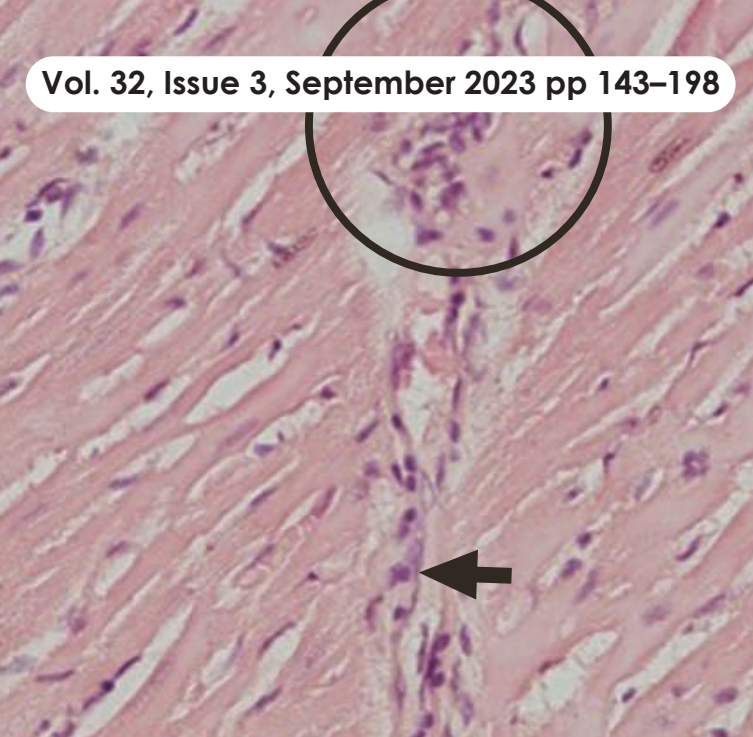
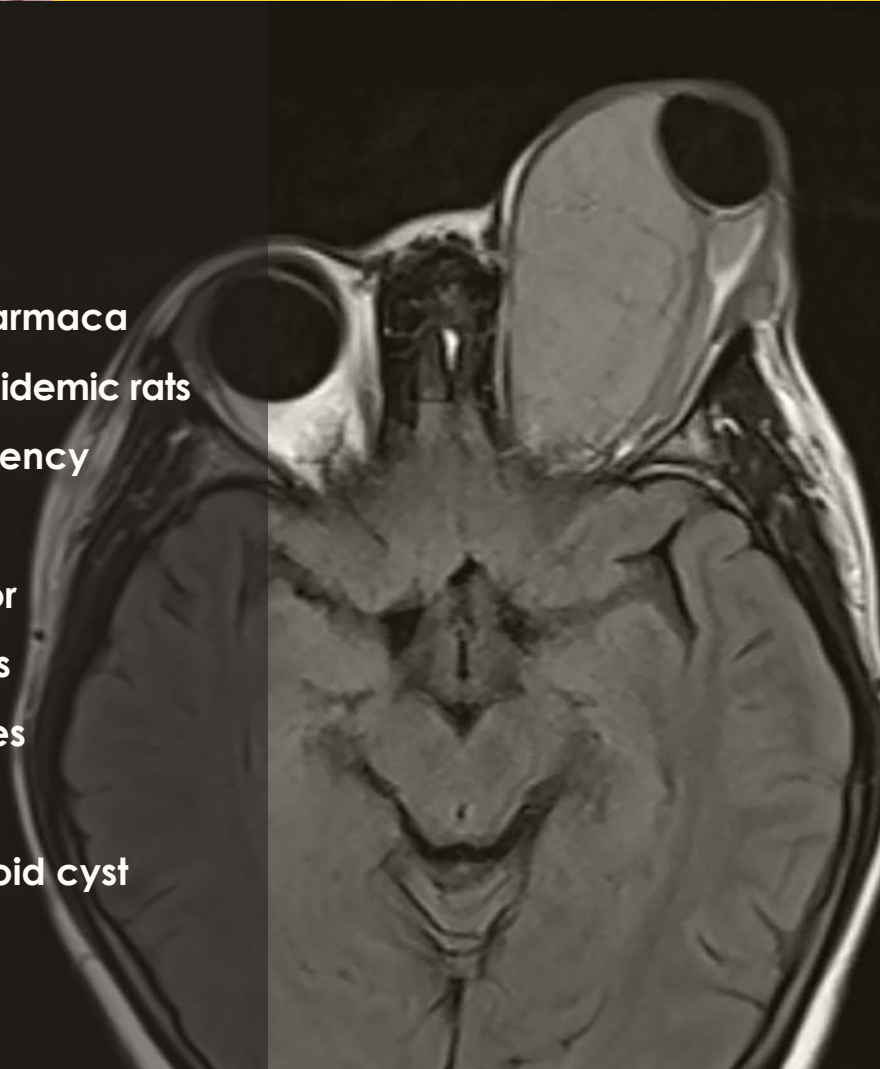


# Medical Journal of Indonesia



- ✓ Editor's note
- ✓ Kidney transplantation in Indonesia
- ✓ Diabetic cardiomyopathy phytopharmaca
- ✓ Effect of mango peel extract in dyslipidemic rats
- ✓ Vigna subterranea for protein deficiency
- ✓ Indonesian version of the IBDQ-9
- ✓ Facial profile of  $\beta$ -thalassemia major
- ✓ Vitamin D, depression, and diabetes
- ✓ Profile of elderly with pressure injuries
- ✓ Atypical orbital meningioma
- ✓ Endoscopic fenestration for arachnoid cyst



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# Medical Journal of Indonesia

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# Medical Journal of Indonesia

Volume 32 • Number 3 • September 2023 • page 143–198 • pISSN: 0853-1773 • eISSN: 2252-8083

## Contents

### Editorial

- 143 Editor's note  
*Hans Joachim Freisleben*

### Commentary

- 146 Development of kidney transplantation as a healthcare development model to achieve Indonesia Emas 2045  
*Nur Rasyid, Endang Susalit, Arry Rodjani*

### Basic Medical Research

- 150 Effects of methotrexate, *Moringa oleifera*, and *Andrographis paniculata* extracts on the myocardial and aortic tissue of streptozotocin-nicotinamide-induced hyperglycemic rats  
*Dimas Bathoro Bagus Pamungkas, Viskasari Pintoko Kalanjati, Abdurachman, Dwi Martha Nur Aditya, Muhammad Husni Fansury Nasution, Maya Rahmayanti Syamhadi*
- 157 Effect of *arum manis* mango peel extract on cholesterol and triglyceride levels in dyslipidemic Sprague-Dawley rats  
*Taufik Saputra, Haidar Satya Naufal, Astika Widy Utomo, Nyoman Suci Widyastiti, Muhammad Farhan Kurniawan, Arfianty Nur Azizah*
- 161 Bambara groundnut ameliorates kidney histology in female mice with protein deficiency  
*Vykra Aulia Firdiana, Rimonta Febby Gunanegara, Sunarti, Ardaning Nuriliani*

### Clinical Research

- 168 Validity and reliability of the Indonesian version of the 9-item Inflammatory Bowel Disease Questionnaire (IBDQ-9)  
*Dekta Filantropi Esa, Hamzah Shatri, Cleopas Martin Rumende, Adityo Susilo, Hasan Maulahela, Achmad Fauzi, Marcellus Simadibrata*
- 173 Lateral facial profile of  $\beta$ -thalassemia major in Javanese children: a photogrammetric analysis  
*Wulan Geraldine Parengkuan, Sri Kuswandari, Indah Titien Soeprihati*
- 177 Vitamin D levels and depression in type 2 diabetes mellitus patients: a cross-sectional study  
*Rudi Putranto, Kresna Adhiatma, Tri Juli Edi Tarigan, Cleopas Martin Rumende, Hamzah Shatri, Iris Rengganis, Pringgodigdo Nugroho, Ikhwan Rinaldi*
- 183 Characteristics of pressure injuries among geriatric patients at an Indonesian tertiary hospital: a cross-sectional study  
*Shannaz Nadia Yusharyahya, Lili Legiawati, Rinadewi Astriningrum, Reganedgary Jonlean, Vega Andhira*

## Case Report/Series

- 190 Atypical orbital primary optic nerve sheath meningioma with severe disfiguring proptosis: an alternative surgical approach  
*Sylves Patrick, Yeap Boon Tat, Muhamad Zarif Mohd Amin, Maftuhim Addenan, Shuaibah Ab.Ghani, Hanida Hanafi*
- 194 Transventricular transforaminal endoscopic fenestration with cysto-ventriculoperitoneal shunt to manage a third ventricular arachnoid cyst: a case report  
*Nia Yuliatri, Ingrid Ayke Widjaya, Alphadenti Harlyjoy, Gibran Aditiara Wibawa, Satyanegara*

## Correction

- 198 Corrigendum: Quadrigeminal plate arachnoid cyst presenting with eye movement related migraine: a rare case report  
*Yemima Graciela, Robert Shen, Mardjono Tjahjadi*

**Front Page:** Histopathology of left ventricle myocardium in rats given methotrexate (MTX) showed necrotic centers (arrow) described as cardiomyocyte cytoplasmic disintegration and inflammatory cell infiltration, with interstitial edema and myocardial fiber disorientation (in circle), as reported by Pamungkas et al, and MRI brain and orbit with contrast showed left orbital mass measuring 6.7 cm × 4.7 cm × 4.9 cm with severe left eye proptosis and distorted eyeball, as reported by Patrick et al. These are published in this issue.

# Contents

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**See the journal website for contents.**



# Medical Journal of Indonesia

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- Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. *Brain Res.* 2002;935(1-2):40–6.

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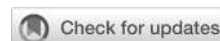






## Lateral facial profile of $\beta$ -thalassemia major in Javanese children: a photogrammetric analysis

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### ABSTRACT

**BACKGROUND** Impairment of globin chain synthesis in patients with  $\beta$ -thalassemia major causes ineffective erythropoiesis. This condition triggers bone marrow hyperplasia and can lead to craniofacial bone abnormalities. This study aimed to evaluate the lateral facial profile of  $\beta$ -thalassemia major, identify any differences when compared with a control group of similar age and ethnicity, and reveal the facial profile of  $\beta$ -thalassemia major in Javanese children.

**METHODS** This cross-sectional study included 35  $\beta$ -thalassemia major children aged 7–15 years. They were divided into 3 groups based on their age. Lateral facial photogrammetry was taken by measuring the forehead protrusion and nasolabial angle. Data were then mapped to the normal group of children in the same age group and descriptively analyzed using SPSS software.

**RESULTS** The 1 and 2 SD group had a higher prevalence of  $\beta$ -thalassemia major in children aged 7–9 years for both sexes. The older age group had a closer mean value to those of children without thalassemia.

**CONCLUSIONS** The forehead and maxillary profile of Javanese  $\beta$ -thalassemia major children tended to be protrusive, especially in the 7–9 years age group, while the older age groups had closer mean values to those of children without thalassemia.

**KEYWORDS** beta-thalassemia, facial bones, photogrammetry

Thalassemia is a common genetic blood disorder in Indonesia. Thalassemia cases have increased from 4,896 in 2012 to 8,761 in 2018.<sup>1,2</sup>  $\beta$ -thalassemia major, the most severe thalassemia, causes severe anemia due to impaired hemoglobin synthesis,<sup>3</sup> stimulating the bone marrow to increase erythrocyte production due to ineffective red blood cell formation. Subsequently, bone expansion may result in cortical thinning, bone distortion, and fragility, often leading to characteristic skeletal and oral and maxillofacial deformities.<sup>1</sup>

The most visible facial characteristics of patients with  $\beta$ -thalassemia major are maxillary protrusion and

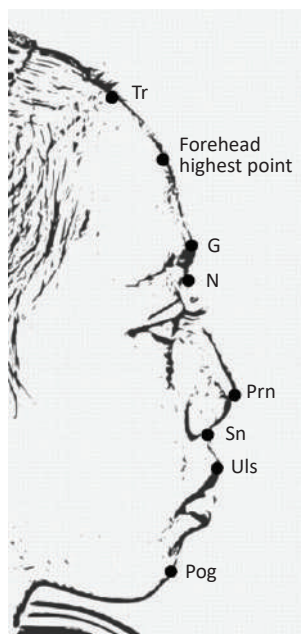
a prominent forehead or frontal bossing,<sup>4</sup> which can be identified using facial photography. Photogrammetry is an effective method to evaluate external craniofacial structures, including soft tissue involvement,<sup>5</sup> and measure the angular facial profile.<sup>6</sup>

Studies regarding the facial profile characteristics of patients with  $\beta$ -thalassemia major, especially in Indonesia, remain unclear. This study aimed to identify the lateral facial profile of Javanese children with  $\beta$ -thalassemia major and elucidate the forehead and maxilla as the clinical predictors in pediatric dentistry for diagnosing  $\beta$ -thalassemia major.

## METHODS

This study was approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Dr. Sardjito General Hospital, Yogyakarta (approval number: KE/FK/0697/EC/2021). Informed consent was obtained from the patients' parents.

This quantitative study included 35 Javanese children (18 males and 17 females, aged 7–15 years) at the Division of Hematology and Oncology, Department of Pediatrics, Dr. Sardjito General Hospital, Yogyakarta, who underwent blood transfusions every 2–3 weeks and were treated during September 2021. The patient's demographic data, medical history, body weight, and height were recorded. Photographs of the lateral aspect of the face were obtained at a distance of 150 cm from the tip of the patient's nose for standardization using a mirrorless camera (Sony  $\alpha$ 7 mark II, Sony, Japan). The patients were seated upright on a chair without a backrest in a resting position, with their eyes looking straight ahead. All of the photographs were obtained by one photographer in the same setting using microlens placed on a tripod at the eye level. The facial midline and interpupillary line were aligned with vertical and horizontal lines on the camera to correct for facial deviations. A cephalostat modification was used to maintain the position of the head so that the



**Figure 1.** Facial landmarks of patients with  $\beta$ -thalassemia major (lateral view). G=glabella; N=nasion; Pog=pogonion; Prn=pronasal; Sn=subnasal; Tr=trichion; Uls=upper lips

Frankfurt horizontal plane was parallel to the floor, and the camera direction was perpendicular to the patient's face. Other photographic parameters were also standardized (aperture: F/4.5; shutter speed: 1/125; and ISO: 2000). Adequate lighting was used for all photographs.

The forehead protrusion (trichion [highest point of the forehead]–nasion) and nasolabial angle (NLA) were measured on the photographs using CorelDRAW 2021 (Corel Corporation, Canada) (Figure 1). The forehead protrusion angle was measured from the intersection of the trichion–glabella line and the line drawn from the glabella along the edge of the forehead to the trichion. The NLA was formed by the intersection of pronasal with the subnasal line and subnasal with the upper lips line.

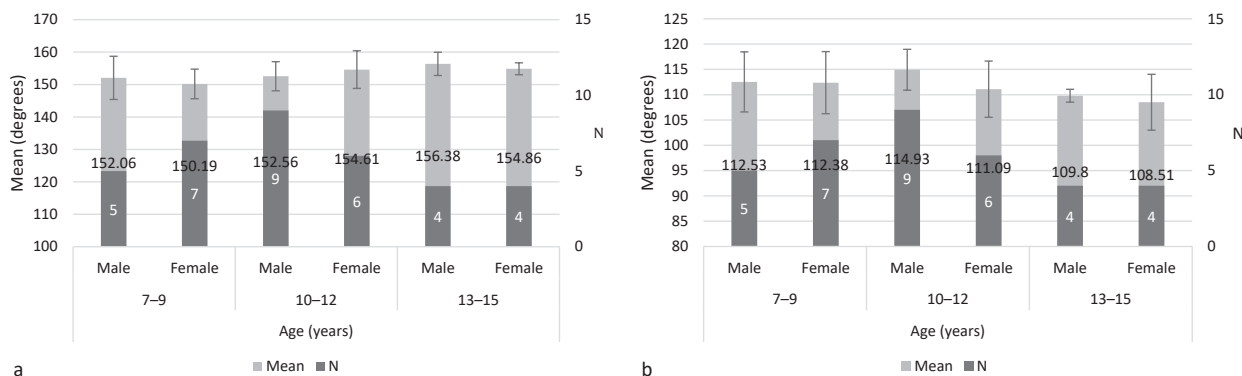
The patients were divided into three dental age groups: 7–9, 10–12, and 13–15 years. The patient characteristics were compared with children without thalassemia in the same age group who were of Javanese ethnicity, lived in Yogyakarta or its surrounding areas, had a normal body mass index, had no history of orthodontic treatment, and had an externally normal jaw. The mean and standard deviation (SD) of the control group's measurements were calculated by SPSS software version 26 (IBM Corp., USA) and classified into four categories: mean, -1 SD, -2 SD, and -3 SD value groups. The individual score of thalassemia patient was mapped into control group's graphs.

The photographs were processed using Adobe Photoshop (Adobe Systems Incorporated, USA). Facial profile photos were evaluated using CorelDRAW 2021 (Corel Corporation) at a 1:1 magnification. All photographs were re-evaluated by the examiner after 1 week. The data were analyzed using SPSS software version 26 (IBM Corp). Statistical significance was set at  $p < 0.05$ .

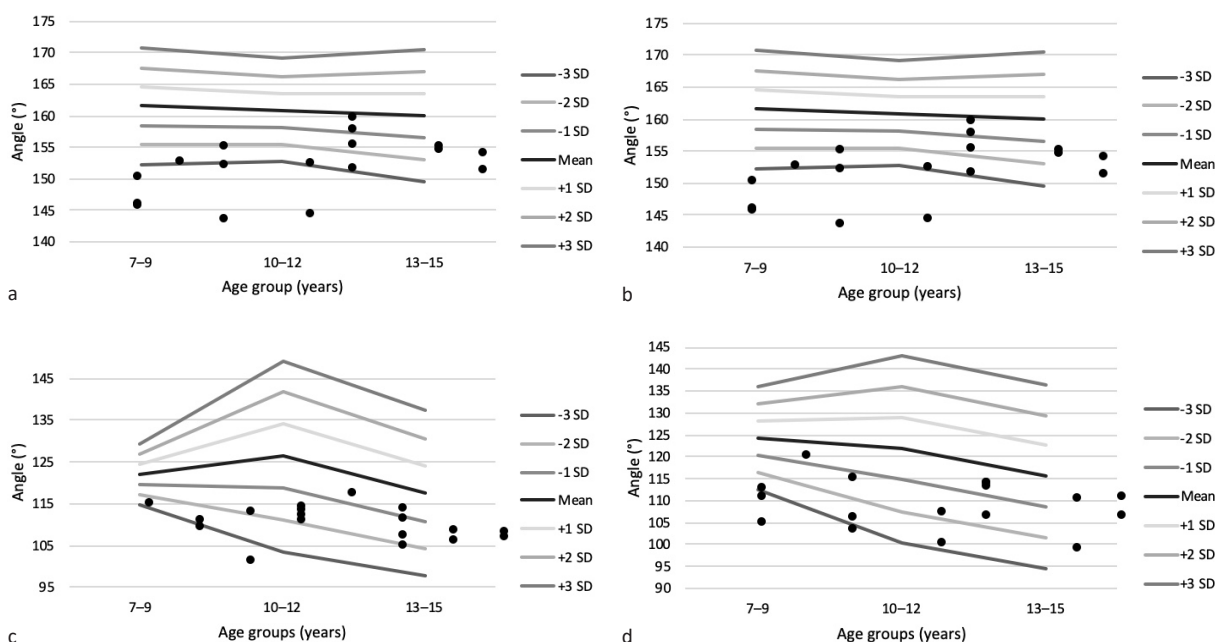
## RESULTS

Of 35 children with thalassemia major, 17 were in the 7–9 age group, 13 in the 10–12 age group, and 8 in the 13–15 age group. The NLA and forehead protrusion angle were distributed across the three age groups, and the mean value for each group can be seen in Figure 2. The highest mean value of the forehead protrusion angle for males and females was observed in the 12–15 age group.

The mean value for each control group and the mapping results showing the distribution of each



**Figure 2.** Average of forehead protrusion (a) and NLA (b) measurements of patients with  $\beta$ -thalassemia major based on age groups. NLA=nasolabial angle; SD=standard deviation



**Figure 3.** Mapping distribution of patients with and without  $\beta$ -thalassemia major. Forehead protrusion angle in male (a) and female (b); nasolabial angle (NLA) in male (c) and female (d). Dots showing the mapping distribution of individual  $\beta$ -thalassemia major data against the control group

$\beta$ -thalassemia major individual in the control group are shown in Figure 3. The 1 and 2 SD group had a higher prevalence of  $\beta$ -thalassemia major in children aged 7–9 years for both sexes. The older age group (10–12 and 13–15 years) had closer mean values to those of children without  $\beta$ -thalassemia major.

## DISCUSSION

Based on the mapping chart of the forehead protrusion and NLAs, patients aged 7–9 years with  $\beta$ -thalassemia had protrusive features compared with those without thalassemia. Forehead protrusion or

frontal bossing is a common characteristic of patients with  $\beta$ -thalassemia major.<sup>4</sup> Ineffective erythropoiesis leads to bone marrow hyperplasia, resulting in wall thinning, bone expansion, and protruding frontal bones in the forehead and maxilla.<sup>7</sup> These protrusions typically appear between 6 and 24 months of age.<sup>8,9</sup> Therefore, differences in bone structure can be observed in children aged 7–9 years. Abnormal bone structure affects the development of the paranasal sinuses and mastoids and often affects the maxillary, sphenoid, and frontal sinuses, which are distinctive radiographic findings in patients with  $\beta$ -thalassemia major that are not observed in healthy individuals.<sup>10</sup>

Furthermore, a previous cephalometric photographic analysis study<sup>7</sup> demonstrated a more prominent forehead in children with  $\beta$ -thalassemia major.

In this study, patients with  $\beta$ -thalassemia major aged 10–12 or 13–15 years had less prominent facial features; their measurements were closer to those of children without thalassemia. This may be due to the growth of the neurocranium being nearly complete, allowing the facial complex to develop in a more typical pattern by this age, similar to the growth pattern of children without thalassemia.<sup>10</sup> No previous photogrammetry studies regarding the forehead protrusion angle in children without thalassemia have been reported. While some studies have reported the NLA, the patient population in those studies does not align with that of the current study. In addition, some previous studies used the pronasal point of the nose, as in this study, while others used the columella when determining the NLA. Varying NLAs were reported for 12-year-old children in southern China, though the NLAs were based on the columella, and the SD was wide (maximum NLA: 120–130°).<sup>11</sup>

Several factors, such as blood transfusions, may influence the condition of patients with thalassemia. Blood transfusion is the main treatment for severe anemia in patients with  $\beta$ -thalassemia major as it suppresses ineffective erythropoiesis. The variations observed in the current study may have been caused by the duration, frequency, and regimen of blood transfusions in each patient. Notably, 55% of patients with thalassemia who received adequate transfusions did not develop facial bone deformities,<sup>12</sup> indicating that adequate treatment can prevent such deformities.

