

**Original Article**

**Trend Analysis of Clinical Characteristics of COVID-19 with Diabetes Based on Disease Severity**  
Batari Retno Minanti, Soebagijo Adi Soelistijo, Agung Pranoto

**Case Series**

**Transition of Care of Disorders of Sexual Development: A Twist of Two Cases with Ambiguous Genitalia**

Marshall Tendean, Nanny Natalia. M Soetedjo, Maya Kusumawati, Ervita Ritonga, Hikmat Permana

**Case Report**

**Diabetic Ketoacidosis as The First Manifestation of a Young Adult with Diabetes: A Clinical Approach to Distinguish Different Types of Diabetes Mellitus**

M. Ikhsan Mokoagow, Anak Agung Arie Widiastuti, Jerry Nasarudin, Marina Epriliawati, Ida Ayu Made Kshanti, Nobian Andre, Adlina Hafidzati, Vania Tryanni

**Does Severe Hypokalemia Worsen the Outcome of Diabetic Ketoacidosis?**

Pamela Sandhya De Jaka, Dias Guita Alantus

**Diagnostic and Management of Idiopathic Panhypopituitarism: A Case Report**

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**Primary Adrenal Insufficiency due to Tuberculosis Infection: Pitfalls in Diagnosis and Management**

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**Pregnancy Following Recent Radioactive Iodine Ablation in Thyroid Cancer Patient: A Case Report**

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**Hypokalemia Periodic Paralysis in Subtle Thyrotoxicosis with Renal Insufficiency**

Indah Sagita Isna Putri, Dadang Herdiana, Pipik Ripa'I, Miko Galastri

**Challenges in the Diagnosis and Management of Adrenal Insufficiency**

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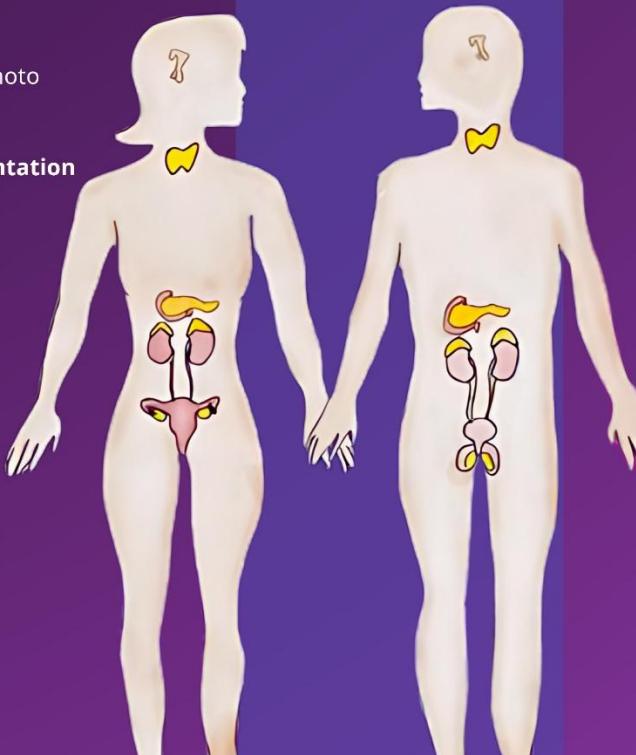
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## Editorial

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Dear readers and contributors,

It is our great pleasure to introduce this first edition of a new scientific journal named “Indonesian Journal of Endocrinology Metabolism and Diabetes” or abbreviated as InaJEMD (Indones J Endocrinol Metab Diab). The journal publish articles in the field of the endocrinology, metabolism, and diabetes from clinical, community, and public health studies and perspectives.

First of all, we would like to express our gratitude for those who contributed to the publication of the first edition, especially for the authors. We take this opportunity to thank all authors who submitted articles into our journal. We also want to thank peer reviewers, editors, and staffs who make our dream of having PERKENI’s own journal accomplished.

One of the objectives of this journal is to encourage publication from different streams of research that helps to enrich further the discourse on endocrinology, metabolism, and diabetes. In this issue, several papers are presented. The first is the original article. It is a study by Batari Retno Minanti from the Department of Internal Medicine, Faculty of Medicine Airlangga University, Surabaya. It details research of the pattern of clinical and laboratory features of diabetes mellitus patients based on the severity of Covid-19 infection. This article demonstrated about how diabetes increases the risk of Covid-19's severity and mortality than those without diabetes.

Diabetes mellitus is one of the most common comorbidities worldwide. It is not rare for people infected with Covid-19 during the pandemic to also have diabetes as their comorbidity. The differences in prognosis and what would be affected in people who have diabetes and those who do not have any comorbidities when infected by Covid-19, have an interesting issue to be investigated. These findings could be fill out studies in the era of the Covid-19 pandemic, especially those involving diabetes as a comorbid condition. While the Covid-19 pandemic is going to be over, and turning into an endemic, the discussion about Covid-19 is still important as a prevention and further management of patients with diabetes in the future, so that the treatment of Covid-19 in patients with comorbidities, including diabetes, is carried out more aggressive.

In this issue we also bring out interesting case reports in the endocrinology field. These case reports are two cases of ambiguous genitalia, two cases of primary adrenal insufficiency, diabetic ketoacidosis in young adult with diabetes, idiopathic panhypopituitarism, and pregnancy following recent radioactive iodine ablation for thyroid cancer. We also publish review article about artificial intelligence for managing diabetes in Indonesia and also a clinical practice on how to manage severe hypertriglyceridemia.

Finally, once again, we would like to thank all the readers, authors, reviewers, and editorial board members for your invaluable support and contributions. We hope this journal would be beneficial for all parties, especially for the readers.

Sincerely,

Prof. DR. Dr. Ketut Suastika, SpPD, K-EMD, FINASIM  
Editor in Chief

## Trend Analysis of Clinical Characteristics of COVID-19 with Diabetes Based on Disease Severity

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### ABSTRACT

Diabetes Mellitus (DM) increases the risk of COVID-19's severity and mortality than those without DM. The aim of this study was to determine the characteristics and trends by disease severity of DM patients with COVID-19. A cross-sectional study examining retrospective medical records was conducted in patients with diabetes mellitus who were confirmed to have COVID-19 by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). All adult patients (age > 18 years) with DM and COVID-19 registered and treated at the Surabaya Hajj General Hospital from May 2021 to the end of December 2021 were included in this study. Trends in each subject's characteristics are displayed in a graph with a trendline based on the severity of COVID-19. The highest proportion of disease severity of DM patients with COVID-19 is mild and moderate cases (72.2%), with 27.8% severe and critical cases. The average age of the subjects was  $56.38 \pm 9.60$  years. The age group with the highest proportion was 50-59 (42.6%). There are slightly more female than male patients (50.4% vs. 49.6%). The tendency is that the disease's severity increases with BMI, increasing HbA1C level, low sodium level, high chloride level, and high CRP and D-dimer levels. The pattern of clinical and laboratory features of DM patients based on the severity of COVID-19 infection shows the tendency for the disease severity worsens with increasing BMI, HbA1C level, low sodium level, high chloride level, and high CRP and D-dimer levels.

**Keywords:** COVID-19 severity, clinical characteristics, bmi, glycaemic control, diabetes

## INTRODUCTION

Diabetes mellitus (DM) is one of the most common comorbidities in patients infected with COVID-19 and significantly affects mortality.<sup>1-3</sup> DM increases 2.20-fold the risk of COVID-19's severity and increases mortality 2.52-fold compared with patients without DM.<sup>4</sup> In one study, COVID-19 patients with DM required a more extended hospital stay (14.4 days) than their counterparts (9.8 days).<sup>5</sup>

In DM patients, there is an increased expression of Angiotensin Converting Enzyme 2 (ACE-2) and furin receptors as well as immune system disturbance due to decreased T-cell function and increased interleukin-6 (IL-6) levels, leading to increased patient severity.<sup>6,7</sup> In addition, ACE-2 receptors are also found in various organs, such as on the surface of pancreatic beta cells, causing hyperglycemia, as well as in various other organs, so that multiple organ damage may develop (kidneys, liver, lungs, and other organs), which increases the severity of COVID-19 patients with DM. Moreover, the inability of the host to eliminate the virus due to DM and the dysfunction of the immune system will lead to a severe cytokine storm in COVID-19; hence the endothelial damage will increase.<sup>7,8</sup> All these eventually lead to organ hypoperfusion, tissue hypoxia, mitochondrial dysfunction, apoptosis, and necrosis, resulting in sepsis, multiple organ dysfunction syndrome (MODS) to acute respiratory distress syndrome (ARDS)<sup>3,9,10</sup>, and eventually increases the severity of COVID-19 patients.

The severity of COVID-19 infection in DM patients is influenced by hosts, pathogens, and the environment conditions. Host factors influencing glycemic control include older age<sup>11</sup>, comorbid conditions (obesity)<sup>3</sup>, electrolyte abnormalities, hypercoagulable states<sup>12,13</sup>, and macrovascular and microvascular complications in DM.<sup>2,4</sup> HbA1c levels and blood glucose levels can assess the glycemic control of DM patients concerning disease severity, as they describe the glycemic state in the body.<sup>14</sup> Hyperglycemic states lead to immune system dysfunction and

trigger oxidative stress and inflammatory processes that manifest as endothelial damage. Persistent endothelial damage leads to coagulation disorders causing both macrovascular and microvascular damage, a chronic complication of DM.<sup>13,14</sup> This study delves into the relationship between COVID-19 severity and DM, a critical comorbidity that hasn't been extensively studied, particularly in Indonesia. The study also investigates various clinical and laboratory factors to add to the growing research on the specific features affecting disease outcomes in this high-risk group.

## METHODOLOGY

### Study Design and Research Subject

This study is part of a larger research project that has been previously published.<sup>15</sup> The previous study established the epidemiological profile of COVID-19 in DM patients with various comorbidities associated with increased severity and death. Meanwhile, in this study, we examine the trends in clinical characteristics in DM patients with COVID-19 based on the severity of the disease. A cross-sectional study examining retrospective medical records was conducted in patients with diabetes mellitus who were confirmed to have COVID-19 by reverse transcription- quantitative polymerase chain reaction (RT-qPCR). All adult patients (age > 18 years) with DM and COVID-19 registered and treated at the Surabaya Hajj General Hospital from May 2021 to the end of December 2021 were included in this study. A diabetic patient is defined as an individual who has random blood sugar (RBS) >200 mg/dL on admission, and this level persists until discharge from the hospital. The Institutional Ethics Commission has approved all research procedures with the number 073/30/KOM.ETIK/2021.

### Variables

The severity of COVID-19 in this study was divided into four criteria, mild, moderate, severe, and critical, referring to the classification of the Decree of the Minister of

Health of the Republic of Indonesia (HK.01.07/MENKES/4641/2021) and World Health Organization (WHO).<sup>16</sup>

Patient demographic characteristics such as age and gender were collected. Clinical characteristics related to the severity of COVID-19 refer to previous studies, including Body Mass Index (BMI [kg/m<sup>2</sup>]), hemoglobin levels (g/dL), albumin (mg/dL), random blood glucose (g/dL), HbA1c (%), electrolyte levels (potassium, sodium, chloride), renal profile (e-GFR), and several clinical biomarkers for inflammation and infection such as procalcitonin (%), creatinine reactive protein (CRP [mg/L]) and D-dimers (μg/dL).

WHO Asia Pacific criteria<sup>17</sup> are used in classifying BMI into underweight (<18.5 kg/m<sup>2</sup>), normal (18.5 - <25 kg/m<sup>2</sup>), overweight (25 - <30 kg/m<sup>2</sup>), obesity class 1 (30 - <35 kg/m<sup>2</sup>), class 2 obesity (30 - <40 kg/m<sup>2</sup>), and class 3 obesity (≥40 kg/m<sup>2</sup>).

## RESULT

A hundred and fifteen DM patients in whom COVID-19 was confirmed between May 2021 and December 2021 were included in this study. The distribution of severity in DM patients infected with COVID-19 at Surabaya Haji Hospital found 2 (1.7%) cases of mild COVID-19, moderate degree, the highest number of cases of 81 (70.4%) cases, 26 (22.6%) severe cases, and 6 (5.2%) critical cases.

The age characteristics of the patients in this study averaged  $56.38 \pm 9.60$  years. The youngest affected person was 36 years old, and the oldest was 83 years old. The age group with the highest proportion was 50-59 (42.6%). There are slightly more female than male patients (50.4% vs. 49.6%). The mean BMI of patients in this study was  $25.20 \pm 2.81$  kg/m<sup>2</sup>, with 41.7% belonging to the BMI category of class 1 obesity, followed by 30.5% overweight (Table 1).

**Table 1.** Subject Characteristics

Characteristics	Frequency	%	Characteristics	Frequency	%
Age (Years) [x±SD; Min-Max]	56.38±9.60	36-83	HbA1C (%) [x±SD; Min-Max]	10.85±1.99	6.40-15.40
<40	5	4,3	≤7	1	2.5
40-49	18	15,7	>7	39	97.5
50-59	49	42,6	Natrium (mmol/L) [x±SD; Min-Max]	132.56±6.34	108-151
60-69	35	30,4	<136	79	69.2
≥70	8	7	136-145	33	29
Sex			>145	2	1.8
Male	57	49.6	Kalium (mmol/L) [x±SD; Min-Max]	4.86±5.75	2.5-6.5
Female	58	50.4	<3.5	6	5.3
BMI (kg/m <sup>2</sup> ) [x±SD; Min-Max]	25.20±2.81	19.5-34.31	3.5-5.0	92	81.4
Normal	26	22.6	>5.0	15	13.3
Overweight	35	30.5	Chloride (mmol/L) [x±SD; Min-Max]	93.10±16.69	64-110
Obese Class 1	48	41.7	<96	57	50.4
Obese Class 2	6	5.2	96-106	49	43.4
Hb (g/dL) [x±SD; Min-Max]	13.45±2.36	4.10-18.50	>206	7	6.2
<10	8	7	Procalcitonin (%) [x±SD; Min-Max]	0.58±1.36	0.02-9.87
≥10	106	93	<0,05	6	11.5
Albumin (mg/dL) [x±SD; Min-Max]	3.43±0.44	2.4-4.3	≥0,05	85	88.5
<3,5	50	52.6	CRP (mg/L) [x±SD; Min-Max]	131.70±195.00	1.1-1,338.0
≥3,5	45	47.4	<5	5	5.4
RBG (g/dL) [x±SD; Min-Max]	302.18±139.12	53-830	≥5	88	94.6
<70	1	0.9	D-dimer (μg/dL) [x±SD; Min-Max]	3.99±7.16	0.40-63.00
70-200	20	17.5	<1	22	23.2
>200	93	81.6	≥1	73	76.8
			e-GFR(mL/min) [x±SD; Min-Max]	76.81±44.95	6.45-261.81

Most patients had a Hb level (g/dL)  $\geq 10$  (93%) and an albumin level  $< 3.5$  mg/dL (52.6%). The glycaemic control of the DM patients in this study was poor, with a proportion of 81.6% RBG  $> 200$  mg/dL and 97.5% HbA1C values  $> 7\%$ . The

electrolyte level results showed that most patients had sodium levels  $< 136$  mmol/L (69.2%), potassium levels 3.5-5.0 mmol/L (81.4%), and chloride levels  $< 96$  mmol/L (50.4%). Most patients had elevated levels for

inflammatory markers: Procalcitonin  $\geq 0.05\%$  at 88.5%, CRP  $\geq 5\text{ mg/L}$  at 94.6%, and D- dimer  $\geq 1\text{ }\mu\text{g/dL}$  at 76.8%. The mean e-GFR of patients was  $76.81\pm44.95\text{ mL/min}$  (Table 1). Trends in clinical characteristics of DM patients based on COVID-19 severity.

Based on age, the trend analysis showed a tendency for the severity of the disease to decrease with increasing age (Fig. 1A.). This shows that the older age group in this study is not always linear with higher COVID-19 severity. The BMI trend found that the higher the BMI, the higher the severity of the disease (Figure. 1B).

Analysis of the blood glucose levels shows that the severity of the disease tends to decrease with higher random blood glucose levels (Figure. 2A). In contrast, the graph shows the disease worsening with increasing HbA1C levels (Fig. 2B.). Based on the hemoglobin level of the patients, the severity of the disease tends to increase with higher Hb levels (Figure. 2C). Analysis of the albumin level revealed a trend pattern indicating an increase in severity the higher the albumin level (Figure. 2D).

Electrolyte level testing involves the analysis of sodium, potassium, and chloride. Analysis of the trend pattern of sodium electrolyte levels revealed a trend pattern that showed an increase in severity as the sodium level increased. When the potassium electrolytes were examined, there was no clear trend pattern of potassium values at different severity levels. In addition, when the chloride level was examined, a trend pattern showed an increase in severity with increasing chloride levels. In this study, the assessment of chronic kidney disease stages was calculated based on glomerular filtration rate (e-GFR), as shown in the graph below, which shows a pattern of increasing disease severity in patients with decreasing e-GFR (Fig. 4A-D). Examination of inflammatory markers showed a trend toward decreasing severity with increasing procalcitonin levels. In contrast, CRP and D-dimer levels analysis showed that disease severity tended to worsen with increasing both markers levels (Figure. 5A-C).

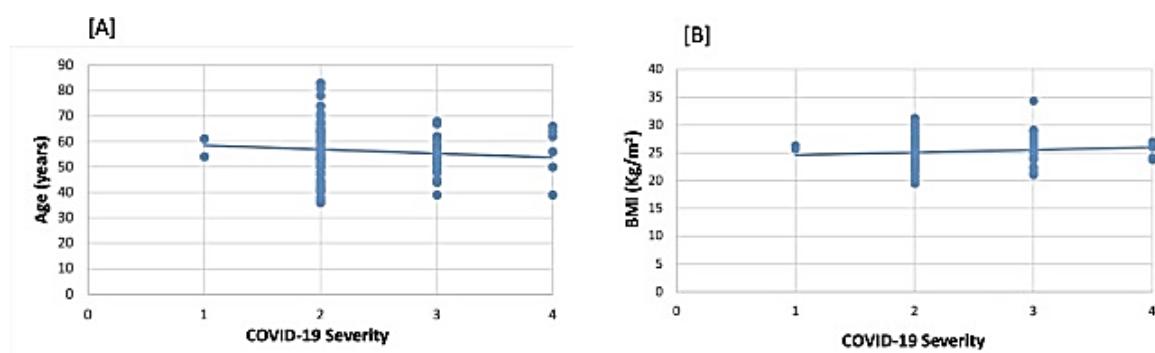


Figure 1. Trend in Age (years) and BMI (kg/m<sup>2</sup>) by COVID-19 Severity

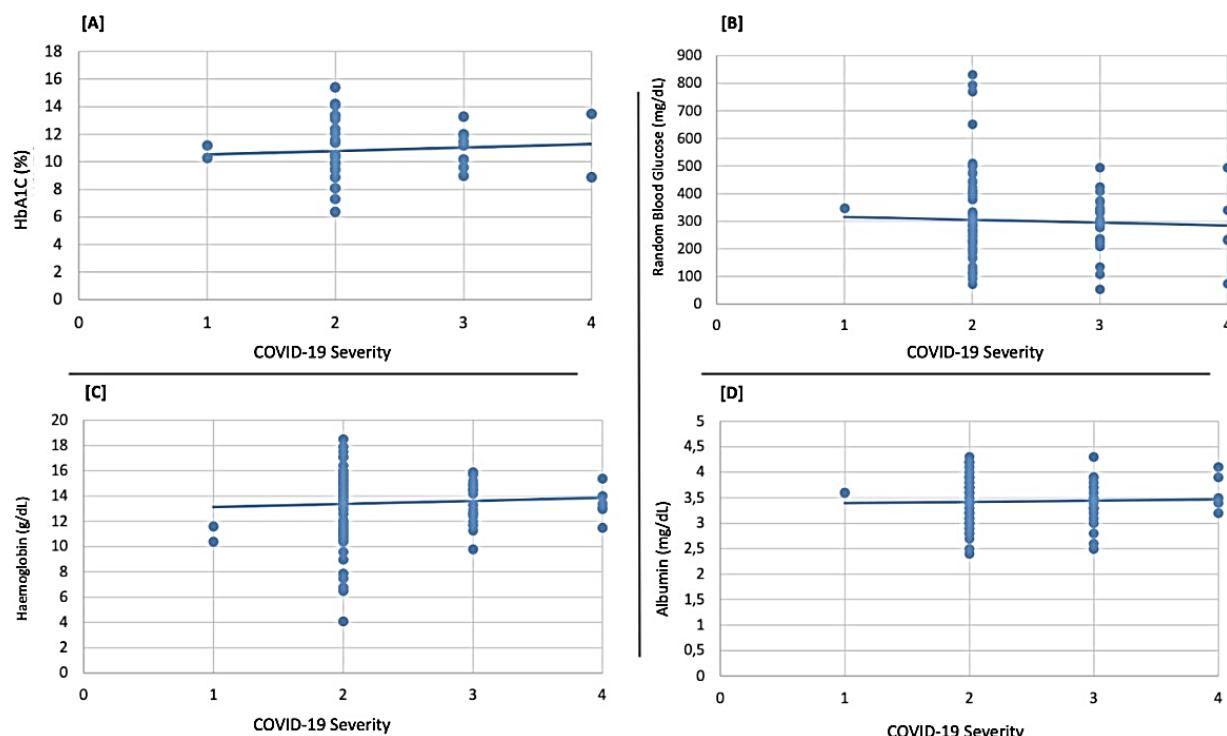


Figure 2. Trend in HbA1C (%), RBG (g/dL), Hemoglobin (g/dL) and Albumin (mg/dL) by COVID-19 Severity

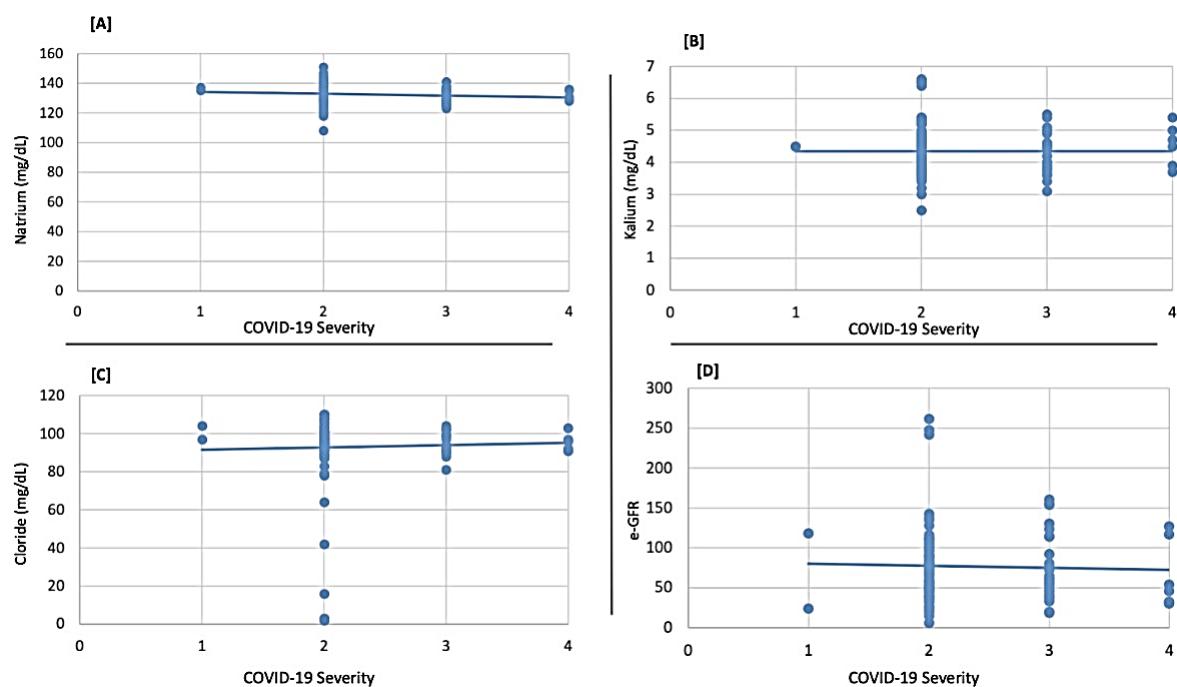


Figure 3. Trend in Natrium, Potassium, Chloride (mmol/L) and e-GFR (mL/minute) by COVID-19 Severity

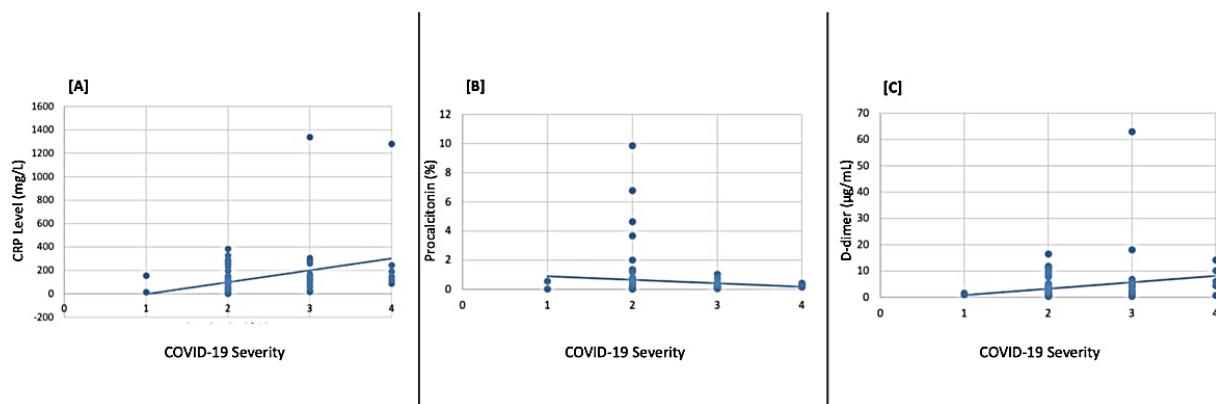


Figure 4. Trend in CRP (mg/L), Procalcitonin (%), and D-dimer ( $\mu$ g/mL) by COVID-19 Severity

## DISCUSSION

From the analysis results, it was found that the trend of disease severity was sloping with age but increased with higher BMI. A study with the same research subject, COVID-19 patients with type 2 DM, by Zhang et al. (2020) obtained different results that the older the age, the degree of severity would increase ( $p=0.012$ ), with the median age in the severe group being 72 years.<sup>18</sup> Another study also reported that Older age was independently associated with a higher risk of death ( $\geq 80$  vs  $<40$  years: odds ratio [OR], 11.15,  $p<0.05$ ).<sup>19</sup> A meta-analysis in China involving 3027 COVID-19 patients also showed that age  $>65$  was a risk factor for disease progression to severe (OR 6.06, 95% CI: 3.98–9.22,  $p<0.00001$ ).<sup>18</sup> This could be due to the variation in the age of the patients who visited the hospital, where most of the patients who came to the Hajj Hospital were in the 50–59 year age group.

A study in New York using 504 samples stated that overweight and obesity in COVID-19 patients increased the risk of severity and mortality compared to patients with normal nutritional status. Obesity increases the risk of complications in the age group of 45–64 years.<sup>20</sup> Meta-analytic studies state that obesity in COVID-19 patients increases severity and mortality.<sup>21</sup> The mechanism that causes them is that obesity reduces the expansion of the diaphragm, which reduces the total lung capacity. Obesity increases levels of proinflammatory IL-6, leading to a cytokine storm.<sup>22</sup> The hormone leptin also increases. Increased leptin causes leptin resistance, and

the maturation of B cells decreases, resulting in decreased immune response.<sup>23</sup> Adipose tissue increases in obese patients, which aligns with the increase in ACE-2 receptors so that the virus can quickly enter the body.<sup>24,25</sup> ACE-2 receptors are expressed in the gastrointestinal, lung, liver, and kidney pathways. Obese patients are associated with comorbidities such as DM, hypertension, and heart disease.<sup>26,27</sup>

The trend analysis also illustrated the sloping disease severity trend along with higher random blood sugar levels. On the other hand, the disease's severity worsens as the HbA1C level increases. These results contrast a study by Kandinata et al., where RBG levels were independently related to the severity, and HbA1C was not significantly related. The study explained the primacy of RBG risk factors concerning the severity of COVID-19 in DM patients; RBG modulates the inflammatory response and exacerbates cytokine storm, endothelial damage, and glucotoxicity, which causes interstitial lung damage and increases the risk of ARDS and death.<sup>28</sup> The different results may be affected by the different RBG variations, and the significance analysis used. This study examined only trends without analysis and control for possible confounding variables.

