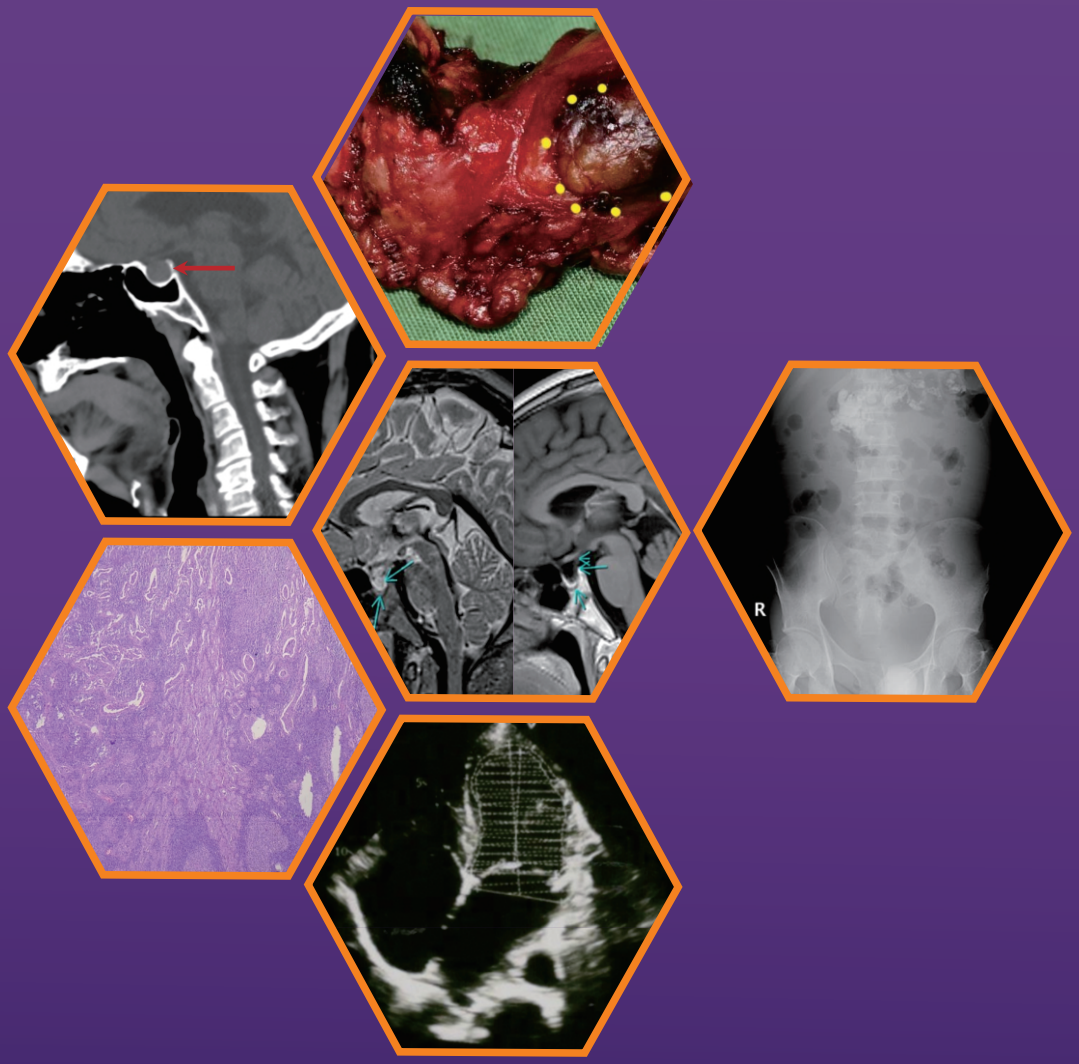
Volume 2 ¦ No. 2 ¦ December, 2025

eISSN 3048-3271
pISSN 3063-1408

InaJEMD

Indonesian Journal of Endocrinology Metabolism and Diabetes



Published by The Indonesian Society of Endocrinology
Official Journal of The Indonesian Society of Endocrinology

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes
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Outcome of Graves' Disease Patients Treated with Radioactive Iodine Therapy at RSCM: Preliminary Study

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ABSTRACT

Introduction: Graves' disease (GD) constitutes 60-80% of all cases of thyrotoxicosis worldwide, typically managed with anti-thyroid drugs (ATD) as first-line therapy. If a patient failed to achieve remission after 18 months or had an ATD allergy, can continue to choose radioactive iodine (RAI^{131}) as definitive therapy. Research on the use of RAI in GD remains limited in Indonesia, and nuclear medicine facilities are not yet widely distributed.

Aim: To assess the treatment outcome of fixed-dose RAI^{131} 10 mCi and the contributing factors involved.

Methods: This was a retrospective observational study involving 10 GD patients who underwent RAI at RSCM. Secondary data were collected consecutively from medical records. The outcome study was the prevalence of hypothyroidism in the 3rd and/or 6th month following RAI. Serum free T4 and TSHs levels were evaluated at baseline, and at 3, 6, and 12 months post-RAI. Inclusion criteria consisted of GD patients who failed to achieve remission with ATD and subsequently underwent RAI at the Department of Nuclear Medicine, RSCM.

Results: At 3 months post-RAI^{131}, 40% of subjects achieved hypothyroidism, 40% had subclinical hyperthyroidism, and 20% reached euthyroid status. At 6 months, 80% of subjects remained with subclinical hyperthyroidism, 10% experienced worsening hyperthyroidism and 10% had developed permanent hypothyroidism. No worsening of Graves' ophthalmopathy (GO) was observed during the study period.

Conclusion: RAI^{131} is a safe and effective definitive treatment for GD. Nevertheless, good interdisciplinary collaboration is essential to ensure the successful hypothyroidism achievement as primary therapeutic goals.

Keywords: Graves' disease, hyperthyroidism, radio-active iodine

INTRODUCTION

Graves' disease (GD) is one of the most common endocrine pathologies.[1] As an organ-specific autoimmune thyroid disorder, it's characterized by typical clinical manifestations named Merseburger trias: diffuse goiter, thyrotoxicosis and ophthalmopathy.[2,3] And the diagnoses are made based on signs, symptoms, and the result of the ancillary laboratory tests.[3]

GD prevalence is around 60-80% of hyperthyroidism cases. Data from Cipto Mangunkusumo Hospital (RSCM), a national referral hospital, indicates that GD prevalence among all thyroid issue cases was 21% in 2004, and is projected to have grown since then. And the pathogenesis is caused by hyperfunction of the thyroid gland, which results in thyrotoxicosis and enlargement of the thyroid gland. GD often recurs, resulting in a longer duration of treatment.[3,4] Therefore early diagnosis and management of Graves' disease can prevent severe complications such as atrial flutter, atrial fibrillation, high output cardiac failure and Graves' ophthalmopathy (GO).[5,6]

Clinicians ought to be aware of systemic manifestations of Graves' disease and the different modalities available for treatment.[6] There are 3 modalities, namely anti-thyroid drugs (ATD), radioactive iodine (RAI), and thyroidectomy.[4] The choice is based on several factors such as patient age, goiter volume size, availability of modalities, response to therapy and other comorbidities.[7] In Indonesia GD is usually managed initially with ATDs, such as propylthiouracil (PTU) or Methimazole (MMI). Remission achieved in approximately half of patients after a 12–18 month duration of treatment, although it occurs in only 20-25% GD patients.[2,4,8] Patients with persistently high TSH receptor antibody (TRAb) at 12–18 months can continue ATD for the next 12 months, or choose for definitive therapy with RAI or thyroidectomy. RAI has the advantage of being non-invasive and relatively safe for all ages.[8] And its main purpose is to treat hyperthyroidism by creating hypothyroidism condition through sufficient radiation dose to reach the thyroid tissue.[2]

Nuclear medicine has not been utilized optimally in Indonesia. Currently, nuclear medicine facilities are only available at 17 hospitals from 11 provinces of Indonesia, and more than half of them are in Jakarta. There are already around 60 nuclear medicine specialists in Indonesia, and may need to be increased.[9] Furthermore there are few research on the use of RAI in GD pretreated ATD in Indonesia. This preliminary study aim to assess the outcome treatment of fixed dose RAI^{131} 10 mCi and evaluate the factors that play roles in 10 GD patients underwent RAI at Cipto Mangunkusumo General Hospital.

METHOD

This study is a retrospective observational analysis involving 10 GD subjects who failed to achieve remission with ATD and subsequently underwent RAI at RSCM as tertiary hospital. Secondary data were collected consecutively from patient medical records. Subjects previously treated with ATD were asked to stop therapy five days before RAI. All subject were given fixed 10 mCi dose of RAI as standard treatment in our hospital and follow-up was performed at 3 months, 6 months and 12 months after. The outcome of this study was the prevalence of hypothyroid conditions in the 3th and/or 6th month after RAI. Inclusion criteria were GD patients who underwent RAI therapy at the Department of Nuclear Medicine RSCM. Successful treatment was considered when subjects achieved hypothyroid (FT4 level range < 0,7 ng/dL or TSHs level range > 5 uIU/mL) condition in the 3th to 6th after RAI [4]. The collected data were then displayed in the form of graphs and tabulations.

RESULT

Table 1. Characteristic data study

Variable (n=10)	Median (min-max)
Age, years	48.5 (20-59)
Uptake Thyroid Scan	34.3 (7,8-64,1)
Thyroid volume (n=8, cc)	32.3 (25,7-78,5)
TRAb (n=5)	23.6 (1,32-40)

Around 10 subjects with GD were enrolled in this preliminary study (80% female, and 20% male) as seen on table 1, all male involved having smoking habits and similar GO prevalence was seen in smoking variables. TRAb data obtained before RAI in 5 subjects with high average, and only 1 normal TRAb subject present with mild inactive GO. By 6 months RAI therapy, 20% subject start required levothyroxine (LT4) therapy, 60% decrease ATD doses, and 10% remaining increased dose. Overall in 3 months follow-up 40% of subjects obtained hypothyroidism targets, 40% subclinical hyperthyroidism and 20% reached euthyroid status. And during 6 months 80% subclinical hyperthyroidism, 10% worsening hyperthyroidism and 10% permanent hypothyroidism. No worsening of GO was observed during the study period. One subject with severe inactive GO at baseline showed no deterioration of ophthalmic symptoms throughout the 12-month evaluation.

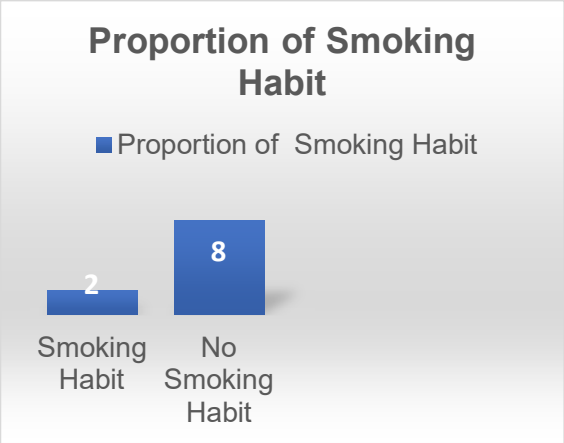

Figure 1. Proportion of smoking habit

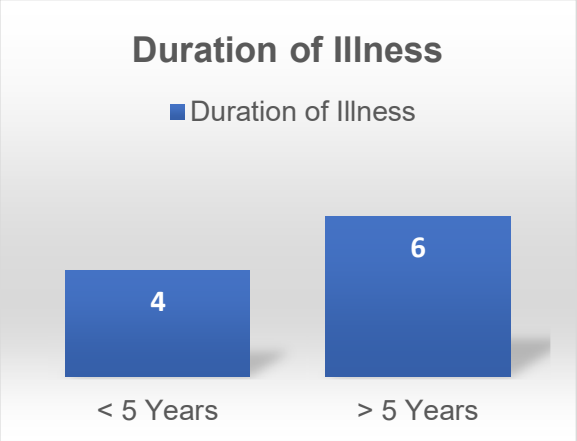

Figure 2. Duration of illness

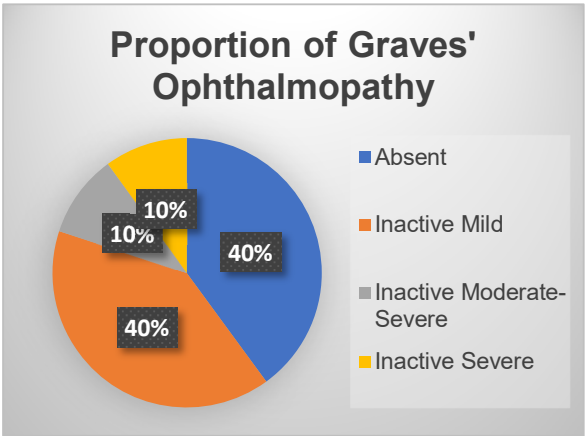

Figure 3. Proportion of Graves' ophthalmopathy

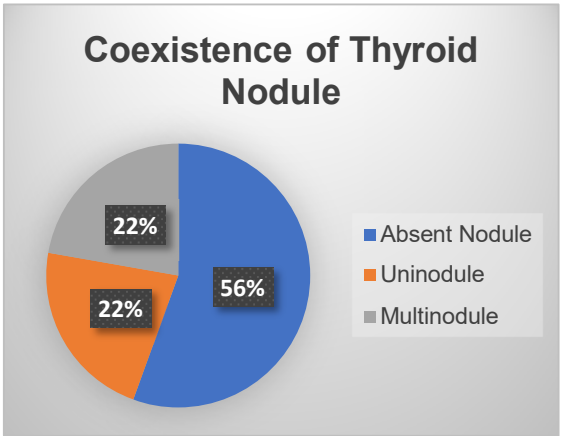

Figure 4. Coexistence of thyroid nodule

DISCUSSION

Graves' disease occupies an important position considering that it accounts for 50-80% of hyperthyroidism cases.[10,11] GD is an organ-specific autoimmune disease leading to thyrotoxicosis and goiter as main clinical feature.[2,10] The prevalence is 20–30 annual cases per 100,000 individuals with peak incidence among aged 30–60 years.[4,10] GD occurs more often in women and has a population prevalence of 1–1.5%.[8] Study at RSCM in 2004 showed GD prevalence of hyperthyroidism cases from all thyroid problems were 21%.[2] Around 8/10 samples were female with median age 48 involved in this study, in tune with GD predominance in middle-aged women.

TRAb has 99% sensitivity and specificity.[5] It is a rapid and accurate diagnostic tool for Graves' hyperthyroidism. High TRAb level is also one of prognostic for posttherapy flare-up.[8] Around 4/5 samples data of this study showed TRAb level > 1.75 which confirmed high disease activity status, and failed to convert at 6 months follow up. The remaining subject showed a low result that can be found in very mild GD. According to European Thyroid Association (ETA) guideline, there are no absolute indications for RAI therapy, but it is often recommended for patients with side-effects to or recurrence after a course of ATD.[5,8] Some clinical situations that favor RAI including ATD allergy, patients with periodic thyrotoxic hypokalemic paralysis, or cardiac problem.[4] It also may be considered for long standing GD (> 10 years) with small to medium goiter and inactive GO.[5] In our study almost all sample are indicated due to failed after > 18 months pretreated ATD, and only 1 subject with ATD allergy. And in line with preparation before the procedure, ATD therapy needs to be stopped 5-7 days before and may continue after in order not to decrease its efficacy.[8]

RAI efficacy has been reported in various studies ranging between 50-90% after single therapeutic dose.[2] RAI therapy success rate depend on some factors such as uptake scan, thyroid gland size, male, elderly, smoking habit, and previous ATD treatment.[5] In our study, successful outcome obtained in 40% subjects during 3 months post exposures while only 10% subject achieved permanent hypothyroidism with LT4 supplementation in 6 months. The cure rate is lower than the reported by Mohamadien et al, Yang et al, De Jong et al, and Karyampudi et al (79,7% ; 76%; 74%; 61,1% respectively).[2,12,13,14] The possible discrepancy causes are small sample size, lower fixed-dose given and delayed second dose administration. Proven by 3 among 9 failed subjects received second RAI after > 9 months follow-up obtained persistent hypothyroidism with LT4 supplementation. European Association of Nuclear Medicine (EANM) guideline stated higher fixed-dose may be required when the thyroid volume > 40 cc, high TRAB level, male, younger age and smoker.[5] If hyperthyroidism persists after 6 months, then a repeat RAI treatment may be needed.[6] Large thyroid volumes and high uptake are positively associated with recurrent hyperthyroidism following RAI therapy. Higher success rates can be achieved when account is taken of these poor prognostic factors.[13] Therefore good interdisciplinary collaboration is needed to maximize this goal, that all physicians engaged in therapy must be knowledgeable and incompliance with applicable law and regulations.[15] And patient need to be informed prior to aim and strategy of RAI, and final functional outcome including possible subsequent retreatment.[5]

There are 2 concepts for RAI therapy, functional dose concept which is correct subclinical or overt hyperthyroidism by reaching euthyroidism as soon as possible, and ablative dose concept to achieve hypothyroidism as soon as possible. But to date, EANM guideline favor the implementation of the ablative dose

concept for all GD patients due to unsatisfactory long-term outcome of GD patients treated with functional dose concept, that resulting in a higher incidence of recurrent hyperthyroidism and the risk of possible GO worsening.[5] Along with this, SNMMI guideline also denoted that decreasing the administered therapeutic activity in an effort to achieve euthyroidism can lead to prolongation of hyperthyroidism with adverse clinical sequelae.[15]

So far there is no general consensus on the determination of I^{131} dose or standardization.[12,15] Meanwhile several studies also have shown comparable results of RAI in fixed-dose and calculated dose.[14] Fixed-dose regimen commonly in range 5-15 mCi, have the advantage of being more simple, more convenient and lower cost. While calculated-dose using 3 factors influencing therapeutic RAI activity: the RAI uptake, the thyroid size and the radiation quantity. In patients without adjunctive ATD, randomized controlled trials found 74% success with 10 mCi (370 MBq), 81% with 15 mCi (555 MBq), and 86% with 15.7 mCi (580 MBq) RAI. [4,16] In one of ETA recommendations stated no dose calculation can secure long-term euthyroidism and it's fully acceptable to offer a fixed dose of RAI.[8] Higher administration dose especially suitable for patient with nodular goiter, very large toxic diffuse goiter.[15]

Most patients respond to RAI therapy with a normalization of thyroid function tests (TFT) and improvement of clinical symptoms within 4-8 weeks. Hypothyroidism may occur from 4 weeks on, with 40% of patients being hypothyroid by 8 weeks and >80% by 16 weeks. This transition can occur rapidly but more commonly between 2 and 6 months, and the timing of thyroid hormone replacement therapy should be determined by results of TFT, clinical symptoms, and physical examination. Transient hypothyroidism following RAI therapy can manifest in 2-5 months after therapy, with subsequent complete recovery of thyroid function or recurrent hyperthyroidism.[4,5] Differentiating between transient and permanent hypothyroidism in the early months following RAI therapy remains a clinical puzzle that requires adequate clinical and laboratory follow-up to establish the optimal treatment plan, especially for GD patients with orbitopathy.[5]

RAI can have side effects including transient thyrotoxicosis, neck discomfort due to radiation-induced thyroiditis, sialadenitis, dysgeusia, permanent hypothyroidism, and new onset or worsening of Graves' ophthalmopathy. It is contraindicated in pregnant and lactating women.[10] RAI is well tolerated and complications are rare, except for those related to orbitopathy. Nwatsock et al found that RAI was associated with 3.7% of GO occurrence mainly in those who developed an early (1-2 months after RAI) and prolonged (1-4 months) hypothyroid period.[16] In our study, baseline ophthalmopathy did not affect the rates of hypothyroidism after RAI. One subject was enrolled with severe inactive GO, and did not show any deterioration of ophthalmopathy during 12 months evaluation. This was in concordance with Pamnani et al study, the same reason is one subject had already been pretreated with corticosteroid before.[16] Further studies, including larger prospective or retrospective cohorts, are needed to better understand the clinical outcomes of GD after RAI treatment, as well as to assess their post-treatment quality of life.

CONCLUSION

RAI is a safe and effective definitive treatment for GD. Nevertheless, good interdisciplinary collaboration is essential to ensure the successful hypothyroidism achievement as primary therapeutic goals.

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ORIGINAL ARTICLE

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Indonesian Journal of Endocrinology Metabolism and Diabetes

Triglyceride-Glucose Index as a Predictor of Diabetic Foot Ulcer Severity in Type 2 Diabetes Mellitus: Cross-Sectional Study

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ABSTRACT

Introduction: Diabetic foot ulcers are a complication of type 2 diabetes mellitus that has a high global prevalence. Insulin resistance in type 2 DM patients tends to cause chronic wounds and can delay wound healing. TyG index is currently used as a surrogate biomarker to evaluate insulin resistance because it is easy to perform and low cost.

Methods: Analytic observational research with a cross-sectional approach at Diabetic Foot Poly Ulin Hospital Banjarmasin. The study sample was all patients diagnosed with type 2 DM and undergoing wound care at the Diabetic Foot Polyclinic of Ulin Hospital Banjarmasin starting in December 2024 who met the inclusion and exclusion criteria with a total of at least 74 people. Data analysis was performed with a simple binomial logistic regression test to estimate crude Prevalence Odds Ratio (POR) with 95% confidence intervals, and multiple binomial logistic regression tests were performed to estimate adjusted POR and 95%CIs.

Results: Compared with the lowest one-third TyG Index score, study subjects with the middle one-third TyG Index score were associated with a lower risk of severe diabetic foot ulcer incidence by 85.9% (Adj POR 0.141, 95% CI: 0.011-1.802). Subjects with the highest third TyG Index value were also associated with a lower risk of diabetic foot ulcer incidence of 87.1% (Adj POR 0.129, 95%CI: 0.008-1.959). The mean value of TyG Index+SD was 4.8872 + 0.4230 at severe foot ulcers.

Conclusion: TyG index is not a predictive factor for the severity of diabetic foot ulcers in type 2 DM patients at the Diabetic Foot Clinic of Ulin Hospital Banjarmasin ($p>0.05$).

Keywords: TyG index, type 2 DM, diabetic foot ulcers

INTRODUCTION

Diabetic foot ulcers are complications of type 2 diabetes mellitus (DM) that usually occur due to neuropathy and peripheral arterial disease with a high global prevalence. The occurrence of diabetic foot ulcers stems from the interaction between impaired tissue regeneration, vasculopathy, neuropathy, and inflammation caused by insulin resistance. Insulin resistance is a condition in which insulin exerts a lower biological effect than expected in both experimental and clinical settings.[1-4]

The global prevalence of diabetic foot ulcers is 6.3%. Nearly 15% of type 2 DM patients suffer from foot ulcers and the amputation rate of type 2 DM patients is 15 to 40 times higher than the general population. Diabetic foot ulcers are more common in men than women. Patients with diabetic foot ulcers have a lower body mass index, longer duration of diabetes, and more with a history of smoking than patients without diabetic foot ulcers. Previous studies have shown that insulin resistance is one of the important risk factors for cardiovascular diseases, such as hypertension, vascular stiffness, and is associated with the development of atherosclerosis.[1,3,5,6]

Individuals with insulin resistance tend to experience several metabolic abnormalities, such as hyperglycemia, dyslipidemia, and hypertension, all of which are strongly associated with cardiovascular disease. Currently, there is no specific method for accurate determination of insulin resistance. The gold standard euglycemic insulin clamp and intravenous glucose tolerance testing are invasive and expensive and, although used in academic studies, are not applied in clinical practice. Homeostasis model assessment insulin resistance (HOMA-IR) index is widely used today but has limited value in subjects receiving insulin treatment or those without functioning beta cells. To overcome these limitations, the TyG index was developed and shown to be superior to HOMA-IR in assessing insulin resistance in individuals with and without diabetes. According to previous studies, the TyG index is a simple, easy, and low-cost surrogate, does not require insulin quantification, and can be used in all subjects regardless of their insulin treatment status.[7]

Previous research on the relationship between TyG Index and the severity of diabetic foot ulcers was conducted by Zhang et al in 2023 at Wenzhou University Hospital China.[8] This study was conducted at Diabetic Foot Poli Ulin Hospital Banjarmasin with different population and demographics from previous studies. As far as the author's research is concerned, this research is the first research conducted at Ulin Hospital, Banjarmasin.

RESEARCH METHODS

Design

This research design is analytical observational research with a cross-sectional approach. This study was conducted at the Diabetic Foot Polyclinic of the Regional General Hospital Ulin Banjarmasin starting in December 2024 until the minimum sample size was met. Minimum sample at least 74 people. Inclusion Criteria: Patients diagnosed with type 2 DM with diabetic foot ulcers who seek treatment at the Diabetic Foot Clinic of Ulin Hospital Banjarmasin, Patients with age >18 years and Patients agree to participate in the study as evidenced by the signature on the informed consent sheet. Exclusion Criteria: Patients with type 1 DM or other types of DM with diabetic foot ulcers who seek treatment at the Diabetic Foot Clinic of Ulin Hospital Banjarmasin. This research has a Medical and Health Research Ethics Committee of FKIK ULM No.242 /KEPK- FKIK ULM/EC/ XII/2024, a certificate of ethical feasibility of research from RSUD Ulin Banjarmasin No.194/ XII-Reg Research/RSUDU/24, and a research permitNo.188/PPDS.IPD/Litbang/RSUDU/ XII/2024 dated December 28, 2024.

Table 1. The samples were classified according to wagner's criteria:[9]

Wagner's Classification	
Grade 0	The skin is intact but the bone abnormalities cause "risky feet."
Grade 1	Superficial ulcers
Grade 2	Deeper, with full thickness extension
Grade 3	Deep abscess formation or osteomyelitis
Grade 4	Partial gangrene of the forelegs
Grade 5	Extensive gangrene

The incidence of diabetic foot ulcers is categorized into 2 groups:[8]

1. Mild-Moderate: Wagner 0-2
2. Heavy (Severe): Wagner 3-5

The cutoff point for the TyG Index as a marker of insulin resistance is ≥ 4.5.[10]

Variable Identification

a. Independent variable: TyG index
b. Dependent variable: severity of diabetic foot ulcers
c. Confounding variables: age, gender, BMI, smoking habits, duration of suffering from DM, use of oral antihyperglycemic therapy and/or insulin, and antilipid therapy.

Data Analysis

All statistical analyses were performed using IBM SPSS version 27 statistical software. Data analysis was performed with a simple binomial logistic regression test to estimate crude Prevalence Odds Ratio (POR) with 95% confidence intervals, and multiple binomial logistic regression tests were performed to estimate adjusted POR and 95%CIs.

RESULT

Table 2. Baseline characteristics of study participants (n = 74)

Characteristics	Total n (%)
Age, mean (year, ± SD)	56.31 ± 9.12
Gender	
Male	32 (43.2)
Female	42 (56.8)
IMT	
Underweight	0 (0,0)
Normal	28 (37.8)
Overweight	18 (24.3)
Obesity	28 (37.8)
Smoker	
Yes	17 (23.0)
No	57 (77.0)
DM duration	
≤10 years	53 (71.6)
>10 years	21 (28.4)
Antihyperglycemic therapy	
Oral	18 (24.3)
Insulin	48 (64.9)
Combination	8 (10.8)
Antilipid	
Yes	41 (55.4)
No	33 (44.6)
Triglyceride	
Normal (<150 mg/dl)	52 (70.3)
Borderline (150-199 mg/dl)	11 (14.9)
High (>200 mg/dl)	11 (14.9)
Fast Blood Glucose	
Low (< 70 mg/dl)	4 (5.4)
Normal (70-125 mg/dl)	23 (31.1)
High (> 126 mg/dl)	47 (63.5)
HbA1C Level	
No data	32 (43.24)
HbA1C < 7,0	12 (16.22)
HbA1C ≥ 7,0	30 (40.54)

Table 2 shows that the average age of type 2 DM patients with diabetic foot ulcers involved in this study was 56.31 years (± 9.12). Female gender is more than male gender 42 people vs 32 people (56.8% vs 43.2%). Normal BMI and obesity (37.8%), overweight (24.3%) and none of the research subjects were underweight. Most of the study subjects did not smoke (77.0%) and had DM <10 years (71.6%). Most of the research subjects used antihyperglycemic therapy in the form of insulin (64.9%) and used antilipid therapy (55.40%). Most of the research subjects had normal triglyceride levels (70.3%). Most of the research subjects had high fasting glucose levels as 47 people (63.5%). Most of the research subjects had HbA1C levels > 7.0, as many as 32 people (40.54%).

Table 3 shows the bivariate analysis between the independent variables and other influencing variables with the dependent variable (severity of diabetic foot ulcers). For data with a numerical scale, namely age, a normality test was first performed using the Kolmogorov Smirnov statistical test p<0.05. This indicates that the data is normally distributed. Furthermore, an

Table 3. Association between TyG Index and diabetic foot ulcer severity

Characteristics	Classification of Diabetic Foot Ulcers (Wagner)		*p-value*
	Mild-Moderate (n =52)	Heavy (n= 6)	
Age, mean (year, ± SD)	**57,53 ± 9,11**	**51,88 ± 7,93**	**0,027[a]***
Gender			
Male	23 (71,9)	9 (28,1)	0,236[b]
Female	35 (83,3)	7 (16,7)	
BMT			
Underweight	0 (0,0)	0 (0,0)	<0,001[b]*
Normal	23 (82,1)	5 (17,9)	
Overweight	8 (44,4)	10 (55,6)	
Obesity	27 (96,4)	1 (3,6)	
Smoker			
Yes	12 (70,6)	5 (29,4)	0,502[c]
No	46 (80,7)	11 (19,3)	
DM duration			
≤10 years	39 (73,6)	14 (26,4)	0,132[c]
>10 years	19 (90,5)	2 (9,5)	
Antihyperglycemic therapy			
Oral	16 (88,9)	2 (11,1)	0,938[d]
Insulin	35 (72,9)	13 (27,1)	
Combination	7 (87,5)	1 (12,5)	
Antilipid			
Yes	33 (80,5)	8 (19,5)	0,632[b]
No	25 (75,8)	8 (24,2)	
Triglyceride			
Normal (<150 mg/dl)	39 (75,0)	13 (25,0)	0,966[d]
Borderline (150-199 mg/dl)	9 (81,8)	2 (18,2)	
High (>200 mg/dl)	10 (90,9)	1 (9,1)	
Fast Blood Glucose			
Low (< 70 mg/dl)	4 (100,0)	0 (0,0)	1,000[d]
Normal (70-125 mg/dl)	17 (73,9)	6 (26,1)	
High (> 126 mg/dl)	37 (78,7)	10 (21.3)	

Notes: *= statistically significant; a= unpaired t-test; b= Chi-square test; c= Fisher-exact test; d= Kolmogorov-Smirnov test; SD=...; BMI= Body Mass Index; DM= Diabetes Mellitus

Table 4. Association between TyG index and diabetic foot ulcer severity (logistic regression model)

TyG Index Category	Mild–Moderate DFU n (%)	Severe DFU n (%)	Adjusted POR (95% CI)	p-value
Lowest tertile (T1)	5 (71.4)	2 (28.6)	1.00 (Reference)	-
Middle tertile (T2)	39 (78.0)	11 (22.0)	0.141 (0.011–1.802)	0.132
Highest tertile (T3)	14 (82.4)	3 (17.6)	0.129 (0.008–1.959)	0.140

Adjusted for age, sex, BMI, smoking status, duration of diabetes, and medication use. DFU: diabetic foot ulcer; POR: prevalence odds ratio.

Table 5. Table of the relationship of tyg index values with the incidence of diabetic foot ulcers according to wagner

TyG Index	Classification of diabetic foot ulcers (Wagner)		Relationship between TyG index and diabetic foot ulcers			
	Mild-moderate (n=58)	Heavy (n=16)	Crude POR (95%CI)	p-value	Adj.* POR (95%CI)	p-value
TyG index, mean ± SD	4.8872 ± 0.4230	4.7881±0,3676	0.994 (0.980-1.008)	0.393	0.987 (0.969-1.004)	0.133

Adj. = Adjusted; CI = Confidence Interval; POR = Prevalence Odds Ratio; SD= Standard Deviation
*Adjusted for age, gender, BMI, smoking status, duration of DM, use of antihyperglycemic and antilipid medications.

unpaired t-test was conducted and the two- sided pvalue = 0.027 (<0.05). This indicates that the mean age of the study sample in mild moderate foot ulcers and severe foot ulcers is statistically significantly different.

Tables 3 and 4 show the results of bivariate and multivariate analyses of the association between TyG index and severity of diabetic foot ulcers using binomial logistic regression to estimate crude PORs and 95% CIs. A multiple binomial logistic regression test was then performed by incorporating confounding variables into the analysis, to adjust for conventional risk factors.

Table 3 shows the estimated Odds Ratio for the incidence of diabetic foot ulcer severity in patients with TyG Index one- third highest (T3) and one-third middle (T2), compared with one-third lowest (T1). Compared with the lowest one-third TyG index value, study subjects with the middle one-third TyG Index value were associated with a lower risk of severe diabetic foot ulcer incidence by 85.9% (Adjusted POR 0.141, 95% CI: 0.011-1.802). Study subjects with the highest one-third TyG Index score were also associated with a lower risk of diabetic foot ulcer incidence of 87.1% (Adjusted POR 0.129, 95%CI: 0.008-1.959). However, this association of severe diabetic foot ulcer incidence with both TyG Index values 2 and 3 was not statistically significant when compared to the association of severe diabetic foot ulcer incidence in patients with TyG Index value 1.

DISCUSSION

In this study, the average age of research subjects was 56.31 ± 9.12 years. In accordance with several previous studies such as that conducted by Hicks et al (2020), the incidence of diabetic foot ulcers mostly occurs at the age of 50 years and over (average 59.2 years). However, this is also related to the duration of DM, the cumulative effect of hyperglycemia, and the high prevalence of macro and microvascular complications in this age range.[11,12]

In this study, female gender was more than male gender, in line with the results of research conducted by Deltty A et al (2020), that women in physical activity tend to move less and use less glucose. Insulin resistance is exacerbated when activity is lacking, and glucose intake increases. This involves AMPK (AMP- activated protein kinase) which does not work properly which will cause women to tend to be at higher risk of developing type 2 DM compared to men. In the process of pregnancy there is also an increase in insulin resistance, so women tend to suffer more from type 2 DM than men. This is different from previous studies by Hicks et al (2020) and Roosboth et al (2020) where men experience more type 2 DM than women. Other risk factors such as blood sugar control status and other complications may also contribute to this difference.[12-15]

Several previous studies have shown that BMI is associated with abnormalities in the distribution of pressure on the surface of the soles of the feet both on the front, middle and rear feet. This mostly occurs in obesity with BMI <35. This study is in line with the results of research by Ananta et al (2023) which showed that most people with Type 2 DM have a normal BMI. This is because at the beginning of Type 2 DM, the patient's BMI will increase first, then because the muscles do not get enough glucose, the muscles cannot develop and convert glucose into energy. Fat and muscle eventually undergo lysis to meet energy needs. Insulin resistance is caused by an excess of fatty acids and proinflammatory cytokines, leading to impaired glucose transport and increased fat breakdown. Hyperinsulinemia results in vasculopathy, resulting in impaired circulation of medium and large blood vessels and limb ulcers or gangrene.[15-17]

The risk factor for smoking is also interrelated with other factors such as gender, duration of

diabetes, BMI, and duration of DM. Several previous studies have shown a link between smoking and the severity of diabetic foot ulcers in relation to peripheral neuropathy, vascular changes and wound healing. One of the mechanisms underlying these effects is oxidative stress. However, diabetic patients with foot ulcers will try to quit smoking to improve the prognosis of diabetic foot ulcers.[15,16]

For the duration of suffering from DM, most of the research subjects with DM duration < 10 years, namely 75.70%, research subjects with DM duration > 10 years, namely 24.30%. This is in accordance with several previous studies which show that diabetic foot ulcers begin to occur after patients suffer from diabetes for more than five years. Several other studies have shown that the longer diabetes, the greater the likelihood of ulcers. Previous research conducted by Safari et al (2023) showed that patients suffering from DM with recurrent diabetic foot ulcers suffered from DM for more than 10 years. Patients who suffer from DM disease for more than 10 years are risk factors that cause diabetic foot ulcers. DM patients who have suffered from DM for many years will experience vascular complications such as microangiopathy which will cause a decrease in blood circulation and then can develop as diabetic ulcers.[15,20,21]

Most of the study subjects used antihyperglycemic therapy in the form of insulin, 64.90%. Oral antihyperglycemic therapy was used in 24.30% of the study subjects, and a combination of oral antihyperglycemics and insulin was 10.80%. The use of antihyperglycemic drugs is related to the patient's blood sugar target that has not been achieved. Previous studies such as those conducted by Balakrishnan et al (2022) stated that the use of insulin in type 2 DM patients with diabetic foot ulcers showed better ulcer improvement than the use of oral antihyperglycemia.[22]

In this study, research subjects with high fasting glucose levels were 66.20%, normal fasting glucose levels were 28.40%, and low fasting glucose levels were 5.40%. Most of the research subjects still had high fasting glucose levels. This is in accordance with several previous studies, such as those conducted by Arismawati et al (2022). which shows the relationship between blood glucose levels and diabetic ulcers where high blood glucose levels can reduce blood vessel elasticity which will result in decreased distal limb tissue perfusion. High blood glucose levels are a fertile environment for the proliferation of anaerobic pathogens because blood plasma in uncontrolled DM patients has a high viscosity. [15]

Research subjects who had HbA1C levels >7.0 were 40.54%, greater than research subjects who had HbA1C levels < 7.0, namely 16.22%. This shows that most research subjects have uncontrolled blood sugar during the last three months. A total of 32 people (43.24%) of the research subjects did not have HbA1C data because the patients were anemic and there was a history of blood transfusion during treatment. Research subjects who used antilipid therapy (55.40%) were more than research subjects who did not use antilipid therapy (44.60%). Most of the research subjects had normal triglyceride levels of 66.20%, low triglyceride levels of 14.90%, and high triglyceride levels of 18.90%. Previous research by Nassaji et al (2017) showed the use of statins as a preventive for diabetic foot ulcers but based on research conducted by O'Dell et al (2024), the use of statins does not affect the healing rate of diabetic foot ulcers.[23,24]

TyG Index as a Predictive Factor of Diabetic Foot Ulcer Severity

Table 9.1 shows that research subjects with the middle third and highest third TyG Index values are associated with a lower risk of diabetic foot ulcer incidence compared to

research subjects with the lowest third TyG Index values, although it is not statistically significant. The results of this study differ from previous studies such as those conducted by Zhang et al (2023) which stated that an increase in TyG index was independently associated with the severity of diabetic foot ulcers. The subjects in this study have routinely undergone treatment and received antihyperglycemic and antilipid therapy which affects fasting blood glucose levels and triglyceride levels so that it can affect the results of this study.[8,10]

In this study, the subjects were type 2 DM patients with diabetic foot ulcers who came regularly to the diabetic foot clinic of Ulin Hospital Banjarmasin. Some underwent foot wound care twice a week and some once a week. During the treatment, changes occurred, namely the improvement of the degree of diabetic foot ulcers according to Wagner. The research subjects had also received routine therapy tailored to the patient's condition every month in the form of antihyperglycemic drugs both oral and insulin, antilipid drugs, antibiotics and other drugs according to other patient complaints such as high blood pressure drugs. This affects the results of the study, namely that some research subjects have fasting blood sugar and triglyceride levels under control, thus updating the results of the TyG index. In this study, the mean value of the TyG Index was 4.8872 (SD + 0.4230) in the classification of mild moderate leg ulcers and 4.7881 (SD + 0.3676) in the classification of severe leg ulcers, as shown in table 9.2. Based on research conducted by Salazar et al in 2017, the cutoff point for TyG Index as a marker of insulin resistance is ≥ 4.5. The results of this study show that both the classification of mild moderate leg ulcers and severe leg ulcers have an average TyG Index value ≥ 4.5 which indicates insulin resistance. Most of the research subjects had TyG Index above the cutoff value associated with the basic characteristics of this research data, namely most of the research subjects had uncontrolled fasting blood sugar levels. 63.5% of the study subjects had high fasting glucose levels. TyG Index is dynamic and may vary over time.[25]

The relationship between TyG Index and glycemic control can be explained through several mechanisms.[27] An increase in free fatty acids is caused by an increase in triglyceride levels which can have an impact on increasing the reflux of free fatty acids from adipose to non-adipose tissue thus affecting glycemic control. Several studies have reported that higher triglyceride levels in muscle and liver may affect glucose metabolism in each target organ. Insulin resistance plays an important role in the pathophysiology of type 2 diabetes; therefore, insulin resistance testing can be used as a marker of diabetes mellitus progression. In health services with limited laboratory facilities, the TyG index can be used as a substitute for predicting the development of diabetes.[26,27]

This study illustrates that by controlling fasting blood sugar levels including through the administration of oral antidiabetics, insulin, or a combination, it is possible to affect the results of the TyG index which will then reduce the risk of diabetic foot ulcers both mild moderate and severe degrees according to research by Balakrisnan et al (2023). Likewise, controlling triglyceride levels through the administration of antilipids is expected to improve the TyG index which is then expected to improve insulin resistance and reduce the risk of diabetic foot ulcers according to research.[21,24] This study has not involved other variables associated with the incidence of diabetic ulcers so that it can affect the results of research such as kidney function, albumin, physical activity of research subjects, diet and education. The subjects in this study have routinely undergone treatment and received antihyperglycemic and antilipid therapy which affects fasting blood glucose levels and

triglyceride levels so that it can affect the results of this study.[8,25]

CONCLUSION

The TyG index was not significantly associated with diabetic foot ulcer severity in Type 2 DM patients. Although it remains a practical indicator of insulin resistance, TyG alone may not predict ulcer severity in patients under comprehensive metabolic therapy. Further multicenter studies are recommended to validate these findings. It is necessary to conduct research by paying attention to other variables that have not been considered as confounding variables in this study.