The variations in the findings of the current study may also be attributed to the unequal distribution of age and sex in each group. Other factors such as poor oral habits and soft tissue thickness, which were not observed in this study, may also have contributed to these variations.

The forehead and maxilla of patients with  $\beta$ -thalassemia major are valuable indicators for recognizing the patient's condition and determining the appropriate treatment options in pediatric dentistry. These clinical predictors are important for diagnosing  $\beta$ -thalassemia major. In addition, extraoral photographs are suitable for assessing patients with thalassemia as they eliminate the need for invasive and lengthy procedures.

In conclusion, the forehead and maxillary profile of Javanese children with  $\beta$ -thalassemia major was protrusive, especially in patients aged 7–9 years. More research with a larger patient population in each age group is needed to complete a statistical analysis of the facial features in this patient population.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

#### Acknowledgment

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## Validity and reliability of the Indonesian version of the 9-item Inflammatory Bowel Disease Questionnaire (IBDQ-9)

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### ABSTRACT

**BACKGROUND** Decreasing the quality of life (QoL) of patients with inflammatory bowel disease (IBD) will increase morbidity and mortality. A valid and reliable instrument is needed to assess the QoL of patients with IBD. This study aimed to analyze the validity and reliability of the Indonesian version of the 9-item Inflammatory Bowel Disease Questionnaire (IBDQ-9).

**METHODS** This cross-sectional study was conducted using the Indonesian version of the IBDQ-9 in adult patients with IBD at the Gastroenterology Outpatient Clinic, Cipto Mangunkusumo Hospital, Jakarta, in November 2022. Patients aged 18 to 59 years who had experienced IBD for at least 2 weeks and provided informed consents were included. The total score of the IBDQ-9 Indonesian version was compared with the 36-item Short-Form Health Survey (SF-36) using the Spearman's correlation test. Reliability tests were examined using Cronbach's alpha and the intraclass correlation coefficient (ICC).

**RESULTS** A total of 124 participants were included in this study. The Spearman's test showed a high and significant result for the IBDQ-9 Indonesian version and the SF-36 ( $r = 0.769$  and  $p < 0.001$ ). Cronbach's alpha and ICC coefficient were equal to 0.883.

**CONCLUSIONS** This study provided evidence of the good validity and reliability of the IBDQ-9 Indonesian version for assessing the QoL of patients with IBD in Indonesia.

**KEYWORDS** inflammatory bowel disease, quality of life

Inflammatory bowel disease (IBD) is a chronic digestive tract inflammatory condition categorized into Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis.<sup>1</sup> The incidence has increased in Asian countries, including Indonesia, over the last two decades. Patients with IBD have poorer quality of life (QoL) than healthy controls. However, Indonesia does not yet have an instrument to specifically measure the QoL of patients with IBD.<sup>2,3</sup>

Hitherto, QoL in Indonesia has been measured using generic instruments, such as the 36-item Short-Form Health Survey (SF-36), which account for various respondent conditions. The SF-36 is widely used to

assess QoL in healthy and diseased populations because it shows good results. However, in assessing the QoL of patients with IBD, several psychometric aspects of the SF-36 may have affected the interpretation of the results. The SF-36 may have limitations in measuring changes in QoL over time based on IBD activity. The SF-36 also does not have an IBD-specific domain related to the severity of gastrointestinal symptoms, which is a risk factor for decreased QoL in patients with IBD. This allows for a floor or ceiling effect in assessing the QoL of patients with IBD using the SF-36. Additionally, the relatively large number of SF-36 questions (36 items) is considered inefficient for each outpatient visit.<sup>4</sup>

Accordingly, an IBD-specific QoL evaluation tool, such as the 9-item Inflammatory Bowel Disease Questionnaire (IBDQ-9), is required in Indonesia. The IBDQ-9 is a self-rated instrument consisting of nine questions representing four domains of QoL: gastrointestinal, systemic, emotional, and social symptoms. The IBDQ-9 is a short form of the IBDQ-36 compiled by Alcalá et al<sup>5</sup> and is the gold standard for examining the QoL of patients with IBD. The validity of the IBDQ-9 showed a high correlation ( $r = 0.91$ ,  $p < 0.01$ ) when compared with the IBDQ-36.<sup>5</sup> With all the advantages of the IBDQ-9 over the SF-36, this study aimed to determine the validity and reliability of the Indonesian version of the IBDQ-9 to assess the QoL of patients with IBD.

## METHODS

This cross-sectional study was conducted online at the Gastroenterology Outpatient Clinic of the Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, in November 2022. The minimum required sample size was 90 participants, determined using a rule of thumb. Patients with a history of IBD who had been on an outpatient basis at the Gastroenterology Outpatient Clinic for more than 2 weeks, aged 18 to 59 years, proficient in Indonesian, and could read and write with or without aids were included in the study. All the participants provided informed consent. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia – Cipto Mangunkusumo Hospital (No: KET-1072/UN2.F1/ETIK/PPM.00.02/2022).

As shown in the Supplementary File, the IBDQ-9 was translated into Indonesian and back-translated into English by independent translators from two different institutions. The results of the IBDQ-9 translation were discussed with four gastroenterology experts to create an appropriate instrument for the Indonesian sociocultural elements. The IBDQ-9 English version was returned to Dr. Francesc Casellas, the instrument's owner, and received no feedback regarding its suitability. Based on this, the Indonesian version of the IBDQ-9 was used for pilot testing in 20 patients with IBD (Supplementary Table 1). Validity and reliability tests were performed using a larger sample size. Data, including sociodemographic and clinical characteristics of the disease, are presented

in a table of proportions. Content validity analysis was performed using the content validity index (CVI), and correlation coefficient assessment for construct validity was performed using Pearson's or Spearman's correlation tests. Internal consistency reliability was assessed by determining Cronbach's alpha and test-retest reliability using the intraclass correlation coefficient (ICC).

## RESULTS

Among the 132 participants who completed the Indonesian versions of the SF-36 and IBDQ-9, 8 were excluded because they were unwilling to sign the informed consent form. Complete data are presented in Table 1.

The Indonesian version of the IBDQ-9 showed good content validity (Table 2). This assessment was qualitatively determined by a panel of experts who evaluated each instrument item. The quantitative approach for CVI scored 1 because all experts gave scale scores of 3 and 4.

Overall, the average total score for the Indonesian version of the IBDQ-9 was 37.3 (10.93) points, with a median of 38 (15–61) points. Good QoL was expressed by a cut-off point of  $>27$  points (on a scale of 63) or  $>50.2$  points (on a scale of 100) on the total score of the Indonesian version of the IBDQ-9 instrument; thus, 96 (77.4%) participants were assessed for their QoL (Table 3; Supplementary Figure 1).

**Table 1.** Characteristics of the participants

| Characteristics | n (%) (N = 124) |
|-----------------|-----------------|
| Age (years)     |                 |
| 18–24           | 11 (8.9)        |
| 25–44           | 73 (58.9)       |
| 45–59           | 40 (32.3)       |
| Male sex        | 33 (26.6)       |
| Residence       |                 |
| Urban           | 95 (76.6)       |
| Rural           | 29 (23.4)       |
| Ethnicity       |                 |
| Javanese        | 48 (38.7)       |
| Sundanese       | 26 (21.0)       |
| Chinese         | 9 (7.3)         |
| Batakese        | 7 (5.6)         |

Table continued on next page



**Table 1.** (Continued)

| Characteristics                        | n (%) (N = 124) |
|--|-----------------|
| Betawinese                             | 8 (6.5)         |
| Ambonese                               | 4 (3.2)         |
| Minangnese                             | 9 (7.3)         |
| Others*                                | 13 (10.5)       |
| <b>Education</b>                       |                 |
| Elementary                             | 5 (4.0)         |
| Junior high school                     | 3 (2.4)         |
| Senior high school                     | 45 (36.3)       |
| Bachelor                               | 64 (51.6)       |
| Postgraduate                           | 6 (4.8)         |
| Doctorate                              | 1 (0.8)         |
| <b>Employment</b>                      |                 |
| Employee                               | 70 (56.5)       |
| Unemployee                             | 54 (43.5)       |
| <b>Good support systems</b>            |                 |
| Yes                                    | 105 (84.7)      |
| No                                     | 19 (15.3)       |
| <b>Diagnosis duration (years)</b>      |                 |
| 0–5                                    | 112 (90.3)      |
| 6–10                                   | 8 (6.5)         |
| 11–15                                  | 2 (1.6)         |
| >15                                    | 2 (1.6)         |
| <b>Type of IBD</b>                     |                 |
| CD                                     | 49 (39.5)       |
| UC                                     | 43 (34.7)       |
| IC                                     | 32 (25.8)       |
| <b>Treatment history</b>               |                 |
| Mesalamine                             | 87 (70.2)       |
| Combination                            | 30 (24.2)       |
| Steroid                                | 1 (0.8)         |
| Others†                                | 6 (4.8)         |
| <b>History of other diseases</b>       |                 |
| Autoimmune                             | 23 (18.5)       |
| Infection                              | 4 (3.2)         |
| Malignancy                             | 4 (3.2)         |
| Others‡                                | 70 (56.5)       |
| None                                   | 23 (18.5)       |
| Surgical history post IBD diagnosis    | 10 (8.1)        |
| Hospitalization prior to IBD treatment | 76 (61.3)       |
| Hospitalization after IBD treatment    | 59 (47.6)       |

IBD=inflammatory bowel disease; IC=indeterminate colitis; CD=Crohn's disease; UC=ulcerative colitis

\*Other ethnicities were Timornese, Arabianese, Malaynese, Minahasanese; †other treatments such as methotrexate and biologic agent; ‡other diseases were psychosomatic, gastroenterology, hematology, and degenerative diseases

Analysis of the IBDQ-9 Indonesian version's total score showed a high correlation with the total score of the SF-36 Indonesian version (correlation coefficient value of 0.769,  $p < 0.001$ ) using the Spearman's correlation test (Supplementary Table 2). A high correlation was also observed when analyzing each IBD diagnosis using Spearman's correlation test ( $r_s = 0.792$ ,  $p < 0.001$ ) (Supplementary Table 3).

This study also compared the QoL of patients with IBD in Indonesia using the validated SF-36 instrument (Supplementary Table 4). In the SF-36 instrument, a good QoL was expressed by a cut-off point of >50 points for the total score of the Indonesian version of the SF-36 instrument; thus, 52 (41.9%) participants were declared to have a good QoL.

The Indonesian version of the IBDQ-9, as measured by internal consistency and test-retest reliability, also showed good results. The IBDQ-9 Indonesian version had a Cronbach's alpha value of 0.883, indicating that all the questions were effectively integrated into the instrument. In addition, the test-retest reliability of the IBDQ-9 Indonesian version was included in the "good" category based on the ICC value of 0.883 (95% confidence interval [CI] = 0.849–0.912).

## DISCUSSION

This study tested the validity and reliability of the IBDQ-9 Indonesian version to assess the QoL of patients with IBD in Indonesia. A specialized instrument with specific indicators of bowel movements and digestive complaints is required to assess the QoL in patients with IBD. Patients with active IBD tend to have more gut symptoms that interfere with daily activities, as well as more illness concerns, perceived stress, and emotional distress. However, poor QoL is not limited to active episodes; even during remission, patients with IBD may experience anxiety relapse, which lowers their QoL. QoL was assessed using the IBDQ-9 Indonesian version. The total score of the IBDQ-9 showed a statistically significant correlation with the total score of the SF-36. This result is in accordance with the results of the IBDQ-9 validation test in Iran by Gholamrezaei et al,<sup>6</sup> which showed a significant correlation with the SF-36 ( $r = 0.524$ ,  $p < 0.001$ ). In addition, this study assessed the instrument's reliability by measuring its internal consistency and test-retest reliability. The internal consistency assessment results were good and aligned with the IBDQ-9 Spanish version by Alcalá

**Table 2.** CVI of the IBDQ-9 Indonesian version

| Domains                   | Questions | Expert 1 | Expert 2 | Expert 3 | Expert 4 | I-CVR | CVR |
|---------------------------|-----------|----------|----------|----------|----------|-------|-----|
| Gastrointestinal symptoms | Q1        | 3        | 4        | 3        | 4        | 1     | 1   |
|                           | Q5        | 3        | 4        | 4        | 4        | 1     | 1   |
|                           | Q7        | 3        | 4        | 3        | 4        | 1     | 1   |
|                           | Q8        | 3        | 4        | 4        | 4        | 1     | 1   |
| Systemic symptoms         | Q2        | 3        | 4        | 4        | 4        | 1     | 1   |
|                           | Q3        | 3        | 4        | 4        | 4        | 1     | 1   |
|                           | Q6        | 3        | 4        | 4        | 4        | 1     | 1   |
| Social function           | Q4        | 3        | 4        | 3        | 4        | 1     | 1   |
| Emotional function        | Q9        | 3        | 4        | 3        | 4        | 1     | 1   |
| Mean I-CVI                |           | 1        | 1        |          |          |       |     |
| S-CVI/UA                  |           | 1        | 1        |          |          |       |     |
| S-CVI/Ave                 |           | 1        | 1        |          |          |       |     |

Ave=average method; IBDQ-9=9-item Inflammatory Bowel Disease Questionnaire; I-CVI=item content validity index; I-CVR=item content validity ratio; CVI=content validity index; CVR=content validity ratio; S-CVI=scale content validity index; UA=universal average method

**Table 3.** Characteristics of IBD patients' QoL score with the IBDQ-9 Indonesian version

| Score                       | Average | Median | Min   | Max   |
|-----------------------------|---------|--------|-------|-------|
| Q1                          | 5.43    | 6.00   | 1.00  | 7.00  |
| Q2                          | 3.15    | 3.00   | 1.00  | 7.00  |
| Q3                          | 4.31    | 5.00   | 1.00  | 7.00  |
| Q4                          | 4.28    | 4.00   | 1.00  | 7.00  |
| Q5                          | 4.04    | 4.00   | 1.00  | 7.00  |
| Q6                          | 3.56    | 3.50   | 1.00  | 7.00  |
| Q7                          | 4.57    | 5.00   | 1.00  | 7.00  |
| Q8                          | 3.81    | 4.00   | 1.00  | 7.00  |
| Q9                          | 4.15    | 5.00   | 1.00  | 7.00  |
| Total score                 | 37.30   | 38.00  | 15.00 | 61.00 |
| Total score (max scale 100) | 57.31   | 57.40  | 36.70 | 86.30 |

IBD=inflammatory bowel disease; IBDQ-9=9-item Inflammatory Bowel Disease Questionnaire; QoL=quality of life

et al<sup>5</sup> (Cronbach's alpha = 0.95 in UC and 0.91 in CD). Gholamrezaei et al<sup>6</sup> also reported an equally good internal consistency value, with a Cronbach's alpha of 0.76.

Patients with active disease have significantly impaired health-related QoL (HRQoL) compared with patients in remission. In contrast, achieving disease remission in CD, either pharmacologically or surgically, is associated with improved HRQoL. Importantly, poor HRQoL is not limited to active episodes alone; it persists even when the disease is inactive.<sup>6-12</sup>

The interaction of various factors, such as genetic susceptibility and changes in the environment of the gastrointestinal tract, is thought to play a role in

impaired gastrointestinal immunity, which causes damage to the gastrointestinal tract.<sup>1-3</sup> This damage in IBD has a distinctive feature, namely, relapse-remission or chronic active phase, so the discomfort that can occur in patients cannot be predicted. Ultimately, this can reduce patients' QoL.<sup>13-17</sup> Thus, increased awareness among physicians and health workers is needed to improve health services for patients with IBD, as well as to maintain and assess their QoL from an early age.

Meanwhile, the IBDQ-9 has various benefits over other instruments, such as predicting fatigue in patients with IBD as an independent variable in multivariate analysis (odds ratio = 0.82; 95% CI = 0.74-0.93).<sup>14</sup> Furthermore, the IBDQ-9 has a good correlation with IBD activity assessment in the UC activity index ( $r = -0.530, p < 0.001$ ) and the CD activity index ( $r = -0.424, p < 0.025$ ).<sup>15</sup> Neubauer et al<sup>6</sup> also described a good correlation between the IBDQ-9 and IBD disease activity, where the correlation in UC was better than in CD. The IBDQ-9 also has the same suitability for assessing HRQoL as the conventional instruments, the IBDQ-36 and SF-36.<sup>16-18</sup> Therefore, the IBDQ-9 not only effectively assesses the QoL of patients but also serves as a predictor of fatigue and an evaluation parameter for IBD disease activity.

This was the pilot study in Indonesia to evaluate the IBDQ-9 instrument to quickly assess QoL that contains questions relevant to IBD characteristics.<sup>19</sup> This measurement tool will be useful for the welfare of patients with IBD by improving the management approaches to some QoL aspects that may have been neglected.<sup>20,21</sup> This study used many participants with various characteristics and was expected to represent

the general population, allowing this instrument to be applied to a broad population.<sup>5</sup> A credible research location, namely Cipto Mangunkusumo Hospital, can increase the certainty of a definitive IBD diagnosis and prevent selection bias.

Nevertheless, this study had several limitations. Owing to time constraints and the cross-sectional design, the IBDQ-9 cannot be used to assess QoL in patients with IBD at various disease activity levels. Additionally, the IBDQ-9 had not been tested for validity and reliability in other populations, such as geriatrics.<sup>5</sup> These limitations could affect the interpretation of the Indonesian version of the IBDQ-9 and should be considered in future research.

In conclusion, the IBDQ-9 Indonesian version was a valid and reliable tool for assessing the QoL of patients with IBD in Indonesia. The results of this study could be considered for the health sector stakeholders in making an algorithm for IBD examination and management, conducting early detection of QoL, identifying risk factors as a preventive measure for IBD complications in health services, disseminating the results of studies on the validity and reliability of the IBDQ-9 in patients with IBD as teaching materials in the field of gastroenterology to general practitioners and participants in internal medicine specialist education, and developing further research to obtain an overview of the comprehensive use of the IBDQ-9 Indonesian version, considering the study design and population variations.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

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# Transventricular transforaminal endoscopic fenestration with cysto-ventriculoperitoneal shunt to manage a third ventricular arachnoid cyst: a case report

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## ABSTRACT

Regular ventriculoperitoneal (VP) shunt is commonly used as the first option to manage a third ventricular arachnoid cyst due to the lack of facilities, unfamiliarity with endoscopic techniques, or misdiagnosis as purely obstructive hydrocephalus. A 9-year-old girl with obstructive hydrocephalus due to a third ventricular arachnoid cyst was treated with a VP shunt. 2 months later, the previous shunt device was removed due to an infection. Following a sterile cerebrospinal fluid analysis culture, we conducted a navigation-assisted transventricular transforaminal endoscopic fenestration and cysto-VP programmable shunt placement. A decrease in ventricular dilatation was seen on follow-up. This approach was justified due to the possibility of establishing communication with normal cisterns, the high rate of cyst elimination, and the potential for achieving shunt independence. Performing an endoscopic fenestration followed by cysto-VP shunt placement could be an optimal option for managing this condition.

**KEYWORDS** cerebrospinal fluid shunt, endoscopic fenestration, transforaminal, transventricular

Arachnoid cysts are benign collections of cerebrospinal fluid (CSF) that result from splitting the arachnoid membrane during childhood. Approximately 9% of all arachnoid cysts are suprasellar arachnoid cysts, arising from either the Lilliequist membrane or an interpeduncular cistern anomaly that develops toward the third ventricle. As a result, the third ventricle enlarges, cyst formation occurs, and dorsal compression of the brainstem may occur.<sup>1</sup> A small percentage of these cysts eventually enlarge to the point of causing clinical symptoms; however, most cysts remain static over time. Patients may exhibit neurological symptoms of a space-occupying lesion and elevated intracranial pressure due to the compression of nearby structures or hydrocephalus.<sup>2</sup> Headache is the most prevalent clinical symptom, occurring in 66% of patients.<sup>1</sup>

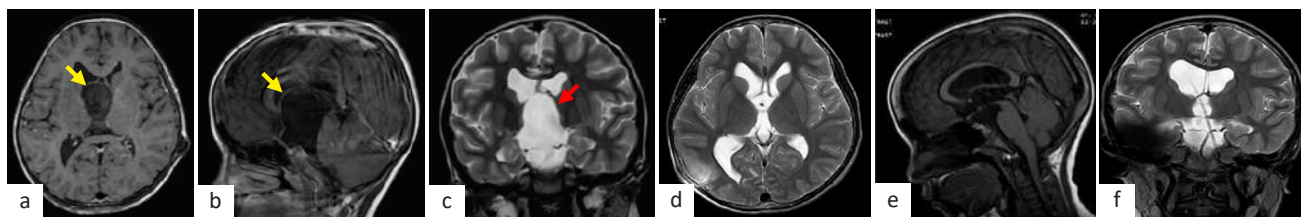
Surgery aims to reduce the cyst volume and the hydrocephalus symptoms. Various treatment methods have been employed, including open craniotomies,

endoscopic procedures, CSF diversion, or a combination of these techniques.<sup>3,4</sup> This case report presented a patient with a third ventricular arachnoid cyst who underwent endoscopic fenestration followed by programmable shunt placement. Endoscopic fenestration is a minimally invasive modality that uses an endoscope to reach the lateral ventricle and foramen of Monro to fenestrate and explore the cystic cavity.