Based on the patient's blood hemoglobin level, it is shown that the severity of the disease tends to increase along with high hemoglobin levels. In several studies, hemoglobin level is associated with the severity of COVID-19 cases. Nonetheless, most studies associate

low Hb levels (<10 g/dL) with disease severity and risk of death.<sup>13,29-31</sup> The study conducted by Sayad et al. yielded slightly different results.<sup>32</sup> His study found an increase in Hb in patients who did not survive, although it was not statistically significant. Similar results were also shown in a study by Sarcia et al., where some patients who did not survive showed elevated Hb levels. The underlying mechanism is unclear, but it is associated with hypercoagulability and polycythemia vera in some COVID-19 patients, which can cause systemic thrombosis.<sup>29</sup>

The results showed an increase in severity with lower sodium levels for electrolyte levels. Nevertheless, the pattern trend is different with potassium levels, and there is no clear pattern of trends at various degrees of severity. Meanwhile, the higher the chloride level, the more likely, the higher disease severity found in the patients. Research reveals that abnormal sodium levels are a risk factor for poor prognosis in COVID-19 patients. In many viral diseases, electrolyte imbalance, especially hypokalaemia, has significant clinical implications in patient management and contributes to the pathogenesis of COVID-19.<sup>33,34</sup> Type 2 DM causes electrolyte balance disturbances such as hyponatremia and hyperkalemia. Patients with type 2DM tend to experience more frequent hyperkalemia due to redistribution into the intravascular fluid, whereas COVID-19 causes hypokalaemia due to increased excretion of K<sup>+</sup> in the urine. Researchers found that chloride levels in critical patients were higher when comparing the number of patients with hypochloraemia and normal chloride. Electrolyte imbalance in COVID-19 patients with Type 2 DM comorbidities can potentially increase the risk of death or more severe COVID-19 disease.<sup>33,35</sup>

Based on the e-GFR, this study found a tendency for the disease to worsen in patients with decreasing e-GFR. A study conducted by Zhang et al. (2020) on the subject of COVID-19 patients with DM found that the severely ill group had a lower median eGFR than those

who were less severe (81 vs. 89, p<0.001).<sup>18</sup> Meanwhile, in another study also conducted by Zhang et al. (2020), it was found that there was no difference in e-GFR values at admission and severity in COVID-19 patients with DM. The examination and analysis of inflammatory markers found that the severity pattern tends to worsen with increasing CRP and D-dimer levels.<sup>36</sup> However, a trend of severity sloping with increasing procalcitonin levels is obtained. Research in COVID-19 patients with type 2 DM found that CRP and procalcitonin were significantly higher in severe cases than in less severe cases (CRP 51.8 vs. 8.7, p<0.001 and procalcitonin 0.19 vs. 0.05, p = 0.012).<sup>36</sup>

Different trends in procalcitonin levels in this study could be due to different examination time points in patients. The results of previous studies showed that the average serum procalcitonin levels were more than four times higher in critically ill patients and more than eight times higher in critically ill patients than in moderately ill patients. However, procalcitonin levels slowly decrease in patients who go home and show improvement.<sup>37</sup> The study suggests that healthcare providers should consider personalized care for COVID-19 patients with diabetes. Factors like BMI, HbA1C levels, and electrolyte imbalances appear to correlate with disease severity, which may help in risk stratification. The findings emphasize the significance of glycemic control for diabetic COVID-19 patients, managing electrolyte imbalances, and monitoring elevated CRP and D-dimer that may help in early risk assessment and targeted interventions.

This study, however, has several limitations. First, the study is limited to a single center; thus, the sample size may not fulfill all variations in DM patients. A multi-center approach must be considered. Second, the nature of the cross-sectional study utilizing retrospective medical records could not show the temporal effect of clinical characteristics by COVID-19 severity.

## CONCLUSION

The pattern of clinical and laboratory features of DM patient based on the severity of COVID-19 infection treated at Haji Surabaya General Hospital shows the tendency that the severity of the disease increases with increasing BMI, HbA1C level, low sodium level, high chloride level, and high CRP and D-dimer levels.

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## Transition of Care of Disorders of Sexual Development: A Twist of Two Cases with Ambiguous Genitalia

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### ABSTRACT

Disorders of sexual development (DSD) is a congenital condition that requires an alteration in the development of chromosomal, gonadal, and anatomical sex is atypical. A report showed most of the patients in the 46XX DSD had congenital adrenal hyperplasia (CAH) at 69.23% followed by unknown under-virilization in the 46XY DSD group at 60.09%. Patient 1 diagnosed as DSD 46XX/non-classic congenital adrenal hyperplasia (NCAH) presented with primary amenorrhea, short stature, over-virilization (Prader 2), and 46XX karyotype. Laboratory examination showed elevated 17-hydroxyprogesterone (17OHP): 166.7 ng/ml (2.83 ng/ml), without salt wasting feature. Patient 2 diagnosed with DSD 46XY/type 2 5 $\alpha$ -reductase deficiency (SAD) presented with cryptorchidism, under-masculinization (Sinecker stage 3b), and 46XY karyotype. Laboratory examination showed elevated testosterone 613 ng/dL (4.6–38.3 ng/dL), decreased dihydrotestosterone (DHT) 11 ng/dL (>20 ng/dL), and elevated testosterone T/DHT ratio 55.73 (8–16). A deep understanding of pathophysiology, and approach to disease in each stage of life is important and warrants special treatment. Comprehensive multidisciplinary team management (MDT) is warranted in DSD management. Disease prognosis varies among each disorder: early detection, treatment compliance, and continuity of care are important to improve patient outcomes.

**Keywords:** Disorders of sexual development (dsd), ambiguous genitalia, case series

## INTRODUCTION

Disorder of sexual development is defined as a congenital condition that requires an alteration in the development of chromosomal, gonadal, and if the anatomical sex is atypical (Table 1).<sup>1,2</sup> The diagnosis of DSD may appear within any stage of patient development from early life to adulthood which owing to discordances genital development, fertility, or even hypertension.<sup>3</sup> The incidence of DSD varies from 1:4500 to 1:5000 birth, with consanguinity marriage as the main risk factor.<sup>4</sup> A study by Walia et al.

identifies 70.3% of patients among 46XX DSD diagnosed as CAH, and 8.8% of patients among 46XY DSD diagnosed with SAD.<sup>5</sup> Report our hospital showed most of the patients in 46XX DSD are CAH 69.23% followed by unknown under virilization in the 46XY DSD group 60.09%.<sup>6</sup> This case report aims to present two DSD cases with ambiguous genitalia due to NCAH and SAD. (Table 2) Hence showed the importance of MDT and the transition of care from pediatric to adult patients with DSD in our institution.

Table 1. Clinical Classification of DSD

Sex Chromosome DSD	46XY DSD	46XX DSD
45X (Turner syndrome and variants)	Disorders of gonadal (testicular) development	Disorders of gonadal (ovarian) development
47XXX (Klinefelter syndrome and variants)	<ul style="list-style-type: none"> <li>• Complete gonadal dysgenesis (Swyer syndrome)</li> <li>• Partial gonadal dysgenesis Gonadal regression Ovotesticular DSD</li> </ul>	<ul style="list-style-type: none"> <li>• Ovotesticular DSD</li> <li>• Testicular DSD (SRY+, dup SOX9)</li> <li>• Gonadal dysgenesis</li> </ul>
45X/46XY (mixed gonadal dysgenesis, ovotesticular DSD)	Disorders in androgen synthesis or action	Androgen excess
46XX/46XY (chimeric, ovotesticular DSD)	<ul style="list-style-type: none"> <li>• Androgen biosynthesis defect (17-hydroxysteroid dehydrogenase deficiency, 5α-reductase deficiency)</li> <li>• Defect in androgen action (CAIS, PAIS)</li> <li>• LH receptor defects (Leydig cell hypoplasia)</li> <li>• Disorders of AMH and AMH receptor (persistent Müllerian duct syndrome)</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal (21- or 11-hydroxylase deficiency)</li> <li>• Fetalplacental (aromatase deficiency, POR)</li> <li>• Maternal (luteoma, exogenous)</li> </ul>
	Other (severe hypospadias, cloacal extrophy)	Other (cloacal extrophy, MURCS)

AMH, anti-Müllerian hormone; CAIS, complete androgen insensitivity syndrome; LH, luteinizing hormone; MURCS, Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia; PAIS, partial androgen insensitivity syndrome; POR, cytochrome P450 oxidoreductase. Adapted from. Lee PA, Houk CP, Ahmed SF, Hughes IA. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 2006 Aug;118(2):e488-500.

## CASE ILLUSTRATION

### Case 1

An 18-year-old female was referred from the pediatric endocrinology clinic with a diagnosis of 46XX DSD/NCAH. The patient was well until the age of 2 when they noticed enlargement of the phallus. Her pregnancy status was a full-term pregnancy, with a birth weight of 3100 grams, and she showed normal genital appearance upon delivery. She was the third daughter among three siblings in the family with a history of consanguineous marriage. She developed as a female with normal intelligence for her age.

Two years prior, she sought a consultation with a pediatric endocrinologist due to genital ambiguity and delayed puberty. Physical examination showed normal vital signs, body height (BH): 143 cm, body weight (BW): 48 kg, father's height (FH): 155 cm, mother's height (MH): 155 cm, mid parenteral height (MPH): 156.5 cm, and arm span (AS): 117 cm. Her secondary sexual evaluation showed breast development tanner stage I (M1), pubic hair tanner stage III (P3), and a Ferriman-Galloway score of 3. Genital examination pre-reconstruction showed a phallus, external urethral orifice, vagina, and

posterior labial fusion (Prader scale 3) (Figure 1). Karyotype examination was compatible with 46XX, and 17-OH progesterone (17-OHP) was elevated at 166.7 ng/ml (2.83 ng/ml). Pelvic ultrasonography (UTZ) revealed a visualized uterus. Magnetic Resonance Imaging (MRI) of the abdomen revealed the presence of an ovary, hypoplastic uterus, and normal adrenal gland. The bone age was consistent with 17 years old (*Greulich-Pyle*). Hydrocortisone 15mg/day was immediately started, and she underwent psychiatric and obstetric evaluation. However, she was non-compliant with treatment, and genital reconstruction was

delayed 1.5 years due to the COVID-19 pandemic.

After 1 year of consultation in an adult endocrinology clinic, despite good compliance, the 17OHP evaluation still showed a high elevation (180.38 ng/mL). As a result, the hydrocortisone dose was increased to 30mg/day. Additionally, a combination of estradiol valerate 2mg and 0.5mg norgestrel preparation was given for 3 cycles to promote the development of her secondary sexual appearance. The psychiatric evaluation confirmed a diagnosis of gender dysphoria in adults, with the patient identifying as female.

A.



B.



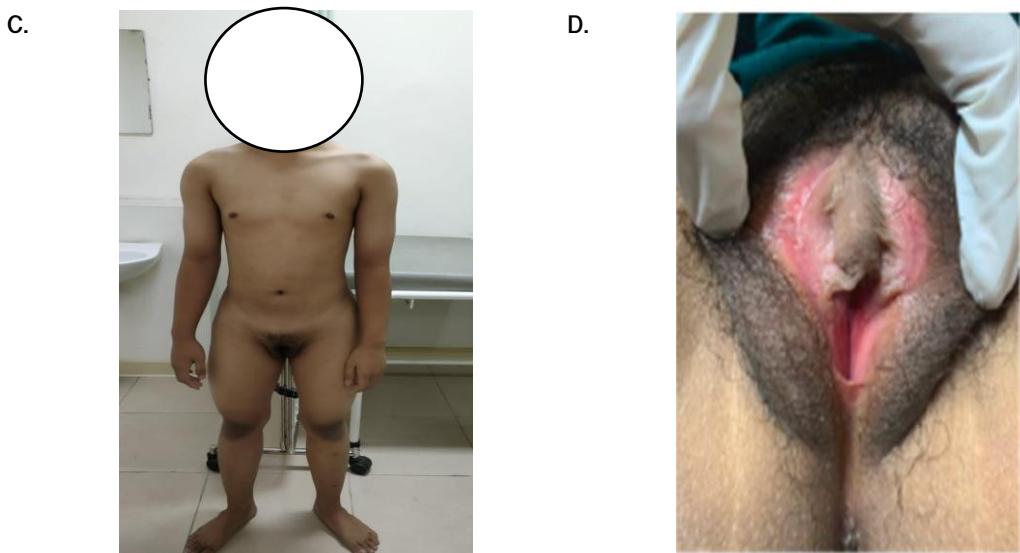


Figure 1. A. Physical appearance of patient 1, and B. Ambiguous genitalia (Prader 2).  
C. Physical appearance patient 2, and D. Ambiguous genitalia (Sinecker 3b)

## Case 2

An 18 year old male was referred from pediatric endocrinology with a diagnosis of 46XYY SRD. Two years prior, he sought consultation to obstetric endocrinology due to primary amenorrhoea. He denied any disorders in micturition and vaginal discharge. He developed as female and showed good physical development and intelligence appropriate for his age. He experienced pubarche and wet dreams at the age of 13. His family history revealed a consanguineous marriage. Among his eight siblings, three of them (his 2<sup>nd</sup> and 4<sup>th</sup> younger siblings) also have the same diagnosis.

Physical examination showed normal vital signs, body weight (BW): 51 kg, body height (BH): 158 cm, arm span (AS): 120 cm, mother's height (MH): 148 cm, father's height (FH): 160 cm, and mid-parental height (MPH): 160.5 cm. No Adam's apple was found during the neck examination. His secondary sexual evaluation revealed breast development tanner stage I (M1), pubic hair tanner stage III (P3), presence of phallus with stretched penile length (SPL) 2.5 cm, perineoscrotal hypospadias, along with vulva, major and minor labia, and palpable gonad (5 ml) in the right labia major (Sinecker score 3b).

Laboratory examination showed elevated FSH at 19.75 IU/mL (2.5-10.2 IU/ml), testosterone at 613ng/dL (4.6-38.3 ng/dl), DHT at 11 ng/dL (>20 ng/dL), and T/DHT ratio of 55.73 (8-16). The testicular biopsy showed testicular tissue with some atrophic fibrosis, and the sperm analysis showed azoospermia. The karyotype test showed 46XY. Pelvic MRI showed bilateral testis, corpus cavernosa, and bulbospongiosus muscle.

The bone age was consistent with 17 years old (*Greulich-Pyle*). The psychiatric evaluation revealed gender dysphoria in an adolescent-adult with a male gender identity. The patient underwent left sided orchidopexy, and DHT 2.5% cream at 5 mg/day was applied over the phallus. After 6 months, the stretched penile length (SPL) extended to 6 cm, and a deeper voice was noticed. The patient will be planned to undergo sinus urogenital reconstruction in conjunction with psycho-supportive care prior to surgery. The ethics committee and the MDT team collaborated patient to fulfil several qualifications for gender disposition.

**Table 2.** Clinical, Radiologic, and Laboratory Examination of 2 Cases

	Patient 1	Patient 2
Age at diagnosis	15 years old	16 years old
Sex upon diagnosis	Female	Female
Secondary Sex Appearance	Breast: Tanner I (M1) Pubic hair: Tanner III (P3) Ferriman-Gallwey Score 3	Breast: Tanner 1 (M1) Pubic hair: Tanner III (P3)
Karyotyping	46XX	46XY
Body dysmorphic, and genital ambiguity	Short stature Prader scale 3	Cryptorchidism Sinecker scale 3b
Sex Hormone		
LH	4.2 IU/ml (1.9-12.5 IU/ml)	12.65 IU/mL (1.8-12.5 IU/mL)
FSH	8.3 IU/ml (2.5-10.2 IU/ml)	19.75 IU/mL (2.5-10.2 IU/ml)
Estradiol	73.17 pg/mL (60- 190 pg/mL)	23.29 pg/mL (Male 10-50 pg/mL)
Testosterone		613 ng/dL (4.6-38.3 ng/dl)
Dihydrotestosterone		11 ng/dL (>20 ng/dL)
T/DHT		55.73 (8-16)
17OHP		
Baseline	166.7 ng/ml (<2.83 ng/ml)	
After 1 year of evaluation	180.38 ng/mL	
Thyroid Function Test		
TSH	1.4 mIU/mL (N: 0.3 - 0.5 mIU/mL)	4.6 mIU/mL (N: 0.3 - 0.5 mIU/mL)
FT4	1.0 ng/dL (N: 0.7 - 1.8 ng/dL)	1.3 ng/dL ( N: 0.7 - 1.8 ng/dL)
Blood Chemistry		
Na/ K/ Glucose	140 mEq/L / 3.9 mEq/L / 104 mg/dL	140 mEq/L / 3.9mEq/L / 85 mg/dL
MRI	Abdominal: Adrenal gland not enlarged. The uterus, vagina, ovaries, corpus cavernosa, and bulbospongiosus are visible.	Pelvis: Bilateral testis (right testes volume 8.3 cc within the inguinal canal, and left testis volume 8.1 cc within labia major), corpus cavernosa, and bulbospongiosus muscle are visible.
Diagnosis	46XX DSD/NCAH	46XX DSD/SAD
Gender Disposition	Female	Male
Medical Treatment	Hydrocortisone 30 mg/day	DHT cream 2.5% 5 mg/day for 6 months
Surgical Management	Feminization clitoroplasty	Orchidopexy left

## DISCUSSION

Ambiguous genitalia among older children is highly suspected in patients with the following conditions: (1) Previously unrecognized ambiguous genitalia; (2) Inguinal hernia in a girl; (3) Delayed or incomplete puberty; (4) Primary amenorrhea or virilization in a girl; (5) Breast development in a boy; and (6) Gross or cyclic haematuria in a boy.<sup>2</sup> Patient 1 presented with signs of virilization (Prader scale 2), and primary amenorrhoea, while patient 2 showed the presence of under-masculinization, hypospadias, and the presence of vulva (Sinecker scale 3b).<sup>7</sup>

Understanding the disease pathogenesis and clinical course at each stage of life

for these two distinct disorders is crucial. In our cases, the androgenic steroid pathway and gene mutations resulting in enzyme (21-hydroxylase, and type 2 5 $\alpha$ -reductase) deficiencies were responsible.<sup>8-10</sup> The diagnoses of our patients followed diagnostic pathways based on paediatric experience for disorder of sex development (DSD).<sup>11</sup> The biological diagnosis is established through biochemical or genetic tests. In patient 1, the diagnosis was determined by an elevated 17OHP level at 08.00 am: 165.7 ng/ml (>10 ng/ml). In borderline cases (2-10 ng/ml), a dynamic test with cortico-tropin stimulation is recommended.<sup>10</sup> In patient 2, the diagnosis was determined by increased T/DHT ratio after human chorionic gonadotropin (HCG)

stimulation (first-line test in infants and pre-pubertal children). The cutoff point for the T/DHT ratio was suggested to be 20, but a ratio of 8.5 after HCG stimulation was found to be more reliable.<sup>8</sup>

Patient 2 had a basal T/DHT ratio of 55.73 ( $>9.5$ ).<sup>12</sup> In cases with inconclusive results, a corticosteroid panel, urine corticosteroid profile, or genetic testing is recommended, although these options are limited in our setting.<sup>10,11</sup> Pelvic UTZ and abdominal MRI were performed in both patients to distinguish between Wolffian or Mullerian structure maturation and adrenal gland enlargement.<sup>6</sup>

The patients were referred for genetic counselling and further genetic testing (karyotyping test) to help classify the DSD into three distinct groups. Subsequently, fluorescence in situ hybridization (FISH), and genetic testing with next-generation sequencing (NGS) were recommended to determine various cases of monogenic DSD (CYP21A2 gene (6p21)<sup>9</sup>, SRD5A2 gene (2p23).<sup>3,8</sup> However, the use of these test is still limited in our institution.

The Chicago Consensus (2006) advocates for a multidisciplinary team (MDT) approach in DSD cases. Medical, surgical, and psychological care are the three main aspects to optimize medical care for DSD patients (Figure 2).<sup>6,13</sup> In our cases, the patients were initially seen by a paediatric endocrinologist and obstetric-endocrinology section. The MDT team consisted of a surgeon, clinical geneticist, psychiatrist, radiologist, pathologist, ethics committee, and pharmacist. Once the patients reach 18 years old, they will be referred to an adult endocrinologist.



Figure 2. The multidisciplinary team model in the management of DSD<sup>16</sup>

Medical management is the cornerstone for various DSD cases. In patient 1, hydrocortisone at a dose of 15mg/day was started to alter androgen synthesis. Glucocorticoids are indicated in patients with early pubarche, increased bone age, and signs of over-virilization. The benefits of glucocorticoid are seen in children below 9 years old (to optimize patient height) and even in adults (to ameliorate hyperandrogenism, infertility, and other related symptoms).<sup>14,15</sup> In cases of severe enzyme deficiency and critical illness, higher doses of glucocorticoids may be required, with consideration of the side effects.<sup>16</sup>

In patient 1, hormonal replacement aimed to develop secondary sexual appearance and treat severe hirsutism. Estrogen replacement (estradiol valerate at a dose of 0.5mg/day, titrated up to 2 mg/day) was initiated after the patient reached puberty. Two years later, consecutive progesterone (medroxyprogesterone 100-200 mg/day, or norethidone 2.5-5 mg/day) can be given in patients with an intact uterus.<sup>17</sup> Alternatively, ovarian or peripheral androgen blockade (using drospirenone or cyproterone acetate) is preferred.<sup>18,19</sup> In patient 2, testosterone replacement for SAD cases is not generally required, as testicular function is preserved. However, high doses of testosterone (testosterone cypionate 200-500 mg twice a week intramuscular (IM) or DHT cream (5-10 mg/day) are given to improve male secondary sexual characteristics.<sup>8</sup> Patient 2 was given DHT cream for 6 months to achieve the maximum effect.

For patient 1, feminization surgery is the treatment of choice, while patient 2 will require sinus urogenital reconstruction and masculinization surgery. Before surgery, both patients receive psycho-supportive treatment. The timing of surgery is debatable, but previous reports suggest that CAH and SAD patients should undergo surgery before 5 years old and 2 years old, respectively. Ethical considerations regarding gender disposition should be considered. After a psychiatric evaluation, patient 1 was suggested for female gender after

feminizing surgery was contemplated, while patient 2 was suggested for male gender disposition.<sup>1</sup> Psychological evaluation is ideally performed before 27 months old, before hormonal or surgical intervention is decided.<sup>8</sup>

The transition from pediatric to adult care is important for DSD patients.<sup>6</sup> Various aspects, including the patient's sexual function, risk of malignant transformation, physiological problems, and information about the patient's illness should be considered.<sup>1</sup> Patient prognosis varies, and early detection, treatment compliance, and long-term management are crucial.

## DISCUSSION

Various cases of disorder of sex development (DSD) with genital ambiguity were encountered from early life to adulthood. It is important to have a deep understanding of the pathophysiology, disease burden, and the approach to managing DSD at each stage of life. Therefore, the management of DSD cases with a MDT approach should be considered to ensure a favourable prognosis.

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## Diabetic Ketoacidosis as The First Manifestation of a Young Adult with Diabetes: A Clinical Approach to Distinguish Different Types of Diabetes Mellitus

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### ABSTRACT

Diabetic ketoacidosis (DKA) is an acute metabolic complication of diabetes. While it most commonly occurs in type 1 diabetes (T1DM), DKA can also occur in other types of diabetes. Encountering a case of DKA prompts further evaluation to determine the type of diabetes and manage patients accordingly. To establish a diagnosis of the type of diabetes in a case with an unusual presentation of DKA through a clinical approach. A 30-year-old male presented to the emergency department with sudden dyspnea. Laboratory examinations showed a blood glucose level of 506 mg/dL, a blood ketone level of 2.6 mmol/L, and a bicarbonate level of 5 mEq/L. His hemoglobin A1c was 15.3%. He had not been previously diagnosed with diabetes mellitus. Studies have shown overlapping clinical and biochemical parameters of DKA among various types of diabetes. Following life-saving management, further clinical and laboratory evaluations should be performed. Measurement of autoantibody titer (i.e.: autoantibodies against glutamic acid decarboxylase, islet antigen-2, zinc transporter 8, and insulin) and c-peptide levels might help determine the type of diabetes in this patient. Establishing the diagnosis of a certain type of diabetes in young adults can be challenging. Based on clinical profile, a presumptive diagnosis of autoimmune diabetes, particularly latent autoimmune diabetes in adults (LADA), was made in this patient.

**Keywords:** Diabetes mellitus, diabetic ketoacidosis, latent autoimmune diabetes in adults, young adult

## INTRODUCTION

One of the most severe acute metabolic complications of diabetes is diabetic ketoacidosis (DKA), characterized by a triad of hyperglycemia, ketonemia, and high anion gap metabolic acidosis.<sup>1</sup> These conditions can lead to dehydration, coma, and death.<sup>2</sup> The American Diabetes Association (ADA) classifies diabetes into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and other specific types of diabetes.<sup>3</sup> Although DKA is typically associated with T1DM, it can also occur in other types of diabetes.<sup>4,5</sup> DKA is a life-threatening complication that can be prevented.<sup>4</sup> Glycemic control intervention should be tailored to the individual patient's needs and diabetes type.<sup>2,3</sup> Therefore, encountering a case of DKA, especially with unusual presentations, necessitates further evaluation to appropriately manage patients and avoid unnecessary therapy.

## CASE ILLUSTRATION

A 30-year-old male presented to the emergency department with an acute onset of dyspnea 6 hours prior to admission. The shortness of breath was continuous, not affected by body position, and not associated with edema. There was no complaint of cough nor fever. His current complaint was accompanied with general weakness, nausea, and vomiting. There were no complaints of dysuria or diarrhea. There was no significant past medical history other than a growing mass on his right upper arm, suspected to be osteosarcoma. This mass developed after a fracture that occurred 4 months prior to admission. The patient was not taking any routine medication and had not received any corticosteroid treatment for his right humeral mass prior to the current admission. Furthermore, the patient reported experiencing polydipsia, polyuria, and a significant weight loss (30 kg) for the last 4 months. He had been previously obese (body

mass index/BMI 30 kg/m<sup>2</sup>). The patient's family history revealed a diabetic father, diagnosed at the age of 38, and has been receiving insulin treatment ever since. There was no grandparental history of diabetes.

On arrival, the patient's vital signs were within normal limit other than tachycardia and a rapid deep breathing pattern. His BMI was 17.6 kg/m<sup>2</sup> (underweight). A thorough physical examination did not reveal any lung and heart abnormalities. There was a mass in his right humerus along with restricted range of motion. Examination of other organs were unremarkable. The complete blood count showed leukocytosis (27.700/µL) and neutrophilia (86%), while the biochemistry examination showed a high random blood glucose level of 506 mg/dL, high hemoglobin A1c (15.3%), a high blood ketone level of 2.6 mmol/L, and a low bicarbonate level of 5 mEq/L. The amylase, lipase tests were increased below threefold of upper normal limit. Renal function, and liver function tests were within normal limit. His urinalysis displayed glucosuria and ketonuria. There were no radiological abnormalities of the heart and lungs from chest radiograph. Electrocardiography showed sinus tachycardia of 140 beats per minute with no other abnormalities.