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CASE REPORT

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

Unexpected Histological Finding of Diffuse Large B-Cell Lymphoma in a Patient with Long-standing Goiter and Hashimoto's Thyroiditis: A Case Report

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Background:
Primary thyroid lymphoma (PTL) is an uncommon malignancy, comprising less than 5% of all thyroid cancers. Hashimoto's thyroiditis (HT) is the most significant risk factor, increasing the risk of developing PTL by 40 to 80 times. Diffuse large B-cell lymphoma (DLBCL) is the most prevalent and aggressive histological subtype, accounting for over 50% of PTL cases. The diagnosis is challenging, as the clinical and sonographic features of PTL can mimic benign thyroiditis.

Case Presentation:
A 60-year-old female with a three-year history of a progressively enlarging goiter and worsening compressive symptoms presented for surgical evaluation. Initial investigations revealed severe hypothyroidism and ultrasound findings of a nodular goiter with features of thyroiditis (TI-RADS 3). She underwent a total thyroidectomy for symptomatic relief. Postoperative histopathology unexpectedly revealed a DLBCL, confirmed by CD20 positivity, coexisting with a background of classic HT. The patient was subsequently treated with six cycles of R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) chemoimmunotherapy and achieved a complete clinical and radiological response.

Conclusion:
This case underscores the diagnostic challenge PTL presents, particularly in patients with pre-existing HT. A high index of suspicion is crucial for clinicians managing HT patients who present with a rapidly enlarging goiter or worsening compressive symptoms. While fine-needle aspiration has limitations, definitive diagnosis often requires a core needle or excisional biopsy to differentiate neoplastic infiltration from the benign lymphocytic infiltrate of HT.

Keywords:

BACKGROUND

Primary thyroid lymphoma (PTL) is a rare neoplasm, accounting for 1-5% of all thyroid malignancies and approximately 2-7% of all extranodal lymphomas.[1,2,8] While papillary thyroid carcinoma is the most common thyroid cancer (85-90%), PTL represents a distinct and important clinical entity.[9] The strongest known

risk factor for developing PTL is pre-existing Hashimoto's thyroiditis (HT), an autoimmune disorder characterized by lymphocytic infiltration, Hürthle cell changes, and germinal center formation.[3,10] Patients with HT have a 40 to 80-fold greater risk of developing PTL compared to the general population.[3,4,11]

The most frequent histological subtype of PTL is diffuse large B-cell lymphoma (DLBCL), which constitutes 50-70% of cases and is considered the most aggressive form.[1,5,6,12] Other subtypes include mucosa-associated lymphoid tissue (MALT) lymphoma, which is also strongly associated with HT and may precede the development of DLBCL.[10,13]

The diagnosis of PTL is frequently challenging. Clinically, patients often present with a rapidly enlarging, painless neck mass and compressive symptoms like dysphagia, dyspnea, or hoarseness.[1,14,15] Sonographically, the features of PTL, especially the diffuse type, can closely mimic those of HT, with findings such as marked hypoechogenicity and echogenic strands present in both conditions, leading to a low positive predictive value for ultrasound alone.[7,16] Definitive diagnosis relies on tissue biopsy with immunophenotypic analysis.[7,17] Management is primarily non-surgical, centered on chemoimmunotherapy and/or radiation therapy, to which these tumors are highly sensitive. Surgery is typically reserved for diagnostic biopsy or to alleviate severe, acute airway compression [7, 14, 18].

Given the strong association between PTL and HT, this report presents the case of a patient with a long-standing goiter and worsening compressive symptoms, in whom total thyroidectomy unexpectedly revealed DLBCL coexistent with HT.

CASE PRESENTATION

A 60-year-old female with a three-year history of a progressively enlarging goiter presented to the oncology surgery polyclinic with worsening compressive symptoms in her neck, including dysphagia. She denied B-symptoms such as fever, night sweats, or significant weight loss.

Clinical and Laboratory Findings Initial laboratory testing revealed overt hypothyroidism with a thyroid-stimulating hormone (TSH) level of 50.4 µIU/mL (normal range: 0.27-4.20) and a free thyroxine (FT4) level of 0.38 ng/dL (normal range: 0.92-1.68). She was started on levothyroxine 100 mcg daily. Prior to surgery, her thyroid function improved, with a TSH of 9.08 µIU/mL and FT4 of 1.27 ng/dL.

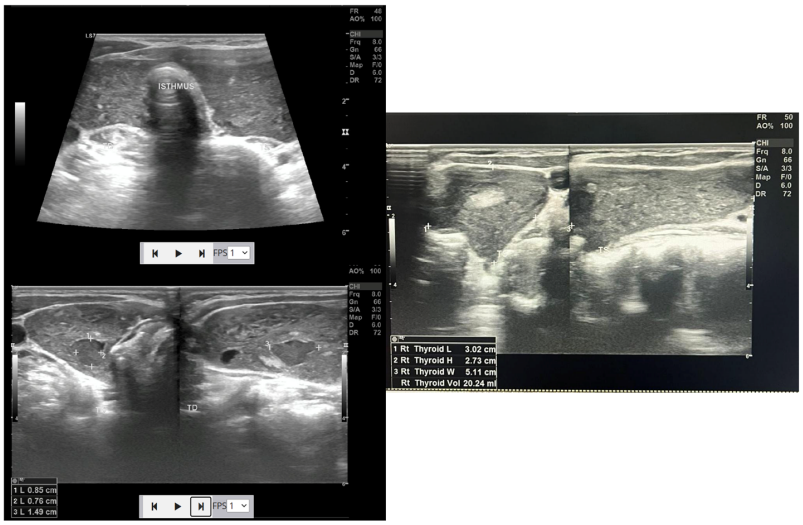

Figure 1. Thyroid Ultrasound. The image shows a bilateral nodular goiter (TI-RADS 3) with calcification in the left thyroid lobe. The parenchyma has a heterogeneous echotexture, suggestive of thyroiditis.

Imaging Preoperative ultrasonography (US) demonstrated bilaterally enlarged thyroid glands containing a nodular goiter classified as TI-RADS 3. The thyroid parenchyma had an inhomogeneous echostructure, a finding consistent with an appearance of thyroiditis.

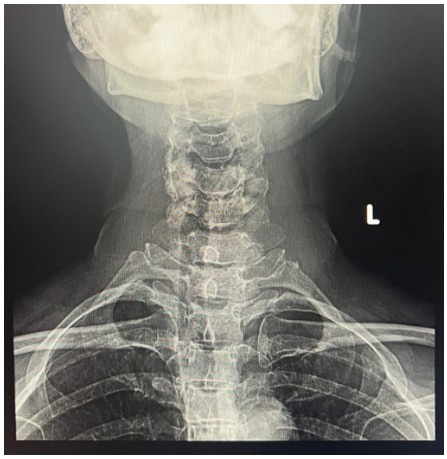

Figure 2. Neck X-ray showing a large bilateral neck mass, more prominent on the left, which deviates the trachea to the right without causing significant airway constriction.

A cervical X-ray showed a bilateral neck mass causing a rightward deviation of the trachea but no evidence of critical airway obstruction.

Surgical Intervention and Histopathology Due to the significant and worsening compressive symptoms, the patient underwent a total thyroidectomy. Postoperative histopathological examination of the specimen unexpectedly revealed a diffuse infiltration of the thyroid parenchyma by medium-to-large atypical lymphoid cells. The background thyroid tissue showed features characteristic of HT, including extensive lymphocytic infiltration with the formation of reactive germinal centers and Hürthle cell metaplasia.[10,20] The immunohistochemical profile of the atypical lymphoid infiltrate was positive for CD20, confirming a diagnosis of DLBCL.[12]

Postoperative Course and TreatmentPostoperatively, the patient's TSH was 30.5 µIU/mL and FT4 was 1.13 ng/dL.

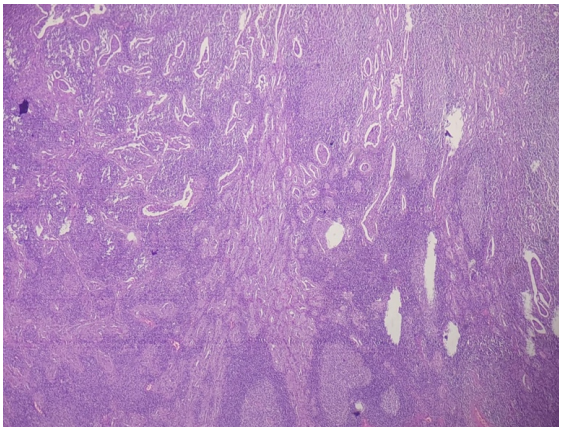

Figure 3. Histopathological Findings of the thyroidectomy specimen (H&E stain).

The micrograph illustrates the dual pathology present within the thyroid tissue. **(A)** A diffuse and infiltrative proliferation of large, atypical lymphoid cells is seen effacing the normal follicular architecture, consistent with Diffuse Large B-Cell Lymphoma. **(B)** The background stroma demonstrates features characteristic of Hashimoto's thyroiditis, including the formation of a prominent lymphoid follicle with a reactive germinal center.

She also developed mild hypocalcemia with a serum calcium level of 1.96 mmol/L (normal range: 2.15-2.5). She was continued on levothyroxine 100 mcg daily and started on calcium lactate 500 mg twice daily. Following her recovery from surgery, she was referred for oncological treatment and completed six cycles of the R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) chemoimmunotherapy regimen. The patient tolerated the treatment well and has maintained a good quality of life with a complete clinical and radiological response.

DISCUSSION

This case highlights the unexpected diagnosis of DLBCL in a patient undergoing thyroidectomy for compressive symptoms attributed to a long-standing goiter in the setting of HT. PTL is a rare disease, but its incidence is significantly elevated in individuals with HT.[3,4,11] Our patient's demographic profile—a female in her seventh decade of life—is consistent with the typical epidemiology of PTL, which predominantly

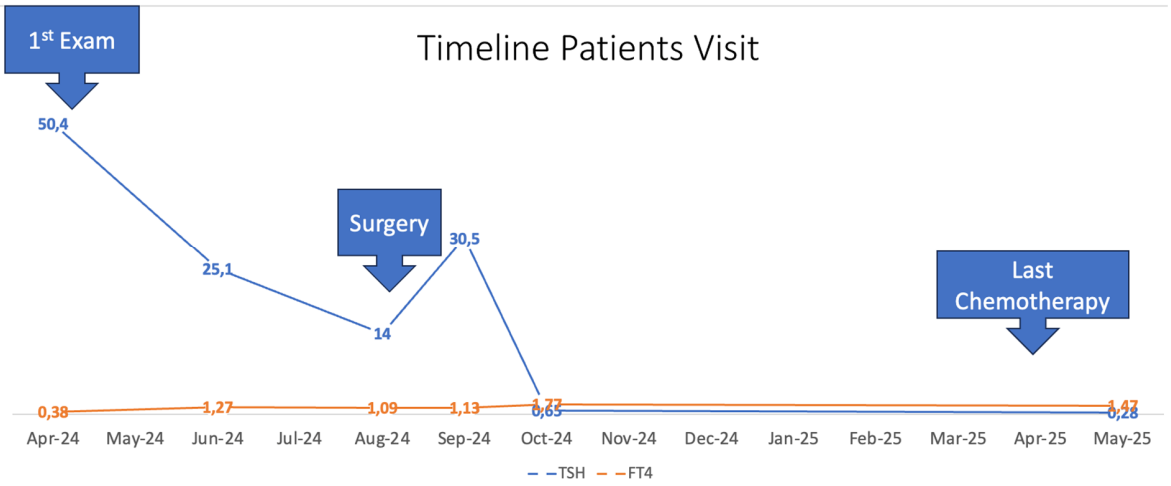

Figure 4. Timeline of patient's thyroid function tests and key clinical events. The line graph illustrates the changes in Thyroid-Stimulating Hormone (TSH, blue line) and Free Thyroxine (FT4, orange line) levels from the initial examination to post-treatment follow-up. At presentation in April 2024, the patient had severe primary hypothyroidism (TSH 50.4 µIU/mL, FT4 0.38 ng/dL). Following levothyroxine initiation, TSH levels decreased leading up to the total thyroidectomy in August 2024. A postoperative TSH spike was observed before stabilizing. The final measurement in May 2025, after completion of chemotherapy, shows a suppressed TSH (0.28 µIU/mL) and a normal FT4 (1.47 ng/dL), consistent with TSH-suppressive therapy.

affects middle-aged to older individuals, with a female-to-male ratio of approximately 3:1 and a mean age at diagnosis of 63–68 years.[1,2,6]

The link between HT and PTL is well-established, with chronic antigenic stimulation of lymphocytes within the thyroid gland thought to be the driving pathogenetic mechanism.[10, 11] This process can be considered a form of acquired MALT.[10] A recent meta-analysis of 38 studies found that 78.9% of PTL cases had evidence of HT, with 64% confirmed on pathology.[3] This strong association suggests a progression model where chronic inflammation in HT leads to the development of MALT lymphoma, which can subsequently transform into the more aggressive DLBCL.[10,13] It is hypothesized that persistent stimulation of B-cells by autoantigens increases the probability of cumulative genetic events, potentially involving the activation of the nuclear factor-κB (NF-κB) pathway.

However, the same meta-analysis also found that the prevalence of HT was significantly lower in pure DLBCL compared to MALT lymphoma (p=0.007) and in mixed DLBCL/MALT cases (p=0.002). This suggests that while many DLBCLs arise from pre-existing MALT lymphoma, a subset of thyroid DLBCL may arise de novo, without a MALT precursor.[3]

The question of whether the lymphocytic infiltrate in HT merely provides fertile ground for lymphoma growth or if the chronic activation directly predisposes lymphocytes to malignant transformation remains a subject of investigation.

A primary challenge in managing these patients is the diagnostic difficulty. The most common presenting symptom of PTL is a rapidly enlarging neck mass with compressive features, as seen in our patient.[1,14,15] However, these symptoms can also be attributed to a benign enlarging goiter. Furthermore, the sonographic features of diffuse PTL and HT demonstrate significant overlap, including a markedly hypoechoic and heterogeneous parenchyma, which complicates diagnosis by imaging alone.[7, 6,21] Advanced imaging techniques, such as contrast-enhanced ultrasound (CEUS) and ultrasomics, are being investigated to better differentiate benign from malignant processes in the setting of HT but are not yet standard practice.[21,22]

Fine-needle aspiration (FNA) is often the initial diagnostic test for thyroid nodules, but its accuracy for PTL is notoriously poor, with sensitivities sometimes as low as 60%.[1,17,23] The cytological similarity between the reactive lymphoid infiltrate of HT and the neoplastic cells of low-grade lymphoma makes a definitive diagnosis challenging on FNA alone.1[1,17,23]

Consequently, a core needle biopsy (CNB) or an excisional surgical biopsy is often necessary to obtain sufficient tissue for accurate histological and immunophenotypic analysis. CNB is considered superior to FNA for diagnosing PTL, with accuracy rates reported as high as 94.3%. In our case, the diagnosis was not established until after total thyroidectomy, which, while not standard for PTL treatment, was clinically indicated for the management of severe compressive symptoms.[7,14]

The standard of care for thyroid DLBCL is systemic chemoimmunotherapy with a regimen like R-CHOP, which has demonstrated high response rates.[1,11,12] Radiotherapy may be used as an adjunct, and dual-modality therapy has been shown to improve survival benefits over single-modality treatment. The excellent response of our patient to R-CHOP is consistent with the known chemosensitivity of this lymphoma subtype.[1,14]

Prognosis in PTL is variable and depends on factors such as histological subtype, disease stage, and patient age. MALT lymphomas generally have a more favorable prognosis than DLBCL.

Although some literature reports poor outcomes, with 50% of reviewed cases resulting in death with the disease within a year, modern multi-modal therapy has significantly improved survival rates, especially for localized disease (Stage I-IIE), which accounts for the majority of presentations. The time interval from a diagnosis of HT to the development of PTL is often long, on the order of 9-10 years, reinforcing the need for long-term vigilance in this patient population.

CONCLUSION

PTL, though rare, is an important differential diagnosis in patients with HT who present with a rapidly growing neck mass or worsening compressive symptoms. The significant overlap in clinical and imaging findings between PTL and benign thyroiditis complicates early detection. This case demonstrates that a definitive diagnosis of PTL may be an unexpected finding following surgery for what is presumed to be a benign goiter. A high index of suspicion and a low threshold for obtaining a core needle or excisional biopsy are essential for timely and accurate diagnosis, allowing for the prompt initiation of appropriate, primarily non-surgical, oncologic therapy.

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CASE REPORT

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

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 the neck and in the 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 gradually recovered and was 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, hyperglycemic hyperosmolar state, hypertriglyceridemia, pancreatitis

INTRODUCTION

The global prevalence of early-onset type 2 diabetes mellitus (T2DM) typically defined as diagnosis before age 40 is rising rapidly, particularly among those with obesity and metabolic syndrome.[1,2] Between 2013 and 2021, the number of individuals aged 20–39 years living with T2DM increased from 63 million to 260 million worldwide.[1] In early-onset T2DM, insulin resistance and beta-cell dysfunction can evolve rapidly, predisposing to acute metabolic decompensations.[3,4] Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) represent two major acute hyperglycemic crises associated with diabetes, both characterized by severe hyperglycemia but differing in the degree of insulin deficiency, presence of ketosis, and plasma osmolality.[5,6] While DKA typically occurs in the context of absolute or severe relative insulin deficiency leading to ketogenesis and metabolic acidosis, HHS arises from profound insulin resistance that is sufficient to suppress lipolysis but not adequate to prevent extreme hyperglycemia and hyperosmolarity.[7,8] Although classically described as distinct entities, a mixed DKA-HHS presentation may occur, particularly in patients with underlying T2DM and superimposed metabolic stress, and is associated with higher morbidity and mortality compared to isolated presentations.[9]

One such precipitating factor is acute pancreatitis, which is itself a rare but recognized complication of uncontrolled diabetes.[10] Among the various etiologies of pancreatitis, hypertriglyceridemia-induced pancreatitis (HTG-AP) accounts for up to 10% of cases and often manifests when serum triglyceride concentrations exceed 1,000 mg/dL.[11] The pathogenesis involves the hydrolysis of excess circulating triglycerides by pancreatic lipase into toxic free fatty acids, which induce direct pancreatic injury, capillary leakage, and systemic inflammation.[12] In patients with poorly controlled diabetes, insulin resistance promotes increased hepatic very-low-density lipoprotein (VLDL) production and reduced lipoprotein lipase activity, further accelerating triglyceride accumulation.[13,14]

Although the patient denied a family history of diabetes or dyslipidemia, genetic predisposition cannot be excluded. Early-onset T2DM is often associated with genetic variants that impair β-cell function and insulin signaling, such as mutations in *TCF7L2*, *KCNJ11*, or *HNF1A*. Similarly, familial combined hyperlipidemia and lipoprotein lipase (LPL) gene polymorphisms may predispose individuals to severe hypertriglyceridemia and pancreatitis under metabolic stress. These factors could partly explain the severity of metabolic derangements in this young patient despite the short history of diagnosed diabetes.[15]

The rare coexistence of HTG-AP triggering a DKA and HHS in a young adult with newly diagnosed type 2 diabetes mellitus highlights a rare and clinically significant metabolic presentation. The inflammatory response triggered by HTG-AP not only worsens glycemic control through elevated counter-regulatory hormones—such as cortisol, glucagon, and catecholamines—but also further impairs insulin secretion.[16–20] As a result, a vicious cycle is initiated in which hyperglycemia, ketosis, acidosis, and hyperosmolarity co-exist, resulting in a mixed DKA-HHS state. This triad is rarely reported and poses a high risk of multiorgan dysfunction, underscoring the importance of early recognition and prompt, multidisciplinary intervention. This case report aimed to describe a 28-year-old male with recently diagnosed but untreated T2DM who presented with overlapping DKA and HHS precipitated by hypertriglyceridemia-induced acute pancreatitis.

CASE DESCRIPTION

A 28-year-old male presented to the emergency department with decreased consciousness and deep, labored breathing

consistent with Kussmaul respiration. According to information provided by family members upon arrival, the patient had been experiencing progressive fatigue, decreased oral intake, excessive thirst, and frequent urination over the past several days. The patient had been diagnosed with type 2 diabetes mellitus two weeks before presentation, but had not initiated pharmacological therapy. The patient denied any prior history of chronic illness and, when conscious, reported no use of alcohol, recent trauma, or intake of medications or herbal products. There was no known family history of pancreatitis, hyperlipidemia, or early-onset diabetes.

On initial physical examination, the patient appeared somnolent but arousable, with vital signs revealing tachycardia (heart rate: 122 bpm) and hypotension (blood pressure: 88/56 mmHg). The respiratory rate was 30 breaths/min with signs of respiratory compensation. Central obesity was evident, with a body mass index of 31 kg/m² and a waist circumference of 112 cm. Dermatological examination revealed extensive acanthosis nigricans involving the posterior neck and bilateral axillary regions.

Initial laboratory investigations demonstrated increased hyperglycemia (798 mg/dL), severe metabolic acidosis (arterial pH: 7.08; bicarbonate: 9 mmol/L; anion gap: 24), and hyperosmolarity (serum osmolality: 336 mOsm/kg). Serum triglyceride level was markedly elevated at 965 mg/dL, and serum lipase was increased to 892 U/L, supporting the diagnosis of acute pancreatitis. Urinalysis showed ketonuria and glucosuria. Based on these findings, the patient was diagnosed with a mixed presentation of DKA and HHS complicated by HTG-AP.

Management was initiated with aggressive intravenous (IV) fluid resuscitation, starting with 0.9% sodium chloride at 1 L/hour for the first few hours, followed by volume titration according to hemodynamic status, with a total of 10 L administered within the first 24 hours. A continuous intravenous infusion of regular insulin was initiated at a rate of 0.1 units/kg/hour. Subsequently, subcutaneous basal insulin was added at a dose of 0.3 units/kg body weight. The total amount of insulin administered until resolution was 224 units. Empiric antibiotic therapy with IV ceftriaxone 2 g once daily was administered due to clinical suspicion of possible pancreatic necrosis.

On the third day of hospitalization, the patient developed acute kidney injury characterized by persistent anuria, reduced estimated glomerular filtration rate (eGFR), and progressive elevation in serum creatinine levels. Subsequently, continuous renal replacement therapy (CRRT) was initiated. Renal function gradually recovered with supportive management. The patient showed progressive metabolic stabilization, resolution of acidosis, and improvement in pancreatic enzyme levels. After 20 days of hospitalization, the patient was discharged in stable condition with instructions for outpatient diabetes management and follow-up with endocrinology.

DISCUSSION

The coexistence of DKA, HHS, and HTG-AP represents a complex and rare metabolic interplay often referred to as an “enigmatic triangle.” Although each condition may occur independently, their convergence—particularly as the initial manifestation of T2DM in a young adult—is exceptionally rare and associated with significant clinical implications. The convergence of DKA, HHS, and HTG-AP represents a pathophysiological continuum driven by profound insulin deficiency, dysregulated lipid metabolism, and systemic inflammation.[15–21] Recognizing the bidirectional associations among these conditions is critical for timely diagnosis and management, particularly in young patients with previously undiagnosed or untreated diabetes.

In young individuals with undiagnosed T2DM, this triad can occur when prolonged insulin resistance—often asymptomatic—is compounded by sudden metabolic stress.[22] In youth and young adults, insulin resistance often appears first, but a swift decline in beta-cell function is a key factor in the rapid worsening of glucose control.[16,17,22] Central obesity, as observed in this patient, enhances insulin resistance, increasing the risk of severe hyperglycemia and dyslipidemia even at an early age.[23] Once beta-cell function declines, the system becomes acutely vulnerable to tipping into ketosis and metabolic crisis, particularly when challenged by triggers such as pancreatitis or infection.[24] The additive effect of obesity, delayed diagnosis, and lack of prior treatment likely contributed to the severity of the presentation.

In the present case, a young patient with T2DM presented with features indicative of a mixed DKA-HHS state. Similar to previous observations in type 1 diabetes, the overlap between these two metabolic emergencies may be exacerbated by the administration of glucose-containing fluids during early resuscitation, which can worsen hyperglycemia and serum osmolality.[25] Such management strategies, although intended to address dehydration, may inadvertently shift the clinical picture toward that of HHS.[26]

The diagnosis of type 2 diabetes in this case was based on the patient's obesity, presence of acanthosis nigricans, and absence of autoimmune history. However, given the acute presentation with ketosis, differential diagnoses such as ketosis-prone type 2 diabetes or latent autoimmune diabetes in adults should be considered. In such cases, measurement of pancreatic autoantibodies and C-peptide levels during follow-up is essential for confirming diabetes classification and optimizing long-term management.[27]

Furthermore, in patients with prolonged and severe dehydration—as observed in this case—significant metabolic acidosis may also occur due to lactic acidosis, secondary to sustained tissue hypoperfusion.[26] This lactic acidosis can contribute to the overall acid-base disturbance, compounding the ketone-driven acidosis characteristic of DKA.[26] However, in the present case, serum lactate levels were low, suggesting that lactic acidosis was not the primary driver of metabolic acidosis. This finding supports the hypothesis that other mechanisms, such as alterations in glucose metabolism and impaired cellular oxygen utilization, may contribute to the acid-base imbalance in mixed DKA-HHS presentations.[26]

In the present case, the patient had high-anion gap metabolic acidosis, as indicated by low serum bicarbonate and elevated anion gap—findings consistent with DKA. However, the history of reduced oral intake suggests a potential contribution from starvation ketosis. This condition typically arises during prolonged fasting and is associated with mild to moderate hyperglycemia and bicarbonate levels below 18 mEq/L.[26] In contrast, DKA is characterized by more severe hyperglycemia, often exceeding 250 mg/dL.[26] Although the patient's serum glucose met the DKA threshold, the acid-base disturbance may represent a mixed picture. Alcoholic ketoacidosis, another differential diagnosis, is less likely given the absence of alcohol use and typically higher serum bicarbonate levels.

The interrelation begins with insulin deficiency, a hallmark of DKA, which promotes unrestrained lipolysis in adipose tissue.[20] This process results in a surge of free fatty acids (FFAs) transported to the liver, stimulating hepatic production of VLDL.[20] Concurrently, insulin deficiency suppresses LPL activity in peripheral tissues, impairing the clearance of circulating triglycerides.[20] The net effect is the

development of severe hypertriglyceridemia, which may surpass 1,000 mg/dL and is sufficient to precipitate acute pancreatitis in susceptible individuals.[11]

The pathophysiology of HTG-AP is multifaceted. Pancreatic lipases hydrolyze excess circulating triglycerides into FFAs.[28,29] When FFA concentrations exceed the buffering capacity of plasma albumin, they self-aggregate into toxic micellar complexes that damage pancreatic acinar cells, vascular endothelium, and platelets.[29] This damage results in pancreatic ischemia, acidosis, and local inflammation, all of which accelerate trypsinogen activation and pancreatic autodigestion.[29] Additionally, hypertriglyceridemia increases serum viscosity, further impairing pancreatic perfusion and amplifying local ischemia.[29]

Conversely, acute pancreatitis can also initiate or worsen DKA and HHS. Pancreatic inflammation induces acute beta-cell dysfunction, causing transient insulin deficiency, which may be sufficient to trigger DKA in patients with underlying glucose intolerance.[9] Furthermore, pancreatitis generates a robust systemic inflammatory response characterized by the release of stress hormones—cortisol, catecholamines, glucagon, and growth hormone—that exacerbate insulin resistance.[9] These hormonal changes not only impair glucose utilization and worsen hyperglycemia but also promote hepatic ketogenesis and dehydration, culminating in the overlapping features of DKA and HHS.

The temporal sequence between these entities is often challenging to establish. Some studies suggest DKA may precede pancreatitis through the pathway of DKA → HTG → AP, while others support the reverse sequence of HTG → AP → DKA, especially when pancreatitis is the initial event in a previously undiagnosed diabetic patient.[30–33] In the present case, the elevated HbA1c supports longstanding, unrecognized hyperglycemia, suggesting that insulin deficiency and hyperglycemia had progressed before the acute event. Thus, it is plausible that the patient developed DKA first, which in turn led to HTG and subsequent pancreatitis. However, acute pancreatitis may have also acted as a precipitating stressor that aggravated insulin deficiency and unmasked the underlying diabetes.

The management of hypertriglyceridemia-induced pancreatitis follows standard acute pancreatitis guidelines, emphasizing aggressive fluid resuscitation, early enteral nutrition, and pain control. According to the 2024 American College of Gastroenterology (ACG) and International Association of Pancreatology (IAP) guidelines, insulin infusion remains a practical approach to rapidly reduce triglyceride levels in diabetic patients, while plasmapheresis is reserved for refractory cases or triglycerides >2000 mg/dL with organ dysfunction.[34]

As a single case report, this study is inherently limited in its ability to establish causality or generalize findings to broader populations. The temporal relationship between diabetic ketoacidosis, hypertriglyceridemia, and acute pancreatitis could not be definitively determined, as serial measurements of insulin, C-peptide, and inflammatory markers were not performed. Moreover, serum β-hydroxybutyrate—the predominant ketone body in diabetic ketoacidosis—was not assessed, limiting the ability to characterize the degree of ketosis accurately. Genetic testing for familial dyslipidemia was also not performed, which may have provided insight into the underlying predisposition to severe hypertriglyceridemia in this young adult.

Another diagnostic limitation was the absence of autoantibody testing (e.g., GAD65, IA-2, ZnT8) and C-peptide follow-up to differentiate between ketosis-prone type 2 diabetes (Flatbush diabetes) and atypical type 1 diabetes. This distinction is fundamental in young adults presenting with mixed DKA-HHS, as overlapping clinical and

biochemical features may obscure classification. Furthermore, serum osmolality and anion gap monitoring were limited to the acute phase, restricting the ability to characterize the dynamic transition between DKA and HHS states fully.[34]

Future research should focus on prospective cohort studies to better define the pathophysiological sequence linking DKA, HHS, and HTG-AP, particularly in young adults with new-onset type 2 diabetes mellitus. Investigating early biomarkers of beta-cell dysfunction and inflammatory mediators in such presentations may help identify individuals at risk for severe metabolic complications. Furthermore, clinical trials evaluating the optimal timing and role of insulin therapy, lipid-lowering agents, and renal support modalities in the management of this triad are warranted to inform evidence-based treatment strategies.

CONCLUSION

This case illustrates a rare yet life-threatening presentation of mixed DKA and HHS, precipitated by HTG-AP in a young, obese adult with newly diagnosed and untreated type 2 diabetes mellitus. The patient's age and obesity reflect a phenotype characterized by marked insulin resistance, β-cell dysfunction, and accelerated lipolysis, contributing to profound hyperglycemia, ketogenesis, and extreme hypertriglyceridemia. These metabolic derangements, compounded by the pro-inflammatory response from pancreatitis, created a vicious cycle of lipotoxicity and systemic inflammation. This case underscores the importance of recognizing the evolving epidemiology and atypical presentations of type 2 diabetes in younger populations. Clinicians should maintain a high index of suspicion for mixed metabolic emergencies in obese individuals presenting with severe hyperglycemia and abdominal symptoms to enable timely diagnosis and coordinated multidisciplinary intervention.

ETHICS APPROVAL

Written informed consent was obtained from the patient before the surgical procedure, including authorization for the intervention and approval for the collection, analysis, and dissemination of clinical data in an anonymized manner for research and academic purposes.

CONFLICT OF INTERESTS

All the authors declare that there are no conflicts of interest.

ACKNOWLEDGMENTS

The authors extend their gratitude to the staff at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, for their expertise and contributions to the management of the patients in this case series.

AUTHOR CONTRIBUTION

TMS: conceptualizing, validation, writing–original draft preparation, review, and editing; ASE.: writing– review, and editing, validation; KWS: validation, supervision, writing–review, and editing; HZ: conceptualizing, supervision, validation, writing–review, and editing. All authors approved the submitted version.

FUNDING

This case report received no external funding.

DATA AVAILABILITY STATEMENT

Derived data supporting the findings of this case report are available from the corresponding author on request.

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CASE REPORT

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

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

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ABSTRACT

Background: 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.

Case Presentation: 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.

Discussion: 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 pituitary atrophy. The combination of central diabetes insipidus (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.

Conclusion: 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

INTRODUCTION

Langerhans cell histiocytosis (LLH) is a rare disease characterized by clonal expansion of myeloid precursors that differentiate into $CD1a^+$/$CD207^+$ in lesions. It can occur at any age with varying degrees of systemic involvement. With a median age upon diagnosis of 3 years, the reported incidence of LCH varies from 2.6 to 8.9 cases per million children under the age of 15 per year. The exact incidence of LCH in adults is much less defined: the only available data are for disseminated disease, with 0.07 cases per million per year. Despite the high cure rate, it can cause serious long-term neurological or endocrine consequences that might impair quality of life.[1]

Recent advances in molecular pathogenesis have identified recurrent oncogenic somatic mutations in LCH that activate the MAPKinase (MAPK) pathway, with BRAF V600E mutation present in approximately 55% of cases. These mutations are associated with disease recurrence and high-risk presentations, confirming that LCH is a neoplastic disorder arising from an expansion of early myeloid cells with constitutive activation of the MAPK RAS/RAF/MEK/ERK cell signaling pathway.[2,3]

Endocrine abnormalities from LCH include excessive thirst and urination caused by damage to the back part of the pituitary gland. This condition is known as diabetes insipidus. If the front part of the pituitary gland is damaged by LCH, the patient may have low levels of thyroid hormone, growth hormone, adrenal stimulating hormone and the hormones that lead to sexual maturation. Bone involvement in children or adult presents as painful areas which may be swollen. In children, the skull is most often affected, followed by long bones of the upper and lower extremity, ribs and spine.[4]

This case report describes an 18-year-old male patient with LCH who developed multiple endocrine complications including empty sella syndrome with CDI, delayed puberty, and central hypothyroidism. The case highlights the importance of recognizing and managing these complications in the context of LCH to improve patient outcomes and quality of life.

CASE PRESENTATION

Patient Information

An 18-year-old male presented to the endocrinology clinic with complaints of polyuria and polydipsia. He had a history of LCH diagnosed at age 10 and was transitioning from pediatric to adult care.

Clinical Findings

The patient reported frequent urination more than 20 times per day with a 24-hour urine volume of approximately 4000 ml. He experienced increased thirst and consequently high fluid intake. He denied symptoms of fatigue, dizziness, hearing disturbances, anxiety, palpitations, muscle cramps, fever, bone pain, nausea, vomiting, or weight changes. He reported never experiencing ejaculation but had noted clear fluid discharge from his genitalia occasionally.

On physical examination, the patient's vital signs were stable: blood pressure 110/70 mmHg, heart rate 88 beats/minute, respiratory rate 18 breaths/minute, and temperature 36°C. His weight was 62.5 kg, height 164 cm, and BMI 23.2 kg/m^2 (normal weight). Notable findings included gynecomastia and Tanner stage 3 genital development with testicular volume of 8 cc.

Timeline and Diagnostic Assessment

The patient's clinical course began at age 10 when he first experienced polyuria and polydipsia, drinking up to 19 liters of water daily with urination frequency exceeding 20 times per day. Initial cranial CT and MRI showed no pituitary abnormalities, but CDI was diagnosed based on clinical symptoms and water deprivation test.

At age 12, he developed a mass in his right thigh. MRI was done and revealed a soft

tissue tumor with lytic lesions in the distal femur metaphysis. Soft tissue biopsy confirmed LCH via CD1a and CD207 immunohistochemical staining. He also frequently experienced generalized weakness and pain in the right shoulder. Laboratory tests showed hypothyroidism with thyroid-stimulating hormone (TSH) 8.663 µIU/mL (reference range 0.35-4.94 µIU/mL) and fT4 0.86 ng/dL (reference range 0.89-1.37 ng/dL) and no palpable thyroid enlargement. Imaging revealed soft tissue masses involving multiple muscles in the right shoulder region with destruction of the first right posterior rib. Chemotherapy was planned at that time but then delayed due to the patient's entry into a boarding school and later by the COVID-19 pandemic. He never had any treatment for 3 years later.