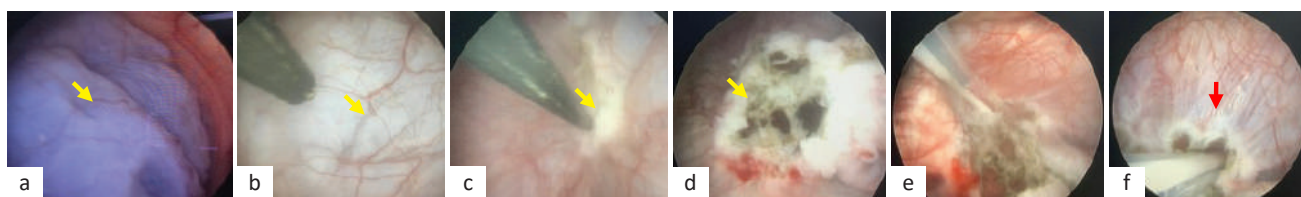
## CASE REPORT

A 9-year-old girl presented with frequent headaches that worsened when coughing, sneezing, or changing positions. No comorbidities or neurological deficits were observed. She showed healthy growth for her age, including refined motor skills, coordination, and muscle control. Her endocrine assessment did not reveal any abnormalities. No precocious puberty, growth

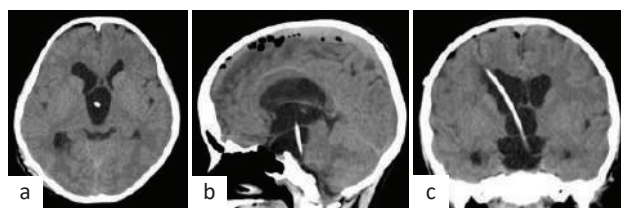




**Figure 1.** Brain MRI. Preoperative MRI showing axial (a) and sagittal (b) post contrast T1 images indicating an enlargement of third ventricle and exposing the cyst membranes (yellow arrows) and a thin-walled cyst (red arrow) (c) with a maximum dimension of 2.6 cm emerging from the quadrigeminal cistern and herniates into the third ventricle, occluding both the foramina of Monro, as shown in the coronal T2 scan; 1 year postoperative MRI acquired in axial (d), sagittal (e), and coronal (f) T1 images. MRI=magnetic resonance imaging



**Figure 2.** Cyst membrane fenestration and cysternostomy. Stages of endoscopic cauterization of the cyst until the foramen of Monro became patent (a–f); the cyst wall was ablated (yellow arrows) (c and d); a VCC was performed (e); a proximal programmable shunt tip (red arrow) was placed in the basal cistern (f). VCC=ventriculocystocisternostomy



**Figure 3.** Postoperative CT images. Brain CT images a week after the procedure revealing decreased cyst size, normalization of the ventricular size, and proximal shunt tip location as planned (a–c). CT=computed tomography

hormone deficiency, or hypothalamic dysfunction was observed. She had previously undergone ventriculoperitoneal (VP) shunt placement at another institution to treat obstructive hydrocephalus caused by a cystic lesion in the third ventricle. Following VP shunt surgery, the headaches were reduced. However, 1 month later, the clinical symptoms recurred. Magnetic resonance imaging (MRI) was performed to enable a detailed analysis of the cyst. Imaging revealed a larger cyst, left ventriculomegaly, and right-slit lateral ventricle (Figure 1a–c). Surgical site infections were also detected. Therefore, we removed the shunt device and performed a CSF examination.

The patient was placed under general anesthesia and positioned at a 30° head-up angle. A semilunar scalp incision (2.5 cm lateral to the midline and 1 cm anterior to the coronal suture) was made on the right frontal

scalp. The right lateral ventricle was cannulated via the anterior horn using a 0° straightforward rigid endoscope (Lotta System, Karl Storz, USA), with the assistance of an image-guided surgery system (Stealth Station S8, Medtronic, USA). Following the identification of the thalamostriate and septal veins, the endoscope was moved toward the foramen of Monro. The cyst wall was pulsating in rhythm with the CSF flow and protruding from the foramen of Monro. Subsequently, navigation-assisted transventricular transforaminal endoscopic fenestration (ventriculocystocisternostomy [VCC]) was performed (Figure 2b–d). A bipolar instrument was used to coagulate the small blood vessels on the cyst wall, and a monopolar instrument was used to fenestrate the apical membrane as extensively as possible. A portion of the cyst wall was excised for histological analysis using forceps, and its contents were aspirated to eliminate the mass effect inside the third ventricle. With navigational assistance, the endoscope was moved into the cyst; fenestration was performed within the third ventricular floor to allow the CSF to reach the basal cistern. Finally, a programmable shunt (Codman Hakim Programmable Valve, Integra, USA) was placed inside the cavity with a regular pressure setting of 1.5. One week after the procedure, a follow-up computed tomography scan showed a collapsed cyst and reduced ventricular size (Figure 3a–c). To avoid postoperative CSF leakage and subdural

collection, the cortical hole was blocked with an absorbable gelatin sponge. After surgery, the patient was transferred to a regular pediatric ward. A follow-up MRI 1 year postoperatively showed a decreased cyst size and good positioning of the proximal shunt tip at the basal cistern (Figure 1d–f).

## DISCUSSION

The best method for treating third ventricular arachnoid cysts in children has been widely discussed, with numerous modalities considered to restore normal CSF flow. The two common methods are microsurgical fenestration and cystoperitoneal shunting (with or without partial cyst excision).<sup>5</sup> Recently, endoscopic fenestration, either with or without CSF diversion, has been widely accepted.<sup>3,6–8</sup>

As a single treatment, CSF diversion using a VP shunt has a low success rate.<sup>9</sup> According to Ma et al,<sup>10</sup> failures in treating third ventricular arachnoid cysts with shunt placement, as evidenced by slit ventricle and cyst enlargement on neuroimaging, are typically due to shunt apparatus malfunction, such as obstruction, infection, or dislocation. Thus, clinical symptoms may recur. By diverting CSF flow into the abdominal cavity, VP shunts may lower intracranial pressure; however, they cannot normalize CSF circulation. Persistent occlusion of the foramen of Monro results in a slit ventricle. Moreover, the pressure difference between the cyst cavity and ventricle may lead to cyst enlargement.<sup>11,12</sup> In the present case, VP shunts were initially considered a promising first-line treatment due to their availability in most neurosurgical centers in Indonesia. However, they are only sustainable in the short term due to the possibility of malfunctioning and the tendency to replace or adjust over time. In the present case, a VP malfunction was observed 3 months after the initial placement. Conversely, although endoscopic surgical treatment is widely accepted, its availability and accessibility in some areas remain limited.

Microsurgical cyst fenestration with open craniotomy for cyst resection can avoid the risk of permanent shunt malfunction.<sup>5,13</sup> Moreover, rapid cyst decompression may cause insufficient CSF absorption and subdural hygromas owing to wide surgical apertures.<sup>14,15</sup> Therefore, the inherent risks of open craniotomy should be considered in patients with minor symptoms related to arachnoid cysts.

Endoscopic fenestration has been widely accepted as a treatment option because of the anatomical proximity of the cyst to the ventricular system and subarachnoid cisterns. This method is less invasive than microsurgical procedure and requires less time. Considering its proximity to important structures, such as the pituitary gland, hypothalamus, and optic nerve, neuronavigation increases patient safety and allows the selection of the best angle when using a rigid endoscope.<sup>9</sup> Ventriculocystostomy (VC) and VCC can be performed using an endoscopic fenestration technique. In VC, the apical membrane of the cyst is fenestrated using an endoscope and instruments, whereas VCC uses the same endoscopic technique to fenestrate the apical membrane before continuing through the inferior membrane, creating a second fenestration that enables the cyst to communicate with the basal cisterns.<sup>3</sup> In the present study, the patient was treated with VCC rather than VC because VCC was associated with a lower incidence of recurrence, risk of infection, and other postoperative problems.<sup>2,5</sup> Although usually successful, VCC may present additional risks to nearby anatomical structures, such as the basilar artery and cranial nerves.<sup>3</sup>

Surgery aims to reduce the size of the cyst and the associated hydrocephalus to normalize CSF flow. CSF hydrodynamics, changes in cyst size over time, and the relationship with the efficacy of this procedure require further investigation. Pitsika et al<sup>16</sup> showed that, after successful endoscopic fenestration of symptomatic arachnoid cysts, the cyst volume markedly decreased in the first few months and reached a plateau in the following 6 months. Despite the cyst not completely disappearing and, in some cases, even remaining large and reaching a state of compensation, the patients may remain asymptomatic in the long term.<sup>16</sup> When El Refaee and Elbaroody<sup>17</sup> performed endoscopic cystocisternostomy in nine cases of arachnoid cysts, four cysts almost completely disappeared, three cysts decreased in size by more than 60%, and two cysts decreased in size by more than 30%. The cysts disappeared after 3–18 months.

The absorption of CSF is not increased by the fenestration of the wall itself. This explains why the prevalence of collapsed cysts is low without shunt therapy.<sup>18</sup> In contrast, cyst wall fenestration occasionally causes subdural CSF accumulation, which may require surgery, as reported by Cinalli et al.<sup>19</sup> The endoscopic procedure may provide a good

fenestration to release CSF trapped inside the cyst, but a rapid increase in circulating CSF volume may not be followed by complete absorption due to the saturated arachnoid villi. Using the CSF diversion method may increase the amount of absorbed CSF.<sup>20</sup>

Endoscopic fenestration combined with programmable cysto-VP shunt placement could reduce cyst volume and restore normal CSF circulation inside the cisternal space.<sup>21</sup> By generating a pressure gradient between the cerebral parenchyma and the cyst while maintaining a negative pressure gradient inside the arachnoid space, the shunt may provide brain expansion.<sup>18</sup>

To reduce shunt dependence, a programmable valve may facilitate shunt weaning by changing the shunt pressure rate, thereby preventing shunt revision and valve removal. Mottolese et al<sup>18</sup> demonstrated that the shunt opening pressure increased after the disappearance of the cyst to facilitate shunt independence. Radiographs were acquired each time the pressure was adjusted. After the shunt was regulated at a higher opening pressure, they waited at least 15 months before finally removing the valve. This approach allowed for complete collapse of the cyst while reducing shunt dependence.

In conclusion, endoscopic fenestration followed by cysto-VP programmable shunt placement was an effective strategy for treating third ventricle arachnoid cysts. This method provides some advantages, such as establishing communication with normal cisternal pathways, a high rate of collapsed cysts, and the possibility of achieving shunt independence. However, a longer follow-up period and a larger number of cases are required to confirm these results.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

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# Atypical orbital primary optic nerve sheath meningioma with severe disfiguring proptosis: an alternative surgical approach

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#### ABSTRACT

Primary optic nerve sheath meningioma is generally a benign tumor. In rare instances, however, the growth rate and intraocular and intracranial extensions can be highly aggressive, especially in children, leading to poor prognosis. Here, we reported a case of a 24-year-old woman who presented with left eye swelling for 3 years. This was associated with blurred vision, retrobulbar pain, and redness. On examination, the left eye was severely proptosed with complete ophthalmoplegia. Magnetic resonance imaging showed an extensive tumor occupying the whole left orbital cavity with a disfigured eyeball. However, no intracranial extension was observed. Interestingly, complete surgical excision was feasible via transconjunctival anterior orbitotomy without bone removal. The histopathological examination confirmed the diagnosis of optic nerve sheath meningioma. Adjunct radiotherapy was given. On a follow-up after 2 years, left enophthalmos with esotropia was observed.

**KEYWORDS** enophthalmos, esotropia, meningioma, ophthalmoplegia

Primary optic nerve sheath meningioma (PONSMS) is a benign tumor originating from the meningotheelial cap cells of the arachnoid villi. PONSMS can develop at any location along the entire course of the optic nerve sheath with practically no mortality rate<sup>1,2</sup> and accounts for approximately 1–2% of all meningiomas and 5–10% of all orbital tumors.<sup>3,4</sup>

The optimal treatment strategy for PONSMS remains controversial. Watchful waiting is recommended in cases with no vision loss, whereas radiotherapy is

indicated when vision is affected. In cases of significantly impaired vision or blindness, disfiguring proptosis, or intracranial extension, surgery alone or in combination with radiotherapy is indicated.<sup>2,5,6</sup> Although benign, PONSMS can exhibit aggressive tumor growth, causing intraocular extension, intracranial extension, and severely disfiguring proptosis, especially in children.<sup>7–9</sup> Various surgical approaches have been described for orbital PONSMS requiring surgery. This case report described our surgical approach of transconjunctival

anterior orbitotomy, sparing the bone, optic nerve, and eyeball for extensive atypical orbital PONSMS. The surgery was less invasive and achieved complete surgical excision in an aesthetically acceptable manner.

## CASE REPORT

Informed consent was obtained from the patient before publishing this case report. A 24-year-old woman with no known medical illness presented with progressive left eye swelling for 3 years, associated with blurred vision, retrobulbar pain, and redness. She denied any history of trauma, loss of appetite, weight loss, or neurological deficits.

The patient's left eye was severely disfigured, proptosed (Hertel exophthalmometry >36 mm), and exposed (Figure 1, a and b). Visual acuity was counting fingers at one foot (CF1FT) with an intraocular pressure of 12 mmHg. Generalized conjunctival redness with signs of exposure keratopathy was also observed. The pupil was mid-dilated with a limited posterior segment view, partly due to severe keratopathy and a distorted eyeball. The left eye showed complete ophthalmoplegia. The right eye and other systemic examination results were unremarkable.

Complete blood count, renal function, and liver function were normal, and tumor markers (alpha-fetoprotein, carcinoembryonic antigen, CA 19-9, and CA 125) were not elevated. Contrast-enhanced magnetic resonance imaging (MRI) of the brain and orbit showed a large left intraconal orbital mass measuring 6.7 cm × 4.7 cm × 4.9 cm with a severely proptosed eyeball (50 mm). The mass showed mild homogeneous contrast enhancement. The extraocular muscles were stretched and displaced with no clear plane between them. The optic nerve was stretched and laterally deviated. Remodeling of the left lamina papyracea was also observed. No intracranial extension was observed (Figure 1c).

The patient underwent tumor removal via bone-sparing transconjunctival anterior orbitotomy. Intraoperatively, a 360-degree conjunctival peritomy was performed. All rectus muscles were isolated. A lateral canthotomy was performed with the disinsertion of the superior and medial rectus muscles to enable better access to the posterior orbit. The mass was separated from the recti muscles, posterior eyeball, and optic nerve before being excised into fragments until to the orbital apex. Total tumor excision was

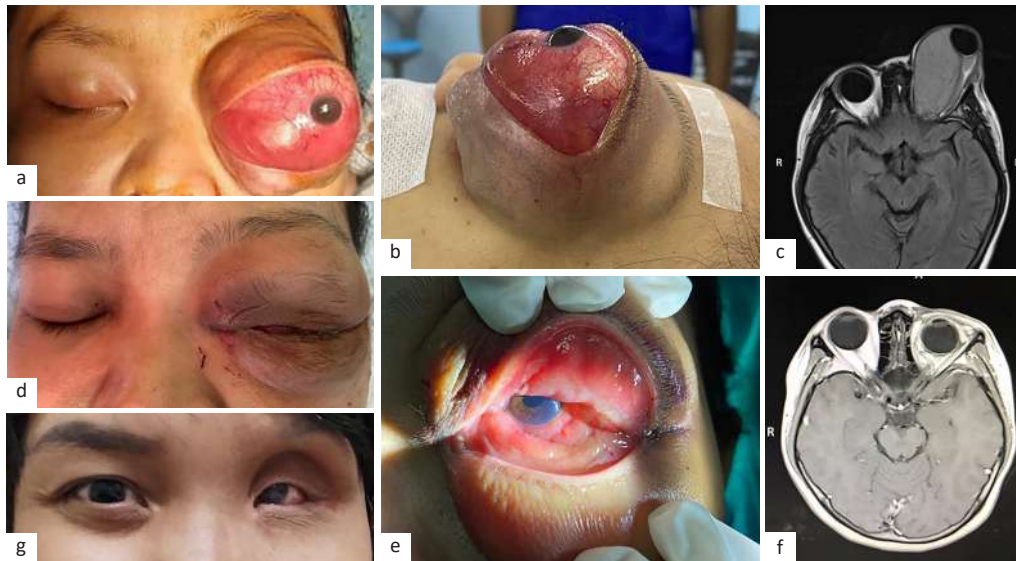
performed by sparing the eyeball, optic nerve, and rectus muscles. The superior and medial rectus muscles were reinserted with Vicryl 6/0 sutures, and the lateral canthotomy was opposed using Vicryl 7/0 sutures. The conjunctival peritomy was sutured using Vicryl 8/0 sutures (Figure 2).

Her hemodynamic status remained stable intraoperatively with no oculocardiac reflex during manipulation of the extraocular muscles and eyeball. The estimated intraoperative blood loss was 700 ml, and she was transfused with one pint of packed cells. Postoperatively, her vision was static, with no signs of anterior segment ischemia. Postoperative eye appearance on Day 1 is shown in Figure 1, d and e. Histopathological examination confirmed the diagnosis of orbital meningothelial meningioma (PONSMS) of the World Health Organization grade 1. Given the large, fast-growing tumor, adjunct radiotherapy was administered to the left eye. Repeated MRI scan of the orbit and brain 18 months post-surgery showed enophthalmos in the left eye with no evidence of recurrence or intracranial extension (Figure 1f). Two years after surgery, visual acuity in the left eye remained at CF1FT, with left eye enophthalmos and esotropia (Figure 1g).

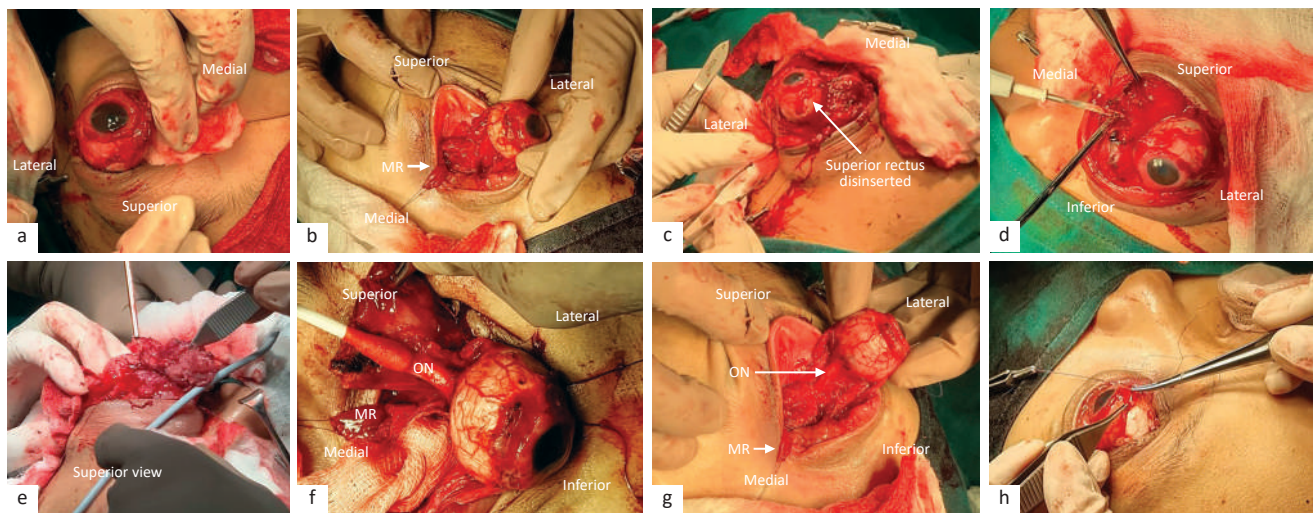
## DISCUSSION

Optic nerve sheath meningiomas commonly present with progressive, painless vision loss, or visual field defect.<sup>10</sup> Proptosis is seldom as the initial presentation. Typically, the proptosis ranges from 2–5 mm.<sup>3</sup> Although rare, severe or extreme proptosis may occur in atypical cases. Amoli et al<sup>7</sup> have histologically confirmed benign PONSMS with aggressive behavior in a 20-year-old woman. The patient presented with severe proptosis with an intracranial and intraocular extension.

Surgery is indicated if PONSMS causes blindness, disfiguring proptosis, or any intracranial extension.<sup>5</sup> However, bleeding from a highly vascularized tumor poses a significant challenge during the surgical excision of severe proptosis or a large tumor. Moreover, bleeding affects the visualization of the tumor and other structures, providing limited space for manipulation during surgery. In the present case, the estimated blood loss was 700 ml, and the patient required a transfusion of one pint of packed cells. The post-transfusion hemoglobin was 10.4 g/dl.



**Figure 1.** Pre- and postoperative ocular features. (a & b) Left eye showing severe disfiguring proptosis, lagophthalmos, and generalized conjunctival redness preoperatively; (c) MRI brain and orbit with contrast showing left orbital mass measuring 6.7 cm × 4.7 cm × 4.9 cm with severe left eye proptosis and distorted eyeball; (d & e) the eye appearance on postoperative Day 1; (f) MRI brain and orbit showing left eye enophthalmos with no evidence of recurrence or intracranial extension; (g) the eye appearance in 2 years postoperative. MRI=magnetic resonance imaging



**Figure 2.** Surgical procedures. (a) Conjunctival peritomy; (b–d) disinsertion of superior and MR; (c) lateral canthotomy; (d & e) separation of the tumor from the ON, recti muscles, and the eyeball with excision of the tumor in fragments; (f & g) the eyeball, ON, and recti muscles were spared; (h) closure of conjunctiva. MR=medial rectus muscle; ON=optic nerve

Separation and manipulation of the extraocular muscles and eyeball from the tumor have a high risk of inducing an oculocardiac reflex during surgery, which was not observed in the present case.<sup>11</sup> If not done meticulously, tumor separation from the eyeball, and more from the optic nerve to achieve complete surgical excision, will further compromise postoperative visual acuity. Postoperative loss of visual acuity occurs in 94% of cases due to a compromised pial vascular plexus,

direct damage to the optic nerve intraoperatively, or incomplete tumor resection with recurrence.<sup>3</sup> In the present case, no worsening of visual acuity was noted postoperatively.

While treating orbital PONSMS, the primary objective is to achieve complete tumor excision without compromising vision or aesthetic components. Many surgical approaches have been described for tumor excision, such as anterior and lateral orbitotomy and



endoscopic endonasal and transcranial approaches, with or without sparing the optic nerve.<sup>12-15</sup> In many instances, mutilating exenteration has been performed for large tumors with severe proptosis.<sup>7,12,14</sup> However, this procedure typically disfigures the patient, which could lead to depression and low self-esteem.<sup>16,17</sup> In the present case, we decided to perform transconjunctival anterior orbitotomy with sparing of the optic nerve and eyeball. The procedure was successful, thus enabling the avoidance of disfigurement following exenteration.

In conclusion, radical surgical interventions, such as exenteration, may not always be the only option in treating orbital PONSMS with severe disfiguring proptosis and blindness. Other options should be considered, particularly in young patients. Follow-up of a patient with an orbital tumor is warranted to detect early recurrence. Our experience in managing this case is worth sharing to benefit the ophthalmic fraternity by enhancing surgical treatment options in orbital PONSMS.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

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## Effects of methotrexate, *Moringa oleifera*, and *Andrographis paniculata* extracts on the myocardial and aortic tissue of streptozotocin-nicotinamide-induced hyperglycemic rats

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### ABSTRACT

**BACKGROUND** Methotrexate (MTX) could lower glucose levels in type 1 diabetes mellitus, while *Moringa oleifera* and *Andrographis paniculata* supplementations have similar effects on hyperglycemia. This study aimed to analyze the effects of MTX, *M. oleifera*, and *A. paniculata* leaf extracts on the myocardial interleukin (IL)-6 and the histopathology of the left ventricle and aorta.

**METHODS** 49 rats were divided equally into 7 groups: negative control and diabetic induced by streptozotocin-nicotinamide (STZ-NA) injection consisting of positive control (STZ-NA only), *M. oleifera* (500 mg/kgBW/day), *A. paniculata* (500 mg/kgBW/day), MTX (7 mg/kgBW/week), MTX (7 mg/kgBW/week)+*M. oleifera* (500 mg/kgBW/day), and MTX (7 mg/kgBW/week)+*A. paniculata* (500 mg/kgBW/day). We analyzed oral MTX, *M. oleifera*, and *A. paniculata* leaf extracts' effects on random blood glucose, myocardial IL-6, and cardiac histopathology of STZ-NA-induced hyperglycemic male rats. Data were analyzed using Wilcoxon and Kruskal–Wallis tests.