The patient was diagnosed with diabetic ketoacidosis (DKA) and received intravenous fluid hydration as well as intravenous insulin infusion. Subsequently, he was admitted to the high care unit. Throughout hospitalization, his condition gradually improved and successful blood glucose control was achieved with subcutaneous fixed-dose insulin. Additional examinations showed a low c-peptide level of 0.11 ng/mL and a negative glutamic acid decarboxylase (GAD) autoantibody of <5.0 IU/mL in this patient. The biopsy of his right arm showed histological findings of high-grade sarcoma suggesting an osteosarcoma. The patient was discharged with a fixed-dose subcutaneous insulin therapy.

## DISCUSSION

The diagnostic criteria for diabetes include several parameters that reflect the condition of hyperglycemia, which are: fasting plasma glucose  $\geq 126$  mg/dL, or two-hour plasma glucose  $\geq 200$  mg/dL during oral glucose tolerance test, or A1c  $\geq 6.5\%$ , or a random plasma glucose  $\geq 200$  mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.<sup>3</sup> In the patient of our case, we found the classic symptoms of hyperglycemia: polydipsia, polyuria, and unintentional weight loss. He also fulfilled other criteria such as A1c  $\geq 6.5\%$  and a presentation of hyperglycemic crisis (DKA).

DKA, an acute metabolic complication of diabetes mellitus, consists of the triad of hyperglycemia (defined as blood glucose  $>250$  mg/dL), ketonemia, and high anion gap metabolic acidosis (bicarbonate  $<18$  mEq/L and anion gap  $>12$ ).<sup>1</sup> The patient of our case fulfilled the criteria of DKA as shown by his laboratory parameters: elevated blood glucose level (506 mg/dL), increased plasma ketone level (2.6 mmol/L), and high anion gap (25 mEq/L), as well as decreased bicarbonate level (5 mEq/L). The age at onset of DKA in our patient was in the early adulthood, making his diabetes type

obscured. DKA was once thought to be a pathognomonic feature of T1DM. This concept has now been reformed as DKA can also be found in T2DM, despite occurring most often in T1DM.<sup>3, 5-7</sup> Another traditional paradigm of T1DM occurring only in children and T2DM being exclusive to adults is also no longer valid as the onset of T1DM may appear in adulthood.<sup>3</sup> In patients who present with DKA, a thorough investigation is recommended for correct diabetes categorization and to determine the lifelong therapy of diabetes.<sup>8</sup> With the challenges in identifying diabetes type, several studies have reported the comparison between DKA in T1DM and T2DM (Table 1) A variety of clinical and laboratory parameters overlapped between DKA in T1DM and T2DM.<sup>5,6,8,9</sup> There is no single marker yet that can distinguish one type from the other. Therefore, we were not able to conclude the diabetes type of our patient up to this point. One clinical algorithm (Figure 1) demonstrates a simple method to determine some commonly encountered diabetes types. Moreover, given the age of our patient was in the young adult category, we also evaluated our patient based on a list of clinical features of several diabetes types that are relevant to our patient (Table 2).

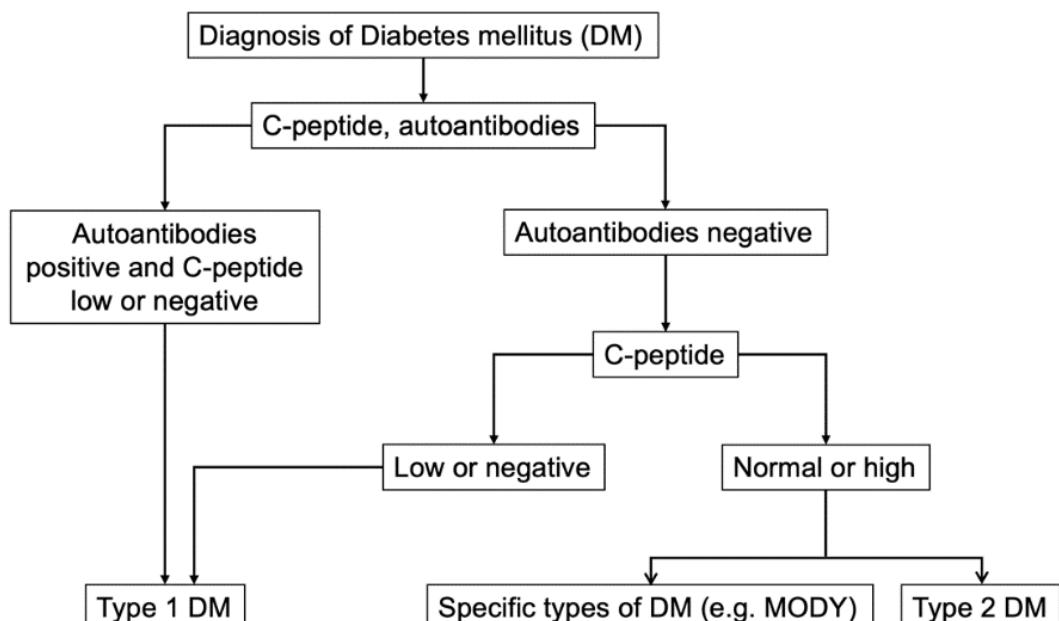


Figure 1. Clinical algorithm for classification of diabetes mellitus.

Adapted from: Hörber S, Achenbach P, Schleicher E, Peter A. Harmonization of immunoassays for biomarkers in diabetes mellitus. Biotechnol Adv. 2020; 39:107359.

Table 1. DKA in T1DM vs. T2DM

	Newton, et al. <sup>6</sup>			Barski, et al. <sup>5</sup>			Wang, et al. <sup>8</sup>			Tan, et al. <sup>9</sup>		
	T1DM	T2DM	p-value	T1DM	T2DM	p-value	T1DM	T2DM	p-value	T1DM	T2DM	p-value
Age on admission (years)	38.2 ± 13.3	42.5 ± 3.3	NS	37.3 ± 16.1	64.3 ± 12.4	<0.001	36.9 ± 3.2	63.0 ± 6.0	0.003	30.24 ± 15.14	56.51 ± 14.05	?
Precipitating factor:												
Insulin-related, n (%)	-	-	-	83 (50)	3 (86)	<0.001	-	-	-	-	-	-
Infection, (%)	? (22)	? (48)	?	49 (29.5)	14 (40)	0.02	4 (50)	10 (56)	NS	-	-	-
BMI >25 kg/m <sup>2</sup> , n (%)	? (21)	? (70)	?	-	-	-	5 (28)	5 (63)	NS	3 (7.30)	63 (35.39)	?
Baseline ischemic heart disease, n (%)	-	-	-	14 (8.4)	12 (34.3)	<0.001	-	-	-	-	-	-
Blood glucose (mg/dL)	461.4 ± 192.3	396.6 ± 191.1	?	543 ± 181	646 ± 250	0.026	651.6 ± 66.6	693 ± 59.4	NS	367.56 ± 231.1	324.54 ± 195.48	?
Bicarbonate (mEq/L)	9.8 ± 5.0	12.0 ± 4.6	?	10.9 ± 3.9	9.7 ± 4.5	0.1	8.0 ± 1.1	13.4 ± 1.9	0.031	-	-	-
Arterial pH	7.19 ± 0.14	7.28 ± 0.03	< 0.1	7.18 ± 0.11	7.14 ± 0.17	0.1	7.11 ± 0.04	7.23 ± 0.06	0.099	7.336 ± 0.158	7.389 ± 0.094	0.028
Creatinine (mg/dL)	1.2 ± 0.5	1.2 ± 0.3	?	1.18 ± 0.78	1.53 ± 0.89	0.036	1.35 ± 0.18	1.62 ± 0.24	NS	-	-	-
Leukocyte (x 10 <sup>3</sup> /µL)	14.1 ± 7.3	10.0 ± 1.3	< 0.1	15.7 ± 7.1	15.6 ± 8.5	0.9	-	-	-	-	-	-

?; not stated; BMI: body mass index; NS: not significant; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

Autoantibodies against a variety of  $\beta$ -cell components are important biomarkers. These include autoantibodies against glutamic acid decarboxylase, islet antigen-2, zinc transporter 8, and insulin.<sup>2</sup> Although common in T1DM, these autoantibodies can occasionally be found in T2DM.<sup>2</sup> The most frequent (>70%) autoantibody in T1DM and latent autoimmune diabetes in adults (LADA) is glutamic acid decarboxylase autoantibody (GADA).<sup>10</sup> Our patient showed a negative GADA result. This does not rule out the possibility. Of the presence of autoantibody to other  $\beta$ -cell components. Due to limited resources, we could not perform the evaluation of other autoantibodies. However, c-peptide measurement would still be useful for diabetes classification regardless of autoantibody result. C-peptide, a molecule generated from the proteolysis of proinsulin, has a longer plasma half-life and a more constant

blood concentration compared to insulin and is mainly used as a marker of  $\beta$ -cell function.<sup>10</sup> The c-peptide level of our patient was decreased (0.11 ng/mL). In T1DM, endogenous insulin release is diminished due to autoimmune-mediated  $\beta$ -cell destruction. In contrast, T2DM patients have normal or increased endogenous insulin synthesis to overcome insulin resistance in the early stage of disease progression.<sup>10</sup> However, advanced impaired glucose tolerance in T2DM may lead to  $\beta$ -cell insufficiency and reduced insulin and c-peptide secretion.<sup>10</sup> Based on his age at onset and the lack of micro-/macrovascular diabetic complications, we did not consider the result of our patient as an advanced stage of T2DM but suspected that the patient has autoimmune-diabetes instead.

Table 2. Features of several types of diabetes.<sup>11-15</sup>

	T1DM	T2DM	LADA	Monogenic diabetes
Age at onset	Commonly in childhood and early adolescence <30 years old	Adulthood, typically >25 years old	Above 30 years old	Usually before 25 years old
Family history of diabetes	Infrequent (5-10%), usually sporadic (>85%)	Strongly positive (75-90%)	Negative or positive	Positive for $\geq 3$ generations
BMI	Usually thin, but can still be like general, non-diabetic population	Overweight or obese (>90%)	Normal, rarely overweight/obese	Like general, non-diabetic, population
Insulin resistance	Absent	Increased	Increased/no change	Absent
C-peptide levels	Low or undetectable after 3 years from diagnosis	Normal-high	Decreased but still detectable	Low-normal
Autoantibodies	Positive in most patients (80-90%)	Negative	Positive	Negative
Insulin dependent	Yes	No	Yes, >6 months after diagnosis	No
Risk of DKA	High	Low, except ketosis-prone subtype	Low	Low

DKA: diabetic ketoacidosis; LADA: latent autoimmune diabetes of adulthood; T1DM: type 1 diabetes; T2DM: type 2 diabetes

T1DM typically appears in childhood and early adolescence with 2 peaks of onset: age group 4-7 years old and 10-14 years old.<sup>16</sup> Meanwhile, LADA appears in people aged 30-50 years old,<sup>17</sup> which is more suitable for our patient. LADA has overlapping features of T1DM and T2DM.<sup>15</sup> On one side, it is immunologically similar to T1DM although the destruction progresses at a much lower rate.<sup>18</sup> On the flipside, it has features similar to T2DM such as onset at adulthood, subclinical/non-acute onset (e.g.: non-dramatic hyperglycemia), insulin independence (at least for the first 6 months of diagnosis), and insulin resistance.<sup>14,18</sup> Patients with LADA have residual c-peptide levels between T1DM and T2DM.<sup>18</sup> This residual endogenous insulin production portrays a slowly progressing  $\beta$ -cell destruction and therefore patients with LADA usually do not require insulin for the initial 6 months after diagnosis.<sup>18</sup>

We made a presumptive diagnosis of autoimmune diabetes, particularly LADA, based on the clinical profile of our patient despite no autoantibody being found (i.e.: age at onset, low c-peptide level in the absence of advanced diabetic complication signs). On one side, our patient was 30 years old, underweight, and his clinical data was in line with the diagnosis T1DM based on algorithms shown above. On the other side, our patient's history of being obese and a positive diabetic family history showed an overlapping T2DM features. These mixed features support the diagnosis of LADA. Owing to the slow progression of  $\beta$ -cell destruction, DKA is usually absent at diagnosis of LADA. However, our patient had demonstrated an insidious onset of diabetes by looking at his symptoms of polydipsia, polyuria, and a significant weight loss over the last 4 months prior to his DKA episode. This is also reflected by his high A1c level in contrast to the average A1c of new-onset T1DM that rarely exceeds 10%.<sup>19,20</sup>

Glycemic control is a key factor for the prognosis of this patient. Patients with LADA may experience a mortality rate as high as T2DM. Chronic exposure to hyperglycemia increases the risk of micro- and macrovascular

complications.<sup>14,18</sup> Chemotherapeutic agents such as doxorubicin may induce hyperglycemia. If poorly controlled, the hyperglycemic condition in this patient may in turn exacerbate chemotherapy-induced neuropathy and nephropathy.

## CONCLUSION

Establishing a diagnosis of certain diabetes type in young adults remains challenging, particularly in patients with unconventional presentation. DKA is not exclusive to T1DM. Currently, there is no distinguishing DKA features that can definitively classify the type of diabetes. Although no autoantibody was found, a presumptive diagnosis of autoimmune diabetes, particularly LADA, was made in this patient based on his clinical profiles.

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## CASE REPORT

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# Does Severe Hypokalemia Worsen the Outcome of Diabetic Ketoacidosis?

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### ABSTRACT

Hypokalemia is an uncommon finding in the initial evaluation of patients with DKA before insulin treatment. However, it can complicate the management of DKA and lead to a worse prognosis. Hypokalemia in DKA may result from a combination of factors, including kaliuresis, secondary osmotic diuresis, inadequate oral intake, and gastrointestinal losses such as vomiting. We report the case of a 31-year-old woman who recently experienced diabetic ketoacidosis with severe dehydration, severe hypokalemia, and sepsis. Unfortunately, her condition deteriorated, and she eventually went into cardiac arrest while receiving treatment in the emergency unit. This case highlights the challenges involved in providing therapy and managing complications that arise in patients, presenting a dilemma for healthcare providers.

**Keywords:** Diabetes, diabetic ketoacidosis, hypokalemia, sepsis, insulin

## INTRODUCTION

Diabetic ketoacidosis (DKA) is an extreme condition within the spectrum of hyperglycemic crisis, serving as an acute metabolic complication of diabetes. It poses a significant risk of morbidity, mortality, and increased hospital costs. DKA can occur due to delayed diagnosis resulting from a failure to recognize diabetes symptoms. It is characterized by a biochemical triad: hyperglycemia, ketonemia, and metabolic acidosis, leading to a high anion gap. DKA most commonly affects patients with type 1 diabetes but can also occur in individuals with type 2 diabetes who experience extreme stress, such as a severe infection, trauma, cardiovascular disease, or other emergencies.<sup>1</sup>

Abnormal electrolyte levels can complicate the management of DKA and contribute to a worse prognosis. One such electrolyte is potassium. Hypokalemia, defined as a plasma concentration of potassium (K+) < 3.5 mEq/L, is an uncommon finding in the initial evaluation of patients with DKA. Hypokalemia in DKA may result from a combination of factors, including kaliuresis, secondary or prolonged osmotic diuresis, inadequate oral intake, and gastrointestinal losses such as vomiting and diarrhea. In general, potassium levels in DKA patients tend to be normal or slightly elevated. However, rare cases of DKA can present with hypokalemia, occurring in only 5% to 10% of DKA patients, with levels below 2.5 mmol/L.<sup>2</sup> A similar rare occurrence was observed in a patient we treated previously, as described in the case below.

## CASE ILLUSTRATION

A 31-year-old woman was referred to the emergency unit of our hospital with hyperglycemia where the blood sugar levels were detected as high index (HI) by a simple glucose meter. The patient complained of feeling weak for about the last 72 hours until she was unable to do some activity. The patient also complained of headaches, tightness on chest, agitation, and a bit nausea and vomiting, with unknown cause. When asked about a history of polyuria, polydipsia, and significant weight loss, the patient denied experiencing these symptoms and explained that she had no complaints of illness. This information was further confirmed by both her mother and husband, who stated that there was no history of diabetes, hypertension, or other diseases, including within the family.

Upon initial examination, the patient was found to be fully conscious, alert with a Glasgow Coma Score (GCS) of E4V5M6. Vital signs measurements were obtained: blood pressure of 140/87 mmHg, heart rate of 100x/minute, respiratory rate of 26x/minute, temperature of 36.1°C and oxygen saturation of 98% without supplemental oxygen. The initial physical examination indicated mild signs of dehydration, with no detectable ketone odor. The blood sugar check conducted in our hospital's emergency unit also showed high levels (HI), necessitating the wait for the results of blood tests, including a complete blood count, biochemical analysis, and blood gas analysis, from the laboratory unit to obtain the specific values. Additionally, an ECG examination was performed, and the results are as follows:

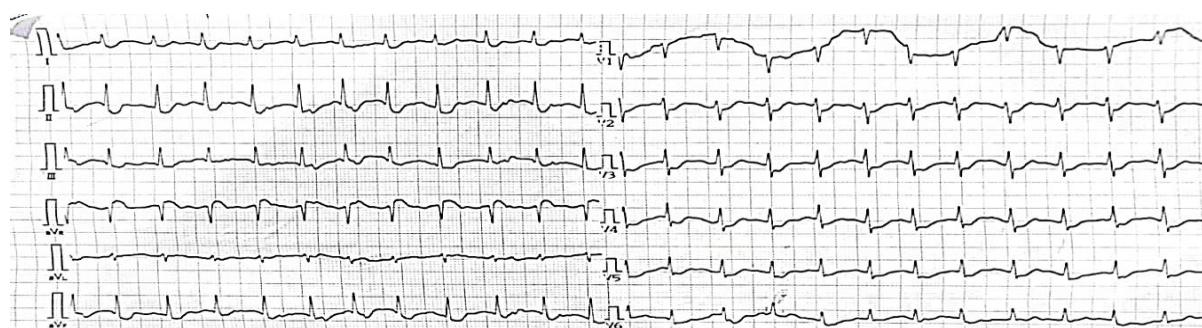


Figure 1: The ECG result showed sinus rhythm with tachycardia HR 120x/minute, predominant depressed ST segment, flattened T wave and prominent U wave suggestive of hypokalemia.

Her blood glucose level is 710.6 mg/dL, potassium level 1.76 mmol/L, pH 7.08, and HCO<sub>3</sub> 17.7 mmol/L. PCO<sub>2</sub> 32.0 mmHg. Her leucocyte 34.750/ $\mu$ L.

Following the objective examination, we began considering a diagnosis of hyperglycemia, suspected diabetic ketoacidosis. Initial therapy was initiated based on the principles of managing hyperglycemic crisis. This involved administering 2000 cc of normal saline for resuscitation within the first hour, administering symptomatic medications, and importantly, inserting a urinary catheter. Upon catheter insertion, we observed a urine output of 200 cc, which appeared a brownish tea-like color and highly concentrated. Simultaneously, the laboratory results were released, providing the following data.

However, the patient's experienced reported a decrease of consciousness. Our team immediately confirmed this by checking the patient. The examination of consciousness showed that the patient was at a somnolent level of consciousness with a GCS of E3V3M6, and started showing signs of shock, while the blood pressure was measured at 108/54 mmHg, heart rate at 46x/minute, respiratory rate at 30x/minute with Kussmaul breathing, oxygen saturation dropped to 88% without supplemental oxygen. The patient presented with cold extremities, reduced, and more concentrated urine output, indicating severe dehydration. In addition, the patient also had the impression of ketone odor, which was not present previously. We started resuscitation measures, starting from administering supplemental oxygen, reloading fluids according to the patient's hemodynamic condition, and putting on an ECG monitor.

We gave her therapy instructions, included double iv line, 500 cc/24 hours of NaCl 3%, 50 meq KCl drip in Ringer Acetate 500 cc/12 hours (4 repetitions), intravenous rapid regulation of 6 units of rapid-acting insulin (4 repetitions) followed by 14 units of rapid-acting insulin subcutaneous before every meals, 20 units long-acting insulin subcutaneous in the night, and 2 gram of ceftriaxone once a day, therapy has been well implemented. However,

after only approximately 15 minutes of therapy and under strict monitoring, the patient experienced respiratory arrest.

## DISCUSSION

We report the case of a 31-year-old woman who had diabetic ketoacidosis with severe dehydration, severe hypokalemia and sepsis resulting in cardiac arrest while she was being treated in the emergency unit.

Diabetic ketoacidosis (DKA) is one of the extreme conditions in the hyperglycemic crisis spectrum as an acute metabolic complication of diabetes. Even though DKA happens more often in people with type 1 diabetes, about a third of all cases of DKA happen in people with type 2 diabetes who do not carry out routine therapy followed by extreme stressful conditions, such as serious infections, trauma, cardiovascular disease, or other emergencies. People who have a higher chance of getting DKA are those who have high HbA1c, have had diabetes for a long time, lower socioeconomic status, presence of psychiatric conditions, teenagers, and girls. Newly diagnosed diabetes may also become the most triggering factor of DKA incidence.<sup>1-4</sup> In fact, in this patient, we cannot confirm whether the patient can be included to, type 1 or type 2 diabetes, due to anamnesis data that was not answered with confidence by the patient or the patient's closest family members, such as whether there was a history of illness since childhood and a history of diabetes in her family. This poor initial modal when the patient came to the emergency room was leading the patient to a deteriorating condition very quickly. So, even optimum care and treatment cannot provide the maximum results we wanted because we were also racing against time to handle this very serious condition.

DKA in general, our body is directed to a major catabolic state by breaking down glycogen stores, hydrolyzing triglycerides from adipose tissue, and mobilizing amino acids from muscles or in other words, in DKA, there is an increase in gluconeogenesis, lipolysis, ketogenesis, and a decreased glycolysis.<sup>5</sup>

Triglycerides and amino acids released from peripheral tissues become substrates to produce glucose and ketone bodies by the liver. Hyperglycemia and the production of ketone bodies lead a central role in developing this metabolic decompensation. The osmolar gradient caused by hyperglycemia in DKA results in a displacement of water from the intracellular to the extracellular space, which causes a decrease in cell volume due to loss of water and electrolytes through the urine, so sufferers of DKA tend to fall into cellular dehydration and decreased electrolyte levels, especially sodium and potassium. In addition, potassium decreases due to intracellular migration is also driven by a state of insulin deficiency and metabolic acidosis.<sup>6</sup> Such a thing has happened to our patient, even though at the beginning of the examination, there were no signs of dehydration in our patient, but during observation, suddenly developed signs of severe dehydration and shock, including decreased mental status, bradycardia, tachypnea with Kussmaul breathing, desaturation, cold extremities and obtained concentrated urine output.

The smell of ketones due to hyperglycemia which increases ketogenesis, also appears when the patient is in shock. Ketogenesis, which results in the excretion of ketone bodies through the urine, is also the cause of a decrease in potassium in the blood (hypokalemia), and it's proven by the result of hyponatremia and hypokalemia of electrolyte serum analysis. This is like the theory that loss of potassium in DKA cases occurs because of osmotic diuresis, reduced NaCl reabsorption, and ketonuria.

In DKA treatment, the important things to do are to give lots of fluids, give insulin, replace electrolytes, and find and treat what caused it in the first place. So that is why the main treatment for hyperglycemia is by administering fluid therapy (rehydration). Fluid therapy for acute hyperglycemia patients will have the effect of reducing blood glucose levels in hyperglycemia patients (80% of patients in the first four hours. The principle of fluid therapy is to initially

improve the balance of ECF (Extra Cell Fluid) in the body and maintain blood flow to the kidneys, if the fluid balances the body is fulfilled, giving fluid therapy will reduce blood glucose levels without depending on insulin and reduce levels of counter-insulin hormones which will ultimately improve sensitivity to insulin<sup>7</sup>.

Hypokalemia may be common in cases of diabetic ketoacidosis, but severe hypokalemia (<2.5 mmol/L) occurring before insulin treatment is extremely rare. Usually, potassium will decrease in greater amounts when followed by insulin treatment because insulin can promote displacements in intracellular potassium and potentially, insulin-like effects of aldosterone on the renal tubules result in increased loss of potassium through the urine (kaliuresis).<sup>8</sup>

Another risk factor that is also closely related to hypokalemia in diabetic individuals is the use of diuretics, especially thiazides and loop diuretics.<sup>9</sup> However, in our patient, it seems to have no effect considering from the anamnesis, the patient has no history of diabetes so there was no previous consumption of any antidiabetic drugs.

Even though we have administered intravenous rapid regulation therapy with insulin, electrolyte serum analysis that showed severe hypokalemia was carried out before insulin was given to the patient. However, based on the theory that insulin can exacerbate hypokalemia, administration of intravenous rapid regulation therapy with insulin aimed at lowering our patient's blood glucose level may exacerbate hypokalemia in these patients. Moreover, it is theorized that when intravenous fluids and insulin are administered to treat hyperglycemia, a rapid decrease in fluid osmolality can cause a reversal of the displacement in intracellular fluid, resulting in cerebral edema.<sup>9</sup>

The most common symptoms of cerebral edema associated with DKA include altered mental status (agitation, confusion, and sleepiness), severe headache, recurrent vomiting, seizures, hypertension, and bradycardia. The incidence of cerebral edema in DKA is closely related to the presence of

factors such as younger patient age, newly diagnosis of diabetes, severity of acidosis, lower pCO<sub>2</sub> values, higher urea levels, administration of bicarbonate, intravenous rehydration, use of hypotonic fluids, and rapid correction of hyperglycemia in the first 24 hours.<sup>10,11</sup>

Our patient met some of these criteria, in which the patient complained of headache and seemed agitated at the initial examination that continued to decreased consciousness in the emergency room and was found to have metabolic acidosis, and a history of administration of large volumes of fluid boluses and IV insulin within the first hours. So even though our patient has not had an imaging examination done, the possibility of cerebral edema may occur.

Other than antidiabetic drugs, in various literatures and several researchers have reported the relationship of ceftriaxone which can increase the development of hypokalemia by increasing the excretion of potassium in the urine.<sup>12</sup> Considering the presence of sepsis in our patient, the administration of antimicrobials in its management is also very necessary, but this does not rule out the possibility that this is a driving factor for increasingly severe hypokalemia.

Given the major role of potassium in the physiology of various tissues, organs and systems, its deficiency can lead to changes in cardiovascular, skeletal muscle, kidney function, even the release and effects of certain hormones.<sup>9</sup> This certainly does not rule out the possibility that the hypokalemic condition in our

patient brought our patient to a drastic deterioration in his condition to the point of cardiac arrest. In this group of patients, cardiovascular disorders are more common due to decreased excitability of myocardial cells and aortic smooth muscle cells and their repolarization which causes atrial and ventricular arrhythmias.<sup>13</sup> Consequently, hypokalemia can affect membrane potential and elicit a decreased response to stressful conditions, such as hypoxia and oxidative stress leading to the cessation of all muscle contractions. The most frequently observed ECG changes include arrhythmias, flattening of the T wave, ST segment depression, prolonged of the QT interval, presence of U waves, and multiple ventricular extrasystoles, which can be seen in up to 20% of patients with severe hypokalemia.<sup>9</sup> We also got the EKG picture clearly from our patient's ECG picture at the initial examination with the findings of sinus tachycardia, predominant depressed ST segment, flattened T wave and prominent U wave.

Our patient case highlights how severe hypokalemia in diabetic ketoacidosis can rapidly worsen a patient's prognosis. Even though all therapies are already given according to the guidelines, the possibility of complications must still be watched out for, especially when one therapy gives adverse effects to each other. For this reason, further research is needed to find the most appropriate combination of therapy that can minimize the occurrence of complications if similar cases are found later.