At age 15, new lesions appeared on his right chest, back, and armpit, which became painful. Bone marrow examination showed hyperactive reticuloendothelial system with hemophagocytosis. He then underwent 12 months of chemotherapy with the LCH protocol (vincristine, etoposide, prednisone), which led to resolution of the painful bone and soft tissue lesions and no evidence of new active disease on subsequent imaging. However, despite clinical remission of LCH, the patient developed long-term endocrine sequelae, including central diabetes insipidus, central hypothyroidism, and hypogonadotropic hypogonadism, suggesting irreversible hypothalamic–pituitary axis damage. During that time, he also experienced gynecomastia grade II with no galactorrhea (figure 1). Testosteron measured and the level was 2.72 nmol/L (reference range 4.94-32.01 nmol/L), Follicle-stimulating hormone FSH 5.4 mIU/mL (reference range 1.5-12.4 mIU/mL) and LH 2.8 mIU/mL (reference range 1.7-8.6 mIU/mL). MRI brain then performed and revealed empty sella grade IV (total empty sella) with thinning of the pituitary gland (figure 2). Bone age assessment with Greulich-Pyle Method showed a bone age of 15 years (chronological age 16.5 years) indicating delayed bone maturation. X-ray of lumbar-sacral vertebrae in 2 positions and thoracic vertebrae in 2 positions at age 17 showed decrease bone density suggested osteopenia and 25-OHD level 12.6 ng/mL showed vitamin D deficiency while ion calcium 0.94 mmol/L showed hypocalcemia. Chest CT scan at age 18 showed right anterolateral rib 1 deformity. No obvious lesion or enhancement is seen around the lesion (figure 3).

Current Medications

The patient is currently managed with desmopressin 4-5 times 0.2 mg daily, levothyroxine 100 mcg daily (Monday-Thursday) and 150 mcg daily (Friday-Sunday), vitamin D3 1000 IU daily,

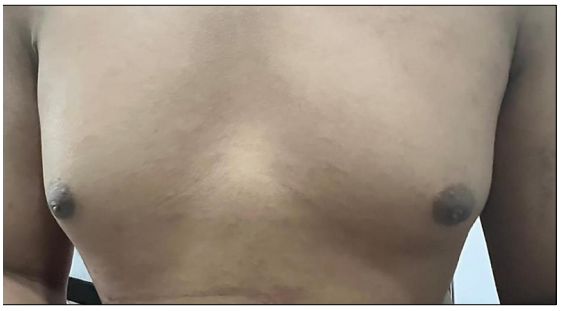

Figure 1. Gynecomastia grade II

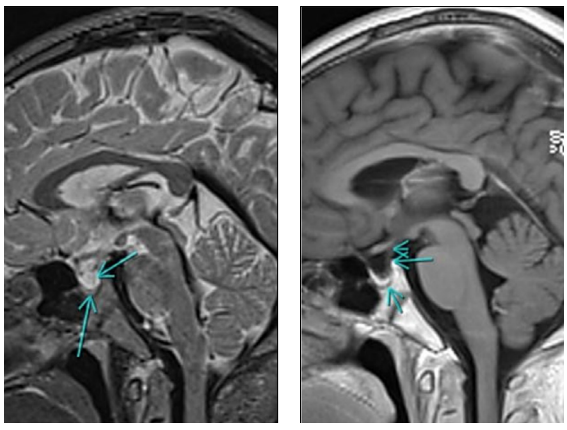

Figure 2. MRI findings are consistent with a grade IV empty sella, characterized by thinning of the pituitary gland and partial filling of the sella turcica with cerebrospinal fluid. The pituitary gland demonstrates homogeneous post-contrast enhancement, with no evidence of mass lesion, abnormal enhancement, or other intracranial pathology.

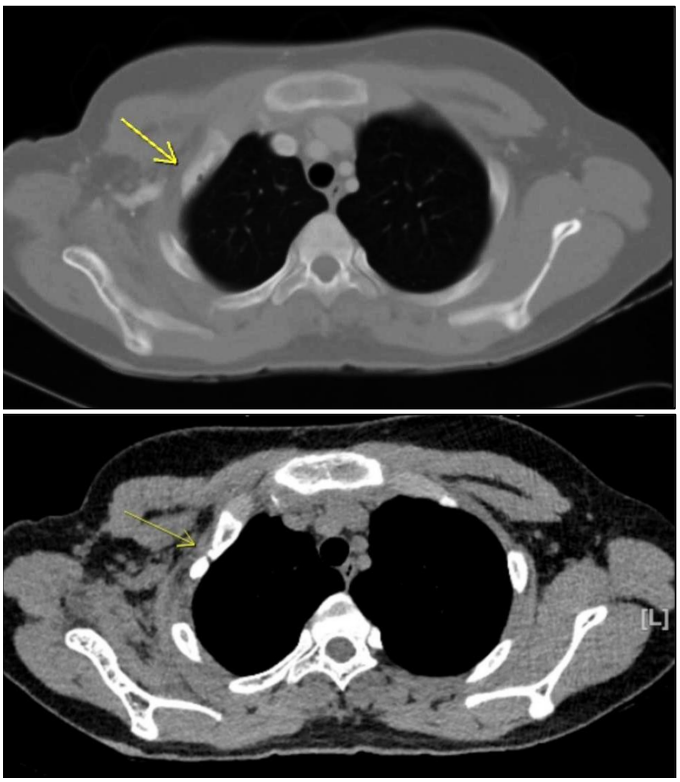

Figure 3. Right anterolateral rib 1 deformity. No obvious lesion or enhancement is seen around the lesion

and calcium carbonate 500 mg twice daily

DISCUSSION

LCH is now recognized as an inflammatory myeloid neoplasia with constitutive activation of the MAPK RAS/RAF/MEK/ERK cell signaling pathway. The MAPK pathway plays a vital role in regulating cell differentiation, proliferation, and apoptosis, particularly in myeloid cell differentiation and maturation. Genomic studies have identified recurrent somatic mutations in LCH, with BRAF V600E mutation present in approximately 55% of cases, while other mutations such as MAP2K1 (10-20%) and rare BRAF splicing mutations have also been reported.[2,3]

The multisystem involvement with bone lesions and soft tissue masses is common characteristic of LCH. In our patient, LCH diagnosis is obtained from immunohistochemistry and chemotherapy is performed for the treatment. Although BRAF V600E testing was unavailable, MAPK pathway activation remains central to LCH pathogenesis, warranting targeted therapies (e.g., BRAF inhibitors) in refractory cases. The pathologic progression aligns with the known disease pattern in LCH, where abnormal proliferation of histiocytes leads to tissue infiltration and damage.[5]

Central nervous system (CNS) involvement in LCH usually occurs with multisystem disease. It can be in the form of either focal mass lesions or progressive neurodegenerative disease. Among the CNS involvement, hypothalamic-pituitary involvement is the most common. CDI represents the most frequent endocrine manifestation observed in patients with LCH, which can present either as an isolated deficiency or in combination with other anterior pituitary hormonal dysfunctions. Across studies, the prevalence of CDI has a wide range, with as high as up to 94% in the presence of one or more other pituitary hormonal abnormalities. Among anterior pituitary dysfunction, growth

hormone (GH) deficiency is the most common, with a prevalence between 53% and 67%, and almost always occurs with CDI. This is followed by gonadotropin deficiency. Although isolated deficiencies have been reported, Central hypothyroidism and adrenal insufficiency are generally seen as a part of panhypopituitarism.[6]

As seen in our case, our patient's persistent polyuria and polydipsia requiring increasing doses of desmopressin (4-5 times 0.2 mg daily) indicate severe CDI. Once CDI develops, it becomes irreversible in most patients, who will require life-long desmopressin replacement therapy. The MRI finding of total empty sella in LCH further supports the correlates with chronic pituitary stalk inflammation and atrophy, as seen in neurodegenerative LCH variants. In LCH, this can result from direct infiltration and subsequent atrophy or from inflammatory processes affecting the pituitary.[7,8]

The patient's central hypothyroidism, evidenced by laboratory result and his requirement for levothyroxine supplementation is another manifestation of pituitary dysfunction. Central hypothyroidism occurs due to insufficient TSH production by the anterior pituitary gland.[6]

Delayed puberty, as manifested by Tanner stage 3 genital development with testicular volume of 8 cc at age 18 is consistent with hypogonadotropic hypogonadism, another consequence of anterior pituitary dysfunction. Normally, puberty should begin by age 14 in males, with progression through Tanner stages occurring over 2-5 years. The patient's bone age of 15 years at chronological age 16.5 years further confirms the developmental delay associated with his endocrine dysfunction.[9] Testosterone therapy will be performed to induce puberty and reduce complications due to its deficiency. It is routinely prescribed in adolescent males with constitutional delay of growth and puberty or hypogonadism. Testosterone plays a critical role in male sexual development and function. It has numerous effects on various tissues and systems. These include the acceleration of linear growth during adolescence, a positive effect on bone mass and accretion, and changes in body composition associated with an increase in lean mass and a reduction and redistribution of fat mass.[10]

The presence of gynecomastia in this patient likely resulted from prolonged glucocorticoid therapy (prednisone) during chemotherapy for LCH. Glucocorticoids can disrupt the estrogen- testosterone balance, leading to breast tissue enlargement. Additionally, central hypothyroidism and delayed puberty (due to hypothalamic-pituitary dysfunction from empty sella) may contribute to hormonal imbalances, though the primary cause here is prolonged glucocorticoid therapy. Osteopenia, documented in the lumbar spine X-ray, may result from multiple factors including the underlying inflammatory disease, endocrine dysfunction (particularly hypothyroidism and hypogonadism), and possibly glucocorticoid therapy received during chemotherapy. [11-12] These manifestations likely result from both hypothalamic–pituitary involvement and the cumulative toxic effects of systemic therapy. Consequently, chemotherapy may indirectly impair linear growth, pubertal progression, and bone mineralization, even after disease remission. [13] Vitamin D deficiency and hypocalcemia in these patients may increase the risk of osteoporotic fractures, especially in the hip. Vitamin D deficiency does not only cause weaker bones due to osteomalacia, but also severe myopathy with loss of muscle strength, selective loss of the rapid type-2 fibres, dyscoordination and consequently increased propensity for falls. It is therefore not surprising that meta-analyses indicate that correction of vitamin D deficiency results in a decreased fall and fracture risk. Daily intake of 400 IU/day is not sufficient, while 800 IU/day reduce falls and fractures significantly. Several reviews have

emphasized the need of addition of calcium to vitamin D for fracture prevention and a dose of calcium 1,000 to 1,200 mg/day was suggested; both vitamin D and calcium therapies has been given to this patient.[14]

A recent multicenter cohort study involving 219 adult patients with LCH demonstrated a 5-year OS rate of 88.7% and a 10-year OS rate of 74.5%, with the median OS not yet reached. The presence of risk-organ involvement (liver, spleen, bone marrow) was associated with significantly poorer outcomes (hazard ratio 10.8), while age at diagnosis also influenced prognosis. In contrast, BRAF V600E mutation status was not associated with OS or progression-free survival. Most LCH-related deaths occurred within the first five years after diagnosis, whereas later mortality was mainly attributed to non-LCH causes such as secondary malignancies, chronic obstructive pulmonary disease, and cardiovascular disease. Consequently, although the disease-specific prognosis is generally favorable, adult LCH survivors remain at higher long-term mortality risk compared with the general population (standardized mortality ratio 2.66). These findings highlight the need for lifelong multidisciplinary follow-up, focusing on prevention of late complications, metabolic health, and endocrine sequelae. In our patient, the absence of new lesions and stable imaging indicate remission, while persistent panhypopituitarism reflects irreversible hypothalamic–pituitary injury requiring lifelong hormonal replacement. [13]

CONCLUSION

This case highlights the complex and multifaceted endocrine complications associated with LCH, particularly when involving the hypothalamic-pituitary axis. Empty sella syndrome with CDI, delayed puberty, and central hypothyroidism are serious long-term sequelae that significantly impact quality of life and require timely diagnosis and ongoing multidisciplinary management. Early recognition of endocrine dysfunction in patients with LCH is crucial for prompt intervention and to prevent further complications. Comprehensive follow-up with endocrine evaluation including annual pituitary MRI, Dual-Energy X-ray Absorptiometry (DEXA scans), and hormonal panels is critical for LCH survivors, especially those with multisystem involvement or central nervous system lesions. Because LCH frequently develops during childhood, endocrine function should be assessed at diagnosis and re-evaluated periodically every 6–12 months throughout growth and puberty to allow early detection and management of evolving pituitary deficiencies.

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CASE REPORT

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

Clinically Non-Functioning Pituitary Incidentaloma Presenting as Recurrent Episodes of Hypoglycemia

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ABSTRACT

A pituitary adenoma is a tumor originating from the adenohypophysis. Pituitary adenomas are mostly discovered incidentally during radiological examinations performed for other purposes. Not all pituitary adenomas are functional. Non-functioning adenomas often present with symptoms due to mass effect and pituitary hormone deficiency. This case report presents a case of a 56-year-old man with type 2 diabetes mellitus who had an accidental finding of pituitary macroadenoma without overt hormone hypersecretion symptoms, but experienced recurrent hypoglycemia. Further investigation revealed low cortisol and insulin like growth hormone-1 levels, suggesting a Houssay phenomenon that leads to 'resolution' of diabetes due to hypopituitarism. Even in patients without overt symptoms of hormone hypersecretion, the possibility of subtle hypopituitarism due to tumor-induced pituitary dysfunction should not be overlooked. Patients with pituitary adenomas require evaluation by a multidisciplinary team involving endocrinology, neurosurgery, and ophthalmology.

Keywords: hypopituitarism, non-functioning pituitary adenoma, pituitary incidentaloma, recurrent hypoglycemia

INTRODUCTION

A pituitary adenoma is a tumor originating from the anterior pituitary (adenohypophysis). This tumor is the most common type of pituitary disorder, accounting for approximately 10–15% of all intracranial tumors.[1, 2] Most pituitary tumors are benign and slow-growing. The pathogenesis of pituitary adenomas remains unclear. The majority of cases are sporadic, with genetic mutations being rarely characteristic of pituitary adenomas. Familial pituitary adenoma cases account for only about 5% of all pituitary tumors.[1]

Most pituitary adenomas are discovered incidentally on imaging performed for other reasons.[1-3] As a result, it is difficult to accurately estimate the prevalence of pituitary adenomas in the general population. Prevalence estimates extrapolated from autopsy and radiological data suggest an average of 16.7%, with autopsy findings at 14.4% and radiological imaging at 22.5%.[1] The detection rate of pituitary incidentalomas varies between 4–20% on CT scans and 10–38% on MRI.[3] A study from the UK reported a prevalence of pituitary adenomas

of 77.6 per 100,000 people[2], while another study from Iceland found an incidence of 115 cases per 100,000 population.[1] Of all pituitary adenomas, approximately 43% are non-functioning, 40% are prolactinomas, 11% secrete growth hormone, and 6% secrete adrenocorticotropic hormone (ACTH).[1] Adenomas that secrete follicle-stimulating hormone (FSH), luteinizing hormone (LH), or thyroid-stimulating hormone (TSH) are rare.[2] The constellation of endocrine symptoms seen in patients with pituitary adenomas includes hormone hypersecretion or, conversely, pituitary hormone deficiency.[2] Functional adenomas can cause clinical syndromes such as acromegaly and Cushing's disease. In contrast, non-functioning adenomas often present with symptoms due to mass effect and pituitary hormone deficiency. Hypopituitarism resulting from the tumor mass that compresses normal anterior pituitary tissue and the pituitary stalk can lead to deficiencies in other pituitary hormones.[4]

This case report presents a pituitary incidentaloma in a 56-year-old man who initially underwent a CT scan for nasopharyngeal cancer evaluation. Although he did not exhibit overt symptoms of hormone hypersecretion, it is possible that he experienced subtle hypopituitarism, particularly given his history of recurrent treatment for hypoglycemia in the context of previously hyperglycemic type 2 diabetes mellitus.

CASE ILLUSTRATION

A 56-year-old male presented to the emergency department with complaints of decreased consciousness and seizures. There was no facial droop or unilateral weakness. Upon arrival at the emergency department, he was found to have low blood glucose. There was no nausea, vomiting, nor anorexia. During hospitalization, an electroencephalogram (EEG) was performed which yielded normal results. The patient also reported that he frequently experienced fatigue, dizziness, and intermittent episodes of blurred vision. These events were accompanied with low blood glucose levels noted over the past several months. Over the past six months, he already had two episodes of hypoglycemia requiring hospitalization.

Previously, the patient was diagnosed with diabetes mellitus since three years prior to admission. He initially presented with dizziness and a blood glucose level of 400 mg/dL at a primary care clinic. He denied previous symptoms of polyphagia, polydipsia, polyuria, nor significant weight loss. He had received regular treatment at Pasar Rebo General Hospital over the past year, with reportedly controlled but generally low blood glucose levels. He occasionally monitors his blood glucose levels at home, typically when experiencing symptoms such as palpitations, fatigue, or cold sweats, with readings ranging from 70–100 mg/dL and a most recent HbA1c of 5.3%. His last prescribed medications were metformin 500 mg once daily and glimepiride 4 mg once daily. His appetite was reported as good, eating three meals daily with no nausea or vomiting. According to his wife, at the time of his hypoglycemic episode, he had not yet taken his diabetes medication prior to being found unconscious.

Seven months prior to admission, the patient sought consultation with an otolaryngologist (ENT) specialist due to frequent epistaxis. There was no history of head or facial trauma. He reported a decline in hearing that had been present for about ten years, previously assessed and attributed to a neural hearing disorder. He denied visual disturbances, a sensation of fullness in the ears, or any neck masses. Nasal endoscopy was performed, but due to difficulty evaluating the retropharyngeal area, a head computed tomography (CT) scan was performed. The CT scan revealed a brain mass, suspected to be a pituitary macroadenoma, and he was then referred to the neurosurgery

department in Fatmawati Central General Hospital. However, due to the absence of any symptoms attributable to the tumor, the patient never visited the neurosurgery clinic. He denied symptoms such as widening of the jaw or face, prominent cheekbones, thickening of the lips or tongue, or enlargement of hands and feet. There was no history of nipple discharge or breast enlargement. He also denied palpitations, hand tremors, insomnia, heat intolerance, exophthalmos, irritability, abdominal or thigh striae, bluish skin rashes, double vision, visual field narrowing, or headache.

On arrival, the patient's vital signs were within normal limits. His body mass index was 30.83 kg/m² (obesity grade II). A thorough physical examination revealed no mandibular enlargement, no increased prominence of the frontal or zygomatic bones, no thickening of the lips or macroglossia, and no moon face. There was no exophthalmos. The thyroid was not palpable, and there was no buffalo hump. Chest examination found no signs of gynecomastia, while abdomen examination found to be distended, with no livid striae discovered. Extremities were within normal limits with no tremors.

A blood sample was then drawn, and the complete blood count, kidney function tests and liver enzymes were within normal limits (urea/creatinine/eGFR: 43/1.24/68, AST/ALT: 73/32 U/L). There was slight hyponatremia of 133 mEq/L. Blood sugar at presentation was low at 35 mg/dL. He received 40% dextrose, which corrected his glucose level temporarily, but he subsequently experienced another episode of hypoglycemia. The following is the trend of his glucose levels.

His HbA1c was 5.3%. This patient had also previously undergone a brain CT scan at five months prior to current admission. The CT scan was initially performed to evaluate for nasopharyngeal carcinoma. However, it revealed a round mass in the sella turcica, measuring 1.4 x 1.7 x 1.4 cm, which showed strong post-contrast enhancement, with a differential diagnosis of pituitary macroadenoma.

The patient was diagnosed with recurrent hypoglycemia in the context of obese type 2 diabetes mellitus, along with a concurrent non-functioning pituitary macroadenoma and suspected hypopituitarism. Further investigation

Table 1. Blood glucose levels

Time	Blood Glucose (mg/dL)	Intervention
01:00	Capillary: Low, Venous: 35	Dextrose 40%, 3 flacons
03:50	63	Dextrose 40%, 2 flacons; Dextrose 10% 500 cc/12 hours
05:05	103	Dextrose 10% 500 cc/12 hours
06:05	27	Dextrose 40%, 2 flacons; meal; Dextrose 10% 500 cc/12 hours
07:20	112	Dextrose 10% 500 cc/12 hours
11:00	110	Dextrose 10% 500 cc/12 hours
13:25	79	Dextrose 10% 500 cc/12 hours
15:52	44	Dextrose 40%, 3 flacons; Dextrose 10% 500 cc/12 hours
17:16	79	Dextrose 40%, 2 flacons; Dextrose 10% 500 cc/12 hours
19:32	96	Dextrose 10% 500 cc/12 hours
22:05	40	Dextrose 40%, 2 flacons; Dextrose 10% 500 cc/12 hours
23:05	50	Dextrose 40%, 2 flacons; Dextrose 10% 500 cc/12 hours
23:59	175	Dextrose 10% 500 cc/12 hours
01:30	50	Dextrose 40%, 3 flacons; Dextrose 10% 500 cc/12 hours
03:10	77	Dextrose 40%, 3 flacons; Dextrose 10% 500 cc/12 hours
04:50	75	Dextrose 40%, 3 flacons; Dextrose 10% 500 cc/12 hours
06:24	82	Dextrose 40%, 4 flacons; Dextrose 10% 500 cc/12 hours
07:45	152	Dextrose 10% 500 cc/12 hours

revealed low cortisol and IGF-1 levels (0.9 mcg/dL and 35 ng/mL, respectively). His prolactin level was 104.7 ng/mL, with a normal TSH (0.69 mIU/L) and normal free thyroxine (1.19 ng/dL). Therefore, we consider that this patient was experiencing subtle symptoms of hypopituitarism due to the compression of normal pituitary tissue by a non-functioning macroadenoma mass, resulting in pituitary hormone deficiency manifested as recurrent hypoglycemia.

Figure 1. Clinical photograph of the patient. The patient showed no signs of prognathism, macroglossia, acral enlargement, buffalo hump, or striae livide.

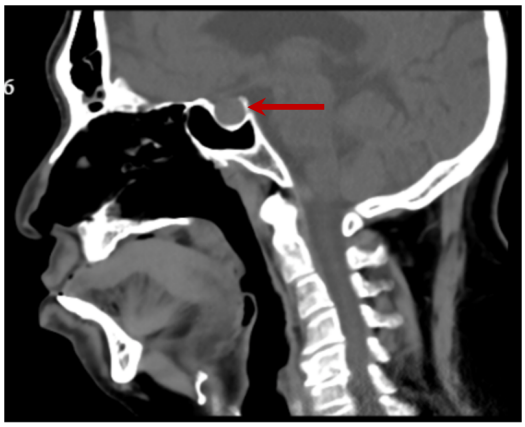


Figure 2. CT scan shows a pituitary adenoma (red arrow).

DISCUSSION

The pituitary gland is located inferior to the hypothalamus, surrounded by the sphenoid bone in a basket-like structure called the sella turcica. It is situated below the optic chiasm.[2] The pituitary gland consists of two lobes: the anterior lobe (also called the adenohypophysis) and the posterior lobe (also called the neurohypophysis). The anterior pituitary produces six hormones: prolactin (PRL), growth hormone (GH), ACTH, LH, FSH, TSH. Pituitary adenoma is a tumor originating from the anterior pituitary (adenohypophysis). These tumors can be classified based on its size, function, and cell of origin:[1, 2]

A. According to size:
    - Microadenoma: diameter <10 mm (<1 cm).
    - Macroadenoma: diameter ≥10 mm (≥1 cm).
    - Giant adenoma: diameter ≥40 mm (≥4 cm).
B. According to functional status:
    - Functional: tumor cells cause increased secretion of one or more anterior pituitary hormones.
    - Non-functional: tumor cells do not secrete excess hormones, but may compress normal anterior pituitary tissue and the pituitary stalk, resulting in deficiencies of other pituitary hormones (hypopituitarism).
C. According to cell origin:

    Pituitary adenomas are neoplasms arising from monoclonal cells, and rarely from a combination of the following cell types:
    - Somatotroph: secretes GH
    - Lactotroph: secretes prolactin
    - Corticotroph: secretes ACTH
    - Gonadotroph: secretes LH/FSH
    - Thyrotroph: secretes TSH

The presentation of pituitary adenomas depends on the size of the tumor (mass effect symptoms) and its functional status (hormonal symptoms). Patients may be asymptomatic if the tumor is small and not hormonally active, as frequently seen in pituitary incidentalomas. Patients with pituitary macroadenomas typically present with symptoms related to mass effect and hormonal disturbances.[1]

A. Symptoms of mass effect:
    - Visual disturbances: suprasellar extension of a pituitary adenoma can compress the superior aspect of the optic chiasm, resulting in visual field defects. Bitemporal hemianopsia is the most common pattern. Involvement of the oculomotor nerves can cause diplopia.[1, 2] Direct invasion of the optic nerve (cranial nerve II) may lead to decreased visual acuity.[2] Therefore, visual function should be clinically evaluated through tests of visual acuity and visual fields.[3]
    - Headache: a nonspecific symptom and may indicate pressure on the dura mater or the sellar diaphragm exerted by the tumor mass. This symptom is more commonly seen in non-functioning adenomas, as these tumors do not secrete enough hormone to cause endocrine symptoms and instead present with mass effect.[2]
    - Cranial nerve palsies: if the adenoma extends laterally into the cavernous sinus, it can compress cranial nerves III (oculomotor), IV (trochlear), and VI (abducens), leading to ocular motor disturbances such as double vision.[2]
    - Hormone deficiency (hypopituitarism): deficiency of one or more anterior pituitary hormones can occur due to compression of the pituitary stalk or destruction of normal pituitary tissue by the tumor mass. Gonadotropin

deficiency causes amenorrhea in women and erectile dysfunction in men. GH deficiency leads to fatigue and weight gain. TSH deficiency results in fatigue, weight gain, cold intolerance, and constipation. ACTH deficiency causes fatigue, weight loss, hypotension, dizziness, nausea, vomiting, abdominal pain, and arthralgia.[1] Symptoms of hypopituitarism are present in about 30% of pituitary adenomas.[2]

B. Symptoms of hormone hypersecretion:
   - Prolactin hypersecretion: in women, this causes oligomenorrhea or amenorrhea and galactorrhea. In men, it leads to erectile dysfunction and gynecomastia. Elevated prolactin also suppresses gonadotropin levels, resulting in infertility, decreased libido, and osteoporosis in both sexes.[1]
   - GH hypersecretion (acromegaly): symptoms include an increase in ring or shoe size, coarse facial features, prominent frontal bone, enlarged nose, prognathism (enlarged mandible), and macroglossia (enlarged tongue). Patients may also present with hypertension and obstructive sleep apnea at diagnosis.[1]
   - ACTH hypersecretion (Cushing's disease): manifestations include weight gain, rounded face (moon face), supraclavicular fat pads, purple (livide) striae on the abdomen, proximal muscle weakness, easy bruising (ecchymosis), bone fractures, and mood disturbances.[1]
   - TSH hypersecretion (central hyperthyroidism): symptoms include palpitations, weight loss, tremor, diarrhea, heat intolerance, and insomnia.[1]
   - Gonadotropin hypersecretion: excess secretion can cause ovarian overstimulation, increased testosterone levels, and testicular enlargement. However, many gonadotropin-secreting adenomas do not produce clinically significant hormone excess and are thus considered non-functioning tumors. These may still cause pituitary insufficiency due to compression of the pituitary stalk or destruction of normal pituitary tissue by the tumor mass.[4]

The detection of pituitary adenomas requires radiographic imaging. Most pituitary adenomas are incidentally detected on CT scans performed for other reasons. However, magnetic resonance imaging (MRI) is the imaging modality of choice for diagnosing pituitary disorders due to its superior sensitivity and specificity for soft tissue evaluation (sensitivity 61–72%, specificity 88–90% for sellar masses).[2, 4] Contrast-enhanced MRI is necessary to differentiate pituitary tumors from aneurysms and assess for intralesional hemorrhage.[1]

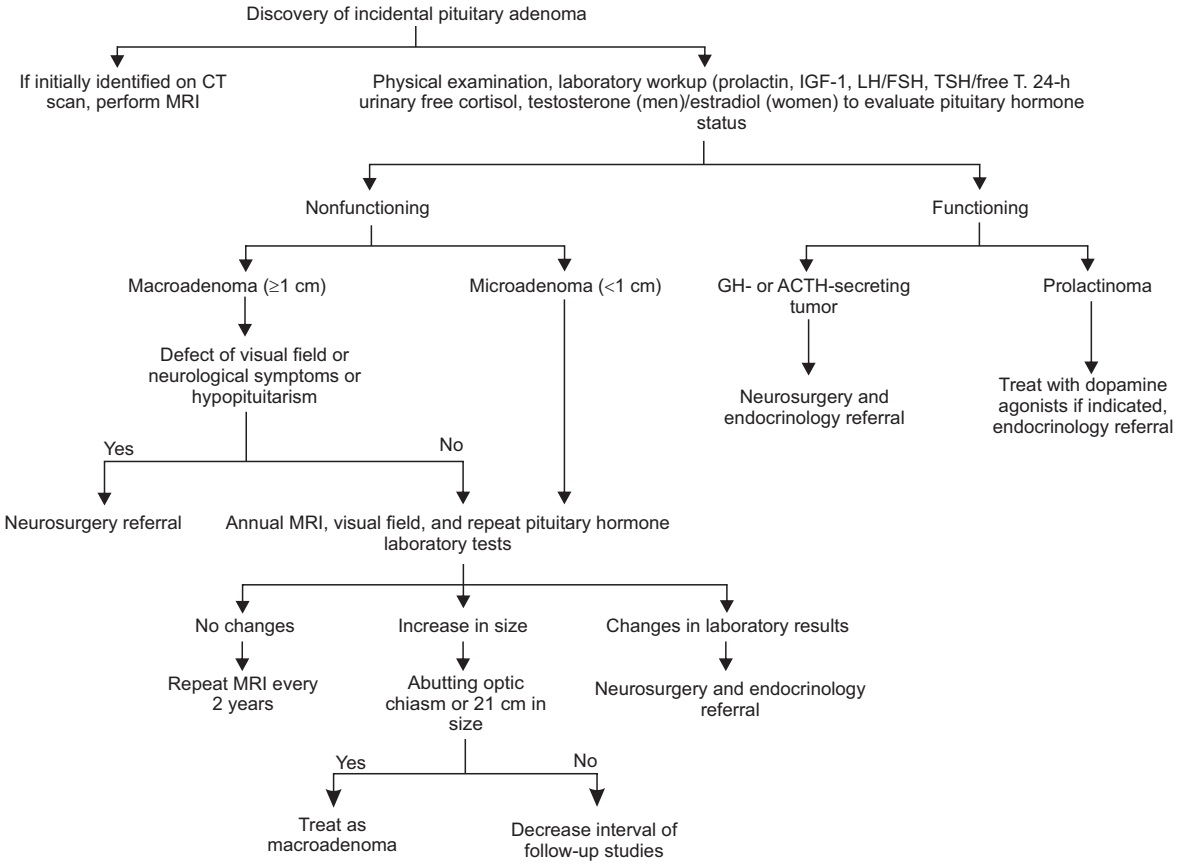
When a pituitary mass is found incidentally, diagnostic workup should determine whether it is functional or non-functional.[2] The 2011 Endocrine Society guidelines for pituitary incidentalomas recommend comprehensive pituitary function assessment, even in asymptomatic patients.[5] Biochemical evaluation includes:[1]

- Prolactin**:** serum levels generally correlate with tumor size. Prolactin <200 ng/mL suggests microadenoma, while levels >200–250 ng/mL indicate prolactin-secreting macroadenoma.[1, 2]
- IGF-1/GH: serum IGF-1 screens for acromegaly. In clinically suspected cases with normal IGF-1, GH levels are measured after a 75 grams of oral glucose tolerance test. Failure to suppress GH below 1 ng/dL confirms acromegaly.[1]
- Morning serum cortisol**:** screening for Cushing's disease includes late-night salivary cortisol, 24-hour urinary free cortisol, or 1

mg overnight dexamethasone suppression test (DST). A post-DST cortisol ≥1.8 mcg/dL indicates hypercortisolism. Biochemical confirmation requires ACTH measurement: elevated ACTH suggests corticotroph adenoma.[1]

- LH, FSH, estradiol, testosterone: Low sex hormones with normal/low LH/FSH indicate hypogonadotropic hypogonadism. Interpretation is confounded by oral contraceptives in women, and FSH naturally rises post-menopause.[1]
- TSH, free T4: TSH-secreting adenomas show elevated T4/T3 with normal/high TSH (central hyperthyroidism pattern).

The finding of a pituitary adenoma in this case report is classified as an incidentaloma because the pituitary mass was discovered during a head CT scan performed for another purpose, in this case, nasopharyngeal malignancy screening by the ENT specialist. With a diameter of ≥1 cm, the lesion in this patient is categorized as a macroadenoma. According to the 2011 Endocrine Society guidelines for pituitary incidentalomas, a comprehensive assessment of pituitary hormone function is necessary for such patients. The clinical approach for pituitary incidentaloma is shown in Figure 3. Clinically, this patient did not exhibit symptoms of anterior pituitary hormone hypersecretion (GH, prolactin, ACTH, TSH). Hormone laboratory tests in this patient also showed normal TSH and free thyroxine levels (0.69 mIU/L and 1.19 ng/dL respectively). Due to several limitations, we could not obtain the LH/FSH as well as testosterone levels in this patient. Although the prolactin level was elevated, it did not reach the 200 ng/mL cutoff required to categorize it as a prolactinoma. Therefore,



ACTH: adrenocorticotropic hormone; FSH: follicle-stimulating hormone; GH: growth hormone; IGD-1: insulin-like growth factor 1: LH: luteinizing hormone; T Thyroxine, TSH: thyroid-stimulating hormone

Figure 3. Flowchart for the evaluation and management of pituitary incidentaloma.[2, 5]

based on the pituitary hormone evaluation, the patient falls into the category of non-functioning macroadenoma.

There are several causes of hypoglycemia in diabetic patients, such as reduced food intake, improper medication administration, decreased kidney function, and hepatic dysfunction. In this case, we attempted to rule out iatrogenic causes of hypoglycemia in a type 2 diabetes mellitus patient who was taking antidiabetic medications. It was noted that the patient was taking metformin, which has a low risk of causing hypoglycemia.[6] Although the patient was also receiving glimepiride, its risk of causing hypoglycemia is relatively lower compared to other sulfonylureas, which are known for their higher hypoglycemic risk. It is also important to note that the patient's hypoglycemic episodes occurred before he took his diabetes medications and there was no history of reduced food intake beforehand. Additionally, the patient's kidney and liver function were relatively preserved, which did not increase the risk of hypoglycemia.

Hormone laboratory tests in this patient showed low cortisol level (0.9 mcg/dL), suggesting an adrenal insufficiency that can lead to hypoglycemia in this patient. Given the presence of a pituitary macroadenoma, it is likely for the adrenal insufficiency to be secondary. However, due to several limitations, we could not obtain the ACTH level in this patient. Furthermore, the occurrence of hypoglycemia in this patient may still be linked to Houssay phenomenon, first described by Dr. Bernardo Houssay in 1931,[7] which involves the resolution of diabetes due to hypopituitarism.[8] This phenomenon explains recurrent hypoglycemia in diabetic patients with hypopituitarism. In this case, hypopituitarism likely involves deficiencies in ACTH, cortisol, and GH—several key counterregulatory hormones that oppose insulin during hypoglycemia. The absence of these hormones disrupts glucose regulation, leading to recurrent hypoglycemia. Laboratory tests in this patient revealed low cortisol level (0.9 mcg/dL) and low IGF-1 level (35 ng/mL), consistent with hypopituitarism secondary to the macroadenoma. These findings align with the mechanism of Houssay phenomenon, where pituitary hormone deficiencies impair counterregulatory responses, resulting in hypoglycemia despite the patient's type 2 diabetes status. Therefore, we propose that the recurrent hypoglycemic episodes encountered in this patient were attributable to a non-functioning adenoma that compresses normal anterior pituitary tissue and the pituitary stalk, causing hypopituitarism.

The management of pituitary adenomas can be divided into functional and non-functional tumors (as shown in Figure 3). For non-functional adenomas, not all cases require surgery. Transsphenoidal resection is indicated in patients with visual field deficits due to tumor compression, other visual abnormalities (e.g., ophthalmoplegia), optic nerve or chiasmal compression on imaging, pituitary apoplexy, loss of endocrine function, and significant tumor growth progression. For non-functioning adenomas not requiring surgery, regular monitoring is essential to assess tumor growth and hypopituitarism development. Head MRI should be performed annually for the first three years, less frequently if stable thereafter.[1, 2] Repeat biochemical testing via endocrine panels is not recommended unless tumor enlargement occurs or patients develop hormone hypersecretion symptoms.[2]

CONCLUSION

Pituitary adenomas are mostly discovered incidentally during radiological examinations performed for other purposes. Tumor size, functional status (hyper- or hypopituitarism), and symptoms of mass effect guide subsequent management. Patients with pituitary adenomas require evaluation by a multidisciplinary team involving endocrinology, neurosurgery, and

ophthalmology. Even in patients without overt symptoms of hormone hypersecretion, the possibility of subtle hypopituitarism due to tumor-induced pituitary dysfunction should not be overlooked.

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CASE REPORT

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

Challenges in The Management of Kallmann Syndrome : A Case Report

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ABSTRACT

Background: Kallman syndrome is combined disorder of hypogonadotropic hypogonadism and anosmia. Incidence of congenital hypogonadotropic hypogonadism is 1-10:100,000 live births, and approximately 2/3 and 1/3 of cases are caused by Kallmann syndrome and idiopathic hypogonadotropic hypogonadism, respectively.

Case illustration: We report a man, 35 years old, with complaints of small penis, small voice, impaired smell, gynecomastia, narrowing of visual field, mustache not growing, little pubic and armpit hair. Patient underwent surgery on both breasts with histopathological results of gynecomastia, no malignancy. Testicular ultrasound results showed bilateral testicular atrophy. Laboratory results showed karyotype 46XY, Follicle-stimulating hormone 1.79 mIU/mL, Luteinizing hormone 1.49 mIU/mL, testosterone <0.03 ng/mL, estradiol 5.0 pg/mL, prolactin 6.75 ng/mL and prostate-specific antigen 0.473 ng/mL. Head CT scan imaging showed bilateral otitis media, mastoiditis and sinusitis. Patient was diagnosed Kallmann syndrome, anxiety and depression symptoms (ADS) chronic tubotympanic suppurative otitis media, sinusitis, oculus dexter and sinister hemianopsia. Patient was treated with testosterone undecanoate injection 1000 mg IM every 3 months, levofloxacin 500 mg PO once daily, avamys nasal spray twice daily.