**RESULTS** Myocardial IL-6 in the *M. oleifera* group was significantly lower compared to the positive control group ( $p = 0.041$ ). Compared to the positive control group, the myocardial necrosis and aortic intima–media thickness in the MTX+*A. paniculata* group were significantly reduced ( $p = 0.005$  and  $0.001$ , respectively).

**CONCLUSIONS** MTX, *M. oleifera*, and *A. paniculata* showed antihyperglycemic effect, both individually and in combination. *A. paniculata* leaf extract had a significant cardioprotective effect in STZ-NA-induced hyperglycemia.

**KEYWORDS** *Andrographis paniculata*, cardiovascular disease, diabetes, methotrexate, *Moringa oleifera*

Diabetic cardiomyopathy (DCM) affects approximately 26 million people worldwide, and its prevalence is constantly increasing.<sup>1–3</sup> The prevalence of heart failure among patients with diabetes mellitus (DM) ranges from 9% to 22%, which is 4 times higher than that among the general population, with a higher incidence in patients with DM aged  $\geq 60$  years.<sup>2</sup> Hyperglycemia in patients with DM increases oxidative

stress within the vascular system and myocardium, followed by the formation of advanced glycation end products, which is cross-link collagen molecules, increasing fibrosis and myocardial stiffness and impairing cardiac relaxation.<sup>2,4</sup> Quercetin and rutin, bioflavonoid substances found in *Moringa oleifera*, and andrographolide in *Andrographis paniculata* possess cardioprotective effects.<sup>4,5</sup>

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Methotrexate (MTX) can reduce myocardial necrosis;<sup>6</sup> however, a more detailed investigation should be done because it also induces myocardial necrosis<sup>4</sup> and lower blood glucose in patients with type 1 DM (T1DM).<sup>7,8</sup> Furthermore, *M. oleifera* and *A. paniculata* leaf extracts significantly lower the blood glucose level in animal models induced with streptozotocin-nicotinamide (STZ-NA).<sup>9,10</sup> The kaempferol in *M. oleifera* extract possesses a hypoglycemic effect by increasing skeletal muscle glucose uptake through phosphoinositide 3-kinase (PI3K) and protein kinase C (PKC) pathways,<sup>11</sup> whereas phytochemicals in the *A. paniculata* leaf extracts have andrographolide that increases glucose transporter type 4 (GLUT4) expression and andrographolide lipoic acid that increases insulin secretion.<sup>10,12</sup> Various studies have reported the cardioprotective effect of *M. oleifera* and *A. paniculata* separately.<sup>5,13</sup> However, their effect in the same study and when combined with MTX as a therapy has yet to be reported. Therefore, this study aimed to analyze the effects of MTX, *M. oleifera*, and *A. paniculata* leaf extracts on myocardial interleukin (IL)-6 levels and the histopathology of the left ventricle (LV) and aorta in DM-induced male rats to determine any potential cardioprotective and antihyperglycemic effects to reduce the risk of DCM.

## METHODS

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine Universitas Airlangga (No. 1/EC/KEPK/FKUA/2022). The sample size was determined using Mead's resource equation.<sup>14</sup> Experimental animal care, intervention, random data collection of body weight and blood sugar levels, and sacrifice were conducted at the Pharmacology Laboratory of the Faculty of Medicine, Universitas Airlangga.

### Experimental

Forty-nine male rats (*Rattus norvegicus*), aged 2–3 months, and weighing 150–250 g, were acclimatized before experimentation and given *ad libitum* standard rodent food (Pokphand CP 593, Charoen Pokphand Indonesia, Indonesia) and drinking water. DM was induced by an intraperitoneal injection of 50 mg/kg STZ (Sigma-Aldrich, Japan), preceded by an intraperitoneal injection of 110 mg/kg NA.<sup>15</sup>

The rats were divided equally into seven groups: negative control and diabetic induced by STZ-NA injection consisting of positive control (STZ-NA only), *M. oleifera*, *A. paniculata*, MTX, MTX+*M. oleifera*, and MTX+*A. paniculata*. MTX (Rheu-Trex, Kalbe Farma, Indonesia) was administered orally once a week at a dose of 7 mg/kg, whereas *M. oleifera* extract (Sido Muncul, batch number EH00012, Indonesia) and *A. paniculata* extracts (Jamu Iboe, batch number SB1081A, Indonesia) were administered orally daily at a dose of 500 mg/kg for 28 days.<sup>16,17</sup> One animal died in each *A. paniculata*, MTX+*M. oleifera*, and MTX+*A. paniculata* groups.

During the treatment period, the rats' body weights were measured 12 times (thrice weekly for 4 weeks) using a triple beam scale (Ohaus Corporation, USA). To measure random blood glucose (RBG), the blood samples were collected through the excision of the blood vessels in the tail. RBG levels were measured 6 times (once before STZ-NA injection, once after STZ-NA injection, and the remaining once weekly during the treatment period) using Model ET-301 glucometer (Guangzhou Easy Touch Technology Co., Ltd, China).

### Tissue extraction and IL-6 measurement

After 28 days of treatment, the rats were sacrificed on Day 29 using an overdose of ether.<sup>18</sup> Then, the heart and aorta attached were extracted. The heart was cut into two pieces at the anterior interventricular sulcus. The right ventricle was processed to measure the IL-6 level using the enzyme-linked immunosorbent assay (ELISA) technique.<sup>19</sup> Right ventricular tissue was sliced into pieces and submerged in a collagenase type IV and DNase solution (Bioenzy, Cat. No. BZ-08185310-EB, Indonesia) to degrade it into component cells. After centrifugation, the cells were resuspended in a growth medium, and the supernatant was discarded. The red blood cells were lysed by dissolving the resulting cell pellets in a solution. A complete culture medium was then applied to the cell pellets after centrifugation, and the supernatant was removed. ELISA was used to detect IL-6 levels, in which samples and standards were added to ELISA plates and incubated. Subsequently, the plate was cleaned, and a color development solution was added, followed by additional incubation. This process was terminated by adding a stop solution. The samples were then scanned using an ELISA reader at a wavelength of 450

nm to determine IL-6 levels. Myocardial IL-6 level was measured using a rat IL-6 measurement kit (Bioenzy, Cat. No BZ-08185310-EB).

### Myocardial necrotic score and aortic intima-media thickness (IMT)

The remaining heart tissue was used for necrotic score measurements at the LV and aortic IMT measurements. The heart was immersed in a fixative solution of 10% formalin buffer prior to the histological process. Paraffin blocks of the LV and aorta were then sliced at 5  $\mu\text{m}$  thickness and stained using hematoxylin and eosin for the myocardium of the LV and Mallory-Azan for the aorta. All histological analyses were performed from 10 visual fields at 200 $\times$  magnification using a light microscope (Olympus CX23 light microscope, Olympus Company, Japan). Images of the myocardium of the LV and aortic walls were processed using CellSense software (Olympus cellSens Software [RRID: SCR\_014551], Olympus Company). Rocha necrosis score was used to calculate myocardial necrosis as follows: 0 = no damage, 1 = early necrotic changes and scattered neutrophilic infiltrate, 2 = one clear area of necrosis, 3 = two or more separate areas of necrosis but <50% of the ventricular wall, and 4 = extensive area of necrosis of >50% of the myocardial thickness.<sup>20</sup>

The myocardial necrotic score was analyzed by two observers blinded to the animal grouping and sample number. The mean necrotic score was used for statistical analysis. The necrotic score was analyzed as previously described.<sup>20</sup> IMT analysis was performed at 200 $\times$  magnification in 10 visual fields, and three random measurements of the aortic wall thickness (the distance between the endothelial cell layer and

the transitional zone of the medial-adventitial layer) were taken.<sup>21</sup> Further attributes have been previously described.<sup>22–24</sup>

### Statistical analysis

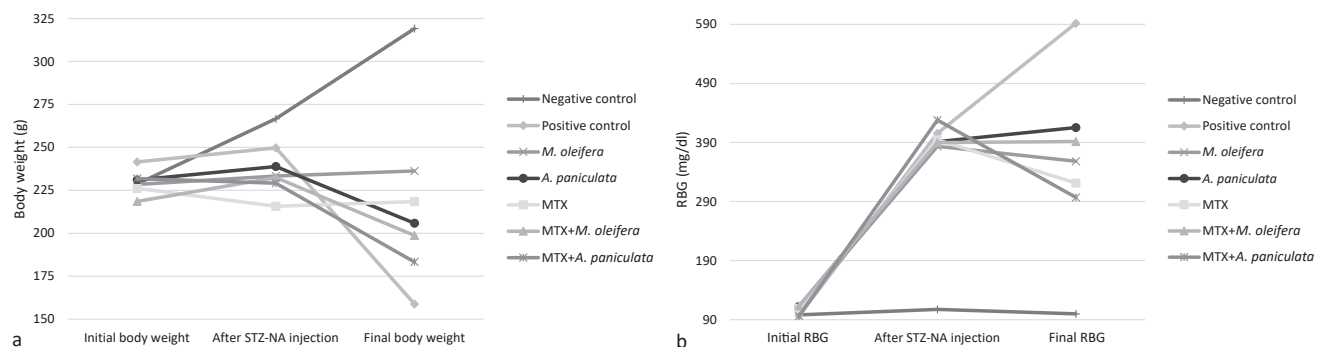
All data were analyzed using SPSS software version 17 for Windows (SPSS Inc., USA).<sup>25</sup> Data were tested for normality using Shapiro–Wilk and for homogeneity using Levene test. The body weight, RBG level, myocardial IL-6 level, Rocha necrosis score, and aortic IMT were compared among the seven groups. Statistical significance was set at  $p < 0.05$ . The post-hoc Kruskal–Wallis test was performed using the Mann–Whitney  $U$  test.

## RESULTS

Body weight in the negative control group was significantly increased but decreased in the positive control group (Figure 1a). All rats induced with STZ-NA had high RBG (Figure 1b).

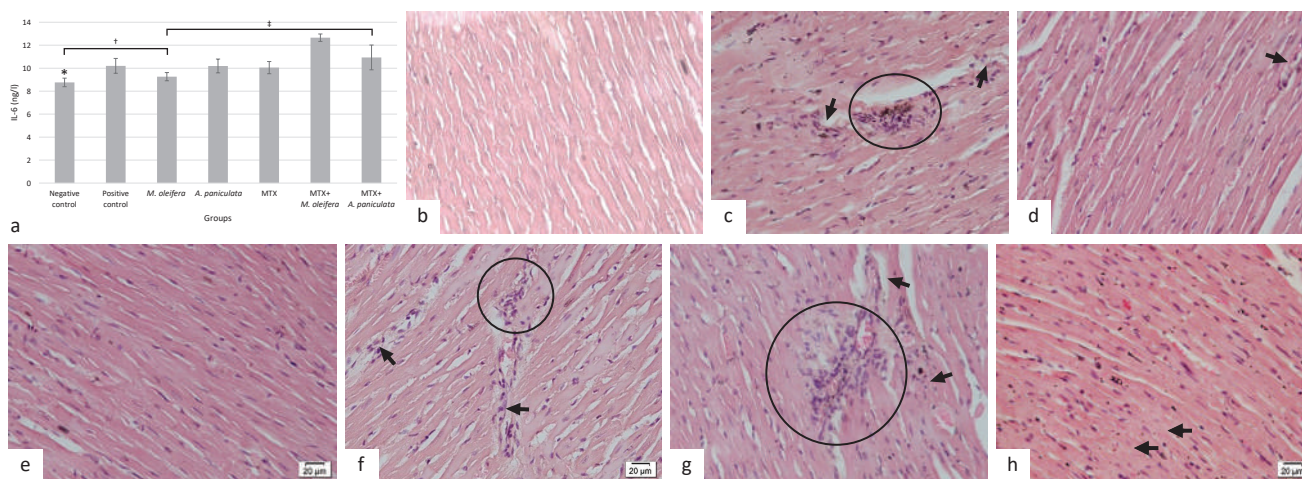
Figure 2 shows the myocardial tissue IL-6 levels and histopathological image of the myocardium. Myocardial IL-6 levels in the negative control group were significantly lower than those in all the hyperglycemic groups ( $p < 0.001$ ). The post-hoc test (not shown) showed significant differences among the groups ( $p = 0.041$ ). The Rocha necrosis score was significantly higher in the MTX+*M. oleifera* group ( $p = 0.002$ ) (Figure 2a). The score was significantly lower in the MTX+*A. paniculata* group than in the positive control group ( $p = 0.005$ , not shown). Myocardial necrosis in each experimental group is shown in Figure 2.

In the negative control group, no necrotic centers, inflammatory cell infiltration, and/or interstitial edema

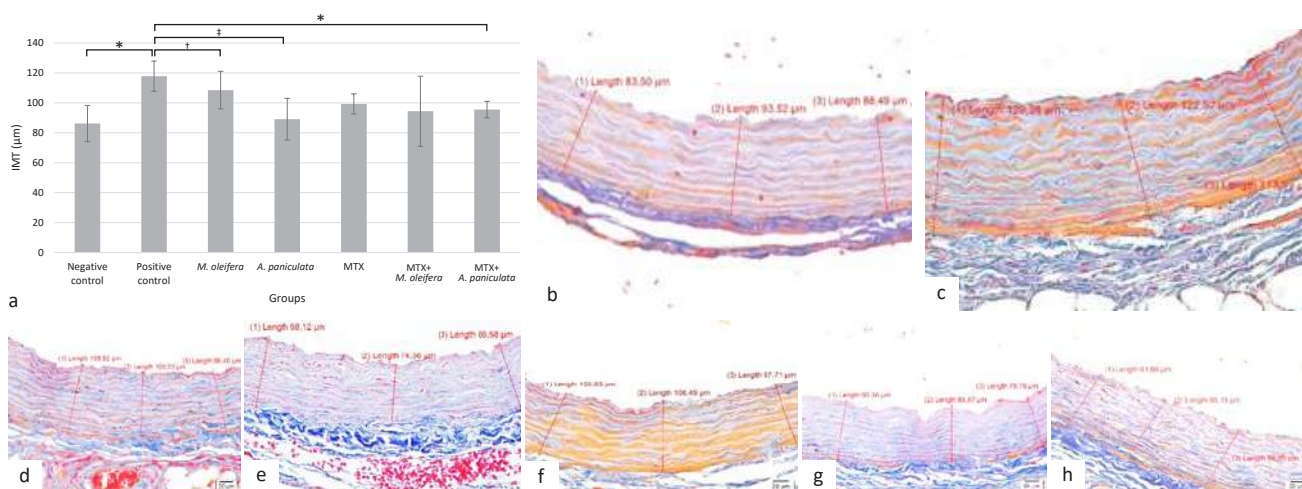


**Figure 1.** Body weight and RBG of the experimental rats. Body weight changes (a) and RBG levels (b) in hyperglycemic rats following *M. oleifera* treatment. Diabetic groups were induced by STZ-NA injection. MTX=methotrexate; RBG=random blood glucose; STZ-NA=streptozotocin-nicotinamide





**Figure 2.** Histopathology of LV myocardium in all groups. (a) Myocardial IL-6 concentration in all experimental groups (mean [SD]); (b) negative control group myocardial tissue showing a normal appearance with regular fibers, without any apparent necrosis or inflammatory cell infiltration; (c) positive control group showing necrotic centers with inflammatory cell infiltration (in circle) and interstitial edema (arrows); (d) *M. oleifera* group showing mild interstitial edema and inflammatory cell infiltrations (arrow); (e) *A. paniculata* group showing near-normal appearance, with mild edema without inflammatory cell infiltration or necrotic centers; (f) MTX group showing necrotic centers (arrows) described as cardiomyocyte cytoplasmic disintegration and inflammatory cell infiltration, with interstitial edema and myocardial fiber disorientation were also apparent (in circle); (g) MTX+*M. oleifera* group showing necrotic centers (arrows) accompanied by severe inflammatory cell infiltration and interstitial edema (in circle); (h) MTX+*A. paniculata* group showing early necrotic signs in the form of focal karyolysis (arrows) with mild inflammatory cell infiltration (H&E staining, 400× magnification). Diabetic groups were induced by STZ-NA injection. H&E=hematoxylin and eosin; IL-6=interleukin-6; LV=left ventricle; MTX=methotrexate; SD=standard deviation; STZ-NA=streptozotocin-nicotinamide. \* $p < 0.001$ ; † $p = 0.002$ ; ‡ $p = 0.005$



**Figure 3.** Histopathology of aorta in all groups. The aortic IMT in all experimental groups (mean [SD]) showing significant differences between negative control and positive control, *M. oleifera*, *A. paniculata*, and MTX+*A. paniculata* groups (a); histology of aorta from the negative control (b), positive control (c), *M. oleifera* (d), *A. paniculata* (e), MTX (f), MTX+*M. oleifera* (g), and MTX+*A. paniculata* (h) groups, respectively. Aortic IMT assessments were done by measuring the distance from the endothelial cell layer to the medial-adventitial layers transition zone. The greatest measurement was shown in the positive control group, while the smallest was seen in the negative control group (in µm, Mallory-Azan stain, 400× magnification). Diabetic groups were induced by STZ-NA injection. H&E=hematoxylin and eosin; IMT=intima-media thickness; MTX=methotrexate; SD=standard deviation; STZ-NA=streptozotocin-nicotinamide. \* $p = 0.001$ ; † $p = 0.014$ ; ‡ $p = 0.010$

were observed in the myocardium (Figure 2b), whereas these pathological features were observed in the positive control group (Figure 2c). Compared with the positive control group, fewer necrotic centers were observed in the *A. paniculata* and MTX+*A. paniculata*

groups, although inflammatory cell infiltration and interstitial edema were still observed. Compared with the *A. paniculata* and MTX+*A. paniculata* groups, the *M. oleifera*, MTX, and MTX+*M. oleifera* groups (Figure 2d-g) showed abundant necrotic centers accompanied

by inflammatory cell infiltration and interstitial edema (Figure 2, e and h).

The aortic IMT measurement results are shown in Figure 3. Compared with the positive control group, the *A. paniculata*, MTX, and MTX+*A. paniculata* groups had significantly thinner IMT.

## DISCUSSION

Body weight was increased significantly in the negative control group but decreased in the positive control group. RBG levels significantly increased after STZ-NA hyperglycemia induction with or without MTX, *M. oleifera*, and *A. paniculata* leaf extract treatments. Previous studies have reported that treatment with *M. oleifera* and *A. paniculata* leaf extracts could significantly decrease the blood glucose levels in STZ-NA-induced hyperglycemic animal models.<sup>9,10</sup> In the present study, reduced RBG levels were observed in rats that received either *M. oleifera* or *A. paniculata* extract compared with STZ-NA-induced only. This may be attributed to kaempferol in the leaf extracts of *M. oleifera* and *A. paniculata*.<sup>11</sup> Kaempferol can reduce blood glucose concentration through PI3K and PKC pathways and translocation of GLUT4 in skeletal muscle. Other studies have also shown that *M. oleifera* extract can increase insulin secretion even higher than metformin.<sup>13,26</sup> In these studies, a methanolic compound of *M. oleifera* extract is suggested to have an antioxidant effect in rats with DM induced by a single intraperitoneal injection of STZ (30 mg/kgBW in 0.1 M citrate buffer [pH 4.5]), with significant increases in plasma insulin, activities of glutathione peroxidase, superoxide dismutase, catalase, and glutathione reductase, and decreases in glutathione content, serum glucose, hydroperoxides, glycated hemoglobin, thiobarbituric acid reactive substances, and conjugated dienes.<sup>13,26</sup> Andrographolide lipoic acid can decrease the production of proinflammatory cytokines through the dampening of nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathway, increase insulin secretion, and promote membrane translocation of GLUT4.<sup>10,12</sup> Consistent with previous studies, the present study also showed the hypoglycemic effect of MTX. In another study, MTX had an antihyperglycemic effect in a T1DM animal model.<sup>27</sup>

In the present study, myocardial IL-6 level was significantly increased in the positive control group compared with the negative control group. A previous

study reported that hyperglycemia modulates specific epigenetic changes, which would regulate the NF- $\kappa$ B activity and, thus, cytokine expression in vascular cells and cardiomyocytes.<sup>28</sup> Elevated circulating level of IL-6 is an independent biomarker of type 2 DM (T2DM) and is associated with inflammation, beta cell dysfunction, obesity, and insulin resistance; however, other studies have shown a contrasting role of IL-6 as an anti-inflammatory cytokine and a cytokine that can help glucose metabolism.<sup>29-31</sup> In a meta-analysis of 15 prospective studies by Bowker et al,<sup>32</sup> higher IL-6 levels were significantly associated with a higher risk of T2DM incidence. The meta-analysis also revealed that IL-6 levels mediated approximately 5% of T2DM cases and a higher body mass index. Furthermore, the reduced myocardial IL-6 level in animals treated with *M. oleifera* extract may be attributed to the inhibition of NF- $\kappa$ B p65, which in turn reduces the synthesis of subsequent inflammatory mediators, including IL-6 and tumor necrosis factor-alpha (TNF- $\alpha$ ).<sup>11,33,34</sup>

The Rocha necrosis score was highest in the MTX+*M. oleifera* group and lowest in the MTX+*A. paniculata* group. The score was significantly lower in the *A. paniculata* group than in the positive control group, possibly due to the potential cardioprotective effect of *A. paniculata* leaf extract on DCM; however, further studies are needed to determine the underlying mechanism. A study by Liang et al<sup>5</sup> showed that andrographolide, one of the components of *A. paniculata* leaf extract, ameliorated DCM in mice by blockage of oxidative damage and inflammation mediated by NF- $\kappa$ B. The cardioprotective effect of andrographolide is due to its capability to restore redox homeostasis by increasing nicotinamide adenine dinucleotide phosphate synthesis in response to hyperglycemia stimulation and the blockage of the messenger RNA expression of several proinflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , and IL-6).<sup>5</sup>

We observed a significant thickening of the aortic IMT in the positive control group compared with the negative control group. However, decreased IMT was observed in the hyperglycemic groups that received any treatment (*M. oleifera* or *A. paniculata* extracts or MTX, either as a single or combination treatment) compared with the positive control group. Notably, the IMT was more reduced in the MTX group than in the *M. oleifera* group. Furthermore, the IMT was more reduced in the *A. paniculata* group than in the positive control group. Another study reported the effect of andrographolide

in the *A. paniculata* extract as an active compound that inhibits blood vessel thickening in mice exposed to cigarette smoke.<sup>35</sup> This effect was obtained by inhibiting the p38MAPK/HO-NF-κB-ERK2 cascade pathway in platelets. MTX monotherapy can reduce blood vessel thickness, mainly by inhibiting proinflammatory cytokines (especially TNF-α, IL-1, and IL-6), increasing the release of IL-10 as an anti-inflammatory cytokine, inhibiting NF-κB, and activating the 5'-adenosine monophosphate-activated protein kinase pathway that improves nitric oxide balance in endothelial cells.<sup>5</sup> Furthermore, the decrease in IL-6 and TNF-α levels was associated with a significant increase in endothelium-dependent vasodilatation and a reduction in vascular cell adhesion molecule-1. Hypertension and dyslipidemia are the common risk factors observed in patients with T2DM and are associated with the development of atherosclerosis.<sup>36-38</sup> MTX possesses a significant antihyperglycemic effect; however, the administration of this drug as a routine treatment to prevent DCM may not be feasible, considering its side effects, particularly in the myocardial tissue.<sup>39,40</sup> This might have also contributed to the death of a few experimental animals in the present study.

