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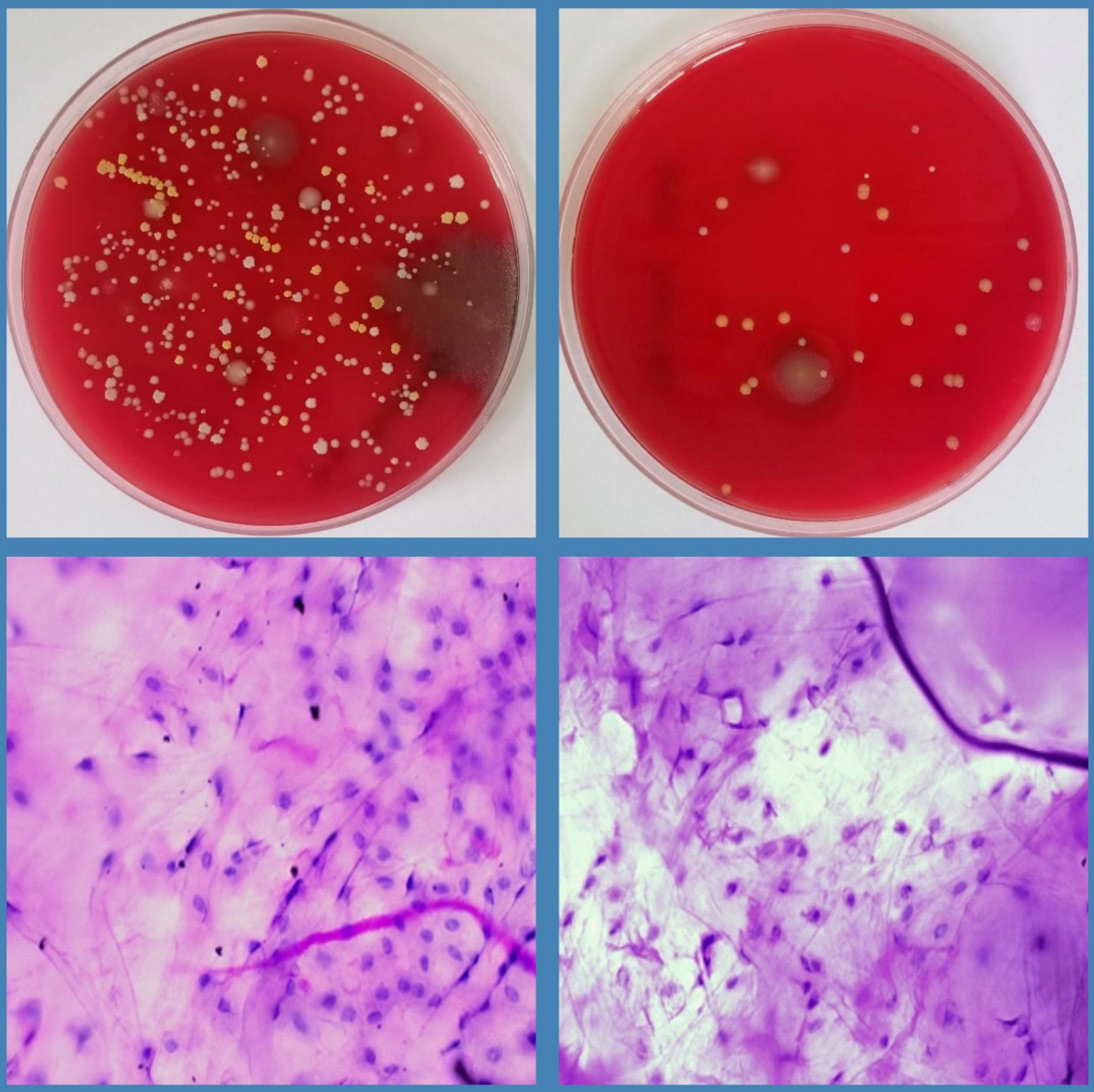

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Decreasing of hand colonization and sterility of refill antiseptic in Dr. Yap Eye Hospital, Yogyakarta

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ABSTRACT

Dr. Yap Eye Hospital, Yogyakarta uses aseptic gel containing 70% ethyl alcohol to refill antiseptic containers during times of antiseptic scarcity. The study aimed to evaluate the effectiveness and sterility of the refill antiseptics in reducing the number of colonization on the hands of nurses. It was a quasi-experimental using pre- and post-control groups design involving 56 nurses who used antiseptics in a bottle sterilized by plasma device (plasma bottle) compare to those washed using detergent (detergent bottle) before being refilled. Sterility tests were performed every two wk for up to two mo. Colonization pre and post hand hygiene practices were determined as an efficacy test and compared using the Mann-Whitney test in STATA 14. Antiseptic in plasma bottles remains sterile until the week8th since refilled, longer than detergent bottles (6th weeks). The pre-handrub colorizations were 0.04-16.92 CFU/cm2 and decreased significantly post-handrub to 0.00-3.08 CFU/cm^2 ($p<0.0001$). Significant decrease pre- vs post-handrub colonization was observed in usage of detergent bottle (0.04-31.04 vs 0.00-10.48 CFU/cm^2, $p=0.0007$). There was no significant difference in Δ colonization for two bottles (0.40-15.76 vs 0.04-30.92 CFU/cm^2, $p=0.8790$). In conclusion, antiseptic in the plasma bottle remains sterile longer than in the detergent bottle since refilled. Both of them are equally effective in reducing colonization after handrub activity.