Discussion: Symptoms of Kallman syndrome can include absent or incomplete pubertal development, anosmia or hyposmia, and low sex steroid levels. KAL1 gene mutations cause Gonadotropin-releasing hormone (GnRH) deficiency, associated with Kallmann syndrome. Testosteron replacement is indicated for men who already have children or have no desire for children. Surgery should be considered as the last option in patients with considerable discomfort, psychological stress, cosmetic problems, long-standing gynecomastia (>12 months) and suspected malignancy.

Conclusion: The aim of testosterone therapy is to reverse the symptoms of hypogonadism, and surgery is last option in patients with considerable discomfort.

Keywords: Kallmann syndrome, small penis, gynecomastia, testosteron undecanoate**,** surgery.

BACKGROUND

Kallmann syndrome (KS) is a clinically and genetically heterogeneous disorder, which combines hypogonadotropic hypogonadism with anosmia.[1,2] Congenital hypogonadotropic hypogonadism is a rare disorder that results from the failure of the normal episodic gonadotropin-releasing hormone (GnRH) secretion, leading to delayed puberty and infertility.[3] Congenital hypogonadotropic hypogonadism is often occurs in adolescence or afterward, and the disease is mostly due to developmental defects in GnRH neuron migration or in the maturation of the GnRH neuronal network and is often associated with congenital features congenital hypogonadotropic hypogonadism hypogonadism.[3]

Hypogonadism can result from a primary testicular disorder (hypergonadism) or occur secondary to hypothalamic-pituitary dysfunction (hypogonadotropic).[2] The incidence of congenital hypogonadotropic hypogonadism is approximately 1-10:100,000 live births, and approximately 2/3 and 1/3 of cases are caused by KS and idiopathic hypogonadotropic hypogonadism, respectively.[2]

CASE ILLUSTRATION

We report a man, 35 years old, with complaints of a small penis, small voice, impaired smell, enlargement of both breasts, mustache not growing, little pubic and armpit hair and narrowing of visual field. In February and April 2023, this patient underwent left and right breast surgery at Wates Regional Hospital with histopathological results of gynecomastia, and no malignancy was found. This patient was referred to Dr. Sardjito hospital and underwent several examinations. Bilateral testicular ultrasound results on June[6th] 2023 were found bilateral testicular atrophy. Laboratory results showed karyotype 46 XY, decreased levels of testosterone

< 0.03 ng/mL, Luteinizing hormone (LH) 1.49 mIU/mL, and estradiol 5.0 pg/mL; Follicle-stimulating hormone (FSH) 1.79 mIU/mL, prolactin 6.75 ng/mL, and PSA 0.473 ng/mL. Head Computed Tomography scan (CT scan) imaging on September[1st] 2023 impressions of bilateral otitis media, bilateral mastoiditis, sinusitis of frontal, ethmoidal, and bilateral maxillary. Evaluation of head Magnetic Resonance Imaging (MRI) results on June[12th] 2024 impression, no visible pituitary adenoma; cavum septum pellucidum et vergae; no visible images of infarction, bleeding, infection or intracranial mass, and no nasal septum deviation visible.This patient was diagnosed with KS, anxiety and depression symptoms (ADS) Chronic tubotympanic suppurative otitis

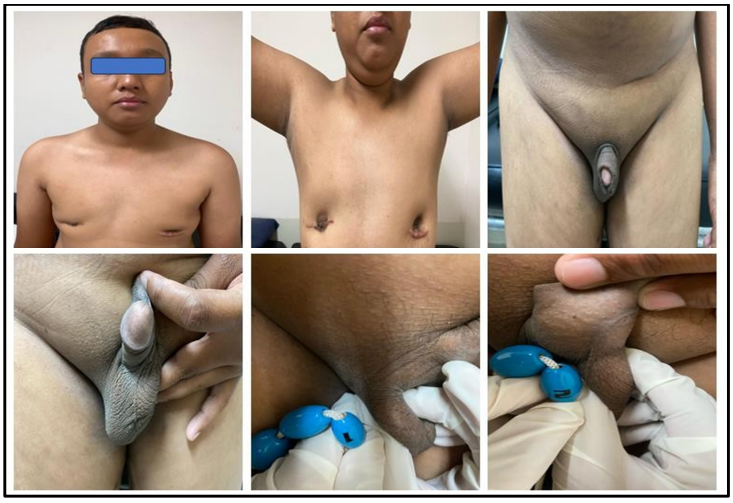

Figure 1. Clinical features of patient with micropenis, and post-mastectomy

Table 1. Patient laboratory results

Laboratory results	26/5/23	6/6/23	30/10/23	18/11/23	27/12/23	17/4/24	10/6/24	Normal range
FSH	1.79							1.5-12,4 mIU/mL
LH	1.49							1.7-8,6 mIU/mL
Estradiol (E2)	< 5.00							11.3-43.2 pg/mL
Testosterone	< 0.03		0.10	1.55	3.27	2.42		2.8-8.0 ng/mL
Prolactin	6.75	2.00						4.6-21.4 ng/mL
Karyotype		46XY						
PSA totals					0.473			≤ 4.0 ng/mL
Urea							12	6-20 mg/dL
Creatinine							0.98	0.67-1.17 mg/dL

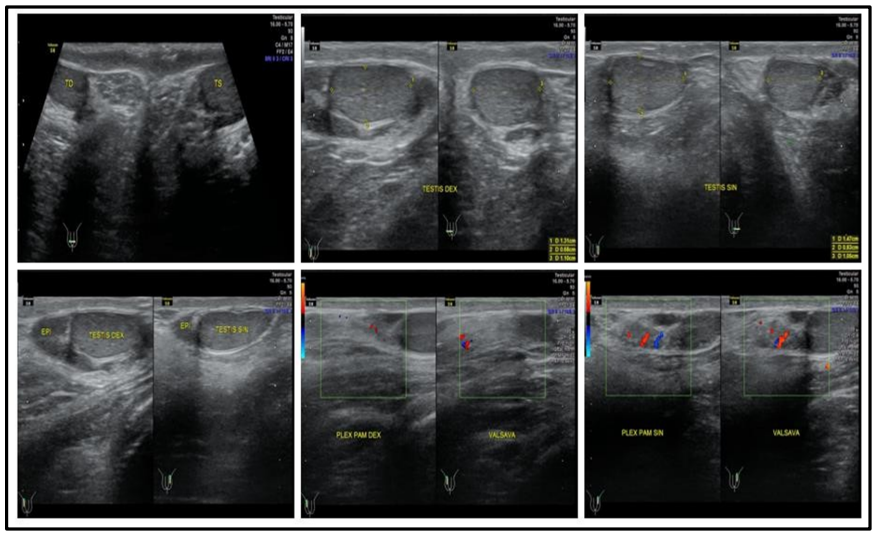

Figure 2. Ultrasound of the patient's testicles on June[6th] 2023, Impression of bilateral testicular atrophy (right testis measuring 1.31 x 0.68 x 1.x 1 cm; left testis measuring 1.47 x 0.83 x 1.05 cm). No varicoceles were seen in the bilateral testicles.

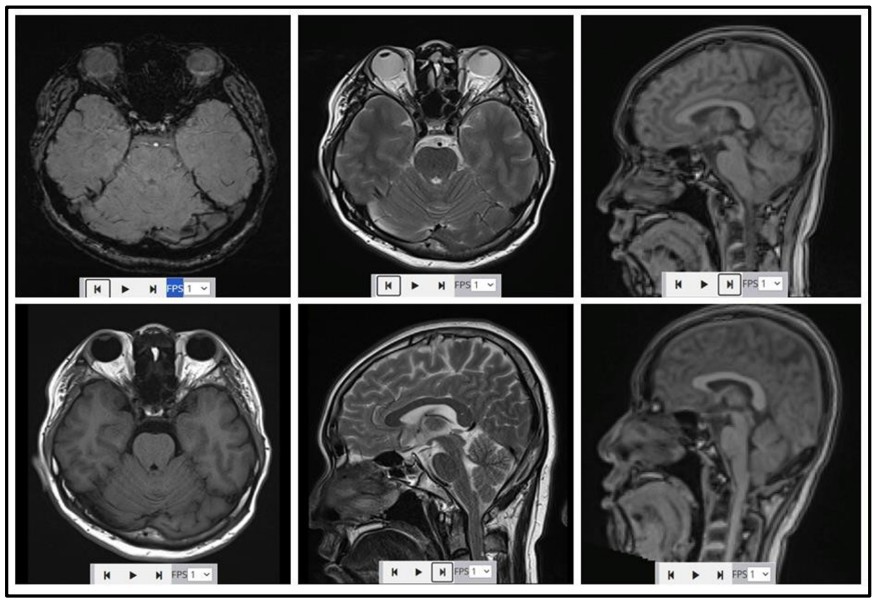

Figure 3. Head MRI results on June[12th] 2024, Impression, no visible pituitary adenoma; cavum septum pellucidum et vergae; no visible images of infarction, bleeding, infection or intracranial mass, and no nasal septum deviation visible.

media, sinusitis, Oculus Dextra et Sinister (ODS) hemianopsia. This patient was consulted to ENT and Ophthalmologist. This patient was treated with testosteron (sustanon) injection 250 mg IM twice a week for 5 months and then continued with testosterone undecanoate (nebido) injection 1000 mg intramuscular (IM) every 3 months, levofloxacin 500 mg peroral (PO) once daily, folic acid 1 mg PO once daily, Avamys nasal spray twice daily. Patient follow-up revealed that the penis size slightly enlarged, voice slightly louder, and testosterone fluctuations increased.

DISCUSSION

Congenital hypogonadotropic hypogonadism is divided into anosmic hypogonadotropic hypogonadism KS and congenital normosmic isolated hypogonadotropic hypogonadism (idiopathic hypogonadotropic hypogonadism).[2] In hypogonadotropic hypogonadism, secretion of GnRH of pituitary is absent or inadequate.[2]

Analysis of KS gene mutations found mutations in KAL1, FGFR1, FGF8, PROK2, PROKR2, CHD7, and WDR11.[4] KAL1 gene mutations cause GnRH deficiency, associated with KS. KAL1 encodes the anosmin-1 protein, which plays a role in regulating GnRH neuron adhesion and axonal migration. This gene is mapped to the X- chromosome Xp22.32.[2] GnRH neurons are an unusual neuronal population, as they originate outside the central nervous system in the olfactory placode, and follow a complex migration route to reach their final destination in the hypothalamus.[3]

To date, a molecular genetic diagnosis is attained in only approximately 30% of Kallmann syndrome patients, which implies the existence of additional genes underlying Kallmann syndrome.[4]

Diagnosis

For male infants, micropenis with or without cryptorchidism can be suggestive of congenital hypogonadotropic hypogonadism, and typically, low serum testosterone, LH, and FSH levels. However, hormonal testing is not routinely prescribed for male infants with micropenis or cryptorchidism.[3] Suspicion of KS in a patient if the following criteria are found:

1. Absent or incomplete pubertal development by the age of 18 years,
2. Anosmia or hyposmia based on either anamnestic information, formal testing (e.g. olfactometry), or testing with familiar odors,
3. Low circulating basal sex steroid levels in association with inappropriately low or normal gonadotropin levels, and subnormal or normal response to GnRH stimulation test.[4]

The symptoms of hypogonadotropic hypogonadism can include decreased libido, impaired erectile function, muscle weakness, increased adiposity, depressed mood, and decreased vitality.[2] Patients with Kallmann syndrome usually lack puberty, but the reproductive phenotype may vary from severe hypogonadism (cryptorchidism or micropenis in male infants) to reversal of hypogonadotropism later in life.[4] Gynecomastia is caused by an imbalance between estrogen and androgen action or an increased estrogen to androgen ratio, due to increased estrogen production, decreased androgen production or both.[5] Gynecomastia causes anxiety, psychosocial discomfort and a fear of breast cancer.[5]

The clinical characteristics of hypogonadotropic hypogonadism are androgen deficiency and delayed pubertal sexual maturation.[2] Complete physical examination can help the diagnosis which includes mirror movement assessment, measurement of testicular volume with a ruler (length × width^2 × 0.52), olfaction was assessed with smell testing (the 40-item smell testing from University of Pennsylvania Smell Identification Test, (UPSIT), where a score < 5 percentile on the UPSIT is classified as anosmic.[4]

A set of laboratory investigations can integrate evaluations such as testosterone, estradiol, sex hormone-binding globulin, LH, FSH, TSH, prolactin, human chorionic gonadotropin (hCG), alpha-fetal protein, liver and renal function tests.[6] Low blood testosterone levels and low pituitary hormone levels confirm the hypogonadotropic hypogonadism diagnosis.[2] In male, circulating testosterone levels in patients with congenital hypogonadotropic hypogonadism are usually low, that is, < 3 nmol/L (86.5 ng/dL).[3]

A prolonged stimulated intravenous GnRH test can be useful.[2] Inhibin B is a hormone secreted by sertoli cells and reflects sertoli cell number and function. Inhibin B is under the control of FSH. Healthy seminiferous tubules after puberty also regulate inhibin B production, likely through the control of spermatids. Most men with congenital hypogonadotropic hypogonadism with absent puberty with or without micropenis and cryptorchidism exhibit low serum inhibin B levels (< 30-60 pg/mL), indicating a reduced sertoli cell population. This is consistent with the absence of GnRH-induced FSH stimulation of the seminiferous tubules during fetal life and minipuberty. Higher serum inhibin B levels are encountered in a minority of patients with absent puberty but are found in most patients with partial puberty or acquired hypogonadotropic hypogonadism, consistent with a robust activation of the hypothalamus-pituitary-gonadal axis during minipuberty. Serum inhibin B levels correlated well with testicular size, and low inhibin B level is a negative predictor of fertility.[3]

During minipuberty, congenital hypogonadotropic hypogonadism infants have low anti mullerian hormon (AMH) levels, which can be normalized by Recombinant Follicle-Stimulating Hormone (rFSH) and Recombinant Luteinizing Hormone (rLH) treatment. rFSH treatment will induce proliferation of immature sertoli cells, and thus increases AMH levels; whereas hCG treatment will increase intratesticular testosterone levels and decreases AMH levels.[3]

Although an orchidometer is often used in clinical practice, testicular ultrasound has the advantage to assess not only testicular size but also testicular localization. The measurement of testicular size with ultrasound is important to determine the severity of GnRH deficiency and track the progress of testicular maturation during fertility treatment.[3] Besides that, ultrasound can assess the structure of the adrenals and kidneys. Cerebral magnetic resonance imaging (MRI) protocol was used to visualize the olfactory bulbs, sulci, and inner ears.[4] In Kallmann syndrome, cerebral MRI can show an anomalous morphology or even absence of the olfactory bulb.[2] Strategy for diagnosis of Kallmann syndrome is shown in figure 4.

Therapy

Early diagnosis and gonadotrophin therapy can prevent negative physical sequelae and mitigate psychological distress with the restoration of puberty and fertility in affected individuals.[7] Therapeutic goals in the adolescent male with congenital hypogonadotropic hypogonadism are to induce virilization, reach optimal adult height, acquire normal bone mass and body composition; achieve normal psychosocial development, and to gain fertility.[3]

There is no uniform KS treatment regimen used internationally.[3] The main medical intervention options include androgen, anti-estrogens, and aromatase inhibitors therapy. In male infants with severe GnRH deficiency, the main goals of hormonal treatment are to increase the penile size and to stimulate testicular growth. HCG therapy with or without a combination of nasal spray of GnRH has been shown to be effective to treat cryptorchidism in neonates and prepubertal boys. Combined gonadotropin therapy in male patients with

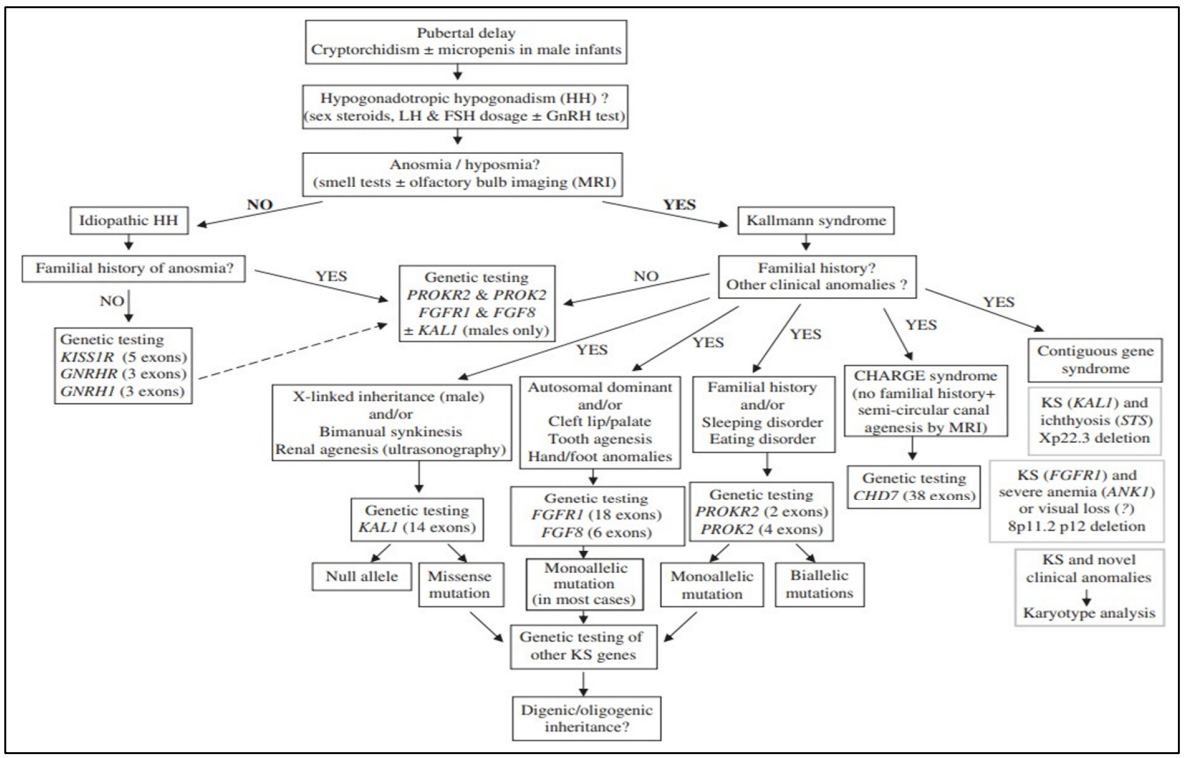

Figure 4. Genetic testing strategy for Kallmann syndrome.[1]

congenital hypogonadotropic hypogonadism during the neonatal period can have a beneficial effect on both testicular endocrine function and genital development, because it can stimulate sertoli cell proliferation and the growth of seminiferous tubules.[3]

Increasing testicular size correlates with the increase in sertoli cell mass, could lead to better outcomes in terms of sperm output during fertility induction in adolescence or adulthood. For patients with congenital hypogonadotropic hypogonadism seeking treatment in later adolescence or early adulthood, a higher dose of testosterone can be used to induce rapid virilization. Initial testosterone doses (such as 100 mg of testosteron enanthate monthly) can be quickly increased to 250 mg IM monthly.[3]

Long-term androgen treatment is required in male patients with congenital hypogonadotropic hypogonadism to maintain normal serum testosterone levels, libido, sexual function, bone density, and general well being. Of note, testosterone treatment does not stimulate testicular growth or spermatogenesis, because intragonadal testosteron production is needed to stimulate spermatogenesis. In contrast, increased testicular growth during testosterone treatment indicates congenital hypogonadotropic hypogonadism reversal and requires treatment withdrawal followed by monitoring of hormone profiling.[3] Fertility induction in male can be accomplished either by long-term pulsatile GnRH therapy or with combined gonadotropin therapy. This therapy will stimulate pituitary gonadotropin secretion and in turn intra gonadal testosterone production, resulting in the initiation and maintenance of spermatogenesis as evidenced by increased testicular volume and sperm output by 12 months of treatment on average.[3]

Induction of testicular maturation in adolescents can be given low doses of hCG (250 - 500 IU twice a week) with increasing increments of 250 – 500 IU every months, and rFSH was added once serum testosterone achieved targeted pubertal level (5,2 nmol/L). This treatment led to a substantial increase

in bitesticular volumes 5 ± 5 to 34 ± 3 mL and induction of spermatogenesis in 91 % of patients.[3] The hormonal treatment options for the induction of puberty in males with congenital hypogonadotropic hypogonadism are presented in table 2.

Table 2. Medical treatment of puberty induction, hypogonadism, and infertility in male patients with congenital hypogonadotropic hypogonadism.[3]

Treatment	Dosing and Administration	Advantages	Disadvantages
Induction of puberty in boys			
T enanthate	Initial dose: 50 mg IM monthly	Standard care with long clinical experience	Premature epiphyseal closure (high dose)
	↑ 50 mg increments every 6–12 mo	Aromatizable to E2: promote bone maturation	Could inhibit TV and spermatogenesis
	Up to 250 mg/mo		Impact on future fertility unknown
Gonadotropin	hCG: initial dose 250 IU SC twice weekly	Stimulate TV growth and spermatogenesis	Not standard treatment
	↑ 250–500 IU increments every 6 mo	Pre-FSH treatment can be beneficial in patients with TV ,4 mL or history of cryptorchidism	Need good compliance in adolescent patients
	Up to 1500 IU three times weekly		Need studies in larger cohorts
	rFSH: dose 75–150 IU SC three times weekly,		
Hypogonadism treatment in adult males			
T enanthate	250 mg IM every 2 to 4 wk	Cost-effective	Relatively frequent IM injection
	Interval adjusted based on trough T	Available around the world	SC route under investigation (302)
		Self-injection	
T undecanoate	1000 mg IM every 10 to 14 wk	Cost-effective	Interval of treatment highly variable follow-up of trough T is important
	Interval adjusted based on trough T	Infrequent injection	Injections by nurses
T gel	50–80 mg/d transdermally	Noninvasive	Risk of transmission by skin contact
		Self-administered	
Treatment of infertility in adult males			
Pulsatile GnRH	SC pump: 25 ng/kg per pulse every 120 min	Most physiological treatment	Not available in many countries
	Dose adapted based on serum T		Require centers with expertise
	Up to 600 ng/kg per pulse		Pituitary resistance (rare)
Gonadotropin	hCG: dose 500–1500 IU SC three times weekly,	Available around the world	Relatively expensive for rFSH
	Dose adjusted based on trough T	For patients with absent puberty (TV ,4 mL):	Frequent injections
	rFSH: dose 75–150 IU SC three times weekly,	Pre-rFSH treatment increases fertility prognosis	
	Dose adjusted based on serum FSH, sperm count		

hCG= Human chorionic gonadotropin ; rFSH= Recombinant Follicle-Stimulating Hormone ; IM= intramuscular ; SC= Subcutaneous

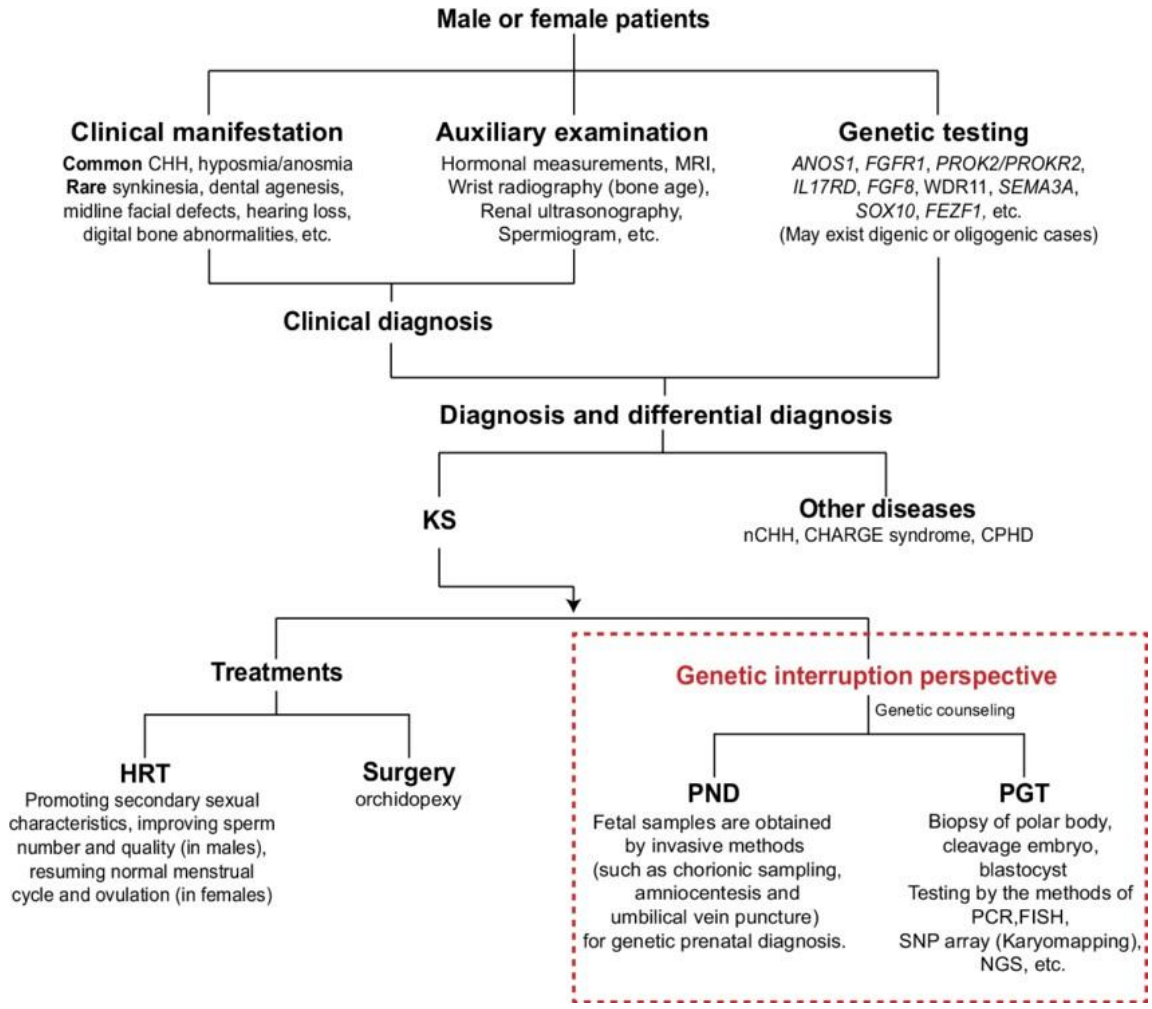

Figure 5. Diagram for clinical management and genetic interruption perspective of Kallmann syndrome.[8]

Cryptorchidism is a factor of poor prognosis for adult fertility and is also a risk factor for testicular malignancy.[3] Surgical orchidopexy is a surgical option for cryptorchidism.[3] Surgery is an option if gynecomastia persists for more than 1 year, complete regression is low due to the predominance of dense fibrous tissue, or gynecomastia is associated with severe pain, tenderness, and psychological distress. Surgery is not recommended in adolescents before the testicles reach adult size, because if surgery is performed before puberty is complete, breast tissue may be regrow.[5] The clinical management of Kallmann syndrome is shown in figure 5.

CONCLUSION

1. Kallmann syndrome is a clinically and genetically heterogeneous disorder, which combines hypogonadotropic hypogonadism with anosmia.
2. The aim of testosterone therapy is to reverse the symptoms of hypogonadism, and GnRH or gonadotropin therapies are an option for men who want to have children.
3. Surgery is the last option in patients with considerable discomfort.

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InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

A Rare Coexistence of Thyrotoxic Cardiomyopathy and Asthma in Graves' Disease: Clinical Challenges and Management Strategies: A Case Report

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ABSTRACT

Graves' disease is the most common autoimmune hyperthyroid disorder. Thyrotoxic cardiomyopathy (TCM) is a rare but potentially lethal complication of thyrotoxicosis, with an incidence of <1%. Beta-blocker is one of the drugs of choice in treating TCM. However, in asthma patient, beta-blocker may induce bronchoconstriction. We report a rare case of a 36-year-old male presented with complaints of shortness of breath, wheezing, cough, and palpitation. The patient had a history of asthma. Physical examination revealed diffuse thyroid enlargement, exophthalmos, tremor, cardiomegaly, irregular heart sounds, rales, wheezing in both lungs, and BMI was underweight. Wayne index was 20 (hyperthyroid) and Burch Wartofsky score was 35 (impending storm). Laboratory results showed low Thyroid-stimulating hormone level and high level of Free-T3, Free-T4, Thyroid-Stimulating Hormone Receptor Antibodies, and N-terminal pro-B-type natriuretic peptide. Chest X-ray showed cardiomegaly. electrocardiogram showed atrial fibrillation RVR. Echocardiography showed segmental wall motion abnormality EF 48%. Patient was diagnosed with Graves' disease with hyperthyroidism, acute asthma exacerbation, Heart failure with mildly reduced ejection fraction NYHA III due to thyrotoxic cardiomyopathy. Patient was treated with methimazole, short-acting beta-agonists, corticosteroid, digitalis, diuretics, anticoagulant, and angiotensin receptor blockers. During follow up, laboratory results, ECG, and clinical symptoms were improved. The management of Graves' disease with hyperthyroidism and TCM focuses primarily on controlling the thyroid hormone levels to prevent further cardiac deterioration. The complex interplay between managing thyroid hormone levels and preventing asthma exacerbation in this patient highlights the need for a multidisciplinary approach to optimize treatment outcomes. Graves' hyperthyroid patients with cardiomyopathy and asthma require holistic, comprehensive, and meticulous drug selection to prevent exacerbation.

Keywords: Graves' disease, hyperthyroidism, asthma, thyrotoxic cardiomyopathy.

INTRODUCTION

Graves' disease is the most common autoimmune hyperthyroid disorder, accounting for 60-80% of hyperthyroid cases. The incidence of Graves' disease is 20-40 cases per 100,000 population per year and is most common in people aged 20-50 years. Graves' disease is more common in women than in men.[1,2] The prevalence of hyperthyroidism in Indonesia is 0.6% in women and 0.3% in men of the total population of Indonesia and is most often caused by Graves' disease.[3] Graves' disease occurs based on an autoimmune process. Thyroid autoantibodies or Thyroid Receptor Autoantibodies (TRAbs) stimulate the Thyroid Stimulating Hormone (TSH) receptor in the thyroid gland, resulting in excessive secretion of thyroid hormone.[4]

Manifestations of hyperthyroidism vary from mild to severe including fatigue, weight loss, palpitations, tremors, and atrial fibrillation. Excessive thyroid hormone levels will affect the cardiovascular system, where uncontrolled hyperthyroidism can cause cardiomyopathy and heart failure. Thyrotoxic cardiomyopathy (TCM) is a rare but potentially lethal complication of thyrotoxicosis, with an incidence of <1%. Graves' disease is most often associated with TCM.[5] TCM causes severe impairment of left ventricular function and can lead to cardiogenic shock.[6]

Early diagnosis of TCM is essential because patients require immediate supportive therapy. The goal of TCM treatment is to restore euthyroidism and manage cardiovascular manifestations. Achieving euthyroid status will improve cardiovascular conditions and provide a better prognosis.[7] Beta-blockers are safe and effective first-line drugs for managing cardiovascular symptoms.[8,9] However, in asthma patients, beta-blockers may induce bronchoconstriction. The use of beta blockers in TCM patients with asthma should be based on individual risk assessment.[10] This case report aims to present a case of Graves' disease with a rare complication of thyrotoxic cardiomyopathy accompanied by asthma.

CASE ILLUSTRATION

A 36-year-old man came to the emergency room with complaints of shortness of breath and wheezing for three days before hospital admission. The symptoms were felt continuously and worsens in the morning, at night, or when exposed to cold temperatures. He also felt shortness of breath when walking more than two meters and sleeps more comfortably with two pillows. He can still speak in full sentences. The patient also complained of coughing for one week ago. The cough is felt to have phlegm but the patient has difficulty expelling the phlegm. He also felt palpitations for two months ago and has worsen in the last week. Palpitations were felt continuously and did not improve with rest. The patient felt hungry often and ate often but lost weight. He has lost about 4-5 kg in the last month. His eyes appeared more prominent. He also felt excessive sweating even though he was sedentary. These complaints have been felt for the past two months. The patient was diagnosed with hyperthyroidism one month ago and was treated with thiamazole 20 mg in the morning and 10 mg at night, propranolol 10 mg three times a day.

Two weeks earlier, the patient was admitted to a private hospital due to a viral infection. Before the scheduled check-up, the patient's asthma relapsed. He has a history of asthma since childhood, but has not had a relapse for almost 20 years. When his asthma relapses, he uses salbutamol. The patient has allergies to dust and seafoods, especially shrimp and crab. There was no history of hypertension and diabetes. The patient defecates 1-2 times a day with normal stool consistency. The patient urinates 4-5 times a day with urine volume of approximately 100-200 ml and clear yellow in colour.

On physical examination, the patient's Body Mass Index (BMI) was 17.9 kg/m^2 (underweight), blood pressure was 123/74 mmHg, heart rate was 110 times/minute, respiratory rate was 30 times/minute, and temperature was 38.7°C. On head examination, atrophy of temporalis muscle and exophthalmos were found in the eyes. The neck examination revealed diffuse thyroid enlargement (Figure 1). Cardiac examination revealed enlarged heart borders and irregular heart sounds. Pulmonary examination revealed rales and wheezing. On extremity examination, tremor was found. The patient's Wayne Index was 20 indicating hyperthyroidism and the Burch Wartofsky Score was 35 indicating impending storm.

Laboratory results showed low TSH level (0.01 ulU/mL) and high levels of Free-T3 (7.99 pmol/l), Free-T4 (46.28 pmol/l), TRAb (>40 IU/L), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (285 pg/ml). ECG showed atrial fibrillation with variable conduction RVR 120

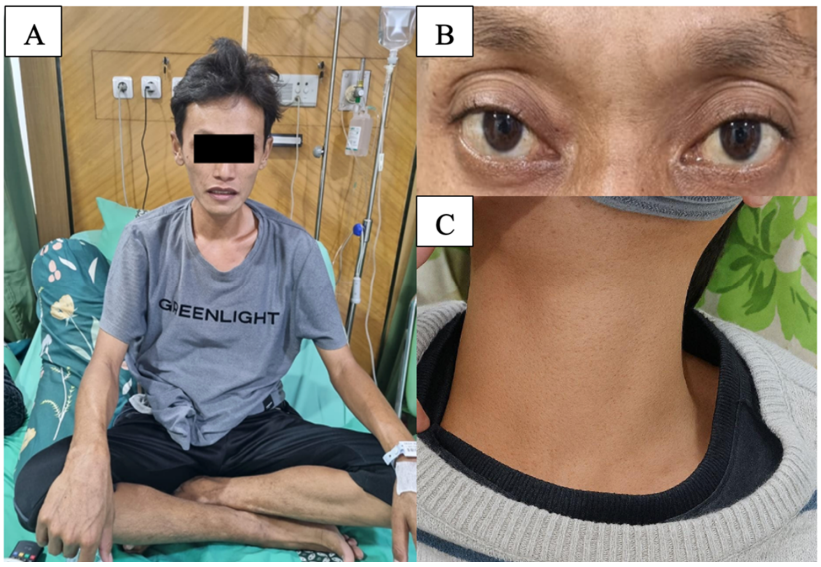

Figure 1. Clinical picture at admission of the patient showing (A) atrophy of temporalis muscle and underweight BMI, (B) exophthalmos, and (C) diffuse thyroid enlargement.

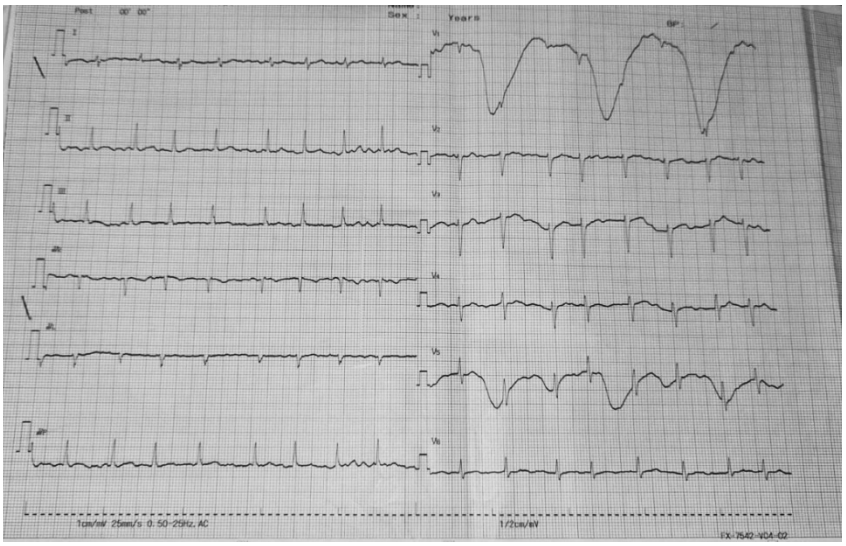

Figure 2. ECG at admission showing atrial fibrillation with variable conduction RVR 120 bpm, normal axis.

bpm, normal axis (Figure 2). Chest X-ray showed cardiomegaly with Cardio-Thoracic Ratio 63% (Figure 3). Echocardiography showed segmental wall motion abnormality with EF 48% (Simpson 46%) (Figure 4).

The patient was diagnosed with Graves' disease with hyperthyroidism, acute asthma exacerbation, and Heart failure with mildly reduced ejection fraction NYHA III due to thyrotoxic cardiomyopathy. He was treated with methimazole 10 mg once daily, valsartan (ARB) 40 mg once daily, spironolactone (aldosterone

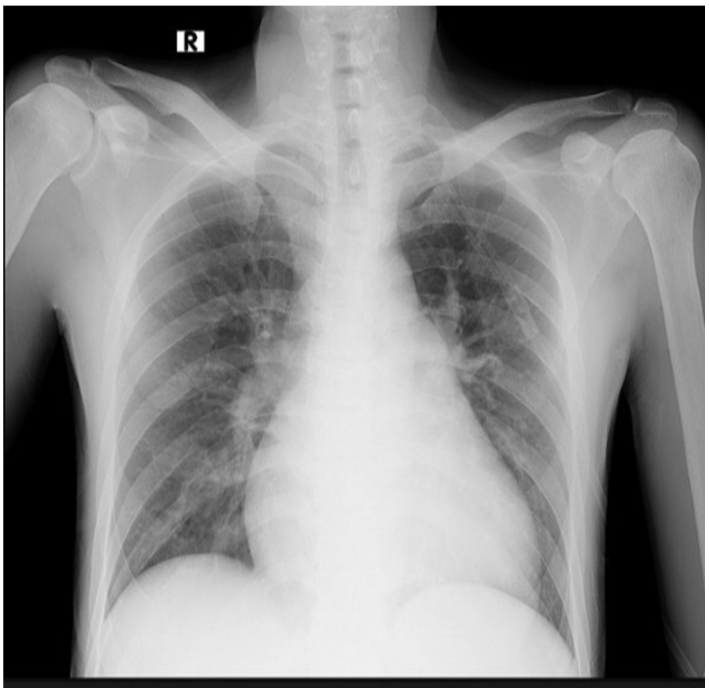

Figure 3. Chest x-ray at admission showing cardiomegaly with CTR 63%.

