the patient was diagnosed with HT with Grave's Disease, also diagnosed as Hashitoxicosis. On the next visit on April 16, 2024, the patient was given Levothyroxine 1x100mg therapy for a month and then on April 18, an anti-TPO and TSH receptor antibodies (TRAB) examination was carried out with the results of anti-TPO>1000 IU/mL and TRAB at 2.46 IU/L. On April 23, TSH and FT4 were rechecked with TSH 0.65 uIU/mL and FT4 86.20 ng/dL. On May 17, TSH 5.97 uIU/mL and FT4 was 1.34 ng/dL.On June 20, TSH 7,41 uIU/mL and FT4 1.06 ng/dL.

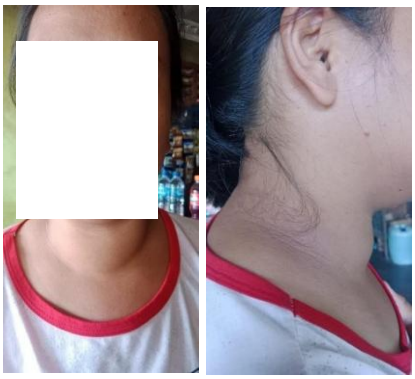

Figure 1. Goiter

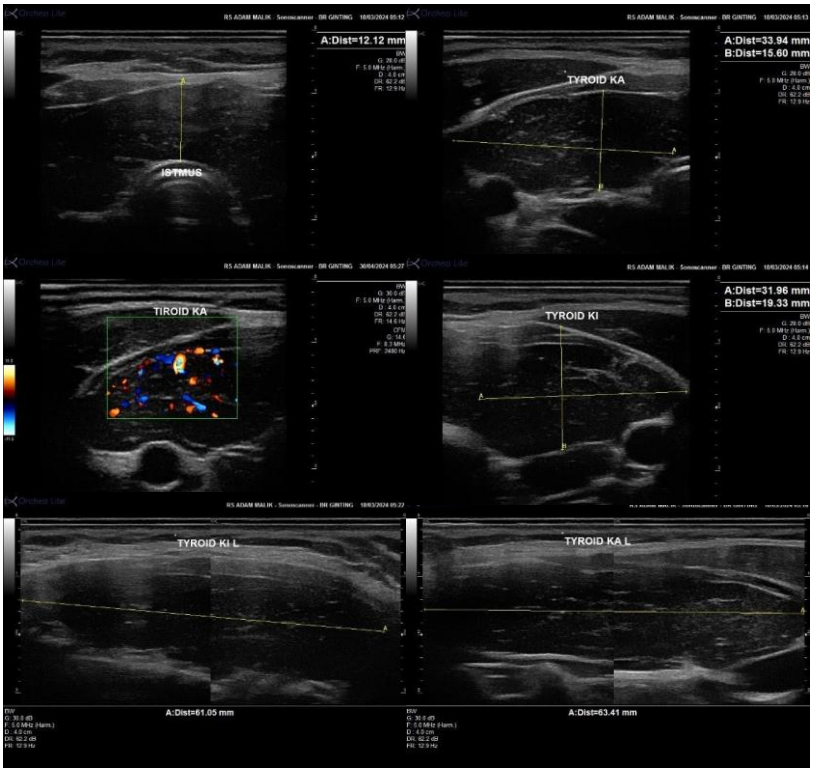


Figure 2. Thyroid ultrasonography

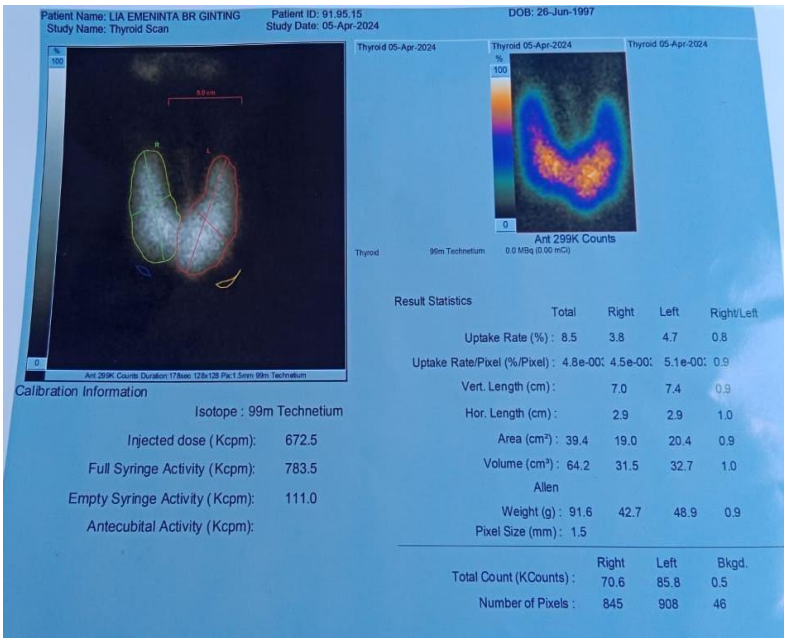


Figure 3. Thyroid Scintigraphy Result

## DISCUSSION

In this case, the patient complained of a lump in the neck, no heart palpitations, and no profuse sweating. This condition caused by signs and symptoms in HT is linked to hypothyroidism they are goiter and decreased T4, cool and dry skin due to atrophy of the sweat glands, yellowish and thickened skin due to accumulation of hyaluronic acid, coarse hair, loss of body hair, hoarse voice due to myxedema of the vocal cord, coarse facial features, facial edema, generalized edema, bradycardia and decreased amplitude of cardiac waves on electrocardiography,

decreased cardiac output, delayed relaxation phase of the deep tendon reflexes, decreased peristalsis leading to constipation or even ileus, hypotonia of the gallbladder and may lead to biliary stone formation. Patients with overt hypothyroidism could present as menorrhagia in women and include altered anovulatory cycles due to impaired conversion of estrogen precursors.[6] Wayne's Index is a scoring tool for hyperthyroidism signs and symptoms. Nine symptoms and ten signs are listed and have positive or negative scores. The score ranges from 45 to −25. A score >19 is toxic hyperthyroidism, while a score <11 is euthyroidism, and a score 11-19 is equivocal. Though arrived at by trial and error, it has shown a diagnostic accuracy of 85%. Wayne's Index was earlier used to help diagnose hyperthyroidism and Grave's disease.[7] In this case, the patient's Wayne's Index is 0, which means it can be assessed as not Grave's disease.

The Billewicz score consists of 13 assessments with a total score of +67 to -47. A score ≥+25 suggests hypothyroidism, -30 to +25 is subclinical hypothyroidism, and a score - of 30 or less excludes the disease. Diminished sweating is assessed in a warm room. Dry skin is defined as dryness of skin noted spontaneously. Cold intolerance is a preference for a warm room or extra clothing. Weight increase and constipation are scored as present. Hoarseness is assessed in speaking and singing, and paresthesia is scored based on subjective sensations. Deafness is defined as a progressive improvement of hearing. Slow movements are noted while observing the patient at present. Coarse skin and thickening are assessed over the hands, forearms, and elbows. Cold skin is assessed by comparing the patient's and examiner's skin. Periorbital puffiness is defined if it obscures the curve of the malor bone. Counting the pulse for the 30s and report bradycardia of the pulse <75/min. They elicit the ankle jerk when the patient kneels on a chair, grasping its back.[8] In this case, the total Billewicz score is 22, which means that based on screening, the patient is concluded to have subclinical hypothyroidism.

In some patients with particularly pronounced thyroid destruction in the initial phase, Hashitoxicosis or HT in the hyperthyroidism stage maybe present due to the release of preformed thyroid hormones from destroyed follicles to the circulation. Primary hypothyroidism is generally considered "overt" when the TSH level is elevated and FT4 is low. Subclinical hypothyroidism is defined biochemically as an elevated TSH accompanied by normal FT4 and FT3. Condition of hypothyroidism is due to thyroid follicular cell destruction by infiltrating immune cells, leading to exposure of thyroid antigens (TPO and thyroglobulin [Tg]), further enhancing antibody production (TgAbs, TPOAbs) and aggravating destruction of thyroid follicles. Anti-TG antibodies attack a protein in the thyroid called thyroglobulin. Anti-thyroperoxidase (TPO) antibodies attack an enzyme called thyroperoxidase in thyroid cells that helps convert T4 to T3. Having TPO autoantibodies in the blood means the body's immune system attacked the thyroid tissue in the past. Most people with HT disease have these antibodies, although people whose hypothyroidism is caused by other conditions do not.[6,9]

The thyroid ultrasound examination results found that the right and left lobes were dilated with heterogeneous parenchyma, no classification, and increased vascularity. There were no nodules, thickened isthmus, and no enlarged lymph nodes. The conclusion of the Thyroid ultrasound examination is diffusa toxic struma. Anti-TPO >1000 IU/mL. Cytologic examination of aspirate samples revealed cystic colloid goiter. Based on the examination, the patient was diagnosed with HT because the diagnosis of HT is based on clinical symptoms of hypothyroidism, the ultrasound features of HT include decreased echogenicity, heterogeneity, hypervascularity, the presence of small cysts, and serum anti-TPOAbs are present. Candanwale et al. found 5 cases of HT with the colloid goiter on FNA examination out of 100 cases they studied. In their case, FNA smears

showed moderate to severe background colloid and lymphocytes infiltrating follicular cell clusters and Hurthle cells.[10,11,6]

In this case, we found TSH 93.40 uIU/mL and FT4 0.39 ng/dL, anti-TPO >1000 IU/mL, and TRAb positive. TRAb suggests clinicians utilize a positive TRAb measurement over their clinical judgment to confirm a Graves' Disease (GD) diagnosis. A meta-analysis of 21 studies showed that the serum TSH-R-Ab concentration's overall pooled sensitivity and specificity measured with second- and third-generation binding assays were 97 and 98%, respectively.[12,13] Thyroid scintigraphy examination, in this case, revealed enlarged lobes with high and even distribution and capture of radioactivity. Diffuse thyroid overactivity with a homogeneous distribution of the tracer, reduced uptake in major salivary glands, and low background, consistent with GD.[14]

In 2010, four case reports illustrated a subtype of Graves' disease where individuals with HT present with Graves' eye disease and elevated blood levels of stimulating antibodies. While the exact reason this occurs is unknown, researchers believe TSH receptors and antibodies are the links. As the concentration of thyroid stimulating and blocking antibodies changes, so does the clinical presentation of thyroid dysfunction. The thyroid cell might be 'attacked' by blocking and stimulating antibodies. Depending on the relative concentrations, hypothyroidism or hyperthyroidism may occur. So, the difference between HD and GD may be gradual and small.[15]

In some cases, as the autoimmune process progresses and the thyroid gland becomes damaged, a person with Graves' disease can develop HT. While symptoms can shift back and forth, it is more common for one clinical presentation to overshadow the other. For instance, in the most common presentation of this situation, there are more thyroid-blocking antibodies than stimulating antibodies, typically causing symptoms of hypothyroidism. It is also possible for a person to have both conditions concurrently. In this case, the immune system produces stimulating and blocking antibodies, leading to fluctuating thyroid hormone levels and variable symptoms that shift between hypothyroid and hyperthyroid. When both conditions are present, one condition is still more likely to dominate in symptoms.[16]

HT usually presents as subclinical or overt hypothyroidism. In some cases, a patient has the signs and symptoms of hyperthyroidism in the initial presentation, and this condition is called Hashitoxicosis. Case report found anti-TPO >1000IU/mL, TSH suppressed, and FT4 elevated.[17] One possible explanation of the unusual hyperthyroidism condition in HT patients was the presence of these stimulating antibodies apart from the destruction of thyroid follicles. [17] In some cases, we found other patients had high TSH, low or normal FT4, and high anti-TPO, so the patients were diagnosed with HT and then got levothyroxine therapy for hypothyroidism. After a few months of therapy, the patient returned for follow-up and found TSH suppressed, FT4 elevated, and TRAb positive. The authors conclude that this condition is called GD following hypothyroidism or conversion of autoimmune hypothyroidism (HT) to GD.[18,19] In a study, 24 patients had hypothyroidism and HT, followed by a phase of hyperthyroidism. They were followed up during the period 2000–2016. Following HT diagnosis, patients developed GD after a mean time of 38 ± 45 months. Levels of fT3, fT4, and TRAb were significantly higher, and TSH levels were significantly lower in the hyperthyroid state.[4]

In another case report, we found a similar case with our patient, a 61year-old woman who was diagnosed with hypothyroidism 30 years ago. Then, the patient returned to the hospital in 2015 with a hypothyroid blood result with anti-TPO 83 IU/mL, elevated TRAb, and a hyperthyroid picture. In 2017, it was found that her TSH was completely suppressed and FT4 elevated. The authors believe that changes in thyroid conditions are related to the balance in the stimulating and blocking activities of antibodies and the thyroid gland's response to these antibodies, causing a pull-push effect

shifting either to hypothyroidism or hyperthyroidism, respectively. A variable behavior of the TRAB with the TSH receptor is responsible for the conversion from hypothyroidism to hyperthyroidism and vice versa. Thyroid damage from an autoimmune phenomenon initially causes thyroid hypofunction, but once enough tissue has recovered, it is stimulated by stimulating antibodies.[5] Based on the findings of several cases and studies, we diagnosed this patient with HT with Grave's Disease, or we also diagnosed it with Hashitoxicosis.

The patient was given levothyroxine 1x100mg therapy for the condition of hypothyroidism. Hypothyroidism should be treated with thyroid hormone replacement therapy. Initial LT4 dose ranges between 1.4 and 1.8 mcg/kg body weight. On May 17, TSH was 5.97 ulU/mL and FT4 1.34 ng/dL; this indicates a response to the therapy given. The substitution therapy must be taken for life to maintain normal TSH levels.[1,6,20]

## CONCLUSION

A patient with HT diagnosed based on thyroid ultrasound with high anti-TPO was reported. A combination of clinical features and thyroid function tests can help diagnose HT. Based on the patient's clinical and laboratory features, treatment may also be considered.

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CASE REPORT

# Multiple Autoimmune Syndrome (Graves' Disease, Autoimmune Hepatitis, SLE) in Young Male with ASD Secundum: A Rare Case

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**ABSTRACT**

Multiple autoimmune syndrome (MAS) is characterized by the presence of at least three autoimmune diseases, presenting complex clinical challenges due to overlapping conditions and varied manifestations. Multiple autoimmune syndrome is rarely reported in men, particularly with the combination of Graves' disease, systemic lupus erythematosus (SLE), and autoimmune hepatitis (AIH). We report a case of a 22-year-old male who presented with symptoms of jaundice, significant weight loss, and classic signs of hyperthyroidism, including palpitations and tremors. Physical examination revealed jaundice, exophthalmos, and an enlarged thyroid gland, and he was diagnosed with Graves' disease, SLE, and AIH. Additional findings included stasis dermatitis and an atrial septal defect (ASD) with a moderate risk of pulmonary hypertension. The patient received thiamazole, propranolol, and corticosteroids, leading to clinical stabilization and symptom resolution. This rare MAS case with concurrent Graves' disease, SLE, and AIH highlights the need for accurate diagnosis and individualized management. The immunological interplay among these diseases contributes to diverse clinical manifestations, requiring a multidisciplinary approach. Our patient's management strategy effectively controlled hyperthyroidism, mitigated hepatic inflammation, and stabilized cardiac function, illustrating the effectiveness of comprehensive therapy. In young patients presenting with multiple autoimmune symptoms, MAS should be considered, especially with unusual combinations. Early detection and tailored treatment approaches, along with interdisciplinary collaboration, are essential to manage MAS and its associated complications.

**Keywords:** Multiple autoimmune syndromes, Graves' disease, *autoimmune hepatitis*, SLE, *atrial septal defect secundum*

## INTRODUCTION

Autoimmune diseases (AIDs) have an estimated global prevalence ranging from 3% to 9.4%. In most cases, AIDs manifests as a single disease (mono autoimmunity). However, clinical observations suggest that some patients may develop additional autoimmune conditions over time or simultaneously experience multiple AIDs, a phenomenon known as polyautoimmunity. The global prevalence of polyautoimmunity is estimated at 0.5%, meaning that approximately 4.4% of individuals with autoimmune diseases are affected by more than one AID.[1]

Multiple autoimmune syndrome (MAS), characterized by the presence of at least three distinct autoimmune conditions and creating complex clinical manifestations, is a rare condition. MAS diagnosis and therapy are challenging due to the overlapping conditions and diverse manifestations. Diagnosing MAS needs a physician's accuracy and depends on the age when the first autoimmune disease appears.[2] Based on the frequency of their association, MAS is categorized into three types.[3] This classification helps in predicting the likelihood of additional autoimmune diseases in patients already diagnosed with two AIDs, offering insights into the underlying pathophysiology of autoimmune disorders.[4]

1. Type I: Myasthenia Gravis, Thymoma, Polymyositis, and Giant Cell Myocarditis;
2. Type II: Sjögren's Syndrome, Rheumatoid Arthritis, Primary Biliary Cirrhosis, Scleroderma, and Autoimmune Thyroid Disease (AITD);
3. Type III: Autoimmune Thyroid Disease, Myasthenia Gravis and/or Thymoma, Sjögren's Syndrome, Pernicious Anemia, Idiopathic Thrombocytopenic Purpura, Addison's Disease, Type 1 Diabetes Mellitus, Vitiligo, Autoimmune Hemolytic Anemia, Systemic Lupus Erythematosus, and Dermatitis Herpetiformis.[3]

This paper aims to describe a rare case with an unusual combination of MAS (Graves' disease, systemic autoimmune disease (SLE), and autoimun hepatitis (AIH)) in a male patient. This case involves a 22-year-old male diagnosed with Graves' disease. Epidemiological data show it occurs more frequently in women than men.[5-7] Studies indicate a 3% risk in women and a 0.5% risk in men, with a peak onset age between 20 and 50.[5,6]

## CASE ILLUSTRATION

A 22-year-old man presented with jaundice and notable weight loss over the past month. He reported yellow discoloration of his body starting with his nails and eyes, eventually spreading to his entire body, worsening over the past week. He also noted bloating and early satiety over the last month, along with a 10-20 kg weight loss within the past three months. Additional complaints included epigastric pain, palpitations for the past month, excessive sweating, cold intolerance, and frequent hand tremors. He felt easily fatigued and experienced shortness of breath with activity. He reported dark patches on both lower legs for the last seven months. There was no history of alcohol use, nor any family history of autoimmune, liver, or cardiac disease.

On admission, the patient was alert with vital signs showing blood pressure of 108/91 mmHg, heart rate of 92 beats per minute, respiratory rate of 20 breaths per minute, temperature of 36.8°C, SpO2 of 100% on room air, and a Visual Analog Scale (VAS) pain score of 2 in the abdominal region. His body mass index was 23.0 kg/m$^2$ (normal weight). The Framingham score included two major and one minor criterion, and Wayne index scored 22, indicating hyperthyroidism. Examination revealed jaundice, exophthalmos, scleral icterus, and a palpable, smooth, mobile thyroid nodule (1 cm$^3$) in the right thyroid lobe without tenderness. Cardiac examination revealed an increased caudolateral impulse, a fixed split second heart sound, and a grade 2 tricuspid murmur. Abdominal examination indicated tenderness in the epigastrium and right hypochondrium. Extremities showed dark lesions on both lower legs and a bilateral hand tremor.

Laboratory results included elevated total bilirubin (13.51 mg/dL), direct bilirubin (2.5

mg/dL), indirect bilirubin (0.3 mg/dL), gamma-glutamyl transferase (GGT, 59 U/L), alkaline phosphatase (ALP, 185 U/L), and free thyroxine (FT4 93.04 pmol/L), supporting the diagnosis of jaundice. ANA immunofluorescence testing was positive for both dsDNA and DFS70 antibodies, with an ANA titer of 1:100. Complete blood count, aspartate aminotransferase (AST), and renal function were normal. Tests for viral hepatitis and antimitochondrial antibody (AMA) M2 were negative.

The patient exhibited thrombocytopenia with a platelet count of 80 $\times 10^3/\mu L$, a common hematologic manifestation of SLE, which may be attributed to immune-mediated destruction or bone marrow suppression. Additionally, an elevated INR (2.36) raised concerns about potential coagulopathy, which could be secondary to AIH-related liver dysfunction or lupus-associated antiphospholipid syndrome.

Imaging included chest x-ray showing cardiomegaly with pulmonary edema, abdominal ultrasound revealing ascites, cystitis, and bilateral pleural effusion. MRCP indicated iron overload (R2* values 50.1-132.9 $s^{-1}$) and grade 1 hepatic steatosis. Thyroid ultrasound revealed bilaterally increased echogenicity and a right-sided thyroid nodule with prominent vascularization, suggesting thyroiditis or Graves' disease.

Electrocardiogram revealed sinus tachycardia with a heart rate of 115 beats per minute, normal axis, transition zone at V3, and complete right bundle branch block (RBBB). Echocardiography showed an atrial septal defect (ASD) with an intermediate risk of pulmonary hypertension (PH). NT-proBNP level was elevated at 1003 pg/mL (normal <49.00 pg/mL).

Histopathological examination of the liver biopsy showed polygonal hepatocytes, inflammatory cell infiltration, erythrocytes, and eosinophils (7 cells/40 high-power fields), with no malignant cells detected, consistent with autoimmune hepatitis. Skin biopsy from the foot revealed hyperkeratosis, mild spongiosis in the epidermis, and dermal fibrosis with hyalinization, confirming stasis dermatitis.

The patient was diagnosed with Graves' disease, systemic lupus erythematosus (SLE), and AIH. Treatment was initiated with thiamazole (20mg-0-20mg), propranolol (20 mg three times daily), methylprednisolone (31.25 mg every 12 hours), and vitamin D3 (5000 IU daily). Conservative management included compression therapy and topical steroids to manage stasis dermatitis. Five days after admission, the patient showed significant improvement; laboratory results revealed normalized bilirubin and thyroid function, prompting a tapering of steroids. ASD closure was scheduled to prevent potential right ventricular volume overload. At a follow-up 28 days post-discharge, the patient continued to show clinical stability and no signs of autoimmune or hepatic complications. Physical examination revealed no jaundice or recurrence of palpitations. Laboratory values remained within normal ranges, and thyroid function was stable. A multidisciplinary approach involving cardiology, dermatology, and endocrinology ensured continued monitoring of potential new autoimmune manifestations. The ASD closure plan remained in place, considering the ongoing pulmonary hypertension risk.