The present study provided data on the potential antihyperglycemic and anti-inflammatory effects of MTX combined with *M. oleifera* and *A. paniculata* leaf extracts on cardiovascular tissues. These combinations exhibited no effect; however, *A. paniculata* leaf extract monotherapy significantly reduced myocardium and aortic wall injuries in the hyperglycemic animal model, whereas *M. oleifera* leaf extract showed promising anti-inflammatory effects on heart tissue. However, further analysis is required. One limitation of this study was that we could not ascertain the specific substances responsible for these findings because we used leaf extracts from whole *M. oleifera* and *A. paniculata* plants. Further study should be conducted to compare the efficacy of the agents used in this study with that of others and the optimum dose for each agent. Therefore, other markers of inflammation and/or myocardial necrosis should be investigated further.

In conclusion, *M. oleifera* leaf extract showed the most beneficial effect in reducing cardiac inflammation, as indicated by decreased IL-6 levels, whereas *A. paniculata* leaf extract showed a greater effect on reducing myocardial injury and aortic wall thickening. In this study, MTX, *M. oleifera*, and *A. paniculata* leaf extracts prevented a decrease in body weight in

STZ-NA-induced hyperglycemic rats; however, the antihyperglycemic effect of each treatment was not evident.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

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## Effect of *arum manis* mango peel extract on cholesterol and triglyceride levels in dyslipidemic Sprague-Dawley rats

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### ABSTRACT

**BACKGROUND** Dyslipidemia is characterized by an increase in low-density lipoprotein (LDL) and triglyceride (TG) levels and a decrease in high-density lipoprotein (HDL). Cholestyramine as an antidyslipidemia has several side effects, so an alternative is needed. Pectin is a natural substance with a mechanism of action similar to that of cholestyramine. Mango peel is one of the sources of pectin, containing 10–15% of this substance. This study aimed to prove the effect of *arum manis* mango (*Mangifera indica* L.) peel extract on LDL, HDL, and TG levels in dyslipidemic Sprague-Dawley rats.

**METHODS** 25 Sprague-Dawley rats were divided into 5 groups. All groups were given high-fat diet for the first 18 days, followed by standard feed (negative control group), cholestyramine (Sequest®) 80 mg/200 g body weight (standard treatment group), and mango peel extract (M-90 [90 mg/day], M-180 [180 mg/day], and M-360 [360 mg/day] groups) for the next 15 days. LDL and HDL levels were analyzed using the cholesterol oxidase-phenyl aminopyrazolone method and TG level using the glycerol-3-phosphate-oxidase-phenol-aminophenazone method.

**RESULTS** The M-360 group reduced the LDL level ( $p = 0.015$ ), while the standard treatment group increased the HDL level ( $p = 0.042$ ). Although significant TG level changes were found in the negative control, standard treatment, and M-360 groups ( $p = 0.042$ ), the mean differences of LDL, HDL, and TG levels between groups were not significantly different ( $p = 0.245, 0.328, \text{ and } 0.454$ , respectively).

**CONCLUSIONS** *M. indica* peel extract reduced LDL and TG levels at 360 mg/day.

**KEYWORDS** cholestyramine, high-density lipoprotein, low-density lipoprotein, mango, pectin, triglyceride

Dyslipidemia is a lipid metabolism disorder characterized by an increase in total cholesterol, low-density lipoprotein (LDL) and triglyceride (TG) levels and a decrease in high-density lipoprotein (HDL) level.<sup>1</sup> The management of dyslipidemia is mainly through lifestyle modification by adopting a low-fat diet and regular physical activity. If non-medical treatment is deemed inadequate, antidyslipidemic medicines, such as cholestyramine, which acts as a bile acid sequestrant, are used.<sup>2,3</sup> However, this medication has several adverse effects, including bloating and

constipation. An alternative therapy with a similar mechanism of action is needed.<sup>4</sup> Pectin has been reported to effectively decrease cholesterol levels.<sup>5</sup>

Mango peel is a potential pectin source, comprising approximately 10–15% pectin.<sup>6</sup> Thicker peels tend to have a higher pectin level.<sup>7</sup> While mango pulp is commonly consumed, mango peel is often discarded and remains underutilized. Previous studies regarding orange, apple, and guava peel extracts have been conducted, although no research regarding the effect of pectin in *arum manis* mango (*Mangifera indica* L.)

peel extract on LDL, HDL, and TG levels has been reported. This study determined the effects of *M. indica* peel extract on LDL, HDL, and TG levels in dyslipidemic Sprague-Dawley rats.

## METHODS

### Design and subject

This study used a pre- and post-test randomized controlled group design. Twenty-five healthy Sprague-Dawley male white rats (age: 12–16 months; weight: 200–350 g) were obtained from the Laboratory of Experimental Animals at the Faculty of Medicine, Universitas Diponegoro. This study was conducted from September to November 2020. The dependent variables were LDL, HDL, and TG levels of the dyslipidemic Sprague-Dawley rats, and the independent variable was *M. indica* peel extract at stratified doses of 90, 180, and 360 mg/day.

### Experimental design

One week prior to treatment, the rats were provided standard rat feed and water *ad libitum*. Twenty-five rats were randomly assigned to five groups that were fed a high-fat diet for 18 days, followed by standard feed (negative control group), cholestyramine (Sequest®, Novell Pharmaceutical Laboratories, Indonesia; 80 mg/200 g body weight [standard treatment group]), or mango peel extract (M-90 [90 mg/day], M-180 [180 mg/day], and M-360 [360 mg/day] groups) for the subsequent 15 days. The treatment was administered via oral gavage.

### Mango peel extract production

The mango peel extract (Baki Fruit Garden, Sukoharjo, Indonesia) was made by drying, washing, mashing, sieving, and adding 500 ml of citric acid to the mango peel. Next, the mango peel flour was extracted at 90–95°C for 180 min, according to a previous study.<sup>8</sup> After the extraction, the filtrate was cooled and precipitated for 24 hours with 96% ethanol. The precipitate was separated from the solution and placed in an oven at 50°C for 24 hours. The mango peel extract powder was dissolved in aquadest (Agarindo Biological Company, Indonesia) for oral administration to the rats. This method produced a galacturonic content of 74.16%, surpassing the threshold of 35%. The galacturonic content measured the purity of the obtained pectin. Higher galacturonic content indicated higher quality and purity.<sup>9</sup>

### Biochemical assays

Blood was collected from the rats at two timepoints: on Day 18 after the induction of a high-fat diet and on Day 33 after treatment. The amount of blood collected was 1% of the body weight of each rat. The blood was obtained from the retro-orbital plexus of the rats. The LDL and HDL levels were measured using the cholesterol oxidase-phenyl aminopyrazolone method. The TG level was measured using the glycerol-3-phosphate-oxidase-phenol-aminophenazone method.<sup>9</sup>

### Statistical analysis

The LDL, HDL, and TG levels at different timepoints were compared using the paired *t*-tests for normally distributed data and the Wilcoxon test for data with abnormal distribution. A one-way analysis of variance test was used to compare the mean difference of LDL, HDL, and TG levels before and after treatment ( $\Delta$ LDL,  $\Delta$ HDL, and  $\Delta$ TG) between the groups. When the data had an abnormal distribution, the Kruskal–Wallis test was used. The SPSS software version 26 (IBM Corp., USA) was used to analyze the data, with a cut-off point of  $p < 0.05$ .

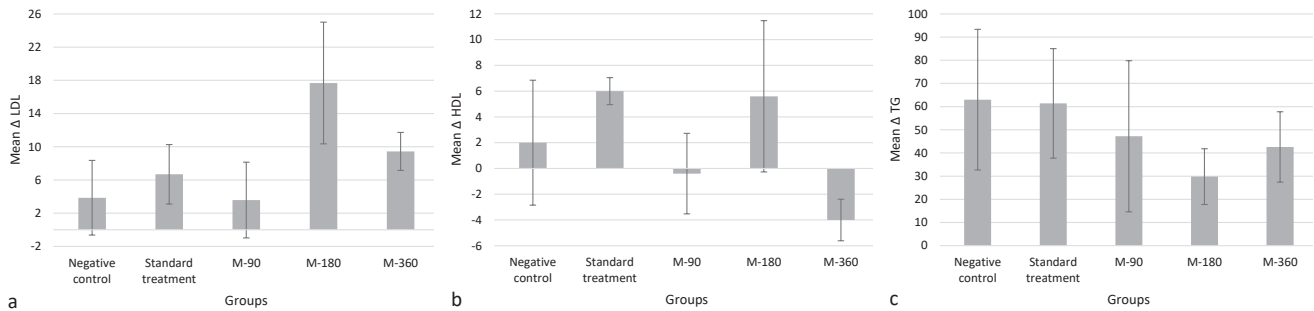
### Ethics

This study was approved by the Health Research Ethics Commission, Faculty of Medicine, Universitas Diponegoro (approval numbers 70/EC/H/FK-UNDIP/VII/2020 and 75/EC/H/FK-UNDIP/VII/2020). All experimental animals were treated according to the Declaration of Helsinki. After treatment, the rats were anesthetized using ether and sacrificed by dislocating the atlanto-occipital joint.

## RESULTS

The LDL level was decreased after treatments in all groups, though the difference was significant only in the M-360 group (from 34.32 mg/dl to 24.88 mg/dl,  $p = 0.015$ ) (Figure 1a). The leveled dose of mango extract did not cause a significant change in the LDL, HDL, and TG levels between the groups ( $p = 0.245, 0.102, \text{ and } 0.454$ , respectively). The HDL level was increased in the negative control, standard treatment, and M-180 groups after treatments, though the increase was only significant in the standard treatment group (from 35.20 mg/dl to 41.20 mg/dl,  $p = 0.042$ ) (Figure 1b). The TG level was decreased after treatments in all groups,





**Figure 1.** Changes in cholesterol levels after 15 days of treatments. Value are expressed in terms of mean difference ( $\Delta$ ) in LDL (a), HDL (b), and TG (c) levels. Standard treatment was given 80 mg/200 gBW cholestyramine (Sequest®). The treatments were administered for the subsequent 15 days. M-90=mango peel extract at 90 mg/day; M-180=mango peel extract at 180 mg/day; M-360=mango peel extract at 360 mg/day. One-way analysis of variance:  $p = 0.015$  for LDL changes,  $p = 0.042$  for HDL changes; Kruskal–Walis test:  $p = 0.043$  for TG changes

with a significant reduction in the negative control (from 106.80 mg/dl to 43.80 mg/dl,  $p = 0.043$ ), standard treatment (from 105.60 mg/dl to 44.20 mg/dl,  $p = 0.043$ ), and M-360 groups (from 92.80 mg/dl to 45.00 mg/dl,  $p = 0.043$ ) (Figure 1c).

## DISCUSSION

In this study, the LDL level was increased in rats fed a high-fat diet, indicating that the acclimatization and high-fat diet for the first 18 days were successful, where the level of normal LDL cholesterol in rats was 2–27 mg/dl. The LDL level after treatment was significantly decreased only in the M-360 group. This may be due to the suboptimal feeding method using tube feeding.

Mango peel extract is difficult to dissolve in room-temperature water, often leading to clogs in the feeding tube, which may affect the dose of mango peel extract ultimately administered to the rat. In addition, the decrease indicated the presence of pectin in mango peels. Pectin can bind bile acids, which are the final products of cholesterol metabolism, resulting in increased excretion of bile acids. Pectin is a water-soluble fiber that can form a thick layer on the intestinal wall, inhibiting the reabsorption of bile acids and cholesterol in the intestine. The subsequent conversion of cholesterol to bile acids increases, decreasing free cholesterol in the liver. To compensate for cholesterol levels in the liver, LDL receptors in the liver increase LDL uptake, resulting in a decrease in serum LDL concentration.<sup>10,11</sup>

In the standard treatment group, the LDL level did not change significantly after administering cholestyramine. This may be due to an insufficient

dose of cholestyramine. The cholestyramine dose used in this study was obtained by converting the human dose to the rat dose. Increasing the dose may increase the effectiveness of cholestyramine for reducing LDL level.<sup>12</sup>

The HDL level is typically >35 mg/dl in rats.<sup>11</sup> In a recent study, a high-fat diet reduced the HDL level in rats.<sup>13</sup> In the current study, the HDL level was <35 mg/dl in all rats fed a high-fat diet except for the standard treatment and M-360 groups. This may be because the HDL level in the M-360 group was higher than those in the other groups prior to the high-fat diet. However, this could not be confirmed as the HDL level was not assessed before the administration of the high-fat diet. In this study, the HDL level was not significantly increased after the administration of mango peel extract. These results correspond with those of previous studies regarding the effect of pectin from guava on cholesterol levels<sup>14</sup> and may be due to the cholesterol-lowering mechanisms of pectin, which increases cholesterol excretion.<sup>10</sup>

In this study, the rat TG levels remained normal (26–145 mg/dl) after the high-fat and standard diets. This may be because the duration of the high-fat diet was relatively short. A previous study reported an increased TG level after 22 weeks of a high-fat diet.<sup>15</sup> In addition, the rats were fed through a feeding tube, which was not optimal. The mixture of pork oil and egg yolk often clogs the feeding tube. However, the TG levels significantly decreased in the standard treatment, negative control, and M-360 groups, indicating that the mango peel extract can significantly reduce TG level. This finding is in accordance with those of previous studies that tested the effects of

pectin from guava, orange, peanut, and pomegranate on TG level in adult male Sprague-Dawley rats.<sup>16,17</sup>

The leveled dose of mango extract was not significantly effective in lowering TG levels between the groups in this study, suggesting that administering various doses of mango peel extract and cholestyramine did not lead to significant changes in TG level. This result contradicts those of previous studies and may be attributed to the natural fluctuation of TG level or the influence of several factors, including stress. Rats tend to experience stress when fed via oral gavage, leading to increased cortisol and blood sugar levels, and prolonged stress may lead to increased TG level.<sup>18</sup> In addition, pectin, as a bile acid sequestrant, can bind to and increase the excretion of bile acids in the feces, decreasing the availability of bile acids in the intestine and preventing cholesterol absorption. Decreased cholesterol absorption in the intestine results in decreased TG synthesis.<sup>8</sup>

This study had several limitations. First, it was conducted only in rats. The high-fat diet was only administered for 18 days before the administration of the drug and mango peel extract; therefore, it was unclear whether the treatment effects were due to the drug and extract or due to the cessation of the high-fat diet. Therefore, a high-fat diet should be administered throughout the study period, and various doses of medication and extract are needed to determine the optimal benefits of the pectin contained in the peel extract in future studies. In addition, mango peel extract requires special preparation for its dissolution in room-temperature water. The pectin levels, pharmacodynamics, pharmacokinetics, therapeutic doses, therapeutic windows, and adverse effects of the mango peel extract must be determined.

In conclusion, the administration of 360 mg/day of *M. indica* peel extract reduced the LDL and TG levels in dyslipidemic Sprague-Dawley rats. However, the HDL level did not change, and the mean LDL, HDL, and TG levels were not significantly different after mango peel treatment.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

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## Vitamin D levels and depression in type 2 diabetes mellitus patients: a cross-sectional study

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### ABSTRACT

**BACKGROUND** The prevalence of type 2 diabetes mellitus (T2DM) is increasing and commonly accompanied by comorbidities, such as depression. Vitamin D levels have been associated with T2DM and depression although the mechanism is uncertain. This study aimed to compare vitamin D levels between patients with T2DM with and without depression in the Indonesian community, where such research is rare.

**METHODS** This cross-sectional study was conducted at Cipto Mangunkusumo Hospital. The participants who met the inclusion criteria on an outpatient basis were screened for depression using the Beck Depression Inventory-II (BDI-II) questionnaire and then divided into 2 groups: patients with T2DM with (BDI-II  $\geq 14$ ) and without (BDI-II  $< 14$ ) depression. Both groups were examined for vitamin D levels using the ELISA method, and an analysis of the mean difference between both groups was performed.

**RESULTS** Of 60 patients, 23 (38%) experienced depression. The median vitamin D levels were 21.8 ng/ml (IQR 14.9–26.6) in the depression group and 26.5 ng/ml (IQR 23.96–34.08) in the non-depression group ( $p = 0.001$ ). After performing multivariate analysis with confounding variables, the adjusted OR of variables (sex, sun exposure score, and body mass index) was 1.123 (95% CI: 1.003–1.259;  $p = 0.045$ ).

**CONCLUSIONS** Vitamin D levels were significantly lower in patients with T2DM with depression. Future studies should be carried out to determine the benefits of vitamin D supplementation in patients with T2DM with depression and their pathophysiology.

**KEYWORDS** depression, type 2 diabetes mellitus, vitamin D level

Patients with type 2 diabetes mellitus (T2DM) are at risk for depression, with a higher prevalence rate (11–17.6%) than the general population (3–4%).<sup>1,2</sup> Furthermore, 41% of patients with T2DM experience depression.<sup>2</sup> Theoretically, depression could be exacerbated by diabetes treatment. Diabetes causes anatomical changes in the brain, including cerebral atrophy and lacunar infarctions, blood flow variations (hypoperfusion and hyperperfusion), and an increased risk of depression.<sup>3</sup> Depression in patients with

T2DM greatly influences medication adherence, diet control, and blood glucose monitoring, thus increasing the treatment cost and lowering the quality of the prognosis of the disease course.<sup>2–4</sup> Despite the condition, using tricyclic antidepressants might impair glucose metabolism in patients with diabetes and increase their body weight.<sup>5</sup>

Vitamin D is a fat-soluble vitamin commonly involved in bone and calcium metabolism and known for its anti-inflammatory and immunomodulatory

properties. Various studies have shown that vitamin D deficiency correlates with various diseases, such as DM, cardiovascular diseases, cancer, autoimmune diseases, and depression.<sup>6–8</sup> Vitamin D plays a crucial role in regulating insulin levels and maintaining proper glucose metabolism, which is essential for the prevention and management of diabetes. Furthermore, individuals with depression tend to have higher blood sugar levels, indicating a potential connection between depression and T2DM. Therefore, addressing vitamin D deficiency could positively impact mental health and prevent T2DM.<sup>6,7</sup>

The association between vitamin D and depression has been reported in several studies, including a systematic review by Ju et al,<sup>9</sup> which reported that an increase in vitamin D levels by 10 ng/ml was associated with improved depressive symptoms and reduced depression risk. Lower levels of vitamin D have also been reported in patients with depression than in the controls.<sup>10,11</sup> It has been proposed that hypovitaminosis D may contribute to depression. Vitamin D metabolites protect neuronal integrity by upregulating neurotrophic factors (nerve growth factor, neurotrophin [NT]-3, and NT-4) in the hippocampus and neocortex. Furthermore, vitamin D affects inflammatory pathways (downregulating autoimmune processes, releasing proinflammatory cytokines, and increasing anti-inflammatory pathways through vitamin D receptor-mediated gene transcription), which are associated with depression.<sup>10</sup>

Notably, vitamin D levels have not been compared between patients with and without depression who have T2DM in Indonesia. To address this knowledge gap, the present study aimed to investigate the relationship between vitamin D levels and T2DM in patients with and without depression. This would provide a better understanding of the association between vitamin D deficiency and the co-occurrence of T2DM and depression.

## METHODS

This cross-sectional study was conducted at the Metabolic Endocrine and Diabetes Clinic of the Department of Internal Medicine, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, between July and August 2022. This study analyzed data collected from interviews and laboratory tests of the included participants.

### Selection and characteristics of the participants

Patients with T2DM aged  $\geq 18$  years (adult) who visited the clinic were enrolled in this study. The sample was obtained through consecutive sampling until the number of participants reached the required size. Patients with a known history of comorbidities, such as cancer, autoimmune disease, and stages 4 and 5 chronic kidney disease, and pregnant and lactating women were excluded from this study. Patients who received vitamin D supplementation, antidepressants, or immunosuppressant therapy and who declined to participate in this study were also excluded.

### Study procedure

Eligible outpatients with T2DM were screened for depression by conducting an interview using the Beck Depression Inventory-II (BDI-II) questionnaire and weekly sun exposure scoring, as reported by Husna.<sup>12</sup> The skin area exposed to sunlight each day for a week was multiplied by the old score (length of exposure) to determine the sun exposure score. Subsequently, history-taking and physical examinations were conducted. Based on the BDI-II scoring results, the participants were divided into two groups: patients with T2DM with (BDI-II score  $\geq 14$ ) and without (BDI-II score  $< 14$ ) depression. The Indonesian version of the BDI-II questionnaire was validated by Ginting et al,<sup>13</sup> with good specificity and sensitivity. Patients were then prepared for serum vitamin D analysis using laboratory analysis. A 3 ml blood sample from a peripheral venipuncture was assessed for 25-hydroxyvitamin D (25[OH]D) serum at the Cipto Mangunkusumo Laboratory using the enzyme-linked immunosorbent assay (ELISA) method.<sup>14</sup> The procedure was performed only once without any therapeutic intervention or any other invasive procedure to minimize hemorrhage after blood puncture.

### Laboratory analysis

Serum vitamin D tests were performed using a sandwich ELISA. Two antibodies were used to capture the target antigens. The test was performed using the DiaSino® 25(OH)D Total ELISA Kit (DiaSino Laboratories Co., Ltd, China). The microplate was then prepared for absorbance reading using a light wave of 450 nm in the microplate reader 30 min after the addition of the stop solution. The absorbance was extrapolated to a reference value based on the manufacturer's instructions.



### Statistical analysis

Statistical analyses were performed using Microsoft Excel 2016 (Microsoft Corp., USA) and SPSS software version 20.0 (IBM Corp., USA). Categorical data are presented as frequencies and percentages, whereas numerical data are presented as mean (standard deviation [SD]) for normally distributed data or median (min–max) for data with non-normal distribution. Data normality was determined using the Kolmogorov–Smirnov test. The comparison or significant difference in the 25(OH)D of each independent and confounding variable was analyzed using bivariate analysis, utilizing an independent *t*-test for normally distributed data and the Mann–Whitney *U* test for data with non-normal distribution. Data are presented as mean, SD, and *p*-value using a 95% confidence interval [CI] (statistical significance was set at  $p < 0.05$ ). Confounding variables were analyzed using multivariate logistic regression analysis.