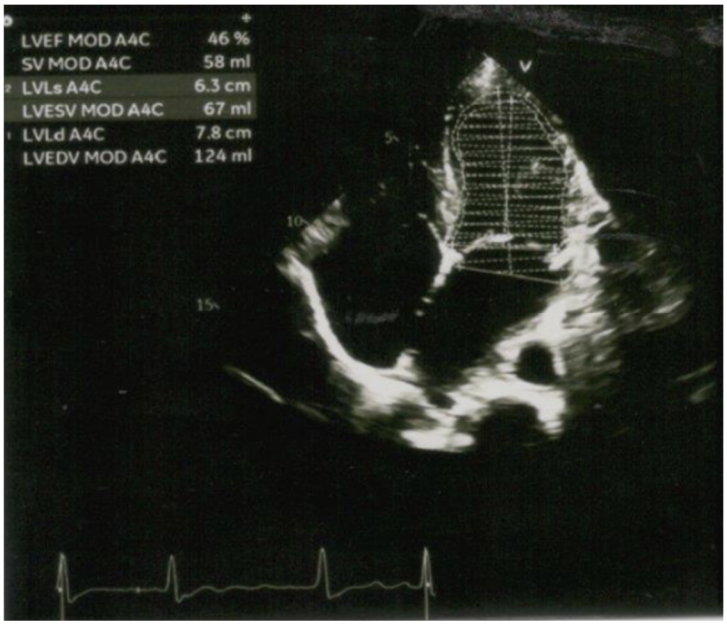

Figure 4. Echocardiography at the second day of hospital stay showing segmental wall motion abnormality with EF 48% (Simpson 46%).

antagonist) 25 mg once daily, furosemide (diuretic) 20 mg once daily, digoxin 0.25 mg once daily, warfarin (anticoagulant) 1 mg once daily, nebulized budesonide and salbutamol every 8 hours. During treatment follow ups, the patient reported that his symptoms had improved significantly. Clinically, the symptoms of hyperthyroidism and TCM gradually subsided. Treadmill test after one month of treatment showed normal resting electrocardiogram (ECG), above average (>20%) functional capacity, and appropriate responses of heart rate and blood pressure to exercise. There were no chest pain, arrhythmias, or ST changes during testing (Figure 5). Serial laboratory results showed decrease of FT4 level and increase of TSH level (Figure 6).

DISCUSSION

Asthma is a disorder in which there is chronic inflammation of the respiratory tract that causes hyperreactivity of the bronchi, characterized by recurrent episodic symptoms of wheezing, coughing, shortness of breath, and tightness in the chest especially at night or early morning, which are generally reversible.[11] In this case, the patient has a history of asthma since childhood but rarely relapses. An acute asthma attack is an episode of sudden worsening of asthma. Triggers for asthma attacks can be caused by a number of factors including allergens, viruses, and irritants. Risk factors for asthma are divided into genetic factors (atopy, gender, race) and environmental factors (dust, food, beta-blocker drugs, excessive emotional expression, cigarette smoke, air pollution, and weather changes).[12] In this case, the triggers for the patient's asthma attack were the use of beta-blocker drugs and cold air. In asthma attacks, bronchodilator drugs and systemic corticosteroids can be given. In this case, the patient was given nebulized budesonide (Pulmicort) and salbutamol (Ventolin) every 8 hours.

Graves' disease is an autoimmune disorder that develops due to the interaction between TRAbs and the TSH receptor resulting in excessive thyroid hormone secretion (hyperthyroidism). Graves' disease is the most common cause of hyperthyroidism and is more common in women with a female to male ratio of 6-7:1. Genetic factors account for 60-80% of the risk of Graves' disease.[13,14] Clinical manifestations of Graves' hyperthyroidism include tremor, palpitations, fatigue, poor concentration, weight loss, sweating, and hyper defecation. Physical signs include tachycardia, hypertension, diffuse thyroid enlargement with thyroid bruit, exophthalmos, atrial fibrillation, signs of heart failure, fine tremor, hyperkinesia, hyperreflexia, warm and clammy skin, palmar erythema, and pretibial myxoedema.[1] In this patient, there were signs and symptoms of hyperthyroidism such as palpitations, excessive sweating, weight loss

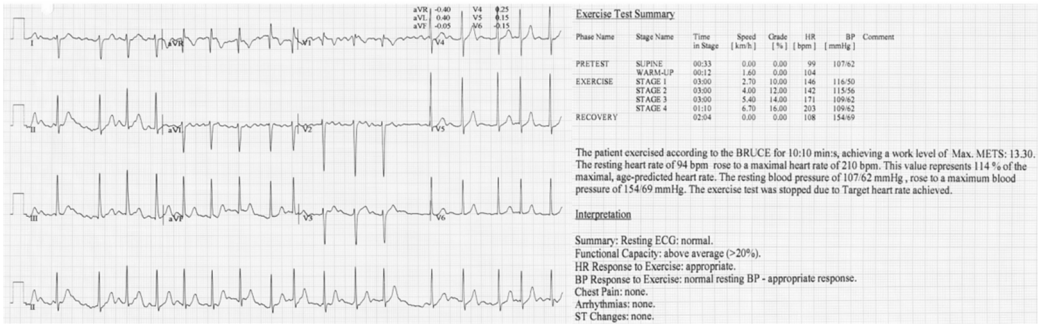

Figure 5. Treadmill test after one month of treatment.

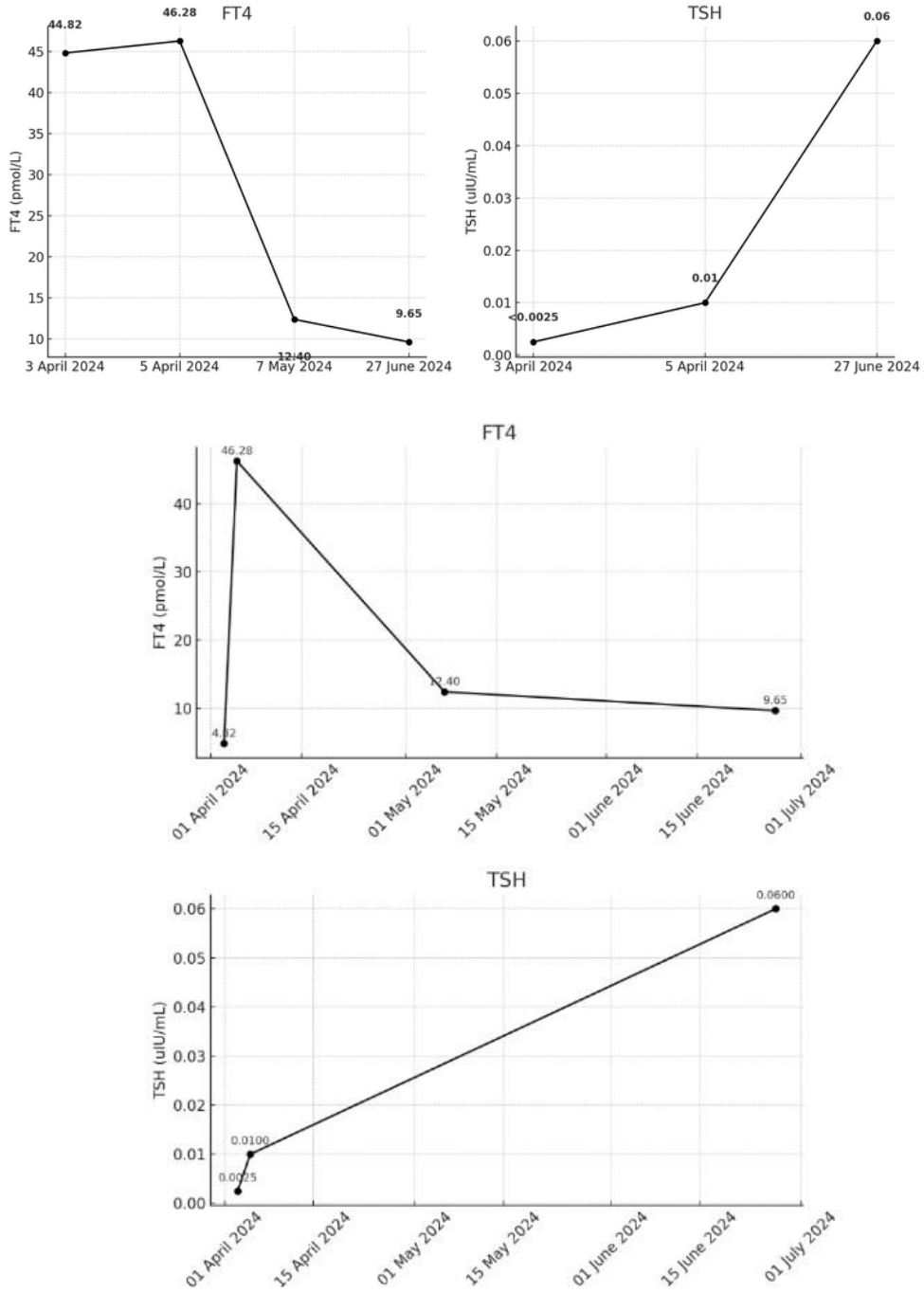

Figure 6. FT4 and TSH levels monitoring at admission, during hospital stay, and follow up: FT4 levels increased from 44.82 pmol/ to 46,28 pmol/l on the fourth day of hospital stay, decreased to 12,4 pmol/l after one month later, and decreased thereafter reaching normal levels. TSH levels were <0,0025 uIU/ml at admission, increased to 0,01 uIU/ml on the fourth day of hospital stay, and returned to normal afterwards

despite increased appetite, diffuse thyroid enlargement, tachycardia, exophthalmos, and atrial fibrillation.

To diagnose hyperthyroidism clinically, the Wayne Diagnostic Index can be used as a reference, which is a simple diagnostic tool. If the total Wayne Index score is >19, the patient is considered to have hyperthyroidism, a score of 11-19 is equivocal, and <11 implies euthyroidism.[15] In this case, the total Wayne Index score is 20 therefore the patient has hyperthyroidism. The diagnosis of hyperthyroidism can be confirmed by determining serum TSH and FT4 levels. A person is considered to have hyperthyroidism if the TSH level is below the reference value and the FT4 level is higher than the reference value. In this case, serum TSH level decreased and FT4 increased, thus meeting the criteria for a diagnosis of hyperthyroidism. The American Thyroid Association recommends that one or more of three methods can be used to diagnose Graves' disease, including TRAb examination, radioactive iodine uptake, or the presence of diffuse increased vascularity on Doppler ultrasonography. TRAb examination has sensitivity of 97% and specificity of 99% for the diagnosis of Graves' disease.[13,16] In this case, TRAb level was elevated, fulfilling the criteria for diagnosis of Graves' disease.

Treatment of hyperthyroid disease may involve antithyroid drugs, radioactive iodine, or surgery. Antithyroid drugs that can be used are methimazole or propylthiouracil (PTU). The duration of action of methimazole is longer and more potent than PTU so it can be given in a single dose per day. The initial dose of PTU is 100-200 mg three times daily and methimazole is 10-30 mg once daily. In this case, the patient was given methimazole 10 mg once daily. Antithyroid drugs is given until the euthyroid state is achieved, usually 1-3 months, then the dose is gradually reduced and continued with the lowest possible maintenance dose. Evaluation of thyroid function is done by monitoring serum FT4 and TSH levels every 4-6 weeks. If serum TSH, FT4, and total T3 levels remain normal after one year, the patient is in remission.[17]

Thyroid hormones affect cardiac muscle cells and the contractile function of the heart. Hyperthyroidism can increase cardiac output and decrease systemic vascular resistance, resulting in systolic hypertension. A shorter cardiomyocyte refractory period can lead to sinus tachycardia and atrial fibrillation which can then complicate into heart failure.[9] In this case, the patient had symptoms of shortness of breath and tachycardia during light activity. Physical and supporting examinations showed rhonchi, cardiomegaly, decreased ejection fraction, and increased natriuretic peptide concentrations. In this case, the patient met the criteria for a diagnosis of NYHA III heart failure with the cause of thyrotoxic cardiomyopathy, in which heart failure is caused by uncontrolled thyroid hormones.

TCM occurs in less than 1% of thyrotoxicosis patients. TCM is characterized by ventricular chamber dilation and decreased cardiac contractility. Identification of TCM should be done promptly because as it is a reversible cause of heart failure and heart function can recover after reaching euthyroid state.[9,18,19] The management of Graves' disease with TCM focuses primarily on controlling the thyroid hormone levels to prevent further cardiac deterioration. Beta-blockers are commonly used in the treatment of TCM due to their ability to control heart rate and reduce the workload on the heart. Beta-blockers are the first choice in TCM cases. However, beta-blockers are contraindicated in this patient due to asthma. Selective beta-blockers may be considered. Other treatment options for TCM include the use of digitalis, diuretics, ARB, and anticoagulants, which can be tailored to the patient's clinical

condition. Digitalis helps in controlling heart rate, diuretics manage fluid overload, ARB provide afterload reduction, and anticoagulants prevent thromboembolic complications associated with atrial fibrillation.[9,20] In this case, the patient was treated with valsartan (ARB) 40 mg once daily, spironolactone (aldosterone antagonist) 25 mg once daily, furosemide (diuretic) 20 mg once daily, digoxin 0.25 mg once daily, and warfarin (anticoagulant) 1 mg once daily. Warfarin is the most widely used anticoagulant drug for stroke prevention in atrial fibrillation. During treatment follow ups, all clinical symptoms, ECG treadmill test, and laboratory results improved significantly.

CONCLUSION

Graves' hyperthyroid patients with thyrotoxic cardiomyopathy and asthma require holistic, comprehensive, and meticulous drug selection to prevent exacerbation. Beta-blocker is one of the drugs of choice for treating TCM. Propranolol is a non-selective beta-blocker that might induce bronchoconstriction in asthmatic patient. Selective beta-blockers should be considered in Graves' hyperthyroid patients with TCM and asthma to prevent exacerbation. The complex interplay between managing thyroid hormone levels and preventing asthma exacerbation in this patient highlights the need for a multidisciplinary approach to optimize treatment outcomes.

ACKNOWLEDGEMENTS

The authors wish to thank the endocrinology, pulmonology, and cardiology divisions of Dr. Moewardi hospital for their support to the research.

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CASE REPORT

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

Mitigating Hungry Bone Syndrome: Case Reports on Best Practices After Parathyroidectomy

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ABSTRACT

Background: Severe hyperparathyroidism caused by prolonged high levels of parathyroid hormone (PTH) can be managed by removing the gland. One of the critical complications related to parathyroidectomy is hungry bone syndrome (HBS), an emergency morbidity which may be fatal if not promptly and adequately managed. HBS is defined by a rapid and profound decline in serum calcium levels following surgery, as the bones avidly uptake calcium and phosphate in the absence of high PTH levels. It may present as worsened bone pain, carpopedal spasm, severe hypocalcemia, hypophosphatemia, and hypomagnesemia. This report highlights two patients who underwent parathyroidectomy and had different postoperative outcomes for HBS.

Case studies: The first case involves a 19-year-old male who had a history of recurrent fractures and bone pain. In 2019, he got a fracture from a fall, and in 2020, he experienced another fall leading to shoulder dislocation and further fractures. By late 2021, he was diagnosed with severe hyperparathyroidism due to parathyroid adenoma and the gland was removed. Two days post-parathyroidectomy, he developed HBS. He was treated with calcium and vitamin D supplementation. Over two years of follow-ups, his bone density and mobility improved significantly. The second case involves a 46-year-old male with uncontrolled hypertension and chronic kidney disease stage 5 on hemodialysis, presenting with bone pain and deformities. This patient had a long-standing history of bone pain and fractures. He underwent a similar surgical intervention for tertiary hyperparathyroidism but did not develop HBS postoperatively. Careful perioperative monitoring of electrolytes, vigorous supplementation of calcium and vitamin D, and the use of antiresorptive therapies before surgery had been employed.

Discusson: These cases underline the variety of postoperative outcomes and the importance of tailored management strategies. Early intervention, appropriate surgical management, and aggressive postoperative supplementation are crucial to prevent and manage HBS in patients with severe hyperparathyroidism. Multidisciplinary approach and the utilization of various imaging modalities and intraoperative PTH monitoring are mandatory in managing such complex cases. Applying these approaches will reduce the risk of HBS while guaranteeing excellent postoperative care for individuals following parathyroidectomy.

Keywords: Primary Hyperparathyroidism; Tertiary hyperparathyroidism; Chronic kidney disease; Osteoporosis, Haemodialysis.

INTRODUCTION

Parathyroidectomy is the definitive treatment for severe hyperparathyroidism, particularly in cases of primary caused by parathyroid adenomas or tertiary hyperparathyroidism caused by chronic kidney disease (CKD).[1] However, one of the critical challenges post-parathyroidectomy is managing hungry bone syndrome, a condition that can significantly complicate recovery. Hungry bone syndrome (HBS) is a potentially life-threatening condition characterized by a rapid decrease in serum calcium levels as the bones, which have been under-mineralized due to prolonged high levels of parathyroid hormone (PTH), suddenly absorb calcium and phosphate when PTH levels drop post-surgery.[2] This can result in severe hypocalcemia, hypophosphatemia, and hypomagnesemia, necessitating immediate medical intervention. The symptoms such as muscle cramps, tetany, and even cardiac complications can occur if not properly managed. The severity and onset of HBS can vary significantly between patients, making it crucial to adopt personalized management strategies.[3]

CASE ILLUSTRATION

Patient 1. Mr. SP, a 19-year-old man presented to the endocrinology clinic in November 2021, with multiple pathological fractures in all four extremities. His medical history revealed a series of untreated or inadequately treated fractures over the past 2 years, which had significantly impacted his quality of life. In 2019, he got fracture of ankle in a motorbike accident. The fracture was managed with traditional massage therapy, which was insufficient for proper healing. In 2020, he suffered a shoulder dislocation after falling out of bed. Again, he sought treatment from a traditional healer, leading to pain. Radiographs showed significant osteoporosis, indicative of severe underlying metabolic bone disease. His family history was unremarkable for metabolic bone disorders or endocrinopathies. He reported significant distress due to his progressive disability and dependency on caregivers. His inability to ambulate normally affected his education which forced him to halt the study in university.

Blood pressure was 137/94 mmHg, heart rate 91 bpm, respiratory rate 16/min, temperature 36°C. He was obese with a Body Mass Index (BMI) of 33 kg/m^2. Physical examination revealed disalignment of cruris dextra and sinistra due to multiple closed fractures. Laboratory findings preoperative showed hypercalcemia, hypophosphatemia, markedly elevated intact parathyroid hormone (iPTH) (576 pg/mL), and Vitamin D insufficiency (13.5 ng/mL). X-Rays showed multiple fractures with lytic lesions and sclerotic borders in the femur, pelvis, and humerus. Bone mineral density (BMD) revealed a Z-score of -3.0. Neck ultrasound revealed multiple heterogeneous lesions in the right and left parathyroid, suspected parathyroid adenoma. He was diagnosed with primary hyperparathyroidism (pHPT) caused by parathyroid adenoma, multiple pathological closed fractures on hip, cruris dextra and sinistra, and secondary osteoporosis.

Bisphosphonate therapy with 4 mg of zolendronat acid injection was initiated, followed by internal fixation of the fracture by the orthopedic . Subsequently, the parathyroid gland was removed by the oncologic surgeon. Intra-operative PTH level dropped to 20 pg/mL which marked the successful marker of the surgery. Two days post parathyroidectomy , he developed hungry bone syndrome, characterized by hypocalcemia, hypophosphatemia, and hypomagnesemia. To manage this, high dose calcium (1 g of calcium gluconate thrice daily) and 5000 IU of vitamin D were delivered the event was resolved after 3 days later. Injection of acid was continued every 6 months for 2 years and was transitioned to oral bisphosphonate

(risedronate), as his condition stabilized. The BMD improved with a Z-score of -2.0 (from -3.0 the previous year). The patient also underwent extensive rehabilitation, leading to significant improvements in mobility.

By early 2023, he could walk with a walker and perform daily activities independently. By 2024, the patient had achieved significant functional recovery, with improved bone density and a more stable overall condition. His care plan included ongoing monitoring, calcium and vitamin D supplementation, and a tailored rehabilitation program to maintain mobility and prevent future fractures. The integration of psychiatric support helped address the emotional toll of his condition, contributing to a more holistic recovery.

Patient 2. Mr. AH, 46-year-old male with (CKD) stage V on haemodialysis (HD), presented with progressive skeletal deformities, multiple fractures, and severe bone pain. He experienced a persistent right thigh pain for the past year, accompanied by skeletal deformities and difficulty walking. He was diagnosed with hypertension 15 years ago, with poorly controlled blood pressure, often reaching systolic levels of 230 mmHg due to poor compliance to antihypertensive medications. CKD Stage V was diagnosed 10 years ago and the patient started hemodialysis twice weekly, later increased to thrice weekly. Four years ago, he got a pelvic fracture for which a total hip replacement was performed. One year ago, he developed a facial mass over the upper jaw, leading to malocclusion, speech changes, and difficulty chewing. He also reported a shortened stature due to spinal curvature and shortened ribs, with finger and toe deformities. The appetite was decrease and progressive weight loss was occurred (from 68 kg to 45 kg).

Physical examination revealed blood pressure 180/117 mmHg, heart rate 86 bpm, respiratory rate 16/min, temperature 36.1°C. He was normoweight with a BMI of 19.5 kg/m². Prominent maxillary bone with downward displacement of the soft palate was noticed in his head. The chest was in barrel-shaped with thoracic kyphosis. He has limited range of motion in his low extremities due to pain. Laboratory findings revealed iPTH level >5000 pg/mL, serum calcium 9.8 mg/dL, phosphate 3.7 mg/dL, vitamin D (25-OH) 10.2 ng/mL (severely deficient) and The Estimated Glomerular Filtration Rate (eGFR) 13.6 mL/min/1.73 m². BMD showed severe osteoporosis with a T-score of -5.1 at the lumbar spine, -6.8 at the left hip, and -6.6 at the femoral neck. X-rays showed bilateral femoral deformities consistent with renal osteodystrophy, including a "Shepherd's crook" deformity in the right femur. Neck ultrasound showed hypoechoic lesions in the posteroinferior thyroid lobes, suggesting parathyroid adenomas. Neck Computed Tomography (CT Scan) revealed suspicious for left inferior parathyroid adenoma and brown tumors in the mandibula and maxilla. He was diagnosed with tertiary hyperparathyroidism with suspected parathyroid adenoma, CKD Stage V on HD with mineral and bone disorder, severe osteoporosis with a history of multiple fractures, and uncontrolled hypertension.

He was planned to undergo parathyroidectomy. While waiting for this surgery , percutaneous ethanol injection was performed as a bridging therapy, and it was successfully decreasing the iPTH level from >5.000 pg/mL initially to 3.069 pg/mL. He also received clonidine, amlodipine, bisoprolol, irbesartan for hypertension, calcium carbonate and calcitriol for calcium and vitamin D supplementation, oral risedronate for osteoporosis, as well as HD thrice weekly, and was scheduled for parathyroidectomy. Due to renal function concerns, the surgery was postponed several times for oncological surgery clearance. With a great concern on his renal status, a careful and well plan surgery was conducted. Parathyroidectomy was performed on July 2024 with intra-operative iPTH level

showed more than 50% decrement from 2.863 pg/mL to 870 pg/mL which marked a successful operation. Post operative, closed monitoring on calcium level was successfully prevent him from HBS. The next plan for this patient was to monitor calcium and phosphate every 3 months, iPTH level 6 months after surgery, and BMD 1 year after surgery to prevent recurrence of metabolic bone disease given his underlying CKD stage V. His osteoporosis remains severe, and fracture risk persists, necessitating long-term bisphosphonate therapy and calcium-vitamin D supplementation.

DISCUSSION

The two cases have a different outcome post-surgery. Mr. SP's case illustrates the challenges of managing a young patient with severe bone involvement and a high iPTH level, where postoperative supplementation alone was insufficient to prevent HBS. In contrast, Mr. AH's outcome was likely influenced by the comprehensive preoperative management, including bisphosphonate therapy and careful monitoring.

Several risk factors have been identified that may predispose individuals to develop HBS after parathyroidectomy. Preoperative biochemical parameters, such as elevated alkaline phosphatase levels prior to surgery are more likely to experience postoperative hypocalcemia and HBS.[3, 4] Additionally, the presence of severe bone disease, as indicated by high turnover markers, has been shown to increase the likelihood of developing HBS, as these patients often have a greater demand for calcium postoperatively due to enhanced bone formation.[5] Age and the size of the parathyroid adenoma also play a critical role in the risk of HBS. It was reported that older patients are at an increased risk, possibly due to the cumulative effects of prolonged hyperparathyroidism on bone metabolism.[1] Larger adenomas are associated with higher levels of PTH and calcium prior to surgery, which lead to a more significant drop in serum calcium levels after the adenoma is removed.[6] Furthermore, vitamin D deficiency has been associated with a higher incidence of HBS, as it exacerbates the hypocalcemic state following parathyroidectomy.[7] The preoperative levels of calcium and PTH are also significant; patients with low preoperative calcium levels and high PTH levels are more susceptible to HBS, as the sudden withdrawal of PTH disrupts the balance between bone formation and resorption, favoring the former.[8]

In the above cases, the one who develop HBS is younger than other which was contradict the literature. The reason could be due to multiple factors. This age population tends to exhibit higher rates of bone turnover, which can lead to a more pronounced influx of calcium into the bones following the rapid decrease in PTH levels after surgery.[1] The increased osteoblastic activity in younger individuals can result in a more significant deposition of calcium in the bone matrix, exacerbating the hypocalcemic state that characterizes HBS.[8] Moreover, younger patients

Table 1. Risk factors for developing Hungry Bone Syndrome

Primary Hyperparathyroidism[9-11]	Secondary/tertiary Hyperparathyroidism[1, 12, 13]
- High pre-operative PTH - Elevated alkaline phosphatase - High blood urea nitrogen (BUN) - Older age - Skeletal involvement (brown tumors, osteitis fibrosa cystica) - Large parathyroid adenomas - Prolonged surgical time - Co-presence of osteoporosis	- High pre-operative PTH - Elevated alkaline phosphatase - Younger age at surgery - Normal or low pre-operative serum calcium - Long duration of pre-surgery dialysis - Obesity (inconsistent evidence)

PTH= Parathyroid hormone

often present with less severe pre-existing bone disease compared to older patients, which can result in a more dramatic response to the sudden cessation of PTH.[13]

The management of HBS after parathyroidectomy should involve a multidisciplinary approach, including endocrinologists, surgeons, and dietitians, to ensure optimal outcomes. The following strategies are recommended :[10]

1. Preoperative Management:

Calcium and Vitamin D Supplementation. Patients with evidence of preoperative vitamin D deficiency should receive adequate supplementation. Prophylactic administration of calcium and vitamin D is not universally recommended but is crucial in those with elevated iPTH or alkaline phosphatase levels, particularly in patients with Graves' disease or other high-risk conditions .[10] In this report, patient 1 (PHPT) received aggressive calcium and vitamin D supplementation before surgery due to profound vitamin D insufficiency and severe osteoporosis, as recommended, while patient 2 secondary hyperparathyroidism (SHPT), optimized calcium and vitamin D levels and controlled secondary complications of CKD, per guideline recommendations.

2. Intraoperative Management

A rapid decline in iPTH during surgery is predictive of postoperative hypocalcemia. Employ intraoperative iPTH monitoring to assess the adequacy of parathyroidectomy and predict the likelihood of postoperative HBS. Regular monitoring of serum calcium, phosphate, and magnesium levels during and after surgery is essential to detect and manage electrolyte imbalances early.[10] In both cases, intraoperative iPTH monitoring showed a rapid decline (more than 50% from baseline), allowing the surgical team to confirm parathyroidectomy, anticipate postoperative hypocalcemia, and immediately monitor and manage calcium.

3. Immediate Postoperative Care

Intensive monitoring of serum calcium, phosphate, and magnesium levels should be initiated immediately after surgery. Intravenous calcium may be required in severe cases, followed by oral calcium and vitamin D supplementation.[10] In this report, patient 1 developed hungry bone syndrome, which was detected early through close postoperative monitoring and promptly managed with intravenous calcium and ongoing supplementation to prevent severe complications, whereas patient 2, who was at high risk due to underlying CKD, received intensive monitoring and timely intravenous calcium administration, successfully preventing the development of hungry bone syndrome.

Steps for hypocalcemia management post parathyroidectomy:[14]

- Assess whether the patient is symptomatic or asymptomatic.
- For Symptomatic hypocalcemia, the first intervention is administering 1 ampoule of calcium intravenously (IV) over 5 minutes. Then reassessment, if symptoms persist after 15 minutes, administer another ampoule of calcium IV over 5 minutes. If symptoms continue, proceed with a calcium IV infusion (5 ampoules in 5% glucose solution over 8 hours) along with oral calcium (Ca 500mg in a 2-2-2 tablets dosing regimen) and calcitriol (0.25 µg per 24 hours).
- Monitor and suspend the calcium IV infusion once the total calcium level exceeds 7.5 mg/dL.
- For asymptomatic hypocalcemia with total ca < 7.5 mg/dL, the patient should be managed similarly to the symptomatic pathway, with calcium IV infusion, oral calcium, and calcitriol.
- For asymptomatic hypocalcemia with total ca < 8 mg/dL, examine the presentation

of Chvostek's and Trousseau's sign, if it is positive, then start oral calcium 500 mg (2-2-2 tablets regimen) and calcitriol (0.25 µg per 24 hours). Reassess in 12 hours. If it is negative, then evaluate ionized calcium (Ca2+). If Ca2+ is low, then manage similarly with oral calcium and calcitriol. If it is normal, then reassess in 12 hours.

- If there is no improvement after 24 hours of treatment, consider increasing the dose of calcium and assess for magnesium deficiency, which can complicate hypocalcemia management.
- If total calcium > 8 mg/dL, continue with the current management and consider to discharged the patient and adjusted to a less intensive outpatient management regimen, as their calcium levels have stabilized.

4. Long-term Follow-up

Regular monitoring of bone mineral density and serum calcium levels is essential to adjust supplementation and prevent recurrence of hypocalcemia or the development of hypercalciuria. The use of bisphosphonates, such as zoledronic acid, can be considered in patients with severe bone disease, although this should be tailored based on the patient's overall clinical status and risk of fractures.

CONCLUSION

Hungry Bone Syndrome remains a significant challenge in the postoperative management of patients undergoing parathyroidectomy for severe hyperparathyroidism. The cases presented illustrate the variability in HBS presentation and the importance of a personalized, evidence-based approach to postoperative care. By adopting best practices in preoperative planning, intraoperative monitoring, and postoperative management, healthcare providers can mitigate the risks associated with HBS and ensure better outcomes for their patients.

Effective management of tertiary hyperparathyroidism in CKD requires a comprehensive approach, including surgical intervention, medical management, and close monitoring of bone health. This case underscores the need for individualized treatment plans to prevent further complications and improve patient outcomes.

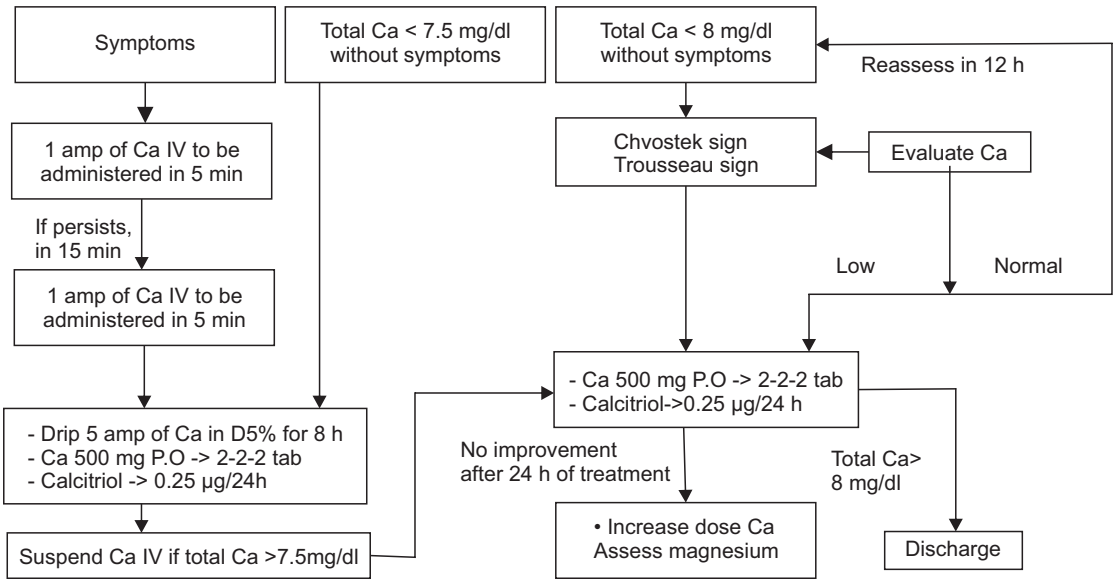

Figure 1 Algorithm for the acute management of hypocalcemia post parathyroidectomy.[14]

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CASE REPORT

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

Recurrent Severe Hypoglycemia in a 43 Year Old Extreme Obese Woman with Insulinoma: A Case Report

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ABSTRACT

Insulinomas are very rare neuroendocrine tumors (4 cases per million individuals per year) leading to insulin hypersecretion and occurring more often in women at any age. A 43 year old extreme obese woman was referred to Dr Kariadi General Hospital with complaints history of repeated unconsciousness due to recurrent episodes of symptomatic severe hypoglycaemia (previously been hospitalized several times in regional hospitals in last six years). Physical examination: Body Mass Index Class II obesity (Asia-Pacific). Laboratory: recurrent hypoglycaemia (random blood glucose range 30-50 mg/dL), Fasting Blood Glucose 105 mg/dL (n: 80-109), 2 hours Postprandial Blood Glucose 44 mg/dL (n: 80- 140), C-peptide levels (taken during hypoglycaemia) 13.59 ng/ml (n:1.1-4.4). Abdominal Ultrasonography : grade 2 fatty liver, Fibroscan: no fibrosis or steatosis, Plain Head MSCT: no visible abnormalities, contrast abdominal magnetic resonance imaging: solid lesion in the body of pancreas (AP 1.2 x LL 1.2 x CC 1.3 cm) tends to be a picture of insulinoma. Patient underwent distal pancreatectomy with immunohistochemical results of an insulinoma. Post surgery the patient never had hypoglycaemia. We described a 43 year old extreme obese woman with recurrent episodes of symptomatic severe hypoglycaemia. Laboratory (low random blood glucose, high C-peptide) and imaging examinations (solid lesion in the body of the pancreas on Contrast Abdominal MRI) support the diagnosis of insulinoma. Surgery is the treatment of choice for insulinomas. Patients with recurrent severe hypoglycemia, increase in C-peptide levels and solid lesion in pancreas are clinical manifestations of Insulinoma.

INTRODUCTION

Insulinomas are the most common, yet still rare, hormone-producing pancreatic neuroendocrine neoplasms (panNEN) with a reported incidence of 0.7 to 4 cases per million per year and the incidence is slightly higher in women than in men. More than 99% of insulinomas are located in the pancreas, where its tumor locations are evenly distributed. Most insulinomas present with the Whipple triad: (1) symptoms, signs, or both consistent with hypoglycemia; (2) a low plasma glucose measured at the time of the symptoms and signs; and (3) relief of symptoms and signs when the glucose is raised to normal.[1] We herein described an case report from Dr. Kariadi Hospital Semarang regarding recurrent severe hypoglycemia in a 43 year old extreme obese woman with insulinoma. The aim of this case report is to make us more aware and able to diagnose and carry out the management cases of insulinoma.

CASE ILLUSTRATION

A 43 year old extreme obese woman was referred to emergency departments of Dr Kariadi Hospital from the regional hospital with complaints history of repeated unconsciousness due to recurrent episodes of symptomatic severe hypoglycemia. Patient had previously been hospitalized several times in regional hospitals due to recurrent episodes of symptomatic severe hypoglycemia (loss of consciousness) in the last six years. Patient has not history of diabetes mellitus. On Physical examination she was fully alert. Her weight was 125 kg and her height was 155 cm, with Body Mass Index (BMI) of 52.09 kg/m^2 (Class II Obesity Asia-Pacific). Heart, lung and abdominal examination were normal. Laboratory tests were obtained recurrent hypoglycaemia (random blood glucose range 40-60 mg/dL), fasting blood glucose 105 mg/dL (n: 80-109), 2 hours post prandial blood glucose 44 mg/dL (n: 80-140),

HbA1c 4,5% (n < 5.7), serum glutamic oxaloacetic transaminase (SGOT) 169 U/L (15-34), serum glutamic pyruvic transaminase (SGPT) 539 U/L (15-60), C-peptide levels (taken during hypoglycaemia) 13.59 ng/ml (n: 1.1-4.4). Abdominal ultrasound shows grade 2 fatty liver, no fibrosis or steatosis on fibroscan, no pancreatic mass was visible on contrast abdominal multi-slice computed tomography (MSCT), solid lesion in the body of the pancreas (size ± AP1.2 x LL1.2 x CC1.3 cm) tends to be a picture of insulinoma on contrast abdominal magnetic resonance imaging (MRI) (**Figure 1**), no visible abnormalities on Plain Head MSCT.

Preoperative management consisted of Dextrose 10% infusion 20 drops per minute, Dextrose 40% 3 flasks if blood glucose is less than 70 mg/dL, Dextrose 40% 2 flasks if blood glucose is less than 100 mg/dL, Dexamethasone injection 5 mg twice daily intravenous and giving snacks every 4 hours. Monitoring blood glucose in patients every 4 hours. During the operation a mass was found in the cauda of the pancreas so patient underwent distal pancreatectomy (**Figure 2**) with immunohistochemical results of an insulinoma (**Figure 3)**.