Table 1. Related Studies

No	Title	Authors	Year Published	Highlights
1.	Diabetic Ketoacidosis with Severe Hypokalemia and Persistent Hypernatremia in an Adolescent Girl with COVID-19 Infection <sup>2</sup>	Badawy MK, Viswanath V, Khetriwal B, Pradhan S, Williams RM, Pathan N, Marcovecchio ML	2022	Hypokalemia in DKA likely results from a combination of kaliuresis, secondary to prolonged osmotic diuresis, inadequate oral intake, and gastrointestinal losses from diarrhea or vomiting. Kaliuresis is also driven by secondary hyperaldosteronism from profound losses of sodium and extracellular volume.
2.	Profound Hypokalemia	Davis SM, Maddux AB, Alonso GT,	2016	Total body potassium depletion is expected in DKA largely due to osmotic renal losses.

Associated with Severe Diabetic Ketoacidosis <sup>12</sup>	Okada CR, Mourani PM, Maahs DM	Measurement of extracellular serum potassium in DKA patients with severe acidosis greatly underestimates the total body potassium deficit in these patients due to the extracellular potassium shift caused by insulin deficiency and metabolic acidosis. In normal adults, approximate total body content of potassium is 50 mEq/kg and 98% is contained intracellularly. In DKA patients with severe hypokalemia, potassium deficit can reach 10 mEq/kg. Treatment with insulin usually results in a decrease in the measured serum potassium due intracellular potassium shifts and, potentially, an aldosterone-like effect of insulin on the renal tubule that further increases urinary potassium losses.
3. The Clinical Caveat for Treating Persistent Hypokalemia in Diabetic Ketoacidosis <sup>13</sup>	Khiatah B, Frugoli A, Carlson D	According to a study conducted at the University of Southern California, the prevalence of hypokalemia in patients with DKA is 5.6%. It has been a clinical challenge to treat DKA patients with profound refractory hypokalemia. With the current guideline advising against initiating insulin therapy due to fear of cardiac arrhythmia, many patients face another life-threatening acidosis, cardiac arrhythmia due to hypokalemia, and severe neural complications.

However, the patient's condition is quite complex. There are many conditions that accelerate worsening conditions. Severe dehydration in the patient leads to decreased urine output and increased urine concentration, resulting in reduced tissue perfusion and a rapid decline in the patient's overall condition. Additionally, severe hypokalemia further complicates the management of lowering blood sugar levels, as insulin administration can lower potassium levels by increasing Na-K-ATPase activity. Aggressive insulin therapy aimed at reducing blood sugar levels can exacerbate the patient's hypokalemia, potentially affecting the functioning of the heart. Furthermore, the presence of sepsis in this patient has progressed to septic shock, leading to a significant and rapid deterioration compared to the patient's initial condition.

In cases of suspected diabetic ketoacidosis (DKA), optimal treatment of hypokalemia requires identification of underlying

causes and management of associated disorders. Key guidelines for potassium replacement emphasize the importance of blood gas and renal function tests to guide replacement therapy. Initial rehydration with normal saline solution is recommended until serum potassium levels normalize. Insulin administration should be withheld if blood potassium levels are below 3.3 mmol/L to prevent insulin-induced hypokalemia.

## CONCLUSION

The management of diabetic ketoacidosis patients with severe hypokalemia indeed poses a serious dilemma. Administration of intravenous fluids and insulin intended to treat hyperglycemia can cause intracellular fluid displacement and produce hypokalemia. Meanwhile, severe hypokalemia can lead to the cessation of all muscle contractions and cerebral edema which ends in cardiac arrest. Therefore, it is crucial to investigate any

potential causes of hypokalemia in patients to prevent the exacerbation of their condition and improve outcomes.

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## Diagnostic and Management of Idiopathic Panhypopituitarism Patient: A Case Report

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### ABSTRACT

Hypopituitarism is marked by decreased secretion of one, several, or all anterior or posterior pituitary hormones. A rare disorder, panhypopituitarism indicates the loss of all the pituitary hormones but often is used in clinical practice to describe a patient's deficiency in growth hormone, gonadotropins, corticotropin, and thyrotropin in whom the posterior pituitary function remains intact. Hypopituitarism may occur because of diverse etiologies and lead to substantial morbidity and mortality. Despite advances in the diagnosis and management of pituitary disorders, hypopituitarism is still associated with increased long-term cardiovascular mortality. We report a rare case of a 22-year-old boy with idiopathic panhypopituitarism. The patient has deficiency of growth hormone, gonadotropin, corticotropin, and thyrotropin, yet the underlying etiology remains unknown in this patient because of lack of imaging data. This is very challenging to do prompt diagnosis and management of panhypopituitarism. The management needs multiple hormone replacement therapy, based on the result of pituitary hormone laboratory examination. Prompt treatment is needed to prevent further morbidity and mortality in this patient.

**Keywords:** Panhypopituitarism, hypoadrenalinism, hypogonadism, hypothyroidism, growth hormon

## INTRODUCTION

Hypopituitarism is a deficiency of one or more hormones secreted by the anterior or posterior pituitary gland.<sup>1,2</sup> Panhypopituitarism indicates loss of all pituitary hormones but is often defined in clinical practice as a deficiency of growth hormone (GH), gonadotropins, corticotropins, thyrotrophins with intact posterior pituitary hormone function.<sup>2,3</sup> Hypopituitarism is a rare condition with a prevalence of 46 cases per 100,000 population.<sup>4</sup> In Spain, the prevalence is 45.5 cases per 100,000 population. The incidence is 4.2 cases per 100,000 population per year and increases with age.<sup>4</sup> According to the National Institutes of Health, a rarer condition, panhypopituitarism, affects only 200,000 patients in the United States.<sup>3</sup> Causes of hypopituitarism include pituitary tumors (61%), non-pituitary lesions (9%), and non-cancerous causes (30%), including 11% of idiopathic causes. Other causes that are classically rare are perinatal insults, genetics, or trauma.<sup>5</sup>

Given the complexity of hypopituitarism, it is very important for clinicians to be able to correctly diagnose this condition. Therefore, this case report will discuss the diagnosis and management of a case of panhypopituitarism suffered by a 22-year-old man. Hopefully this case report can increase clinician knowledge in terms of diagnosing and managing panhypopituitarism, so that mortality can be reduced.

## CASE ILLUSTRATION

A male patient aged 22 years, Lombok ethnicity, came with the chief complaint of a delay in height growth that has been felt since the patient he was 9 years old. It is said that his height increases more slowly than his peers. The patient also complained that the small penis and the left testicles smaller than the right testicles. The testicles of the patient on the left are also smaller than the testicles on the right.

The patient's voice sounded like a child for the last 7 years or so. The patient also said that he had not experienced secondary sexual growth such as pubic and armpit hair and had no libido. It was said that his intellectual abilities

also did not develop well, so the patient missed several grades at the elementary and junior high school levels. Patients also complained of weakness all the time, even when he was not active. The patient did not complain of visual or olfactory disturbances, and no appetite disturbances. The patient did not experience appetite disturbances and activities can be carried out as usual. Complaints of headaches, dizziness, nausea, and vomiting were denied.

The patient was in first grade of high school and the patient was the fourth child of four siblings. Both of his parents are normal and do not experience any hormonal disturbances, so do the patient's three siblings. The patient was said to have been born via vaginal delivery (breech presentation) and during delivery there were no notable complications. The patient was born healthy. He had a history of seizures accompanied by fever when he was 6 months old, but the family did not know the cause of the febrile seizures. The history of drug use and accidents as well as head trauma were denied by the patient and the patient's family. History of other diseases such as diabetes mellitus, congenital heart disease or kidney disease were denied by the patient and his family. At 9-year-old the patient went to a hospital in Surabaya and received hormone therapy, but the treatment was stopped voluntarily.

On physical examination, the general condition was good, and the patient was alert. Blood pressure was 110/70 mmHg, pulse rate was 88 times per minute, respiratory rate was 18 times per minute, axillary temperature was 36.7°C. The head and neck examination were within normal limits, no lymph nodes enlargement. Examination of the chest impression was within normal limits. Abdominal examination was also within normal limits, no enlargement of the liver or spleen. Extremities felt warm. There were no signs of secondary sex growth including axillary hair. Examination of the genitalia region showed the absence of pubic hair, the penis was small, and the left testicle was smaller (left testicles was barely palpable) than the right one (right testicles still palpable).

Anthropometric measurements taken on July 2020 found as such: height 147 cm, body weight 39 kg, head circumference 56 cm, upper arm circumference 22 cm, abdominal circumference 72 cm. The height of the patient's biological father was 170 cm while the patient's biological mother was 165 cm. The calculation of the genetic potential height of a boy was

$[(\text{Mother's Height (cm)} + 13 \text{ cm}) + \text{Father's Height (cm)}] / 2 \pm 8.5 \text{ cm}$ . So, the patient's genetic potential height calculation is  $[(165 + 13 \text{ cm}) + 170] / 2 \pm 8.5 \text{ cm}$  resulting in 165.5-174 cm. Currently, the patient's height can be categorized as having not reached the genetic potential height.



The first laboratory examination was carried out at the Endocrine clinic on August 25, 2019. The result of hormone examination were as follow: Thyroid-Stimulating Hormone (TSH) 2.311  $\mu\text{IU}/\text{mL}$  ( $N = 0.35$ - $4.94 \mu\text{IU}/\text{mL}$ ), free T4 (FT4) 0.61 ng/dL ( $N = 0.79$ - $1.34 \text{ ng/dL}$ ), testosterone  $\leq 2.5 \text{ ng/ mL}$  (normal levels depending on Tanner stage), prolactin 6.07 ng/ml ( $N = 4.3$  - $23.04 \text{ ng/ml}$ ), morning serum cortisol  $<0.8 \mu\text{g/dL}$  ( $N=3.7$ - $19.4 \mu\text{g/dL}$ ), IGF-1  $<15$

ng/mL (57-426 ng/ mL). The HbA1c level was 4.6% ( $N \leq 6.5\%$ ). Follicle stimulating hormone (FSH) levels were found to be 0.1 mIU/ml ( $N= 0.49$ - $9.98 \text{ mIU /ml}$ ), luteinizing hormone (LH)  $<0.5 \text{ mIU/mL}$  ( $N= 0.78$ - $4.93 \text{ mIU/mL}$ ).

Complete blood results showed the following values: leukocyte levels  $5.91 \times 10^3/\mu\text{L}$  ( $4.10$  - $11.0 \times 10^3/\mu\text{L}$ ), lymphocytes  $3.00 \times 10^3/\mu\text{L}$  ( $1.00$ - $4.00 \times 10^3/\mu\text{L}$ ), monocytes  $0.32 \times 10^3/\mu\text{L}$ .

$^3/\mu\text{L}$  ( $0.10-1.2 \times 10^3/\mu\text{L}$ ), eosinophils  $0.53 \times 10^3/\mu\text{L}$  ( $0.00-0.5 \times 10^3/\mu\text{L}$ ), basophils  $0.07 \times 10^3/\mu\text{L}$  ( $0.00-0.1 \times 10^3/\mu\text{L}$ ), neutrophils  $1.99 \times 10^3/\mu\text{L}$  ( $2.50-7.50 \times 10^3/\mu\text{L}$ ), hemoglobin  $10.38 \text{ g/dL}$  ( $13.5-17.5 \text{ gr/dL}$ ), hematocrit  $30.6\%$  ( $41-53\%$ ), MCV  $76.32 \text{ fL}$  ( $80-100 \text{ fL}$ ), MCH  $25.89 \text{ pg}$  ( $26-34 \text{ pg}$ ), platelets  $216.2 \times 10^3/\mu\text{L}$  ( $150-440 \times 10^3/\mu\text{L}$ ), Serum Glutamic Oxaloacetic Transaminase (SGOT)  $77.0 \text{ U/L}$  ( $11-33 \text{ U/L}$ ), Serum Glutamic Pyruvic Transaminase (SGPT)  $53.2 \text{ U/L}$  ( $11-50 \text{ U/L}$ ), Blood Urea Nitrogen (BUN)  $8.4 \text{ mg/dL}$  ( $8-23 \text{ mg/dL}$ ), serum creatinine  $0.71 \text{ mg/dL}$  ( $0.7-1.2 \text{ mg/dL}$ ), sodium  $137 \text{ mmol/L}$  ( $136-145 \text{ mmol/L}$ ) and potassium  $4.14 \text{ mmol/L}$  ( $3.5-5.1 \text{ mmol/L}$ ). Considering that the Hb level is less than the normal range, the peripheral blood smear, Serum Iron (SI), TIBC, and ferritin were examined. Examination of the peripheral blood smear found normochromic normocytic erythrocytes, normal leukocyte count, no

immature cells, and toxic granulosa, negative vacuolization, normal platelet count, and no giant platelets. Conclusion of peripheral blood with normochromic normocytic anemia. Meanwhile SI levels were  $97.38 \text{ ng/dL}$  ( $65-175 \text{ ng/dL}$ ), TIBC  $289 \text{ ng/dL}$  ( $261-478 \text{ ng/dL}$ ), ferritin  $84.64 \text{ (30-400 ng/dL)}$ . Hepatitis virus marker examination was also carried out due to an increase in liver enzymes but was found to be negative for both HbsAg and anti HCV. This liver enzyme examination was repeated, and other liver function tests were also carried out. On repeat examination, levels of SGOT  $28.1 \text{ U/L}$  ( $11-33 \text{ U/L}$ ), SGPT  $20.3 \text{ U/L}$  ( $11-50 \text{ U/L}$ ), total bilirubin  $0.34 \text{ mg/dL}$  ( $0.30-1.30 \text{ mg/dL}$ ), direct bilirubin  $0.15 \text{ mg/dL}$  ( $0.00-0.3 \text{ mg/dL}$ ), indirect bilirubin  $0.19 \text{ mg/dL}$ , alkaline phosphatase  $105 \text{ U/L}$  ( $53-128 \text{ U/L}$ ), total protein  $7.6 \text{ g/dL}$  ( $6.4-8.3 \text{ g/dL}$ ), albumin  $4.8 \text{ g/dL}$  ( $3.2-4.5 \text{ g/dL}$ ), gamma GT  $25 \text{ U/L}$  ( $11-49 \text{ U/L}$ ).

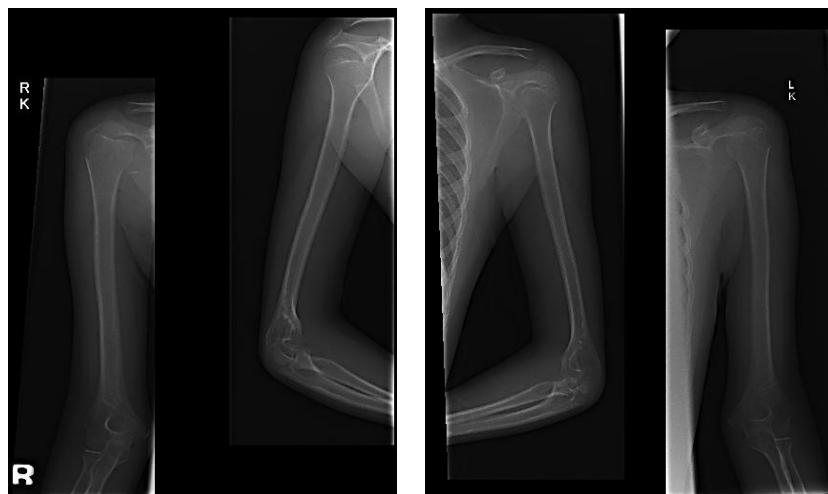


Figure 1. Left: X-ray photo of the right elbow; Right: X-ray photo of left elbow.

Due to sub optimal height compared to the genetic potential, a radiological examination was carried out to determine bone age and epiphyseal plate closure. Plain AP/lateral x-ray of the right and left elbows showed that the epiphyseal plate of both proximal radius bone, no fractures or dislocations were seen at the location of both elbows (Figure 2). Plain AP/lateral x-ray of the right and left femurs showed growth plates on both femur bones, and

no bone fractures or joint dislocations were seen (Figure 3). Meanwhile, on the AP/lateral manus x-ray, a bone age picture of a 13-year-old boy was obtained (according to the Atlas of Hand Bone Age) (Figure 4). From the history, physical examination, results of hormonal and radiological examinations performed on this patient, it can be concluded that the patient suffered from panhypopituitarism.

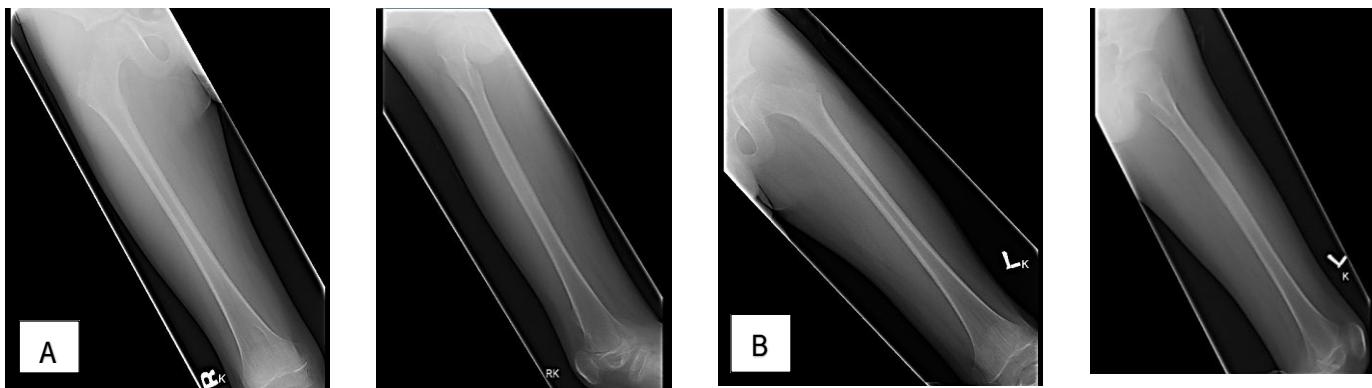


Figure 2. A, AP/lateral plain radiograph of the right femur; B, AP/lateral plain radiograph of the left femur.

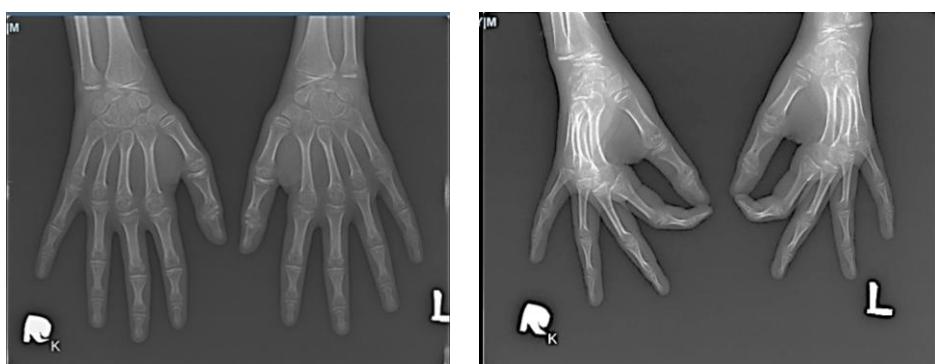


Figure 3. AP/lateral manus plain radiograph X-ray.

The patient also underwent several imaging tests. Figure 4 shows the results of an ultrasound imaging of the testicles with a picture of the right scrotum, testicles measuring  $1.15 \times 0.67 \times 1.03$  cm (volume 0.56 cc), normal echoparenchime with no visible nodules or masses or calcifications, normal epididymis, no intrascrotal abnormal free fluid. In the

left scrotum, testis measuring  $1.24 \times 0.7 \times 0.8$  cm (0.49 cc volume), normal echoparenchime, no visible nodules/ mass/ calcifications, normal epididymis, no intrascrotal abnormal free fluid. From the results of testicular ultrasound, it can be concluded that the size and volume of the right and left testicles matched the testicles in children aged 9 months to prepuberty.

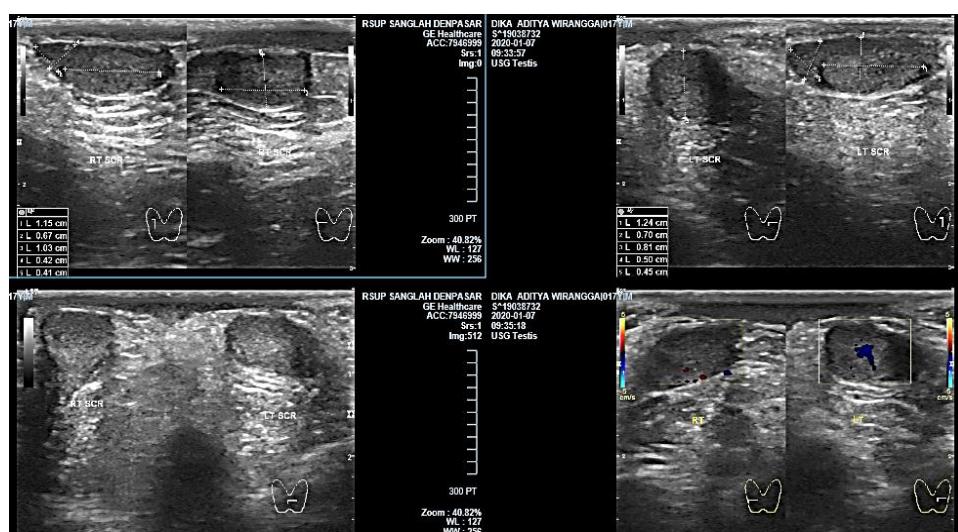


Figure 4. Ultrasoundography result of patient's testicles

After the first pituitary hormone examination, the patient was then given hydrocortisone treatment (10 mg in the morning and 5 mg in the afternoon) and planned to receive GH. However, due to the patient's busy school activities, GH administration could only be given from July 2020 at a dose of 0.2 mg subcutaneous injection per day. GH therapy

which had been done for 30 days, later was discontinued due to insurance issues. The patient also received levothyroxine therapy 100 mcg per day and testosterone hormone replacement 250 mg intramuscularly per month. Figure 5 is a summary of the patient's disease history and treatment.

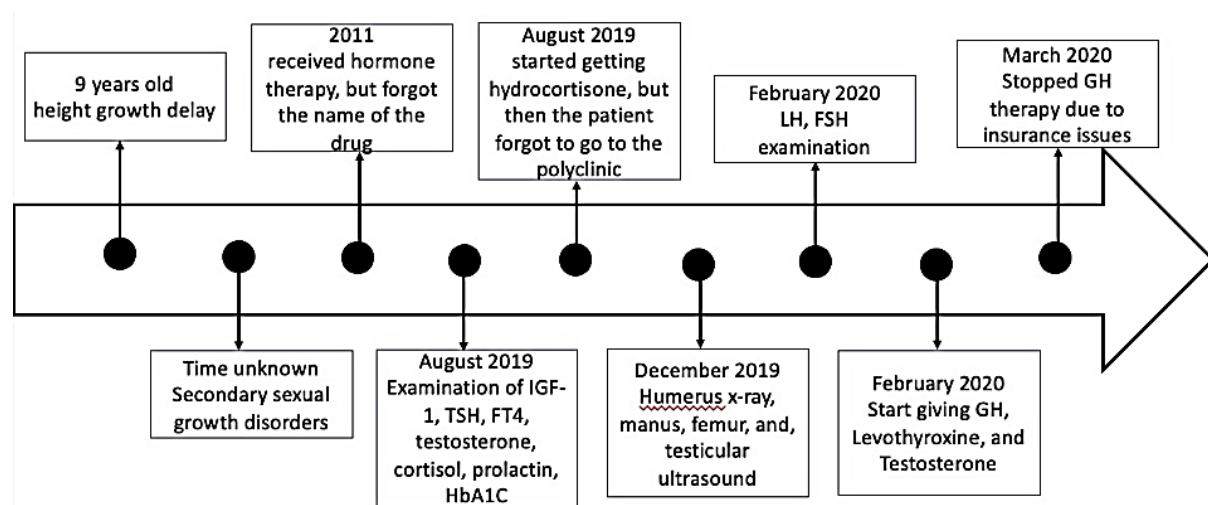


Figure 5. Timeline and course of the disease.

## DISCUSSION

The pituitary gland itself is supplied by blood that comes from branches of the internal carotid artery. These branch vessels form a plexus in the region of the median eminence of the hypothalamus. Blood from this branching area then reaches the anterior pituitary via the pituitary stalk. The middle and inferior pituitary arteries supply the pituitary stalk and neurohypophysis. However, the anterior lobe is not included in the blood supply of this artery; it receives oxygenated blood via the internal plexus and external median eminence. Through the regulation of hypothalamic releasing factor, hypothalamic inhibiting factor, and peripheral hormonal negative feedback inhibition, the anterior pituitary produces adrenocorticotrophic hormone (ACTH), thyrotropic hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), and GH. The posterior pituitary is a storage organ for the hypothalamic antidiuretic hormone (ADH) and oxytocin hormones.

The mechanism by which hypopituitarism (including panhypopituitarism) develops depends on the cause of the disease and may not be fully understood in some cases. Table 1 shows the causes of hypopituitarism. In determining the cause of hypopituitarism, it is recommended to perform pituitary imaging. In this case magnetic resonance imaging (MRI) of the sella is the first choice for assessing the sella region.<sup>1</sup> In this case, an MRI examination has not been carried out, so the exact cause of hypopituitarism is not yet known. In making the diagnosis of panhypopituitarism, it is necessary to evaluate the clinical picture and examination of the pituitary hormone. Pituitary hormone deficiency will cause various clinical symptoms depending on the hormone deficiency that occurs (Table 2). In this case, the patient showed symptoms of deficiency of corticotropin, thyrotropin, gonadotropin, and GH hormones in the form of chronic weakness, delayed puberty, loss of libido, cognitive delay, and growth retardation. Symptoms of ADH deficiency were not found.

**Table 1.** Causes of hypopituitarism<sup>3</sup>

Cause of hypopituitarism	
<b>Brain damage</b>	<b>Infection</b>
<ul style="list-style-type: none"> <li>- Traumatic brain injury</li> <li>- Subarachnoid hemorrhage</li> <li>- Neurosurgery</li> <li>- irradiation</li> <li>- Strokes</li> </ul>	<ul style="list-style-type: none"> <li>- Apoplexia</li> <li>- Sheehan's Syndrome</li> <li>- <b>Autoimmune Disease</b></li> <li>- Pituitary lymphocytic</li> </ul>
	<b>Haemochromatosis, granulomatous disease, histiocytosis</b>
<b>Pituitary tumors</b>	<b>Empty sella</b>
<ul style="list-style-type: none"> <li>- Adenomas</li> <li>- Etc.</li> </ul>	<b>Perinatal insult</b>
<b>Non-pituitary tumor</b>	<b>Pituitary hypoplasia or aplasia</b>
<ul style="list-style-type: none"> <li>- Craniopharyngiomas</li> <li>- Meningioma</li> <li>- Glioma</li> <li>- Chordoma</li> <li>- Ependymoma</li> <li>- Metastases</li> </ul>	<b>Genetic cause</b>
	<b>Idiopathic cause</b>

Thyrotropin deficiency can be diagnosed by testing TSH and free T4 (FT4). In panhypopituitarism, central hypothyroidism will be found, in which FT4 level is low and TSH level is low or normal (Table 3).<sup>1</sup> Examination of

thyroid function in this case showed that the patient had central hypothyroidism, considering that the Free T4 level was 0.61 ng/dL (low) and TSH was 2.311 µIU/mL (normal).