### Ethical clearance

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital (No. KET-348/UN2.F1/ETIK/PPM.00.02/2022). The participants were informed of the study procedure and signed an informed consent form prior to data extraction.

## RESULTS

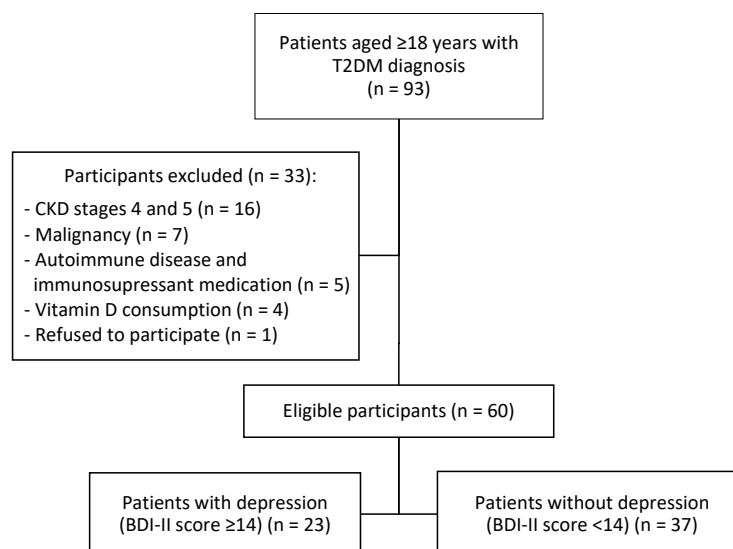
Of the 93 patients enrolled in this study, 60 were finally included (Figure 1). Participants' baseline characteristics are presented in Table 1.

Age and body mass index (BMI) were similar between patients with T2DM with and without depression. However, those who had depression were predominantly females. Higher median sun exposure scores and lower vitamin D levels were observed in the depression group (Table 2).

The lower the vitamin D level, the higher the risk of depression (crude odds ratio [OR]: 1.107; 95% CI: 1.031–1.189;  $p = 0.005$ ). This remained significant after adjusting for sex, sun exposure score, and BMI (adjusted OR: 1.123; 95% CI: 1.003–1.259;  $p = 0.045$ ).

## DISCUSSION

This study found a significantly increased risk of depression in patients with T2DM with vitamin D deficiency. Vitamin D levels were lower in the depression group than in the control group. In contrast, Westra et al<sup>15</sup> found no correlation between vitamin D deficiency and the risk of depression in patients with T2DM. Other studies have shown different vitamin D levels in patients with obesity experiencing depression compared with those without depression.<sup>16</sup> The results are consistent with other studies on depression in patients with several comorbidities, such as liver disease and perinatal or postpartum depression.<sup>17–25</sup> Furthermore, Wang et al<sup>26</sup> found a median vitamin D level of 10.2 ng/ml (interquartile range [IQR]: 7.6–15.2) among patients with T2DM with depression, compared with 14.6 ng/ml (IQR: 10.7–19.8) among those without depression. No significant associations were found between vitamin D levels and the duration of T2DM, therapy, or sociodemographic factors.



**Figure 1.** Participants' enrollment flowchart. BDI-II= Beck Depression Inventory-II; CKD=chronic kidney disease; T2DM=type 2 diabetes mellitus



**Table 1.** Baseline characteristics of the participants

| Variables                                  | N = 60              |
|--|---------------------|
| Male sex, n (%)                            | 31 (52)             |
| Age (years), median (min–max)              | 59 (52–63)          |
| BMI (kg/m <sup>2</sup> ), median (min–max) | 26.9 (24.65–28.85)  |
| Obese, n (%)                               | 43 (72)             |
| Depression, n (%)                          | 23 (38)             |
| Vitamin D levels (ng/ml), median (min–max) | 24.95 (18.95–32.17) |
| Vitamin D level, n (%)                     |                     |
| Deficiency                                 | 15 (25)             |
| Insufficiency                              | 27 (45)             |
| Normal                                     | 18 (30)             |
| Sun exposure score, median (min–max)       | 16 (9–20)           |
| GFR, median (IQR)                          | 81.45 (57.25–92.7)  |
| HbA1C, median (IQR)                        | 7.9 (7.0–9.1)       |

BMI=body mass index; GFR=glomerular filtration rate; HbA1c=glycosylated hemoglobin; IQR=interquartile range

Regarding the confounding variables in the present study, there were no significant differences in age and BMI. However, significant differences were observed in sex and sun exposure. The depression group comprised females predominantly, which is consistent with the study of Salk et al,<sup>22</sup> in which a 3 times higher risk of depression was observed in females than in males, particularly in the teenage age group (12–16 years old). Females are more prone to depression because of higher stress, cognitive instability owing to hormonal imbalance, and a higher risk of comorbidities of anxiety and somatic symptoms, particularly during peripartum and postpartum periods.<sup>23,24</sup> However, Al Qusaibi et al<sup>25</sup> found an insignificant incidence between males and females.

Sun exposure is a significant confounding factor that increases serum vitamin D levels and lowers the proportion of vitamin D deficiency.<sup>27,28</sup> Notably, sun exposure might also affect depressive symptoms and other mental disorders because it has a dose-response effect, with lower exposure correlating with worsening cognitive status.<sup>29</sup> This finding is consistent with that of other reports on the efficacy of sun exposure in improving depressive symptoms and quality of life.<sup>30,31</sup> This phenomenon might be explained by an increase in anti-inflammatory cytokines, which might explain the improvement in mood progression. In addition, sun exposure is correlated with increased cortisol levels and circadian rhythm regulation, thereby improving mood and depressive symptoms.<sup>32–34</sup>

Diabetes is associated with vitamin D deficiency. The significance of vitamin D in sustaining accurate insulin release by pancreatic beta cells in patients with diabetes involves the establishment of insulin resistance. Beta cells can overcome this resistance by releasing more insulin, thus preventing hyperglycemia. However, when hyperactivity increases, the cells exhibit increased Ca<sup>2+</sup> levels and reactive oxygen species signaling, leading to cell death and diabetes. Vitamin D deficiency contributes to initial insulin resistance and subsequent onset of diabetes caused by beta cell apoptosis. Vitamin D prevents inflammation, which is a major factor in insulin resistance.<sup>35</sup> The use of vitamin D supplementation has also been reported to positively impact mental health and depressive symptoms in patients, particularly those with insufficient vitamin D.<sup>36–38</sup> According to several studies, vitamin D supplementation may reduce depression in patients with T2DM.<sup>39–42</sup>

This study had several limitations. First, the study design did not cover the causes of depression or vitamin D deficiency. Second, this study did not

**Table 2.** Multivariate analysis of depression in patients with T2DM

| Variables                                  | Depression       |                    | p       |
|--|------------------|--------------------|---------|
|  | Yes              | No                 |         |
| Age (years), median (min–max)              | 59 (55–65)       | 59 (48–63)         | 0.342*  |
| Male sex, n (%)                            | 5 (16.1)         | 26 (83.9)          | <0.001† |
| Sun exposure score, median (min–max)       | 9 (7–15)         | 18 (12–22)         | <0.001* |
| BMI (kg/m <sup>2</sup> ), median (min–max) | 26.3 (23.1–30.0) | 27.1 (25.7–28.8)   | 0.186*  |
| Vitamin D levels (ng/ml), median (min–max) | 21.8 (14.9–26.6) | 26.5 (23.96–34.08) | 0.001*  |

BMI=body mass index; T2DM=type 2 diabetes mellitus

\*Mann–Whitney U test; †chi-square test

include the diet consumption variable despite the probable increase in vitamin D based on a suitable diet. However, several studies have reported non-significant differences owing to diet differences in vitamin D levels.<sup>43,44</sup>

In conclusion, this study reported significantly lower vitamin D levels in patients with T2DM with depression. Future studies should be conducted to determine the benefits of vitamin D supplementation in patients with T2DM with depression and their pathophysiology.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

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None.

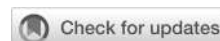
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## Bambara groundnut ameliorates kidney histology in female mice with protein deficiency

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### ABSTRACT

**BACKGROUND** Protein deficiency (PD) can lead to kidney damage. Consuming plant-based proteins may improve this condition. Bambara groundnut (*Vigna subterranea*) has an essential amino acid score of 80%, which is higher than other legumes; thus, it is potent in overcoming malnutrition. This study aimed to determine the effect of Bambara groundnut supplementation on kidney histology in adult female mice with PD.

**METHODS** The study was conducted for 2 months in randomly selected female mice. These mice were grouped into the control, PD, and PD supplemented with Bambara groundnuts at 100, 200, and 300 g/kg of feed. 1 day after the last treatment, the kidneys of the mice were collected and processed histologically using the paraffin method (stained with hematoxylin and eosin and Masson's trichrome). Parameters for observation included histopathological scoring (glomerular and interstitial space fibrosis and tubular damage), kidney histomorphometry, and organ index. Semi-quantitative data were analyzed using the Kruskal–Wallis test, while quantitative data were analyzed using one-way ANOVA (followed by Tukey's test) and nested t-test. Statistical analysis was performed using SPSS software version 20 (IBM Corp., USA) ( $p \leq 0.05$ ).

**RESULTS** PD caused cell sloughing (moderate level) and dilatation (severe level) of the kidney tubules. It also reduced glomerular diameter and area by approximately 17.66% and 29%, respectively. PD and Bambara groundnut administration had no significant effects on the glomerular number, cortex and medulla thickness, distal and proximal tubule diameter, and kidney organ index ( $p > 0.05$ ).

**CONCLUSIONS** Bambara groundnut (*V. subterranea*) administration prevented damage to the kidney's histological structure of protein-deficient mice.

**KEYWORDS** female, histology, kidney, mice, protein deficiency, *Vigna subterranea*

Protein deficiency (PD) is reportedly experienced by approximately half of the world's population,<sup>1</sup> especially women. Women are vulnerable to malnutrition due to higher nutritional requirements during certain conditions, such as menstruation, pregnancy, and breastfeeding.<sup>2</sup> Inadequate protein intake in women can lead to malnutrition in their offspring.<sup>3</sup>

PD adversely reduces the effectiveness of the immune system and disturbs the endocrine, digestive,

and circulatory systems. A lack of protein intake additionally impairs the function of the brain, lungs, stomach, intestines, and kidneys.<sup>4,5</sup> PD may cause structural damage to the glomeruli, tubules, blood vessels, or interstitial spaces. As a result, the kidneys cannot perform optimal blood filtration, as indicated by a decrease in glomerular filtration rate (GFR), renal blood flow, and renal vascular resistance, and inflammation arises.<sup>6–9</sup> Leukocyte infiltration, cast

formation, fibrosis in the glomeruli and interstitial space, and tubular damage have been reported in the kidneys of protein-deficient mice.<sup>10–12</sup>

The consumption of legumes with high protein contents can improve malnutrition. Most residents of developing countries consume legumes, such as soybean, peanuts, peas, and chickpeas,<sup>13</sup> as an alternative protein source to replace expensive animal protein and meet their protein intake needs.<sup>14</sup> One legume with a complete nutrient content that remains underutilized for overcoming PD is the Bambara groundnut (*Vigna subterranea*). This groundnut contains 49–63.5% of carbohydrates, 4.5–7.4% of fat, 15–25% of protein, 5.2–6.4% of fiber, and 3.2–4.4% of ash.<sup>13,15</sup> Additionally, the Bambara groundnut has an essential amino acid score of 80%, which is higher than that of soybeans (*Glycine max*; 74%), peanuts (*Arachis hypogaea*; 65%), and cowpea (*Vigna unguiculata*; 64%).<sup>16</sup>

The Bambara groundnut has been primarily consumed as a roasted or boiled snack to ameliorate vision problems and joint pain, reduce nausea, diarrhea, and sexually transmitted infections, treat inflammation, and inhibit the development of cancer cells.<sup>17–19</sup> The Bambara groundnut is abundant and easily accessible in Indonesia, and is, therefore, a potential food supplement to overcome PD.<sup>20</sup> Hence, ascertaining the safety level of Bambara groundnut consumption for overcoming PD is essential. This study aimed to examine the effects of Bambara groundnut supplementation on the histological structure of the kidneys of female mice with PD.

## METHODS

This animal experimental study was conducted in the Animal House, Pharmacology Laboratory, Biochemistry Laboratory of the Faculty of Medicine, Public Health, and Nursing, and the Animal Structure and Development Laboratory of the Faculty of Biology, Universitas Gadjah Mada, from December 2021 to June 2023.

### Experimental animal preparation

This collaborative research was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, under the protocol KE/FK/0913/EC/2022 (amendment). Twenty female mice (*Mus musculus* L.) of the Swiss-Webster strain aged

1 month and weighing approximately 20 g were randomly selected. The sample size was determined based on a previous study by Arifin and Zahiruddin<sup>21</sup> and was calculated as 10, divided by the number of treatment groups, and added by one.

### Mice acclimatization

All mice were acclimatized for 7 days to standard feed (2 g/20 g body weight [BW] of AIN-93M) prepared by the author (S) and drinking water *ad libitum*. The standard feed was obtained from Department of Biochemistry, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Indonesia. The mice were then randomly divided into five groups, and each group was maintained in a plastic cage (40 × 50 × 50 cm<sup>3</sup>) containing husks. Cages were placed in a room with a 20–24°C temperature, 45–65% humidity, and 12-hour day/night periods.

### Feed preparation and administration

PD feeds containing Bambara groundnuts were prepared by the author (S). The Bambara groundnuts used in this study were obtained from the Bambara Groundnut Research Center, Gresik, East Java. Five types of feed, differing in protein content, were employed, as follows: control (14% protein), PD (10% protein), PD supplemented with 100 g Bambara groundnuts (PD-100; 11.289% protein), PD supplemented with 200 g Bambara groundnuts (PD-200; 12.578% protein), and PD supplemented with 300 g Bambara groundnuts (PD-300; 13.867% protein). Feeding was performed for 2 months at a rate of 2 g/20 gBW.

### Kidney collection

On the day after the last feeding, the 3-month-old female mice were euthanized via intraperitoneal ketamine (100 mg/kgBW) and xylazine injections (10 mg/kgBW), followed by neck dislocation. Twenty right and 20 left kidneys were collected and fixed in 10% neutral-buffered formalin.

### Histological preparation

The kidneys were processed using the paraffin method to produce tissue sections with 6 µm thickness in cross-section (right kidney) and longitudinal section (left kidney). Staining of the preparations was performed with hematoxylin and eosin (Ehrlich hematoxylin [Merck, Germany] and eosin Y 1% [Merck]) to observe general tissue damage



and Masson's trichrome (Ehrlich hematoxylin [Merck], acid fuchsin [Merck], phosphomolybdic acid [Merck], aniline blue [BDH Chemicals Ltd., United Kingdom], and glacial acetic acid [BDH Chemicals Ltd.]) to assess the presence of fibrosis.

### Data analysis

The kidney tissues were observed under a light microscope (Leica ICC50 E [Leica Microsystems, Germany]). Tissue damage was observed in the longitudinal section of the kidney, while the number, diameter, area of the glomeruli, the thickness of the cortex and medulla, and the diameter of the distal convoluted tubule (DCT) and proximal convoluted tubule (PCT) were observed in the cross-section. ImageJ software (National Institutes of Health, USA) was used to measure the thickness, diameter, area, and glomerular number.

Tissue damage was evaluated by the authors (VAF and AN) using a modified ordinal scoring method,<sup>22</sup> as follows: 0 for none; 1 for  $\leq 1\%$  field of view (minimal); 2 for 1–5% field of view (mild); 3 for 6–10% field of view (moderate); and 4 for 11–15% field of view (severe). Semi-quantitative scoring data were analyzed using the Kruskal–Wallis test and Dunn's test of significant differences. Quantitative data were analyzed using one-way analysis of variance and nested t-test with Tukey's test for significant differences. Statistical analyses were performed using SPSS software version 20 (IBM Corp., USA) at a significance level of 5%.

## RESULTS

The PD feed resulted in moderate tubular cell sloughing and severe tubular lumen dilatation (Figure 1). In contrast, Bambara groundnuts resulted in better kidney tissue by reducing cell sloughing and tubular lumen dilatation. Addition of 200 and 300 g of Bambara groundnuts to the protein-deficient feed prevented damage and ensured renal tissue close to normal conditions. However, the present study found no fibrosis in the glomerulus or interstitial space of the kidney after PD treatment. Similarly, administration of Bambara groundnuts did not result in the presence of collagen fibers in the kidney tissue (Figure 2a–e).

The PD feed resulted in mice renal cortex and medulla with the most negligible thickness, 1,433.91 (113.26)  $\mu\text{m}$  and 2,445.04 (591.01)  $\mu\text{m}$ , respectively, although there were no differences compared to

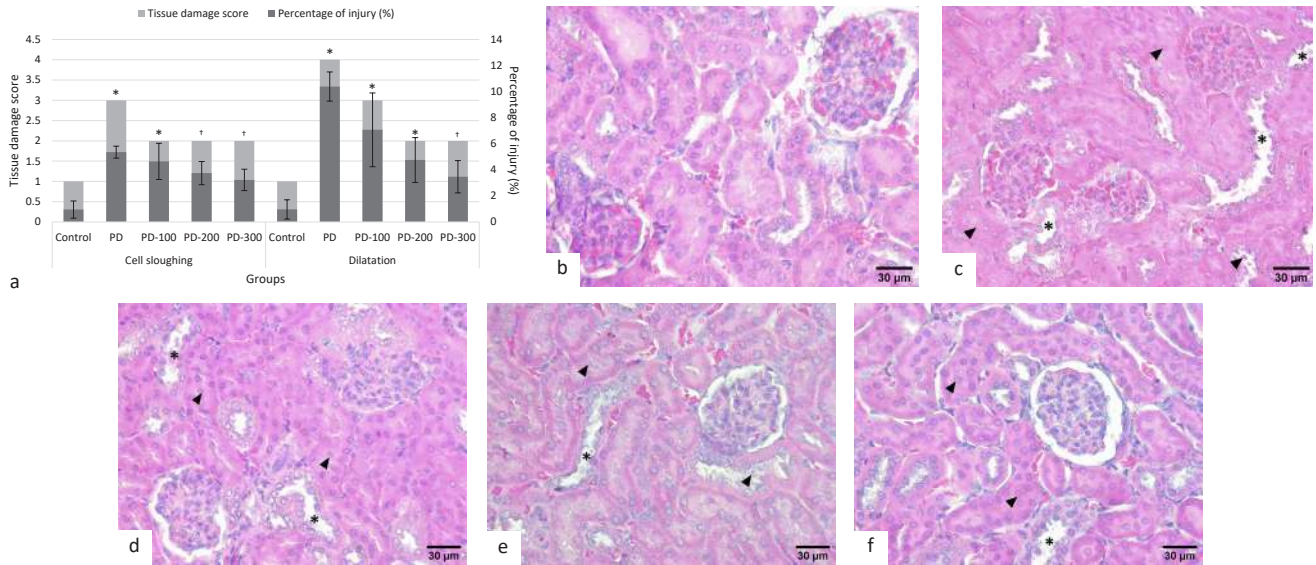
the control group. However, the thickness of the renal cortex and medulla increased after Bambara groundnut administration. The PD-300 group had the thickest cortex (1,673.33 [122.80]  $\mu\text{m}$ ), while the PD-200 group had the thickest medulla (2,916.87 [678.66]  $\mu\text{m}$ ). Although differences in size occurred, the thicknesses of the renal cortex and medulla between the PD diet and Bambara groundnut supplementation groups were not significantly different (Figure 2f).

The PD feed resulted in a smaller proximal tubule diameter than all Bambara groundnut treatments. Meanwhile, the distal tubule diameter in the PD group was greater than that in the PD-200 group. Groups fed with the PD diet and administered Bambara groundnuts had larger distal and proximal tubule diameters than the control group. Nonetheless, the variation in diameter among all groups was not significantly different (Figure 2g).

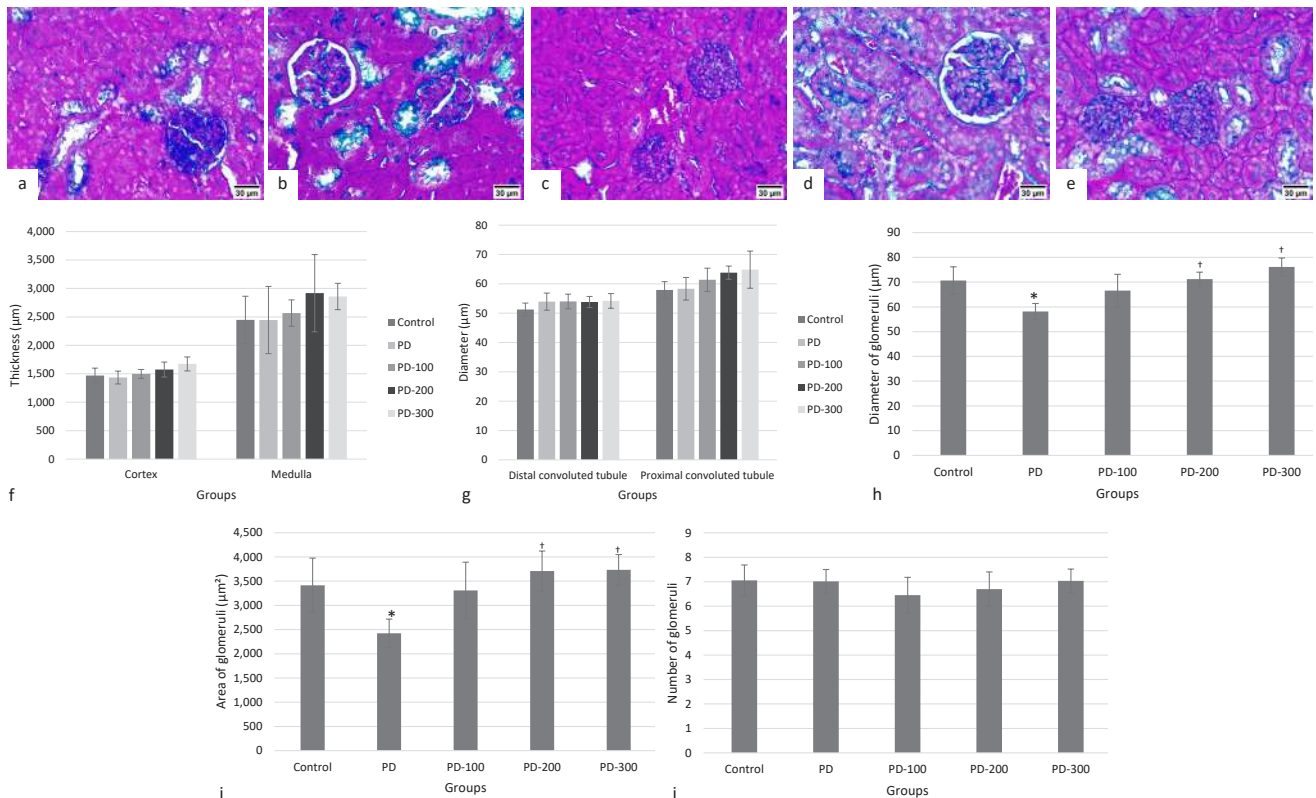
The glomerular diameter decreased with the PD treatment, which represented a 17.66% reduction compared to the standard diameter in the control group. The PD group also showed the smallest glomerular area among all treatments, with a decrease of approximately 29% from normal conditions. The glomerular diameter and area in the PD group differed significantly from those in the control, PD-200, and -300 groups. The addition of Bambara groundnut to protein-deficient feed progressively increased the glomerular diameter and area. The PD-300 group had the greatest diameter and glomerular area. However, the glomerular diameter closest to normal condition was observed in the PD-200 group (Figure 2h), and the glomerular area closest to normal was found in the PD-100 group (Figure 2i).