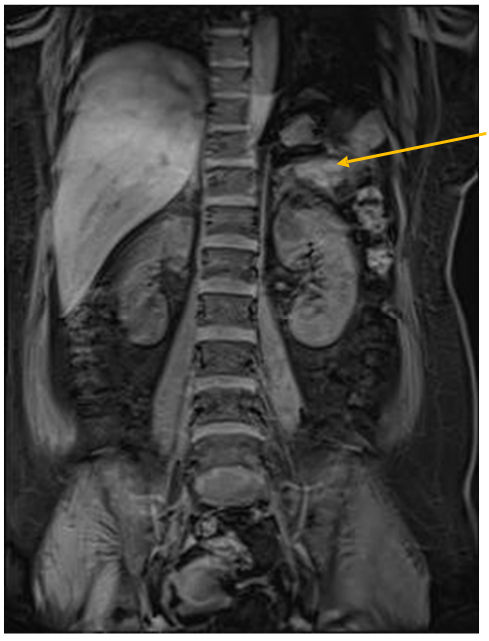

Figure 1. Contrast abdominal MRI

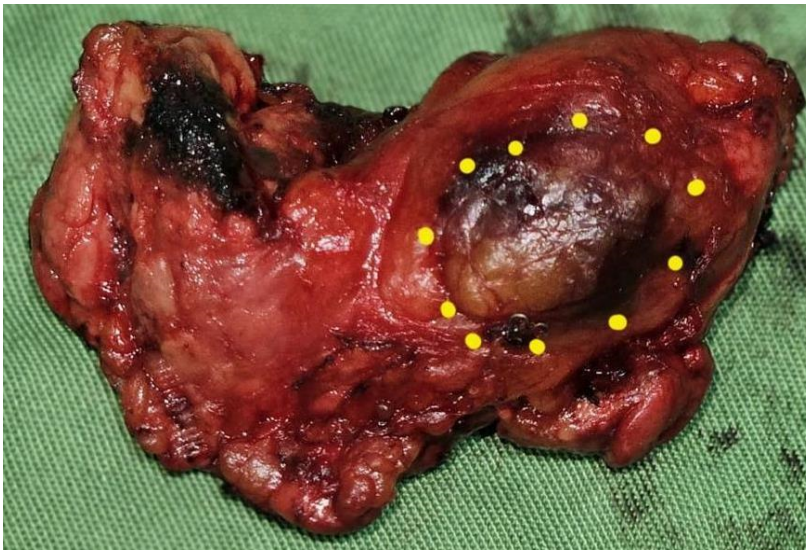

Figure 2. Distal pancreatectomy

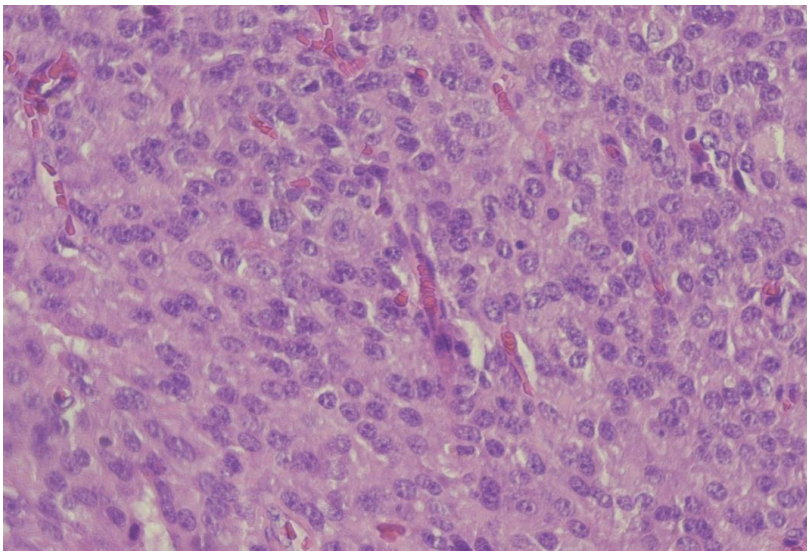

Figure 3. Immunohistochemical of an insulinoma

Patient is treated in a regular ward after distal pancreatectomy. Patient consciousness is composmentis, condition and hemodynamics were stable and patient has a drain installed. Patient never experienced hypoglycaemia after surgey, blood glucose tests had increased. Postoperative management in regular ward consisted of Nacl 0.9% infusion 20 drops per minute, Ranitidine injection 50 mg twice daily intravenous, metformin 500 mg twice daily oral, Vitamin B12 1 tablet twice daily oral. Patient was discharge home then 6 days later. One week later the patient was checked into the clinic and blood glucose monitoring was normal.

DISCUSSION

Hypoglycemia is a common presentation in the primary care setting and accounts for about 16 of every 1000 visits to the emergency department. In patients without diabetes, it is important to rule out common precipitating factors such as medications (e.g., indomethacin or antibiotics), alcohol, caloric restriction and systemic illness. In the absence of an obvious

cause, further investigation for causes of endogenous hyperinsulinemia is warranted.[2] Insulinoma is the most common pancreatic F-NET, deriving from β-pancreatic islet cells that secrete insulin, and is associated with hypoglycemic neuroglycopenic and sympathetic-overstimulation symptoms. Insulinomas are most commonly benign, well-differentiated NETs, whereas malignant neoplasms account for approximately 5-10% of all cases. Insulinomas may occur at any age, mainly during the 5th decade of life, and have a slight female predominance. Insulinomas present with signs and symptoms early in their course and thus during diagnosis their size ranges between 0.5 cm and 2 cm. The diagnostic hallmark of insulinoma, the so- called “Whipple’s triad” or “triad of insulinoma”, was first described by Allen Whipple and Virginia Kneeland Frantz in the 1930s and consists of symptoms caused by hypoglycaemia, low blood glucose level during the episodes, symptoms relief upon blood glucose level normalization through glucose administration.[3] Patients with insulinomas suffer from recurrent episodes of hypoglycemia. The most frequent symptoms are neuroglycopenic (altered mental status, abnormal behavior, visual disturbances). Autonomic, adrenergic, and cholinergic symptoms are less frequent. The diagnosis of insulinomas can be challenging as patients are first examined in neurologic and psychiatric departments due to neuroglycopenic symptoms. Symptoms occur mainly in the fasting state, but up to 20% of patients also described postprandial symptoms.[4] In this case, the patient had a history of hospitalized several times in regional hospitals due to recurrent episodes of symptomatic severe hypoglycaemia (loss of consciousness and seizure) since 2018. Weight gain is found in only 25% - 42% of patients and monthly changes in body weight are significantly correlated with the tumor size and serum insulin concentration. Weight gain in insulinoma can be attributed to overeating to treat the hypoglycemia symptoms.[5]

Laboratory investigations for the cause of hypoglycemia, including endogenous insulin overproduction, should be ordered. Initial investigations at the time of a hypoglycemic episode include levels of serum glucose, C-peptide, insulin and β-hydroxybutyrate. Insulin is generated in the pancreas when its precursor, proinsulin, is cleaved into insulin and C-peptide. In patients with insulinoma, endogenous insulin overproduction occurs independent of serum glucose level, resulting in elevated insulin and C-peptide levels, which precipitates hypoglycaemia.[2] Patients with insulinoma characteristically develop symptoms while fasting (73%- 80%) but 6% of patients report symptoms only in the postprandial state, and 21% of patients report symptoms in both the postprandial and fasting states. Although fasting hypoglycemia has been considered the main trait of insulinoma, postprandial hypoglycemia has also been occasionally reported as the predominant feature.[5] Laboratory examination in this case found recurrent hypoglycaemia (random blood glucose range 40-60 mg/dL), fasting blood glucose 105 mg/dL (n: 80-109), 2 hours post prandial blood glucose 44 mg/dL (n: 80-140), C-peptide levels (taken during hypoglycaemia) 13.59 ng/ml (n: 1.1-4.4).Computerized tomography is currently considered the first-line imaging diagnostic test in the insulinoma visualization procedure. In this case, Contrast Abdominal MSCT was not found pancreatic mass but from Contrast Abdominal MRI found solid lesion in the body of the pancreas (size ± AP1.2 x LL1.2 x CC1.3 cm) tends to be a picture of insulinoma. MRI is a highly sensitive localization technique for seemingly occult, indolent, localized insulinomas and has become increasingly popular. Contrast Abdominal MRI is emerging as an appropriate, safe, non-invasive alternative with high sensitivity

in the localization of insulinomas.[3]

Patient management consisted of Dextrose 10% infusion 20 drops per minute, Dextrose 40% 3 flasks if blood glucose is less than 70 mg/dL, Dextrose 40% 2 flasks if blood glucose is less than 100 mg/dL, Dexamethasone injection 5 mg twice daily intravenous and giving snacks every 4 hours. Monitoring blood glucose in patients every 4 hours. Regular meals or snacks rich in slow carbohydrates, also ante noctem, are generally recommended. The inclusion of a bedtime or late night meal is sufficient in most patients, but nocturnal tube feeding might be required to avoid nocturnal hypoglycemia in severely symptomatic patients. IV glucose administered via a central IV indwelling catheter might be needed for the control of severe recurrent hypoglycemia. Glucocorticoids are sometimes used to control the hypoglycaemia. A continuous glucose monitoring system can support patients in recognizing hypoglycemic events and prevent serious complications, especially during the night.[1]

The definitive treatment of insulinoma is surgical resection. Most insulinomas are benign and confer an excellent prognosis after tumour resection, with disease-specific survival of 98% at 1 year, 92% at 5 years and 90% at 10 years.[2] The type of surgical treatment depends on the localization and size of the tumor. Enucleation is indicated in smaller tumors without contact with the main pancreatic duct. The other possibility is a left- side pancreatectomy, with or without splenectomy. A central resection of the pancreas can be performed in some specific case.[4] In this case, patient underwent distal pancreatectomy with immunohistochemical results of an insulinoma.

CONCLUSION

We described a 43 year old extreme obese woman who had suffered from recurrent episodes of symptomatic severe hypoglycaemia. Laboratory (low random blood glucose, high C-peptide levels) and imaging examinations (solid lesion in the body of the pancreas on Contrast Abdominal MRI) with immunohistochemical results support the diagnosis of insulinoma. Surgery is the treatment of choice for insulinomas.

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CASE REPORT

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

Turner Syndrome Mosaicism 46,Xx/45,X with Graves' Disease: A Case Report

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ABSTRACT

Background: Turner syndrome (TS) is a condition in females missing the second sex chromosome (45,X) or parts thereof. It is a rare genetic condition with a wide range of clinical stigmata, such as short stature, delayed puberty and infertility, congenital malformations, and endocrine disorders. TS with chromosomal mosaicism (TSM) is a less severe and less frequent form of TS, who has less pronounced signs and symptoms than the classic TS.

Case Illustration: A 21-year-old woman with TSM and Graves' disease (GD) is reported. She presented with fatigue, sweating, palpitation, tremor, and the absence of menstruation or breast development. Further investigation reveals diffuse enlargement of thyroid gland and hyperthyroidism symptoms. Laboratory testing shows elevated fT4, low TSH, and elevated TSH receptor antibody levels. Previous chromosomal analysis showed a mosaicism: 46,XX,dup(X)(q28q21.2)[36]/45,X[4]. She is then treated with thiamazole and oral beta-blocker.

Discussion: Thyroid abnormalities is common in TS, especially in adult females. This including Hashimoto's thyroiditis and GD. But TS presenting with hyperthyroidism is rare, with most of the cases were reported happens in adult females. Mosaicism in TS resulted in less severe signs and symptoms than the classic TS. Therefore, based on the variabilities, it is often undetected.

Conclusion: We reported a rare case of TSM with GD. We observed that mosaicism in this TS patient resulted in less severe GD symptoms, and the response to conventional treatment with thiamazole and oral beta-blocker was satisfactory.

Keywords: Turner's syndrome, mosaicism, Graves' disease, Hyperthyroidism

BACKGROUND

Turner syndrome (TS) is a condition among phenotypic females with a karyotype containing one X chromosome and complete or partial absence of the second sex chromosome, associated with one or more typical clinical manifestations of TS, such as evidence of growth failure, short stature or has a strong likelihood of short stature (e.g., short parents and short predicted adult height or already pubertal at

the time of diagnosis), hypergonadotropic hypogonadism, congenital malformations, infertility, and a constellation of other disorders that are common in TS.[1] It was described by many scientists but it now carries the name of Henry H. Turner, who in his report in 1938, described the syndrome with the triad of infantilism, webbing of the skin and neck, and deformity of the elbow (*cubitus valgus*).[2] Later in 1959, it was found that the disease was caused by sex chromosomal abnormality.[3]

TS affects 25-50 per 100.000 females and can involve multiple organs through all stages of life, necessitating a multidisciplinary approach to care. It is the only viable monosomy syndrome caused by partial or complete loss of one of the two sex chromosomes.[1,4] It is generally accepted that 45% of TS cases are classic TS that is associated with non-mosaic monosomy (45,X), while the remainder is associated with mosaic aberrations of chromosome X in 20–35% of cases, and with X chromosome rearrangements in 10–35% of cases. The presence of mosaic in chromosomal karyotyping in TS is often called Turner syndrome with mosaicism (TSM).[5] Monosomy or classic TS is diagnosed earlier than other sex chromosome aneuploidies, such as Klinefelter syndrome. Median age of TS diagnosis is at 15 years, on average is 12 years earlier than other. This probably due to a more severe phenotype that may already be present in the fetus.[5]

Autoimmune thyroid diseases (AITD) are the most prevalent organ-spesific state and the occurrence of thyroid peroxidase antibodies indicates the presence of autoimmune thyroid disease.[6] Several mechanisms have been proposed to explain the increased susceptibility to autoimmune disease in TS, including haploinsufficiency of X chromosome-related genes. On the X chromosome, there at least ten genes that are involved in immunoregulatory functions. Haploinsufficiency of the *FOXP3* gene, located in the Xp11.23 region, may contribute to increasing the susceptibility of TS women to AITDs.[7] Additionally, alterations of both humoral and cellular immunity profiles have been suggested as possible mechanism leading to autoimmunity in TS.[9]

AITDs had been reported to be more frequent in women with TS than in the general population. They include Hashimoto's thyroiditis (HT) - which is considered the most common AITD in TS, and Graves' disease (GD) - which causes hyperthyroidism.[9] A recent meta-analysis revealed that the prevalence of AITDs among TS population was 38.6%,[10] higher than previous reviews done by Gravholt that reporting 15% as the prevalence.[11] Although a higher incidence of GD might also be expected in TS patients, based on the perspectives of pathogenic mechanism in AITD, this syndrome is significantly more infrequent than expected. The aim of this case report is to report a rare case of GD in a woman with TSM.

CASE ILLUSTRATION

A 21-year-old woman came to our hospital and complained of fatigue, sweating, palpitations, and tremors lasting for more than 2 months. Previous medical history was Turner syndrome, diagnosed based on chromosomal karyotyping in 2019. The sampling from 40 cells revealed mosaic 46,XX,dup(X)(q28q21.2)[36]/45,X[4]. During the initial physical examination, the patient's heart rate was 124 beats/minute, the blood pressure and body temperature were of normal value. Family history showed nothing that was relevant. We also found diffuse thyroid gland enlargement and fine finger tremor, but exophthalmos was not present. Her height was 142 cm, weight was 41.9 kg, and body mass index was 20.77 kg/m^2 (normal). Further examination revealed amastia (Tanner stage 1) and insubstantial pubic and axillary hair (Tanner stage 2). Oral estradiol has been prescribed in

the past due to primary amenorrhea, but with unsatisfactory results.

Hormonal tests, pelvic and thyroid ultrasound, and chest x-ray were performed. Thyroid function analysis presented that the sensitive thyroid stimulating hormone (TSH) level was <0.005 mIU/mL (normal range 0.350-4.940 mIU/mL), the free T4 (fT4) level was 6.48 ng/dL (normal range 0.93-1.70 ng/dL), and TSH receptor antibody (TRAb) level was 10.1 IU/L (normal range <= 1.75 IU/L). Other hormonal tests were also performed, with prolactin level was 5.04 ng/mL (normal range 5.18-26.53 ng/mL), luteinizing hormone (LH) level was 37.01 mIU/mL (normal range <= 15.97 mIU/mL), follicle stimulating hormone (FSH) level was 118.37 mIU/mL (normal range 0.57-8.77 mIU/mL), and estradiol level was <20 pg/mL (normal range <62 pg/mL for Tanner stage 2). Thyroid ultrasound revealed enlargement of the thyroid gland with hyper vascular activity. Pelvic ultrasound by a gynecologist presented that the uterus and both ovaries were relatively small. Chest x-ray was of normal state.

Based on the result, we diagnosed the patient with Graves' disease, Turner syndrome mosaicism, and hypergonadotropic hypogonadism. Thiamazole treatment was soon started and the dose was adjusted accordingly based on the thyroid hormone level that was regularly monitored. An oral beta-blocker was given based on the clinical presentation. Nine months after initial therapy, hyperthyroid symptoms were absent and the thyroid function analysis was of normal value. Her body weight has increased to 54 kg, but the height remains the same as before. We planned long-term follow-up on this patient since the patient and her parents refused definitive treatment option. As of the latest follow-up, the euthyroid state is maintained with a low dose thiamazole.

DISCUSSION

This report describes a young woman with clinical signs and symptoms of classical GD and TSM. The karyotype was 46,XX,dup(X)(q28q21.2)[36]/45,X[4] with evidence of mosaicism (Fig.1). Mosaicism in TS resulted in a less severe phenotype than monosomy TS, because in mosaic individuals only some cells express the mutant allele while others express only normal alleles.[1] Most women with 46,XX/45,X mosaicism were detected incidentally and usually would not require a follow-up. The phenotype in these women was often unremarkable. While they were slightly shorter on average, this group of women went through menarche and menopause at an average age, had an average number of children, and were not at increased risk of pregnancy loss.[13] TSM cases, on average, were diagnosed 8 years later than the monosomy cases. This was due to a less severe clinical signs and symptoms.[14] Our patient was diagnosed with TSM during adolescence, with a lack of secondary sex characteristics becoming the primary concern at the time. No cardiovascular anomaly or kidney abnormalities were present, as many of classic TS patients would have. Additionally, hyperthyroidism symptoms were only noted more than 4 years after TS diagnosis was established.

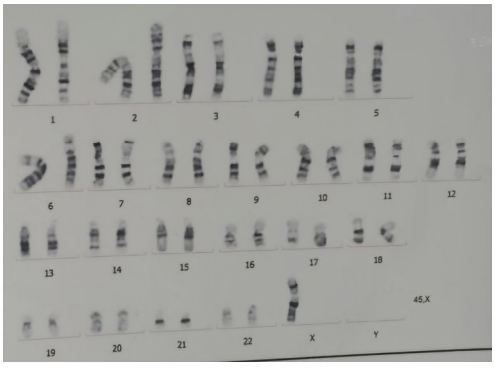

Figure 1. Cytogenetic analysis

The association of thyroid dysfunction and TS was well established, with the first report dated back to 1961.[15] Since then, there were many reports of AITDs on patient with TS, although most of them were the case of hypothyroidism. A long-term follow-up study of 30 years found that hypothyroidism was present in 24% case of TS, but hyperthyroidism only present in 2.4% of the TS patients.[16] Other report showed lower percentage, where there was only 2 out of 119 TS patients (1.7%) was confirmed hyperthyroidism due to GD.[17]

Currently, it is generally agreed that GD, especially during childhood and adolescence, is relatively rare. It is occurring mostly in patients with a family history of AITDs or other associated autoimmune disorders. It has been hypothesized that the incidence and frequency of chromosomal abnormalities are higher in patients with HT than in those with GD, however this is still poorly understood.[18] In this case, we found no evidence of AITDs or other autoimmune disorders in the family history.

It is also worth noting that some of GD cases in TS had been preceded earlier by HT, just like in general population, where exists a continuum between HT and GD. A mechanism that has been hypothesized to account of these changes is the alteration in the biological activity of TRAbs, from predominantly thyroid-blocking antibodies during the HT phase to thyroid-stimulating antibodies when GD manifests itself.[19] This hypothesis however, did not explain why the conversion from HT to GD was observed more frequently in chromosomopathies condition. The possible explanation could be that the switch was detected more frequently in the selected population with these chromosomopathies because these patients were already being monitored for thyroid disorders before GD presentation.[20] In this case, the patient had no record of prior hormonal tests, hence the preceding HT could not be concluded.

Biochemical picture at diagnosis and the clinical course of GD in TS patients were not different from general population. Valenzise et al. showed that the methimazole dose required to maintain euthyroidism during the therapy, and remission dan relapse rates did not significantly differ from those observed in non-TS patients.[21] All of the case reports on GD in TS patients used methimazole as a first line treatment, with satisfactory result. But in some cases, this treatment resulted in toxic hepatitis or other intolerances. Radioactive iodine therapy (RAIT) thus indicated in these cases. However, there were only very few reports have been published on RAIT in TS patients, so this option should be considered individually with taking into account of potential RAIT complications.[22] Our patient showed significant improvement after 3 months of thiamazole treatment. The symptoms were absent after 6 months and her body weight was increased 12 kgs after 9 months. And since the patient and her parents refused definitive treatment, we planned for long-term follow-up focusing in clinical and biochemical profiles. Currently the euthyroid state is maintained with a low dose thiamazole.

CONCLUSION

We report a rare coexistence of TS mosaicism (46,XX/45,X) and Graves' disease in a young woman. AITDs in TS patients are higher than in the general population, but the presence of GD is relatively rare. In our case, thiamazole treatment showed significant improvements, and currently the patient is in euthyroid state with a low-dose thiamazole. However, the underlying mechanism of higher frequency of AITDs, especially GD, in TS patients is still poorly understood. The prognosis is relatively good, although comorbidities such as cardiovascular complications remain a problem. We recommend close follow-up on TSM patients with GD for a better quality of life.

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SPECIAL ARTICLE

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

Fibrocalculous Pancreatic Diabetes (FCPD) : A Rare Type of Pancreatogenic Diabetes

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ABSTRACT

Background. FCPD is a rare form of secondary diabetes. FCPD is mainly found in the tropical region; it is characterized by diabetes, chronic abdominal pain, calcification of the pancreas, and steatorrhea. The Incidence of FCPD is often misdiagnosed with type 2 or type 1 diabetes mellitus.

Case Illustration. A 46-year-old man came with chief complaints of chronic abdominal pain. Abdominal radiography showed calcification in the pancreas. The patient was malnourished. Abdominal X-ray revealed pancreatic calcification, which was confirmed by an abdominal MSCT scan. C-Peptide decreased with an intermediate degree. The patient was given supportive therapy, and insulin was given to control his diabetes.

Discussion. FCPD is a morphological pancreas change caused by chronic tropical pancreatitis. The aetiology of chronic tropical pancreatitis is unknown. FCPD can be diagnosed by history taking and supporting examinations such as abdominal X-ray examination, ultrasound and abdominal CT Scan. C-peptide was examined to assess the function of pancreatic beta cells. The primary treatment for FCPD is insulin therapy; metformin or Sulfonylureas can be used in the early phase of diabetes. In reducing pain, non-steroidal analgesics are used as an option. The use of pancreatic enzyme supplementation can improve the nutritional status of patients.

Conclusion. FCPD is a rare case, occurring mainly in tropical countries and in people who are malnourished. The primary treatment for FCPD is insulin therapy.

Key words : Fibrocalculous Pancreatic Diabetes, Diabetes Mellitus, Chronic Pancreatitis

INTRODUCTION

The highest prevalence of diabetes is type 2 diabetes mellitus and type 1 diabetes mellitus. About 1-5% of diabetes is caused by other causes, such as endocrinopathy and pancreatic disorders.[1,2] Fibrocalculous Pancreatic Diabetes (FCPD) is common in countries with tropical climates. The study conducted by Geeverghese is the first to describe cases of FCPD on a large scale in the Indian state of Kerala, with a prevalence of 29.3% among total diabetes registered in the medical college in 1960. However, the prevalence decreased drastically, with a prevalence of 0.36% in 2001-2003 and 0.2% in 2001 - 2006.[3] There are no studies in Indonesia that explain the prevalence of FCPD.

The cause of FCPD is unknown. Several hypotheses regarding its aetiology exist, including the malnutrition hypothesis, the casava hypothesis, familial and genetic factors, deficiency of essential elements, oxidative stress, and autoimmunity.[4–6] FCPD is an often overlooked diagnosis. Most of the patients with FCPD were diagnosed as type 1 or type 2 diabetes mellitus before the exact diagnosis was known. FCPD has a variety of symptoms, and the disease is not widely recognized by medical personnel.

CASE ILLUSTRATION

A 46-year-old man came to Dr Moewardi Hospital with chief complaints of left abdominal pain 2 weeks ago. Abdominal pain was intermittent and accompanied by nausea and vomiting. He had lost 12 kilograms of weight in the last 2 months. One month earlier, he had been hospitalized in a regional hospital, and he was diagnosed with chronic pancreatitis and type 2 diabetes mellitus. He received oral therapy with metformin to control his blood sugar.

The average blood pressure during the physical examination was above normal. The patient appeared malnourished with a BMI of 16.5 kg/m2. Daily fasting blood glucose monitoring was 98-130 mg/dl, while postprandial blood glucose examination was 160-180 mg/dl. Lipid profile, liver and kidney function within normal limit. C-peptide level decreased to 0.5 ng/ml. The abdominal ultrasound examination was normal. A plain photo examination of the abdomen showed multiple opacities in the left hypochondriac region to the epigastrium as high as corpus vertebrae thoracal 12 mid clavicula sinistra to corpus vertebrae lumbal para vertebrae dextra, which leads to pancreatic calcification (Figure 1). The patient's abdominal computer tomography (CT) scan supported the diagnosis of chronic pancreatitis with multiple calcifications in the pancreas (Figure 2). Based on the criteria, this patient was diagnosed with FCPD.

The patient was educated on medical nutrition therapy. The patient's blood glucose monitoring was still above average, so it was decided to use basal-bolus insulin to control the patient's blood sugar. He also received pancreatic enzyme supplementation to prevent absorption disorders in the patient. NSAIDs were given to reduce abdominal pain experienced by the patient. After 2 months of evaluation, HbA1c level decreased to 7.0%, fasting blood sugar 119 mg/dl and postprandial blood sugar 149 mg/dl. The patient's symptoms have decreased, but he lost follow-up and returned to his home area for economic reasons.

DISCUSSION

FCPD is a form of diabetes that is rarely encountered in clinical practice. FCPD is generally found at a young age. In men, the diagnosis of FCPD occurs in the range of 10 years to 40 years old. Whereas in women, the average diagnosis occurs at the age of 17 years old.[7] Most patients with FCPD are malnourished and typically occur in tropical countries. The classic symptoms of FCPD are diabetic symptoms accompanied by chronic abdominal pain, stones or calculi in the pancreas, and the emergence of steatorrhoea.[2,8] The diagnostic criteria for FCPD include : [1,9]

1. It happens in developing countries
2. Diabetes diagnosis based on WHO Study group criteria
3. There is evidence of chronic pancreatitis, which includes clinical and radiological examinations that include the following three criteria:
   a. Abnormal pancreatic morphology according to radiological examination
   b. Chronic abdominal pain
   c. Abnormal pancreatic function
   d. Steatorrhea

4. There were no other causes of chronic pancreatitis, such as alcoholism, hepatobiliary disorders, and primary hyperthyroidism

Abdominal pain is the main symptom that often occurs since childhood. Abdominal pain is usually episodic and improves with sitting and bending. However, the frequency of abdominal pain that occurs gradually decreases with the development of diabetes. In our case, the criteria for the diagnosis of FCPD have also been met with the incident taking place in a tropical country (Indonesia), the diagnosis of diabetes according to the WHO study group criteria, evidence of chronic pancreatitis through clinical and laboratory studies, and no other causes of chronic pancreatitis that occur such as alcohol use and hepatobiliary disease.[10]

The physical examination often found in patients with FCPD is known as the classic triad of FCPD, including parotid gland enlargement, abdominal distension, and cyanosis of the lips. However, the physical examination results with the triad are rarely found to have more heterogeneous properties. Malnutrition with a BMI below the average value is often seen in FCPD patients.[11] Examination of the abdomen shows various symptoms; it can be normal, or there is pain when pressed in the epigastric region and right hypochondriac.

Radiological examination plays a vital role in diagnosis. Some radiological examinations used are plain abdominal radiographs, ultrasound, CT scans, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound, and magnetic cholangiopancreatography. Ultrasound shows dilatation of the pancreatic duct and increased echogenicity secondary to fibrosis of the gland. Abdomen X-ray examination showed pancreatic calcification.[1,12,13] CT scan is an ideal examination to diagnose chronic pancreatitis.

Increased blood sugar levels, characterized by increased levels of HbA1c and an increase in postprandial blood glucose, are caused by a decreasing number of residual pancreatic beta-cells.[8] The examination used to assess pancreatic beta-cell function is done using a C-peptide assay. C-Peptide levels in FCPD patients tend to decrease to an intermediate degree.[4]

Non-opioid analgesics are used to reduce the pain experienced. The primary choice in the management of FCPD is the administration of insulin. Insulin is given in a combination of rapid-acting and long-acting insulin, adjusted to the patient's needs. [1,9] The diabetic oral drug can be given, especially in the early phase of diabetes. A long-acting insulin secretagogue is not recommended because it increases the risk of hypoglycemia. Metformin can be given but needs to be considered for gastrointestinal side effects. Incretin-based drugs are not recommended. Only a few literatures have discussed the effect of thiazolidinediones and SGLT-2 administration in FCPD patients. Giving patients pancreatic enzyme supplementation can improve their nutritional status.[1,14]

CONCLUSION

FCPD is a rare case, often occurring in young adults, characterized by malnutrition, diabetes and chronic pancreatitis. Initial management can be given oral antidiabetic drugs, but at an advanced stage, insulin is used to control blood glucose. Adequate glycemic control, reduced pain, and improved pancreatic function are the main treatments that improve the patient's quality of life.

ACKNOWLEDGEMENTS

We thank the patient for consenting to be featured in this manuscript.

AFFILIATIONS

All authors are staff of the Endocrine, Metabolic and Diabetes Division of Dr. Moewardi Hospital Surakarta / Faculty of Medicine, Sebelas Maret University.

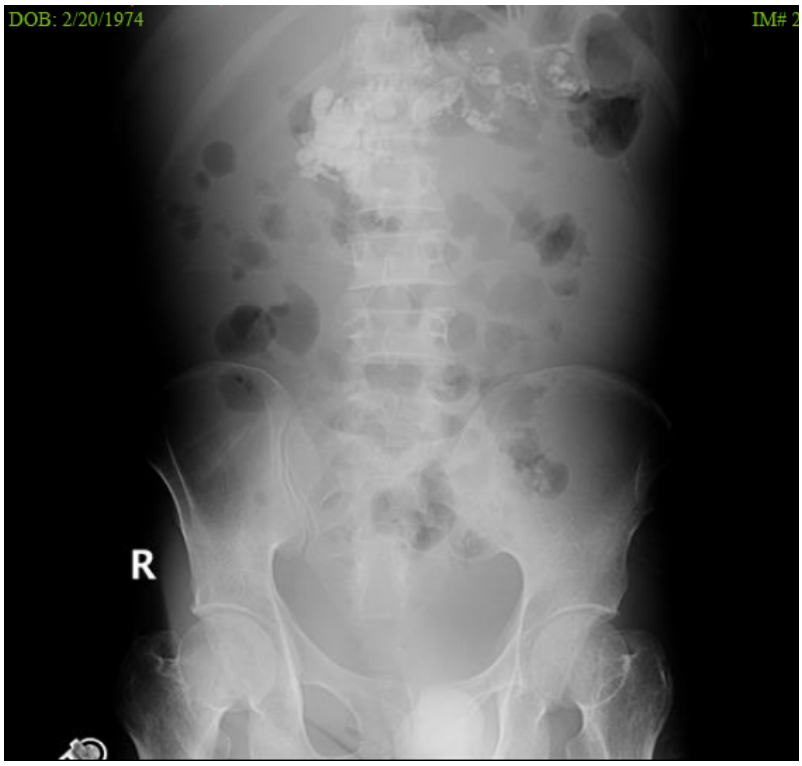

Figure 1. Calcification of pancreas appear in abdominal X-ray

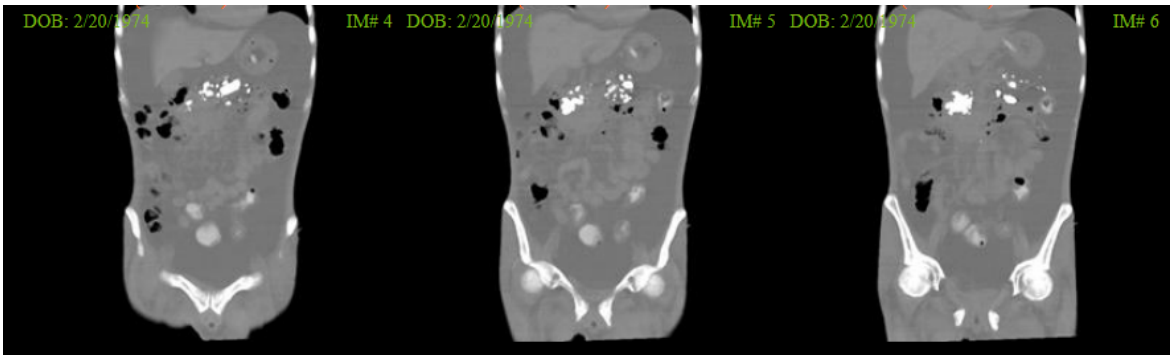

Figure 2. CT Scan Shows Multiple Calcification of pancreas

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REVIEW ARTICLE

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

Evaluating the Effects of Testosterone Therapy on Cardiometabolic Health and Well-being in Men with Hypogonadism

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ABSTRACT

Testosterone is crucial for male health, and hypogonadism is prevalent, particularly in men with metabolic comorbidities. While Testosterone Therapy (TTh) is used to manage symptoms, its effects on cardiometabolic health and overall well-being remain debated. This review aimed to synthesize current evidence on the impact of TTh on cardiometabolic parameters, cardiovascular safety, and quality of life in men with hypogonadism. A literature search (2015-2025) across multiple databases identified relevant studies, including Randomized Controlled Trials (RCTs) and observational data, which were narratively synthesized. Results show TTh consistently improves body composition (reduced fat, increased muscle) and aspects of sexual function (libido, activity). However, its effect on glucose metabolism remains controversial, with conflicting findings. While large RCTs indicate no increased risk of major adverse cardiovascular events over the medium term, TTh is associated with increased specific risks including pulmonary embolism, atrial fibrillation, acute kidney injury, and polycythemia. Benefits on mood/energy are modest, and effects on other quality of life domains are limited. In conclusion, TTh offers clear benefits for body composition and sexual function. Clinicians must balance these with controversial glucose effects and increased specific adverse event risks, requiring careful patient selection and monitoring. Further long-term research is needed.

Keywords: Testosterone Therapy, Hypogonadism, Cardiometabolic Health, Quality of Life, Adverse Cardiovascular Events

INTRODUCTION

Testosterone is the principal androgen hormone in men, playing a central role in the regulation of male sexual differentiation, the development and maintenance of secondary sexual characteristics, spermatogenesis, and fertility.[1] Beyond its well-established reproductive functions, testosterone exerts widespread effects on numerous physiological systems. It is a key modulator of body composition, promoting muscle mass, reducing fat mass, and influences glucose and lipid metabolism, thereby contributing significantly to overall metabolic health.[2] Moreover, adequate testosterone levels are associated with cardiovascular health, as low testosterone has been linked to increased cardiovascular risk factors, including insulin resistance, dyslipidemia, hypertension, and

visceral adiposity.[3] Testosterone is also involved in various neuropsychological processes, contributing to mood regulation, energy levels, cognitive function, and general well-being, highlighting its systemic importance.

Physiologically, testosterone levels decline gradually with advancing age, in a process commonly referred to as late-onset hypogonadism or age-related testosterone deficiency. This age-related decline is often compounded by comorbid conditions such as obesity, type 2 diabetes mellitus (T2D), metabolic syndrome (MetS), and chronic illnesses, as well as by lifestyle factors, certain medications, and genetic predispositions.[4] A substantial proportion of men with these metabolic comorbidities exhibit low testosterone levels, with estimates suggesting that up to 50% of obese men or those with T2D or MetS are affected.[5,6] The relationship between testosterone and adiposity is complex and bidirectional: increased visceral fat leads to higher aromatase activity and conversion of testosterone to estradiol, suppressing the hypothalamic-pituitary-gonadal axis, while testosterone deficiency itself contributes to fat accumulation and metabolic derangements.[7] Similarly, men with MetS, characterized by central obesity, hyperglycemia, insulin resistance, hypertension, and dyslipidemia, often exhibit significantly lower testosterone concentrations compared to metabolically healthy individuals.[8]

In light of testosterone's diverse physiological roles and the high prevalence of hypogonadism among men with metabolic disorders, testosterone therapy (TTh) has gained substantial attention as a potential therapeutic strategy. The primary aim of TTh is to restore serum testosterone levels to a physiological range to alleviate symptoms of hypogonadism, such as sexual dysfunction, low energy, depressive symptoms, and loss of muscle mass. However, the potential benefits of TTh extend beyond symptomatic relief, with growing interest in its metabolic and cardiovascular effects. Several clinical studies and observational reports have suggested that TTh may enhance insulin sensitivity, lower fasting glucose and glycated hemoglobin (HbA1c), improve lipid profiles by reducing total cholesterol and triglycerides, and favorably influence body composition by decreasing fat mass and increasing lean mass.[4,9] These findings indicate that TTh may offer cardiometabolic benefits, particularly for men with comorbid conditions such as T2D or MetS. Nonetheless, the safety of TTh remains controversial, as some reports have raised concerns about increased cardiovascular risk, especially in older men or those with underlying cardiovascular disease. Additionally, TTh can lead to increased hematocrit levels, raising concerns about the risk of erythrocytosis and venous thromboembolism.[10]

Given these potential benefits and risks, there is a critical need for a comprehensive and balanced synthesis of the current literature to guide clinical practice. This review aims to evaluate the most recent and robust evidence regarding the effects of testosterone therapy in men with hypogonadism, with a specific focus on its impact on cardiometabolic health (including metabolic parameters, cardiovascular outcomes, and safety considerations) as well as on broader quality-of-life measures such as sexual function, mood, and vitality. Additionally, this review seeks to identify gaps in the existing body of research and highlight areas where further investigation is warranted, particularly in high-risk populations and long-term therapeutic contexts.

METHODOLOGY

The authors conducted a literature search across databases such as PubMed, Scopus, ProQuest, EBSCO, and Google Scholar to identify studies related to the use of therapy TTh and its impact on cardiometabolic health in men, with a publication date range from 2015 to 2025. The search was performed using Boolean

operators with keywords such as ("testosterone therapy" OR "testosterone replacement therapy" OR "TTh" OR "TRT") AND ("cardiometabolic health" OR "cardiovascular risk" OR "metabolic syndrome" OR "insulin resistance").