Table 1. Laboratory Results on the 1st Day of Admission

| Parameter | Result | Unit | Normal Value |
|---|---|---|---|
| **Hematology** | | | |
| Hemoglobin | 11.1 | g/dL | 13,5 - 17,5 |
| Hematocrit | 30 | % | 33 - 45 |
| Leucocyte | 6.3 | $10^3/\mu L$ | 4,5 - 11,0 |
| Platelets | 80 | $10^3/\mu L$ | 150 - 400 |
| Erythrocyte | 3.59 | $10^6/\mu L$ | 4,5 - 5,9 |
| MCV | 83.7 | fL | 70 - 96 |

| Parameter | Result | Unit | Normal Value |
|---|---|---|---|
| MCH | 30.9 | pg | 28,0 - 33,0 |
| MCHC | 36.9 | g/dL | 33,0 - 36,0 |
| Eosinophil | 1.70 | % | 2-4 |
| Basophil | 0.60 | % | 0,0- 2,0 |
| Neutrophil | 52.60 | % | 55,0-80,0 |
| Lymphocyte | 35.70 | % | 22,0-44,0 |
| Monosite | 9.40 | % | 0,0-7,0 |
| PT | 30.3 | seconds | 10-15 |
| APTT | 39.8 | seconds | 20-40 |
| INR | 2.360 | seconds | |
| **Chemistry** | | | |
| SGOT | 55 | u/l | <35 |
| SGPT | 40 | u/l | <45 |
| Albumin | 2.5 | g/dl | 3.5-5.2 |
| Creatinin | 0.3 | mg/dL | 0,6 - 1,2 |
| Ureum | 23 | mg/dl | >50 |
| Blood Natrium | 133 | mmol/l | 136-145 |
| Blood Potassium | 3.7 | mmol/l | 3.3-5.1 |
| Blood Chloride | 109 | mmol/l | 98-106 |

**Table 2. Monitoring of Total Bilirubin, TSH, and FT4**

| Laboratory Examination | Results (2024) | | | | | | Reference | Unit |
|---|---|---|---|---|---|---|---|---|
| | 24 Apr | 29 Apr | 17 May | 24 May | 31 May | 24 July | | |
| Total Bilirubin | 13,51 | 15,83 | 12,54 | 4,22 | 2,11 | 1,25 | 0.00-1.00 | mg/dl |
| TSH | 0,01 | | | 0,01 | | 0,07 | 0.40-4.20 | ulU/ml |
| FT4 | 93,04 | | 77,22 | | 24,57 | 14,68 | 10.30-34.70 | pmol/l |

**Tabel 3. Simplified AIH Criteria.[30]**

| Variable | Score |
|---|---|
| ANA or SMA/F-actin | |
| ≥1:40 | +1 |
| ≥1:80 or | +2 |
| LKM ≥ 1:40 or | +2 |
| SLA (+) | +2 |
| IgG serum | |
| > Upper normal limit | +1 |
| >1.1 × Upper normal limit | +2 |
| Histological findings | |
| Compatible AIH | +1 |
| Typical AIH | +2 |
| Negative viral hepatitis markers | +2 |

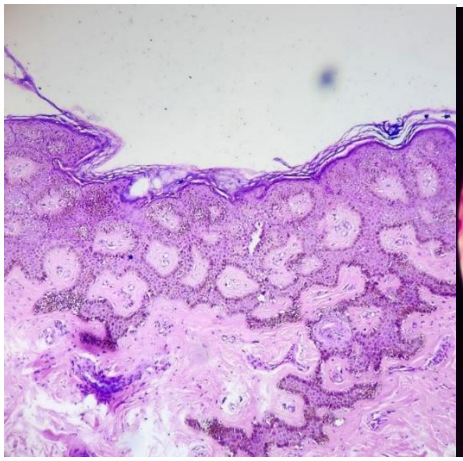

Figure 1. Skin Biopsy Showed Epidermal Hyperkeratosis and Dermal Hyalinizing Fibrosis

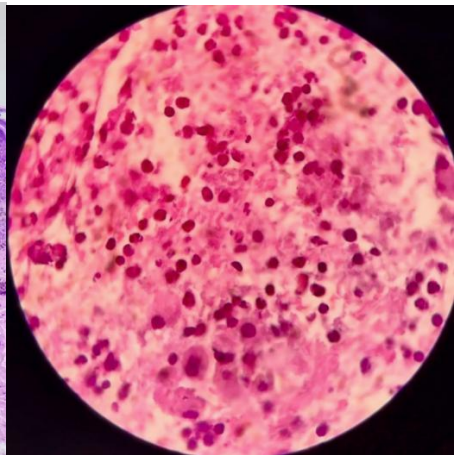

Figure 2. Liver Biopsy Showed Hepatocyte Rosette, Emperipolesis, and Plasma Infiltration

Referee: 2405170111 SLO Test: Ana Profile3 plus DFS70
Results from: 20/05/2024 Strip Number: 287-68

| Antigen | Class | o | (+) | + | ++ | +++ |
|---|---|---|---|---|---|---|
| RNP/Sm (RNP/Sm) | o | | | | | |
| Sm (Sm) | o | | | | | |
| SS-A native (60 kDa) (SSA) | o | | | | | |
| Ro-52 recombinant (52) | o | | | | | |
| SS-B (SSB) | o | | | | | |
| Scl-70 (Scl) | o | | | | | |
| PM-Scl100 (PM100) | o | | | | | |
| Jo-1 (Jo) | o | | | | | |
| Centromere B (CB) | o | | | | | |
| PCNA (PCNA) | o | | | | | |
| dsDNA (DNA) | (+) | | | | | |
| Nucleosomes (NUC) | o | | | | | |
| Histones (HI) | o | | | | | |
| Ribosomal Protein (RIB) | o | | | | | |
| AMA-M2 (M2) | o | | | | | |
| DFS70 (DFS70) | + | | | | | |
| Control (Ko) | +++ | | | | | |
| Label (ET) | | | | | | |

Figure 3. ANA Profile Results

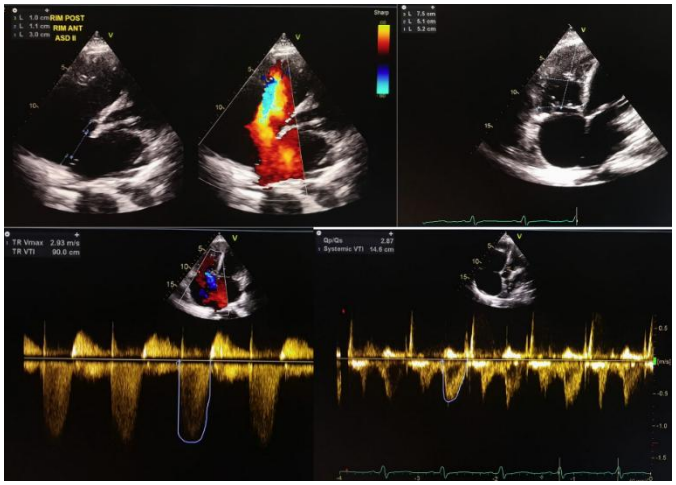

Figure 4. Echocardiography (ASD II L To R shunt, LV Concentric Remodeling with good LV Contractility EF 65 % (Simpson 62 %), Grade I Diastolik Dysfunction, TR dan MR Moderate dan PR Mild, Intermediate Probability of PH)

Figure 5. Clinical Presentation on the 1st Day of Admission

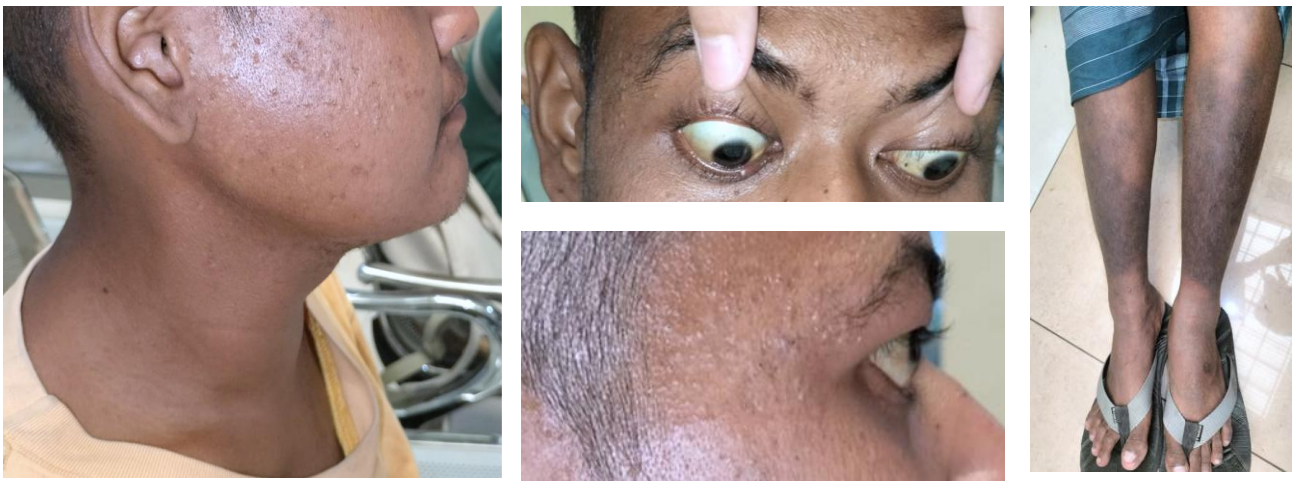

Figure 6. Follow-Up 28 Days After Hospital Discharge

## DISCUSSION

This case presented symptoms of autoimmune thyroid disease (Graves' disease), SLE, and AIH, which is classified as an unusual combination of MAS with additional skin involvement to form stasis dermatitis. MAS refers to the coexistence of three or more autoimmune disorders in a patient, classified into types based on the associated diseases. [8] This patient's condition falls into MAS type III, which includes autoimmune thyroid diseases, SLE, and other autoimmune diseases, a group first described by Humbert and Dupond (1988),[3] such as those in this case, share common immunologic and genetic mechanisms that involve the breakdown of immune tolerance, leading the body to attack its tissues. This phenomenon is often termed "autoimmune tautology," describing how these diseases, despite distinct clinical manifestations, may share underlying mechanisms, often presenting in what is called a "kaleidoscope of autoimmunity". Studies show that approximately 25% of patients with one autoimmune disease may develop another, underscoring the importance of monitoring for emerging autoimmune manifestations.[8]

Graves' disease is a disorder with systemic manifestations primarily affecting the heart, skeletal muscles, eyes, skin, bones, and liver. Failure to diagnose Graves' disease promptly can predispose to thyroid storm, leading to high morbidity and mortality in patients. The symptoms of our patient included a 10-20 kg weight loss over the past three months, palpitations for one month even at rest, profuse sweating daily, preference for cold

environments, fatigue during activities, tremors, and consistently sweaty palms. These complaints are classic signs and symptoms of hyperthyroidism.[6,9,10] Physical examination revealed right thyroid enlargement and exophthalmos, known as Graves ophthalmopathy.[11] Thyroid ultrasound can assist in diagnosis, particularly when nodules are detected, as it is susceptible in identifying lesion/nodule size and differentiating solid from simple or complex cystic lesions.[12]

In suspected thyrotoxicosis, additional testing is needed to confirm diagnosis, assess severity, and guide therapy. Investigations include TSH, FT4, T3, and FT3; thyroid isotope uptake; thyroid isotope scanning; thyroid ultrasound; and antithyroid antibodies.[10,13,14] Thyroid function tests in our case indicated hyperthyroid (TSH <0.05 IU/ml; Free T4 93.04). Positive results on TSH-Receptor-Thyrotropin receptor antibody (TRAb) testing strongly support Graves' disease. TRAb testing in our case showed positivity (>40 IU/L), with ANA immunofluorescence positive results for dsDNA and DFS70, while 14 other panels were negative.[12]

The presence of DFS70 antibodies in the ANA profile is noteworthy. Their presence in isolation, without other disease-specific autoantibodies, tends to suggest a lower likelihood of SLE.[15] However, in this case, the co-occurrence of anti-dsDNA positivity alongside thrombocytopenia and systemic symptoms strongly supported an SLE diagnosis, minimizing the potential confounding effect of DFS70 positivity. The clinical relevance of anti-DFS70 antibodies remains a subject of debate.[16] While some studies, such as Mahler et al. (2012), have found no significant differences in clinical or laboratory findings between SLE patients with and without anti-DFS70,[17] other studies, including Dai et al. (2022), suggest an association between anti-DFS70 positivity and a higher frequency of anti-dsDNA antibodies. Additionally, a correlation between anti-DFS70 and anti-dsDNA titers has been reported. This suggests that while DFS70 antibodies alone may not be indicative of SLE, their coexistence with disease-specific autoantibodies, as observed in this patient, warrants careful consideration.[16]

The treatment options for Graves' disease are (1) Iodine-131 therapy; (2) hormone synthesis blockade by antithyroid drugs; and (3) thyroid surgery.[7,10,18] Our patient received thiamazole as an antithyroid drug.[19] Antithyroid drug therapy allows on avoid damage to the thyroid (and parathyroid or nerve), as well as radiation exposure and surgery. The disadvantages of this antithyroid treatment are the need for commitment to comply with the treatment for months or years, increased doctor visits for control, possible side effects of the drugs, and most importantly, a very low rate of permanent remission.[18]

Our case patient received beta-blocker therapy in the form of propranolol and carvedilol. Beta-blockers should be given to most hyperthyroid patients who do not have contraindications to their use. Beta-blockers are relatively or, depending on the severity of the disease, absolutely contraindicated in patients with asthma or chronic obstructive pulmonary disease, severe peripheral vascular disease, Raynaud's phenomenon, bradycardia, second- or third-degree heart block, and diabetics who are susceptible to hypoglycemia. If there are no contraindications, beta blockers can be given immediately after the diagnosis of hyperthyroidism is established, even before a definite diagnosis of the etiology of thyrotoxicosis is obtained. Propranolol is a non-selective beta-1 and beta-2 blocker used in hyperthyroidism and thyroid storms because of its effect on blocking the peripheral conversion of inactive T4 to the active form T3.[20]

Beta blockers can also be useful in controlling heart rate in ASD II Left to Right shunt conditions suffered by patients. Previously, the patient denied a history of heart disease. This may be because ASD is the most common congenital heart disease diagnosed in adulthood, accounting for 25-30% of diagnoses. ASD shows a direct connection between the atrial chambers, allowing blood flow between the systemic and pulmonary circulations. A unique feature of ASD is its slow clinical

progression with most children and young adults being asymptomatic, causing a delay in diagnosis.[21]

Patients with ASDs <5 mm often experience spontaneous closure of the defect within the first year of life. Defects >1 cm are more likely to require medical/surgical intervention to close the defect. Other indications for therapy include stroke, significant hemodynamic shunting greater than 1.5:1, and evidence of systemic oxygen desaturation.[22] If the ASD requires closure, options include percutaneous transcatheter and surgical intervention.[21] According to the European Society of Cardiology guidelines, the best treatment outcomes are with ASD repair at age <25 years.[23] When the ASD is closed percutaneously, patients require antiplatelet therapy for the next 6 months.[22]

Transcatheter closure of ASD (tcASD) in patients with pulmonary arterial hypertension (PAH) has been shown to improve PAH severity, enhance cardiac functional capacity, and reduce atrial arrhythmias. However, some patients may experience residual PAH (rPAH) or worsening PAH following ASD closure.[24] Askeer *et al.* (2020) reported a decline in the prevalence of combined PH from 44% at baseline to 18% post-closure, with a follow-up duration ranging from 15 to 60 months.[25] Chronic left-to-right shunting contributes to pulmonary vascular remodeling and increased pulmonary artery pressure, which may persist even after ASD closure. Risk factors for rPAH post-procedure include advanced age and high pulmonary vascular resistance (PVR). Long-term management should emphasize lifelong monitoring for emerging autoimmune conditions and cardiac complications, including pulmonary hypertension, given the risk of persistent pulmonary vascular changes even after ASD closure.[24]

Jaundice (hyperbilirubinemia) serves as an indicator of liver disease.[26] Jaundice in Graves' disease is rare and multifactorial.[7,27] Direct and indirect mechanisms contribute to liver dysfunction in hyperthyroidism, including hepatotoxicity from hormone exposure, hepatocyte anoxia, free radical damage, accelerated decomposition of glycogen, autoimmune, congestive hepatopathy, underlying liver disease, and antithyroid drug-induced hepatotoxicity.[27] The patient's test results (HBsAg non-reactive, anti-HCV non-reactive, anti-HBc total negative) excluded viral hepatitis etiology. Magnetic resonance imaging (MRI) of the whole abdomen with contrast showed hepatomegaly with hyperhidrosis and grade 1 hepatic steatosis, which is useful for identifying iron overload, especially in the liver. Iron overload, though mild, may be associated with chronic liver disease and metabolic syndrome.[28]

Since this patient had no history of antithyroid drug use a liver biopsy was necessary to confirm the diagnosis, which was consistent with AIH. The liver biopsy result was consistent with AIH. AIH is a chronic, immune-mediated liver disease with complex etiology rooted in genetic susceptibility and environmental triggers, such as viral infections and microbiome alterations along the gut-liver axis. These factors contribute to an immune dysregulation that underpins the inflammation of hepatic tissue, evidenced by circulating autoantibodies, elevated IgG, and characteristic histological findings like interface hepatitis and plasma cell infiltration. Untreated AIH carries a significant mortality risk, underscoring the need for prompt intervention, even in asymptomatic cases, to reduce morbidity and mortality.[29] The diagnostic process for AIH is nuanced due to its broad spectrum of clinical manifestations and serological markers. Patients often present with unexplained elevated serum aminotransferase levels, yet about 25-34% are asymptomatic, complicating early diagnosis. Notably, untreated asymptomatic individuals have a markedly lower 10-year survival rate than those who receive timely therapy (67% vs. 90%).[30]

In addition to liver enzymes, diagnosis is further refined through autoimmune markers like *antinuclear antibodies* (ANA), *smooth muscle antibodies* (SMA), *liver/kidney microsomal antibody type 1* (anti-LKM1), and the simplified AIH scoring system, which integrates these

findings with histology to confirm the diagnosis and exclude other liver pathologies. Histology remains indispensable, revealing interface hepatitis, periportal necrosis, and other distinctive changes. Non-invasive imaging modalities, such as elastography and MRI, are valuable for staging fibrosis and assessing inflammatory activity without the need for repeated biopsies. The simplified scoring system requires four variables, namely autoimmune antibodies, hyper-gammaglobulinemia, histology, and exclusion of viral hepatitis. Definite AIH is defined as ≥7 points, and probable AIH is defined as ≥6 points. Although these systems are helpful in excluding AIH in patients with other conditions, they are less sensitive in identifying atypical cases.[29,30]

Management goals in AIH include achieving remission, reversing fibrosis, and preventing disease progression. Induction therapy typically begins with corticosteroids, with prednisolone as the preferred agent due to its potent anti-inflammatory effects, achieving biochemical response within a week in most cases. This rapid response contrasts with alternatives like budesonide, which show slower efficacy, reinforcing prednisolone's utility as a first-line therapy. The common initial dose of prednisolone is 0.5 mg/kgBW. Once remission is reached, azathioprine is introduced for maintenance, reducing the risk of steroid-induced adverse effects. The recommended dose is 1-2 mg/kgBW. Dose adjustments are guided by patient tolerance and metabolite monitoring, especially in those with thiopurine methyltransferase (TPMT) deficiency, who are prone to azathioprine toxicity. In cases resistant to first-line therapy, options include mycophenolate mofetil, inhibitor calcineurin-inhibitor (cyclosporin, tacrolimus), mercaptopurine, and biologic agents (rituximab, infliximab) can be considered.[29,30]

For select patients, long-term therapy may be unnecessary if remission is maintained; approximately 10-20% can eventually discontinue immunosuppressive treatment under close medical supervision. Relapse remains a concern, making gradual tapering essential to sustain remission. Supplementary vitamin D is also beneficial, contributing to improved disease outcomes. AIH may progress to cirrhosis and liver failure, requiring liver transplantation in advanced cases. Though recurrence post-transplant occurs in a notable proportion (8-12% within the first year, 36-68% within five years), outcomes are generally favorable. Close monitoring and individualized treatment approaches are paramount in managing AIH to improve survival and quality of life.[29,30]

Diagnosing Systemic Lupus Erythematosus (SLE) requires clinical evaluation supported by standardized classification criteria, such as the American College of Rheumatology (ACR) 1997, Systemic Lupus International Collaborating Clinics (SLICC) 2012, or the European League Against Rheumatism (EULAR)/ACR 2019 criteria. Assessment of disease activity is critical in guiding treatment, with scoring tools like the SLEDAI and MEX-SLEDAI helping to quantify disease severity and guide therapy. Severe cases of SLE, indicated by SLEDAI scores over 12 or MEX-SLEDAI scores between 10 and 13, require comprehensive evaluations to rule out other potential causes, including infections, given their impact on both morbidity and treatment choices. Management of severe SLE typically involves immunosuppressive therapy, including intravenous methylprednisolone or oral prednisolone (≤1 mg/kg/day). Additionally, vitamin D supplementation has shown benefits in improving SLE-related outcomes.[31]

Our patient received methylprednisolone 31.25 mg every 12 hours. The methylprednisolone dosing was chosen to balance the need for effective immunosuppression in the context of AIH and SLE while mitigating the risks associated with high-dose corticosteroids, such as infection, hyperglycemia, and gastrointestinal bleeding.[32,33] Given the patient's elevated INR, corticosteroid therapy posed an increased risk of gastrointestinal bleeding, necessitating close monitoring and potential gastroprotective

measures such as proton pump inhibitors (PPIs) or H2 receptor antagonists.[34] To mitigate this, our patient received intravenous omeprazole (40 mg every 12 hours).

In cases of lower extremity lesions, differential diagnoses might include stasis dermatitis, scleroderma, and vasculitis. In this patient, a biopsy confirmed stasis dermatitis, a chronic inflammatory skin disease caused by chronic venous insufficiency (CVI) and frequently affecting the lower extremities of elderly patients. Stasis dermatitis develops when venous plexus dysfunction in the legs causes blood to reflux into the superficial venous system, resulting in venous hypertension, skin inflammation, and potential complications like venous ulcers.[35] The widely accepted CEAP classification system (Clinical, Etiologic, Anatomic, and Pathophysiologic) helps assess the severity of varicose vein-related issues, which often underlie stasis dermatitis.[36]

In this patient, the stasis dermatitis may be related to chronic venous insufficiency secondary to an atrial septal defect (ASD) II with a left-to-right shunt. Normally, systemic and pulmonary circulations handle equal blood volumes (Qp/Qs = 1). However, with a left-to-right shunt, "back-leak" blood flows from systemic to pulmonary circulation, resulting in a higher pulmonary flow (Qp/Qs >1). This pulmonary overload can lead to chronic venous insufficiency, contributing to stasis dermatitis development.[37]

Treatment for stasis dermatitis aims to manage the venous insufficiency, reduce edema, alleviate inflammation (itching and pain), and improve skin lesions or heal ulcers. Initial therapy includes lifestyle modifications, such as exercise, walking, and leg elevation, which are generally effective for mild cases. Compression therapy, a cornerstone of treatment, employs high-pressure wraps or stockings (approximately 60 mmHg) to reduce ambulatory venous pressure and mitigate venous hypertension.[35]

The diagnosis of MAS presents significant challenges due to the need for specialized tests that are not readily available in all hospitals. Although our hospital is a type a facility, certain diagnostic tests, such as TRAb and ANA Profile had to be sent to an external laboratory for confirmation. This highlights the financial and logistical barriers to timely diagnosis. Additionally, the patient, a self-employed person with a lower-middle income, faced economic constraints that made an extensive diagnostic workup difficult. Culturally, the patient also struggled with regular follow-ups due to work obligations and difficulty obtaining leave. Furthermore, he was an orphan, having lost both parents during the COVID-19 pandemic two years ago, which added to his socioeconomic burden and limited access to continuous care.