**Table 2.** Clinical features and investigation findings of hypopituitarism<sup>1,5</sup>

	Investigative findings
<b>Corticotropin Deficiency</b>	
Chronic: Chronic weakness, pallor, anorexia, weight loss	Hypoglycemia, hypotension, anemia, lymphocytosis, eosinophilia, hyponatremia
Acute: Acute weakness, spinning dizziness, nausea, vomiting, circulatory collapse, fever, shock	-
Children: delayed puberty, failure to thrive	-
<b>Thyrotropin Deficiency</b>	
Fatigue, intolerance to cold, constipation, hair loss, dry skin, hoarseness, cognitive delay	Weight gain, bradycardia, hypotension
Children: growth and development disorders	-
<b>Gonadotropin Deficiency</b>	
Women: oligomenorrhea, loss of libido, dyspareunia, infertility	Osteoporosis
Men: loss of libido, loss of sexual function, absence of facial, scrotal and trunk hair	Decreased muscle mass, osteoporosis, anemia
Child: delayed puberty	-
<b>Growth Hormon Deficiency</b>	
Reduced muscle mass and strength, visceral obesity, fatigue, decreased quality of life, impaired attention and memory	Dyslipidemia
Child: growth retardation	-
<b>Prolactin Deficiency</b>	
Women: failure to lactate in post-partum conditions	-
Man: no consequence	-
<b>Anti Diuretic Hormon deficiency</b>	
Polyuria, polydipsia	Decreased urine osmolality, hypernatremia, polyuria

Secondary hypogonadism or hypogonadotropic hypogonadism (HH) is a condition that occurs due to deficiency of gonadotropins (FSH and LH). The diagnosis of HH is established in the second or third decade (after the age of 18 years), in which the patient will experience clinical symptoms in the form of loss of libido, delay or absence of signs of secondary sex growth which include eunuchoid body proportions, infertile, unilateral and/or bilateral cryptorchidism and micropenis in man.<sup>5</sup> The symptoms and clinical manifestations of HH in these patients are decreased libido and tend to be absent altogether, as well as secondary sex development disorders (absence of hair on the armpits and penis, and micropenis). The diagnosis of HH is established when there is a decrease in the levels of the hormones FSH, LH, and testosterone. In our case we found very low

testosterone levels of <2.5 ng/dL, FSH level of 0.1 mIU/ml (N= 0.49–9.98 mIU/ml), and LH <0.5 mIU/mL (N= 0.78–4.93 mIU/mL).

In general, to diagnose GH deficiency, stimulation examination is required (Table 3), unless all pituitary axes are deficient and IGF-1 levels are low. According to Schneider HJ et al., An insulin tolerance test is the best choice, but it should be noted that not all GH deficiency tests are 100% reliable.<sup>5</sup> The probability that GH deficiency will be proven through this test will increase as the number of pituitary hormone deficiencies increases. In our case, patient showed clinical growth retardation, the patient also had low IGF-1 levels (IGF-1 <15 ng/mL). Our patient also has other pituitary axis deficiencies, thereby strengthening the diagnosis of a GH deficiency.

Table 3. Endocrine examination to evaluate pituitary function<sup>1,5</sup>

	Hormone deficiency criteria
<b>Corticotropin Function</b>	
• Morning cortisol	<100 nmol/L: hypocortisolism; >500 nmol/L: hypocortisolism excluded
• ACTH in the morning	Below normal reference range: secondary adrenal insufficiency
• Insulin tolerance test	Cortisol <500 nmol/L
• 250 µg ACTH test	Cortisol <500 nmol/L after 30 minutes
<b>Thyrotropic Function</b>	
• Free T4	Low (<11 pmol/L)
• TSH	Low or normal (sometimes slightly increased)
<b>Gonadotropic Function</b>	
• Woman	Oligomenorrhea, estradiol <100 pmol/L, low LH and FSH
Clinical	
Post menopause	Low LH and FSH
• Man	
Testosterone	Low (<10-12 nmol/L), LH and FSH
<b>Somatotropic Function</b>	
• IGF-1	Below normal value
• Insulin tolerance test	Adult: GH ≤3 µg/L Child: GH≤10 µg/L Transition phase: GH ≤5 µg/L
• GHRH + arginine test	Underweight or normal BMI (BMI<25): 11.5 µg/L Overweight (BMI ≥ 25 to <30): 8 µg/L Obesity (BMI ≥30): 4.2 µg/L
• GHRH+GHRP-6 test	GH≤10µg/L
<b>Prolactin function</b>	
• prolactin serum	Not detected
<b>Posterior Pituitary Function</b>	
• Basal urine, plasma samples	Urinary volume (≥40 ml/kg/day) + urine osmolality <300 mOsm/kg + hypernatremia
• Water deprivation test	Urinary osmolality <700 mOsm/kg; urine to plasma osmolality ratio <2

The principle in management of panhypopituitarism is in the form of hormone replacement therapy that mimics the normal physiological pattern of hormones as much as possible. For conditions of corticotropin deficiency (ACTH), according to the recommendations of the Endocrine Society Clinical Practice Guideline, patients can be given oral hydrocortisone 15-20 mg per day in single doses or divided doses.<sup>7</sup> In this case the patient was given oral hydrocortisone therapy 10 mg in the morning then 5 mg in the afternoon (total 15 mg per day). Meanwhile, for thyrotropin (TSH) deficiency, initiation of levothyroxine administration can be done when Free T4 levels begin to decrease (no need to wait until FT4 levels are below normal). In this case, the patient was given 100 mg of levothyroxine per day and this dose was in accordance with the recommended dose in young patients (without evidence of heart disease), which is 75-100 mcg per day (1.6-1.8 mcg/kg/day).<sup>7,8</sup>

The management of HH in this patient is to replace the existing hormone deficiency and improve the patient. This patient received testosterone hormone replacement at a dose of 250 mg intramuscularly monthly. The presence of androgen hormones will improve male libido and erectile function. Another effect is to increase muscle mass and strength, increasing bone density and homeostasis which will prevent early osteoporosis in men.<sup>9</sup>

GH deficiency in this patient had been treated by subcutaneous injection of GH at a dose of 0.2 mg per day. Before it was decided whether this patient can be given GH or not, bone age must be checked, and the epiphyseal plate must be identified whether it had closed or not. Through radiological examination, it was found that the patient's epiphyseal plate had not closed yet, and the patient had not reached his genetic height, so GH administration was indicated. According to the Endocrine Society Clinical Practice Guideline, the recommended initial dose for patients younger than 60 years is 0.2-0.4 mg per day.<sup>7</sup> The dosage recommendation for GH is different from the

dosage recommendation issued by the Pediatric Formulary Committee, which is 23-39 mcg/kg/day.<sup>10</sup> The patient was finally unable to continue GH injections due to cost issues.

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## Primary Adrenal Insufficiency due to Tuberculosis Infection: Pitfalls in Diagnosis and Management

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### ABSTRACT

Primary adrenal insufficiency (PAI) is a chronic condition in which both adrenal glands cannot produce steroid hormones. In this article we reported a 20-year-old male with history of soft tissue tumor in thoracal region and general hyperpigmentation of skin and mucous. Laboratory findings showed hypocortisolism and adrenal computed tomography (CT) scan showed bilateral enlargement of adrenal with multiple necrotic nodular lesion and calcification, suggesting adrenal metastasis or tuberculosis infection. The interferon gamma release assay (IGRA) and histopathology review of the specimen from soft tissue tumor in thoracal region showed confirmed the diagnosis of adrenal tuberculosis. Antituberculosis drugs were started, and hydrocortisone dose were frequently adjusted. Five months after therapy the patient is clinically improved with a minimal dose of steroid.

**Keywords:** Addison disease primary, adrenal insufficiency, hypocortisolism, adrenal, tuberculosis

## INTRODUCTION

Primary adrenal insufficiency (PAI) is a chronic condition in which both adrenal glands are not able to produce steroid hormones. Back in 1855, Thomas Addison described six cases of bilateral adrenal destruction due to tuberculosis infection. As an anti-tuberculosis drug was introduced, the incidence of adrenal tuberculosis worldwide rapidly decreased. Nowadays in the western world, the most common cause of primary adrenal insufficiency is autoimmune disease, yet in many developing countries bilateral adrenal infection including tuberculosis, histoplasmosis, and human immunodeficiency virus is still common. Left undiagnosed and untreated, this will lead to fatal condition of adrenal crisis.<sup>1,2</sup>

Commonly, adrenal tuberculosis is secondary to tuberculosis infection elsewhere and affects both adrenals. It spreads through hematogenous route to adrenal glands. Symptoms of adrenal tuberculosis are not specific and slowly developed due to the chronic nature of *M. tuberculosis* bacteria. To give full-blown symptoms of adrenal insufficiency, both adrenal glands must have been destroyed up to 90%.<sup>3</sup> General symptoms of tuberculosis such as anorexia, malaise, fever are not specific and often overlooked by most patients. Both computed tomography scan (CT-scan) and magnetic resonance imaging (MRI) cannot precisely differentiate between adrenal tuberculosis and other bilateral adrenal pathologies such as adrenal malignancy, metastasis, hemorrhage, or fungal infections.

The commonly used of fluorodeoxyglucose positron emission tomography (FDG-PET) scan to diagnose malignancy can also lead to falsely positive results because any underlying chronic inflammation will also be shown as hot spots in FDG-PET scan indicating possible malignancy.<sup>4</sup> Definitive histology diagnosis through laparoscopic biopsy is quite invasive, expensive, not widely available, and easily turned down by many patients. In this paper, we report a diagnostic difficulties and management of primary adrenal insufficiency in a young-

male patient, highlighting the need of aggressive trait of suspiciousness from clinicians in the setting of limited resources.

## CASE ILLUSTRATION

A 20-year-old male patient was referred to Endocrinology Clinic of Cipto Mangunkusumo Hospital with a two-year history of general hyperpigmentation of the skin. The hyperpigmentation started from fingers, toes, gum, and continued spreading to whole skin. Fever, malaise, and anorexia were absent although patients complained about not gaining weight over the years. Other symptoms of low energy level, worsening fatigue, salt craving, loss of libido, and erectile dysfunction were also absent. The patient denied having contact with tuberculosis patients or any people with chronic cough. The patient also complained of having soft tissue tumor in his chest. Previous illness and family history were unsignificant. The patient was not on any medication or substances. At that point, the patient consulted a skin specialist and was given systemic and topical treatment for the hyperpigmentation yet did not show any improvement. As for the tumor in the chest, the patient had it removed, and the histopathology showed non-specific chronic inflammation.

One year later, the patient complained of having anorexia, unintended weight loss up to 10 kg, and easily feeling tired during exercise. Patient consulted to private hospital and was suspected to have hormonal problems. The patient was then referred to Cipto Mangunkusumo Hospital. On his first visit to our hospital, physical examination showed general hyperpigmentation of skin and gum. Vital signs and other organ examinations were within normal limit. Considering history and physical findings, we were suspicious that the patient had low level of cortisol and began the investigation for adrenal insufficiency.

Initial laboratory findings showed very low level of morning cortisol (1.1 ug/dL) and low blood sugar level (2-hour-post meal 95 mg/dL). Sodium, potassium, and calcium levels were still within normal limit. To confirm the diagnosis and

determine the cause of hyporcortisolism, cosyntropin stimulation test (CST) along with

basal adrenocorticotrophic hormone (ACTH) level measurement were scheduled.



Figure 1. General hyperpigmentation and scar of post-removal soft tissue tumor in thoracal region.

During that waiting period, the patient experienced worsening fatigue with blurry vision and was rushed to the emergency room. At admission, the patient was found lethargic and hypotensive (blood pressure 90/60 mm/Hg). Laboratory findings showed severe hyponatremia (111 mEq/L), hypoglycemia (70 mg/dL), and hyperkalemia (5 mEq/L). The patient was assessed with adrenal crisis and started given intravenous hydrocortisone. The initial dose of hydrocortisone given was 100 mg twice

daily for three days and tapered off accordingly. We also obtained measured ACTH level and the result was within normal limit (14 pg/mL). However, this result was neither reliable nor valid as it was taken after the patient had been given intravenous hydrocortisone for 3 days. After being hospitalized for seven days, the patient was clinically improved and discharged with oral hydrocortisone. The total hydrocortisone dose given during hospitalization was 900 mg.

Table 1. Laboratory Findings

	Reference	Initial (April 4 <sup>th</sup> )	Emergency room (June 27 <sup>th</sup> )	Hospital ward (June 30 <sup>th</sup> )
Cortisol	3.7 - 19.4 ug/dL	1.1		128*
ACTH	6 - 40 pg/mL			14*
TSHs	0.35 - 4.94 µIU/mL	3.392		
Prolactin	3.46 -19.4 ng/mL	31.2		
Potassium	3.5 - 5.1 mEq/L	3.5	5	
Natrium	136 - 145 mEq/L	135	111	
Fasting blood glucose	<100 mg/dL	85		
Post-prandial glucose	<200 mg/dL	95		

\*Sample was taken while patient on intravenous hydrocortisone

On his follow-up visit at endocrinology clinic, the investigation of adrenal insufficiency was resumed aiming to find the root of the condition while continuing oral hydrocortisone. The abdominal CT-scan showed bilateral enlargement of adrenal with multiple necrotic nodular lesion and calcification, suggesting adrenal metastasis or adrenal tuberculosis. Laparoscopic biopsy of adrenal was considered, but the patient and his family preferred any non-invasive diagnostic method and put surgery as the last option. Evaluation of several tumor markers such as carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), lactate dehydrogenase (LDH), and cyfra-21 came back negative. The viral marker for chronic hepatitis infection and antibody against HIV infection also showed negative results. The Interferon Gamma Release Assays (IGRA) test was positive suggesting tuberculosis infection. This finding was strengthened by the re-expertise result of histopathology specimen from soft tissue tumor in thoracal region that showed granuloma, Datia Langhans cell, and caseous necrosis area compatible with chronic tuberculosis infection.



Figure 2. Adrenal contrast CT-scan showing bilateral adrenal enlargement with calcification and necrosis.

Following these findings, the patient was started with category 1 anti-tuberculosis drugs (ATD) and adjusted dose of oral hydrocortisone was continued accordingly. There were not either significant side effects of ATD or drug interaction between ATD and hydrocortisone. Three months after initiation of ATD and the oral hydrocortisone dose was tapered to only 10 mg once daily. Evaluation of

morning plasma cortisol level was obtained by previously putting off hydrocortisone one day before the examination and the result of morning plasma cortisol level was 8.2 ug/dL. Even though the result was quite promising, the ultimate target of treatment for this patient is to have a- working-hypophyseal-adrenal axis. To evaluate this axis, a short synacten test will be the most appropriate approach. So, the patient was scheduled to have the test when the daily hydrocortisone dose used is close to physiologic dose of endogenous cortisol secretion and clinically stable. Anatomic improvement of adrenal gland will also be evaluated using abdominal CT scan and was scheduled after completion of ATD.

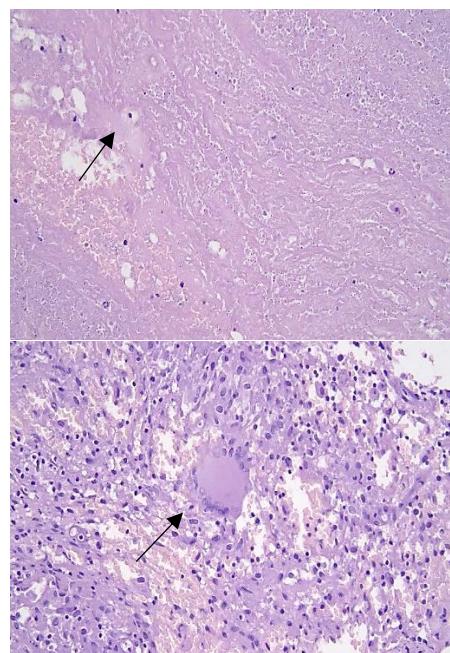


Figure 3. Histopathology finding of thoracal soft tissue tumor showing Datia Langhan's cell and caseous necrosis.

## DISCUSSION

Primary adrenal insufficiency is a condition when both adrenal glands were destroyed poor enough to not be able to produce enough cortisol and other adrenal hormones. The destruction of the glands can be caused by autoimmunity, malignancy, surgery or trauma, hemorrhage and thrombosis, infiltration, or chronic infection. Table 2 showed different causes of primary adrenal insufficiency.<sup>5</sup>

Different from western world where autoimmune diseases are the most common cause of PAI, in many developing countries including Indonesia,

chronic infection such as histoplasmosis, histiocytosis, tuberculosis, and HIV are the most frequent culprit.<sup>1,2</sup>

Table 2. Causes of primary adrenal insufficiency<sup>5</sup>

Causes	Prevalence (%)
Autoimmune adrenalitis <ul style="list-style-type: none"> <li>• Isolated adrenal insufficiency</li> <li>• PAS type I, II</li> </ul>	70-90
Infectious adrenalitis <ul style="list-style-type: none"> <li>• Tuberculosis</li> <li>• HIV infection</li> <li>• Fungal infection</li> <li>• Syphilis</li> </ul>	20
Metastatic cancer (lung, breast, stomach, colon, lymphoma)	10
Adrenal hemorrhage/infarction	-
Drugs (ketoconazole, fluconazole, rifampin, phenytoin, barbiturate)	-
Others <ul style="list-style-type: none"> <li>• ALD/AMN</li> <li>• Congenital adrenal hypoplasia</li> <li>• Familial glucocorticoid deficiency/resistance</li> </ul>	

PAS: polyglandular autoimmune syndrome, ALD/AMN: adrenoleukodystrophy/Adreno myeloneuropathy

Symptoms of adrenal insufficiency include hyperpigmentation of skin and mucous, low energy level, salt craving, loss of libido, erectile dysfunction, and fatigue. In PAI, these symptoms are not always clearly shown until after 90% of both adrenal glands are destroyed. The patient presented in this case was first complained of chronic general hyperpigmentation of skin and gum that were not improved despite medication from skin

specialist. Other symptoms of adrenal hormone deficiency were not present until after some years later. Hyperpigmentation in PAI is due to increased production of  $\alpha$ -melanocyte-stimulating-hormone ( $\alpha$ MSH). Both ACTH and  $\alpha$ MSH are made from the same pro-hormone called peptide pro-opiomelanocortin (POMC) in which its production is triggered by hypocortisolism.

Table 3. Sign and symptoms of adrenal tuberculosis<sup>3</sup>

Signs and symptoms	Prevalence (%)
Anorexia	75-100
Fever	72-94
Weakness	72-100
Fatigue	70-100
Hyperpigmentation	65-94
Gastrointestinal symptoms (nausea, vomiting, abdominal pain, constipation, diarrhoea)	58-92
Hypotension (systolic blood pressure <110 mmHg)	50-90
Salt cravings	5-16
Giddiness	4-12
Vitiligo	10-120
Muscle or joint pain	5-10

Proper diagnosis of adrenal insufficiency is obtained through cosyntropin stimulation test (CST). Hypocortisolism is confirmed when cortisol level, either at 30 minutes or 60 minutes after 250 ug cosyntropin injection, is below 18 - 20 ug/dL. High level of baseline ACTH confirms the diagnosis of PAI while low level of ACTH suggests either secondary or tertiary adrenal insufficiency. Some reviews showed that morning cortisol level below 3 ug/dL is a strong predictor for adrenal insufficiency, yet CST is still needed.<sup>7,8</sup> The patient had initial morning cortisol level as low as 1.1 ug/dL and was prepared to have CST. At that time, the physician was not yet starting hormone replacement because other laboratory findings were still within normal limit and the patient was clinically stable. Adrenal crisis took place when certain trigger happened in a restricted cortisol availability condition. In this patient, vigorous physical activity was thought to be the trigger of the crisis and intravenous hydrocortisone was started immediately in the emergency department. Whenever signs and symptoms of adrenal crisis were found in suspected PAI patients, hormone replacement must never be delayed for diagnosis confirmation. Keeping one serum sample before administering steroid is a crucial step to ensure the validity of cortisol and ACTH level results.<sup>9</sup>

Determining the cause of PAI can be tricky as there are several differential diagnoses. Most endocrinology guidelines recommend detecting 21-OH-antibody in all adult patients suspected with PAI and proceed with abdominal CT if the antibody is not detected.<sup>6</sup> What must not be forgotten is that chronic infection such as tuberculosis is epidemiologically common in developing country and reasonable to be first considered as the cause of PAI. Adrenal tuberculosis is almost always secondary to primary tuberculosis elsewhere. Consequently, the effort to find the primary tuberculosis, either active or latent infection, in any other organ should be done vigilantly.<sup>1,2</sup> There were no specific imaging finding of adrenal tuberculosis. Bilateral enlargement, calcification, and necrosis can be suggestive but not conclusive. Laboratory findings may show elevated erythrocyte sedimentation rate (ESR), lymphocytosis, positive IGRA and purified protein derivative (PPD) test. Histopathology finding from laparoscopic surgery can confirm the diagnosis.<sup>1,3</sup> In this case report, test detection for 21-OH antibody was not performed due to resources limitation. Adrenal CT-scan showed atypical findings, as expected. However, positive results of IGRA and classic histopathology findings from thoracal soft tissue tumor led to confirmation of previous tuberculosis infection.

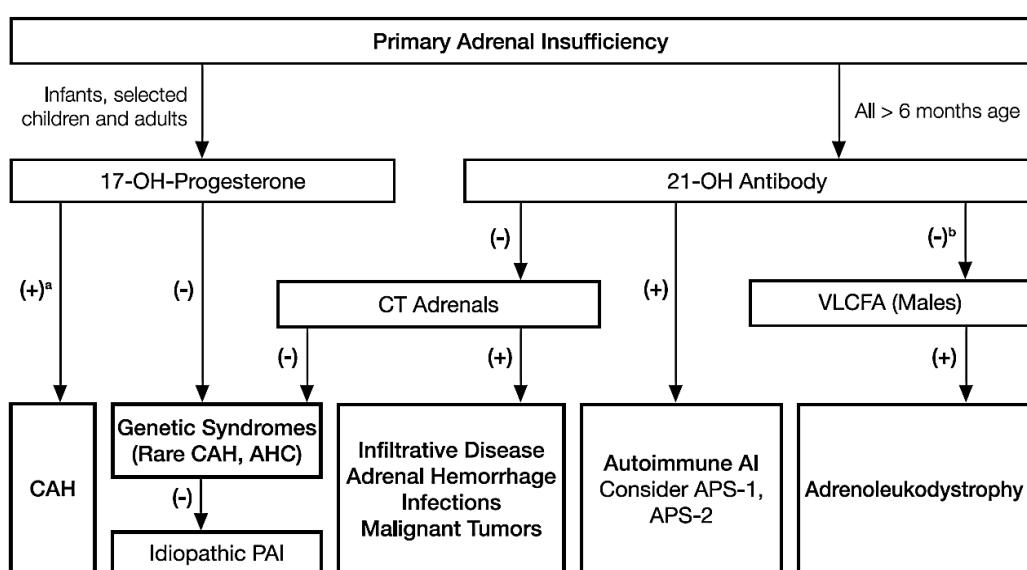


Figure 4. Diagnostic algorithm of primary adrenal insufficiency<sup>7</sup>

With chronic infection and overt adrenal insufficiency, antituberculosis drugs do not always successfully restore hormonal function.<sup>10</sup> Younger age, shorter disease duration, and less severe clinical symptoms might result in better outcome.<sup>11</sup> Not all those criteria were fit with this patient, so there is possibility that the adrenal function might not be fully recovered, and long-term hormone replacement will be needed. To encourage better chance in adrenal function reversibility, earlier initiation of ATD can result in better recovery of adrenal function.

However, one must always be aware of the effect of rifampicin on glucocorticoid metabolism. Rifampicin is a potent inducer of hepatic enzyme and failing to adjust the dose of glucocorticoid replacement therapy while initiating ATD may result in baneful adrenal crisis.<sup>12</sup>

## CONCLUSION

Tuberculosis infection should be considered in young patients with overt clinical signs and symptoms of PAI. High index of suspiciousness is necessary to confirm primary tuberculosis infection elsewhere. Anti-tuberculosis drug along Glucocorticoid replacement is the mainstay treatment and- might give a better outcome when given at earliest time of diagnosis.

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## Pregnancy Following Recent Radioactive Iodine Ablation in Thyroid Carcinoma Patient: A Case Report

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### ABSTRACT

Well-differentiated thyroid carcinoma (DTC) is common among females of reproductive age. Pregnancy is associated with hormonal (TSH and HCG) and metabolic changes that might affect the thyroid gland. Information regarding the outcome of babies born to mothers who have recently undergone radioactive iodine-131 ablation (RAI) is scarce. A 24-year-old pregnant woman with a history of thyroid cancer was consulted by the obstetrics and gynecology for further evaluation. She complained of a lump under the left jaw, and a thyroid nodule was found from further examination. Postoperative pathology of the right thyroid tissue revealed follicular and solid variant papillary thyroid carcinoma. Postoperative Thyroglobulin (Tg) level before ablation was 16.14 ng/mL. Ablation with iodine-131 of 100 mCi was performed. Whole-body scintigraphy (WBS) indicated remaining functional thyroid tissue in the right thyroid field and thyroid tissue metastases in the left supraclavicular area. The patient was pregnant 3 months after the radioablation. Fetal-maternal examination results 6 months pregnancy revealed fetal biometry according to gestational age (31 - 32 weeks) with an estimated fetal weight of 1787 grams and fetal doppler was normal. The patient is treated with levothyroxine 125 µg once daily, folic acid 400 µg twice daily, calcium lactate twice daily, and aspirin 80 mg once daily. The TSH level was 0.01 (0.55 - 4.78) µIU/mL and the fT4 was 1.14 (0.7 - 1.48) ng/dL. The latest thyroid ultrasound indicated no discrete mass in the thyroid fossa and non-specific lymphadenopathies. The baby was born normally, weighed 2680 grams, with normal thyroid function tests (neonatal TSH 1.02 µIU/mL, fT4 2.6 ng/dL).

**Keywords:** Thyroid carcinoma, pregnancy, radioactive iodine ablation

## INTRODUCTION

Thyroid cancer is commonly diagnosed in younger individuals, especially in females of reproductive age. Papillary thyroid carcinoma (88%) and follicular thyroid carcinoma (9%) are the most common types of thyroid cancer, both categorized as DTC.<sup>1,2</sup> Over the past three decades, the incidence of DTC has increased by more than 5% per year globally. In addition to the raised awareness of the diagnosis, environmental variables (such as obesity and radiation exposure) are also responsible for this phenomenon.<sup>2</sup>

Due to its rising incidence, DTC became the second most common malignancy diagnosed in pregnancy, with a prevalence of 3.6 to 14 per 100,000 live births.<sup>3</sup> Approximately 10% of thyroid carcinoma cases are diagnosed during pregnancy or in the postpartum period. Pregnancy is associated with hormonal (TSH and HCG) and metabolic changes that might affect the thyroid gland. However, the relationship between these changes and the progression of thyroid carcinoma, especially DTC, is still controversial.<sup>1</sup>

The prognosis of DTC is favorable, with mortality less than 2% at 5 years; however, diagnosis of malignancy during pregnancy might raise anxiety regarding the optimal timing of the recommended therapies.<sup>1</sup> In general, the management of DTC consists of surgery (lobectomy and total thyroidectomy with or without lymph node dissection), selective use of radioiodine ablation, and levothyroxine suppression therapy.<sup>2</sup>

The 2015 American Thyroid Association (ATA) guidelines for adult patients with DTC recommend that women of childbearing age receiving RAI treatment should have a negative screening evaluation for pregnancy before RAI administration and avoid being pregnant for at least 6 months following RAI. This is due to the concern of increased risk for miscarriage and fetal malformation.<sup>4</sup> Therefore, our recent case report aimed to describe how pregnancy might affect the progression of DTC and the outcome of babies born to mothers who have recently (< 6 months) undergone RAI treatment.

## CASE ILLUSTRATION

A 24-year-old pregnant woman with a history of thyroid cancer was consulted by the ob-gyn at our endocrine clinic for further evaluation. At the beginning of 2022, the patient complained of a lump under the left jaw. Upon ultrasound examination of the neck, in addition to a lump in the left sub-mandible, a nodule was discovered in the right thyroid. Then, surgery was performed to remove the lump in the neck and thyroid. The patient was given Iodine-131 ablation therapy at a dose of 100 mCi. Furthermore, the patient is being planned to repeat WBS with or without RAI. However, the patient was already pregnant three months after radio ablation therapy. The patient has no complaints of symptoms currently. Her history of illness was unremarkable. Her current medication was levothyroxine 125 µg once daily, folic acid 400 µg twice daily, calcium lactate twice daily, and aspirin 80 mg once daily. Her family history of illness was unremarkable.