The PD group showed an average number of kidney glomeruli within a 50,000  $\mu\text{m}^2$  field of view lower than that of the control group. The PD-100 and -200 groups had a lower number of glomeruli than the PD group. The PD-300 group had a higher number of glomeruli than that in the PD group, which is closest to that in the control group. However, the mean number of glomeruli in all PD groups was not significantly different (Figure 2j).

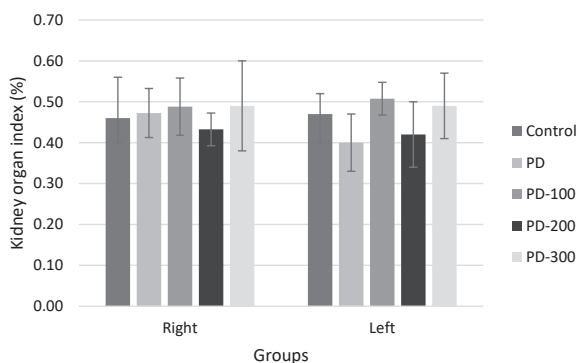
The PD group had a lower left kidney index value than the control, PD-300, -200, and -100 groups. Meanwhile, the PD group had a slightly higher right kidney index value than the control and PD-200 groups, with minimal differences of 0.01 and 0.04, respectively. In general, Bambara groundnut administration increased the right and left kidney organ indices



**Figure 1.** Kidney histological structure damage in female protein-deficient mice after Bambara groundnut supplementation. PD treatment resulted in damage to the kidney’s histological structure (a) in the form of cell sloughing (arrowheads) and tubular lumen dilatation (asterisks) in the control (b), PD (c), PD-100 (d), PD-200 (e), and PD-300 groups (f) (H&E stain; scale bar 30 μm). Results are expressed as mean (SD). \* $p \leq 0.05$ , compared to control; † $p \leq 0.05$ , compared to PD. H&E=hematoxylin and eosin; PD=protein deficiency; PD-100=protein deficiency supplemented with 100 g of Bambara groundnuts; PD-200=protein deficiency supplemented with 200 g of Bambara groundnuts; PD-300=protein deficiency supplemented with 300 g of Bambara groundnuts; SD=standard deviation



**Figure 2.** Effect of PD and Bambara groundnut supplementation on kidney histological structure, kidney's cortex and medulla thickness, urinary tubule diameter, and glomerular diameter, area, and number in female mice. Kidney histological structure appearance without glomerular and interstitial fibrosis in the control (a), PD (b), PD-100 (c), PD-200 (d), and PD-300 groups (e) (Masson's trichrome stain; scale bar 30 μm). No effect on thickness of cortex and medulla (f) and diameter of DCT and PCT (g). There were significant differences in glomerular diameter (h) and area (i) without significant difference in glomerular number (j). Results are expressed as mean (SD). \* $p \leq 0.05$ , compared to control; † $p \leq 0.05$ , compared to PD. DCT=distal convoluted tubule; PCT=proximal convoluted tubule; PD=protein deficiency; PD-100= protein deficiency supplemented with 100 g of Bambara groundnuts; PD-200=protein deficiency supplemented with 200 g of Bambara groundnuts; PD-300=protein deficiency supplemented with 300 g of Bambara groundnuts; SD=standard deviation



**Figure 3.** Bambara groundnut supplementation in female mice with PD showing no effect on the organ index of the right and left kidneys ( $p > 0.05$ ). Results are expressed as mean (SD). PD=protein deficiency; PD-100=protein deficiency supplemented with 100 g Bambara groundnuts; PD-200=protein deficiency supplemented with 200 g Bambara groundnuts; PD-300=protein deficiency supplemented with 300 g Bambara groundnuts; SD=standard deviation

compared to PD conditions, but not significantly different (Figure 3).

## DISCUSSION

Proteins are vital providers of the amino acids needed to execute all biological processes in the body. Adequate amounts of protein are required to support the smooth functioning of organs such as the kidneys,<sup>5</sup> indicating that a diet's protein content should be precisely considered.<sup>23</sup> A lack of protein intake results in the disrupted regulation of physiological renal processes. PD decreases the GFR, which is in line with the decreased concentration of the dissolved Klotho protein. Consequently, reactive oxygen species (ROS) accumulate in the kidney, and the oxidative stress caused by ROS accumulation damages renal tubular cells.<sup>24</sup>

Cell sloughing occurs with the loss of polarity of tubular epithelial cells, causing their detachment from the basement membrane into the lumen.<sup>25</sup> Proximal tubule dilatation, followed by epithelium thinning shows the loss of the brush border, resulting in the tubular epithelium appearing flat with a clear lumen.<sup>26</sup> In the present study, the tissue damage in the PD group was the most severe among all groups. Bambara groundnuts contain phenolic compounds with high antioxidant activities, such as flavonoids, phenolic acids, and anthocyanins. Antioxidant compounds can protect cells from oxidative damage.<sup>15,19</sup> As a result, adding Bambara groundnuts to feed composition

improved the tissular conditions. According to previous studies, legume supplementation can repair damage to the histological structure of the kidneys. Soy protein, for instance, can prevent glomerular hypertrophy in obese rats<sup>27</sup> and alleviate basement membrane changes in the renal tissues of diabetic rats.<sup>28</sup>

No fibrotic damage was identified in the glomeruli or interstitial space of the renal tissue of mice in the PD, PD-300, -200, and -100 groups (Figure 2b–e). This occurred because fibrosis appears solely after severe kidney damage.<sup>5</sup> The present study employed a low protein dose (10%), which is still not classified as chronic PD. Chronic PD with 8% protein content does not cause fibrosis yet induces an increased production of inflammatory cytokines.<sup>5</sup> Fibrosis, in turn, can quickly develop in environments with a high concentration of inflammatory cytokines.<sup>29</sup> The administration of legumes in previous studies showed that soy protein has a protective effect on renal tissue by preventing inflammation through suppression of the production of inflammatory cytokines (nuclear factor- $\kappa$ B) and induction of the expression of anti-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor alpha.<sup>28,30</sup>

PD also causes renal angiotensin system disturbances through increased interactions between angiotensin II and angiotensin II receptor type 1 in renal blood vessels. As a result, the functional surface area of the glomeruli for filtration decreases, with a consequent decrease in GFR.<sup>7</sup> Similarly, the present study observed that the decrease in glomerular size due to PD showed improvement with an increased protein intake through Bambara groundnut supplementation. The raw Bambara groundnut used in this study contained the amino acids lysine, leucine, arginine, histidine, threonine, tryptophan, valine, and methionine, which can inhibit the angiotensin-I-converting enzyme. The inhibited enzyme activity reduces the production of angiotensin II and maintains the concentration of the vasodilator bradykinin, preventing the continuous contraction of the renal vessels.<sup>31</sup>

This study showed that the glomeruli number was not affected by the amount of protein consumed. The final glomeruli number in the mouse kidneys depends on the successful nephrogenesis during the gestational phase. Improper nephrogenesis due to inadequate nutrient intake during pregnancy causes a decrease in glomeruli.<sup>32</sup> The thickness of the cortex and medulla is determined by nephrogenesis and is influenced by the



amount of protein intake. High levels of protein intake can increase the thickness of the cortex and medulla to compensate for the lower water concentration.<sup>33</sup> Administration of additional protein from Bambara groundnuts in this study led to increased thickness of the cortex and medulla and greater distal and proximal tubules diameters, yet not significant. This may have occurred because of an insufficient protein content in the Bambara groundnut feed, resulting in an absence of significant difference in the outcomes. The feed can be categorized as high in protein if it contains more than 25% protein.<sup>23</sup>

In line with the results from the present study, a previous report showed no significant differences in kidney cortex volumes, as well as glomeruli number, in rats with low protein intake ( $\leq 0.88$  g/kgBW) compared to rats with regular protein intake (0.89–1.13 g/kgBW).<sup>34</sup> In another study, rats with a low protein intake (6%) showed a significant difference in cortical thickness compared to rats fed a normal diet (20% protein intake). However, the diameters of the glomeruli and proximal renal tubules were not significantly different between protein-deficient and normal mice.<sup>35</sup>

The low-protein diet and Bambara groundnut supplementation did not affect the right and left kidney indices in mice. The kidney index was obtained from the organ and BW ratio. Notably, BW positively correlates with kidney size; therefore, an increased BW impacts kidney weight gain.<sup>36</sup> Mice with PD caused by consuming feed with a 6% protein content had a higher energy intake, thereby increasing the total fat weight and reducing lean body mass compared to normal mice consuming 20% protein.<sup>37,38</sup> A lack of protein intake causes increased hunger, resulting in a tendency to consume large amounts of food. Such occurs because proteins can create a longer-lasting feeling of fullness than carbohydrates and fats.<sup>39</sup>

In this study, the protein content of Bambara groundnuts did not significantly affect the ratio of kidney weight to BW of female mice. This can be explained by the presence of tannins, phytic acid, and antitrypsin compounds in the feed, which act as anti-nutritional factors. Such compounds can inhibit the activity of protein-breaking enzymes, hampering protein digestion. Therefore, the high protein and essential amino acid contents of Bambara groundnuts cannot be optimally utilized.<sup>15</sup>

In the present study, a PD diet caused cell sloughing, tubular dilatation, and decreased glomerular diameter

and area in the histological structure of the renal tissue of mice. Nevertheless, PD treatment did not affect the glomerular number or renal morphometry, namely, the thickness of the cortex and medulla, and the diameter of the DCT and PCT. Bambara groundnut supplementation prevented such damage and the decrease in glomerular size.

This study had several limitations. Treatment with a protein-deficient diet was conducted in a subchronic manner to enable the cells to retain their adaptability to stress conditions. Consequently, damage to the histological structure of the kidney remained minimal and likely reversible. At this stage, gross morphometry, including the thicknesses of the renal cortex and medulla, were not yet affected. Additionally, the anti-nutritional factors of Bambara groundnuts may impede its use as a dietary supplement. Therefore, a long-term study of the effect of Bambara groundnut supplementation on the histological structure of the kidney in protein-deficient mice is recommended. Furthermore, determining the levels of anti-nutritional factors in Bambara groundnuts is necessary to guarantee their suitability for consumption.

In conclusion, Bambara groundnut (*Vigna subterranea*) administration prevented damage to the kidney histological structure in protein-deficient mice with respect to cellular injuries (cell sloughing and dilatation) and reduction in the diameter and area of renal glomeruli.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

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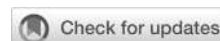
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## Characteristics of pressure injuries among geriatric patients at an Indonesian tertiary hospital: a cross-sectional study

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### ABSTRACT

**BACKGROUND** Pressure injury develops due to sustained pressure at the bony prominence of the skin and tissues. Geriatric patients often have multiple comorbidities, predisposing them to pressure injury. Data on the characteristics of the geriatric with pressure injuries are still limited. This study aimed to report the characteristics of geriatric patients with pressure injuries admitted at a tertiary hospital in Indonesia.

**METHODS** This cross-sectional study used medical records of geriatric patients admitted with all stages of pressure injuries consulted to the Department of Dermatology and Venereology at a tertiary hospital in Indonesia between January 2017 and April 2021. Pressure injuries were classified based on the 2019 National Pressure Injury Advisory Panel guideline.

**RESULTS** 39 patients presented with varied pressure injury characteristics. The sacral region was the most reported site (36%), with stage 2 pressure injury being the most commonly found stage in the patients (74%). Interestingly, 22% of the patients had pressure injuries found on the atypical sites due to prolonged surgery or the pressure of medical devices. More than half of the patients used conventional dressings (51.3%). Immobility was found in 35.9% of the patients due to being bedridden.

**CONCLUSIONS** No characteristics were found as a significant risk factor for pressure injury formation during or outside the admission period. However, a history of surgery might be related to pressure injury formation during admission.

**KEYWORDS** geriatrics, Indonesia, inpatients, pressure ulcer

Pressure injury or pressure ulcer is a societal burden<sup>1</sup> that typically occurs due to sustained and prolonged pressure at the bony prominences of the skin and tissues, leading to insufficient blood flow.<sup>2</sup> Contributing factors to pressure injury include shearing forces, friction, and a moist environment, and pressure injury can extend to the muscle and bone.<sup>3</sup> According to the National Pressure Injury Advisory Panel (NPIAP), pressure injuries are staged from 1–4, with higher stages indicating more severe injuries. There are two other stages, unstageable and

deep tissue pressure injuries. A systematic and meta-analysis<sup>6</sup> reported the global prevalence of pressure injuries as 12.8% in hospitalized adult patients. In comparison, the prevalence of pressure injuries in four hospitals in Indonesia was 8%, with almost half of the patients (44%) having one or more pressure injuries upon admission; therefore, the prevalence of nosocomial pressure injuries in Indonesia was 4.5%.<sup>7</sup>

Geriatric patients (those aged ≥60 years) are more vulnerable to pressure injuries due to the progressive decline in skin integrity and function as

the dermoepidermal junctions flatten, affecting the nutritional and oxygen transport of the skin.<sup>8</sup> These patients tend to develop chronic illnesses, making them immobile for extended periods.<sup>9</sup> Geriatric patients also develop syndromes that may contribute to weight loss, malnutrition, and immobility. The use of medical devices, such as respiratory devices, diapers, restraining devices, medical catheters, and medical tubes attached to the patients, also contribute to developing pressure injuries.<sup>10–12</sup>

Cipto Mangunkusumo Hospital is a top tertiary and referral hospital in Indonesia. However, no studies have been reported on the prevalence and characteristics of patients with pressure injuries at Cipto Mangunkusumo Hospital. A previous study reported the prevalence of pressure injuries in older people living in nursing homes in Barcelona as 3.5%.<sup>13</sup> Hossain et al<sup>14</sup> reported that 75.4% of critically ill patients with pressure injuries admitted to a tertiary hospital were 61 years or older. Ke et al<sup>15</sup> reported that pressure injuries were observed in 5.6% of patients aged 65 years or older who are admitted to the emergency department in an Asian hospital. As pressure injuries are a common complication in inpatient geriatric patients that are associated with significant morbidity, identifying the characteristics of geriatric patients with pressure injuries is essential to reduce the physical and financial burdens on the patient and healthcare system.<sup>16,17</sup> Data regarding the features and potential factors associated with pressure injuries in geriatric inpatients in Indonesia are rare. This study aimed to report the characteristics of geriatric patients admitted to Cipto Mangunkusumo Hospital for the dermatological treatment of pressure injuries.

## METHODS

This cross-sectional study included geriatric patients with pressure injuries admitted to the Department of Dermatology and Venereology at Cipto Mangunkusumo Hospital, Jakarta, between January 2017 and April 2021. Due to the complexity of care received by patients in central hospitals and the emergence of the coronavirus disease 2019 pandemic, the data were collected retrospectively using medical records. This study included Indonesian patients admitted to inpatient care units (inpatient wards, emergency rooms, and intensive care units) to obtain more generalized results. Geriatric patients with all stages of confirmed pressure injuries were included in

this study. Pressure injuries were defined and staged using 2019 NPIAP guidelines: stage 1, pressure injuries manifested as an ulcer with non-blanchable erythema of intact skin; stage 2, pressure injuries manifested as an ulcer with partial-thickness skin loss with the exposed dermis; stage 3, pressure injuries manifested as an ulcer with full-thickness skin loss; and stage 4, pressure injuries manifested as an ulcer with full-thickness skin and tissue loss. Unstageable ulcers were defined as ulcers with full-thickness skin and tissue loss, and deep tissue injuries were defined as ulcers with persistent, non-blanchable deep red, maroon, or purple discoloration. Potential confounders in this study were ulcers with etiologies other than constant pressure, such as diabetes and venous ulcers. The NPIAP guidelines and the hospital's internal diagnostic standards were used to differentiate pressure injuries from other ulcers.

Data from medical records included patient age, sex, anatomical site of pressure injuries, stage, causes and duration of bedridden patients, and treatment modalities. The patients were classified based on the setting where the pressure injury was first detected (during or outside admission). Although this study exclusively examined geriatric patients, the patients were subdivided into three groups based on age: 60–69 years, 70–79 years, and ≥80 years. The anatomical sites of the pressure injuries were categorized using the three most common locations. Pressure injuries found in other locations were classified as “atypical sites.” In addition, the duration of hospitalization was categorized as <1 month, between 1–6 months, and >6 months. The causes and settings in which the pressure injuries were diagnosed were determined by the dermatovenereologist, which was reported in the medical records. The treatment modalities used in this study included dressings (conventional, modern, or both). Conventional dressings referred to the application of saline solution wet dressings or gauze twice daily for 15–20 min each, whereas modern dressings referred to the application of hydrocolloid, antimicrobial, or foam dressings. All patients who fulfilled the inclusion criteria were included in this study to represent the entire population of geriatric patients with pressure injuries at Cipto Mangunkusumo Hospital between 2017 and 2021.

This study was approved by the ethical committee of Cipto Mangunkusumo Hospital (No: 16.02/221/0775/2020) and Faculty of Medicine

Universitas Indonesia (No: 20-05-0564, amendment number: ND-141/UN2.F1/ETIK/PPM.00.02/2021). The study design was based on the Strengthening the Reporting of Observational Studies in Epidemiology for cross-sectional studies and was prepared according to the recommendations of the International Committee of Medical Journal Editors.

Data are presented descriptively. The SPSS software version 26 (IBM Corp., USA) was used to analyze the data descriptively without using any specific statistical test to plot the percentages of each assessed parameter, with  $p < 0.05$  being set as a cut-off point of significance when necessary.

## RESULTS

A total of 39 patients (50 pressure injuries) aged 60–89 years were included in this study (Table 1). The number of female (51%) and male (49%) patients were similar. Most patients developed pressure injuries outside the inpatient hospital stay. Some patients developed more than one type of pressure injury. The distribution of patients who developed pressure injuries during and outside hospital admission was not significantly different based on the patient's sex or age.

The three most common anatomical sites for the formation of pressure injuries were the lumbosacral region, back, and gluteus. Nearly one-fourth (24%) of the pressure injuries were located in atypical sites due to prolonged operation or the pressure of medical devices, such as urine catheters. The location of the pressure injuries did not differ significantly between the two groups. More than half of the patients had stage 2 pressure injuries. Only one patient experienced a stage 4 pressure injury, which occurred outside of the hospital admission period. Another patient had an unstageable pressure injury during hospital admission. No deep tissue pressure injuries were observed. The distribution of the stages of pressure injury was not significantly different between the two groups.

Each patient was treated according to the pressure injury stage and associated infections. Most patients were treated via conventional dressings. However, eight patients treated with conventional dressings received additional antimicrobial therapy, including six (16%) who received antifungal therapy and two (6%) who received antibiotic therapy due to infection. The treatments were not significantly different between the two groups.

**Table 1.** Patient characteristics and the pressure injuries

| Patient characteristics (N = 39)                      | During admission, n (%) | Outside of admission, n (%) |
|---|-------------------------|-----------------------------|
| <b>Sex</b>  |                         |                             |
| Female  | 11 (28)                 | 9 (23)                      |
| Male  | 11 (28)                 | 8 (21)                      |
| <b>Age (years), mean</b>                              |                         |                             |
| 60–69, n (%)  | 10 (26)                 | 12 (31)                     |
| 70–79, n (%)  | 8 (21)                  | 7 (18)                      |
| >80, n (%)  | 1 (3)                   | 1 (3)                       |
| <b>Regions (n = 50)</b>                               |                         |                             |
| Lumbosacral   | 8 (16)                  | 9 (18)                      |
| Back  | 6 (12)                  | 5 (10)                      |
| Gluteus   | 5 (10)                  | 5 (10)                      |
| <b>Atypical sites</b>                                 |                         |                             |
| Scalp & facial  | 2 (4)                   | 1 (2)                       |
| Neck  | 1 (2)                   | -                           |
| Abdominal   | 1 (2)                   | -                           |
| Upper extremity                                       | 1 (2)                   | 2 (4)                       |
| Lower extremity                                       | 2 (4)                   | 2 (4)                       |
| <b>Stages of pressure injury (n = 50)</b>             |                         |                             |
| 1   | 4 (8)                   | 4 (8)                       |
| 2   | 17 (34)                 | 20 (40)                     |
| 3   | 2 (4)                   | 1 (2)                       |
| 4   | -                       | 1 (2)                       |
| Unstageable   | 1 (2)                   | -                           |
| <b>Treatments for pressure injury</b>                 |                         |                             |
| Conventional dressings                                | 16 (41)                 | 17 (44)                     |
| Modern dressings                                      | 1 (3)                   | 1 (3)                       |
| Conventional and modern dressings                     | 2 (5)                   | 2 (5)                       |
| <b>Others (in addition to conventional dressings)</b> |                         |                             |
| Antifungal topical/systemic therapy                   | 3 (8)                   | 3 (8)                       |
| Antibacterial topical/systemic therapy                | 1 (3)                   | 1 (3)                       |

All patients were bedridden for various causes and durations (Table 2). Immobility was the main cause of being bedridden. Patients with pressure injuries during admission had significantly more injuries due to being bedridden after a postoperative procedure. Most patients were bedridden for less than 1 month. The

**Table 2.** Causes and durations of bedridden

| Causes and durations of bedridden (N = 39) | During admission, n (%) | Outside of admission, n (%) |
|--|-------------------------|-----------------------------|
| <b>Causes of bedridden</b>                 |                         |                             |
| Immobility                                 | 6 (15)                  | 8 (21)                      |
| Weakness due to diseases                   | 4 (10)                  | 6 (15)                      |
| Post-surgery                               | 9 (23)                  | -                           |
| Loss of consciousness                      | 3 (8)                   | 3 (8)                       |
| <b>Durations of bedridden (month)</b>      |                         |                             |
| <1   | 11 (28)                 | 12 (31)                     |
| 1–6  | 5 (13)                  | 7 (18)                      |
| >6   | 2 (5)                   | 2 (5)                       |

duration of being bedridden was similar between the two groups.