Initially, the patient believed that his symptoms were purely gastrointestinal in origin, as his primary complaint was jaundice, leading him to seek consultation with a gastroenterologist. He was unaware that he had underlying thyroid dysfunction and multiple autoimmune conditions until further investigations were conducted. After receiving treatment, the patient reported a significant improvement in his overall health and clinical condition. He also acknowledged the complexity of his illness and understood the necessity of long-term follow-up to achieve remission and prevent complications.

During hospitalization, the patient experienced a thyroid storm, a severe and life-threatening complication of Graves' disease. The diagnosis was confirmed using the Burch-Wartofsky score, which indicated a high probability of thyroid storm. The patient was promptly treated with PTU, Lugol's iodine solution, and intravenous methylprednisolone, leading to significant clinical improvement within five days.

The patient's overall prognosis depends on multiple factors, including the control of thyroid disease, autoimmune hepatitis, and SLE. The presence of an ASD further complicates long-term outcomes, as it increases the risk of pulmonary hypertension. While the intermediate probability of pulmonary hypertension was identified in this case, the patient's long-term prognosis will be influenced by the progression

of his autoimmune conditions and cardiovascular status. With adequate management and long-term follow-up, remission and prevention of complications are achievable.

This case demonstrated the complex interplay between multiple autoimmune disorders and congenital cardiac anomalies, providing valuable insight into the management of such rare presentations. However, a key limitation is that the patient should ideally undergo ASD closure to prevent long-term complications, but this procedure was postponed due to the need for stabilization of thyroid metabolism and autoimmune conditions. Additionally, despite medical recommendations, the patient expressed reluctance toward undergoing ASD closure due to fear of the procedure and challenges with regular follow-ups due to work constraints.

## CONCLUSION

This case report highlights a rare presentation of MAS in a young male patient with an unusual combination of Graves' disease, SLE, and AIH. The complex, multisystemic manifestations necessitated a comprehensive approach. The patient's jaundice, stasis dermatitis, and cardiac anomaly (ASD) contributed additional challenges to the diagnosis and treatment. The management approach focused on targeted therapies for each autoimmune disorder. Thiamazole successfully controlled hyperthyroidism, while methylprednisolone was effective in reducing the autoimmune response associated with SLE and AIH. Propranolol provided symptomatic relief for hyperthyroid symptoms and mitigated cardiovascular risks associated with ASD. This case underscores the importance of early diagnosis and individualized, multidisciplinary treatment for MAS, as timely intervention can significantly improve outcomes. Continued follow-up is essential, as MAS patients may experience the emergence of new autoimmune manifestations or complications over time. This case report emphasizes the need for vigilance in managing MAS due to its complex nature, particularly in young male patients, where atypical presentations and rare autoimmune combinations may occur.

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CASE REPORT

# Pituitary Macroadenoma with Hypogonadism in 30-year-old Liver Cirrhosis Patient: A Case Report

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**ABSTRACT**

Pituitary macroadenomas can suppress pituitary hormone secretion, one of which is the gonadotropin hormone, causing hypogonadism. The condition of hypogonadism can increase the risk of non-alcoholic fatty liver disease (NAFLD), which can then become liver cirrhosis. A 30-year-old man came to the hospital with decreased consciousness and hematemesis melena. From physical examination, laboratory, and pituitary magnetic resonance imaging (MRI). The patient was diagnosed with pituitary macroadenoma, hypogonadotropic hypogonadism, primary hypothyroidism, acute adrenal insufficiency, and liver cirrhosis. The patient was given hydrocortisone therapy, correction of electrolyte levels, hypoglycemia protocol, levothyroxine 100 mg/day, and management of hematemesis melena. After that, Sustanon 250 mg was given every two weeks intramuscularly. The patient went home in good condition and was planned for neurosurgery consultation for transsphenoidal resection. After the injection of Sustanon, the patient experienced increased penile length and testicular volume. The condition of hypogonadism in patients with pituitary macroadenoma can be a risk factor for NAFLD, which can then progress to liver cirrhosis. NAFLD and liver cirrhosis also can cause hypogonadism in men by several mechanisms. The patient has been well-managed and experienced clinical improvement.

**Keywords**: pituitary macroadenoma, hypogonadism, liver cirrhosis, therapeutic intervention

## INTRODUCTION

A pituitary adenoma is the most common type of pituitary tumor. Based on the size of the widest diameter, pituitary adenomas can be divided into microadenoma (<1 cm) and macroadenoma (>1 cm). Pituitary adenoma can be classified as non-functioning pituitary adenoma (NFPA) and functioning pituitary adenoma, based on their hormone-secreting capabilities. Both pituitary adenomas can suppress the secretion of pituitary hormones, one of which is the gonadotropin hormone, causing hypogonadism. In men, hypogonadism is a condition of testosterone deficiency.[1,2] Testosterone deficiency in men is associated with increased visceral adipose tissue (VAT) and insulin resistance, which are some of the factors that cause metabolic syndrome. VAT and insulin resistance are important in non-alcoholic fatty liver disease (NAFLD) pathogenesis. Chronic liver damage in NAFLD can lead to the progression of NAFLD to non-alcoholic steatohepatitis (NASH), advanced fibrosis, and liver cirrhosis.[3] One of the most common causes of liver cirrhosis is NAFLD. Therefore, this case is discussed to see the relationship between hypogonadism and possibly acromegaly that arises due to pituitary macroadenoma and the incidence of liver cirrhosis in this patient.[4]

## CASE ILLUSTRATION

A 30-year-old man comes to the hospital with a decreased level of consciousness and hematemesis-melena. From the anamnesis, this patient complained of child-like voice, small penis size and, no axillary and pubic hair growth. The patient did not complain of chronic headaches and visual field disturbances. From the physical examination, he was somnolent, with blood pressure 100/75 mmHg, pulse 78 times/minute, respiratory rate 20 times/minute, temperature $37^0$C, body weight 53 kg, height 166 cm, and body mass index (BMI) 19.23 kg/$m^2$. Other physical examination findings were pale conjunctiva, collateral veins, Schuffner grade 4 spleen, ascites, bilateral pretibial edema, penile length 1 cm, right testicular volume 3 cc, and left testicular volume 2 cc.

From laboratory examination, hemoglobin 4.4 gr/dl, hematocrit 16%, platelets 112,000 $mm^3$, random blood glucose 73 mg/dl, sodium 115 mmol/l, potassium 3.9 mmol/l, chloride 79 mmol/l, HbsAg (-), and antiHCV (-). On further laboratory tests, we found LH <0.09 mIU/ml (0.57 - 12.07 mIU/ml), FSH 0.14 mIU/ml (0.95 - 11.95 mIU/ml), testosterone <2.5 ng/ml (249 - 836 ng/ml), TSH 5.7 ·IU/ml (0.27 - 4.2 mIU/ml), free T4 6.94 pmol/L (12 - 22 pmol/l), ACTH 7.5 pg/ml (7.2 - 63.3 pg/ml), cortisol 7.5 ·g/dl (3.7 - 19.4 ug/dl), IGF-1 18 ng/ml (41 - 246 ng/ml), GH < 0.05 ng/ml (< 3 ng/ml), and prolactin 5.01 ng/ml (3.46 - 19.4 ng/ml). An abdominal ultrasound examination revealed liver cirrhosis, and esophagoduodenoscopy revealed grade I-II esophagol variceal with portal hypertension gastropathy. On pituitary MRI examination, it was found suggestive of a macroadenoma with size 17.04 x 17.07 x 13.26 $mm^3$.

The patient was diagnosed with pituitary macroadenoma, hypogonadotropic hypo-gonadism, primary hypothyroidism, acute adrenal insufficiency, and hepatic cirrhosis with hematemesis melena. The patient was given hydrocortisone therapy, correction of electrolyte levels, hypoglycemia protocol, levothyroxine 100 mg/day, and management of hematemesis melena. After that, Sustanon 250 mg every two weeks intramuscularly. The patient went home in good condition and was scheduled for another pituitary hormone examination and neurosurgery consultation for transsphenoidal resection. At the follow-up after six times of injection of Sustanon, he has experienced deepening voice and erection. In physical examination, it was found that the penis had increased in length to 5 cm, and the volume of the right and left testicles had increased to 4 cc and 3 cc, respectively. However, the patient still has not experienced axillary and pubic hair growth.

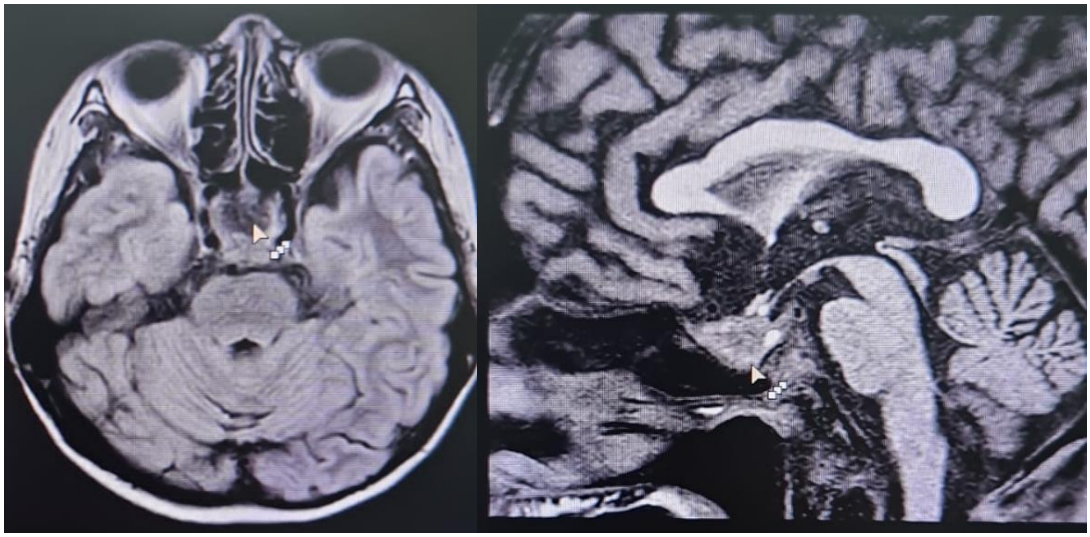

Figure 1. Pituitary MRI Result

Figure 2. Patient profile

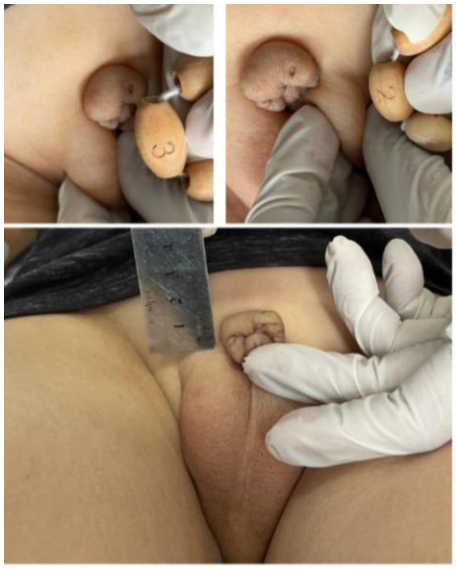

Figure 3. Genital examination before Sustanon therapy

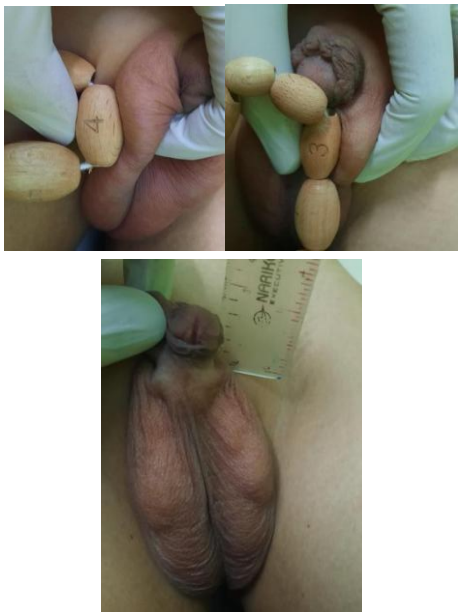

Figure 4. Genital examination after Sustanon therapy

## DISCUSSION

A pituitary adenoma is the most common cause of pituitary tumors. The most common types of pituitary adenomas are prolactinoma and non-functioning pituitary adenoma (NPFA). NPFA is a tumour originating from adenohypophysis cells characterized by the absence of hypersecretion from these cells. In NPFA, there can be suppression of some pituitary cells, which will then cause a deficiency of one or several pituitary hormones. Thus, it is recommended for patients with NPFA and other pituitary tumours to check the pituitary hormone panel. Pituitary hormone deficiency can be asymptomatic, so by examining the pituitary hormone panel, disorders that can occur due to pituitary hormone deficiency can be managed earlier. In this patient, it is planned to examine IGF-1, ACTH, and prolactin to determine the condition of other pituitary hormones.[1,5]

Approximately 30% of NPFA patients are asymptomatic and diagnosed with NPFA based on incidental findings on MRI. Symptoms of headache and visual field disturbances are found in approximately 60% of NPFA patients. The incidence of NPFA with hypogonadism is about 60%. Hypogonadism and growth hormone (GH) deficiency are the most common hormonal abnormalities in NPFA.[1,5] Hwang et al. (2023) stated that several hormone deficiencies that result from NPFA are associated with NAFLD, which are GH, thyroid, and testosterone. Testosterone deficiency is associated with the occurrence of metabolic syndrome.[6] Testosterone deficiency in men is associated with increased visceral adipose tissue (VAT) and insulin resistance, which are some of the factors that cause metabolic syndrome. VAT and insulin resistance have an essential role in the pathogenesis of NAFLD. Several other studies support the relationship between testosterone deficiency and NAFLD. NAFLD is a chronic liver disorder that can then progress to liver cirrhosis.[3,6]

Liver cirrhosis is a condition of liver fibrosis with several causal factors. Some common factors that cause liver cirrhosis are hepatitis B and C infection and NAFLD. In this patient, markers of hepatitis were negative. The natural progression from acute infection to cirrhosis takes 20-30 years. Thus, liver cirrhosis in this patient is suspected to be caused by the metabolic syndrome experienced by the patient due to testosterone deficiency.[4] A liver biopsy examination is the gold standard to prove liver cirrhosis caused by NAFLD. However, this patient was not able to undergo the procedure because of the mortality risk due to this procedure.[7]

Several studies have also reported the effect of hepatic cirrhosis on hormonal disorders. Kim et al. (2017) reported that liver cirrhosis can cause hypogonadism in men with impaired LH pulsatility, blunted gonadotropic response, and downregulation of GnRH production due to increased proinflammatory cytokines. Estrogen in male patients with liver cirrhosis increases due to decreased estrogen clearance, increasing the estrogen/androgen ratio.[8]

In NAFLD conditions, several hypotheses emerge, such as the bidirectional relationship between metabolic syndrome and hypogonadism and the hypothesis of a low sex hormone binding globulin (SHBG) relationship in NAFLD, which is the cause of decreased testosterone levels. The SHBG theory is supported by Song and Choi (2022), who reported that sex hormone dysfunction has a role in the pathogenesis of NAFLD. SHBG is associated with low testosterone levels in men.[8,9]

In addition, Punekar et al. (2018) reported that liver cirrhosis can cause clinical hypothyroidism. The liver has an essential role in the peripheral conversion of T4 to T3 because type 1 deiodinase is a liver enzyme. The liver also plays a role in the synthesis of thyroid-binding globulin.[10] This patient also had acute adrenal insufficiency. Wentworth and Siragy (2022) reported that adrenal insufficiency is an underrecognized endocrine dysfunction in liver disorders. The circadian rhythm of cortisol is disrupted in liver cirrhosis, likewise with the metabolism of cortisol and the production of binding globulin. Another hypothesis linking adrenal insufficiency with liver cirrhosis is deficient intrinsic adrenal enzymatic activity and the suppressive effect of proinflammatory cytokines on the HPA axis.[11]

The pituitary macroadenoma in this patient was planned for transsphenoidal resection surgery. Two surgical techniques can be performed, which are transsphenoidal and transcranial. Transsphenoidal can be done through endoscopic and microscopic. Some research results state that transsphenoidal provides better results than transcranial.[5,12,13]

According to Penn (2017), indications for surgery for patients with NFPA are the presence of neurological disorders, vision, ophthalmoparesis, and obstructive hydrocephalus, asymptomatic tumors but threatening the occurrence of visual disturbances, signs of hypopituitarism, and acute pituitary apoplexy. This operation aims to decompress the optic nerve and chiasm and restore normal pituitary function.[12,13]

According to the guidelines of the Endocrine Society, it is recommended that male patients with hypogonadism receive testosterone to induce and maintain secondary sex characteristics and improve symptoms of testosterone deficiency. There are several preparations for administering testosterone, such as intramuscular, transdermal, pellets, and intranasal. Testosterone administration was continued and followed up in these patients despite tumor resection surgery.[14]

This patient was given an intramuscular injection of Sustanon 250 containing 30 mg of testosterone propionate, 60 mg of testosterone phenylpropionate, 60 mg of testosterone isocaproate, and 100 mg of testosterone decanoate every two weeks. After giving it six times, it has been found that the patient has experienced deepening voice, erections, and an increased in penile length and the testicular volume. However, the patient still has not experienced axillary and pubic hair growth.

Liver cirrhosis and hematemesis melena experienced by patients have been given therapy, and clinical improvement was obtained, likewise with acute adrenal insufficiency and hypothyroidism. During treatment, the patient experienced improvement and continued treatment at the outpatient clinic. Levothyroxine and hydrocortisone therapy was continued, and clinical improvement was found on follow-up. Sustanon, hydrocortisone, and levothyroxine will be given until the patient undergoes transsphenoidal resection for pituitary macroadenoma. After surgery, pituitary hormones level will be remeasured to determine the need for long-term therapy.

## CONCLUSION

The condition of hypogonadism in patients with pituitary macroadenoma can be a risk factor for NAFLD, which can then progress to liver cirrhosis. The patient has been well-managed and experienced clinical improvement. The patient is prepared for transsphenoidal tumour resection.

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CASE REPORT

# Varicella Zoster-Induced Severe Diabetic Ketoacidosis

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**ABSTRACT**

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes. There are not many cases reported relate to this case. This case report aims to present a case of DKA which is a common and potentially life-threatening complication in T1DM and can be the first sign of undiagnosed diabetes. A 36-year-old female presented with altered mental status and breathing difficulty. The patient's three children had recently contracted varicella (chickenpox). The patient was diagnosed with type 1 diabetes mellitus 8 months ago, with irregular adherence to treatment. Vital signs included a blood pressure of 84/60 mmHg on norepinephrine at 12 mcg/min, heart rate of 135 bpm, respiratory rate of 33 breaths/min, and temperature of 38.9°C. Physical examination revealed multiple lenticular, circumscribed vesicles with an erythematous base across the entire body. Laboratory results showed leukocytosis (leukocytes: 16,000 x $10^3$/µL), hyperglycemia (random blood glucose: 273 mg/dL), severe metabolic acidosis (pH: 7.002, HCO3: 5.7 mEq/L, BE: -23.6 mEq/L), hypoxemia (pO2: 38 mmHg, SaO2: 52.8%), hypoalbuminemia (albumin: 3.48 g/dL), and stage I acute kidney injury (creatinine: 1.36 mg/dL). Urinalysis revealed the presence of ketone bodies. The patient was subsequently diagnosed with severe diabetic ketoacidosis, varicella zoster infection, septic shock with multiorgan failure, and type 1 diabetes mellitus. Despite initial treatment efforts, the patient's condition continued to deteriorate, with no signs of clinical improvement. After 3 days, the patient deceased. In conclusion, although varicella zoster infection is an uncommon precipitant of DKA, the present case report highlights the critical role of varicella zoster vaccination and optimal glycemic control in DMT1 to prevent infection-related DKA progression.

**Keywords**: Varicella, diabetic ketoacidosis, vaccine, complication

## INTRODUCTION

Diabetes mellitus (DM) is a global health concern with significant prevalence, contributing to high morbidity and mortality rates worldwide.[1-3] Diabetic ketoacidosis (DKA) is the most frequent and potentially life-threatening acute complication of diabetes mellitus.[4] The primary precipitating factors for DKA include infections and inadequate insulin therapy.[5] Infections account for more than 50% of DKA cases, with specific infections such as pneumonia and urinary tract infections frequently identified as triggers.[6,7] In patients with uncontrolled DM, the likelihood of developing DKA is markedly increased, and these patients are also more susceptible to infections, which serve as major triggers for DKA.[8,9] The physiological stress induced by infections elevates the body's insulin requirements, and failure to meet these demands can precipitate DKA.[10]

Diabetic patients are more susceptible to infections due to an immunocompromised state, which is exacerbated by hyperglycemia that impairs immune function and may lead to more severe infections.[11,12] Varicella zoster virus infections commonly affect immuno-compromised patients, with diabetes mellitus associated to increased risk, particularly in those with poorly controlled blood glucose levels.[13] Although skin complications associated with DKA are uncommon, those specifically triggered by varicella zoster infections are exceedingly rare.[14] To the best of our knowledge, only one case of DKA triggered by varicella zoster have been reported in the literature.[14] This case report aimed to present a case of varicella zoster-induced DKA in a patient with uncontrolled type 1 diabetes mellitus. The present case report was prepared in accordance to case report (CARE) guideline.[15]

## CASE ILLUSTRATION

A 36-year-old female patient presented to the Emergency Unit of Dr. Zainoel Abidin Hospital in Banda Aceh, Indonesia, with gradually altered mental status and breathing difficulty, unaccompanied by seizures, projectile vomiting, or severe headache. The patient reported experiencing a fever for 5 days prior to admission, followed by the development of painful blistering skin lesions and vesicular rashes that began on the neck and subsequently spread across the entire body. The patient did not self-administer any medications for symptomatic relief prior to hospital admission. The patient's family reported that the patient's three children had recently contracted varicella (chickenpox). The patient denied any prior history of varicella infection or varicella vaccination. The patient has a history of recently diagnosed type 1 diabetes mellitus, identified approximately 8 months ago, with irregular adherence to treatment and HbA1c levels of 10%.