Upon physical examination, the patient appeared well and alert. Her blood pressure was 118/84 mmHg, pulse was regular, 105 beats/minute, respiration rate 20 times/minute, and the axillary temperature was 36.8°C. Her body weight was 68 kg with a height of 156 cm, and a body mass index of 27.94. Her head-neck examination was unremarkable apart from the postoperative scar tissue (Figure 1). Her latest thyroid function test (TFT) indicated a TSH level of 0.01 (0.55 - 4.78) µIU/mL and an fT4 level of 1.14 (0.7 - 1.48) ng/dL. The serum calcium level was 9.2 mg/dL. Her postoperative Tg level before ablation was 16.14 ng/mL. The WBS imaging following the administration of Iodine-131 ablation therapy indicated functional thyroid tissue remnants in the right thyroid field and thyroid tissue metastases in the left supraclavicular area (Figure 2). Detailed post-partial thyroidectomy pathology reports were as the following: right thyroid indicated papillary thyroid carcinoma (PTC), follicular and solid variant, with tumor size of 2.3 x 1.7 x 1.5 cm, without lymphangion-invasion nor perineural invasion (limited growth in the thyroid); left submandibular indicated fibro lipoma.

Fetomaternal examination results on 6 months pregnancy, revealed fetal biometry according to gestational age (31 - 32 weeks) with an estimated fetal weight of 1787 grams and fetal doppler was normal. Her current assessment was primigravida and stage I PTC (pT2N1M0, age < 55 years old) with intermediate risk of recurrence and indeterminate response of therapy. Then, she was prescribed levothyroxine 125 µg once daily along with previous medications, and a thyroid ultrasound examination was ordered. Two weeks later, the thyroid ultrasound revealed no discrete mass in

the thyroid fossa and non-specific lymphadenopathies. Three weeks later, the baby was born normally, weighed 2680 grams, with normal thyroid function tests: neonatal TSH 1.02 µIU/mL (normal: < 9 µIU/mL), and fT4 2.6 ng/dL (normal: 0.83–3.09 ng/dL). During follow-up, a stimulated serum Tg level performed by stopping levothyroxine for 4 weeks revealed a negative result (< 0.04 ng/mL), with the anti-Tg level also negative (44.3 IU/mL). The patient was then classified as having an excellent response to therapy.



Figure 1. The head-neck examination showed postoperative scar tissue

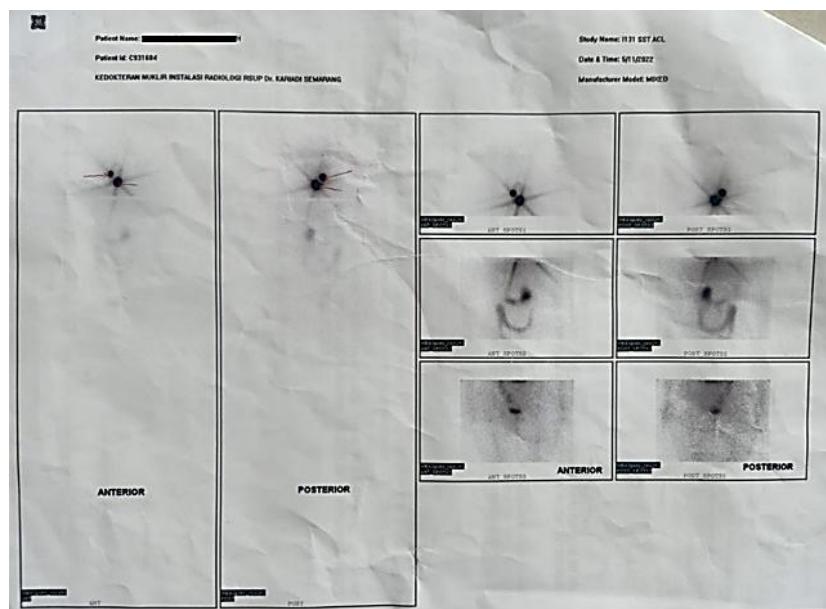


Figure 2. Whole-body scintigraphy imaging following administration of Iodine-131 ablation therapy indicated functional thyroid tissue remnants in the right thyroid field and thyroid tissue metastases in the left supraclavicular area

## DISCUSSION

Papillary thyroid carcinoma is an epithelial neoplasm featuring evidence of differentiated follicular cells and a set of distinctive nuclear characteristics. There are several risk factors associated with PTC, namely ionizing radiation exposure (especially in childhood), genetics, obesity, and high dietary iodine intake. Papillary thyroid carcinoma is mostly diagnosed in middle-aged adults with a 3:1 female-to male ratio. RET protooncogene, NTRK1, and MET gene overexpression are several molecular

derangements related to PTC. Mutation in the BRAF gene, particularly BRAFV600E, have also been identified in the pathophysiology of PTC and correlated with its prognosis.<sup>5</sup> Papillary thyroid carcinoma commonly presents as a painless thyroid lump with or without enlargement of cervical lymph nodes. Physical examination usually reveals a painless hard lesion that is less than 5 cm in size. Nodal metastases of ipsilateral lymph nodes are frequently reported in 27% of patients at presentation, although lateral lymph node

involvement is occasionally reported in some cases.<sup>6</sup>

The favored initial diagnostic approach for PTC is fine needle aspiration (FNA). Thyroid function tests have little role in the diagnosis of PTC because most patients have normal TFT at diagnosis. The preferred imaging technique for PTC is ultrasound, where microcalcification is a highly specific finding.<sup>5</sup> As primary treatment, the extent of surgery is decided after determining preoperative risk, which includes clinical, imaging, and cytological data. Following surgery, the risk of recurrence of the disease is determined according to ATA 2015 guidelines to decide further needs for RAI treatment. In general, low-risk patients do not need RAI adjuvant treatment, while intermediate and high-risk patients might be given RAI adjuvant treatment using selective doses. In this case, the patient has an intermediate risk of disease recurrence because of the presence of uptake in the neck on post-treatment WBS. Lifelong thyroid hormone replacement using levothyroxine is needed after thyroidectomy to achieve suppression of thyrotropin.<sup>4</sup>

Overall, the management of PTC during pregnancy can be categorized into two clinical scenarios: pregnant women who are newly diagnosed with PTC and pregnant or planning-to-be pregnant women with a history of PTC.<sup>3</sup> In our case, the patient has already received primary treatment (partial thyroidectomy) and has been given RAI treatment. Radioiodine (Iodine-131) administration during pregnancy is contraindicated due to the risks of fetal hypothyroidism, deformities, growth abnormalities, malignancies (leukemia), and other fatal changes. Additionally, it should not be administered to nursing mothers due to the significant accumulation of Iodine-131 in the lactating breast. Due to the slow-growing nature of PTC, further RAI therapy may be postponed allowing nursing for at least 6 to 8 weeks after the cessation of breastfeeding in nursing women.<sup>3,4</sup> Depending on the dose of Iodine-131 given, the patients need to be separated from the infant (approximately 6 feet) for at least 6 - 23 days.<sup>7</sup>

Before administering the first dose of RAI, it is recommended to measure the Tg level three to four weeks after surgery. A Tg level of  $> 30$  ng/mL indicates disease persistence and is associated with recurrence, early treatment failure, distant metastases, and increased mortality. In a subset of patients with non-total thyroidectomy as primary treatment, the trend of Tg levels is used instead of a definite cutoff value.<sup>4</sup> However, Tg levels can significantly increase during pregnancy and return to preconception levels following delivery therefore, increasing levels of Tg should be interpreted carefully during pregnancy.<sup>8</sup> Neck ultrasound should be performed at 6 and 12 months, then the frequency is adjusted according to the patient's risk. Our present case was categorized as having an excellent response to therapy based on the nonspecific findings on imaging (neck US), and the stimulated Tg evaluation was negative following delivery. To maintain a TSH level in the range of 0.1 - 0.5 mU/L for appropriate thyrotropin suppression and to prevent fetal hypothyroidism, the levothyroxine dose should be adjusted every 4 weeks.<sup>9</sup>

The association between estrogen, HCG, and DTC has long been proposed due to the evidence that females of reproductive age are more likely to develop DTC.<sup>10</sup> Other studies also suggested the association between high parity and the increased risk of DTC.<sup>11</sup> In early pregnancy, the level of HCG increases, and simultaneously, the estrogen level also increases; therefore, theoretically, pregnancy will likely increase the risk of DTC. Some *in vitro* studies reported a proliferative effect of estrogen on thyroid cancer cells, while others reported the effect only on adenomatous and normal thyroid. Another study reported a higher incidence of DTC in women using estrogen oral contraceptives and hormone replacement therapy, while others did not.<sup>12</sup> Meanwhile, in a large cohort study, the use of clomiphene, a fertility agent, in parous women is not linked to an increased risk of DTC.<sup>13</sup> In this case, pregnancy-related hormonal changes did not seem to affect the progression of PTC, as the

result from the neck ultrasound evaluation indicated no structural evidence of disease.

The 2015 ATA guidelines for adult patients with DTC recommend that women of childbearing age should avoid being pregnant for at least 6 months following RAI due to the concern of negative pregnancy outcome.<sup>4</sup> A meta-analysis confirmed that the negative outcomes of pregnancies that occurred after a year following RAI treatment was not significant.<sup>14</sup> Another large-scale cohort study in Korea also reported the poor outcome of pregnancy after RAI was not significant if the interval was more than 6 months.<sup>15</sup> Following RAI administration, the ovaries are exposed to radiation from the blood, bladder, bowel, and, if any, metastases adjacent to the ovaries.<sup>16</sup> The effect of radiation absorbed by the ovaries can be categorized into deterministic effects, which are dose-dependent, and stochastic effects, which might occur at any radiation dose.<sup>17</sup> The 2017 ATA guidelines for the diagnosis and management of thyroid disease during pregnancy and the postpartum recommended all infants born to mothers with thyroid illness be screened for hypothyroidism 2-5 days after birth.<sup>18</sup> A neonatal TSH value of < 9 µIU/mL is considered normal and not associated with neonatal hypothyroidism, while the normal reference for fT4 in neonates is 0.83-3.09 ng/dL.<sup>19</sup> In this case, even though the pregnancy resulted in no apparent fetal malformation, further evaluation and active surveillance are needed for future negative outcomes. Women who recently underwent RAI also need to get effective contraception to prevent pregnancy under 6 - 12 months.

## CONCLUSION

The management of intermediate-risk DTC in pregnancy following surgery and RAI treatment involves levothyroxine suppression therapy and active surveillance using Tg and neck ultrasound. Hormonal and metabolic changes during pregnancy might not affect the progression of intermediate-risk DTC. Recent radiation exposure (less than 6 months) due to RAI treatment to the female gonadal tissue

might not increase the risk for miscarriage and fetal malformation in the pregnancy.

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## CASE REPORT

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# Hypokalemia Periodic Paralysis in Subtle Thyrotoxicosis with Renal Insufficiency

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## ABSTRACT

Hypokalemia is one of the frequently observed electrolyte imbalances in clinical practice. The clinical manifestations range from asymptomatic to significant manifestations, such as paralysis. Here we report a case of 31-years-old female admitted to our emergency department with chief complaint of acute onset of paralysis in lower extremities. Vital signs showed slight tachycardia. The physical examinations were all normal. Motoric examination showed paraparesis in lower extremities with normal sensory function. Upon admission, laboratory tests showed severe hypokalemia (1.5 mmol/L) with renal insufficiency. The patient got hypokalemia corrected with both potassium oral supplementation and potassium infusion. Thyroid function tests showed hyperthyroidism and the diagnosis of thyrotoxic periodic paralytic (TPP) was made. This case report highlights the importance of early diagnosis and prompt treatment of hypocalcemia in TPP patients.

**Keywords:** Periodic paralysis, hypokalemia, primary hyperthyroidism, subtle thyrotoxicosis

## INTRODUCTION

Hypokalemia stands out as a frequently observed electrolyte imbalance in the field of clinical medicine. The prevalence of hypokalemia varies from 6.7% to 21%.<sup>1-3</sup> The existing guidelines establish the standard range for lower potassium levels as 3.5 to 3.8 mmol/L and for upper levels as 5.0 to 5.5 mmol/L.<sup>4</sup> This abnormality has broad clinical manifestations, from asymptomatic to significant manifestation such as paralysis, called hypokalemia periodic paralysis (HPP).

Hypokalemia periodic paralysis (HPP) is characterized by episodic of flaccid muscle weakness of variable duration and severity with intact sensory functions. The prevalence of HPP is rare, approximately 1 in 1.000 and most of HPP cases identified as sporadic and more prevalent in male, with ratio of 9:1.<sup>5,6</sup> Theoretically, testosterone can increase the activity of the sodium/potassium (Na<sup>+</sup>/K<sup>+</sup>) pump resulting in hypokalemia.<sup>7</sup> Most cases of HPP are hereditary, caused by the mutation in either calcium or sodium ion channel. HPP could also occurred secondarily due to thyrotoxicosis, called thyrotoxic periodic paralysis (TPP). TPP is a rare, yet extremely dangerous complication observed in patients with thyrotoxicosis. Any cause of thyrotoxicosis can lead to TPP, including Graves' disease, toxic nodular goiter, solitary toxic nodule, iodine-induced thyrotoxicosis, thyroiditis, excess exogenous thyroxine use, drug-induced thyrotoxicosis, etc.<sup>9</sup>

Timely identification of hyperthyroidism in patients experiencing hypokalemic paralysis is crucial to administer suitable treatment and prevent the potential danger of rebound hyperkalemia resulting from unnecessary and excessive potassium supplementation. This article presents a scenario involving

hypokalemic periodic paralysis caused by asymptomatic hyperthyroidism.

## CASE ILLUSTRATION

A female 31 years old was administered to the emergency department (ED) with acute onset of paralysis in bilateral lower extremities. The symptoms occur when she wakes up from sleep. The symptoms were followed by chest tightness and vomiting. A few hours prior to the onset of symptoms, she didn't engage in any excessive physical activity. The patient mentioned that she had consumed fried rice before going to sleep. There was no fever, diarrhea, sore throat, or cough. There were no indications of weight loss, heat intolerance, alterations in bowel habits, or any other symptoms associated with hyperthyroidism reported. She had a history of similar symptoms in the past 2 years. No history of previous illness such as hypertension, diabetes mellitus, hyperthyroidism, or nervous system disease. No family member has similar symptoms.

Upon admission, the patient was alert. Her vital signs; blood pressure (BP) 101/73mmHg, pulse 118 beat per minute, respiratory rate 24 breaths per minute, saturation 98% with three liters of nasal canula, and body temperature of 37°C. During the physical examination, her thyroid appeared to be of regular size and texture. Listening to the thyroid did not reveal any abnormal sounds. There were no signs of bulging eyes (exophthalmos) or changes in the skin. Motoric examination showed paraparesis in lower extremities with normal sensory function. Electrocardiography demonstrated sinus tachycardia (Figure. 1). Chest x-ray showed no abnormalities.

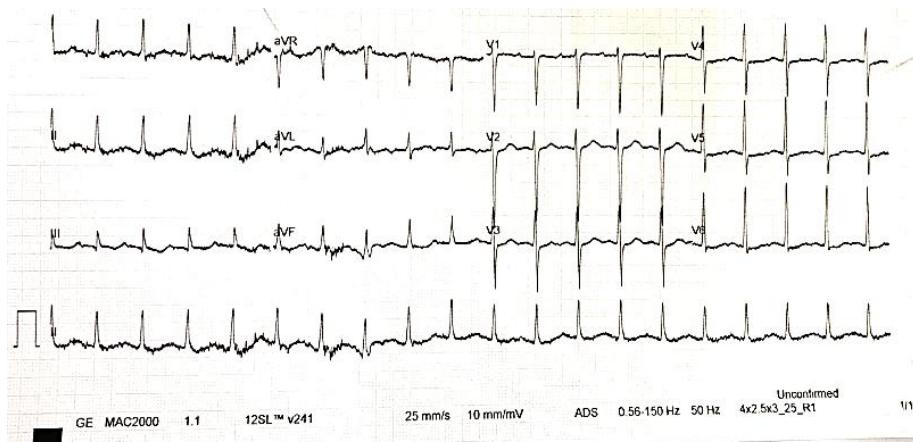


Figure 1. Electrocardiography of the patient upon admission

Complete blood count showed leukocytosis. Biochemical examination showed hyperglycemia, slightly elevated liver enzyme, and azotemia. Electrolyte examination showed severe hypokalemia of 1.5 mmol/L. The details are shown in Table 1.

Table 1. Laboratory Findings Upon Admission

Examination	Normal Range	Result
Blood chemistry		
AST	<35 U/L	56 U/L
ALT	<35 U/L	76 U/L
BUN	10–50 mg/dL	133 mg/dL
Cr	0.45–0.75 mg/dL	2.68 mg/dL
Glucose	70–140 mg/dL	242 mg/dL
Na	135–147 mmol/L	139 mmol/L
K	3.5–5.0 mmol/L	1.5 mmol/L
Cl	95–105 mmol/L	112 mmol/L
Thyroid function		
Free T4	10.60–19.40 pmol/L	28.0 pmol/L
TSH	0.40–4.20 mIU/ml	0.1 mIU/ml

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; Na: sodium; K: potassium; Cl: chloride; TSH: thyroid stimulating hormone

An initial diagnosis of HPP was made. The patient was initially treated with 20 mEq of intravenous potassium chloride (KCl) as well as 25 mEq of oral potassium in ED. Repeat laboratory testing after eight hours showed potassium of 1.5 mmol/L. The administration of potassium replacement was sustained, and the patient was admitted to the intensive care unit. She was given ringer lactate infusion with 50mEq of potassium infusions, antibiotics, and

oral potassium supplementation. Serial measurement of serum potassium showed improvement with a level of 3.5 mmol/L on third day and 4.3 mmol/L on fifth day. The thyroid function test indicated primary hyperthyroidism, with a thyroid stimulating hormone (TSH) level below 0.1 mIU/ml and a free thyroxine (T4) level of 28.0 pmol/L. Subsequently, a diagnosis of thyroid periodic paralysis (TPP) was established. The patient was given propranolol 10mg t.i.d as well as methimazole 20 mg once daily.

## DISCUSSION

Periodic paralysis refers to a neuromuscular condition linked to dysfunctional muscle ion channels, marked by instances of painless muscle weakness. Most cases are hereditary and follow an autosomal dominant inheritance pattern.<sup>8</sup> Individuals with thyrotoxicosis might occasionally develop hypokalemic periodic paralysis (HPP). Thyrotoxic periodic paralysis (TPP) can occur because of several forms of thyrotoxicosis, but it is most common in Graves' disease. TPP, in contrast to other thyroid disorder, is more common in men and is notably common in Asian populations, with an estimated frequency of roughly 2% in thyrotoxicosis patients.<sup>10</sup>

While the precise mechanism is not fully understood, there is a hypothesis suggesting that individuals with TPP possess an inherent anomaly in their muscle ion channels. This anomaly typically doesn't cause symptoms in individuals with normal thyroid function. Nonetheless, when thyroid hormone levels rise,

they heighten the sensitivity of tissues to beta-adrenergic stimulation. As a result, this amplifies the activity of Na/K-ATPase, leading to the movement of potassium into cells.<sup>11</sup> Excess potassium in the skeletal muscle cells inhibits muscle cell excitability, resulting in weakness. The entry of potassium into muscle cells takes place during the resting phase. This phenomenon could elucidate why patients encounter symptoms during the nighttime or early morning hours while asleep (rest).<sup>12</sup> In this instance, the patient ingested fried rice on the evening prior to the onset of symptoms.

However, the exact quantity of carbohydrates consumed is not specified. Consuming a high-carbohydrate diet serves as a trigger for TPP.<sup>13</sup> Hyperinsulinemia contributes to the escalation of Na/K-ATPase activity and the inhibition of potassium efflux from muscle cells.<sup>14</sup> The patient refutes experiencing any emotional stress stemming from work or family matters. Emotional factors such as stress and trauma can act as triggers for TPP, with stress potentially influencing hormonal responses. Catecholamines impact the activity of Na/K-ATPase and hinder the outward movement of potassium by suppressing the function of inward-rectifying potassium channels.<sup>15,16</sup>

TPP presents as temporary occurrences of painless muscle weakness while maintaining intact consciousness. These episodes generally endure for several hours to a few days. The muscle weakness is widespread, yet frequently more prominent in proximal muscles. Episodes can be intensified by the consumption of high-carbohydrate foods, physical activity, stress, infections, anesthesia, or exposure to extreme temperatures.<sup>17</sup> Less frequent symptoms encompass myalgia, diminished or absent reflexes (hyporeflexia or areflexia), as well as concurrent hyperthyroid manifestations like rapid heart rate (tachycardia). Tachycardia was noted at presentation in one series, differentiating these patients from those with familial HPP.<sup>18</sup>

Electrocardiogram (ECG) changes are common during a TPP attack. These include ST depression, sinus tachycardia, and U waves, as

well as those that are not consistently associated with hypokalemia: an elevated higher heart rate, abnormal PR interval, higher QRS voltage, and first-degree atrioventricular (AV) block.<sup>19,20</sup> Severe arrhythmias such as sinus arrest, second-degree AV block, ventricular fibrillation, and ventricular tachycardia are rarely occurred but are documented.<sup>21</sup>

Typically, the degree of hypokalemia corresponds to the severity of weakness. Laboratory findings include an increase in serum thyroxine (T4) and a decrease in thyrotropin levels (TSH). There have been reports of patients with elevated T3 levels but normal T4 levels.<sup>22</sup> Creatine levels may be normal, but they have been found to be mildly elevated in two-thirds of patients.<sup>23</sup>

TPP should be detected when a patient has paralysis accompanied by hypokalemia and hyperthyroidism. Other causes of acute paralysis, such as myasthenic crisis, botulism, Guillain-Barre syndrome, acute myopathy, and acute thyrotoxic myopathy, should be separated from TPP. In this situation, the patient exhibited normal cranial nerve function, ruling out myasthenic crisis or botulism. Her weakness was diffused, with no rising trend that would indicate Guillain-Barre disease. Her absence of discomfort and non-dermatomal distribution were also inconsistent with acute thyrotoxic myopathy or acute myopathy. Other causes of hypokalemia should be differentiated. Initial 24-hours urine potassium level helps to differentiate between two broad groups, renal-loss related or non-rental-loss.

Based on previous reports, almost 50% of TPP patients had only subtle symptoms of thyrotoxicosis, albeit without systematic assessment.<sup>24,25</sup> Study reported by Chang et al<sup>17</sup> showed that only 17% of TPP patients had toxic thyrotoxicosis (Wayne Score >19), supporting the notion that most TPP patients have equivocal symptoms. In this report, our patient also had subtle symptoms of thyrotoxicosis.

The primary treatment for TPP is potassium administration. Although oral potassium chloride is the favored method, intravenous potassium is suitable for those with

difficulty swallowing. As per a recommended protocol, an oral dosage of 30 milliequivalents is advised at intervals of 15 to 30 minutes until serum potassium levels return to normal.[26] Previous review recommended to no potassium replacement more than 90 meq in 24 hours to avoid overcorrection.<sup>27</sup> Given the frequent occurrence of rebound hyperkalemia, meticulous tracking of serum potassium levels and continuous cardiac monitoring are essential precautions.

For case where potassium replacement proves unresponsive, intravenous propranolol might be beneficial in counteracting the surplus beta-adrenergic stimulation responsible for the potassium shift into cells. Propranolol is also advised to be used in the treatment for TPP. Propranolol is a non-selective beta blocker and works by the mechanism of preventing the intracellular shift of potassium and phosphate, it does this by diminishing the hyper-adrenergic stimulation of Na<sup>+</sup>/K<sup>+</sup>-ATPase.<sup>28-30</sup> Treatment for the cause of thyrotoxicosis is important. This could be through using anti-thyroid medications, radioiodine therapy and thyroidectomy in Graves' disease and toxic nodules. Long-term TPP prevention involves restoring euthyroid status and avoiding the trigger factors, such as excessive activity, high-carbohydrate meals, and alcohol consumption.

## CONCLUSION

In conclusion, timely identification, and intervention in cases of TPP held significance in averting severe cardiac complications. To avoid rebound hyperkalemia, potassium replenishment was performed in stages accompanied by continuous monitoring. Therefore, the ultimate treatment aimed to achieve a euthyroid state, thereby preventing recurring attacks.

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## Challenges in The Diagnosis and Management of Adrenal Insufficiency: A Case Report

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### ABSTRACT

Adrenal insufficiency (AI) is a rare endocrine condition. Primary adrenocortical insufficiency, or Addison disease, reduces the production of crucial hormones, including glucocorticoids, mineralocorticoids, and adrenal androgens. Due to the lack of proper cortisol response in adrenal crises, it can be life-threatening during times of stress, emphasizing the need for a timely diagnosis. Despite this, diagnosing and managing AI still presents significant challenges. We report the case of a middle-aged woman who presented with complaints of weight loss, abdominal pain, lethargy, hyperpigmentation of the skin and mucosa, and a history of repeated hospitalizations for nausea, vomiting, dehydration, and hypovolemia. During the patient's previous hospitalization, Addison's crisis was suspected, and methylprednisolone therapy was administered, rendering the cortisol and ACTH assays inaccurate. The patient's condition subsequently improved. The subsequent monitoring revealed low cortisol levels, but an ACTH stimulation test was unavailable. The presence of pulmonary tuberculosis was indicated by a positive chest X-ray and IFN-Gamma Release Assay (IGRA) test. With a history of repeated hospitalizations, suspected Addison's crisis, hypoglycemia, mineralocorticoid involvement (hypotension, hyponatremia), and the presence of hyperpigmentation, a clinical diagnosis of primary adrenal insufficiency was made with limited conditions and testing tools. The patient was given anti-tuberculosis treatment and the lowest dose of hydrocortisone required to control the disease without causing side effects.

**Keywords:** adrenal insufficiency, addison's disease, hypocortisolism

## INTRODUCTION

Adrenal insufficiency (AI), particularly primary adrenal insufficiency, is a rare endocrine disorder that occurs when the adrenal glands cease producing enough glucocorticoids and, in some cases, mineralocorticoids and androgens.<sup>1,2</sup> AI is less common than other endocrine conditions. There is no prevalence data in Indonesia. In South Korea, the estimated prevalence of PAI was 4.17 cases per million inhabitants, which is much lower than the prevalence recorded in Western countries.<sup>3</sup> However, it is a crucial consideration in acute admissions due to significant morbidity and mortality.

Diagnosing can be challenging due to its varied presentation, and referrals to various specialties often occur before making a diagnosis.<sup>4</sup> Many patients are only diagnosed once admitted in acute primary adrenal insufficiency or Addison's crisis, which makes prompt diagnosis even more important. Crisis can also be triggered by infection sepsis, which can mask symptoms and make the diagnosis more complex.<sup>5</sup>

Several advances have been made over the past several decades in the management of AI. Still, treatment remains suboptimal even after the diagnosis, leading to poor quality of life and increased mortality.<sup>6</sup>

## CASE ILLUSTRATION

A 44-year-old Asian female presented to the outpatient department complaining of four hospitalization episodes due to general weakness, frequent vomiting, abdominal pain, dehydration, and hypotension. She was referred to a cardiologist and given some medications. Thereby, she experienced fever, inability to walk, dehydration, and hypotension. The patient was suspected of Covid infection and was referred to the Tropical Medicine division, but the result came back negative. Afterwards she experienced frequent vomiting, abdominal pain, and back pain. Then she was referred to a Gastroenterologist and underwent a gastroduodenal endoscopy. The result was nonactive, non-atrophy chronic gastritis, and

*Helicobacter pylori* were not found. Two weeks later, she underwent her third hospitalization and moved to another hospital with the same complaints.

Later, she got disorientation, breathlessness, and loss of consciousness. She was admitted to the ICU and somehow needed a pacemaker. From the examination, there were persistent hypotension, hypoglycemia, and hyponatremia. Therefore, the physician suspected her of an Addisonian Crisis. Eventually, she was given intravenous methylprednisolone, and it dramatically improved her condition. The patient was referred to the outpatient clinic at our hospital to get further analysis and treatment. At that time, she was already taking oral methylprednisolone 16 mg daily divided into two times a day since the last hospitalization.