## DISCUSSION

In this study, the characteristics of patients who developed a pressure injury during hospital admission were similar to those of patients who had a pressure injury outside of the hospital stay. The only significant difference between these patient groups was the cause of being bedridden, as more patients who developed injury during admission were bedridden due to a procedure. However, surgeries can only be performed in hospitals; therefore, this difference is not unexpected. In addition, due to the small patient population, it cannot be determined if being bedridden after a surgical procedure is a significant risk factor for developing pressure injuries during hospital stay. The results of this study provide evidence regarding the natural disease history of pressure injuries, specifically in geriatric inpatients in Indonesia.

Most pressure injuries in this study were categorized as stage 2 injuries. Patients with pressure injuries upon hospital admission were less likely to be discharged home.<sup>18</sup> Therefore, a thorough examination must be conducted to ensure that geriatric patients with pressure injuries receive prompt treatment to improve their prognosis. Pressure injuries are the leading etiology of ulcerative diseases requiring emergency geriatric dermatology consultations in Indonesia.<sup>19</sup> Patients typically develop pressure injuries after prolonged hospitalization, including patients receiving post-surgical and intensive care. In the present study, all

patients who underwent surgery for pressure injuries developed injuries during hospital admission. Pressure injuries are a common complication in elderly patients hospitalized after undergoing various surgeries.<sup>20–22</sup> Hyun et al<sup>23</sup> reported an increased number of drugs, a poor sedation status, and the use of feeding tubes as risk factors for hospital-acquired pressure injuries.

Several patients in this study developed multiple pressure injuries depending on their general conditions and comorbidities associated with wound formation. The sacral region was the most common anatomical site of pressure injuries in this study, which is consistent with findings from other studies.<sup>6,24,25</sup> A meta-analysis by Hu et al<sup>26</sup> reported that the sacrococcygeal region was the most common site of pressure injury, and the hip was the third most common site. However, the heel was the second most common site reported in that study. Differences in anatomy and adipose tissue distribution may explain these differences.<sup>27</sup> The sacrum is typically the most affected region due to several factors, including thinner skin layers, constant pressure from the sacral bony prominence, impaired blood flow and perfusion, and a constant shearing force on the skin surface.<sup>28,29</sup> In this study, a significant proportion of pressure injuries were observed at atypical sites, such as the scalp, face, posterior neck, abdomen, upper extremity, and lower extremity. Pressure injuries may develop on the head and neck due to positioning or medical devices.<sup>30</sup> A previous study reported that facial pressure ulcers developed in 27% of patients who underwent surgery in the prone position for more than 3 hours, mainly occurring in the bony prominences of the face.<sup>31</sup> As excessive pressure on the interface between a supporting surface and the skin is a pivotal mechanism of pressure injury development,<sup>32</sup> pressure injury on the abdomen may develop in patients lying prone for an extended period. However, pressure injuries in the extremities usually develop due to medical devices.<sup>33</sup> Pressure injuries are more frequently observed in the lower extremity than in the upper extremity and are most common on the ankle, heel, and hip.<sup>34–36</sup>

At Cipto Mangunkusumo Hospital, a higher number of patients received conventional dressings because they are usually more affordable and easily accessible than modern ones.<sup>37</sup> Modern dressings include hydrocolloid, antimicrobial, or foam dressings and are used based on the condition of the injury. Modern dressings in combination with other



treatments are used more frequently for pressure injuries of various stages.<sup>38-40</sup> However, these dressings are considered prophylactic rather than therapeutic.<sup>41</sup> Modern dressings facilitate healing by providing a moist environment, controlling excessive exudate and bacterial contamination, and reducing pain.<sup>42,43</sup> In some patients, both conventional and modern dressings were used simultaneously or alternately. Other treatments, such as topical antibiotics or antifungals, were administered to the patients depending on the presence or type of local infection. However, antimicrobial agents should not be routinely used as prophylaxis in patients with pressure injuries without a confirmed infection, as their efficacy is unclear.<sup>44</sup>

All patients included in this study were bedridden for various durations and causes; however, these could not be investigated due to a lack of documentation. Immobility is an intrinsic risk factor that affects the formation of pressure injuries. A prolonged period of immobilization causes constant pressure from solid surfaces, impairs vascularization, and ultimately induces pressure injury formation.<sup>8</sup> Furthermore, incorrect body positioning synergizes with immobilization to aggravate pressure injury formation, especially in geriatric patients after surgery.<sup>45</sup> Older patients with lower body mass index and Braden scores are at an increased risk of developing pressure injuries.<sup>46,47</sup> Lower skin pH and stratum corneum moisture content are major skin barrier factors affecting the formation of pressure in patients who are bedridden, including geriatric patients.<sup>48</sup>

This study was limited by its small sample size, as not all geriatric patients with pressure injuries were referred to the Department of Dermatology and Venereology. Patients who consulted to the Department of Dermatology and Venereology typically had stage 1 or 2 pressure injuries. In contrast, patients who developed stage 3 and higher pressure injuries were often referred to the Department of Reconstructive and Aesthetic Plastic Surgery. Furthermore, some patients with pressure injuries were treated by other departments without being consulted to the Department of Dermatology and Venereology, which introduced selection bias and further reduced the potential sample pool.

The findings of this study are significant for the rising burden of pressure injuries on healthcare systems. A healthcare economics study by Padula and Delarmente<sup>49</sup> reported that pressure injuries represent

a significant financial burden on healthcare system, with more than half of the total funding spent on treating a small percentage of stage 3 and 4 injuries, which can be attributed to the poor quality of healthcare facilities and early prevention systems. Understanding the characteristics of geriatric patients with pressure injuries can significantly reduce the healthcare costs. Therefore, geriatric patients with relevant features should be observed more closely, allowing early interventions to prevent pressure injuries. Educating patients and their caregivers may increase awareness regarding the characteristics of patients with pressure injuries. Robineau et al<sup>50</sup> concluded that education programs on pressure injury prevention yielded positive results, especially in geriatric patients, as older adults developing pressure injuries had a 2-fold higher 3-year risk of mortality.<sup>51</sup> The findings of this study can be incorporated into clinical practice guidelines at healthcare facilities in combination with other relevant prevention strategies to prevent or treat pressure injuries at earlier stages, reducing unnecessary financial burdens for both the patient and the healthcare system.<sup>17,52</sup>

In conclusion, neither patients with pressure injury during nor outside admission had significant characteristics that might act as a risk factor. However, pressure injuries are a significant burden in every hospital, and a history of surgery may increase the risk of developing pressure injuries during an inpatient stay.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

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## Development of kidney transplantation as a healthcare development model to achieve Indonesia Emas 2045

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Kidney failure is a medical condition where the kidneys lose their ability to perform vital functions such as filtering blood, removing waste, and regulating the body's electrolyte and fluid balance. Kidney failure can occur suddenly (acute) or develop gradually over some time (chronic).<sup>1</sup>

The frequency of declining kidney function is on the rise due to changes in human behavior and lifestyle, as well as the lack of a widespread and structured non-communicable disease prevention program implemented by the government in the general population through health promotion and prevention programs. Various diseases resulting from these changes contribute to the decline in kidney function.<sup>2,3</sup>

Based on data from the Ministry of Health of the Republic of Indonesia in 2020, by comparing the number of kidney failure cases in the national health insurance program (JKN) to the total population of Indonesia, approximately 1,602,059 individuals had kidney failure out of a population of 271,066,366, resulting in a prevalence rate of 0.59%. According to the basic health research (*Riskesmas*) findings, the prevalence of chronic kidney disease (CKD) cases increased from 21,000 individuals in 2013 to 381,000 individuals in 2018, and it further increased to 591,000 individuals in 2020. Expenditure on CKD remains in the fourth position, amounting to 2.1 trillion Indonesian Rupiah (11.48% of the total burden of the social security agency on health [BPJS]).<sup>4</sup>

Early diagnosis, changes in behavior and lifestyle, and prompt treatment are crucial to slowing down the progression of kidney failure. Unfortunately, if end-stage kidney failure (stage 5) has already occurred, there is no other option than to undergo kidney replacement therapy. Renal replacement therapy could

be in the form of hemodialysis, peritoneal dialysis, or kidney transplant.

### History of kidney transplantation

The historical journey of kidney transplantation dates back to March 13, 1902, when Erich Ullmann conducted the first recorded clinical kidney transplantation, as documented in the 'Wiener klinische Wochenschrift.' The true milestone came in 1933 when Yuri Voronoy in Ukraine achieved the first successful human-to-human renal transplant. However, it was not until December 23, 1954, when Dr. John Murray, who later received the Nobel Prize in Medicine, performed the groundbreaking first successful kidney transplant at Brigham and Women's Hospital in Boston, saving a 23-year-old patient with end-stage renal disease.<sup>5</sup>

In Indonesia, the inaugural kidney transplantation took place on November 11, 1977, at Cipto Mangunkusumo Hospital under the supervision of a Japanese urologist from Tokyo Women Medical College. Indonesia's path in kidney transplantation has not always been smooth, with challenges including economic downturns such as the Rupiah decline in 1983, the 1998 economic crisis, and a surge in illegal organ trafficking in the early 2000s. These issues prompted the Indonesian government to enact new laws and regulations, creating a clear organ transplantation guideline.<sup>5</sup>

The landscape began to change in 2011 with the introduction of laparoscopic living donor nephrectomy (LLDN) in Indonesia, leading to increased kidney transplant procedures. Government insurance through BPJS is pivotal in making transplantation accessible to lower-income individuals. With the official establishment of Cipto Mangunkusumo Kanigara Hospital, kidney

transplant patients covered by BPJS insurance now have access to two new dedicated operating rooms for urological surgeries. This development has increased transplantation frequency from four to six–eight times per week, thereby reducing the waiting queue from a year to 8 months.<sup>5</sup>

### **Advancement in kidney transplantation**

In the realm of kidney transplantation in Indonesia, a significant turning point came in October 2011 with the introduction of the pioneering LLDN technique. This groundbreaking approach revolutionized the process, substantially reducing postoperative recovery time and donor discomfort. Families and potential donors found renewed confidence in this innovative method, especially compared to the traditional open surgical procedures often subjecting donors to 2–3 months of pain. With LLDN, donors could return to normal activities within just 1 week.<sup>5</sup>

A novel technique known as retroperitoneal kidney laparoscopy emerged as a viable alternative, focusing on minimizing donor complications. Fast forward to 2020, retroperitoneal laparoscopic donor nephrectomy has become the gold standard at Cipto Mangunkusumo Hospital, largely due to the influence of the coronavirus disease 2019 (COVID-19) pandemic. This strategic shift in surgical practice was prompted by the discovery that the virus resides in the gastrointestinal tract.

On the recipient's side, the kidney transplantation technique has remained relatively unchanged since 1954. The standard practice involves connecting the renal vein of the donor's kidney to the recipient's external iliac vein end-to-side, a technique consistently followed across various centers. However, the approach to connecting the renal artery initially mirrored the venous anastomosis. A significant transformation occurred in May 2013 with the first pediatric kidney transplantation in Indonesia, marking the beginning of changes in arterial anastomosis techniques.<sup>5</sup>

The end-to-side anastomosis technique is employed when a notable difference occurs in blood vessel diameters. This method relies on basic equipment readily available in all Indonesian operating rooms, including a 14G venous cannula and a 3.5 Fr nasogastric tube. It was further perfected through microsurgical techniques by the Department of Urology, Cipto Mangunkusumo Hospital.<sup>6</sup>

### **Multidisciplinary team**

Successful kidney transplantation relies on the team's commitment to professional growth. Aside from nurses and urologists, Indonesian anesthesiologists are sent abroad to further hone anesthesiology in transplantation. Advanced anesthesia equipment and monitoring systems enable precise anesthesia depth, circulation, fluid levels, and tissue oxygenation measurements. This progress allows rapid kidney functionality, often with urine output minutes after vascular anastomosis. Radiological imaging also plays a vital role in evaluating potential living kidney donors. Computed tomography (CT) scans with contrast are a commonly used imaging technique for assessing the kidneys before surgery and are considered the standard of excellence. Contrast-enhanced CT scans provide detailed images of focal and diffuse kidney parenchymal diseases. Furthermore, they offer information about the anatomy and anomalies in the urinary tract and blood vessels of the kidneys.<sup>7–9</sup>

### **Government role in kidney transplantation**

The involvement of the Ministry of Health of the Republic of Indonesia in increasing the number of centers performing transplants began on June 7–8, 2013, with the first-ever “The 1st National Symposium and Workshop on Kidney Transplantation,” in collaboration with the Department of Urology, Faculty of Medicine, Cipto Mangunkusumo Hospital. Government hospitals entered into bilateral memoranda of understanding with Cipto Mangunkusumo Hospital as the supporting hospital, signed by both hospital directors and the Director-General of Medical Services.<sup>5,10</sup>

From 2014 to 2019, the Cipto Mangunkusumo Hospital kidney transplantation team supported kidney transplantation programs at seven hospitals. In the first phase, all supported hospital teams visited Cipto Mangunkusumo Hospital to learn about the kidney transplantation process and administration. If the hospital met the minimum service standards, the Cipto Mangunkusumo Hospital transplantation team would visit the hospital. Afterward, they supported the kidney transplantation procedures at the local hospital. The success of this program depended on the commitment and dedication of the transplantation team and all stakeholders at the supported hospitals, resulting in varying levels of implementation, with some hospitals completing it once and others four or five times.<sup>5,6,10</sup>

The journey of creating regulations to protect kidney transplantation in Indonesia began in 2005 with various drafts such as government regulations (PP). By 2016, the Regulation of the Minister of Health of the Republic of Indonesia (PERMENKES-RI) Number 38 was issued, which became the foundation for organ transplantation services in Indonesia. This regulation led to the formation of the national transplantation committee, providing legal protection and certainty for donors, recipients, transplant hospitals, and healthcare providers involved in organ transplantation.<sup>10,11</sup>

PERMENKES-RI Number 38 Year 2016 also includes the overall organ transplantation service flow. However, the kidney transplantation service flow must be adapted to the working rules and cultures of each transplantation center to ensure the sustainability of kidney transplantation services. The legal framework for organ and tissue transplantation has been strengthened with the issuance of Government Regulation Number 53 in 2021.<sup>10,11</sup>

As of now, kidney failure patients who have been indicated for kidney transplantation must seek their own donors. Subsequently, the patient and donor will meet with a kidney transplantation coordinator to undergo the advocacy process. The advocacy team includes medical-legal, ethical-legal, legal, psychiatric, and layperson members. The decision of the full board meeting of the advocacy team determines whether someone is eligible to be a donor. Following this, the donor and recipient pair undergo more detailed examinations to prepare for transplantation, including laboratory matching, radiology imaging, and operational tolerance assessments from various other disciplines based on the patient's comorbidities.<sup>10</sup>

### **Kidney transplant during the pandemic era**

During the COVID-19 pandemic in Indonesia, the last transplantation at Cipto Mangunkusumo Hospital was performed in the second week of March 2020. In an online meeting on April 8, 2020, involving countries conducting kidney transplantation and those affected by COVID-19, protocols were discussed for initiating transplantation in the COVID-19 pandemic era. Although these protocols were not fully established and recognized worldwide, they could be implemented when all requirements were met. Implementing these protocols was challenging at Cipto Mangunkusumo Hospital, where COVID-19 patients were also being treated and managed, as it required categorizing areas

into red, yellow, and green zones according to the risk of COVID-19 transmission. The Cipto Mangunkusumo Hospital team, which also performed transplantation at a private hospital meeting the criteria of a green hospital in the COVID-19 era and complying with kidney transplantation protocols during this time, managed to conduct the procedure in early May 2020.

### **Collective reflection in the field of kidney transplantation**

The lesson of kidney transplantation development in Indonesia is a miniature depiction of how various components of the healthcare profession or those related to the healthcare world interact to achieve a common vision that addresses the needs of patients and the national healthcare requirements. However, vision alone is not enough; concrete steps require collective sacrifices. This is evident in the early phases of transplantation development. To progress, it is necessary to consider the well-being of all involved components. Continuous innovation is required even after success is achieved. Lastly, the lessons from the development of kidney transplantation in Indonesia should serve as a lesson for all nations in providing healthcare.

Part of this paper was presented at Professor Nur Rasyid's inauguration, June 22, 2023, Jakarta.

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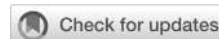


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## Editorial

### Editor's note

Hans Joachim Freisleben<sup>1,2,3</sup>



Recently, the World Association of Medical Editors (WAME) Board invited to participate in an important multi-journal project by publishing an editorial on nuclear risk and health. The editorial should be published within 3 months after the anniversary of the Hiroshima bomb on August 6.

As a member of the WAME, I signed up for the list of medical journals on behalf of Medical Journal of Indonesia after reconfirmation by our Editor-in-Chief, Agus Rizal A. H. Hamid, and our Managing Editor, Felix F. Widjaja, to participate in publishing this editorial. (<sup>2,3</sup>Hans Joachim Freisleben, for MJI and the German-Indonesian Medical Association [DIGM])

According to the United Nations, the risk of nuclear weapons use is higher than at any time since the Cold War. At this moment of extreme danger, we are preparing to distribute an editorial on the role of health professionals in reducing nuclear danger. We hope to time the announcement of the release of this editorial on the anniversary of the bombing of Hiroshima on August 6 to underline the very real danger that nuclear weapons may be used again.

The editorial was co-authored by a group of journal editors and other supporters of the Nobel-

prizewinning International Physicians for the Prevention of Nuclear War listed below. All of the authors' journals will be publishing the editorial. The WAME Board agreed to support the publication of this editorial as widely as possible and to encourage all WAME members to join us in this unique declaration by the medical community.

Having so many respected journals around the world publishing the editorial should attract political and media attention. We hope that giving health professionals a more prominent voice in this debate will encourage profound changes in the system of nuclear arms control that has resulted in the current dangerous situation that threatens the health of people and planet. (<sup>1</sup>Chris Zielinski, Project Manager, WAME)

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### Reducing the risks of nuclear war—the role of health professionals

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In January, 2023, the Science and Security Board of the Bulletin of the Atomic Scientists moved the hands of the Doomsday Clock forward to 90s before midnight, reflecting the growing risk of nuclear

war.<sup>1</sup> In August, 2022, the UN Secretary-General António Guterres warned that the world is now in a time of nuclear danger not seen since the height of the Cold War.<sup>2</sup> The danger has been underlined

by growing tensions between many nuclear armed states.<sup>1,3</sup> As editors of health and medical journals worldwide, we call on health professionals to alert the public and our leaders to this major danger to public health and the essential life support systems of the planet—and urge action to prevent it.

Current nuclear arms control and non-proliferation efforts are inadequate to protect the world's population against the threat of nuclear war by design, error, or miscalculation. The Treaty on the Non-Proliferation of Nuclear Weapons (NPT) commits each of the 190 participating nations “to pursue negotiations in good faith on effective measures relating to cessation of the nuclear arms race at an early date and to nuclear disarmament, and on a treaty on general and complete disarmament under strict and effective international control”.<sup>4</sup> Progress has been disappointingly slow, and the most recent NPT review conference in 2022 ended without an agreed statement.<sup>5</sup> There are many examples of near disasters that have exposed the risks of depending on nuclear deterrence for the indefinite future.<sup>6</sup> Modernization of nuclear arsenals could increase risks: for example, hypersonic missiles decrease the time available to distinguish between an attack and a false alarm, increasing the likelihood of rapid escalation.

Any use of nuclear weapons would be catastrophic for humanity. Even a “limited” nuclear war involving only 250 of the 13,000 nuclear weapons in the world could kill 120 million people outright and cause global climate disruption leading to a nuclear famine, putting two billion people at risk.<sup>7,8</sup> A large-scale nuclear war between the USA and Russia could kill 200 million people or more in the near term and potentially cause a global “nuclear winter” that could kill five to six billion people, threatening the survival of humanity.<sup>7,8</sup> Once a nuclear weapon is detonated, escalation to all-out nuclear war could occur rapidly. The prevention of any use of nuclear weapons is therefore an urgent public health priority and fundamental steps must also be taken to address the root cause of the problem—by abolishing nuclear weapons.

The health community has had a crucial role in efforts to reduce the risk of nuclear war and must continue to do so in the future.<sup>9</sup> In the 1980s

the efforts of health professionals, led by the International Physicians for the Prevention of Nuclear War (IPPNW), helped to end the Cold War arms race by educating policy makers and the public on both sides of the Iron Curtain about the medical consequences of nuclear war. This was recognized when the 1985 Nobel Peace Prize was awarded to the IPPNW.<sup>10</sup>

In 2007, the IPPNW launched the International Campaign to Abolish Nuclear Weapons, which grew into a global civil society campaign with hundreds of partner organizations. A pathway to nuclear abolition was created with the adoption of the Treaty on the Prohibition of Nuclear Weapons in 2017, for which the International Campaign to Abolish Nuclear Weapons was awarded the 2017 Nobel Peace Prize. International medical organisations, including the International Committee of the Red Cross, the IPPNW, the World Medical Association, the World Federation of Public Health Associations, and the International Council of Nurses, had key roles in the process leading up to the negotiations, and in the negotiations themselves, presenting the scientific evidence about the catastrophic health and environmental consequences of nuclear weapons and nuclear war. They continued this important collaboration during the First Meeting of the States Parties to the Treaty on the Prohibition of Nuclear Weapons, which currently has 92 signatories, including 68 member states.<sup>11</sup>

We now call on health professional associations to inform their members worldwide about the threat to human survival and to join with the IPPNW to support efforts to reduce the near-term risks of nuclear war, including three immediate steps on the part of nuclear-armed states and their allies: first, adopt a no first use policy;<sup>12</sup> second, take their nuclear weapons off hair-trigger alert; and, third, urge all states involved in current conflicts to pledge publicly and unequivocally that they will not use nuclear weapons in these conflicts. We further ask them to work for a definitive end to the nuclear threat by supporting the urgent commencement of negotiations among the nuclear-armed states for a verifiable, timebound agreement to eliminate their nuclear weapons in accordance with commitments in the NPT,

opening the way for all nations to join the Treaty on the Prohibition of Nuclear Weapons.

The danger is great and growing. The nuclear armed states must eliminate their nuclear arsenals before they eliminate us. The health community played a decisive part during the Cold War and more recently in the development of the Treaty on the Prohibition of Nuclear Weapons. We must take up this challenge again as an urgent priority, working with renewed energy to reduce the risks of nuclear war and to eliminate nuclear weapons.

This Comment is being published simultaneously in multiple journals. For the full list of journals see: <https://www.bmj.com/content/full-list-authors-and-signatories-nuclear-risk-editorial-august-2023>.

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## Corrigendum

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## Corrigendum: Quadrigeminal plate arachnoid cyst presenting with eye movement related migraine: a rare case report

Yemima Graciela, Robert Shen, Mardjono Tjahjadi

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In the original version of this article, the corresponding author's email address was incorrectly typed as "mardjonotjahjadi@gmail.com". It should be corrected as follows "mardjono.tjahjadi@atmajaya.ac.id".