The patient's vital signs upon examination were as follows: blood pressure of 84/60 mmHg while on norepinephrine at 12 mcg per minute, heart rate of 135 beats per minute, respiratory rate of 33 breaths per minute, and a temperature of 38.9°C. This patient weighs 70 kg and has a body mass index (BMI) that falls within the overweight category. Physical examination revealed multiple lenticular, circumscribed vesicles with an erythematous base across the entire body. Laboratory results showed leukocytosis (leukocytes: 16,000 x $10^3$/µL), anemia (hemoglobin: 16.4 g/dL, hematocrit: 22%, erythrocyte: 2.6 x $10^3$/µL), hyperglycemia (random blood glucose: 273 mg/dL), severe metabolic acidosis (pH: 7.002, HCO3: 5.7 mEq/L, BE: -23.6 mEq/L), hypoxemia (pO2: 38 mmHg, SaO2: 52.8%), hypocalcemia (calcium: 7.6 mg/dL) and corrected with Ca gluconate 1g/12 hours, hypoalbuminemia (albumin: 3.48 g/dL), stage I acute kidney injury (creatinine: 1.36 mg/dL), electrolyte imbalances (sodium: 134 mEq/L, potassium: 4.6 mEq/L, chloride: 105 mEq/L). Urinalysis revealed the presence of ketone bodies.

The patient was subsequently diagnosed with severe diabetic ketoacidosis, varicella zoster infection, septic shock with multi-organ failure, stage I acute kidney injury, and type 1 diabetes mellitus. In the emergency department, the patient was administered 4,000 mL of 0.9% NaCl over the first 6 hours and was started on

an insulin drip with rapid-acting insulin aspart 2 IU/hour. Throughout the treatment, the patient was continuously monitored for vital signs, urine output, blood glucose, and electrolyte levels. Blood glucose was checked hourly, and ketone levels were monitored to assess the effectiveness of the treatment. The insulin dose was titrated based on blood glucose levels. The random blood glucose levels during the infusion were 235 mg/dL in the first hour, decreasing to 213 mg/dL in the second hour, then to 210 mg/dL, 186 mg/dL, and eventually stabilizing at 160 mg/dL. This patient's urine output is 1500/24 hours. Additionally, acyclovir was given at an oral dose of 800 mg five times daily (4.000 mg daily). Despite initial treatment efforts, the patient's condition continued to deteriorate, with no signs of clinical improvement. The patient was urgently referred to the Respiratory Intensive Care Unit at Dr. Zainoel Abidin Hospital in Banda Aceh, Indonesia. Intensive supportive care was provided, including mechanical ventilation to manage respiratory failure and intravenous meropenem 1000 mg every 8 hours to combat potential bacterial infections. Despite these aggressive interventions, the patient's condition remained critical. After 3 days in the respiratory intensive care unit, the patient deceased.

## DISCUSSION

The present case report identified a severe case of varicella zoster-induced DKA with septic shock and multi-organ failure in a patient with uncontrolled type 1 diabetes mellitus. Despite these aggressive interventions, the patient's condition continued to deteriorate. After 3 days in the respiratory intensive care unit, the patient deceased. The association between infections and the onset of DKA is well-established, with infections often serving as a significant precipitating factor for DKA.[8,10,11] The mechanism underlying infection-induced DKA involves the body's stress response, which triggers the release of counter-regulatory hormones such as glucagon, cortisol, catecholamines, and growth hormone.[16] These hormones oppose insulin action and dysglycemia, leading to insulin resistance.[17] Glucagon, in particular, promotes hepatic gluconeogenesis and glycogenolysis, increasing blood glucose levels, and it additionally induces ketone production.[18] Simultaneously, catecholamines and cortisol reduce glucose uptake in peripheral tissues, exacerbating hyperglycemia and precipitating DKA due to insufficient insulin activity.[19] In addition to promoting hyperglycemia, these counter-regulatory hormones also stimulate lipolysis, the breakdown of triglycerides into free fatty acids, in adipose tissue.[20] Free fatty acids are subsequently transported to the liver, where glucagon stimulation promotes the conversion into ketone bodies, primarily acetoacetate and β-hydroxybutyrate, serving as an alternative energy source in the absence of sufficient insulin.[21] The accumulation of ketone bodies leads to metabolic acidosis, one of the hallmarks of DKA.[22] Furthermore, the infection-induced inflammatory response exacerbates insulin resistance and promotes hyperglycemia.[23] Proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), are released in response to infection and contribute to the impairment of insulin signaling pathways, further reducing the effectiveness of insulin and worsening hyperglycemia.[24-26] This cascade of events ultimately overwhelms the body's compensatory mechanisms, leading to the clinical manifestation of DKA.[27]

Varicella zoster infection, though rare, is a notable trigger of DKA.[14] To the best of our knowledge, only one case of DKA triggered by varicella zoster have been reported in the literature.[14] A 17-year-old male patient presented with DKA exacerbated by a varicella zoster infection.[14] Despite a decade-long history of type 1 diabetes mellitus, the patient developed severe DKA, characterized by vomiting, dehydration, and a generalized vesicular rash indicative of chickenpox.[14] Upon admission, the patient required intensive management, including aggressive fluid replacement, intravenous insulin therapy, and electrolyte monitoring.[14] The chickenpox was

treated with intravenous acyclovir and supportive care.[14] Despite initial complications, including hypokalemia and renal impairment, the patient's metabolic parameters gradually stabilized, and his condition improved.[14] The patient was subsequently discharged with outpatient follow-up and continued antiviral therapy.[14] Unlike previous case report, the present case report highlights the severe and potentially fatal consequences of varicella zoster-induced DKA, highlighting how this condition, particularly when combined with other factors septic shock and multi-organ failure, can rapidly deteriorate a patient's health. Despite aggressive medical interventions, the disease's progression can be relentless, ultimately leading to death.

Although varicella zoster-induced DKA is rare, caution is also needed with herpes zoster-induced DKA, as both can cause severe metabolic disturbances, potentially leading to fatal outcomes. To the best of our knowledge, the existing literature documents only two case reports of herpes zoster-induced DKA, each originating from different years and countries.[28,29] These cases offer unique insights into this uncommon complication. The present case report is similar to a 2018 case involving a 75-year-old female patient from Indonesia who presented with declining consciousness and skin lesions consistent with herpes zoster.[28] Despite a history of uncontrolled type 2 diabetes mellitus, the patient had not been compliant with insulin therapy.[28] Upon admission, the patient was diagnosed with DKA triggered by herpes zoster infection.[28] The treatment included intravenous fluids, insulin, ceftriaxone for pneumonia, and acyclovir for the herpes zoster.[28] Unfortunately, despite initial improvement, the patient succumbed to complications from sepsis during hospitalization.[28] Another case, a 17-year-old female patient from the United Kingdom, presented in 1991 with diabetic ketoacidosis precipitated by a genital herpes infection.[29] The patient's symptoms included vulval soreness, drowsiness, and hypothermia.[29] The patient was treated with intravenous insulin and acyclovir, which led to a slow recovery over 72 hours.[29]

The risk of varicella virus infection is elevated in elderly or immunocompromised patients.[30,31] The 2022 American Association of Clinical Endocrinology Clinical Practice Guideline recommends varicella vaccination for patients with type 2 diabetes mellitus.[32] Hata et al found that demonstrated that varicella zoster vaccine safely enhanced varicella zoster virus specific immunity in elderly people with or without diabetes.[33] However, the detailed procedures, efficacy, and safety of the varicella zoster vaccine in type 1 diabetes mellitus patients have not yet been fully established.

The current recommendation specifically pertains to herpes zoster vaccination for immunocompromised patients.[34-36] Immuno-compromised individuals experience a higher incidence of herpes zoster and related complications.[37-39] Herpes zoster has a 25-30% lifetime risk and can lead to severe complications, including death.[40] Advisory Committee on Immunization Practices (ACIP) recommended the Zoster Vaccine Recombinant, Adjuvanted (Shingrix, GlaxoSmithKline [GSK], GSK Research Triangle Park, North Carolina, USA), a 2-dose subunit vaccine initially approved by Food and Drug Administration (FDA) for preventing herpes zoster in immunocompetent adults aged ≥ 50 years, with moderate to high vaccine efficacy and an acceptable safety profile.[36] Additionally, National Advisory Committee on Immunization (NACI) in Canada recommended the recombinant zoster vaccine for adults over 50 without contraindications and noted it may be considered for immunocompromised adults.[34] However, in 2022, the FDA broadened the vaccine's use to include adults aged 18 years and older at increased risk due to immunodeficiency or immunosuppression, which is also relevant for patients with type 1 diabetes mellitus.[35] Furthermore, a meta-analysis by Racine et al confirmed that the recombinant subunit herpes zoster vaccine has a favorable safety profile and effectively induces

immunity in a significant proportion of immunocompromised patients aged 18-49.[41]

However, recent literature advises caution when using the live attenuated zoster vaccine. A case report by Alexander et al highlighted that live zoster vaccination (Zostavax, Merck & Co., Inc, New Jersey, USA) in an immunocompromised patient led to disseminated varicella-zoster virus infection and death, underscoring the need for a non-live vaccine for immunocompromised patients.[42] Li-Kim-Moy et al demonstrated that disseminated varicella-zoster virus can be life threatening and primarily affects individuals with severe immunosuppression following the live attenuated herpes zoster vaccine.[43] ACIP deferred recommendations of recombinant zoster vaccine for immunocompromised patients until more data were available.[35]

A limitation of the present case report is the absence of polymerase chain reaction (PCR) testing to confirm the varicella zoster infection, primarily due to financial constraints, which could have provided more definitive diagnostic clarity. Future research is recommended to conduct large scale studies evaluating the efficacy and safety of varicella zoster vaccines in diverse immunocompromised populations, including those with specific conditions such as type 1 and type 2 diabetes mellitus.

## CONCLUSION

Varicella zoster infection rarely precipitates DKA, yet it may occur due to an ineffective immune response to the varicella-zoster virus in patients with diabetes mellitus. The present case report highlights the critical role of varicella zoster vaccination and optimal glycemic control in DMT1 to prevent infection-related DKA progression.

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# Author Guidelines
# Indonesian Journal of Endocrinology Metabolism and Diabetes
# (InaJEMD or Indones J Endocrinol Metab Diab)

## Author Guideline

- **General principles**
  1. Manuscripts submitted to Indonesian Journal of Endocrinology Metabolism and Diabetes (InaJEMD) should neither be published before nor be under consideration for publication in another journal.
  2. InaJEMD only **accept the clinical, basic science, community medicine, or public health manuscripts in the field of endocrinology, metabolism, and diabetes.** Others are accepted if only correlate to **endocrinology, metabolism, and diabetes.**
  3. Manuscripts must be submitted in English.
  4. Authors whose native language is not English should be seek a proofreading consultant, before submitting their manuscripts. Make sure that issues about publication ethics, research ethics, copyright, authorship, figure formats, data and references format have been appropriately considered.
  5. Ensure that all authors have approved the content of the submitted manuscript.
  6. We accept eight types of articles:
     1) Original article
     2) Review article
     3) Systematic review
     4) Case report
     5) Case series
     6) Case illustration
     7) Special article
     8) Clinical practice
     9) Point of view
     10) Editorial
     11) Community/public health study

- **Writing guideline**

  Manuscripts are written on A4 pages, double-spaced in all parts of the manuscript, with margin of 2.54 cm of all sides, using Times New Roman 12. Articles must be submitted in the following structural order: title page and authorship, abstract, main text, conflicts of interest, acknowledgments, funding disclosure, references, tables, figures, and legends (if any).

**Editorial/Point of View should be presented in sections:**

To stimulate thought about any cutting-edge topics that relate to endocrinology and metabolism.

1. **Word count:** up to 1200 words.

2. **Illustrations/tables:** no illustration and/or tables.
3. **References:** up to 10-30

**Article Research (Original Article/Community Study/Public Health research) should be presented in sections:**

These represent a substantial body of laboratory or clinical work. Extended reports should not exceed 3000 words plus references; articles that exceed this word limit may be returned for revision before peer review. Additional data may be presented as supplementary information, which will be published online only should the article be accepted (this can be in any format: text, tables, images, etc.).

1. **Title of The Article**
2. **Abstract:** No more than 250 words summarizing the problem being considered, how the study was performed, the salient results and the principal conclusions under subheadings background and purpose of the study, methods, results, and conclusion. Please define abstract in two version languages (Bahasa Indonesia and English).
3. **Key words:** No more than 5 words or short phrases.
4. **Introduction:** Without subtitle, state the rationale for the study, identify a problem main problem/the study purpose, establish a gap in the current knowledge/state the novelties, and articulate a hook that convinces readers that this gap is of consequence. Brief description of the background that led to the study (current results and conclusions should not be included).
5. **Methods:** Please state the study design. Details relevant to the conduct of the study. Wherever possible give numbers of subjects studied (not percentages alone). Statistical methods should be clearly explained at the end of this section and its analyses must be explained on the methods used. Relying solely on statistical hypothesis testing, such as p values should be avoided; instead, important information about effect size and precision of estimates should be provided.
6. **Results**: Work should be reported in standard international units. Undue repetition in text and tables should be avoided. Commenting on validity and significance of results is appropriate.
7. **Discussion:** The nature and findings of the study are placed in context of other relevant published data. Caveats to the study should be discussed. Avoid undue extrapolation from the study topic.
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9. **Acknowledgments and affiliations**: Individuals with direct involvement in the study but not included in authorship may be acknowledged. The source of financial support and industry affiliations of all those involved must be stated.
10. **References:** (usually below 30). Please see References for further style guidance. Consist of references of minimal 10 years recently and in the form of essay.
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**Case (Case Reports/Case Series/Case Illustration) should be presented in sections:**
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- **Tables and figures:** Total of tables and figures are advisable not to exceed 6 in number. Tables should be numbered in Arabic numerals with brief captions clearly indicating the purpose or content of each table. Provide a footnote to each table, identifying in alphabetical order all abbreviations used. Explain all nonstandard, abbreviations and explanatory matters in footnotes, and for explanatory matters use the following symbols "*, **".

- **Figures:** should be either professionally drawn or photographed, and submitted in a format (JPEG, TIFF, GIF, or EPS) in the following resolutions [grayscale or colour in RGB (red, green, blue mode) at least 300 dpi (dots per inch). For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send sharp, glossy, black-and-white or colour photographic prints, usually 127 x 173 mm (5 x 7 inches). Figures should be made as self-explanatory as possible; titles and detailed explanations belong in the legends-not on the figures themselves. Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify, and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs. Photographs of potentially identifiable people must be accompanied by written permission to use the photograph.

- **Study Ethics:** All submitted papers containing animal experiments and/or involving human subjects should have obtained approval from an independent ethics committee. The copy of approval should be provided to the editorial office as mentioned above.

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# Ethical Statement

## Journal of Endocrinology Metabolism and Diabetes (InaJEMD)

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4. All authors in this manuscript have stated that there is no conflict of interest related to the manuscript and have known the process of sending manuscripts to the Indonesian Journal of Endocrinology Metabolism and Diabetes (InaJEMD).

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# Patient Consent Form for Case Report/Case Series

For patient's consent to publication for information about them in
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Name of person described in article in photograph: _____

Title of article: _____

I_____ [insert full name] give my consent for this information about **myself or my child or ward/my relative** [insert full name]: _____, relating to the subject matter above the Information to appear in a journal article.

I understand the following:

1. The Information will be published without my name/child's name/relatives name attached and every attempt will be made to ensure anonymity. I understand, however, that complete anonymity cannot be guaranteed. It is possible that somebody somewhere - perhaps, for example, somebody who looked after me/my child/relative, if I was in hospital, or a relative - may identify me.
2. The Information may be published in a journal which is read worldwide or an online journal. Journals are aimed mainly at health care professionals but may be seen by many non-doctors, including journalists.
3. The Information may be placed on a website.
4. The Information has been committed to publication it will not be possible to withdraw the consent.

Signed,

_____,_____

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Signature of the Doctor or Health care worker,

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# Supplementary Abstract

Forum Endokrinologi Nasional Ke-13
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"Advancing clinical practice and exploring emerging trends in Endocrinology and Diabetes"

Yogyakarta
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001

## A Case Report of Refractory Hypokalemia in a Young Adult: Diagnostic Challenges

**Anugrah Riansari[1], Zaki Mita Kusumaadhi[1], Yohana Prima Ceria Anindita[1], Tania Tedjo Minuljo[1], K. Heri Nugroho HS[1]**

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**Abstract**

Refractory hypokalemia is a persistent low serum potassium level despite supplementation. It often indicates an underlying renal tubular disorder or other systemic pathology affecting potassium homeostasis. It often indicating underlying renal tubular disorders such as Bartter syndrome or Gitelman syndrome. Differentiating these syndromes is crucial for appropriate management. A 20-year-old male presented with recurrent fatigue for the previous five years. Laboratory tests revealed severe hypokalemia, hypochloremia, and mild hypomagnesemia. Imaging and clinical evaluation excluded secondary causes. The patient received potassium. Despite treatment, hypokalemia persisted, consistent with refractory hypokalemia. Close monitoring and supportive care were continued, with gradual clinical improvement. This case underscores the importance of thorough evaluation in refractory hypokalemia and highlights the need to differentiate Bartter syndrome from Gitelman syndrome and other causes for targeted therapy.

**Keywords**: Refractory hypokalemia, Electrolyte imbalance, Potassium deficiency, Renal tubular disorder, Hypokalemia management.

002

## Persistent Pituitary Macroadenoma Manifesting as Acromegaly Previously Treated with Surgery, Radiotherapy and Medical Therapy

**Andi Rahmat Hidayat, Himawan Sanusi, Makbul Aman, Husaini Umar, Fabiola MS Adam**

Division of Endocrine, Metabolic and Diabetes, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

**Abstract**

Acromegaly is a rare disease characterized by excessive production of growth hormone (GH) and insulin-like growth factor (IGF-1), which causes systemic disorders. A 48-year-old woman presented to the endocrinology department with the main complaint of progressive enlargement of her body, which had become more noticeable over the past three years. Additionally, she experienced intermittent headaches and reported loss of visual field on the left side of her left eye. She had been experiencing amenorrhea for the past ten years and had been undergoing treatment for hypertension for the past three years. She was diagnosed with acromegaly in 2023 and subsequently underwent transsphenoidal surgery in 2023, followed by radiation therapy in 2024. She exhibited classic acromegaly features such as a prominent forehead, prominent lower jaw, prominent cheekbones, enlarged nose, diastema, and enlargement of both hands and feet. Initial laboratory results at diagnosis showed GH 107 ng/ml, IGF-1 258 ng/ml, prolactin 5.70 ng/ml, FT4 0.78 ng/dl, and TSH 0.80 mIU/ml. The first brain MRI showed a macro pituitary adenoma (3.0x4.0x3.8 cm). Histopathological analysis confirmed the pituitary adenoma. Recent laboratory results showed IGF-1 332 ng/ml, FT4 0.65 ng/dl, TSH 0.95 mIU/ml, FSH 0.89 mIU/ml, and LH 0.2 mIU/ml. Follow-up brain MRI showed a persistent macro pituitary adenoma (3.85x2.58x3.60 cm) despite prior treatment with surgery, radiotherapy, and medical therapy. Pharmacological therapy for acromegaly includes somatostatin analogs, GH receptor antagonists, and dopamine receptor agonists. Reoperation is considered if residual tumor is accessible and causing mass effect and hormonal excess.

**Keywords**: Pituitary macroadenoma, acromegaly.

003

## Synchronous Bilateral Adrenalectomy in a Rare Bilateral Pheochromocytoma: Focus on Perioperative Management

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**Abstract**

Pheochromocytoma is a neuroendocrine tumor originating from the adrenal medulla, typically

unilateral and hereditary in nature. A 34-year-old man presented to our clinic with complaints of sudden-onset right-sided abdominal pain, headaches, and uncontrolled hypertension for two years despite ongoing treatment. On examination, he also reported episodes of cold sweats, pallor, nausea, palpitations, and blood pressure exceeding 180/110 mmHg, particularly during exercise or under stress. His plasma free metanephrine level was 1732 (< 57) and normetanephrine 1398 (< 148), while morning serum cortisol, electrolytes, and urea creatinine levels were within normal limits. CT scan of the abdomen and MIBG scintigraphy revealed bilateral adrenal masses (right 7.4 x 7 x 7.2 cm and left 3.3 x 1.9 x 2.5 cm) without metastatic processes. After the diagnosis of bilateral pheochromocytoma was confirmed, appropriate antihypertensive management was initiated, including Terazosin 3 mg once daily at bedtime, Bisoprolol 2.5 mg once daily in the morning, and Amlodipine 10 mg once daily. The multidisciplinary team initially planned a adrenalectomy preserving the cortex. However, due to intraoperative challenges, a bilateral synchronous adrenalectomy was ultimately performed. Histopathological examination confirmed bilateral pheochromocytoma without vascular invasion or calcification. Hypertension was fully resolved, and the patient began lifelong oral hydrocortisone replacement therapy. Comprehensive education regarding medication adherence and sick day rules was provided to minimize morbidity and mortality from acute adrenal insufficiency.

**Keywords:** Bilateral pheochromocytoma, resistant hypertension, elevated plasma metanephrines, bilateral adrenalectomy, steroid replacement therapy.

004

## Osteomalacia in Renal Tubular Acidosis Type 1, Hypokalemic Periodic Paralysis, Vitamin D Deficiency, Toxic Nodose Struma

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**Abstract**
Renal tubular acidosis (RTA) is a group of disorders characterized by metabolic acidosis and hypokalemia. RTA can cause long-term complications such as osteomalacia and kidney stones. This case report describes RTA accompanied by hyperthyroidism and vitamin D deficiency. A 41-year-old woman presented with complaints of back pain and leg weakness. Since the age of 18, she had been diagnosed with hypokalemic periodic paralysis, and at the age of 36, she was diagnosed with hyperthyroidism. A decrease in height of 10 cm over 20 years. Back deformity (-), tenderness (+), limited active and passive movement, Lasseuge sign (+), Patrick sign (+), Patrick counter (+). TSH 0.025 mEq/L, AGD metabolic acidosis, urine K 25.6 mmol, urine Ca 51.2 mg/dL, urine P 5.2, TTKG 16 (distal), urine anion gap 76.6 (positive), urine pH 6.5. Lumbosacral X-ray: Compression of lumbar vertebrae and Th 12, right-left nephrolithiasis. Thoracolumbar X-ray: Osteoporosis and compression fractures at the T12-L3 level. Z-score BMD of the spine -4.3, Z-score BMD of the femoral neck -3.8. Urological CT scan: Right hydronephrosis. Calcium oxide stones in the middle calyx and bilateral nephrocalcinosis. Thyroid ultrasound: A mass measuring 0.6 x 0.5 x 1.2 cm in the right thyroid (TIRADS 4). The body attempts to neutralize this by mobilizing calcium and phosphorus from bones through stimulation of osteoclasts and inhibition of osteoblasts, leading to bone demineralization, osteopenia, osteoporosis, and osteomalacia. Vitamin D deficiency impairs calcium absorption, increases PTH, leading to bone demineralization, hypercalciuria, and kidney stones.
**Keywords**: RTA, Hypokalemia, Osteomalacia, Vitamin D Deficiency, Hyperthyroidism.