Moreover, a history of similar complaints on and off for the past few years, wherein the local doctor treated him on the lines of gastrointestinal disorder, mainly gastritis. There was a history of weight loss (about 10 kgs in the last 12 months). On inquiry, history of skin hyperpigmentation, mainly elbows, and knees, for two years ago. Lips and oral mucosa became hyperpigmented over the last six months. Furthermore, the patient complained of frequent coughing during the past month. Her periods were coming monthly, with normal flow. But there was decreased libido. No history of tuberculosis, diabetes mellitus, thyroid disorders, liver disease, or other comorbid illnesses.

Physical examination showed a well-appearing woman who weighed 49.5 kg and was 156 cm tall, with a body mass index of 18.7. Her recumbent blood pressure was 105/70 mmHg, her heart rate was 74/min, her respiratory rate was 20/min, and her temperature was 36.5°C. No finding of pallor, lymphadenopathy, or neck swelling. Generalized hyperpigmentation on the face, palmar creases, knuckles, and elbows did not seem clear, but hyperpigmentation in oral mucosa was noted (Figure 1). The remaining physical examination findings were normal.

On examination of the abdomen system, there was no tenderness, guarding, or rigidity. The systemic examination of the respiratory, neurological, and cardiovascular systems was normal. Investigations were done for further evaluation.

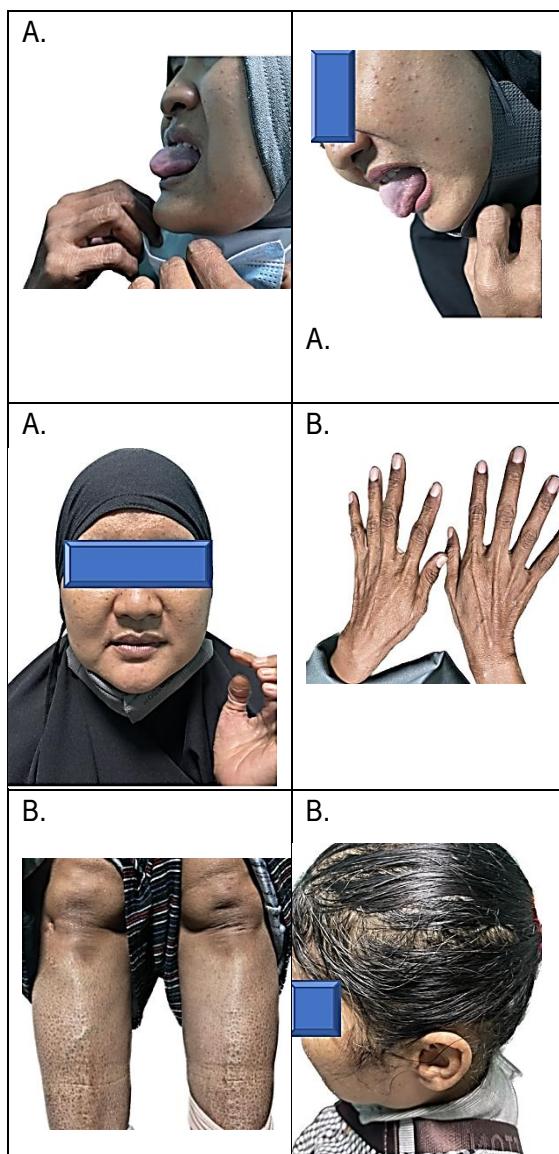


Figure 1: (a) Hyperpigmented lips and tongue, (b) Hyperpigmentation skin, anorexic and thinly built, hair fell.

Laboratory findings from previous hospitalization, showed a hemoglobin 10.1 g/dL, a total leukocyte count  $3.37 \times 10^3/\mu\text{L}$ , differential counts and platelet level were normal. The patient was hyponatremic with serum sodium 120 meq/L (130-142 meq/L) and potassium 3.9 meq/L (3.5-5.5 meq/L), chloride 82.9 meq/L (95-

110 meq/L). Renal function tests were essentially normal. The random blood sugar was 59 mg/dL (80-110 mg/dL). The liver function tests were in the normal range. The next day after methylprednisolone intravenous was given, the condition dramatically improved; the laboratory findings showed serum sodium 136 meq/L (130-142 meq/L) and potassium 3.59 meq/L (3.5-5.5 meq/L), chloride 103.3 meq/L (95-110 meq/L). Early morning 8 am serum cortisol level was normal in this first course, 20.08  $\mu\text{g}/\text{dL}$  (normal >18  $\mu\text{g}/\text{dL}$ ). Due to limited resources, the Cosyntropin test, plasma renin activity, and serum aldosterone level could not be examined. These average results of the cortisol level might be because the patient had already been given intravenous methylprednisolone intravenously and orally in the hospital due to the Addisonian crisis.

On the evaluation, laboratory investigations showed the hyponatremia was improved with serum sodium 137 meq/L (130-142 meq/L), potassium 4.8 meq/L (3.5-5.5 meq/L), chloride 105.0 meq/L (98-107 meq/L), the calcium 8.1 meq/L (8.5-10.5 meq/L), and magnesium 2.10 meq/dL (1.8-2.4 meq/L). Plasma ACTH level was normal 44.6 pg/ml (7.2-63.3 pg/ml).

Another lab investigation to rule out etiological factors for Addison's disease was done. Thyroid function tests showed Free T4 1.12 ng/dL (0.83-1.43) and a normal thyroid stimulating hormone TSH level 0.71  $\mu\text{U}/\text{mL}$  (0.02-132.7). HbA1C was 5.1%, serum calcium, and magnesium were 8.1 mg/dL (8.5-10.5) and 2.10 mg/dL (1.8-2.4). Autoantibodies against adrenal glands and serum levels for light chain fatty acids could not be performed. The three methods of anti-HIV examination were non-reactive, Toxoplasma IgG and IgM were non-reactive, CMV IgG was reactive 163.4 AU/mL ( $\geq 6$ ), and CMV IgM was non-reactive. We followed up and reexamined the morning cortisol serum; the result fell to < 1.0  $\mu\text{g}/\text{dL}$  (3.7-19.4); the patient was still on methylprednisolone 16 mg/day since her last admission. The electrocardiography was normal; the sinus rhythm was 74 bpm. The summary of echocardiograph was normal left

ventricle diastolic and systolic function, ejection fraction of 59%, mild mitral regurgitation, tricuspid regurgitation, and good right ventricle contractility. The chest X-ray showed infiltration in the right and left perihilar and paracardial, suggesting pulmonary tuberculosis.

Abdominal MSCT scan and magnetic resonance imaging with contrast were utilized to conduct tests and eliminate any possibilities of adrenal abnormalities. The outcome of the tests revealed no adrenal mass detected. The test showed hepatomegaly, cholelithiasis, spondylosis thoracolumbar, bronchiectasis type varicose, and cystic on the lower of the left lung. Because adrenal tuberculosis is the most frequent cause of primary adrenal insufficiency in developing countries, we ran an IFN-Gamma Release Assay (IGRA), and the result came back positive. However, Xpert MTB-RIF assay showed MTB not detected.

With the foregoing facts, we hypothesized adrenal insufficiency which was the case of primary or Addison disease, and pulmonary TB. The patient was finally given the anti-tuberculosis drug regimen and a drug switch from methylprednisolone to hydrocortisone 20 mg in the morning and 10 mg in the afternoon. After a month, she mentioned that all her symptoms had significantly improved. She also gained 6 kilograms and noticed an improvement in hyperpigmentation. She felt her cheeks grow fat, and her hair fell out (Figure 1). Later, she was feeling well, and her weight had not increased too fast, although the morning cortisol serum was still  $<0.1$   $\mu$ g/dl. Her hydrocortisone dose was reduced to 10 mg in the morning and 5 mg in the afternoon; we plan to give the smallest dose to control the disease without relapsing her symptoms.

## DISCUSSION

Adrenal insufficiency (AI) is a relatively uncommon but serious condition characterized by decreased production of glucocorticoids and/or mineralocorticoids and adrenal androgens due to adrenal gland destruction or absence of stimulation. It is subdivided into primary adrenal insufficiency (PAI), also known

as Addison's disease, secondary adrenal insufficiency (SAI), and tertiary adrenal insufficiency (TAI) based on whether the disease affects the adrenal cortex, anterior pituitary gland, or hypothalamus, respectively.<sup>1,6-8</sup>

SAI and TAI are most typically caused by exogenous steroid treatment, which suppresses ACTH production. It is a pituitary-dependent decrease in ACTH secretion that leads to a decrease in glucocorticoid production. Mineralocorticoid secretion, including aldosterone, however, remains relatively normal. They are more common than primary insufficiency. Symptoms frequently appear after the steroid has been discontinued.<sup>9</sup>

Primary adrenal insufficiency, or Addison's disease, is uncommon. Annually, the incidence is 0.6 per 100,000 individuals in the population. The incidence rate of this condition varies between 4 and 11 per 100,000 individuals globally at any given time. The typical age of onset in adults is between 30 and 50 years. It is more prevalent among females.<sup>9</sup> In Western countries, the prevalence of Addison's disease ranges from 82 to 144 cases per million persons.

Autoimmune disorders account for 70% to 90% of PAI patients, with tuberculosis accounting for just 7% to 20%. However, in developing nations, adrenal TB is still the leading cause of PAI.<sup>10</sup> In South Korea, the estimated prevalence of PAI was 4.17 cases per million inhabitants, which is much lower than the prevalence recorded in Western countries. The cause of Korea's low incidence of PAI is unknown; nevertheless, it appears that some racial or regional variables may impact the disease's occurrence, given that the incidence of PAI in Korea is like that recorded in Japan (0.15 per million per year).<sup>3</sup> Several infectious processes associated with AIDS, including Cytomegalovirus, *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, *Toxoplasma gondii*, *Mycobacterium avium* intracellular, *Pneumocystis jiroveci*, and *Histoplasma capsulatum*, may cause adrenal gland destruction. Ketoconazole (an antifungal) and etomidate (a general anesthetic) are two medications that can induce AI.<sup>7</sup>

Doctors are poor at recognizing adrenal insufficiency, with two-thirds of patients presenting with symptoms of adrenal failure three or more times before receiving the correct diagnosis.<sup>2</sup> This illustrates the adage, "If you think of adrenal failure, rule it out". The diagnostic difficulty lies in that cortisol secretion has a circadian rhythm, so the sampling timing impacts the result. As a 'stress hormone,' cortisol secretion depends on the patient's health. Generally, a random serum cortisol of over 400 nmol/L at any time of the day makes adrenal insufficiency highly unlikely, while a morning serum cortisol of less than 100 nmol/L strongly suggests adrenal failure. In interpreting such results, one must consider the patient's current and prior steroid usage and conditions affecting cortisol-binding globulin, such as pregnancy or oral estrogen therapy, which can result in falsely reassuring cortisol concentrations.<sup>5</sup>

About half of the patients with Addison's disease are diagnosed only after an acute adrenal crisis. It is a medical emergency often precipitated by an infection or other forms of stress in an undiagnosed or inadequately treated patient with Addison's disease.<sup>8,11</sup> Patients present acutely unwell with severe dehydration, hypotension, or circulatory shock in this condition.<sup>12</sup>

The diagnosis of Addison's involves simple blood tests; however, in the acute setting, random cortisol can sometimes provide sufficient information. If in doubt, intravenous steroids can be given if there is a high index of suspicion without blood tests.<sup>11-13</sup>

Initially, the cortisol results in our patient were inappropriate because she had an adrenal crisis in the previous episode and had received methylprednisolone therapy without waiting for the cortisol level results. ACTH levels were also normal. However, we found that the cortisol levels were low during later follow-up.

A deficient cortisol in the presence of clinical features of Addison's disease should prompt a diagnosis, and a trial of hydrocortisone may confirm this. The key diagnostic test is a short synacthen test<sup>13,14</sup>. However, this can be

difficult in the crisis scenario since intravenous hydrocortisone should be started immediately.<sup>11,12</sup>

Unfortunately, the ACTH stimulation test is not available in our center. We were planning a re-examination of ACTH in this patient. In the case of a low or normal ACTH, a pituitary magnetic resonance imaging scan should be obtained, along with the measurement of anterior pituitary hormones.<sup>5</sup>

Hyperpigmentation of the skin and mucosae resulting from the melanocyte-stimulating activity of lipotropin, which derives from the same precursor as ACTH, is observed only in primary AI. Although hyperkalemia is observed only in primary AI, hyponatremia can also occur in secondary AI due to reduced glomerular filtration rate, increased antidiuretic hormone secretion, and possible concomitant central hypothyroidism. Patients with primary AI caused by autoimmune adrenalitis are at risk for other manifestations of autoimmune disease, such as vitiligo, Hashimoto thyroiditis, pernicious anemia, and type 1 diabetes mellitus.<sup>7</sup>

Secretion of adrenal mineralocorticoid aldosterone is regulated mainly through the renin-angiotensin system or dietary potassium. Lack of adrenal mineralocorticoid leads to increased renin release by the juxtaglomerular cells of the kidneys. ACTH does not play a significant role in the long-term regulation of mineralocorticoid secretion. However, it does stimulate aldosterone secretion acutely and transiently but to a lesser extent than angiotensin II and potassium.<sup>6</sup>

SAI is usually milder than PAI as aldosterone secretion remains intact. Hyponatremia can occur in PAI and SAI, although the underlying etiology differs in each case. In PAI, hyponatremia (and hypovolemia) is caused by aldosterone deficiency. In contrast, in SAI, hyponatremia is due to inappropriate vasopressin secretion (and water retention) due to the lack of cortisol, which leads to dilutional or hypervolemic hyponatremia.<sup>6</sup>

In this case, the Abdominal CT and MRI findings were negative, and Addison's adrenal TB as the primary infection is still questionable,

confusing the etiology of adrenal insufficiency. We found TB presentation in chest X-ray and Interferon- $\gamma$  release assays (IGRAs) positive results support pulmonary TB diagnosis.

Availability such as adrenal autoantibodies and endoscopic ultrasound for guide needle biopsy may sharpen the lack of diagnostic procedures. Some data present inaccurate percutaneous core needle biopsy of adrenal was 0-30%.<sup>15</sup> We did not use guided CT or MRI adrenal fine needle biopsy because reaching the adrenal without injuring the visceral organ was difficult. Measurement of anti-adrenal antibodies may help the diagnosis of autoimmune adrenalitis. This test is highly specific but not 100% sensitive.<sup>7</sup> Unfortunately, this test is not available in our area.

Alongside the difficulties in diagnosing this case, we faced additional challenges in its management. In the last admission, the patient was in the intensive care unit for five days and then shifted to the ward for further follow-up and management. Injections were given to correct all deranged parameters. Acute treatment included intravenous hydrocortisone, aggressive fluid resuscitation in normal saline, and inotropic support to treat hypotension.<sup>5,16</sup>

Serum cortisol level should always exceed 18  $\mu$ g/dL in severely stressed patients. Albumin and cortisol-binding globulin generally bind 90% of serum cortisol, except in severe hypoproteinemia. Free cortisol is a better AI indicator than total blood cortisol in such cases. Unfortunately, direct measurement of free serum cortisol is not widely available, and there is no formula to correct it for albumin or total protein levels. Before starting lifelong glucocorticoid medication, intensive care unit patients with serum cortisol-based AI diagnoses should be retested in the outpatient setting.<sup>7</sup>

The glucocorticoid doses commonly used during significant stress (major surgery, severe infection, myocardial infarction)—80 to 100 mg of hydrocortisone every 8 hours—are probably excessive and not based on clear evidence. Patients with intact adrenal function secrete between 75 and 150 mg/d in response to major surgery. Therefore, the maximal dose

recommended is 50 mg of hydrocortisone every 8 hours. When such a dose is administered, there is no need to prescribe fludrocortisone, even in patients with primary AI, because the high amounts of hydrocortisone will activate the mineralocorticoid receptor.<sup>6,7</sup>

Glucocorticoids are the primary therapy for all forms of AI. Although several kinds of glucocorticoids can be used, hydrocortisone (10-12.5 mg per day) is preferred because its short half-life mimics the normal cortisol circadian rhythm most closely. This dose of hydrocortisone is not associated with reduced bone mineral density. The downside is that hydrocortisone must be given twice or thrice daily.<sup>7,14</sup> The classic dose of 30 mg/d (20 mg in the morning and 10 mg in the afternoon) is probably excessive in most patients.

Medications with a long half-life, such as dexamethasone, beclomethasone, and deflazacort, can readily lead to overtreatment and should therefore be avoided. None of the currently available glucocorticoid preparations can mimic physiology exactly, and overtreatment with glucocorticoids is a common side effect. In addition, no reliable biochemical parameters exist for monitoring under or overtreatment. During glucocorticoid replacement, serum cortisol, ACTH, and 24-hour urinary-free cortisol excretion are inadequate indicators of tissue exposure to cortisol. Daily practice uses clinical judgement to determine the appropriateness of glucocorticoid dosage. Patients should be observed for weight gain, glucose intolerance, moon face, double jawline, thin skin, decreased bone mineral density, and osteoporotic fractures. The overuse of glucocorticoids can increase cardiometabolic risk and mortality.<sup>1,5</sup>

Moreover, patients with exogenous suppression of the HPA axis ('tertiary adrenal failure') may paradoxically exhibit Cushingoid symptoms due to the withdrawal of steroid medication, resulting in functional adrenal failure. For at least three weeks, steroid doses equivalent to 7.5 mg of prednisolone can cause adrenal suppression.<sup>5</sup> Due to the presence of adrenal insufficiency, the use of steroids in

tuberculosis is a definitive indication; therefore, the use of steroids must be more cautious, in addition to contemplating the adverse effects.<sup>17</sup>

## CONCLUSION

This case highlights the importance of reviewing previous admissions and considering other differential diagnoses, especially when the presenting symptom is similar. The patient had been initially referred to cardiologist and gastroenterologist, then underwent four hospitalizations, the last one with a suspicion of adrenal crisis. The more cardinal features, such as skin or mucous membrane pigmentation, may be missed, although these may not always be present. Eventually, primary AI was diagnosed almost one year after symptoms presented. Diagnosis is usually late, leading to increased morbidity and mortality. An adrenal crisis is a life-threatening emergency that requires immediate recognition and treatment.

In developing countries, adrenal tuberculosis remains the leading cause of primary adrenal insufficiency. In this case, the Abdominal CT and MRI were negative, and Addison's adrenal TB as the underlying infection is still dubious, challenging the adrenal insufficiency etiology. Chest X-ray and IGRA findings confirmed pulmonary TB. Pulmonary TB was clinically diagnosed in this patient. Anti-tuberculosis treatment was provided to the patient.

The patient was diagnosed with primary adrenal insufficiency following the occurrence of multiple Addisonian crises. The patient received hydrocortisone replacement therapy, with a dosage of 20 mg in the morning and 10 mg in the afternoon. One month later, he stated that all his symptoms had shown remarkable improvement. Our intention is to administer the minimal dosage necessary to manage the disease while preventing the reoccurrence of symptoms.

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## Artificial Intelligence for Managing Diabetes Mellitus in Indonesia: Implementation Challenge in Resource-Limited Settings

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### ABSTRACT

The existence of Artificial Intelligence (AI) has shaped a significant transformation in healthcare. In the field of endocrinology, AI has been used in the treatment of diabetes mellitus which categorized as one of the leading causes of death in Indonesia. This study is based on a general article review that uncovered the function of AI and its utilization on diabetic care. Currently, AI has grown into a facility that plays a role in health care, such as screening, diagnosis, and recognizing problems. In the scope of diabetes, several AI-based methods and applications have been investigated and played a role in diabetes management such as monitoring blood sugar, setting therapy targets, and dietary adjustment in diabetic patients. Despite the sophistication of AI, there are still several potential risks and barriers, notably in Indonesia, where the limited resources still be an impediment to the use of advanced technology. Lack of data integration and limited accessibility are the common challenges to AI implementation in limited-resources areas. Nevertheless, the application of AI offers numerous prospective benefits, particularly in terms of convenience of use and its efficacy in diabetes management to optimize diabetes care with standardized digital data records, resource improvement, and workload decrease.

**Keywords:** Artificial intelligence, diabetes, resource limited settings

## INTRODUCTION

Diabetes is a health problem that has been a concern for a long time in Indonesia with various complications. The prevalence of diabetes in Indonesia reached 6.2% with 10 million people living with diabetes, which is one of the leading causes of death in large numbers.<sup>1</sup> This can affect individual productivity and affect social scope if neither the intervention nor the proper management is provided. Indonesia is a developing country that still struggles to face the reality of limited facilities and infrastructure in some regions in supporting health management, including information provision, availability of diagnostic tools, and availability of access to monitor patient conditions. This also happens in diabetes management, where limited access to disease management can lead to an increase in comorbid diseases. It can be caused by the distance to reach adequate health facilities and the level of education that still varies within society.

Technology in the healthcare industry is continuously advancing, including the presence of Artificial Intelligence (AI). AI is a system that combines computer science, machinery, and adequate datasets to solve a problem.<sup>2</sup> AI has the potential to further improve patient care due to its ability to interpret more detailed and comprehensive data.<sup>3</sup> AI applications in medicine are emerging worldwide in resource-rich and resource-limited regions, including Indonesia. The Indonesian government strongly supports and encourages the use of AI as a part of digital transformation technology for public health in the future. Digital transformation is an influential agenda to encourage the realization of a Healthy Indonesia through data and technology.<sup>3</sup>

In the context of endocrinology, AI, and digital health intersection, type 2 diabetes mellitus (T2DM) is the most common non-infective, chronic disease observed in Indonesia, and remains the leading cause of morbidity and mortality. At present, AI has developed into a 'promising' technological advancement program in improving diagnosis and patient care. Regarding diabetes

management, a study stated that the use of AI can be used to detect complications, support clinical decisions, and provide self-management tools.<sup>4,5</sup> It is expected that AI performs to help afford access to diabetes care in areas with limited resources. The purpose of this review is to provide a view about the utility of AI and its implementation challenges regarding diabetes management in resource-limited settings.

## DISCUSSION

### AI in health digital transformation

Artificial Intelligence (AI) is a field of computer science that combines machinery and computer systems to think like human cognitive functions. An adequate dataset and specific computer codes were required to instruct machines how to interpret data and make conclusions or decisions. AI has the potential to further improve patient care due to its ability to analyze information and process complexity in a wide range of applications.<sup>3,6</sup>

AI is a human-made intelligence using some predictive algorithm properties. Through Machine Learning (ML) algorithms, computers can learn from experience without exact instructions by using large data inputs and outputs. This subclass of AI investigates the association among given training datasets and recognizes repetitive patterns. ML emphasizes to create autonomous resolutions on newly seen datasets.<sup>6,7</sup>

Deep Learning (DL) is a new concept of advanced AI and a more complex form of ML that emulates the neuronal connections of the brain by creating an Artificial Neural Network (ANN). This algorithm learns from unstructured and unlabeled inputs without supervision and segregates data input from low-relevance variables. In unsupervised learning, unlabeled datasets are explored and used as unidentified patterns or clusters to predict unknown outputs.<sup>7,6</sup>

DL has been widely applied to pattern recognition such as image analysis, given its computational power in analyzing data via intricate neural networks. Other forms of DL

include Deep Neural Network (DNN) and Convolutional Neural Network (CNN). DNN which contains multiple hierarchical levels of ANN, is required to improve data predictions and allow the development of models without explicitly programmed directions, while CNN is used for computer vision tasks including medical image analysis.<sup>7,8</sup>

One must consider the risks associated with AI, potentially causing harm to an individual or inadvertently revealing a patient's confidential information when collecting and studying data with AI. In order to create a safer AI technology, it is essential to include safe designs, safety buffers, and structured safeguards. It is also important to pinpoint any uncertainties with potential technical systems to prevent errors. Wearables, cell phones, and other technical gadgets can be advantageous for doctors to assist patients with health issues through their capability to keep track of symptoms and the development of the condition.<sup>9</sup>

Doctors can direct and help patients to choose applicable AI-supported treatment for their condition and obtain patients' consent for the interest of effective medical service. The challenges include paving the way for early implementation, not paying attention to the patient's perspective, and guaranteeing continuous utilization within the digital healthcare system. The realization of the digital health transformation also requires various parties, including health workers, the government, ministries/agencies from other sectors, academics, communities, and volunteers to work together for more effective health services.<sup>3,6</sup>

Indonesia's government strongly supports and encourages the use of AI as a part of digital transformation technology for health services in the future. The "Health Technology Transformation Roadmap" arranged by the Ministry of Health Indonesia is divided into some main activities. The roadmap plan activities for

2023 includes an increase in the number of individual data variables from the previous year, 2022. This increase will be made possible through implementing an AI-based analysis system. The introduction of this technology will be marked by the growth of licensing for biotechnology products and their implementation in hospitals, enhancing telemedicine services in First Line Healthcare Facilities (FKTP), and a policy for digital health.<sup>10</sup>

### Utilization of AI in diabetic care

In this modernization era, AI has evolved into a facility that plays a role in health care, such as conducting screening, establishing diagnosis, and identifying complications. AI is defined as the science and engineering of making intelligent machines, through algorithms or a set of rules, which the machine follows to resemble human cognitive functions, such as learning and problem-solving.<sup>11</sup> AI has the potential to deal with issues as they come up and, as such, operate in an intelligent and adaptive manner.<sup>12</sup> The strength of utilizing AI is its ability to learn and recognize patterns in massive datasets. For instance, AI systems are capable of translating a patient's entire medical record into a single number that indicates a likely diagnosis.<sup>13</sup> Subsequently, AI has been crucial in the acceptance of these systems as common therapeutic tools for diabetes patients.<sup>14</sup>

In recent decades, the use of AI in diabetes management has undergone transformation with the latest technologies used, such as continuous glucose monitoring devices, artificial pancreatic development, and early detection of diabetic retinopathy with retinal camera.<sup>14,15</sup> Numerous AI-based methods (Table 1) have been used in the treatment of diabetes. The diagnosis of diabetes has advanced since the development of AI besides blood glucose levels and HbA1c tests.

**Table 1.** AI-Based Methods In Diabetic Care

Methods	Utilities
Case-based reasoning (CBR)	CBR is an artificial intelligence technique to support physicians in their clinical decision-making process by customizing and optimizing insulin administration for various meal situations. CBR learns from previous comparable meal experiences, which are characterized in cases using a set of parameters (e.g., meal timing, exercise). <sup>16</sup> It also makes automated recommendations to the patient to enhance their habits and understanding of the condition based on the collected data and physician preferences. <sup>17</sup> The example of CBR-based tool is Advanced Bolus Calculator for Diabetes (ABC4D) in smartphone, with the ability to recommend the insulin doses given to the patient by measuring the amount of meal intake and various parameters such as alcohol and exercises. <sup>18</sup>
Machine learning	Digital help for diabetes treatment has been developed using a variety of machine learning techniques. They consist of k-nearest neighbor, support vector machine, artificial neural network, naive bayes, decision tree, random forest, classification and regression trees, and artificial neural network. <sup>5</sup> Machine learning enables mobile applications to connect with users in very engaging ways, hence promoting treatment adherence. An example is a program that suggests appropriate foods based on a person's current glucose levels and past glycemic responses. <sup>19</sup>
Artificial neural networks	A 'neural network' portrays data as a large number of linked neurons, comparable to the human brain; hence, such models may approach clinical problems in a similar way to a clinician by combining several sources of divergent information and offering a personalized solution. <sup>14</sup> The researchers developed a regression model based on ANN, an exercise guidance for diabetes' patients, that could be used to automatically evaluate the activity levels of patients using accelerometers and heart monitors, as well as track changes in glucose levels that happened while the participants were exercising. <sup>16</sup>

Several applications in the area of diabetes are currently designed and used to optimize the management of diseases listed in Table 2.