All authors conducted an initial screening of titles and abstracts obtained electronically, followed by independent assessment of the full texts of studies that potentially met the inclusion criteria. Inclusion criteria encompassed observational studies, randomized controlled trials (RCTs), meta-analyses, and systematic reviews that evaluated the effects of testosterone therapy on cardiometabolic health parameters (such as insulin resistance, blood glucose levels, lipid profiles, body composition, cardiovascular events, and related safety) and/or quality of life outcomes (such as sexual function, mood, and energy levels) in men. Only studies with complete data available in either Indonesian or English were included.

Data extracted from each study meeting the inclusion criteria included study characteristics (e.g., study design), participant population characteristics (including age and comorbid conditions), details of the testosterone therapy protocol (including dosage, route of administration, and duration of therapy), relevant outcomes (metabolic parameters, cardiovascular events, adverse effects, and quality-of-life indicators), and other key findings. All extracted data were then synthesized and reported narratively in the Results and Discussion section. Any disagreements that arose among the authors during the screening, full-text assessment, or data extraction processes were resolved through discussion until consensus was reached.

RESULT

Study Characteristics

A summary of the study characteristics is presented in Table 1. A total of 13 studies from various literature sources were included, consisting of diverse study designs, including RCTs and longitudinal observational studies. The interventions examined involved the use of TTh in various formulations (intramuscular injections, transdermal gels, and subcutaneous pellets) with differing doses and durations.

These studies involved male participants with hypogonadism, which in many cases was associated with metabolic comorbidities such as type T2D, MetS, and obesity. Participant ages varied widely, although most were from the middle-aged to elderly groups. The relationship between hypogonadism and metabolic comorbidities is bidirectional, with hypogonadism potentially being either a cause or consequence of these conditions. Two studies included men with various health conditions without specific criteria related to hypogonadism or comorbidities, while one study specifically involved hypogonadal men with cardiovascular risk.

Despite disparities in the types of testosterone preparations, dosing regimens, administration routes, baseline comorbidities, and testosterone levels across studies, these parameters were still generally comparable. Key clinical outcomes such as changes in body composition, metabolic parameters, sexual function, and major cardiovascular events remained objective parameters that could be assessed statistically.

Cardiometabolic and Functional Implications of Testosterone Deficiency

Testosterone deficiency in men is associated with a range of adverse health outcomes, affecting metabolic processes, cardiovascular health, and overall quality of life. The decline of this crucial hormone triggers a cascade of interconnected physiological changes that can significantly impair well-being.

Table 1. Study characteristics.

Author (Year)	Country	Study Design	Intervention	Population	Age (years)	Sample Size (n)	Formulation	Dose	Follow-up Duration
Malyar Emranian (2015)	US	Case-Ctrl Study	TTh	Various men	70.4 (case), 71.0 (control)	934,243	Various (injection, gel, patch, oral)	N/A	N/A
Geoffrey Hackett (2019)	UK	Longit Obs Cohort	TTh	Men w/ T2D & Hypog	Avg 64.6 yrs	857	Various	1000 mg	N/A
Christopher J.D Wallis (2016)	Canada	Pop-Based Retro Cohort	TTh	Various men	≥66 yrs	10,311 (TTh) vs 28,029 (control)	All T formulations	N/A	63.6 months
Jemma Hudson (2022)	Global	MA (RCT, IPD)	TTh	Men w/ Hypog	≥18 yrs (avg 65)	5601	All T formulations	Varies	Varies across studies
Yuliya Tishova (2024)	Russia	DB PC RCT	TTh	Men w/ MetS & Hypog	35–70 yrs	184	Parenteral TU	1000 mg	34.5 months
Aksam Yassin (2019)	Germany, UAE	LT Obs Registry	TTh	Men w/ preDM & Hypog	Avg 61.5 (TTh), 61.6 (control)	319	Parenteral TU	1000 mg	126 months
Karim Sultan Haider (2020)	Germany, UAE	LT Obs Registry	TTh	Men w/ preDM & Hypog	Avg 51.5–54.4 (TTh), 53.7–54.9 (control)	356	Parenteral TU	1000 mg	132 months
Gary Wittert (2021)	Australia	DB PC Phase 3b RCT	TTh + lifestyle intervention	Obese/ overweight men w/ low T or T2D	56.1–56.5 yrs	1007	Parenteral TU	1000 mg	24 months
Shalender Bhasin (2024)	US	PC RCT Substudy	TTh	Men w/ Hypog + preDM/DM	68.8 ± 1.9 yrs	5204	T gel	1.62%	48 months
A.M. Lincoff (2023)	US	Multicenter DB RCT	TTh	Men w/ Hypog + preDM/DM	63.3–77.9 yrs	5204	T gel	1.62%	Avg 3.2 yrs
Karol M. Pencina (2023)	US	DB RCT Substudy	TTh	Men w/ Hypog + CV risk	63.7 (7.6) yrs	1161	T gel	1.62%	Avg 3.3 yrs
Shalender Bhasin (2024)	US	Noninferiority RCT Substudy + Phase 4	TTh	Men w/ Hypog + preDM/DM	45–80 yrs	2643	T gel	1.62%	Avg 3.2 yrs
Mathis Grossmann (2024)	Australia	Secondary analysis of T4DM Trial	TTh + lifestyle intervention	Obese/ overweight men w/ low T/T2D	Avg 56.0 yrs	648	Parenteral TU	1000 mg	24 months

Avg: Average, Case-Ctrl Study: Case-Control Study, CV: Cardiovascular, DB: Double-Blind, DM: Diabetes Mellitus, Hypog: Hypogonadism, IPD: Individual Participant Data, LT Obs Registry: Long-term Observational Registry, Longit Obs Cohort: Longitudinal Observational Cohort, MA: Meta-Analysis, MetS: Metabolic Syndrome, N/A: Not Available, PC: Placebo-Controlled, Pop-Based Retro Cohort: Population-Based Retrospective Cohort, preDM: Prediabetes, RCT: Randomized Controlled Trial, Retro: Retrospective, T gel: Testosterone gel, TTh: Testosterone Therapy, TU: Testosteron undecanoat, T2D: Type 2 Diabetes, US: United States, UK: United Kingdom, w/: with, yrs: years.

Metabolic implications

Testosterone deficiency significantly disrupts metabolic homeostasis, primarily by reducing insulin sensitivity and altering lipid profiles, while also contributing to a bidirectional negative relationship with obesity. Low testosterone levels impair the body's ability to respond to insulin through several key mechanisms. A decrease in Glucose Transporter Type (GLUT4) expression in skeletal muscle and subcutaneous adipose tissue limits glucose uptake, while disturbances in insulin signaling pathways further worsen glucose control and glycogen synthesis. In adipose tissue, heightened activity of inflammatory pathways promotes the release of pro-inflammatory cytokines such as Interleukin-6

(IL-6) and Monocyte Chemoattractant Protein-1 (MCP-1), which further impair insulin function and exacerbate metabolic dysfunction. In the liver, increased regulation of lipogenic enzymes drives fat accumulation (steatosis), further contributing to systemic insulin resistance.[11–13]

Testosterone deficiency also adversely affects lipid metabolism, resulting in an atherogenic lipid profile. Reduced activity of lipoprotein lipase (LPL) hinders triglyceride clearance, while increased release of free fatty acids from visceral adipose tissue prompts the liver to produce more triglycerides. Enhanced hepatic lipogenesis leads to greater secretion of VLDL-TG, worsening dyslipidemia. Moreover, low testosterone levels reduce HDL cholesterol by disrupting the expression of key proteins involved in reverse cholesterol transport. Dysregulation of nuclear receptor signaling pathways associated with lipid metabolism further exacerbates this imbalance.[11]

The relationship between testosterone deficiency and obesity is bidirectional and forms a vicious cycle. Obesity reduces testosterone levels through several mechanisms, including increased aromatase activity in visceral fat tissue, which converts testosterone into estradiol and suppresses the hypothalamic-pituitary-testicular axis. Additionally, the release of pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha and IL-6 from visceral fat disrupts hormonal signaling to the testes. Insulin resistance and hyperinsulinemia associated with obesity lower the production of sex hormone-binding globulin, reducing total testosterone levels. Changes in adipokine levels also play a role: hyperleptinemia leads to leptin resistance, reducing hypothalamic hormonal stimulation, while decreased adiponectin impairs Leydig cell function in testosterone production.[9,14–16]

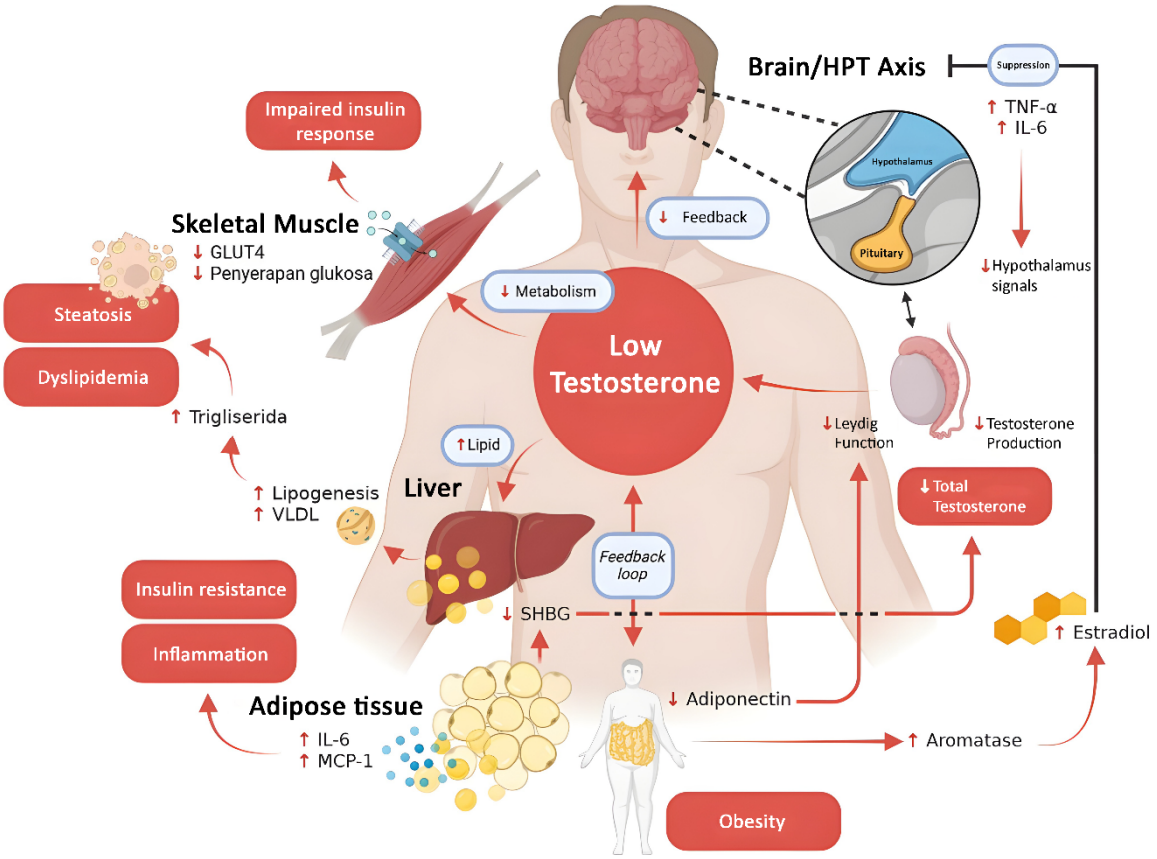

Figure 1. Multifactorial interactions between testosterone deficiency and metabolic disorders.

Conversely, low testosterone actively promotes the development of obesity by triggering fat accumulation and disrupting lipid metabolism. Testosterone plays a critical role in regulating body composition by suppressing the formation of adipocytes, particularly in visceral tissue. When testosterone levels are low, this process is impaired, making preadipocytes more likely to differentiate into mature fat cells. Additionally, low testosterone increases triglyceride uptake into adipose tissue and reduces the body's ability to break down and burn fat due to decreased activity of key enzymes involved in lipolysis and fat oxidation. These disturbances are compounded by the loss of lean muscle mass, which is a major site of energy metabolism. Clinically, low testosterone levels are a strong predictor of increased visceral fat over time.[9,15–17]

Cardiovascular implications

Testosterone deficiency has detrimental effects on the cardiovascular system, primarily by triggering endothelial dysfunction and creating a pro-inflammatory vascular environment. One of the key mechanisms is the reduced bioavailability of nitric oxide (NO), a vital vasodilator produced by the enzyme endothelial nitric oxide synthase (eNOS). Low testosterone levels decrease eNOS activity and increase oxidative stress, which further suppresses NO production and generates reactive oxygen species that can damage endothelial cells directly or by inactivating NO. In addition, low testosterone levels promote increased synthesis of endothelin-1 (ET-1), a potent vasoconstrictor, disrupting the balance between NO and ET-1 and worsening vascular dysfunction. This condition is also accompanied by elevated levels of adhesion molecules such as vascular cell adhesion molecule-1 and increased leukocyte–endothelium interactions, which indicate vascular inflammatory activation. This pro-inflammatory status is further evidenced by elevated levels of systemic inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and TNF-α, as supported by findings in animal models. This feed-forward loop of inflammation is exacerbated by cytokines like IL-6 and TNF-α, which upregulate the expression of adhesion molecules and reinforce vascular damage.[18–21]

Quality of life implications

One of the most prominent effects of low testosterone is a decline in sexual function, which can significantly reduce quality of life. Clinically, this often manifests as erectile dysfunction, decreased sexual desire hypoactive sexual desire disorder, or delayed ejaculation. These issues rarely occur in isolation; they are frequently associated with systemic health conditions and an increased risk of mortality, making them an important indicator of overall male well-being.[22]

Table 2. Cardiovascular implications of testosterone deficiency

Mechanism	Effect of Testosterone Deficiency	Cardiovascular Impact
Endothelial Function	↓ eNOS Activity, ↑ Oxidative Stress	↓ Nitric Oxide (NO), Endothelial Dysfunction
Vascular Tone Regulation	↑ Endothelin-1 (ET-1), ↓ NO	Vasoconstriction, ↑ Vascular Resistance
Inflammatory Markers	↑ hs-CRP, TNF-α, IL-6	Chronic Vascular Inflammation
Cellular Adhesion Molecules	↑ VCAM-1, ↑ Leukocyte interaction with Endothelium	Atherosclerosis worsening
Forward Inflammation Loop	Cytokines amplify Oxidative Stress and Endothelial Damage	Progressive Vascular Damage

eNOS: Endothelial Nitric Oxide Synthase, ET-1: Endothelin-1, hs-CRP: High-Sensitivity C-Reactive Protein, IL-6: Interleukin-6, NO: Nitric Oxide, TNF-α: Tumor Necrosis Factor alpha, VCAM-1: Vascular Cell Adhesion Molecule-1, ↑: Increased/Elevated, ↓: Decreased/Reduced.

Table 3. Implications of testosterone deficiency for quality of life

Aspect	Specific Effect	Impact
Sexual Function	**↓ Libido, ED, Delayed Ejaculation**	**Decreased sexual satisfaction, ↓ Self-Esteem**
Mood & Emotion	↑ Depression, fatigue, irritability, ↓ vitality and motivation	Impaired daily activities and social relations
Cognition & Behavior	↓ Drive for dominance, ↓ assertiveness, impaired stress response	Impaired work performance, impaired decision-making
Neurobiological	Neurotransmitter and brain plasticity impairment	↓ Psychological resilience
Genetic Factors	Variation in CAG repeat length in androgen receptor affects hormone sensitivity	Symptom and treatment response variability

CAG: Cytosine-Adenine-Guanine, ED: Erectile Dysfunction, ↑: Increased/Elevated, ↓: Decreased/Reduced.

Beyond sexual health, low testosterone also affects psychological and behavioral aspects. Men with testosterone deficiency are more susceptible to dysphoria, chronic fatigue, irritability, decreased vitality and assertiveness, and even depression. Testosterone functions as a neuroactive steroid, influencing neurotransmitters, brain plasticity, and the modulation of stress and emotional responses. These symptoms can profoundly affect daily life, but TTh has been shown to improve energy levels, mood, and vitality. This hormone also plays a role in motivated behaviors such as dominance and status-seeking, which can influence self-perception and social interactions. These effects may also be modulated by genetic factors, such as the length of coronary angiography repeats in the androgen receptor gene, which can alter hormonal sensitivity in the brain.[23]

Effects of Testosterone Therapy on Metabolic Parameters

TTh has demonstrated various effects on metabolic parameters in men, particularly those with hypogonadism, prediabetes, type 2 diabetes (T2D), or metabolic syndrome (MetS), as shown in multiple studies. Several investigations have highlighted its potential benefits on glucose metabolism.

One study involving men participating in a lifestyle program found that TTh significantly reduced the incidence of T2D over two years compared to placebo (12% vs. 21%) and led to greater improvements in 2-hour glucose levels after an oral glucose tolerance test (OGTT).[24] Similarly, an eight-year registry study reported that long-term TTh in hypogonadal men with prediabetes prevented progression to T2D, with 90% achieving normal glucose regulation (HbA1c <5.7%), compared to 40.2% who progressed in the untreated control group. This study also noted improvements in fasting glucose and HbA1c following TTh administration.[25] Furthermore, an eleven-year registry study observed T2D remission (defined as HbA1c <6.5% without medication) in 34.3% of hypogonadal men with T2D receiving TTh, along with significant and sustained reductions in fasting glucose and HbA1c levels, changes not observed in the control group.[26]

Improved insulin sensitivity has also been reported. TTh significantly reduced homeostatic model assessment of insulin resistance (HOMA-IR) (a marker of insulin resistance) from baseline in hypogonadal men with MetS, primarily by lowering fasting insulin levels more than fasting glucose levels.[27] The eleven-year registry study also documented significant reductions in fasting insulin and HOMA-IR in the TTh group, indicating improved insulin sensitivity, while these markers worsened in the control group.[26] Additionally, the triglyceride-glucose index and lipid accumulation product also declined with TTh in the eight-year registry study.[25]

However, not all studies support TTh's role in glycemic control or diabetes prevention. A major substudy from the TRAVERSE RCTs found no

difference between TTh and placebo in the risk of progression from prediabetes to T2D over up to 48 months. This study also did not show significant increases in glycemic remission rates among men with existing diabetes, nor improvements in fasting glucose or HbA1c levels compared to placebo in middle-aged and older men with hypogonadism.[28] Supporting these findings, a study by Wittert et al. (2021), despite showing benefits for T2D incidence and OGTT glucose, found no significant difference in HbA1c changes between the TTh and placebo groups over two years.[24]

Regarding body composition and anthropometric parameters, the findings generally indicate improvements with TTh. Studies consistently reported greater reductions in waist circumference in men receiving TTh compared to controls or placebo.[24–27] Weight loss and reductions in body mass index (BMI) were also observed in long-term registry studies.[25,26] Moreover, TTh was associated with greater reductions in total fat mass and abdominal fat mass, along with increases in total muscle mass and arm muscle mass. This shift from fat mass to lean mass may explain why overall weight loss is not always significant, as seen in the Wittert et al. (2021) study, where fat loss was offset by gains in muscle mass.[24]

Improvements in lipid profiles have also been reported, particularly in long-term registry studies. TTh was associated with significant improvements in total cholesterol, Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), triglycerides, triglyceride-to-HDL ratio, and non-HDL cholesterol compared to untreated controls.[25,26] Remnant cholesterol levels also declined significantly with TTh in the eleven-year registry study.[26]

Effects of Testosterone Therapy on Cardiovascular Risk

The cardiovascular safety profile of (TTh) presents a complex picture, with recent large-scale trials offering valuable insights, alongside findings from observational studies and meta-analyses. The key result from the TRAVERSE RCTs, which involved middle-aged and older men with hypogonadism and high cardiovascular risk, was that TTh was non-inferior to placebo in terms of major adverse cardiac events (MACE)—a composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The incidence of first MACE events was similar between the TTh group (7.0%) and the placebo group (7.3%) over an average follow-up period of about three years.[29] This finding aligns with results from a meta-analysis that found no evidence that TTh increased the overall risk of cardiovascular or cerebrovascular events compared to placebo in the short- to medium-term (mean follow-up of 9.5 months), with comparable event rates (7.5% in TTh vs. 7.2% in placebo).[30] Furthermore, a large pharmacoepidemiological study focusing on myocardial infarction did not find any statistically significant association between either current or past use of TTh and myocardial infarction risk.[31]

Regarding mortality, some observational evidence suggests potential benefits of TTh. A study in men with T2D and low testosterone levels found that TTh was associated with a significant reduction in all-cause mortality compared to untreated men, particularly among older individuals or those who were less overweight, despite no improvements in conventional cardiovascular risk factors such as lipid profiles or blood pressure.[30] Another observational cohort study also showed that TTh use overall was linked to lower mortality, with the effect strongly dependent on the duration of therapy; long-term use (>35 months) was associated with a significantly reduced risk of death compared to controls.[32] However, in meta-analyses, although fewer deaths were observed in the TTh group (0.4% vs. 0.8%), this difference did not reach statistical significance, likely due to the short

duration of follow-up and low event rates in the analyzed trials.[30]

The timing and duration of TTh exposure may influence cardiovascular risk, although most findings derive from observational data that are prone to bias. One cohort study reported that short-term exposure to TTh (median of 2 months) was associated with increased mortality and cardiovascular events, whereas long-term exposure (median of 35 months) was associated with reduced risk for both outcomes compared to controls.[32] Similarly, a pharmacoepidemiological study found a small but statistically significant increased risk of myocardial infarction in new users of TTh (within the first 90 days of therapy), a risk not observed in long-term users. The absolute increase in risk was considered low (Number Needed to Harm, 305).[31] These findings suggest a potential early hazard or risk with short-term use, which contrasts with the possible benefits of long-term use. However, interpreting these results requires caution while awaiting confirmation from more robust RCTs.

Although the TRAVERSE trial did not find an increased risk of MACE, it did identify higher incidences of certain specific adverse events in the TTh group compared to placebo. Notably, there was a higher incidence of pulmonary embolism (0.9% vs. 0.5%), atrial fibrillation (3.5% vs. 2.4% as reported by investigators; 5.2% vs. 3.3% for nonfatal arrhythmic events requiring intervention after adjudication), and acute kidney injury (2.3% vs. 1.5% per investigator report) in the TTh group.[29] In line with known physiological effects, meta-analyses also reported a significant increase in hematocrit/hemoglobin levels (leading to higher rates of polycythemia) and a greater incidence of edema in the TTh group, although no overall increase in venous thromboembolism events was observed in the short- to medium-term data analyzed.[30]

Effects of Testosterone Therapy on Quality of Life

TTh demonstrates specific, though not universal, benefits on aspects of quality of life (QoL) in men with hypogonadism. The most consistently reported improvements are found in the domain of sexual function. One study found that TTh significantly enhanced overall sexual activity and sexual desire (libido) compared to placebo in middle-aged and older men with hypogonadism, with these positive effects sustained over a 2-year period.[33] This improvement in sexual well-being was accompanied by a significant reduction in the overall burden of hypogonadism symptoms, as measured by the Hypogonadism Impact of Symptoms Questionnaire (HIS-Q), indicating broader symptom relief.[33] However, it is important to note that the same study did not find a significant difference between TTh and placebo in the improvement of erectile function scores (IIEF-5).[33]

Regarding mood and energy levels, evidence shows mild improvements with TTh. A sub-study of the TRAVERSE trial reported a small but statistically significant increase in mood and energy compared to placebo, particularly evident in men who had depressive symptoms at baseline.[34] However, the positive impact on mood appeared limited, primarily benefiting men with mild to moderate depressive symptoms (baseline PHQ-9 scores between 5–14), and showing no significant advantage over placebo in those with moderate to severe depression.[34] Based on these findings, TTh is generally not considered a primary treatment for clinical depressive disorders.[34]

TTh benefits appear less evident or absent in other QoL domains. Studies using HIS-Q domains did not find significant improvements attributable to TTh in perceived cognitive function or sleep quality compared to placebo.[28] Moreover, in a 2-year trial involving overweight or obese men

participating in a lifestyle modification program, TTh did not produce consistent improvements in broader health-related QOL(HR-QOL) measures, such as the physical and mental component scores of the SF-12, or in psychosocial function indicators like personal mastery and subjective social status relative to society, when compared with placebo. Although temporary improvements in self-cohesion and relative social status among peers were observed midway through the study, these effects did not persist until the end of the study.[35]

Interestingly, other factors such as lifestyle changes may have a greater impact on QoL than TTh in certain populations. The study by Grossmann et al. (2024) clearly demonstrated that weight loss achieved through accompanying lifestyle interventions significantly improved mental quality of life, personal mastery, and subjective social status, indicating that weight management exerted a more positive influence on these aspects than TTh alone in overweight or obese men. This study also highlighted that better baseline psychosocial health predicted greater success in weight loss programs.[35]

DISCUSSION

This literature review aimed to evaluate the current evidence regarding the impact of (TTh) on cardiometabolic health and overall well-being in men with hypogonadism. Analysis of relevant studies highlights the complexity of TTh effects, with findings varying depending on the measured parameters, study design, and population characteristics. Physiologically, testosterone plays a critical role in regulating glucose and lipid metabolism, body composition, and cardiovascular function, providing a biological rationale for the expected cardiometabolic benefits of TTh in men with hormone deficiency. However, clinical evidence presents a more nuanced picture.

In terms of metabolic parameters, TTh consistently shows benefits on body composition, with significant reductions in waist circumference, fat mass (particularly abdominal fat), and increases in muscle mass reported across various studies, including clinical trials and long-term registry studies.[24–27] Positive effects on lipid profiles, such as improvements in total cholesterol, LDL, HDL, and triglycerides compared to controls, have also been reported in long-term registry data.[25,26] However, the impact of TTh on glucose metabolism remains a subject of debate. While some observational and long-term registry studies suggest TTh may help prevent progression to T2D, induce T2D remission, and improve glycemic control and insulin sensitivity,[24–27] large-scale RCTs, such as the TRAVERSE substudy, found no significant benefit of TTh over placebo in terms of diabetes progression, glycemic remission, or improvements in HbA1c and fasting glucose over a follow-up period of up to 48 months.[28] These differing results may be attributed to variations in methodology, follow-up duration, or population characteristics across studies, highlighting the need for further research to clarify the role of TTh in glycemic management.

Regarding safety and cardiovascular risk, the TRAVERSE RCT provides important evidence that TTh is not inferior to placebo in terms of MACE in middle-aged and older men with hypogonadism and high cardiovascular risk over approximately three years.[29] This finding is supported by meta-analyses and pharmacoepidemiologic studies that also found no overall increase in MACE risk.[30,31] Some observational studies even suggest a potential reduction in mortality with long-term TTh use,[32,36] although short-term trial meta-analyses did not find statistically significant differences in mortality rates.[30] Nevertheless, the safety profile of TTh is not without concerns. The TRAVERSE trial identified increased incidences of venous

thromboembolism (particularly pulmonary embolism), atrial fibrillation, and acute kidney injury in the TTh group.[29] Increases in hematocrit and hemoglobin, leading to heightened risks of polycythemia and edema, are also known and confirmed side effects.[30] Observational data suggesting a potential elevation in cardiovascular risk during early or short-term therapy warrant further confirmation through RCTs.[31,32]

Assessment of TTh's impact on well-being and quality of life indicates benefits primarily in the domain of sexual function. TTh has been consistently reported to improve overall sexual activity and sexual desire (libido), and to reduce the symptom burden of hypogonadism.[33] However, these benefits do not extend to improvements in erectile function as measured by IIEF-5.[33] There is also evidence of small but statistically significant improvements in mood and energy levels, especially among men with mild to moderate depressive symptoms at baseline,[34] although TTh is not indicated as a primary therapy for clinical depression. TTh appears to offer little or no benefit in other quality-of-life domains, such as perceived cognitive function, sleep quality, or broader HR-QOL measures.[34,35] Interestingly, in overweight or obese men, lifestyle interventions such as weight loss have shown a greater impact on mental and psychosocial quality of life than TTh alone.[35]

While the TRAVERSE trial provides compelling evidence regarding the cardiovascular safety of TTh, some experts have expressed nuanced perspectives that merit consideration. Khera et al. acknowledged the trial's significance in advancing testosterone research and providing valuable safety and efficacy insights.[37] However, Krishnan et al. cautioned against overly simplistic interpretations for real-world application, citing limitations such as high discontinuation rates and short treatment duration.[38] Budoff further emphasized trial shortcomings, including early termination and inadequate testosterone restoration, which could create a false sense of security.[39] Despite these concerns, Hackett and Ramachandran suggested that the positive findings may justify the relaxation of cardiovascular warnings on testosterone products.[40] These differing viewpoints underscore the ongoing debate about balancing the observed benefits of TTh, particularly in enhancing sexual function and libido, with the need for careful interpretation of safety data and awareness of potential risks.

CONCLUSION

In conclusion, this review synthesizes current evidence on the impact of (TTh) on cardiometabolic health and overall well-being in men with hypogonadism, highlighting a complex picture. TTh consistently demonstrates benefits in body composition (reduction in fat mass, increase in muscle mass) and sexual function, particularly in libido and sexual activity. However, its effects on glycemic control remain controversial, with conflicting findings between observational studies and large clinical trials, indicating the need for further research.

In terms of cardiovascular safety, trials such as TRAVERSE show that TTh is non-inferior to placebo for MACE, but they also indicate increased risks of specific adverse events, including venous thromboembolism, atrial fibrillation, acute kidney injury, and polycythemia. The benefits of TTh on mood and energy are moderate, while its impact on other aspects of quality of life is limited.

Therefore, while TTh offers meaningful benefits, careful consideration of its risk-benefit profile remains essential. Research gaps that need to be addressed include confirmation of long-term safety, clarification of its precise role in glycemic management, understanding the mechanisms behind specific adverse effects, evaluating effectiveness in particular subpopulations, and assessing quality of life using

appropriate instruments. This body of evidence is crucial to support more personalized clinical decision-making for men with hypogonadism.

ACKNOWLEDGEMENT

None

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REVIEW ARTICLE

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

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

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ABSTRACT

Background: The rising prevalence of diabetic retinopathy (DR) among diabetic patients necessitates innovative therapeutic strategies. Fenofibrate, primarily known for its lipid-lowering effects, has gained attention for its potential role in mitigating DR progression. This study aims to evaluate the efficacy of fenofibrate in reducing the progression of diabetic retinopathy.

Method: A comprehensive search was done on three electronic databases, including PubMed, Scopus, and ProQuest up to 3 January 2025. We included all studies that are clinical trials or observational by design published within the last 15 years. The outcome of interest in this study is the progression or worsening of DR. All eligible studies were assessed using the Cochrane risk of bias tool 2.0 for randomized clinical trials, and the risk of bias in non-randomized studies - of interventions.

Result: A total of 5 studies encompassing 2 RCT and 3 retrospective cohort studies with a total of 250.835 patients, consisting of 101.026 (40.3%) males, with an overall mean age of 64.3 ± 9.5 years old. Based on the risk of bias assessment, all five studies fall in the low to moderate risk of bias. Four studies show that fenofibrate significantly reduces the risk of DR progression, while one study shows no significant reduction. Two studies also indicate the efficacy of fenofibrate in reducing the development of macular edema.

Conclusion: This study solidifies the efficacy of fenofibrate in reducing the risk of DR progression and the development of macular edema.

Keywords*:* Fenofibrate, diabetic retinopathy, macular edema

INTRODUCTION

Diabetic retinopathy (DR) stands as a leading cause of vision impairment among adults worldwide, particularly affecting those with diabetes mellitus. This microvascular complication arises from prolonged hyperglycemia, leading to progressive retinal damage and, if untreated, potential blindness. The global burden of DR is substantial; in 2020, approximately 103 million individuals were affected, with projections estimating an increase to 160.5 million by 2045.[1] The pathophysiology of DR involves complex mechanisms, including inflammation, oxidative stress, and the breakdown of the blood-retinal barrier. Traditional management strategies have focused on stringent glycemic control, blood pressure regulation, and lipid management to mitigate the risk of DR development and progression. Despite these measures, the incidence of DR remains high, underscoring the need for additional therapeutic interventions.[2,3]

Fenofibrate, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, is conventionally utilized for its lipid-modifying properties, particularly in reducing triglyceride levels and increasing high-density lipoprotein cholesterol. Beyond its lipid-lowering effects, fenofibrate has demonstrated potential benefits in ocular health. Notably large-scale randomized controlled trials, such as the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.[4] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study.[5], have reported a significant reduction in the progression of DR among patients with type 2 diabetes treated with fenofibrate.[6]

The FIELD study, encompassing 9,795 participants, revealed that fenofibrate therapy led to a notable decrease in the requirement for laser treatment for DR, independent of baseline lipid levels. Similarly, the ACCORD Eye study corroborated these findings, indicating that fenofibrate reduced the progression of DR, suggesting mechanisms beyond mere lipid modulation.[4,5]

The exact pathways through which fenofibrate exerts its protective effects on the retina are not entirely elucidated. Proposed mechanisms include anti-inflammatory actions, inhibiting vascular endothelial growth factor (VEGF) expression, and preserving the blood-retinal barrier integrity. These pleiotropic effects position fenofibrate as a promising adjunctive therapy in DR management.[7] In light of these findings, this systematic review aims to comprehensively evaluate the efficacy of fenofibrate in attenuating the progression of diabetic retinopathy.

METHODOLOGY

This systematic review and meta-analysis were conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[8,9] A thorough systematic literature search was conducted on three electronical databases such as PubMed, ProQuest, and Scopus. Keywords associated with literature searching are summarized in Table 1. This systematic review includes randomized controlled trials, non-randomized controlled trials, observational studies, and pilot studies published in the last 15 years.

Table 1. Keywords associated with literature searching for databases.

Databases	Search terms
PubMed	("fenofibrate"[MeSH Terms] OR "fenofibrate"[All Fields] OR "fenofibrates"[All Fields] OR "fenofibric"[All Fields]) AND ("diabetic retinopathy"[MeSH Terms] OR ("diabetic"[All Fields] AND "retinopathy"[All Fields]) OR "diabetic retinopathy"[All Fields])
ProQuest	fenofibrate AND (diabetic retinopathy OR retinopathy diabetic OR Retinopathy of diabetes)
Scopus	fenofibrate AND (diabetic retinopathy OR retinopathy diabeticum OR Retinopathy of diabetes)

In this study, studies associated with the use of fenofibrate in patients with diabetic retinopathy that were published in English in the last 15 years are included. We excluded studies with irrelevant outcome measurements, animal or cadaveric studies, review articles, meta-analyses, case reports, case series, and publications not in English. Two researchers working in pairs independently did study selection and data extraction from published papers. Any disagreements were settled by conversation or involving the third researcher through discussions until a consensus was reached. In this study, we performed quality assessments using the Cochrane risk of bias tool (ROB) 2.0 for randomized clinical trials (RCT) and the risk of bias in non-randomized studies - of interventions (ROBINS-I).[10,11] The risk of bias or quality assessment for each study was conducted by three researchers, with any differences resolved through discussion until a consensus is reached. Outcomes measured for this systematic review are progression of diabetic retinopathy, defined as diabetic retinopathy that has progressed into proliferative diabetic retinopathy or any progression that significantly affects the patients.

RESULT

A total of 893 studies were obtained from three databases. After removing duplicates, totaling 543 entries, and assessing publications based on their titles and abstracts, 288 articles were deemed unfit and are therefore not included in further research. After careful consideration, 62 articles were chosen for additional analysis. Of those, 51 reports could not be received, leaving 11 publications; a thorough evaluation was performed on their whole texts, excluding 6 articles. The reasons for exclusion included 2 articles having different outcomes of interest (e.g., the incidence of DR), 1 article with unclear intervention protocol, and another 1 with other tools to measure the outcome and 1 is not published within 15 years. Five papers met the specific criteria for inclusion. Therefore, these papers were chosen for additional examination and data extraction, as shown in figure 1.

The composition of the study design is as follows: 3 were randomized controlled trials, and 3 were cohort studies. The origin of each survey is varied, with six conducted in the United Kingdom, Canada, Korea, USA, and Taiwan. The characteristics of the included studies and patient demographics are described in Table 2. A total of 250,835 patients were included, with a mean age of 64.3 ± 9.5 years old across 5 studies and gender predominance towards the males (40.3%). Two studies used a regimen of fenofibrate 200 mg once daily, two used 160 mg once daily, and one study used 145 mg once daily. Based on the risk of bias assessment, all studies fall into the low to moderate risk of bias. (Figure 2 and 3)

Four studies show that fenofibrate significantly reduces the risk of DR progression, while one study shows no significant reduction when compared to placebo. One study also showed that fenofibrate as an addition to statin therapy significantly reduced DR progression compared to statin + placebo. A study by Preiss, et al.[12] stated that patient in the fenofibrate group are 0.73 times more likely to experience progression of diabetic retinopathy or maculopathy and 0.50 times more likely to develop macular edema compared to placebo. No significant effect was observed in terms of visual function, quality of life, or visual acuity. The ACCORD study group expresses similar findings, with patients receiving fenofibrate 0.67 times progressing their diabetic retinopathy compared to placebo.[5] Stepping into the cohort studies, Kim, et al found that patient receiving statin – plus fenofibrate are 0.88 more likely to experience the development of their diabetic retinopathy compared patient receiving statin only, in addition, they are also

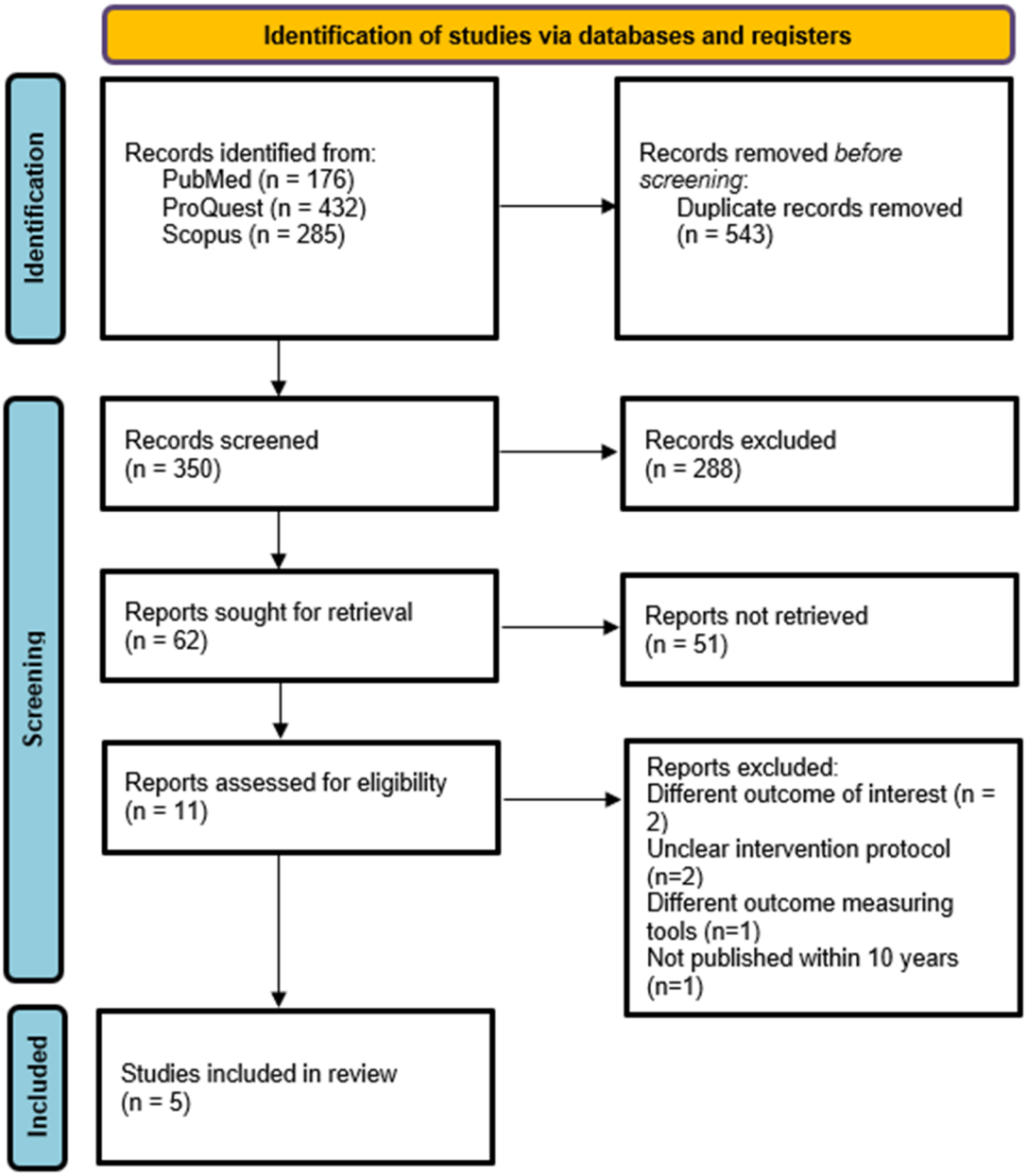

Figure 1. PRISMA diagram Depicting The Detailed Process of Study Selection for The Systematic Review and Meta-analysis.