005

## Late Diagnosis of Classic Turner Syndrome Associated with Adrenal Insufficiency and Immune Thrombocytopenia Purpura: Case Report

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**Abstract**
Classic Turner syndrome (TS) known as X monosomy (45,X) is a rare genetic condition in female. TS is often delayed being diagnosed so treatment given is not optimal. So, this case needs to be displayed. Female, 30 years old consulted from haematologist

with diagnosis primary amenorrhea. No history of menstruation, no axilla and pubic hair. She has been diagnosed as immune thrombocytopenia purpura (ITP). Physical examination body height 140 cm, body weight 45 kg, short stature, blood pressure 95/68 mmHg, epicanthic fold, webbed neck, broad chest. Tanner scale prepubertal. Laboratory of estradiol <5pg/mL, LH 15.48mIU/mL, FSH 56.12mIU/mL, serum cortisol <1mcg/dL, IGF-1 206ng/mL. Bone age retarded girl, gynaecology ultrasound uterine hypoplasia, karyotyping 45,X. Patient was diagnosed with classic Turner syndrome, adrenal insufficiency, and ITP. Treatment is oral estradiol 2 mg once daily and methylprednisolone as haematologist instruction. Chromosome X is not only important in determining sex gender but also related to some genes for growth. In TS, patient does not suffer from true growth hormone deficiency, but patient has good response with growth hormone therapy given in appropriate time. Aberration of chromosome X is also related to autoimmunity. In this case, autoimmunity of adrenal and hypophysis still need some evaluations. Diagnosis of TS need to be performed earlier so the treatment given optimally. Evaluation of autoimmunity is also needed.

**Keywords**: Turner syndrome, adrenal insufficiency.

006

## Allergic Acute Coronary Syndrome (Kounis Syndrome) Induced by Rifampicin in A Type 2 Diabetes Mellitus Patient: A Case Report

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**Abstract**

Kounis syndrome is characterized as an uncommon ethology of acute coronary syndrome resulting from systemic allergic or hypersensitivity reactions. An allergic reaction brought on by mediator release and mast cell degranulation coexists with the complex multisystem disorder. The most identified Kounis Syndrome cases have been provoked by medications on elderly male patients. The Kounis syndrome rate was calculated at 11.12 per 1,000 individuals, while the mortality rate was determined to be 7.47%. Herein, we present a case of KS in an elderly diabetic type 2 male without chest pain. A 69-year-old male, a diabetic type 2 patient with a medical history of dermatitis exfoliativa induced by Rifampicin started 6 months prior to admission. The patient presented to the emergency department complaining of delirium and dysphagia that started 3 days before admission. He was admitted due to the presence of ST segment depression in the chest leads V2-6 confirmed by a repeat ECG, with Hs Troponin T level 1985 ng/L. Echocardiogram showed decreased wall motion in the apicoseptal, apicolateral, and basal inferolateral. Acute management of ACS was started and without steroid was given. The patient was discharged with the diagnosis of Kounis syndrome with delirium also induced by Isoniazid adverse event. KS is a complex and underdiagnosed disease that should be considered as a differential diagnosis in acute coronary syndrome associated with an allergic reaction. Diabetes was one of the most prevalent comorbidities.

**Keywords:** Kounis syndrome, allergic myocardial infarction, type 2 diabetes mellitus, isoniazid-induced delirium, acute coronary syndrome without chest pain.

007

## Sudden Visual Loss in Giant Macroprolactinoma Patient Treated with Bromocriptine

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**Abstract**

Prolactinomas are the most common functioning pituitary adenomas. While they typically present with symptoms related to hormonal imbalance or mass effect, acute visual loss is rare and may indicate pituitary apoplexy. A 32-year-old male with a history of macroprolactinoma diagnosed four years prior, on

bromocriptine therapy, presented with a 6-week history of progressive visual difficulties, specifically describing difficulty seeing objects to either side and frequent collisions with obstacles, Physical examination: Visual field testing revealed bitemporal hemianopsia. Cranial nerve examination was normal, and there were no signs of meningeal irritation. Laboratory examination: Prolactin < 0.50 ng/mL (N = 3 - 25 ng/mL), morning cortisol 54.39 ug/dL (N = 48.2 - 195 ug/dL), TSH 1.20 uIU/mL (N = 0.27 - 4.2 uIU/mL), electrolytes within normal limit. MSCT Scan Abdomen: A well-defined, homogenous mass is seen in the sellar-suprasellar region forming a snowman appearance. The size is approximately 4.2 x 3.8 x 4.8 cm (previously 2.9 x 2.9 x 3.9 cm). The superior part of the mass compresses the optic chiasm. No Evidence of Pituitary Apoplexy. The patient was undergoing endoscopic transsphenoidal surgery (ETSS). Postoperatively, his visual field defect improved gradually. Although prolactinomas typically respond to dopamine agonists such as bromocriptine and cabergoline, the large tumor size and progressive visual symptoms in this case necessitate early surgical intervention via ETSS. This highlights the need for close monitoring in patients with macroprolactinoma and timely neurosurgical referral when mass effect symptoms evolve, even in the absence of apoplexy.

**Keywords**: visual loss, prolactinoma, bromocriptine.

008

## A Young Female with Pheochromocytoma: Challenges of Diagnostic, Management and Follow up

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**Abstract**

Pheochromocytoma is a rare catecholamine-secreting tumor of adrenal medullary chromaffin cells. Although classic symptoms of paroxysmal hypertension, palpitations, and diaphoresis are well described, less than a third of patients have these classic symptoms, making the diagnosis especially difficult in younger patients. Early diagnosis helps prevent life-threatening cardiovascular events. A 21-year-old female presented with treatment-resistant hypertension, palpitations, anxiety, and diaphoresis. Abdominal CT showed a 63 mm right suprarenal mass. Laboratory evaluation revealed markedly elevated 24-hour urinary norepinephrine (1486 µg), normetanephrine (5139 µg), and metanephrine (5274 µg). She was started on pre-operative alpha- and beta-adrenergic blockade followed by right adrenalectomy. Histopathology showed pheochromocytoma with Zellballen architecture and positive immunohistochemistry for Chromogranin and S100. She subsequently developed perioperative hypotension, which was treated with fluid resuscitation and norepinephrine. Genetic testing was not performed due to insurance reasons. At three-month follow-up, the patient was normotensive without antihypertensive therapy and had normal urinary catecholamines. This case highlights the diagnostic difficulties and perioperative management of pheochromocytoma in young adults. Although rare, pheochromocytoma should be considered in young patients with treatment-resistant hypertension and classic symptoms. Early biochemical testing and appropriate pre-operative adrenergic blockade is critical to minimize surgical risk. Histopathological confirmation and post-surgical monitoring are imperative. Genetic analysis can provide guidance to determine follow-up and family screening but should not delay definitive treatment.

**Keywords**: Pheochromocytoma, adrenal tumour, catecholamines, resistant hypertension, adrenergic blockade, young adult, Zellballen.

009

## Diagnostic Aspect and Management of Pancreatic Neuroendocrine Tumour with Suspicious of Insulinoma

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**Abstract**

Insulinoma is a rare neuroendocrine tumor of the pancreas that is a major cause of endogenous

hypoglycemia. This case report presents a 60-year-old female patient experiencing recurrent episodes of hypoglycemia, which led to the diagnosis of an insulinoma located in the pancreatic tail. The patient presented with neuroglycopenic symptoms, including weakness, dizziness, and confusion, often occurring during fasting or after physical exertion. Initial laboratory results showed marked hypoglycemia with high fasting insulin, while imaging studies using abdominal Magnetic Resonance Imaging (MRI) with contrast revealed a 4.2 x 3.3 cm solid mass in the cauda of the pancreas, suspicious for an insulinoma. Further evaluation confirmed the diagnosis of insulinoma with metastatic lesions to the liver and bones, indicating an aggressive progression of the tumor. Advanced diagnostic modalities and a multidisciplinary approach are essential for optimizing patient outcomes.

**Keywords:** insulinoma, recurrent hypoglycaemia, neuroendocrine tumour.

010

## Mixed hyperglycemic crisis in a young obese diabetic triggered by hypertriglyceridemia-induced pancreatitis: A case report and review of pathophysiology

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**Abstract**

Mixed diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS), accompanied by hypertriglyceridemia-induced pancreatitis, represent a rare but life-threatening complication of type 2 diabetes mellitus (T2DM). This case report aimed to illustrate a young adult in whom these three critical conditions converged, highlighting the complexity of such presentations. A 28-year-old male presented with altered consciousness and Kussmaul respiration. The patient was diagnosed with T2DM two weeks earlier but had not yet initiated treatment. Physical examination revealed obesity (BMI: 31 kg/m$^2$) and acanthosis nigricans on neck and in axillary regions. Laboratory results showed hyperglycemia (798 mg/dL), metabolic acidosis (pH: 7.08; anion gap: 24), ketonuria, hyperosmolarity (336 mOsm/kg), severe hypertriglyceridemia (965 mg/dL), and elevated lipase (892 U/L). A diagnosis of mixed DKA-HHS secondary to hypertriglyceridemic pancreatitis was established. Treatment included aggressive intravenous (IV) fluid resuscitation of 0.9% sodium chloride (6 L in the first 12 hours) and insulin infusion (0.1 units/kg/hour). During hospitalization, the patient developed acute kidney injury, necessitating continuous renal replacement therapy (CRRT). The patient was gradually recovered and discharged after 20 days. In obese T2DM patients, insulin resistance drives severe hyperglycemia typical of HHS. However, metabolic stress caused by acute pancreatitis induces relative insulin deficiency, triggering lipolysis, ketogenesis, and hypertriglyceridemia, leading to overlapping DKA. Severe hypertriglyceridemia exacerbates systemic inflammation, insulin resistance, and ketosis, creating a vicious cycle that worsens mixed DKA-HHS. This case report highlights the importance of recognizing that T2DM can occasionally present with atypical, life-threatening metabolic complications, necessitating prompt diagnosis and multidisciplinary management.

**Keywords**: Young obese diabetes, diabetic ketoacidosis, hyperglycaemic hyperosmolar state, hypertriglyceridemia, pancreatitis.

011

## Unmasking Insulinoma in a Patient with Recurrent Neuroglycopenic Episodes: A Case Report

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**Abstract**

Insulinoma is a rare pancreatic neuroendocrine tumor characterized by endogenous

hyperinsulinemic hypoglycemia. Timely diagnosis is critical due to the risk of neuroglycopenic symptoms and potential morbidity. A 56-year-old woman presented with a five-year history of recurrent hypoglycemic episodes, manifesting as blurred vision, weakness, confusion, palpitations, diaphoresis and occasional syncope. Despite multiple hospitalizations and symptomatic management, including dextrose infusion, somatostasin injection and corticosteroids, hypoglycemia persisted recurrently. Biochemical evaluation during a supervised prolonged fasting test showed plasma glucose 24 mg/dL, result elevated fasting insulin (93.1 µIU/mL), high C-peptide (9.5 ng/mL), and markedly elevated proinsulin levels (261.6 pmol/L), consistent with endogenous hyperinsulinemia. Beta-hydroxybutyrate was suppressed (< 0.1 mmol/L). Dynamic contrast-enhanced abdominal MRI revealed a 1.7 cm hypervascular nodule at the junction of the pancreatic body and tail, suggestive of insulinoma, without metastasis or lymphadenopathy. Initial management included frequent small meals rich in complex carbohydrates, blood glucose monitoring, and continuation of antihypertensive and lipid-lowering therapy. However, hypoglycemia recurred. The patient subsequently underwent successful enucleation of the tumor in May 2025, with a favorable outcome. This case highlights the importance of maintaining a high index of suspicion for insulinoma in patients with recurrent unexplained hypoglycemia. Modern imaging modalities such as dynamic MRI and biochemical tests are critical for diagnosis. Surgical resection remains the definitive treatment with a higher cure rate compared to radiofrequency ablation. Insulinoma should be considered in patients with recurrent fasting hypoglycemia and confirmed through biochemical and imaging evaluations. Surgical resection remains the treatment of choice.

**Keywords**: Insulinoma, Recurrent Hypoglycemia, Prolonged Fasting Test, Endogenous Hyperinsulinemia.

012

## Euthyroid Graves' Ophthalmopathy in A 44 Year Old Woman with Positive TSH Receptor Antibodies: A Rare Clinical

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**Abstract**

Graves' ophthalmopathy (GO) is an autoimmune disorder of the retrobulbar orbital tissues, most associated with hyperthyroidism in Graves' disease. A small proportion of patients exhibit characteristic GO eye symptoms despite normal thyroid function, a condition known as Euthyroid Graves' Ophthalmopathy (EGO). A 44-year-old woman was reported to have bilateral proptosis that had persisted for more than six years. She did not report any visual disturbances or systemic symptoms indicative of thyroid dysfunction, such as weight loss, palpitations, tremors, or heat intolerance. There was no family history of autoimmune disease. Clinical examination revealed bilateral proptosis consistent with NOSPECS class 3 and a Clinical Activity Score (CAS) of 0. There were no signs of conjunctivitis, chemosis, or ophthalmoplegia. Thyroid function tests were within normal limits: FT4 1.23 ng/dL (0.89-1.76), TSH 1.17 µIU/mL (0.35-4.94), and FT3 2.88 pg/mL (2.3-4.2). However, thyroid receptor antibodies (TRAb) were positive with a titer of 4.79 IU/L (<1.75 IU/L). Neck ultrasound showed a right thyroid nodule measuring 0.74 × 0.64 × 0.95 cm (TIRADS-3). Orbital MRI showed bilateral hypertrophy of the lateral rectus muscles and left medial rectus muscle, confirming GO. A diagnosis of EGO was made, and the patient was treated with mycophenolate mofetil 500 mg twice daily, selenium 200 mg daily, and artificial tears as recommended by the ophthalmologist. This case highlights the importance of considering EGO in the differential diagnosis of proptosis, even in the presence of normal thyroid function, and underscores the significance of TRAb levels and orbital imaging in diagnosis. We have reported “Graves ophthalmopathy in an euthyroid state” in a 44-year-old woman with positive TSH receptor antibodies.

**Keywords**: euthyroid graves' ophthalmopathy, TRAb.

013

## When Giants Meet Sugar: A Case of Diabetes Mellitus in Acromegaly Coincidence or Causality?

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**Abstract**

Acromegaly is a rare disorder, usually due to a pituitary adenoma, resulting in elevated growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels. It is frequently associated with metabolic complications, including diabetes mellitus (DM), which may be misclassified as type 2 DM. A 51-year-old woman with a 3-year history of type 2 DM and hypertension, previously treated with insulin and oral agents (biguanides, dipeptidyl peptidase-4 inhinitor, sulfonylurea) but poorly controlled (HbA1c ~7.3%), developed progressive acral enlargement, coarsening of facial features, macroglossia, and voice deepening over the past year. Investigations revealed elevated IGF-1 (773 ng/mL) and a pituitary macroadenoma on MRI, confirming acromegaly. She underwent transsphenoidal surgery with marked postoperative improvement in 6 weeks: IGF-1 dropped to 393 ng/mL and HbA1c to 5.3%, allowing de-escalation of antidiabetic therapy. Diabetes mellitus, often a complication of acromegaly, arises mainly from insulin resistance and pancreatic β-cell dysfunction induced by elevated levels of GH and IGF-1. At present, no specific test can clearly differentiate type 2 diabetes from acromegaly-induced hyperglycemia. Continued observation is necessary to assess whether the patient's diabetes will remit fully following GH normalization, helping clarify the true etiology. This case underscores the challenge in distinguishing type 2 DM from secondary diabetes due to acromegaly. The overlap may obscure diagnosis and delay appropriate intervention. Improvement in glycemic control after surgical treatment supports a causal link with GH excess. A thorough clinical and biochemical evaluation, along with longitudinal monitoring, remains essential to determine the underlying cause and guide long-term management.

**Keywords**: Acromegaly, Diabetes mellitus, secondary diabetes, antidiabetic therapy, IGF-1.

014

## Diagnosing Primary Hyperparathyroidism: The Role of Tc-99m Sestamibi Scintigraphy in Revealing Ectopic Parathyroid Adenomas with Negative Conventional Imaging - A Theranostic Approach

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**Abstract**

Primary hyperparathyroidism (PHPT) is a common endocrine disorder resulting from autonomous overproduction of parathyroid hormone (PTH), leading to hypercalcemia and systemic complications. The condition is frequently underdiagnosed or diagnosed late due to its nonspecific clinical manifestations such as fatigue, bone pain, and nephrolithiasis. While ultrasound and MRI are frequently used as first-line imaging tools, their sensitivity for identifying small or ectopic parathyroid adenomas is limited. A 45-year-old woman presented with persistent fatigue and generalized bone pain lasting for the past two months. She had a prior history of three times bilateral nephrolithiasis treated surgically in. She suffered a low-impact fall resulting in a left femur fracture, followed by surgical fixation. Laboratory investigations revealed marked hypercalcemia (total calcium: 13 mg/dL) and a significantly elevated intact PTH level (963 pg/mL), suggestive of PHPT. However, MRI of the neck failed to identify any parathyroid abnormality. Further evaluation using Tc-99m sestamibi SPECT/CT demonstrated a hyperfunctioning parathyroid lesion located inferolaterally to the left thyroid lobe, consistent with an aberrant parathyroid adenoma. This case

highlights the diagnostic limitations of conventional anatomical imaging in PHPT, particularly in patients with small, aberrant or ectopically located adenomas. Functional imaging, such as Tc-99m sestamibi scintigraphy, offers superior sensitivity in adenoma localization, especially when PTH levels are markedly elevated. Early diagnosis is essential to prevent severe complications such as osteoporosis, recurrent fractures, and nephrolithiasis. In patients with hypercalcemia and nonspecific musculoskeletal symptoms, PHPT should be considered even in the absence of radiological abnormalities on conventional imaging. Tc-99m MIBI remains a critical tool in localizing parathyroid adenomas and guiding curative surgical intervention.

**Keywords**: Primary hyperparathyroidism, Tc-99m sestamibi SPECT/CT, aberrant parathyroid adenoma, diagnostic imaging, theragnostic approach.

015

## Addison's Disease Without Imaging Abnormalities: A Diagnostic Challenge - Case Report

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**Abstract**

Addison's disease or primary adrenal insufficiency is a rare endocrine disorder characterized by inadequate production of glucocorticoids and mineralocorticoids. Clinical manifestations are often nonspecific and progressive, leading to delayed diagnosis until adrenal crisis occurs. Hormonal evaluation and adrenal imaging are essential to establish the diagnosis and investigate the underlying etiology. A 54-year-old woman presented with chronic hyperpigmentation, fatigue, and weight loss, along with recurrent episodes of altered consciousness associated with hypotension, hypoglycemia, and hyponatremia. Hormonal evaluation revealed elevated ACTH levels (1295 pg/mL) and low morning serum cortisol 4.3 µg/dL. Imaging studies (CT and MRI) of the adrenal glands revealed no abnormalities. The patient was diagnosed with Addison's disease and initiated on oral hydrocortisone therapy, resulting in significant clinical and biochemical improvement within three months. This case emphasizes the diagnostic complexity of Addison's disease, particularly in the presence of vague early symptoms and unremarkable adrenal imaging findings. Clinical signs such as hyperpigmentation and metabolic abnormalities can provide important clues, however hormonal evaluation remains essential for a definitive diagnosis. Further workup is essential to determine the underlying etiology, including potential autoimmune, infectious, or infiltrative causes. Lifelong glucocorticoid replacement remains the mainstay of therapy, with regular clinical monitoring required to prevent adrenal crises and ensure optimal disease control. Addison's disease should be considered in patients with chronic nonspecific systemic symptoms, electrolyte imbalances and hyperpigmentation. Early diagnosis and appropriate hormone replacement therapy are essential to prevent life-threatening complications and improve clinical outcomes.

**Keywords**: Addison's disease, primary adrenal insufficiency, hyperpigmentation, glucocorticoid therapy.

016

## The Effectiveness of Diacerein Addition on Interleukin-1β Levels and Glycemic Control in Patients with Uncontrolled Type 2 Diabetes Mellitus at Mohammad Hoesin Hospital Palembang

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**Abstract**

Interleukin-1β (IL-1β) plays a key role in worsening insulin resistance. Diacerein, as an IL-1β inhibitor, has the potential to reduce inflammation and improve glycemic control. This study aimed to evaluate the efficacy of diacerein on IL-1β levels and glycemic control in uncontrolled T2DM patients. This double-blind randomized clinical trial was conducted from July to October 2024 at the Endocrine Metabolic

Diabetes Polyclinic, Outpatient Installation of Mohammad Hoesin Hospital, Palembang. A total of 34 uncontrolled T2DM patients were randomly divided into two groups, namely the diacerein group (n=17) and the placebo group (n=17) using the block-permuted randomization method. Patients received 50 mg of diacerein or placebo twice daily for 90 days. Assessments were carried out before and after the intervention, including serum IL-1β levels, glycated hemoglobin (HbA1c), and fasting blood sugar (FBS). Of the 34 patients recruited, 4 patients (2 from each group) dropped out of the study, resulting in a final analysis of 30 patients (15 patients per group). Baseline characteristics of both groups were comparable ($p>0.05$). After 90 days, the diacerein group showed significant reductions in HbA1c (-0.7%; $p=0.002$) and FBG (-66.47 mg/dL; $p=0.004$) compared to the placebo group, which showed no significant changes. IL-1β levels showed minimal changes in both groups without statistical significance ($p>0.05$). Multivariate analysis confirmed diacerein as an independent predictor of reductions in HbA1c and FBG ($p=0.025$ and $p=0.019$). No serious adverse events were found, with only mild gastrointestinal symptoms in the diacerein group. The addition of diacerein significantly improved glycemic control (HbA1c and GDP) in uncontrolled T2DM patients without significant effect on IL-1β levels.