**Table 2. AI-Based Applications In Diabetic Care**

Applications	Utilities
Automated retinal screening	AI-based retina screening is a viable, accurate, and widely recognized tool for detecting and monitoring diabetic retinopathy. The automated screening of the retina has a high sensitivity and specificity of 92.3% and 93.7%, respectively. The system integrates the results of numerous, partially dependent biomarker detectors, some of which employ convolutional neural networks. <sup>20,21</sup> It included separate algorithms for quantifying image quality and the detection of haemorrhages, exudates, cotton wool spots, neovascularisation, and irregular lesions. <sup>22</sup>
Clinical decision support	Clinical decision support systems based on supervised machine learning have been created to predict short- and long-term HbA1c response following insulin initiation in patients with type 2 diabetes mellitus. These techniques also aid in the identification of clinical factors that may impact a patient's HbA1c response. <sup>23</sup>
Predictive population risk stratification	Predictive models have been developed to use big data analytics to evaluate the likelihood of problems developing in diabetic patients. Many similar models have been created to predict both long-term (eg, retinal, cardiovascular, and renal) and short-term (eg, hypoglycemia) diabetic problems. <sup>24</sup> Given an example of application called <i>FootSnap</i> with its objectivity in standardizing the capture of diabetic foot photographs for longitudinal/follow-up investigations of the plantar surface of the diabetic foot. <sup>25</sup>
Genomic	Advanced molecular phenotyping, genomics, epigenetic changes, and the development of digital biomarkers may be used in the approach to diagnosis and management of diabetes, where large data sets are created due to the disease's heterogeneous character and chronic duration. <sup>9</sup> For the past decade, the analysis of array-based genome-wide association studies (GWAS) has given the most powerful way to identifying genetic variations contributing to the risk of complex characteristics such as type 2 diabetes (T2D). This method has enabled the finding of many thousands of linked regions spanning hundreds of characteristics, including >120 loci increasing type 2 diabetes risk. <sup>26</sup>

## Telehealth

Remote monitoring by Telehealth helps shortening follow-up visits and provides for better real-time monitoring of the patient's glycemic condition as well as general health. Virtual engagements and remote monitoring have the potential to replace 50%-70% of typical follow-up healthcare appointments.<sup>27</sup>

## Visual dietary application

Mobile applications appear to be a useful approach to help young people with diabetes grasp the fundamentals of their condition and manage it with treatment challenges. Given the example of an application called *DiaMob*. This application uses smartphone camera to capture the actual diet of the patients and targets carbohydrate evaluation and insulin dosages. Actual insulin dose appropriate for the meal they planned to consume was input, and the app then launched the camera feature on the mobile phone, photographing the portion.<sup>28</sup>

AI enables informed and empowered patient engagement. As they affect patient comorbidities, behaviors, time spent in healthcare facilities, and interaction with healthcare professionals, digital solutions have a significant impact on the healthcare systems.<sup>27</sup> Patients have the opportunity to interact and gain knowledge from one another through online diabetic communities and support groups. Patients' desired results and general well-being are impacted by this cooperative approach to learn more about various conditions, which is interesting for both patients and caregivers.<sup>29</sup>

### AI-based diabetic care in Indonesia: Potentials and Limits

Indonesia's AI National Strategy has identified five key areas, including healthcare. AI may provide several benefits to the health industry, particularly in accelerating the diagnostic procedure to achieve findings.<sup>30</sup> The usage of technology in the form of telecommunications network devices in Indonesia is still on the rise, by means of improvements in multimedia, images, computers, information systems, and telecommunications.<sup>31</sup> The Ministry of Health Indonesia has a vision to digitize the health sector which is stated in the Regulation of the Ministry of Health Republic of Indonesia

(Permenkes RI) No. 21 of 2020 concerning Health Governance Reform including the integration of information systems, health development, and research.<sup>10</sup>

AI-based tools might possibly minimize the costs of screening and treatment plan selection for disorders that need expensive technology and specialized skills that are not accessible in most low or middle-income countries, particularly in rural and remote locations.<sup>32,33,34</sup> Indeed, when new digital technologies, like AI, are available in local contexts, they can allow the creation of more inexpensive, higher-quality, and accessible innovations while overcoming the local resource-constrained environment.<sup>35</sup>

Routine data integration is a crucial part of digital services. The lack of sufficient data to build logical and accurate algorithms is a frequent challenge in diabetes care with AI. More than 80% of health service facilities in Indonesia have not yet implemented digital technology. Although technology is still not optimally used in Indonesia, it is essential for the adoption of AI in health services.<sup>10,36</sup>

Incomplete, inconsistent, and inaccurate data recording is the main factor affecting the quality of digital patient management. More than 270 million patients' data is still documented manually and not

integrated digitally. Several regions in Indonesia still use paper to record medical history, prescriptions, and health-finance claims. To create effective solutions by AI, datasets need to be increasingly developed and structured. The seamless acceptance of digital applications in the treatment of diabetes is also being constrained by patients' worries about security, data protection, and regulatory issues. Indonesia still lacks regulations regarding the standardization of data input and output flows, protection, and rights of privacy from patients' data.<sup>10,36,37</sup>

Cost, access, and implementation are also obstacles to using AI for the treatment of diabetes. Indonesia is one of the developing countries with rural areas which may lead to unequal access to AI-powered technologies due to the inadequate infrastructure, lack of public health worker training in AI, lack of computational resources, skilled labor, or internet access.<sup>38</sup> Meanwhile, until 2023, Indonesia has more than 400 healthcare-related applications. Interoperability is a typical possible impediment to the use of a rising number of devices and applications in diabetes care. Many health applications have been created by the central government, local governments, and the commercial sector separately, resulting in fragmented data that is dispersed across very diverse systems, incomplete, and inefficient services.<sup>9,39,40</sup>

Diagnostic and screening machine learning applications are designed to assist physicians in enhancing their skills. However, relying solely on AI to automate patient care without reviewing or updating the latest healthcare research may lead to deskilling physicians by introducing dependence on AI and potentially replacing healthcare workers.<sup>41-43</sup> Nevertheless, most studies claim that AI is unlikely to replace healthcare workers since the development and adoption of healthcare AI applications are slow, and healthcare work still requires a combination of cognitive and emotional skills.<sup>44,45</sup> Moreover, AI in diabetic care is still in need of regular refinement by professionals.<sup>6</sup> Physicians must be adaptable

and consider both the causes and effects of medical issues, as well as the methods and models used to assist them in their decision-making process.<sup>6,37</sup>

Currently, The Ministry of Health Indonesia has formulated a Blueprint for Digital Transformation Strategy 2024 with collaboration from various parties in the health sector and industry under the Indonesia Health Services (IHS) platform. This platform is a system that provides data connectivity, analysis, and services to support and integrate various Indonesian health applications. It provides Indonesia with a way to achieve a measurable and focused digital transformation for the development of an integrated and sustainable healthcare system.<sup>10</sup>

## CONCLUSION

A large amount of health data input, routine data integration, and routine refinements by professionals are still required for the training of the AI model especially for AI-based diabetic care in Indonesia. However, Indonesia still confronts various challenges in integrating AI-diabetic management due to low-resource areas that do not have equitable access to technology. Complete and standardized digital data records also facilitate evidence-based AI development, improve the competence of staff in health services, and reduce administrative workload.

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## Management of Severe Hypertriglyceridemia

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### INTRODUCTION

Hypertriglyceridemia is a condition characterized by increased fasting plasma triglyceride levels with or without other lipoprotein disturbances. Based on The Endocrine Society (ESC) 2010 levels of triglyceride levels are divided into five, namely: normal (<150 mg/dL), mild (150-199 mg/dL), moderate (200-999 mg/dL), severe (1000-1999 mg/dL), and very severe ( $\geq$ 2000 mg/dL).<sup>1</sup>

Acute pancreatitis is one of the complications of hypertriglyceridemia, along with cardiovascular complications. After gallstones and alcohol, Hypertriglyceridemia is the third most common cause of acute pancreatitis, with an incidence of 4-10%. The incidence of acute pancreatitis increases by up to 4% for each 100 mg/dL increase in triglycerides.<sup>2</sup> A large-scale study reported that the incidence of acute pancreatitis was 3.2 times greater in the group with triglyceride levels  $>500$  mg/dL compared to those with triglyceride levels  $<150$  mg/dL.<sup>2</sup>

The prevalence of hypertriglyceridemia is higher in men than in women, with a ratio of 28.7% for men and 21.5% for women, with the highest age in men between 40 and 59 years of age and in women over 60 years of age.<sup>3</sup>

This paper discusses the management of severe hypertriglyceridemia, especially in special conditions such as pregnancy and acute pancreatitis complications.

### ETIOLOGY AND DIAGNOSTIC CRITERIA

Hypertriglyceridemia can be caused by excessive triglyceride production in the liver, decreased hepatic clearance of chylomicrons and VLDL, inefficient lipolysis, or a combination of these three. Triglyceride levels are affected by environmental and genetic factors. Persistent hypertriglyceridemia is typically caused by monogenic, polygenic, or genetic factors with unknown causes. Secondary hypertriglyceridemia is caused by a specific disease condition or the influence of drugs.<sup>3</sup>

Based on etiology, hypertriglyceridemia is divided into primary and secondary. Primary Hypertriglyceridemia caused by genetic disorders, by Fredrickson, is divided into five types, namely: familial chylomicronemia (type 1), familial combined hyperlipoproteinemia (type 2 B), familial dysbetalipoproteinemia (type 3), familial Hypertriglyceridemia (type 4), and primary mixed hyperlipidemia (type 5), while secondary Hypertriglyceridemia is caused by several conditions such as nephrotic syndrome, type 2 diabetes mellitus, hypothyroidism, chronic kidney disease, alcoholism, pregnancy, and consumption of certain drugs, namely corticosteroids, oral contraceptives, protease inhibitors (for people with HIV), antihypertensive drugs (thiazides and beta blockers).<sup>4</sup>

Diagnostic criteria for hypertriglyceridemia based on the National Cholesterol Education Program Adult Panel

Treatment (NCEP-ATP III) are divided into four levels, namely: normal (<150 mg/dL), borderline (150–199 mg/dL), high (200–499 mg/dL), very high (>500 mg/dL). Meanwhile, based on ESC 2010, triglyceride levels are divided into five,

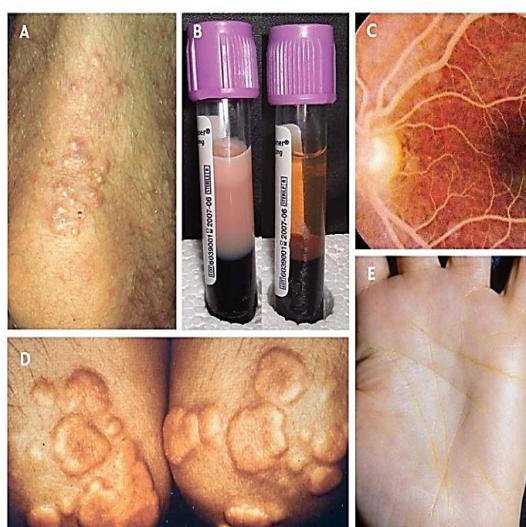
namely: normal (<150 mg/dL), mild (150–199 mg/dL), moderate (200–999 mg/dL), severe (1000–1999 mg/dL), and very severe ( $\geq 2000$  mg/dL).<sup>5</sup>

**Table 1.** Diagnostic Criteria for Hypertriglyceridemia Based on NCEP-ATP III and The ESC 2010<sup>5</sup>

NCEP ATP III (3)			The Endocrine Society 2010 <sup>a</sup>		
Normal	<150 mg/dl	<1.7 mmol/liter	Normal	<150 mg/dl	<1.7 mmol/liter
Borderline-high triglycerides	150–199 mg/dl	1.7–2.3 mmol/liter	Mild hypertriglyceridemia	150–199 mg/dl	1.7–2.3 mmol/liter
High triglycerides	200–499 mg/dl	2.3–5.6 mmol/liter	Moderate hypertriglyceridemia	200–999 mg/dl	2.3–11.2 mmol/liter
Very high triglycerides	$\geq 500$ mg/dl	$\geq 5.6$ mmol/liter	Severe hypertriglyceridemia	1000–1999 mg/dl	11.2–22.4 mmol/liter
			Very severe hypertriglyceridemia	$\geq 2000$ mg/dl	$\geq 22.4$ mmol/liter

## CLINICAL OVERVIEW

Until triglyceride levels reach  $>1000$  mg/dL, the clinical manifestations of Hypertriglyceridemia are typically asymptomatic. A portion of the clinical picture that emerges can have an impact on various systems. In the central nervous system as mood and neurocognitive disorders, lipemia retinalis; in the gastrointestinal system as nausea, vomiting, and hepatosplenomegaly; and in the musculoskeletal system as eruptive xanthoma and xanthoma striata palmaris. (Figure 1).<sup>6</sup>



**Figure 1.** Clinical manifestations of hypertriglyceridemia<sup>6</sup>

## Triglyceride Metabolism

There are two primary pathways for triglyceride metabolism in the body: exogenous and endogenous. The exogenous pathway begins in the small intestine and concludes in the liver, where chylomicrons containing triglycerides derived from food in the small intestine are formed. Chylomicrons then enter the bloodstream through the thoracic duct. Triglycerides and chylomicrons in fat tissue are hydrolyzed by lipoprotein lipase to produce free fatty acids (FFA) and glycerol, which then enter peripheral tissues and are stored as adipocytes and energy sources.<sup>7</sup>

The endogenous pathway is the next step in the synthesis of triglycerides. In this pathway, the liver synthesizes triglycerides from glycerol and FFA derived from three main sources: adipocytes, remnant chylomicrons, and fat derived from food absorbed directly from the small intestine through the portal vein. 10% of healthy individuals undergo de novo lipogenesis, whereas 22% of patients with insulin resistance and nonalcoholic fatty liver disease (NAFLD) do. The liver then releases triglycerides and VLDL into the plasma, where VLDL undergoes lipolysis, produces remnant particles, as with chylomicrons, or complete lipolysis, and is converted into LDL. Extra LDL will accumulate in the blood vessels and cause atherosclerosis. Lipoprotein lipase plays an important role in the lipolysis of triglycerides and VLDL.<sup>7,8</sup>

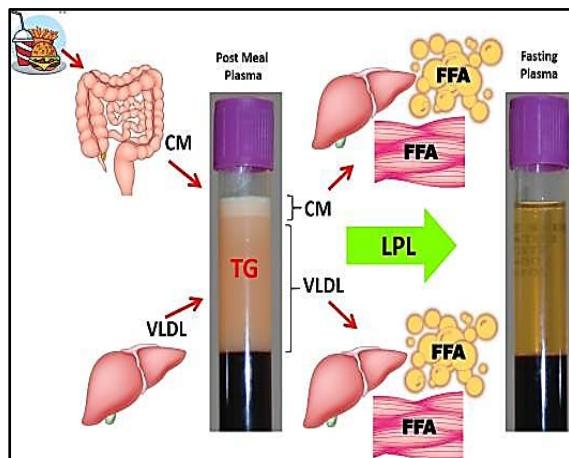


Figure 2. Triglyceride metabolism: exogenous pathway and endogenous pathway<sup>7</sup>

### Management of Hypertriglyceridemia

Hypertriglyceridemia management aims to reduce the incidence of acute pancreatitis and cardiovascular complications. Two hypotheses explain the occurrence of hypertriglyceridemia-related acute pancreatitis. The first theory is that high triglycerides cause an increase in chylomicrons, which are then hydrolyzed into free fatty acids (FFA). FFA aggregates micellar structures that cause damage to platelets, vascular endothelium, and acinar cells, which then trigger ischemia and acidosis, then activate trypsinogen, which causes pancreatitis. The second theory posits that increased chylomicrons will increase plasma viscosity, resulting in capillary damage, tissue ischemia, and acidosis, all of which will initiate pancreatitis.<sup>9</sup>

In conditions of severe hypertriglyceridemia, triglycerides must be lowered immediately to prevent further complications. Management in the form of nutritional intervention, anti-hyperlipidemic drugs, and plasmapheresis can be performed in emergency conditions such as acute pancreatitis due to hypertriglyceridemia.<sup>10</sup> The following is the management of hypertriglyceridemia in certain conditions.

### Management of Hypertriglyceridemia in Pregnancy

Hypertriglyceridemia is associated with elevated levels of estrogen and human placenta lactogen (HPL) during pregnancy. Estrogen causes an increase in VLDL, while HPL increases the hydrolysis of adipose tissue, resulting in an increase in FFA levels; consequently, triglyceride synthesis increases in the liver. Acute pancreatitis caused by hypertriglyceridemia is more prevalent in the third trimester of pregnancy since triglyceride levels increase with gestational age, increasing two to fourfold and reaching a peak in the third trimester.<sup>11,12</sup>

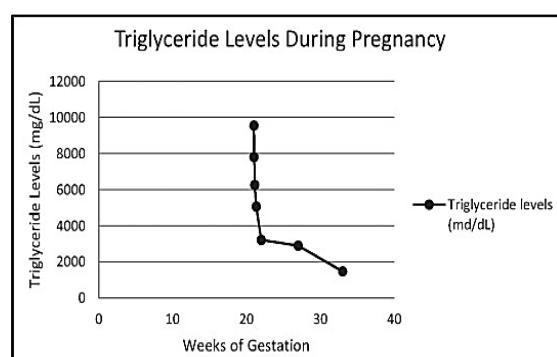


Figure 3. Triglyceride levels during pregnancy<sup>13</sup>

Multidisciplinary disciplines, including nutrition, obstetrics, gynecology, and endocrine metabolism, should be involved in managing acute pancreatitis caused by Hypertriglyceridemia during pregnancy to prevent complications for both the mother and the fetus.

#### a. Diet and nutrition therapy

To reduce chylomicron levels, the diet must be isocaloric, low in fat, and the total calorie requirement from fat must be <20%. Parenteral nutrition (NP) may be used to optimize the nutrition of pregnant women. It is believed that NPs are effective due to the delivery of systemic lipids through the portal system, which permits peripheral metabolism and transplacental fat release. The diet must contain at least 300 mg of EPA and DHA because a deficiency increases the risk of brain disorders and visual

development in the fetus by <2%. Since omega-3 fatty acids contain EPA and DHA, which decrease liver lipogenesis and increase fatty acid oxidation in the liver and skeletal muscle, they are the nutritional therapy of choice. Several studies have found that nutritional therapy can reduce triglyceride levels by 25 to 30 percent.<sup>12,13</sup>

### **b. Pharmacological therapy**

#### **b.1. Niacin**

Niacin is also known as nicotinic acid or vitamin B3. Niacin inhibits diacylglycerol acyl transferase 2, which is involved in the enzymatic esterification of triglyceride production in hepatocytes. Niacin inhibits hepatocyte HDL catabolism receptors, thereby preventing damage to HDL apo A I due to a decrease in triglyceride synthesis-induced intracellular apo B degradation. The recommended daily intake of niacin during pregnancy is 18 mg/day, but a pharmacological dose of niacin is required to achieve lipid reduction (2 to 3 g/day), and there are no studies on the effects of pharmacological doses of niacin during pregnancy. Niacin is a pregnancy category C drug.<sup>12,13</sup>

#### **b.2. Heparin**

Heparin administered intravenously can decrease triglyceride levels by releasing LPL from endothelial cells into the plasma. Intravenous administration of heparin is still controversial because the increase in LPL is only temporary and rebound Hypertriglyceridemia will occur shortly after therapy is discontinued. Furthermore, the risk of pancreatic bleeding is very high, meaning heparin is not recommended for the treatment of acute pancreatitis in pregnancy.<sup>12</sup>

#### **b.3. Insulin**

Insulin therapy administered intravenously can reduce triglyceride levels by accelerating chylomicron degradation, activating LPL enzymes, and inhibiting hormone-sensitive lipase (HSL). Reduced HPL activation will decrease the breakdown of adipocytes and

triglycerides, decreasing circulating FFA and reducing the pancreas' toxic and inflammatory effects. Insulin is administered at a 0.1–0.3 U/kg/hour dose, while blood sugar, electrolytes, and triglycerides are monitored every hour and 12 hours, respectively. Insulin can reduce triglycerides by 50% to 75% in two to three days.<sup>14,15</sup>

#### **b.4. Plasmapheresis**

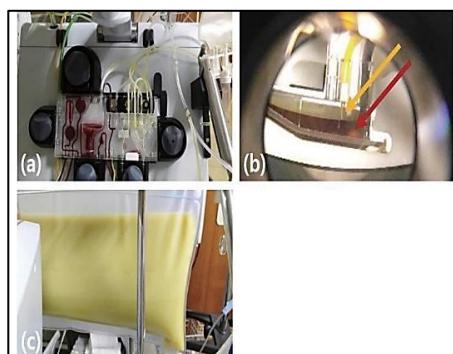
Plasmapheresis as a therapy for severe Hypertriglyceridemia was first introduced by Betteridge et al. in 1978, indicated in emergency conditions such as pancreatitis due to hypertriglyceridemia in pregnancy with triglyceride levels > 1000 mg/dL. Plasmapheresis can reduce triglyceride levels by 50–80% in the first 24 hours.<sup>10,16</sup> In addition to rapidly reducing triglyceride levels, plasmapheresis can also inhibit proinflammatory cytokines and adhesion molecules, which play a significant role in the pathogenesis of pancreatitis. This action is extremely safe and effective for treating hypertriglyceridemia-related pancreatitis during pregnancy. Possible adverse effects include urticaria, hypotension, headache, and chills.<sup>17,18</sup>

### **Management of Acute Pancreatitis Due to Hypertriglyceridemia**

The third cause of acute pancreatitis, after gallstones and alcohol, is Hypertriglyceridemia. The clinical manifestations are identical: nausea, vomiting, and heartburn; however, the resulting complications and organ damage are significantly more severe. There are currently no standard guidelines for the treatment of acute pancreatitis caused by hypertriglyceridemia.<sup>10,16</sup>

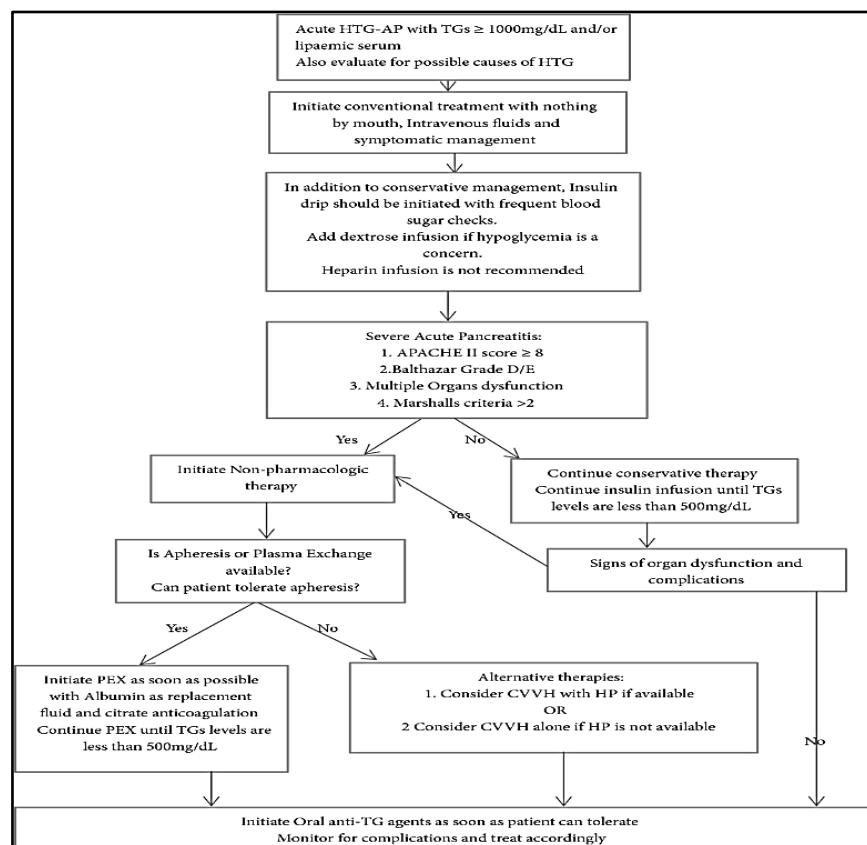
Management of acute pancreatitis generally consists of stopping oral intake, adequate fluid hydration, correction of electrolyte imbalance, administration of adequate analgesia, administration of antibiotics if needed, and specific therapy depending on the cause.<sup>17</sup> Plasmapheresis is the primary treatment option for hypertriglyceridemia related

acute pancreatitis. Plasmapheresis can reduce triglycerides more rapidly than other conservative therapies, such as intravenous insulin and heparin, as well as reduce morbidity and mortality. One plasmapheresis session usually reduces triglycerides by 50–80%. Plasmapheresis removes triglyceride-rich plasma through filtration or centrifugation and replaces it with colloidal fluid components (albumin, plasma, or crystalloids).<sup>19, 20</sup>



**Figure 4.** Plasmapheresis: a. Plasmapheresis process b. The patient's blood is separated into two parts c. The bag contains triglyceride-rich plasma after plasmapheresis<sup>22</sup>

Other conservative treatment options are intravenous insulin or heparin. Intravenous insulin therapy is considered more minimally invasive and easy to do with a dose of 0.1–0.3 U/kg/hour while monitoring blood sugar every hour and triglycerides every 12 hours, given 5% dextrose if the blood sugar level is <200 mg/dL. For the heparin used is unfractionated heparin (UFH) at a dose of 60 U/kg bw, or low molecular weight heparin (LMWH) at a dose of 1 mg/kg of weight in several studies showing the same effect on both UFH and LMWH in the treatment of acute pancreatitis due to Hypertriglyceridemia.<sup>21</sup> Insulin is preferred even in non-diabetic patients due to the risk of pancreatic bleeding and rebound Hypertriglyceridemia associated with administering heparin.<sup>16</sup> The following is an algorithm for the management of acute pancreatitis due to Hypertriglyceridemia.



**Figure 5.** Algorithm for the management of acute pancreatitis due to hypertriglyceridemia<sup>16</sup>

## SUMMARY

Hypertriglyceridemia is characterized by elevated fasting plasma triglyceride levels with or without other lipoprotein abnormalities. Acute pancreatitis is one of the complications of hypertriglyceridemia, along with cardiovascular complications. After gallstones and alcohol, hypertriglyceridemia is the third most common cause of acute pancreatitis.

In general, the treatment of acute pancreatitis includes cessation of oral intake, adequate hydration, correction of electrolyte imbalance, administration of adequate analgesia, administration of antibiotics if necessary, and specific therapy based on the underlying cause.

Plasmapheresis is the primary treatment option for hypertriglyceridemia-related acute pancreatitis. Plasmapheresis can reduce triglycerides more rapidly than other conservative therapies, such as intravenous insulin and heparin, as well as reduce morbidity and mortality.

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- **General principles**

1. Manuscripts submitted to Indonesian Journal of Endocrinology Metabolism and Diabetes (InaJEMD) should neither be published before nor be under consideration for publication in another journal.
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5. Ensure that all authors have approved the content of the submitted manuscript.
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  - 3) Systematic review
  - 4) Case report
  - 5) Case series
  - 6) Case illustration
  - 7) Special article
  - 8) Clinical practice
  - 9) Point of view
  - 10) Editorial
  - 11) Community/public health study

- **Writing guideline**

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

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

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

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2. **Illustrations/tables:** no illustration and/or tables.
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2. **Abstract:** No more than 250 words summarizing the problem being considered, how the study was performed, the salient results and the principal conclusions under subheadings background and purpose of the study, methods, results, and conclusion. Please define abstract in two version languages (Bahasa Indonesia and English).
3. **Key words:** No more than 5 words or short phrases.
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10. **References:** (usually below 30). Please see References for further style guidance. Consist of references of minimal 10 years recently and in the form of essay.
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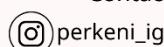


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