Table 2. Study and patient characteristics

No.	Author	Year	Study Design	Country	Fenofibrate regimen	Patients (N)	Male (%)	Age [Mean (SD)]
1	Preiss, et al (LENS trial)	2024	RCT	UK	145 once daily	1.151	43.6%	N/A
2	ACCORD study group	2010	RCT	Canada	160 once daily	1.593	68.5%	61.9 (6.2)
3	Kim, et al	2023	Retrospective Cohort	Korea	200 once daily	65.586	67.5	54.9 (11)
4	Meer, et al	2022	Retrospective Cohort	USA	160 once daily	150.252	51.3%	65.3 (10.4)
5	Lin, et al	2020	Retrospective Cohort	Taiwan	200 once daily	32.253	50.3%	60.7 (12.8)

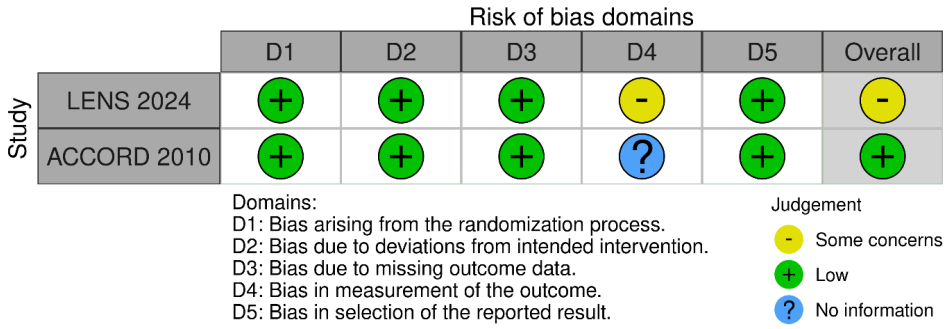

Figure 2. Study assessment of RCT using ROB 2.0

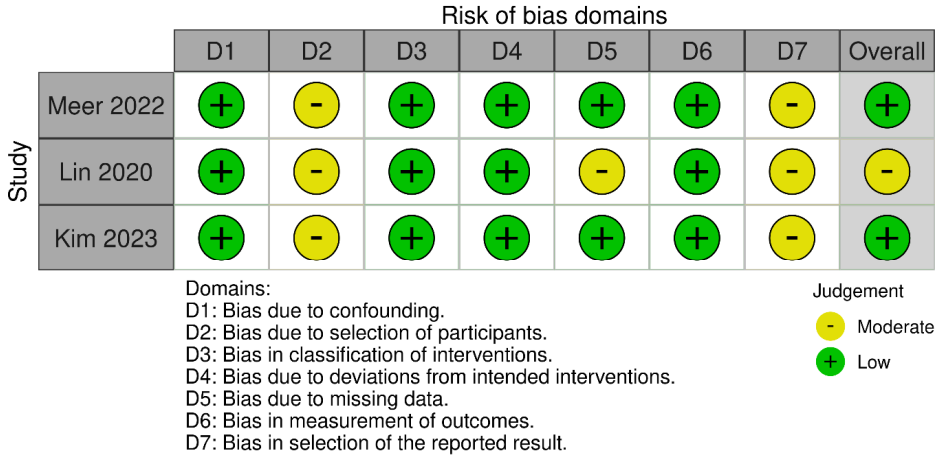

Figure 3. Study assessment of cohort studies using ROBINS-I

Table 3: Summary of the findings in each study

No.	Author	Key results	Additional results
1	Preiss, et al (LENS trial)	Fenofibrate reduced progression of diabetic retinopathy compared with placebo among participants with early retinal changes	Reduces incidence of macular edema
2	ACCORD study group	Demonstrated that fenofibrate, when added to statin therapy, slows the progression of diabetic retinopathy in patients with type 2 diabetes	N/A
3	Kim, et al	Fenofibrate reduces DR progression	less likely to experience vitreous hemorrhage, needing laser photocoagulation and intravitreous injection
4	Meer, et al	No significant difference between the group that receives fenofibrate vs the placebo	No significance in reducing macular edema
5	Lin, et al	Significant reduction in DR progression in the group that received fenofibrate vs placebo	Decreases risk of developing macular edema

significantly less likely to experience vitreous hemorrhage, needing laser photocoagulation, and intravitreous injection therapy.[13] Meer, et al., standing out from the other study, found that those in the fenofibrate group are not significantly different compared to the control group in terms of progression (HR:0.99; 95% CI 0.93-1.05; p=0.67), they also found no significant difference in terms of macular edema development.[14] Lastly, a study by Lin, et al shows a hazard ratio of 0.59, favouring the fenofibrate group in terms of DR progression, compared to other medications.

They also find that fenofibrate significantly decreases development of macular edema.[15] Table 3 summarises the findings of each studies.

DISCUSSION

The present systematic review evaluated the impact of fenofibrate on the progression of DR by analyzing six studies, including two RCTs and three retrospective cohort studies, encompassing 250.835 patients. Most of these studies indicate that fenofibrate significantly reduces the risk of DR progression, with five out of six studies demonstrating a beneficial effect. Additionally, two studies reported that fenofibrate contributes to a reduction in the development of macular edema. These findings reinforce the potential of fenofibrate as an adjunctive therapy in DR management.

The protective effects of fenofibrate on DR appear to extend beyond its traditional lipid-lowering properties. As a PPARα agonist, fenofibrate modulates several metabolic pathways that may contribute to its retinal benefits.[16] One proposed mechanism involves reducing oxidative stress and inflammation, which play significant roles in DR progression.[17,18] Fenofibrate has been shown to inhibit the activation of nuclear factor-kappa B (NF-κB), a key regulator of inflammatory cytokines contributing to retinal damage.[19] Additionally, fenofibrate is believed to exert anti-angiogenic effects by downregulating VEGF, a key mediator of pathological neovascularization in DR. The suppression of VEGF expression could explain the observed reduction in macular edema among fenofibrate-treated patients.[20,21] Furthermore, fenofibrate may help preserve the integrity of the blood-retinal barrier, reducing vascular leakage and preventing the accumulation of extracellular fluid in the retina.[22] These pleiotropic effects position fenofibrate as a promising pharmacological intervention for DR beyond conventional glucose and lipid control.

When comparing fenofibrate with other pharmacological treatments for DR, anti-VEGF agents such as aflibercept, bevacizumab, and ranibizumab have been extensively studied.[23–25] They are considered the standard of care, particularly for diabetic macular edema (DME). The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study compared these three agents in patients with center-involved DME. At the one-year mark, all three drugs improved visual acuity, with aflibercept showing superior outcomes in patients with worse baseline vision (20/50 to 20/320). By the two-year follow-up, aflibercept remained superior to bevacizumab but not to ranibizumab in this subgroup. These findings highlight the efficacy of anti-VEGF therapies in managing DME, though they require repeated intravitreal injections, which can be burdensome and carry potential risks such as endophthalmitis and retinal detachment.[26]

Corticosteroids, including triamcinolone acetonide and dexamethasone intravitreal implants, have also been evaluated for DR treatment due to their potent anti-inflammatory effects. The MEAD trial demonstrated that dexamethasone implants significantly improved visual acuity and reduced central retinal thickness in patients with DME.[27] However, these benefits were accompanied by increased risks of cataract formation and elevated intraocular pressure.[28,29] Compared to fenofibrate, corticosteroids provide localized treatment but are associated with ocular side effects, limiting their long-term use.

Traditional glucose-lowering therapies, such as metformin and sodium-glucose co-transporter-2 (SGLT2) inhibitors, have been investigated for their potential retinal benefit.[30] A retrospective cohort study reported that metformin use was associated with a lower risk of DR progression in patients with type 2 diabetes, independent of glycemic control.[31] In observational studies, SGLT2 inhibitors have

been linked to improved vascular function and a reduced incidence of DR progression.[32,33] However, the direct effects of these therapies on retinal health remain inconclusive, and unlike fenofibrate, they have not been the primary focus of DR-specific interventional trials.

Despite the promising findings, several limitations and potential biases should be considered. Including both RCTs and retrospective cohort studies introduces variability in study design, which may affect the consistency of the findings. While all six studies were assessed to have a low to moderate risk of bias, inherent biases in retrospective studies, such as selection and information bias, cannot be entirely ruled out. Additionally, differences in the definitions and assessments of DR progression and macular edema across studies may lead to inconsistencies in reported outcomes. Furthermore, variations in the duration of follow-up among studies could influence the observed effects of fenofibrate on DR progression.

CONCLUSION

In conclusion, fenofibrate presents a unique advantage in DR management due to its systemic benefits, anti-inflammatory properties, and ability to preserve the blood-retinal barrier. Compared to anti-VEGF agents and corticosteroids, fenofibrate offers a non-invasive, oral treatment option with fewer ocular complications, making it a viable alternative or adjunctive therapy. However, further well-designed, large-scale RCTs with standardized outcome measures and longer follow-up periods are needed to confirm these findings and to elucidate the underlying mechanisms of fenofibrate's protective effects on the retina.

ACKNOWLEDGEMENT

The authors acknowledge the contribution of the Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University, Manado.

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REVIEW ARTICLE

InaJEMD
Indonesian Journal of Endocrinology Metabolism and Diabetes

Efficacy and Safety of Testosterone Treatment in Male Hypogonadism: a Systematic Review

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ABSTRACT

Male hypogonadism may occur because of either congenital conditions or dysfunction that arises along the hypothalamic-pituitary-gonadal axis. As part of the lifelong management of male hypogonadism, testosterone replacement therapy (TRT) has been the most important therapy, although its effectiveness and safety are subject to controversy. This systematic review was undertaken to investigate the effectiveness and safety of TRT in men with hypogonadism. Searches were conducted in the literature through MEDLINE, CENTRAL, and ScienceDirect. The inclusion criteria were restricted to RCTs reported within five years. Out of 2,471 published articles, 16 were found eligible for analysis. Results showed that TRT is effective in raising serum testosterone levels in male with hypogonadism no matter the mode of administration, whether injected, oral or topical as in gels. In addition, TRT has improved body composition by decreasing fat and lean muscle mass. An increase in PSA commonly occurs in most patients, yet no research proves that TRT increases the development of prostate cancer and cardiovascular disease. Most commonly, the adverse effects are arrhythmias and increase in blood pressure, especially among those who undergo oral TRT. Amelioration of different symptoms such as erectile dysfunction, decreased libido, and fatigue in patients with hypogonadism was also achieved by TRT. Overall, it can be concluded that, TRT is generally safe and effective but requires close monitoring, but also one where monitoring should regularly be performed because of possible side effects, more research is needed.

Keywords: Hypogonadism; Testosterone Replacement Therapy; Safety; Efficacy; Systematic Review.

INTRODUCTION

Male hypogonadism, acquired or congenital, can be caused by defects that interfere with the hypothalamic-pituitary-testicular axis. It is imperative to differentiate between primary and secondary forms of hypogonadism. The presence of decreased spontaneous erections, nocturnal penile flaccidity, diminished libido, and reduced testicular volume are highly suggestive of hypogonadism.[1]

Prevalence of hypogonadism varies widely (between 2.1% and 38.7%) in middle-aged and older men.[2] In Asia, the estimated prevalence of late onset hypogonadism (LOH) was 7.8% among

middle-aged and elderly males in China and significantly increased with age [3]. One method of treatment for hypogonadism is testosterone replacement therapy, but Testosterone therapy has been controversial since its synthesis in the 1930s to the present day [4].

Currently, TRT is available in a variety of forms, including injections, oral medication, and a recently introduced gel formulation. As with any pharmaceutical treatment, TRT carries a certain risk of adverse effects such as mood changes (such as depression), acne, weight gain, arrhythmias, increase risk of acute kidney injury and increase risk of prostate cancer. [5]. Therefore, the purpose of this systematic review is to summarize and determine the efficacy and safety of the use of TRT in patients with male hypogonadism.

METHOD

A total of 1,460 articles from MEDLINE, 828 articles from CENTRAL, and 183 articles from ScienceDirect were identified through the search terms "hypogonadism," "testosterone," and "treatment." The search was limited to five years and 38 journals that met the criteria for free full-text articles and randomized controlled trials (RCTs). Of these, 16 journals were selected for further screening and analysis. This systematic review has been registered PROSPERO CRD42024628103.

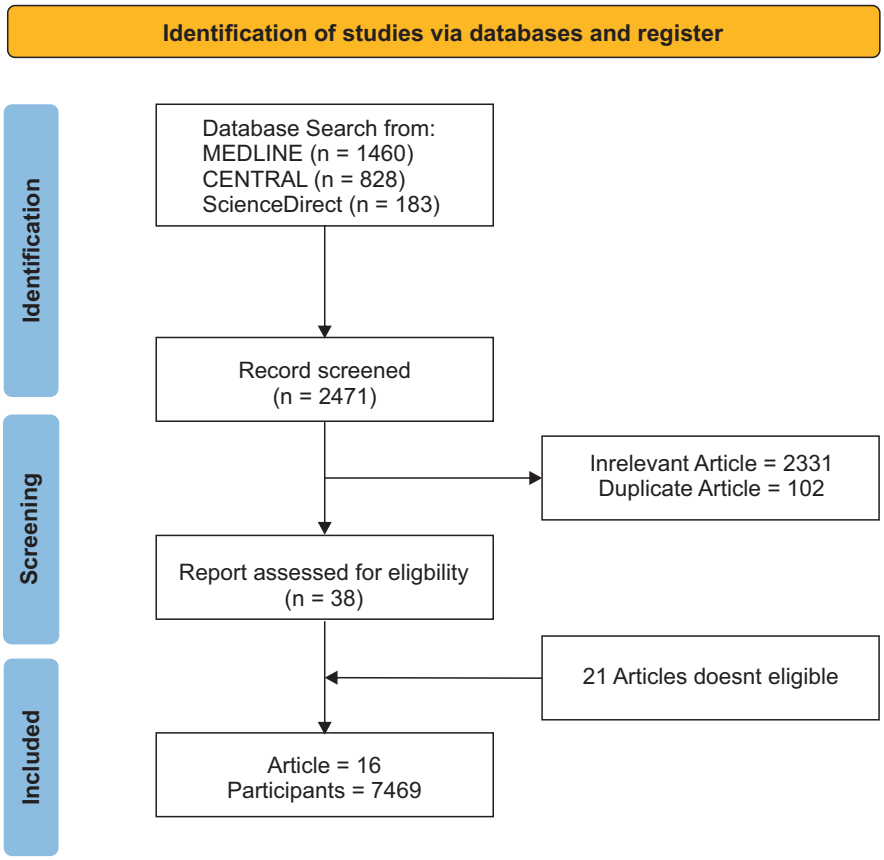

Figure 1. Study selection and inclusion process of safety and efficacy TRT in hypogonadism men

RESULTS

Table 1. Study Characteristic and Outcomes

Author (year)	Sample size		Age (year,mean)		Study design	Testesterone administration	Efficacy	Safety
	IG*	CG*	IG*	CG*				
Dudek et al. (2020)	20	20	54.2	55.6	Randomized clinical trial	testosterone enanthane intramuscular injection every 2 weeks for 12 months	- TRT increased serum testosterone and reduced luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. BMI decreased from 26.6 ± 2.1 to 26.1 ± 1.8 kg/m² ($p < 0.05$), and fat mass decreased from 17.0 ± 4.4 to 15.6 ± 4.0 kg ($p < 0.05$).Serum leptin decreased from 6.2 ± 1.4 to 4.0 ± 1.2 µg/L ($p < 0.05$).Adiponectin increased from 7.6 ± 2.5 to 9.4 ± 2.8 µg/mL ($p < 0.05$).hsCRP decreased from 1.4 ± 1.2 to 1.0 ± 1.0 mg/L ($p < 0.05$). - In the placebo group serum leptin, adiponectin, and hsCRP levels did not change significantly.	- PSA levels increased in the testosterone-treated and the placebo group: from 0.9 ± 0.4 to 1.2 ± 0.5 ng/mL, $p < 0.05$, and from 0.9 ± 0.5 to 1.1 ± 0.5 ng/mL, $p < 0.05$, respectively. Differences between the groups were not statistically significant at any time point - PSA increases did not exceed 1 mg/year or reach levels >4 mg/L in either group.
Bhasin et al. (2023)	2601	2603		63.3	Randomized, placebo-controlled trial	Topical 1.62% testosterone gel	- Change in IPSS did not differ between groups.	- The incidence of high-grade prostate cancer (5 of 2596 [0.19%] in the TRT group vs 3 of 2602 [0.12%] in the placebo; HR 1.62; 95% CI, 0.39-6.77; P = 0.51) did not differ significantly between groups; - The incidences of any prostate cancer, acute urinary retention, invasive surgical procedures, prostate biopsy, and new pharmacologic treatment also did not differ significantly.

Rasmussen RS et al. (2024)	44	34	≥ 70		double-blind, randomized, placebo-controlled intervention trial with a 2 × 2 factorial design	testosterone undecanoate injections for 52 weeks with or without progressive resistance training	- No significant differences between PSA levels. - Comparing performances within a group at baseline, and at weeks 4, 20 and 52 (Friedman Test), only the Combo group improved in the 30-s Sit to Stand Test ($p<0.001$). - Testosterone levels at week 52 correlated with the 30 s Sit to Stand Test performances only in the Combo and TU groups	NA
Cunningham GR et al. (2019)	395	395	72.3	72.1	Double-blinded, placebo-controlled trial.	Testosterone gel for 12 months.	NA	- Testosterone treatment resulted in a significantly greater increase in PSA levels compared to placebo ($P < 0.001$). Serum PSA levels increased from 1.14 ± 0.86 ng/mL (mean ± SD) at baseline by 0.47 ± 1.1 ng/mL at 12 months in the testosterone group and from 1.25 ± 0.86 ng/mL by 0.06 ± 0.72 ng/mL in the placebo group. - Five percent of men treated with testosterone had an increase of PSA ≥1.7 ng/mL and 2.5% of men had an increase of PSA ≥3.4 ng/mL.
Miner M et al. (2024)	210	105	52.6	54.2	multicenter, phase 3, randomized, open-label, active-controlled study	2:1 to oral testosterone undecanoate or 1.62% topical testosterone gel	- 87.4% of patients taking oral testosterone undecanoate (TU) had an average 24-hour testosterone level within the normal male range (300–1140 ng/dL) by week 13. - Oral testosterone undecanoate (TU) showed significantly greater improvements than 1.62% topical testosterone gel in the SF-36 mental component summary (mean change: 3.82 vs. 0.55; $p = 0.009$). - Oral TU also demonstrated numerically greater improvements in vitality (6.89 vs. 3.82), social role functioning (2.17 vs. 0.64), emotional role functioning (0.65 vs. 0.38), and physical role functioning (0.85 vs.0.24).	- The mean change in PSA levels from baseline was 0.2 ng/mL in both the treatment and placebo groups, indicating no significant difference.

Narukawa T et al. (2020)	23	20	59.5	54.9	open-label, randomized, crossover study	intramuscular injection monotherapy (IMIM) of 250 mg testosterone enanthate every 3 weeks over a period of 12 weeks, followed by 12 weeks combination therapy (CT) of TRT with tadalafil (10 mg)	- There was no significant statistical difference in patients preferences between IMIM and CT.	-Patients who experience polycythemia from IMIM, which may hinder continued treatment, might find CT to be an alternative for testosterone replacement.
Pencina KM et al. (2023)	Same sample with Bhasin et al. (2023)				Randomized, placebo-controlled trial	Topical 1.62% testosterone gel	- Testosterone treatment corrected anemia in a significantly higher percentage of men compared to placebo at : 6 months (41.0% vs. 27.5%), 12 months (45.0% vs. 33.9%), 24 months (42.8% vs. 30.9%), 36 months (43.5% vs. 33.2%), and 48 months (44.6% vs.39.2%) (P = 0.002). - Among participants without anemia, a significantly smaller proportion of testosterone-treated men developed anemia.	NA
Bøgehave et al. (2023)	17	20	54	53	double-blinded, placebo-controlled study	24 weeks of testosterone injections	NA	- TRT affects the coagulation system in an anticoagulant direction through suppressed TF pathway. - Between-group differences at 24 weeks were observed for endogenous thrombin potential (P = 0.036), Factor VII (P = 0.044), Factor X (P = 0.015), prothrombin (P = 0.003), protein C (P = 0.004), and protein S (P = 0.038). Within the TRT group, ETP, peak thrombin, FVII, FX, prothrombin, TFPI, protein C, and FXII decreased and protein S increased (all P < 0.05). - Within the placebo group, coagulation outcomes were unchanged.

Groti Antonic K. (2020)	28	27	58	62	two-part prospective observational clinical study (first year: double-blind randomized placebo-controlled trial employing testosterone undecanoate; second year: open-label follow-up with all participants receiving TTh)	intramuscular testosterone undecanoate administered at first visit (baseline), second injection 6 weeks later (second visit), and each subsequent injection 10 weeks after the previous injection.	Bone turnover markers C-telopeptide of type I collagen (CTX) and procollagen I N-terminal propeptide(PINP) levels significantly decreased in both groups after the first year: for CTX from 1055 (mean) to 453 (mean) pmol/L in group P ($p < 0.001$) and from 897 (mean) to 523 (mean) pmol/L in group T ($p < 0.001$). PINP decreased by 4.30 ± 8.05 µg/L in group P ($p = 0.030$) and 4.64 ± 8.86 µg/L in group T ($p < 0.023$). Lumbar spine BMD increased (by 0.075 ± 0.114 g/cm2; $p = 0.019$) in treatment group following 2 years of treatment. No femoral neck BMD changes were observed in both groups.	No adverse events or side effects of TRT have been observed over the course of this trial.
Cauley JA et al. (2021)	105	92	≥ 65		Multicentre placebo-controlled, double-blind trial	Testosterone gel for one year 5g daily	. There was no difference in the percent change in TBS (trabecular bone score) by randomized group: 1.6% (95% CI 0.2-3.9) in the testosterone group and 1.4% (95% CI 0.2-3.1) in the placebo group. In contrast, vBMD (volumetric bone mineral density) increased by 6% (95% CI 4.5–7.5) in the testosterone group compared to 0.4% (95% CI −1.65–0.88) in the placebo groups	NA
Bischoff-Ferrari HA et al. (2024)	46	45	71.8	72.5	2 × 2 factorial design randomized controlled trial	transdermal testosterone at a dose of 75 mg per day and/or monthly 24'000 IU Vitamin D	Transdermal testosterone did not reduce fall risk but improved appendicular lean mass ((0.21 kg/m2 [0.06, 0.37])) and gait speed (0.11 m/s, [0.03, 0.20]) in pre-frail older men.	NA

Swerdloff RS et al. (2020)	151	48	51.6	53.4	Randomized, active-controlled, open-label study.	Oral testosterone undecanoate (TU) vs. topical testosterone product once daily for 3 to 4 months.	- 87% of patients in both groups achieved mean average Testosterone concentration (TCavg) in the eugonadal range. Sodium fluoride-ethylenediamine tetra-acetate plasma T Cavg (mean ± SD) for the oral TU group was 403 ± 128 ng/dL; serum T equivalent, ~489 ± 155 ng/dL; and topical T, 391 ± 140 ng/dL.	- Blood pressure measured by ABPM showed that the oral TU group had significantly greater increases in daytime, nighttime, and 24-hour systolic BP compared to the topical testosterone group. The 24-hour average systolic BP rose by 4.9 ± 8.7 mm Hg in the oral TU group versus 0.2 ± 9.4 mm Hg in the topical group (P = 0.0013). Diastolic BP increases were higher in the oral TU group but not statistically significant. Clinic (cuff) systolic BP increased from baseline to the end of the study in both treatment groups (mean ± SD:oral TU, 2.8 ± 11.8 mmHg; topical Testosterone, 1.8 ±10.8 mm Hg), whereas diastolic blood pressure was essentially unchanged at the final visit for both groups. - Safety profiles were similar in both groups, but oral TU was associated with a mean increase in systolic BP of 3 to 5 mm Hg.
Lincoff AM et al. (2023)	Same sample with Bhasin et al. (2023)				Randomized clinical trial	Topical 1.62% testosterone gel	-	The main cardiovascular safety measure was the first occurrence of death from heart-related causes, a nonfatal heart attack, or a nonfatal stroke, analyzed over time. A secondary measure included these events plus coronary revascularization. With a follow-up period of 33.0 months, primary cardiovascular events occurred in 7.0% of patients in the testosterone group and 7.3% in the placebo group, showing no significant difference (HR 0.96, 95% CI:0.78–1.17; P < 0.001).

Ramachandran S et al. (2020)	86	103		63	A randomized double-blind trial	testosterone undecanoate 1000 mg intramuscular injection at 0, 6, 18, and 30 weeks.	- In the TRT group, significant reductions were found in waist circumference (−3.0 cm, IQR: −5.30/0.0, P < 0.0001), weight (median: −1.0 kg, IQR: −2.75/0.55, P = 0.0014), body mass index (median:−0.3, IQR:−0.90/0.25, P = 0.0032) and total cholesterol (−0.2, IQR:−0.60/0.10, P = 0.0036). In the placebo group, only HbA1c changed, demonstrating a significant increase after 30 weeks (median: +0.10,IQR: −0.20/0.50, P = 0.032).	NA
Tishova Y. et al. (2024)	81	54	49	53	Double blind randomized controlled trial	testosterone undecanoate parenteral 1000 mg	- -Compared to baseline, HOMA-IR was significantly reduced at almost every time point in men receiving TU after only 18 weeks of TU treatment (p<0.0001); - Placebo was not associated with significant changes in HOMAβIR. - -There was a significant decrease in median values of fasting glucose (30 weeks: −2.1%; 138 weeks: −4.9%) and insulin (30 weeks: −10.5%; 138 weeks: −35.5%) after TU treatment.	NA
Gregori G et al. (2021)	42	41	72.6	72.2	parallel, double-blind randomized controlled trial	Testorone gel 1.62% applied once daily	- Global cognition Z score improved more in the LT + Test group compared to the LT + Pbo group (mean change: 0.49 vs. 0.21; 95% CI : -0.45 to -0.11; Cohen's d = 0.74). Attention processing Z-score (0.55 vs. 0.23; 95% CI: -0.55 to -0.09, Cohen's d = 0.49) and memory Z-score (0.90 vs. 0.37; 95% CI: -0.93 to -0.13, Cohen's d = 1.43) showed greater improvements in the LT + Test group.	NA

*IG : Intervention Group
*CG : Comparison Group
NA: Not Available

DISCUSSION

Swerdloff et al. showed that both oral testosterone undecanoate (TU) and testosterone gel are effective, with 87% of patients achieving mean average testosterone concentration (TCavg) within the eugonadal range. The oral TU group demonstrated a TCavg of 403 ± 128 ng/dL in plasma, equivalent to 489 ± 155 ng/dL in serum, which was comparable to the topical testosterone group (391 ± 140 ng/dL). This emphasizes the oral and topical delivery methods are equally effective in maintaining testosterone levels.[6]

Dudek et al. further supported the efficacy of TU injections, reporting a significant increase in serum total testosterone levels from baseline (3.1 ± 0.4 to 7.2 ± 1.3 ng/mL) after 12 months of treatment. Additionally, TU injections effectively suppressed luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels ($p < 0.001$), indicative hypothalamic -pituitary-gonadal axis regulation.[7] Similarly, Miner et al. demonstrated the effectiveness of oral TU, with 87.4% of patients achieving average 24-hour testosterone levels within the normal male range (300–1140 ng/dL) by week 13. The confidence interval (CI) for this result was 81.7%–92.7%, and the lower bound (81.7%) exceeded the target of at least 65% of patients achieving normal testosterone levels.[8] These results collectively establish that oral, topical, and injectable testosterone formulations are effective in achieving and maintaining testosterone levels in the eugonadal range.

Prostate safety

TRT appears to be relatively safe concerning prostate health. Bhasin et al. found that the incidence of high-grade prostate cancer was similar between the testosterone gel treated group (0.19%) and the placebo group (0.12%), with no statistically significant difference [HR 1.62, 95% CI: 0.39–6.77, p = 0.51]. The incidence of any prostate cancer was also similar between the testosterone gel treated group (0.46%) and the placebo treated group (0.42%) [HR 1.07, 95% CI: 0.47-2.42, p=0.87].[9]

Most studies observed minimal increases in PSA levels that remained clinically insignificant. Rasmussen et al. and Miner et al. observed there were no significant differences of prostate-specific antigen (PSA) levels.[8,10] Dudek et al. reported PSA levels increased in both the TRT and placebo groups over 12 months, but the differences between the groups were not statistically significant.[7] Cunningham et al. found that TRT led to a significantly greater increase in PSA levels compared to placebo ($p < 0.001$) with PSA rising 0.47 ± 1.1 ng/mL from baseline at 12 months in the TRT group, compared to 0.06 ± 0.72 ng/mL in the placebo group.[11]

Cardiovascular safety

Testosterone replacement therapy, through complex mechanisms, is known to increase sodium and fluid retention, which may contribute to elevated blood pressure in some men receiving oral testosterone.[12] Swerdloff et al. highlight significant differences in the impact of testosterone replacement therapies on blood pressure, with oral testosterone undecanoate (TU) showing greater increases in systolic blood pressure compared to topical testosterone.[6] The rise in 24-hour systolic blood pressure observed in the oral TU group (4.9 ± 8.7 mmHg) was significantly higher than in the topical testosterone group (0.2 ± 9.4 mmHg, $p = 0.0013$). These differences were consistent across daytime, nighttime, and 24-hour monitoring. Interestingly, clinic (cuff) measurements did not fully reflect the changes seen in ambulatory blood pressure monitoring (ABPM). Both treatment groups experienced modest increases in clinic systolic blood pressure (oral TU: 2.8 ± 11.8 mmHg; topical testosterone: 1.8 ± 10.8 mmHg), while diastolic pressures remained largely unchanged.

This discrepancy between ABPM and clinic measurements underscores the importance of utilizing ABPM in assessing the cardiovascular effects of testosterone therapy (especially oral), as it provides a more comprehensive evaluation.[6]

Over a follow-up period of 33 months, Lincoff et al. found that there were no significant difference in the occurrence of primary cardiovascular events (death from heart-related causes, a nonfatal heart attack, or a nonfatal stroke) in the testosterone and the placebo group.[13] This finding suggests that while testosterone therapy may influence cardiovascular parameters such as systolic blood pressure, these changes do not necessarily translate to an increased risk of major cardiovascular events.

Hematologic effects

A meta-analysis found that all forms of TRT gels, patches, or injections—cause significant increase in hematocrit (HCt), but no type causing an increase over 4.3%. This finding suggests the risk of excessive red blood cell production can be managed with proper monitoring and patient selection. For patients with low to normal baseline HCt levels, the increase is unlikely to be a concern.[15] Venous thromboembolism and major adverse cardiac events are the most concerning risks associated with increased HCt, necessitating close monitoring.[16] When comparing all testosterone formulations, intramuscular testosterone enanthate showed a significantly greater increase in mean hematocrit compared to the patch. However, no differences in hematocrit were observed between the other formulations.[15] Narukawa suggests that patients who develop polycythemia from intramuscular testosterone, potentially interfering with continued treatment, might consider a combination of intramuscular and patch therapy as an alternative for testosterone therapy.[17]

Pencina found that testosterone treatment has a significant effect in correcting anemia compared to placebo. At each assessed interval—6, 12, 24, 36, and 48 months—a greater proportion of testosterone-treated men achieved anemia correction compared to those receiving placebo, with differences being statistically significant (P = 0.002). Furthermore, testosterone treatment was associated with a reduced incidence of new anemia cases among participants without anemia at baseline. These results suggest that testosterone therapy could be a valuable strategy for managing anemia in men with hypogonadism.[18] Moreover, TRT influences the coagulation system by promoting an anticoagulant effect, primarily through the suppression of the tissue factor (TF) pathway. After 24 weeks, significant between-group differences were observed in key coagulation markers. In the TRT group, several markers decreased, including endogenous thrombin potential , peak thrombin, Factor VII, Factor X, prothrombin, protein C, and Factor XII (all $p < 0.05$), while protein S increased. The placebo group showed no significant changes in coagulation factors.[19]

We expanded the systematic review by adding metabolic and musculoskeletal effects that differ from previous reviews, as well as including more recent studies.[20,21] However, conducting a meta-analysis is not feasible due to the high heterogeneity among included studies.

Metabolic effects

Increased serum testosterone may influences metabolic processes, including body mass index, fat mass, and energy expenditure. Dudek observed that TRT cause significant weight loss and decrease fat mass compared to placebo. TRT also reduce leptin and increase adiponectin level significantly. In addition, highly-selective C-reactive protein level decrease significantly in TRT group. The results suggest that TRT may improve systemic metabolic health in patients with hypogonadism.[7]

Similar findings in metabolic effects also observed by Ramachandran who found that in the TRT group, significant reductions were found in waist circumference (−3.0 cm, IQR: −5.30/0.0, P < 0.0001), weight loss (median: −1.0 kg, IQR: −2.75/0.55, P = 0.0014), body mass index (median:−0.3, IQR: −0.90/0.25, P = .0032) and total cholesterol (−0.2, IQR:−0.60/0.10, P = .0036). In the placebo group, only HbA1c changed (median: +0.10, IQR: −0.20/0.50, P = 0.032).[22]

A study conducted by Tishova observed that HOMA-IR was significantly reduced (from baseline) at almost every time point in men after only 18 weeks of Testosterone undecanoate treatment (p<0.0001). There was a significant decrease in median values of fasting glucose (30 weeks: −2.1%; 138 weeks: −4.9%) and fasting insulin (30 weeks: −10.5%; 138 weeks: −35.5%) after TU treatment. Placebo was not associated with significant changes in HOMA-IR. These results suggest that TRT appears to increase insulin sensitivity.[23]

Musculoskeletal effects

Testosterone therapy had a notable impact on bone health, especially in bone mass density. Cauley found that even though there was no difference in the percent change in TBS (trabecular bone score): 1.6% (95% CI 0.2-3.9) in the testosterone group and 1.4% (95% CI – 0.2, 3.1) in the placebo group, the vBMD (volumetric bone mineral density) increased by 6% (95% CI 4.5–7.5) compared to 0.4% (95% CI −1.65–0.88) in the placebo group.[24]

Groti found that both groups (testosterone and placebo) experienced a significant reduction in bone turnover marker, indicating reduced bone resorption. However, only the testosterone group had a significant increase in lumbar spine BMD (following 2 years of treatment), with no changes in femoral neck BMD for either group.[25]

Testosterone is found to significantly improved appendicular lean mass and gait speed in pre-frail older men.[26] Rasmussen reveal insights into the effects of strength training and testosterone supplementation on functional performance, specifically measured by the 30-second STS test. The Combogroup (testosterone injection, training, oral vitamin D, calcium, and protein) showed significant improvement in the 30-second STS test at all time points (p<0.001) compared to no intervention, testosterone injection alone, or training with oral vitamin D, calcium, and protein alone. At week 52, testosterone levels were correlated with the performances in the 30-second Sit to Stand Test exclusively for the Combo and TU injection groups; therefore, higher testosterone levels were associated with better physical performance in older men.[10]

Mental Health and Cognitive Function

Gregori et al. found that combination of lifestyle changes (weight management and exercise) with testosterone therapy had consistently larger improvements in cognitive functions (global cognition, attention processing and memory) than lifestyle changes only. A stronger effect size was reported for memory.[27]

Miner et al. observed oral TU showed significantly greater improvement in the SF-36 mental component summary (3.82 vs. 0.55; p = 0.009) and numerically greater improvements in vitality, social role functioning, emotional role functioning, and physical role functioning compared to 1.62% topical testosterone gel.[8] These results suggested that oral TU could be the answer to the delivery of testosterone in a way that improves performance in many aspects related to mental health and quality of life. However, the lack of statistical significance in the other aspects warrants further investigation.

Limitation: We did not conduct a subgroup-analysis due to a significant heterogeneity among the studies, which may be attributed to variations in measurement methods, outcome

definitions, and small sample sizes. Moreover, the optimal TRT delivery could not be identified because the different comparators were utilized across the studies. Future research: A longer duration of TRT administration, defined as a minimum of ten years, is required to establish long-term effects.

CONCLUSION

TRT effectively improves testosterone levels, symptoms, overall health, and body composition in male with hypogonadism. While generally safe, TRT has been linked to higher PSA and hematocrit levels, necessitating monitoring. However, there's no evidence that TRT increases the risk of prostate disease and cardiovascular disease . More research are needed to explore long-term outcomes of TRT.

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