**Keywords**: Diacerein, Interleukin-1β, Uncontrolled Type 2 Diabetes Mellitus.

017

## Conn's Syndrome: An often-forgotten cause of hypertension

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**Abstract**

Resistant hypertension at a young age is an early sign of secondary hypertensive disease associated with hormonal abnormalities, one of which is caused by primary hyperaldosteronism (Conn's Syndrome) characterised by elevated aldosterone levels, low renin palsma, hypokalemia and metabolic alkalosis. This condition is often overlooked as it requires sophisticated investigations. Female, 46 years old came to the endocrine polyclinic of RSMH Palembang with complaints of headache, weakness and history of high blood pressure since 16 years ago, BP: 160/100 mmHg, consumption of three antihypertensive drugs, laboratory results obtained low serum potassium levels (1,6 mEq/L), increased aldosterone 142,09 ng/dL, low plasma renin activity (PRA) 0,05 ng/mL/h, high Aldosterone renin ratio (ARR) 2.841,8. MSCT abdomen obtained left adrenal mass, the patient refused to do adrenal venous sampling and adrenalectomy, then given additional therapy spironolactone 50 mg, BP: 130/90 mmHg. High levels of aldosterone in the blood interacting with mineralocorticoid receptors on the ductus collectivus will lead to 1) increased excretion of potassium through the urine. 2) Hypertension is caused by increased reabsorption of sodium and water, thus suppressing renin levels. In addition to the use of mineralocorticoid receptor antagonists, adrenalectomy is indicated in the subtypes of Aldosterone-producing adenoma (APA) and Primary/unilateral adrenal hyperplasia (UAH).

**Keywords:** Primary hyperaldosteronism, resistant hypertension, hypokalemia, aldosterone-producing adenoma (APA), mineralocorticoid receptor antagonist.

018

## Association between Triglyceride-Glucose Index with Diastolic Dysfunction, Systolic Dysfunction and Left Ventricular Remodelling in Type 2 Diabetes Mellitus

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**Abstract**

Diabetes mellitus (DM) is the main cause of heart failure. Insulin resistance in type 2 DM is risk factor for diastolic dysfunction, systolic dysfunction and left ventricular remodelling. TyG Index is a simple and relatively new for alternative assessing insulin resistance. The aim of this cross-sectional study was to determine association between TyG index with diastolic dysfunction, systolic dysfunction and left ventricular remodelling. This study was conducted on 56 patients with uncontrolled type 2 DM without cardiovascular symptoms, 30-65 years old at Endocrine Polyclinic, Sardjito General Hospital Yogyakarta, period May1st to October31st 2024.

Echocardiography was performed to assess ventricular dysfunction and left ventricular remodelling. TyG index is calculated with formula, TyG index: ln [fasting blood triglycerides (mg/dL) x fasting blood glucose (mg/dL) /2]. Logistic regression test is used to assess association between independent variables and outcome. A total 56 subjects were included in this study. Echocardiography results of diastolic function showed 66.0% normal, 28.6% grade 1 diastolic dysfunction, 3.6% grade 2 diastolic dysfunction and 1.8% grade 3 diastolic dysfunctions. Echocardiography results of systolic function were in median ejection fraction of 68% (22-79%), which included 80,3% normal ejection fraction (EF > 50), 5,4% ejection fraction 41-49, and 14.3% ejection fraction < 40. Echocardiography of left ventricular remodelling showed 67.8% normal geometry, 14.3% concentric remodelling, 14.3% concentric hypertrophy and 3.6% eccentric hypertrophy. There were no association between TyG index on diastolic dysfunction and systolic dysfunction (p= 0.512 and p= 0.838). Logistic regression tests fined that TyGindex, uric acid levels and obesity were associated with left ventricular remodelling with OR 10,716, p = 0.037 (CI 95%: 1.157-99,290); OR 2,136, p= 0.011 (CI 95%: 1.190-3.837); and OR 0.022, p = 0.003 (CI 95%: 0.002-0.273). There is association between high TyG index and left ventricular remodelling in type 2 DM. There were no association between TyG index with left ventricular diastolic and systolic dysfunction in type 2 DM patients.

**Keywords**: TyG index, insulin resistance, left ventricular dysfunction, remodelling.

019

## Management Of Diabetes Mellitus in Patients Infected with Human Immunodeficiency Virus (HIV)

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**Abstract**

Patient with Diabetes Mellitus (DM) and Human Immunodeficiency Virus (HIV) infection presents unique challenges in diagnosis and management. 49-year-old male patient with HIV infection, syphilis infection, and longstanding T2DM come with blurry vision and tingling in the lower extremities for eight months. Laboratory findings show uncontrolled diabetes (HbA1c 8.3%), positive VDRL and TPHA, and CD4 266 cells/µL. Cerebrospinal fluid analysis supported neurosyphilis. Management for this patient including insulin, antiretroviral therapy (ART) with tenofovir, lamivudin and dolutegravir and *benzathine penicillin G* for syphilis infection. The number of persons taking ART for HIV increasing. As a result, the fatalities have decreased, and those affected longer survival rate. Longer life expectancy for people with HIV followed by a rise in non-communicable diseases such as DM. Diabetes mellitus and metabolic derangement have been connected to HIV infection and ART. HIV is also said to be cognate with an elevated risk of insulin resistance. Patients infected with HIV infection often have different infections, such as tuberculosis (TB) or viral hepatitis, which are also associated with a higher chance of the ailment. Individualizing treatment plans must consider about comorbidities, medication interactions, and potential side effects when managing diabetes concerning HIV. Comprehensive strategies such as lifestyle modifications, regular monitoring, medication management, and integration of multidisciplinary healthcare teams are essential. Appropriate treatment choice, regular monitoring and a multidisciplinary approach are essential for optimizing patient outcomes.

**Keywords**: Diabetes Mellitus, HIV, Syphilis.

020

## The Correlation Between the Degree of Liver Steatosis Using Controlled Attenuation Parameter and Arterial Stiffness Using Brachial-Ankle Pulse Wave Velocity in Type 2 Diabetes Mellitus Patients

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**Abstract**

Type 2 diabetes mellitus (T2DM) patients with liver steatosis had a higher risk of developing microvascular and macrovascular complications. Liver steatosis might increase the risk of cardiovascular disease by inducing vascular damage reflected by an increase in arterial stiffness (AS). Previous studies regarding the relationship between liver steatosis and AS in T2DM patients were controversial. This study aims to analyze the relationship between the degree of liverm steasosis measured controlled attenuation parameter (CAP) and AS measured using brachial-ankle pulse wave velocity (baPWV) in T2DM patients. One hundred and one T2DM patients aged > 30 years at the Endocrine & Diabetes Clinic, RSUD Dr. Soetomo Surabaya, were enrolled in this crosssectional study from August to November 2023. Demographic, clinical, and laboratory data were collected. Fibroscan and baPWV examinations were performed on all subjects. The Pearson correlation test was used to analyze the relationship between CAP values and baPWV values. The mean CAP value of the subjects was 259.11 dB/m, and liver steatosis ≥ S1 was detected in 58.42% of subjects. The mean baPWV value of the subjects was 15.3 m/sec, and AS, characterized by increased baPWV values ≥ 14.0 m/sec, was detected in 72.28% of subjects. A weak positive correlation was found between CAP and baPWV values (r = 0.27; p = 0.006). The correlation remained significant after correction for blood pressure values, and the duration of diabetes Liver steatosis is associated with AS in T2DM patients.

**Keywords**: type 2 diabetes, liver steatosis, transient elastography, arterial stiffness, pulse wave velocity.

021

## First Confirmed case of Maturity-onset Diabetes of the Young (MODY) in Indonesia using In-House Targeted Next Generation Sequencing (tNGS): a Case Report

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**Abstract**

Monogenic diabetes, including maturity-onset diabetes of the young (MODY), results from pathogenic mutations in a single gene and accounts for approximately 1-5% of all diabetes cases. MODY is often misdiagnosed as type 1 or type 2 diabetes due to its mild presentation and overlapping clinical features. Genetic diagnosis plays a crucial role in confirming MODY subtypes and guiding precision treatment, however, access to genomic sequencing remains limited in much healthcare settings. In response to Indonesia's national genomic initiative, the GENESIS-ID study aims to establish a clinical-genomic diabetes registry and develop targeted MODY diagnostic panel. Here, we present the first case of MODY diagnosed using in-house targeted next-generation sequencing (tNGS) in Indonesia. A 19-year-old male with a history of onset of diabetes 2 years prior, presented with neurological deficits following an intracranial hemorrhage due to an arteriovenous malformation. The patient had 3 generations of diabetes, normal BMI and C-peptide levels that rule out DMT1. Genetic testing via tNGS identified a pathogenic c.160C>T variant in the HNF4A gene, confirming MODY3. Subsequent testing revealed the same mutation in his mother and younger sibling. This case represents the first confirmed MODY diagnosis in Indonesia using in-house genomic testing panel. The implementation of targeted genetic diagnostics will advance diabetes care precision medicine in Indonesia.

**Keywords:** Maturity-onset diabetes of the young (MODY), HNF4A mutation, targeted next-generation sequencing (tNGS).

022

## Endocrine Complications in Langerhans Cell Histiocytosis: A Case of Empty Sella Syndrome with Hypopituitarism

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**Abstract**

Langerhans cell histiocytosis (LCH) is a rare clonal myeloid neoplasia characterized by infiltration of

CD1a+/CD207+ dendritic cells, frequently affecting bones, skin, and the central nervous system. Endocrine complications, particularly involving the hypothalamic-pituitary axis, are common in multisystem disease and may result in irreversible dysfunction, impacting growth, development, and overall quality of life. An 18-year-old male diagnosed with LCH at age 10 presenting with polyuria, polydipsia, and delayed puberty. He was found to have central diabetes insipidus, central hypothyroidism, hypogonadotropic hypogonadism, and a grade IV empty sella on brain MRI. The patient had a history of bone and soft tissue involvement and underwent chemotherapy for multisystem LCH. His current therapy includes desmopressin, levothyroxine, vitamin D, calcium supplementation, and planned to given testosterone replacement. This case illustrates the classic progression of endocrine complications in LCH with hypothalamic-pituitary axis involvement. Central diabetes insipidus is often the first manifestation followed by anterior pituitary hormone deficiencies. The finding of total empty sella on MRI likely reflects chronic inflammatory damage or atrophy of the pituitary. The combination of CDI, central hypothyroidism, and delayed puberty requires lifelong hormonal replacement and regular endocrine follow-up. The case also highlights the importance of addressing bone health and growth delays secondary to hormonal deficiencies and previous glucocorticoid therapy. Early identification and management of endocrine complications in LCH, particularly those involving the pituitary are essential to reduce morbidity and improve patient outcomes. Lifelong monitoring and multidisciplinary care are necessary for optimal management of LCH survivors.

**Keywords**: Langerhans cell histiocytosis, central diabetes insipidus, hypopituitarism, empty sella syndrome, hypogonadotropic hypogonadism, endocrine complications.

023

## Complete Central Diabetes Insipidus in Adulthood: The Combined Role of Water Deprivation Test and Pituitary Imaging

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**Abstract**

Central diabetes insipidus (CDI) results from deficient secretion of antidiuretic hormone (ADH), causing hypotonic polyuria and compensatory polydipsia. Although typically diagnosed in childhood, adult-onset CDI may be underrecognized due to gradual and nonspecific symptoms. In younger adults, primary polydipsia should be considered in the differential diagnosis. Accurate identification requires clinical suspicion, dynamic testing, and neuroimaging. A 25-year-old previously healthy male presented with a seven-month history of persistent polyuria, including nocturia every 1-2 hours, excessive thirst (~8 L/day), 10 kg weight loss, and fatigue. He denied a history of diabetes, head trauma, CNS infections, or psychotropic drug use. Vital signs were stable (BP 110/70 mmHg, HR 78 bpm), and he appeared clinically euvolemic, without signs of dehydration or hormonal deficiencies. Urinalysis revealed a pH of 6.0, specific gravity of 1.000, and no abnormalities. Laboratory findings included sodium 139 mmol/L, glucose 75 mg/dL, serum osmolality 285 mOsm/kg, and urine osmolality 75.2 mOsm/kg. A water deprivation test showed persistently low urine osmolality (75.2-148.9 mOsm/kg), which rose to 530.1 mOsm/kg following administration of desmopressin. MRI revealed absence of the posterior pituitary bright spot and infundibular thickening (2.8 mm). A diagnosis of complete CDI was confirmed, and the patient experienced marked clinical improvement after starting desmopressin therapy. This case highlights the importance of combining dynamic m testing and anatomical imaging in diagnosing adult-onset CDI. The water deprivation test remains a valuable diagnostic tool, particularly in settings where copeptin assays are unavailable.

**Keywords**: Central diabetes insipidus, water deprivation test, pituitary MRI, polyuria, desmopressin.

024

## Development of Clinical Scoring as Predictor of Cardiac Dysfunction in Patients with Graves' Disease on Therapy with Anti-Thyroid Drugs Therapy

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**Abstract**

Graves' disease is the leading cause of hyperthyroidism. This condition, especially uncontrolled and prolonged hyperthyroidism, is at risk for increased cardiovascular disease morbidity and mortality, with the prevalence of thyroid dysfunction in heart failure reported at 35.6%. Thyroid dysfunction is a modifiable risk factor in patients at risk of heart failure. There is no clinical guidance for the selection of second-line therapy, whether to continue ATD or switch to definitive therapy when associated with the incidence of cardiac dysfunction, hence this study. Cross sectional study with subjects of Graves' disease patients on ATD therapy above 9 months who had routine control at the Endocrinology Clinic of Dr. Sardjito Hospital Yogyakarta in April 2024-June 2024, echocardiographic examination was performed, then their medical records were traced from the beginning of their illness. Univariate, bivariate and multivariate logistic regression analyses followed the Spiegelhalter Knill-Jones scoring method. Data analysis obtained 11 predictor variables to build a scoring system, with an initial score of 18, and a cut-off point < 20.5 declared cardiac dysfunction. This scoring obtained a sensitivity of 97.4%, specificity of 91.7%, predicted positive value 97.4%, predicted negative value 91.7, positive likelihood ratio 11.7, negative likelihood ratio 0.03, accuracy 96.1%, with an AUC value of 94.6% (95% CI 84.9%-100.0%) with a pvalue of 0.0001; then this scoring system has excellent diagnostic value. Internal validation obtained the results of sensitivity 81.3%, specificity 88.9%, predicted positive value 92.9%, predicted negative value 72.7%, likelihood ratio positive 7.3; likelihood ratio negative 0.2; accuracy 84%. This study successfully developed clinical scoring as a predictor of cardiac dysfunction in Graves' disease patients under anti thyroid drugs therapy with good
diagnostic test values.

**Keywords**: Graves' disease, anti-thyroid drugs, clinical scoring, therapeutic guidelines.

025

## The Correlation of Free Fatty Acid with Retinopathy Diabetic Incidence and Urine Albumin to Creatinine Ratio (uACR) in Type 2 Diabetes Melitus (T2DM)

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**Abstract**

Microvascular complications of type 2 diabetes mellitus (T2DM), including diabetic retinopathy (DR) and diabetic nephropathy (DN), are contributed by chronic hyperglycemia, which will stimulate inflammatory mediators, matrix production, and nitric oxide (NO) reduction and cause microvascular pathologies. On the other hand, dyslipidemia in diabetes is related to free fatty acid (FFA) elevation, IR, intracellular metabolism alteration, and mitochondrial dysfunction. This study aims to identify the relationship between FFA concentrations with DR or albuminuria in T2DM subjects. This is analytic observational research with a cross-sectional method done in T2DM subject in an outpatient clinic at the endocrinology section RSUP Dr. Hasan Sadikin, RSM Cicendo, and primary care clinic (Wirasakti and Monalisa) from September to December 2024. Baseline characteristics include age, gender, duration of DM, type of medications, comorbidities, chronic complications, and clinical characteristics include HbA1c, LDL, HDL, TG, total cholesterol, creatinine, FFA, uACR) and complications (RD or albuminuria). A total of 96 subjects with T2DM are included in this study. Mean age was 59 years old, with a higher mean in the non-albuminuria group (p=0.016). Most subjects are female 58.3%. However, male sex is higher in the albuminuria group 57.1% (p=0.020). DR subjects showed a lower BMI 25.3kg/m$^2$, and a higher proportion of visceral fat <10 51% (p <0.05). Laboratory examination showed a higher proportion of RD subjects with FFA <0.9meq/L (70.6%) and TG <150mg/dL (66.7%) (p<0.05). On the other hand, subjects with HbA1c >7% have a higher proportion in the albuminuria group 68.6% (p<0.001).

A total of 53% of subjects showed RD complication and 36.4% showed albuminuria. Correlation analysis showed no correlation between FFA concentration and the RD (r:-0.51, p=0.071) or uACR concentrations (r=0.048, p=0.322). The result showed the significance of IR and glycemic control in the pathogenesis of microvascular complications in T2DM subjects. This study showed no significant correlation between FFA concentration and DR or uACR concentration. However, the role of FFA and microvascular cannot be fully ruled out.

**Keywords**: type 2 diabetes mellitus, free fatty acid, diabetic retinopathy, uACR.

026

## A Case of Insulinoma in Elderly Obese Man underwent Distal Pancreatectomy and Laparascopic Sleeve Gastrectomy

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**Abstract**

Insulinoma is one of the most common neuroendocrine tumors. Special considerations related to the elderly are needed for tumor removal and obesity management in this case. A 67-year-old man came to the hospital emergency room with recurrent hypoglycemia with a 40 kg weight gain experienced since 2 years ago. We found 121 kg in weight, 174 cm in height, BMI of 39.8 kg/m$^2$, C-peptide 11.7 ng/ml (0.78-5.19), morning insulin 141.3 μIU/L (5-20), and tumor in the cauda pancreas. The patient was diagnosed with insulinoma and grade II obesity. The patient planned for distal pancreatectomy and laparoscopic sleeve gastrectomy (LSG). Adjusting nutritional intake and administering octreotide 3x100mcg SC prepared the patient for surgery. No hypoglycemia was recorded during the monitoring pre-operative, intraoperative, and postoperative periods. The patient was then discharged after being able to mobilize and experiencing clinical improvement. The patient continued to have regular check-ups up to one year post-operatively and was in good condition, with weight loss and no further hypoglycemia. There is no epidemiological data on the incidence of obesity in insulinoma, although several case reports have reported significant weight gain experienced by patients. There is no difference in insulinoma management for this case. However, obesity in this case requires special attention related to the impact of obesity on the elderly. For the management of obesity, the patient underwent LSG, which is one of the metabolic surgery options.

**Keywords**: insulinoma, obesity, elderly, laparascopic sleeve gastrectomy.

027

## Case Report: Bilateral Adrenal Mass Due to Tuberculosis

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**Abstract**

Adrenal tuberculosis can present without prior evidence of pulmonary or extrapulmonary tuberculosis evidence. Bilateral adrenal enlargement is more frequently observed in cases of adrenal tuberculosis. We report a case of a 55-year-old male who presented with mild abdominal pain and unintended weight loss. No signs or symptoms of adrenal insufficiency were found on clinical examination or biochemical laboratory tests. Non-

contrast CT scan revealed iso- to hypodense lesions with relatively well-defined borders and irregular margins in the right (approximately 6.9 × 4.6 × 8.5 cm) and left (approximately 6.5 × 3.8 × 8.4 cm) adrenal glands. After contrast administration, both adrenal masses showed heterogeneous enhancement. The patient underwent a left adrenalectomy, with 50 mg intravenous hydrocortisone was administered as a bolus intraoperatively after removal of the left adrenal gland. Postoperative cortisol levels remained within normal limits (30.4 µg/dL). The hydrocortisone dose was then gradually tapered, and the patient was discharged to inpatient care with oral hydrocortisone at a dose of 20 mg/day. Histopathology examination confirmed the diagnosis of adrenal tuberculosis. The patient subsequently received anti-tuberculosis treatment from another hospital. However, a few days after initiating the anti-tuberculosis regimen, the patient's condition deteriorated, and he was hospitalized with clinical signs of hyponatremia and a blood pressure of 100/60 mmHg.

**Keywords:** Adrenal Tuberculosis, Adrenalectomy, Non-functional adrenal mass.

028

## Elevated Thyroglobulin and Negative I-131 Whole Body Scan After Total Thyroidectomy: Case Report of Two Patients with TENIS Syndrome

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**Abstract**

Thyroglobulin-elevation, negative iodine scintigraphy (TENIS) syndrome represents a significant diagnostic and therapeutic challenge. Highly sensitive imaging modalities are required to help in the localization of disease, treatment planning, and prognostication. When compared to other imaging modalities, 18-fluoro-2-deoxyglucose positron emission tomography CT has superior sensitivity and specificity in localizing the disease in this subset of patients. Tyrosine kinase inhibitors (TKIs) are now considered first-line therapies for differentiated thyroid cancer refractory to treatment modalities. TKI therapy is a chronic, life-long treatment that requires careful attention to quality of life and side effects. Here we report two cases of TENIS syndrome currently on TKI treatment.

**Keywords**: papillary thyroid carcinoma, TENIS syndrome, thyroglobulin, tyrosine kinase inhibitors

029

## Therapeutic Conundrum: hCG Hormonal Therapy in Obese Males with Non-Specific Hypogonadal Symptoms and Normal Hormonal Profiles, Coexisting with Personality Disorder

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**Abstract**

Hypogonadotropic hypogonadism is typically associated with dysfunction of the hypothalamic-pituitary-gonadal axis. However, prolonged exogenous administration of human chorionic gonadotropin (hCG) may suppress endogenous gonadotropin secretion, leading to iatrogenic hypogonadism. This case highlights the diagnostic and therapeutic complexity of managing non-specific hypogonadal symptoms in an obese male with normal baseline hormonal profiles and coexisting personality disorder. A 30-year-old obese male with a history of bilateral varicocele surgery presented with persistent fatigue, emotional instability, and irritability. Despite having normal total testosterone levels, the patient received prolonged hCG therapy. Semen analysis revealed teratozoospermia. Psychiatric evaluation showed a PHQ-9 score of 13 (suggestive of depression) and an SCL-90-R score of 1.21 (moderate symptoms). Over time, the patient's symptoms worsened, raising concerns of treatment-induced hormonal suppression. The patient's hCG therapy was discontinued. Lifestyle and dietary modifications were initiated alongside supplementation with vitamin

D (1000 IU/day) and Coenzyme Q10. Psychiatric referral and counseling were provided. Within one year, both clinical symptoms and laboratory parameters improved, including increased emotional stability and reduced fatigue. This case illustrates that prolonged hCG therapy in eugonadal men may result in iatrogenic hypogonadotropic hypogonadism. In patients presenting with hypogonadal symptoms and multiple comorbidities such as obesity and behavioral disorders, hormonal therapy must be approached cautiously. A multidisciplinary and individualized treatment strategy is essential to optimize outcomes and prevent further endocrine disruption.

**Keywords**: hCG Theraphy, Hypogonadotropic hypogonadism, Obese, personality disorder.

030

## Secretome of Human MSC Gel Improves DFU Healing through NF-κB p50 and CD163 mRNA Expression

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**Abstract**

Diabetic foot ulcers (DFUS) remain a critical clinical problem and stem cell-derived secretome reared under hypoxic conditions has been shown to play a significant role in tissue repair via immunomodulation. This study aimed to evaluate the secretome of human mesenchymal stem cell gel (SH-MSC gel) in DFU patients with grades 2 and 3 through reduced wound volume and modulation of CD163 and NF-kB p50 mRNA expression. A prospective, randomized controlled clinical trial involved 16 DFU patients with grades 2 and 3. Participants received either a placebo gel or an intervention gel containing secretome from Human Umbilical Cord Mesenchymal Stem Cells (hUC-MSCs) cultured under hypoxic conditions. All patients received standard wound care. Primary outcomes included changes in wound volume and expression levels of CD163 and NF-kB p50 mRNA in wound tissue, assessed using quantitative PCR. The Shapiro-Wilk test assessed normality and for normally distributed data, paired t-tests (within-group) and unpaired t-tests (between-group) were used. One-way ANOVA compared means across groups, while the Kruskal-Wallis test followed by post hoc analysis was employed for non-parametric data ($p<0.05$). Statistical analysis was performed using GraphPad Prism 10. Baseline characteristics of participants did not show significant differences between the groups. Treatment with SH-MSC gel significantly enhanced wound healing compared to the placebo group, evidenced by a marked reduction in wound volume after 7 days (95% CI (0.467 to 1.18), $p<0.001$). The CD163 mRNA expression significantly increased in the SH-MSC gel group post-treatment (95% CI (-2.20 to -1.11), $p<0.001$), while NF-kB p50 mRNA expression significantly decreased (95% CI (0.349 to 0.688), $p<0.001$). The clinical trial results suggested that SH-MSC gel effectively improves wound healing in DFUs. Further research is warranted to explore additional inflammatory markers to better understand DFU treatment.

**Keywords**: Diabetic foot ulcers, stem cells, wound healing, NF-kB p50, CD163 antigen.

031

## Case Report : Progressive Disease Metastatic Pheocromocytoma

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**Abstract**

Pheochromocytoma is rare neuroendocrine tumor of the adrenal medulla, with incidence of 2-8 cases per million annually. It accounts for 90% of adult Pheochromocytoma-Paraganglioma (PPGL) cases and typically presents with episodic hypertension, headaches, palpitations, and diaphoresis. This case involved malignant transformation with metastatic

progression, posing significant therapeutic challenges. A 40-year-old man with long-standing treatment-resistant hypertension presented with paroxysmal symptoms. Test result showed elevated plasma normetanephrines, and imaging confirmed a left adrenal mass. He underwent adrenalectomy in 2022, with temporary normalization of blood pressure and catecholamines. In 2023, PET/CT revealed liver and bone metastases, with elevated urinary noradrenaline. Follow-up imaging revealed progression with additional metastatic lesions in multiple sites. Currently, Patient was treated with lanreotide (120 mg/month), denosumab (120 mg/month), and capecitabine (days 1-14) plus temozolomide (days 11-14). Blood pressure is now controlled with amlodipine, telmisartan, and terazosin. Despite persistent metastases, the patient remains clinically stable. Malignant pheochromocytoma, defined by metastases to non-chromaffin tissues, remains difficult to treat due to limited curative options. In this case, multimodal therapy helped stabilize symptoms and slow progression. In this case, despite the administration of multimodal therapy using targeted agents, somatostatin analogs, bone therapy, and chemotherapy, metastatic progression continues. Metastatic pheochromocytoma is a clinical challenge. While remission is rare, early diagnosis, surveillance, and tailored therapies are key to symptom control and disease stabilization.

**Keywords**: Pheochromocytoma, metastasis.

032

## Unexpected Finding of Hashimoto Thyroiditis in Histological Diffuse Large B Cell Lymphoma

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**Abstract**

Hashimoto's thyroiditis is an autoimmune inflammatory disorder. Histologically, it is characterized by lymphocyte infiltration of the thyroid parenchyma, reactive germinal centers, and Hürthle cell changes. A 60-year-old woman with a goiter for approximately 3 years denied weight loss, fever, or night sweats. Recently, she felt discomfort and worsening compression symptoms in her neck, so she completed all examinations at the oncology surgery clinic. She was advised to undergo total thyroidectomy due to worsening symptoms. Preoperative ultrasound (US): showed bilateral thyroid gland enlargement and nodular goiter TI-RADS 3 with heterogeneous echogenic structures consistent with thyroiditis. Neck X-ray showed bilateral neck masses with right tracheal deviation, without evidence of airway obstruction. Laboratory tests showed hypothyroidism with TSH 50.4 µIU/mL (0.27-4.20); FT4 0.38 ng/dL (0.92-1.68), and the patient was taking levothyroxine 100 mcg once daily to achieve normal levels as much as possible before the scheduled surgery. Postoperative laboratory evaluation showed TSH 9.08 µUI/mL (0.27-4.20); FT4 1.27 ng/dL (0.92-1.68). The patient's clinical presentation, combined with imaging findings, raised concerns about the possibility of malignancy. Postoperative pathology unexpectedly revealed HT coexisting with DLBCL of intermediate to large cell type; the immunohistochemical profile of the thyroid tumor was consistent with DLBCL, CD20+. Postoperative laboratory tests showed TSH 30.5; FT4 1.13. Serum calcium 1.96 mmol/L (2.15-2.5). Levothyroxine 100 mcg qd was continued with calcium lactate 500 mg bid to maintain hypocalcemia. The patient completed 6 cycles of R-CHOP chemotherapy with excellent quality of life. PTL is a rare neoplasm. Patients with HT are at higher risk of developing PTL compared to those without HT.

033

## Chronic Kidney Disease in a 65 Year Old Man with Primary Hyperparathyroidism due to Parathyroid Adenoma

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**Abstract**

Primary hyperparathyroidism affecting 1% of the adult population and 80-85% caused by parathyroid adenoma. The most common manifestations of parathyroid adenoma involve the kidneys and bones due to alteration in bone resorption and calcium deposition in the kidneys. A 65 year old man with chronic kidney disease (CKD) was referred to Dr Kariadi General Hospital to clarify the etiology of CKD. Abnormal Physical and supporting examinations: heart rate 58 beats per minute, increase creatinine (4.28 mg/dL), recurrent hypercalcemia (15.8; 14.3 mmol/L; ), hyperuricemia (11.0 mg/dL), increase serum Parathyroid Hormone (PTH) 405 pg/mL, abdominal USG: chronic process of both kidneys with bilateral nephrolithiasis, renogram: decrease in total Glomerular Filtration Rate (GFR) 46.76, parathyroid USG: left parathyroid lobe adenoma, contrast cervical MRI: parathyroid adenoma of the left lobe thyroid, sestamibi parathyroid scan: parathyroid adenoma (postero-inferior) of the left lobe thyroid, BMD: osteopenia. Patient underwent partial left parathyroidectomy with immunohistochemical results of a parathyroid adenoma. Post surgery serum PTH was normal (16.7 pg/mL). Patient discharge after 2 weeks of treatment in good condition. Primary hyperparathyroidism was suspected because of recurrent hypercalcemia. Increase PTH might cause hypercalcemia due to alteration in bone resorption and calcium deposition in the kidneys resulting in CKD. Definitive therapy in cases of parathyroid adenoma is parathyroidectomy.

**Keywords**: Primary Hyperparathyroidism, Parathyroid Adenoma, Sestamibi Parathyroid Scan.

034

## Correlation Between Body Mass Index, Visceral Adiposity Index, and Body Fat Percentage as Obesity Parameters and Liver Steatosis in Type 2 Diabetes Mellitus Patients

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**Abstract**

To determine the correlation between body mass index (BMI), visceral adiposity index (VAI), and body fat percentage as indicators of obesity and the severity of liver steatosis in patients with Type 2 Diabetes Mellitus (T2DM). This knowledge will enable earlier screening and diagnosis for obesity treatment and prevention of complications related to non-alcoholic fatty liver disease (NAFLD) in T2DM patients. Methods: One hundred three patients with T2DM over 30 years old were included in the study conducted at the Endocrine & Diabetes Clinic, Dr. Soetomo General Academic Hospital Surabaya. The patients were selected using a consecutive sample approach, and the study followed a cross-sectional design. The data collection took place from August to November 2023. Data on demographics, clinical characteristics, and supporting data were gathered from all participants. This included measurements of body mass index (BMI), visceral adiposity index (VAD), and body fat percentage using Bioelectrical impedance analysis (BIA). Additionally, a transient elastography examination was conducted. The correlation test was employed to ascertain the association between BMI, VAI, and body fat percentage with liver steatosis, measured by the Controlled Attenuation Parameter (CAP). In this study involving patients with DMT2, 68.0% of participants failed to attain the glycaemic control target, with a median HbA1c of 8.1%. The prevalence of NAFLD was observed in 65.04% of the research participants. The mean BMI of the participants in this study was 26.49 kg/m2, with 61.2% categorized as obese. A positive correlation was identified between BMI, VAI, and body fat percentage with the extent of liver steatosis. The correlation between BMI and liver steatosis was significant (p=0.00) with a r value of 0.444. The correlation of VAI with liver steatosis was significant in men (p=0.030, r=0.332) but not significant in women (p=0.078, r=0.230). The correlation of body fat percentage with liver steatosis was significant in men (p=0.028, r=0.335) and women (p=0.013, r=0.320). The Body Mass Index, VAI, and body fat percentage are correlated with hepatic steatosis in T2DM patients, allowing these measures to be utilized in conjunction

for early obesity screening to avert additional NAFLD problems.

**Keywords**: type 2 diabetes, liver steatosis, transient elastography, body mass index, visceral adiposity index, body fat percentage.

035

## Heart Stress and Its Associated Factors in Type 2 Diabetes Patients

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**Abstract**

Heart failure is an underestimated but potentially devastating complication of diabetes. Thus, early detection is important. Heart stress is a condition in which a person does not have symptoms of heart failure but is at risk of developing, for example in diabetes population. Here, we evaluate the prevalence of heart stress and factors associated with its development in type 2 diabetes (T2D) patients. A cross-sectional study including 317 T2D patients recruited from the Genomic Study of Young-Onset Diabetes Mellitus database of Dr.Cipto Mangunkusumo National General Health Hospital was performed. Heart stress was defined as NTproBNP > 50 pg/mL. The prevalence of heart stress is 53.6% (95%CI 48,1 - 59,1). Factors significantly associated with development of heart stress in T2D were age [PR 1,29 (95%CI; 1,05 - 1,59; p=0,016)], anemia [1,42 (1,16 - 1,73: p=0.001), hypertension [1,42 (1,09 - 1,84: p=0.010)] and albuminuria [1,561 (1,26 - 1,94: p < 0.001)]. Older age, anemia, hypertension and albuminuria are associated with the development of heart stress in T2D patients. Smoking, hypertriglyceridemia, obesity, chronic coronary syndrome, HbA1c, TyG and NLR are not yet proven to be associated with the development of heart stress in T2D mellitus patients in this study.

**Keywords**: Type 2 Diabetes Melitus; Heart Stress; Subclinical Heart Failure.

036

## Autoimmune Polyglandular Syndrome Type IIID in Identical Twins: A Role for CTLA4 Polymorphism

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**Abstract**

Autoimmune Polyglandular Syndrome Type IIID, involving Graves' disease and systemic lupus erythematosus (SLE), is rarely reported in monozygotic twins. This case highlights the contribution of genetic and immunologic factors to the development of multiple autoimmune disorders. Ms. RI, 21, presented with palpitations, facial redness after sun exposure, hair loss, joint pain, fatigue, and diarrhea >3 times/day. She had malar rash, diffuse goiter, a Wayne index of 23, and an ARA score of 18. Labs showed low TSH, elevated FT4, high TRAb, ANA 1:3200, and elevated anti-dsDNA. Genetic testing revealed CTLA4 G/G polymorphism. Her twin, Ms. RA, also 21, reported palpitations, tremors, excessive sweating, loose stools, and weight loss over 12 months. She had exophthalmos, goiter, Wayne index 21, and ARA score 6. Labs revealed low TSH, elevated FT4, high TRAb, ANA 1:1000, normal anti-dsDNA, and CTLA4 A/G polymorphism. They are monozygotic twins, confirmed by a shared placenta and zygosity testing. Despite identical genetic backgrounds, the twins displayed distinct autoimmune phenotypes. The G/G genotype in Ms. RI correlated with more severe clinical expression, suggesting that specific CTLA4 polymorphisms may influence disease severity. Environmental and epigenetic factors may further modulate disease presentation. CTLA4 polymorphism appears to modulate the severity of autoimmune expression in identical twins.

**Keywords**: Autoimmune Polyglandular Syndrome Type IIID, Monozygotic twins, CTLA4 polymorphism

037

## Isolation, In Vitro Expansion, Cryopreservation of Primary Cells Derived from Human Thyroid Carcinoma

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**Abstract**

Thyroid carcinoma is a malignancy originating from thyroid parenchymal cells and currently ranks fourth in the incidence of newly diagnosed carcinomas in Indonesia. This study focuses on in vitro research aimed at isolating thyroid carcinoma cells for subsequent expansion and storage as a cell culture stock, as well as cryopreservation for future use and reapplication. The study also involved the identification and characterization of cells derived from papillary thyroid carcinoma tissue to determine the presence or absence of mutations that may influence prognosis. Primary cell isolation was conducted using an enzymatic method with collagenase, which successfully separated carcinoma-derived cells from those originating from normal thyroid tissue. Cell proliferation cultures of thyroid carcinoma tissue in this study used DMEM (Dulbecco's Modified Eagle Medium) supplemented with 20% FBS (Fetal Bovine Serum) due to its high growth factor content, which enhances the cell proliferation rate. Cryopreservation of the thyroid carcinoma-derived cells was performed using the slow freezing method. Characterization of thyroid carcinoma cells in this study was conducted using PCRelectrophoresis and alignment sequencing of one BRAF gene and five RAS genes included HRAS exon 2, NRAS exon 2, NRAS exon 3, KRAS exon 2, and KRAS exon 3. The results showed no mutations in any of the BRAF and RAS genes.

038

## Methimazole-Induced Agranulocytosis in a Patient with Graves' Disease: A Case Report

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**Abstract**

Antithyroid drug-induced agranulocytosis is a rare but serious complication of antithyroid drug (ATD) therapy. It occurs in approximately 0.2-0.5% of patients with Graves' disease who are treated with ATDs. A 24-year-old female presented with a 10-day history of fever, sore throat, oral ulcers, and generalized weakness. She had a history of hyperthyroidism and had been taking methimazole 10 mg three times daily for the past three months. On examination, she was febrile, tachycardic, and had a goiter. Laboratory investigations revealed agranulocytosis, suppressed TSH, normal free T4

(fT4), and elevated thyroid receptor antibodies (TRAb). Methimazole was discontinued, and the patient was started on empirical broad-spectrum antibiotics along with subcutaneous granulocyte-colony stimulating factor (G-CSF). Her clinical condition and blood counts improved, and she was discharged after four days. Antithyroid drug-induced agranulocytosis typically occurs within the first three months of ATD therapy, it should be considered in every patient prescribed with any ATD who presents with high fever and other signs of infection. The diagnosis is confirmed by an absolute neutrophil count (ANC) of less than 500/μL in the presence of ATD use. Immediate discontinuation of the offending drug is essential to prevent further complications. Management includes the administration of broad-spectrum antibiotics and, in selected cases, granulocyte-colony stimulating factor (G-CSF). Monitoring and patient education are essential for the early detection of antithyroid drug-induced agranulocytosis, particularly within the first three months of therapy. Prompt and appropriate management is crucial for a good prognosis.

**Keywords:** Antithyroid drug-induced agranulocytosis, methimazole, Graves' disease, granulocyte colony-stimulating factor

039

## Association Between Insulin Resistance and Remnant Cholesterol with Metabolic Associated Fatty Liver Disease (MAFLD)

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**Abstract**

Insulin resistance (RI) and Remnant Cholesterol (RC) are risk factors for cardiovascular and Metabolic Associated Fatty Liver Disease (MAFLD). Insulin resistance combined with increased RC will increase the risk factors for MAFLD. Studies on the relationship between RC and RI with MAFLD are still limited. To determine the relationship between insulin resistance and remnant cholesterol with MAFLD. Cross sectional observational study was conducted at Wahidin Sudirohusodo Hospital and Hasanuddin University Teaching Hospital Makassar from October 2024 to December 2024. The subjects were MAFLD patients who were more than 18 years old. HOMA-IR examination and RC examination were conducted through the RC calculation method=Total cholesterol-LDL-HDL. Results: In the study, 88 samples were divided into MAFLD 45 (51.14%) and Non MAFLD 43 (48.86%). Insulin resistance is a risk factor for MAFLD.(Ods Ratio= 3.4 with 95%, CI =1.41 - 8.15) and RC is a risk factor for MAFLD. (Ods Ratio= 10.3 with 95%, CI =3.71 - 28.51). There was a significant relationship between insulin resistance and RC (r = 0.399 and P = 0.000118. From the results of logistic regression analysis, it was found that high HOMA-IR values with high RC levels were risk factors for MAFLD ($p<0.05$). This study found an association between insulin resistance and RC with MAFLD. Insulin resistance and RS can be used as predictors to assess the risk of MAFLD.

**Keywords:** Insulim resistance, remnant cholesterol, MAFLD.

040

## A 39-year-old woman with a suspicion of Familial Hypercholesterolemia

**Ika Hudayani, Himawan Sanusi*, Andi Makbul Aman*, Husaini Umar*, Fabiola MS Adam*, Sitti Aulia**

**Abstract**

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder characterized by elevated LDL cholesterol levels from birth, placing individuals at high risk for premature cardiovascular disease. Early diagnosis and appropriate therapy are essential to reduce morbidity and mortality. A 39-year-old woman presented with yellowish nodules on her body (xanthomas), chest pain, and significantly elevated total cholesterol (571 mg/dL) and LDL (482 mg/dL) levels. Physical examination revealed corneal arcus and xanthelasma. A family history of similar conditions supported the diagnosis of FH. Based on the Dutch Lipid Clinic Network criteria, the patient scored 20, confirming a definitive diagnosis of FH. The patient exhibited clinical manifestations of heterozygous FH with a high risk of coronary artery disease. Supporting laboratory findings and family history reinforced the diagnosis. High-dose atorvastatin was prescribed to achieve an LDL-C reduction target of ≥50% (<70 mg/dl). Long-term management includes pharmalogical therapy, lifestyle modifications, and close monitoring.

Accurate diagnosis and management of FH can reducr the risk of cardiocascular disease and improve patient life expectancy. Awarenesss of clinical signd and family history is crucial for early detection.

041

## A Rare Case of Insulinoma with suspected MEN Type-1 associated: Diagnostic and Therapeutic Challenges

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**Abstract**
Insulinoma is a rare pancreatic neuroendocrine tumor (NET) from beta cells pancreas which responsible for insulin secretion. Insulinoma characterized by episodes hypoglycemia due to excessive insulin secretion. Few cases of insulinoma reported to be associated with MEN-1 Case illustration: A 44-year-old man admitted to the hospital due to disorientation, cold sweats, and tremors. On admission, his blood glucose (BG) was 34 mg/dL. The patient reported recurrent hypoglycemic with excessive hunger, unable to fast, and weight gain 6 kg over the past two months. No history of diabetes, medication use, or alcohol consumption. A supervised 72-hour fasting test was performed and terminated at 4 hours due to symptomatic hypoglycemia (BG level 38 mg/dl). Laboratories revealed high C-peptide 2.15 ng/ml and fasting insulin 16.8 mU/ml. The FI to glucose ratio was 0.44 and FI to C-peptide ratio was 0.17 suggesting endogenous hyperinsulinemia. Calcium ion 1.6 mmol/L and PTH 145 pg/mL indicate hyperparathyroidism suspected to be associated with MEN-1. Abdominal CT showed mass in the pancreatic tail while neck CT showed right parathyroid hyperplasia. The patient subsequently underwent pancreatectomy and the histopathologic revealed well-differentiated pancreatic NET. Discussion : This rare insulinoma case with MEN-1 features emphasizes the importance of recognizing syndromic associations. Comprehensive evaluation and prompt surgical management significantly improve prognosis in patients with neuroendocrine tumors and endocrine hyperfunction. Conclusion: We presented a rare case of insulinoma associated with MEN-1 characterized by recurrent hypoglycemia. Surgical resection remains the definitive treatment and associated with good prognosis.
**Keywords**: insulinoma, hypoglycemia, MEN-1, C-peptide.

042

## Comparison of the Use of Antidiabetic Therapy (OAD, Insulin, and Combination) on HbA1c and EGFR Profile in T2DM Patients at Rachma Husada Hospital

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**Abstract**
Therapy in T2DM patients greatly varies and is a challenge for the clinician. In T2DM, HbA1c is an indicator of therapeutic accuracy and is checked over a period of at least 3 months. Glycaemic control has a relationship with eGFR as one of the main renal macrovascular complication indicators in patients with DM. This study is a descriptive study comparing the types of drugs consumed with HbA1c and eGFR profiles in patients with T2DM at Rachma Husada Hospital, Bantul. This study is a retrospective cohort study. Data were taken from the EMR of T2DM ambulatory patients who received OAD or insulin or combination therapy at Rachma Husada Hospital during January 2024-March 2025. There were 73 patients who fulfilled the criteria. The results showed that most patients were aged ≥60 years (52%), and were predominantly female (51%). The results of the paired t-test comparing the HbA1c profiles before and after therapy for 3 months showed that patients given OAD had a significant difference compared to insulin and combination drugs (respectively p-*value* 0.047; 0.915; 0.195). Meanwhile in the eGFR profiles there were a significant difference in patients using OAD and combination (respectively p-*value* 0.001 and 0.029). However, changes in HbA1c and eGFR were not influenced by the type of drug consumed by the patient. The result of the correlation test with pearson method showed there was a significant relationship between eGFR and HbA1c with a value of r = -0.236 and p = 0.045. These results showed that if the patient experiences an improvement in HbA1c levels, there will also be an improvement in

the eGFR profile in the patient. In this study, the use of antidiabetic therapy that had a better impact on the HbA1c and eGFR profiles was the OAD type, but in general the type of drug consumed by patients did not have a significant effect on changes in HbA1c and eGFR treated for 3 months. This is possibly because there are still many other factors that influence the success of T2DM patient therapy.

**Keywords**: DM, HbA1c, eGFR, OAD.

043

## GLP-1 Receptor Agonists in the Era of Cardio-Kidney-Metabolic Syndrome: Mapping the Triple Organ Benefit, a Scoping Review

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**Abstract**

Cardio-Kidney-Metabolic (CKM) syndrome is a complex clinical entity defined by interrelated dysfunctions in cardiovascular, renal, and metabolic systems. While significant therapeutic advances have been made for each domain, an integrated CKM management strategy remains underdeveloped. Glucagon-like peptide-1 receptor agonists (GLP-1RA) have emerged as promising agents with multifaceted benefits, extending beyond glycemic control to cardiovascular protection, renal preservation, and metabolic optimization. This scoping review synthesizes current evidence on the therapeutic role of GLP-1RA in CKM syndrome, emphasizing its clinical relevance, mechanistic pathways, and implications for multimodal treatment strategies. A systematic literature search was conducted across PubMed, Embase, Scopus, Cochrane Library, and NCBI databases, following Joanna Briggs Institute (JBI) guidelines and PRISMA-ScR methodology. Eligible studies included randomized controlled trials, cohort studies, systematic reviews, meta-analyses, and narrative reviews published between 2017 and 2025. Extracted data were categorized into cardiovascular, renal, and metabolic domains, followed by thematic synthesis. Analysis of 77 studies indicates that GLP-1RA significantly reduces major adverse cardiovascular events (MACE), enhances heart failure outcomes, and improves vascular function. Renal benefits include albuminuria reduction and glomerular filtration rate stabilization. Metabolic effects encompass glycemic control, obesity reduction, and lipid profile modulation. Notably, combination therapy with SGLT2 inhibitors exhibits synergistic potential in CKM management. GLP-1RA represents a compelling multimodal therapeutic approach for CKM syndrome, warranting further research to refine optimal combination therapies and accelerate integration into clinical practice guidelines.

**Keywords**: GLP-1 receptor agonists, Cardio-Kidney-Metabolic syndrome, MACE, renal, metabolic.

044

## Evaluating the Effect of Fenofibrate Towards the Progression of Diabetic Retinopathy: A Systematic Review

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**Abstract**

Diabetic retinopathy (DR) is increasingly prevalent, prompting interest in alternative treatments like fenofibrate, known for lipid-lowering and potential retinal benefits. This review evaluates its efficacy in slowing DR progression. A systematic search of PubMed, Scopus, and ProQuest identified RCTs and observational studies from the past 15 years. Outcomes focused on DR progression. Risk of bias was assessed using ROB 2.0 and ROBINSI tools. Five studies (2 RCTs, 3 cohorts) with 250,835 patients (mean age 64.3 years) were included. Four studies reported that fenofibrate significantly reduces DR progression, and two showed reduced risk of macular edema. Risk of bias was low to moderate. Fenofibrate offers anti-inflammatory and anti-angiogenic effects, making it a promising systemic alternative to anti-VEGF or steroid therapies. It may complement glucose-lowering drugs, though more evidence is needed. Conclusion: Fenofibrate appears effective in reducing DR progression and macular edema. More clinical trials are needed to confirm its long-term benefits.

**Keywords**: Fenofibrate, diabetic retinopathy, macular edema.

045

## Correlation Between Diabetic Ulcers and Depression in Patients at Prof Dr. R. D. Kandou Hospital Manado

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**Abstract**
Diabetic ulcers are chronic complications of diabetes that impair physical and psychological well-being. Classified by the Wagner criteria, these ulcers range from superficial lesions to extensive necrosis, leading to prolonged treatment and reduced quality of life. Depression, measured by the Hamilton Depression Rating Scale (HDRS-21), may further worsen selfcare, delay healing, and negatively impact prognosis. This cross-sectional analytical study involved 50 diabetic ulcer patients aged ≥18 years, recruited through sequential sampling. Patients with pre-existing mental disorders or severe comorbidities affecting mental status were excluded. Ulcer severity was assessed using the Wagner Classification; depression was measured by HDRS-21. Spearman correlation tested relationships between ulcer severity (independent variable) and depression, age, and education (dependent variables). Most participants were female (60%), with high school education (38%), Wagner grade 4 ulcers (38%), and no depression (42%). Significant correlations were found between ulcer severity and depression ($p < 0.001$, $R = 0.529$), and ulcer severity and age ($p = 0.047$, $R = 0.283$). No significant correlation was observed between ulcer severity and educational status ($p = 0.989$). Severe diabetic ulcers significantly impact mental health, especially in older patients with greater comorbidity burdens and reduced coping capacity. Education did not influence depression severity. These findings highlight the need for integrating mental health support into diabetic ulcer management. Diabetic ulcer severity correlates with depression and age but not with educational status. Keywords: Diabetic ulcer, depression, Wagner, HDRS-21.

046

## A case of primary hyperaldosteronism presenting as haemorrhagic stroke: A Case Report

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RSPAD Gatot Soebroto

**Abstract**
Primary hyperaldosteronism (PA) is a common cause of secondary hypertension, especially in resistant cases. PA characterized by excessive aldosterone secretion from the adrenal glands, leading to hypertension, hypokalemia, and metabolic alkalosis. PA is associated with increased cerebrovascular risk, including stroke, due to vessel injury and impaired endothelial function. A 46-year-old woman with a 5-year history of uncontrolled hypertension was admitted following altered mental status, with left-sided numbness and weakness. Her blood pressure was 219/88 mmHg, and she exhibited 3/5 weakness in her left extremities. She had severe hypokalemia (potassium 1.63 mmol/L) and metabolic alkalosis (pH 7.6). A CT scan revealed a right thalamic intracranial hemorrhage. Laboratory findings showed suppressed plasma renin activity (0.50 ng/mL/h) and elevated plasma aldosterone (68.16 ng/dL). Abdominal imaging identified a cystic mass in the left suprarenal gland, consistent with an aldosteronoma. She underwent adrenalectomy in January 2025, resulting in symptom resolution and improved blood pressure control. PA is prevalent among hypertensive patients and significantly increases stroke risk. Screening with the Aldosterone-Renin Ratio (ARR) is recommended for hypertensive patients with hypokalemia or resistant hypertension. Imaging studies help identify potential adenomas amenable to surgical removal. Adrenalectomy can effectively reduce cerebrovascular events by improving blood pressure and correcting hormonal excess. This case underlines the importance of considering PA in patients with resistant hypertension and stroke. Early diagnosis and surgical management can greatly improve outcomes, emphasizing the need for a multidisciplinary approach. In this patient, adrenalectomy led to clinical improvement, underscoring the benefit of timely intervention. **Keywords**: Primary hyperaldosteronism, secondary hypertension, stroke, adrenalectomy.

047

## A Rare Case Medullary Thyroid Cancer with Normal Calcitonin Level

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**Abstract**
Medullary thyroid carcinoma (MTC) is a rare neuroendocrine malignancy arising from parafollicular cells (C-cells) of the thyroid, typically characterized by elevated serum calcitonin, which serves as a key biomarker for diagnosis and monitoring. However, approximately 6% of cases represent calcitonin-negative MTC (CNMTC), which lacks elevated calcitonin levels, thereby complicating timely diagnosis and appropriate clinical management, as reported in retrospective series and systematic reviews. A 56-year-old woman presented with bilateral thyroid nodules. No other prior medical conditions were noted. She underwent total thyroidectomy, and histopathological analysis confirmed the diagnosis of classical MTC, showing characteristic features such as round-to-oval tumor cells with coarse chromatin and lymphoid follicular architecture. Postoperatively, her serum calcitonin level remained within the normal range (2.8 pg/mL). The patient did not receive chemotherapy but was managed with thyroid hormone replacement and routine nuclear medicine follow-up. Serial wholebody scintigraphy showed no evidence of recurrence or metastasis. She subsequently developed hypothyroidism, vertigo, and mild hoarseness but had no other significant comorbidities. CNMTC is a rare subtype of MTC characterized by normal serum calcitonin levels, posing significant diagnostic and monitoring challenges. In such cases, histopathology and immunohistochemistry become essential for diagnosis. The underlying mechanisms remain unclear, though tumour dedifferentiation or impaired hormone synthesis is suspected. Imaging, particularly nuclear scans, plays a key role in postoperative surveillance when biochemical markers are uninformative.
Keywords: Medullary thyroid carcinoma; Calcitonin-negative; Procalcitonin; Thyroid nodule; Histopathology.

048

## Thyroid Imaging Reporting and Data System (TIRADS) Profile in Patients with Thyroid Nodules

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**Abstract**
Evaluation of thyroid nodules using the Thyroid Imaging Reporting and Data System (TIRADS) classification system in Eastern Indonesia is still limited. This study aims to describe the TIRADS profile in patients with thyroid nodules at Prof. Dr. R. D. Kandou Hospital. Descriptive study reviewing medical records of patients who underwent thyroid ultrasonography during January-June 2024 was conducted. The characteristics assessed include TIRADS category, composition, echogenicity, nodule shape, margin, and echogenic foci. Results: A total of 177 patients were included, the majority were female 160(90.4%) and the average age was 52.41 years. Single thyroid nodules were found in 76(35.5%) patients. The most common TIRADS category was TIRADS 3 in 72(40.7%) patients. The composition of the nodule was dominated by a solid-cystic mixture in 89 (50.3%), isoechoic echogenicity in 43(24.3%), shape wider than tall in 134(75.7%), smooth margin in 91(40.9%), and nodules did not show echogenic foci in 153(86.4%) patients. The majority of thyroid nodules in patients are included in the TIRADS 2 and 3 categories. The dominant finding of smooth nodule margins in the right and left lobes, smooth margins, mixed solid-cystic nodule composition, isoechoic and hypoechoic echogenicity, and wider than tall nodule shape also support the benign profile of this population. Most thyroid nodules in patients were classified as low to moderate risk based on the TIRADS classification. These findings support the importance of using TIRADS in the non-invasive evaluation of thyroid nodules and providing a local epidemiological picture that can strengthen clinical decision-making.
**Keywords**: TIRADS, thyroid nodules, ultrasonography.

049

## A Diagnostic Pitfall Between Acinar Cell Carcinoma and Insulinoma in a Hypoglycemic Young Patient

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**Abstract**

Acinar cell carcinoma (ACC) is a rare exocrine pancreatic tumor that may morphologically resemble pancreatic neuroendocrine tumors. Misclassification can lead to overtreatment and inappropriate prognostication. Timely distinction is essential, as treatment strategies differ significantly. Clinical-pathological correlation is vital, especially when presentations are inconsistent. A 19 year old male presented with a three year history of recurrent hypoglycemia. Laboratory results showed endogenous hyperinsulinemia (insulin fasting 26.78 µU/mL, C-peptide 9.57 ng/mL). Imaging revealed mass in the pancreatic tail. Following distal pancreatectomy, initial histopathology suggested ACC based on solid nests of granular cells. However, this diagnosis was questioned due to strong clinical suspicion of insulinoma. Further immunohistochemical analysis was pursued, revealing chromogranin and synaptophysin positivity, cytokeratin 7 negativity, and a Ki-67 index <2%, confirming insulinoma. This case highlights a significant diagnostic pitfall in pancreatic tumors. Both insulinoma and ACC may exhibit overlapping histological architecture under hematoxylineosin staining. Without immunohistochemical confirmation and clinical correlation, particularly in young patients with classic Whipple's triad, misdiagnosis is possible. Given that ACC is aggressive and insulinoma is typically benign, accurate classification is critical to avoid unnecessary aggressive treatment. In this case, critical thinking in response to inconsistent pathology findings led to diagnostic correction and proper care. When histopathological results appear inconsistent with the clinical presentation, diagnostic re-evaluation is essential. This case underscores how clinical awareness, immunohistochemical support, and multidisciplinary collaboration are key to avoiding misdiagnosis and ensuring optimal outcomes.

**Keywords**: Acinar Cell Carcinoma, Insulinoma, Pancreatic neoplasm, Hypoglycemia.

050

## Burch-Wartofsky Score in a Patient with Cardiogenic Shock and Chronic Hyperthyroidism : Diagnostic Challenge

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**Abstract**

Thyroid storm is a life-threatening endocrine emergency requiring prompt diagnosis and management. Diagnosis is primarily clinical, often assisted by the Burch-Wartofsky Point Scale (BWPS). However, its use can be challenging due to symptom overlap with other critical conditions, such as cardiogenic shock. A 56-year-old man with a history of chronic hyperthyroidism presented with shortness of breath and diarrhea for two days. Initial assessment in the emergency department revealed a heart rate of 139 beats per minute and a body temperature of 38.3°C. Physical examination revealed basilar rales and electrocardiography showed atrial fibriliation. The BWPS score reached 65, raising a strong suspicion of thyroid storm. However, thyroid function tests showed a mildly elevated free T4 and a normal thyroid stimulating hormon (TSH) level. The patient was ultimately diagnosed with cardiogenic shock secondary to thyroid heart disease, rather than thyroid storm. Although a high BWPS score is suggestive of thyroid storm, the patient's thyroid profile did not support the diagnosis. This case underscores the importance of comprehensive clinical interpretation and highlights the limitations of BWPS in patients with complex cardiovascular manifestations. The use of BWPS

should be integrated with additional criteria to improve diagnostic accuracy and therapeutic decision-making. BWPS remains a useful tool in diagnosing thyroid storm; however, its application must be contextualized within the broader clinical picture, especially in patients presenting with overlapping cardiovascular features.

**Keywords**: thyroid storm, Burch-Wartofsky Point Scale, cardiogenic shock, chronic hyperthyroidism.

051

## Therapeutic potential of celastrol in diabetic nephropathy: A systematic review of in vivo and in vivo studies

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**Abstract**

It is estimated that the number of patients with type 2 diabetes mellitus will reach 439 million worldwide by 2030. Approximately 40% of diabetics develop diabetic nephropathy 10 years after diagnosis. Current medical treatment often fails to stop progression. Recent studies show celastrol (Tripterygium wilfordii) as a promising agent to prevent and slow down the progression of diabetic nephropathy This systematic review aims to understand the underlying mechanism of celastrol in diabetic nephropathy progression by pooling related articles from medical journal databases, including PubMed, ScienceDirect, Web of Science, Scopus, and ProQuest. Database searches found four in-vivo and three in-vitro studies meeting inclusion criteria. In-vivo studies found that rats with diabetic nephropathy showed decreased blood glucose, HbA1c, 24h-urinary albumin, and 24h-urinary creatinine after celasterol administration. In-vitro study showed that celastrol reduces expression of MAPK3, TNF, AKT1, and PI3K/Akt/NF-kB pathway which promoted inflammatory and fibrosis response. Another in-vitro study revealed that moderate concentration of celastrol could alleviate the changes in the cell morphology of HG-treated HK-2 cells. Celastrol could improve renal function in diabetic nephropathy and regulates blood glucose. Celastrol also improves abnormal lipid metabolism, oxidative stress and proinflammatory cytokine activity in the kidney. Celastrol affects multiple pathways, creating a renoprotective response. Celastrol improve cell viability, reduce apoptosis, decrease inflammatory cytokines, and enhance antioxidant activities. Preclinical studies show celastrol as a potential therapeutic agent in diabetic nephropathy. However, further studies are needed to confirm its efficacy and safety in humans.

052

## Correlation Between Lipid Profile And Severity Of Diabetic Foot Ulcers

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**Abstract**

Diabetic foot ulcer (DFU) is a cause of morbidity and mortality due to diabetes. There are several risk factors for DFUs, such as peripheral neuropathy, peripheral vascular disease, deformity, and trauma. The risk of developing diabetic ulcers in patients with diabetes mellitus is 19-34%. This study aims to identify the lipid profile in DFU patients and assess its correlation with the Wagner ulcer grade classification. This study is a cross-sectional, retrospective study using a total sampling approach to analyze the medical records of DFU patients treated at Dr Moewardi Hospital in December 2024 with various degrees of severity. All DFU patients had HDL (High-Density Lipoprotein) levels below normal, with a mean of 23.7 ± 1.8 mg/dl. The mean LDL (Low-Density Lipoprotein) level of DFU patients was relatively low at 82.96 ± 7.6 mg/dl. The mean LDL/HDL ratio of DFU patients was 3.8 ± 0.3. Statistical tests showed no significant relationship between LDL, HDL, LDL/HDL ratio, and triglycerides with the severity of DFU based on Wagner classification. HDL has an atheroprotective effect by exerting anti-inflammatory effects and protects against oxidative damage by inactivating lipid hydroperoxides. This study showed that a decrease in HDL occurred in all DFU patients. Increased LDL and Triglycerides are associated with DFU severity, but this study did not show significant results.3-5 Conclusion. DFU patients had low HDL levels. There was no significant association between LDL, HDL, Triglyceride, and LDL/HDL ratio with the severity of DFU.

053

## Hypoparathyroidism Presenting as Recurrent Seizures: A Case Report

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**Abstract**

Chronic hypocalcemia secondary to hypoparathyroidism may present with diverse clinical manifestations, ranging from mild neuromuscular symptoms to more severe neurological and psychiatric disturbances. The absence of head and neck surgery in primary hypoparathyroidism poses a diagnostic challenge, particularly when accompanied with neuropsychiatric features such as seizures and hallucinations. A 29 year old woman was brought to the emergency department with generalized seizures. She had a prior history of hospitalization due to hypocalcemia, without any history of head and neck surgery. Laboratory evaluation revealed severe hypocalcemia (5.5 mg/dL), hyperphosphatemia (5.5mg/dL), and low parathyroid hormone levels (<6 pg/mL). Electrocardiography (ECG) showed prolonged QT interval, and non-contrast head CT scan revealed bilateral basal ganglia calcifications. The patient's condition improved and remained seizure free following calcium correction and vitamin D supplementation. The pattern of biochemical, ECG, and neuroimaging abnormalities pointed toward a chronic metabolic etiology consistent with unrecognised primary hypoparathyroidism. Given the absence of surgical history, idiopathic or syndromic causes such as DiGeorge syndrome were considered. The patient's clinical improvement following prompt metabolic correction highlighted the endocrine basis of the symptoms. Hypocalcemia due to primary hypoparathyroidism can mimic neurological or psychiatric disorders. Electrolyte and parathyroid function assessment should be considered in patients with unexplained seizures, particularly when accompanied by intracranial calcifications suggestive of metabolic etiology.

**Keywords:** Hypocalcemia, Hypoparathyroidism, Vitamin D, Seizures.

054

## Impact of a Giant Meningothelial Meningioma: Anterior PituitarySuppression, Hypothyroidism and Bitemporal Hemianopsia

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**Abstract**

Meningioma is the most common primary brain tumor, typicallybenign and slow-growing. One subtype, meningothelial meningioma (WHOGrade I), accounts for approximately 60% of all cases. Suprasellar tumors cancompress the anterior pituitary and optic chiasm, potentially causingpanhypopituitarism and visual disturbances. Case Illustration: We report a case of a 45-year-old woman with a one-year history of severe headache accompanied by nausea and vomiting. She alsoexperienced bilateral visual field narrowing for the past nine years andamenorrhea for 15 years. Physical examination revealed bitemporal hemianopsiaand headache with a VAS score of 8. Laboratory tests showed primaryhypothyroidism (TSH 10.43 µIU/ml; FT4 7.04 pmol/l), secondaryhypocortisolism (morning cortisol <1 µg/dl; ACTH 15.3 pg/mL), secondary amenorrhea (FSH 0.89 mIU/mL; estrogen <9.77 pg/mL), and prolactin level of 22.00 ng/ml. Head CT and MRI revealed a pituitary macroadenoma (6.1 x 4.5 x 6.1 cm. Histopathological examination confirmed a meningothelial meningioma, WHO Grade I. Treatment included hydrocortisone 20mg-0-0, levothyroxine 100mcg daily, and supportive therapy, followed by linear accelerator radiotherapy and surgical tumor excision. This case illustrates the endocrine and visual impact of a large suprasellar tumor, leading to compression of the anterior pituitary and resulting in hormonal disturbances. Bitemporal hemianopsia reflects compression of the optic chiasm. Delayed diagnosis can worsen functional deficits, therefore comprehensive endocrine and neuro-ophthalmologic evaluation is essential in such patients. Although benign, large meningiomas can cause significant functional deficits. Early diagnosis, hormonal evaluation, and a multidisciplinary

approach are essential for preventing complications and improving outcomes.

**Keywords**: meningothelial meningioma, secondary hypocortisolism, pituitary compression, bitemporal hemianopsia, hypopituitarism

055

## Neutrophil and Platelet to Lymphocyte Ratios in Hashimoto's Thyroiditis: A Systematic Review and Meta-Analysis

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**Abstract**

Hashimoto's thyroiditis (HT) is an inflammatory condition that affects the thyroid gland, ranging from euthyroidism to hypothyroidism. Recently, the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have become increasingly useful as predictive markers in patients with inflammatory conditions but their clinical significance in Hashimoto's thyroiditis remains unclear. This study aimed to investigate the association between NLR and PLR in Hashimoto's thyroiditis. We conducted an updated systematic review and meta-analysis of studies identified in systematic searches of PubMed, Scopus, and ScienceDirect database (through June 2025). The meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Outcomes of interest include NLR and PLR. Data analysis was conducted using Review Manager 5.4. Results This meta-analysis incorporated seven articles including 2122 patients (1074 controls, 691 euthyroid HT, 357 hypothyroid HT). Compared to healthy control, hypothyroid HT and euthyroid HT had significantly higher NLR (WMD 0.25 [p=0.09], WMD 6.34 [p= 0.65]). Discussion The limitations including high heterogeneity, different number of samples for each group might hinder clear interpretation. NLR and PLR may serve as potential indicators of systemic inflammation in patients with both hypothyroid and euthyroid HT. However, further validation through more high-quality clinical randomized trials is required.

056

## Effectiveness and Safety of Myo-inositol and D-chiro-inositol in the Prevention of Gestational Diabetes Mellitus in High-Risk Patients: A Literature Review

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**Abstract**

Myo-inositol and D-chiro-inositol have emerged as potential preventative therapies for gestational diabetes mellitus in high-risk populations. Gestational diabetes mellitus (GDM) is a common metabolic disorder during pregnancy, especially among high-risk patients. Supplementation with myo-inositol and D-chiro-inositol is effective in enhancing insulin sensitivity and reducing the incidence of gestational diabetes. This literature review aims to evaluate the current evidence on the effectiveness and safety of myo-inositol and D-chiro-inositol supplementation in preventing GDM among high-risk patients. The study used scientific articles from PubMed, Google Scholar, and Elsevier for studies published between 2021 and 2025. Eligible studies included randomised controlled trials, cohort studies, systematic reviews, and meta-analyses involving high-risk women receiving myo-inositol, D-chiro-inositol, or both and compared with standard care. Treatment with myo-inositol (1.1 g) and d-chiro-inositol (27.6 mg) in the first trimester does not significantly reduce the incidence of GDM in high-risk patients. In another study, giving 1.75 mg myo-inositol and 200 mg d-chiro-inositol prevented the onset of maternal GDM and macrosomia in newborns. A review of existing research found that myo-inositol and D-chiro-inositol supplementation may improve glucose metabolism in high-risk women, although myo-inositol and D-chiroinositol have different modes of action. Treatment with myoinositol and d-chiro inositol at the recommended dose can minimise the incidence of GDM in patients with high risk factors while having no adverse effects on the mother or newborn.


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