ABSTRAK

Rumah Sakit Mata Dr. Yap. Yogyakarta menggunakan antiseptik isi ulang aseptic gel yang mengandung etil alkohol 70% pada masa kelangkaan bahan antiseptik kebersihan tangan. Tujuan penelitian ini adalah untuk mengevaluasi efektivitas dan sterilitas antiseptik isi ulang dalam menurunkan angka kuman di tangan petugas. Penelitian ini merupakan eksperimental semu menggunakan rancangan *pre and post test* dengan melibatkan 56 perawat yang menggunakan antiseptik isi ulang dalam botol yang disterilkan alat plasma (botol plasma) dibandingkan dengan dicuci detergen (botol detergen) sebelum diisi ulang. Uji sterilitas dilakukan setiap 2 minggu selama 2 bulan. Penghitungan angka kuman sebelum dan sesudah cuci tangan dilakukan sebagai uji efikasi. Perbandingan angka kuman dilakukan dengan uji Mann-Whitney menggunakan STATA 14. Antiseptik dalam botol plasma tetap steril hingga minggu ke-8 sejak diisi ulang, lebih lama dibandingkan botol detergen (minggu ke-6). Angka kuman sebelum cuci tangan dengan botol plasma berkisar antara 0,04-16,92 CFU/cm^2 dan turun signifikan sesudah cuci tangan menjadi 0,00-3,08 CFU/cm^2 ($p<0,0001$). Penurunan yang signifikan terhadap angka kuman sebelum dan sesudah cuci tangan juga terjadi pada penggunaan antiseptik botol detergen (0,04-31,04 vs 0,00-10,48 CFU/cm^2, $p=0,0007$). Tidak ada perbedaan bermakna pada Δ angka kuman kedua botol (0,40-15,76 vs 0,04-30,92 CFU/cm^2, $p=0,8790$). Dapat disimpulkan, antiseptik botol plasma lebih lama steril dibandingkan botol detergen sejak diisi ulang. Kedua antiseptik efektif menurunkan angka kuman setelah aktivitas cuci tangan.

Keywords:
Antiseptic sterility; antiseptic effectiveness; hand colonization; refill antiseptic; handrub

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INTRODUCTION

Infectious diseases are still the leading cause of high morbidity and mortality in the world. Hospital-acquired infections (HAIs) are related directly to patient safety, staff safety, and the hospital environment.[1,2] The HAIs increase morbidity and mortality, long-term disability, and financial burden on health.[1] The incidence of HAIs is reported to be higher in low- and middle-income countries than in high-income countries. The low incidence of HAIs has become one of the target markers for the quality of hospital services, hospital performance indicators, national hospital accreditation standards, and hospital minimum service standards.[3,4] According to the regulation of the Ministry of Health of Republic of Indonesia No.129/2008, the standard of HAIs figures should generally not be more than 1.5%.[5] Meanwhile, the infection control target based on hospital performance indicator dictionary is not more than 5%.[6] Studies showed HAIs rates ranged between 5-10% worldwide. The World Health Organization (WHO) data showed that the incidence of HAIs in Ukraine, Italy, France were 10%, 6.7%, 6.7-7.4%, respectively. In Indonesia, a study in 11 hospitals in Jakarta in 2008 showed that 9.8% of hospitalized patients has HAIs.[7]

Hand hygiene is the key to infection control. All hospital staff members, patients, and visitors must easily practice and readily get access to hand hygiene facilities while in the Dr. Yap Eye Hospital, Yogyakarta. Various studies have shown that hand hygiene is the most important and most cost-effective way to prevent and reduce the transmission of HAIs. Hands are the most common transmission medium for pathogens in hospitals.[8] Hand hygiene can be done in two ways: washing hands with water and soap if hands look dirty and using alcohol-based handrub.[9,10]

Dr. Yap Eye Hospital, Yogyakarta uses an alcohol-based refill antiseptic which was put into refill bottles during times of antiseptic scarcity in COVID-19 pandemic 2020. Preparation of the refill bottles was conducted as needed. High-level disinfection is required to kill spores. One of them uses a low-temperature plasma sterilizer H_2O_2 compatible with a sterilized plastic hand-rub bottle. Bauer-Savage explained the WHO recommendation of alcohol-based hand-rub prepared by putting the hand-rub into a small container (100 - 500 mL) and leaving for 72 h before use so that the spores in the container would die.[10]the World Health Organization (WHO In this study, the handrub was left for two days after being refilled in a bottle.[9] However, unfortunately, the WHO guidelines does not explain how to prepare and clean refill bottles. Meanwhile, the cost of sterilization using plasma is relatively high. Therefore, a cheaper method to clean the refill bottles was needed by washing with detergent. The effectiveness of preparing the refill bottle should be compared.

This study aimed to evaluate the effectiveness and sterility of refill antiseptic in reducing the number of germs on the nurses' hands. This study also compared the bottles sterilized with plasma and those washed with detergent. The results of this study are expected to underlie the rationality of using refill antiseptic and its preparation to support the infection prevention control programs.

MATERIALS AND METHODS

Study design

It was a quasi-experimental using pre- and post-control groups design. Refill antiseptic (active ingredient ethyl alcohol 70%) was used. Two refilled antiseptics were treated differently; bottle 1 was sterilized with a plasma

device (plasma bottle), and bottle 2 was washed with detergent (detergent bottle) before refilling. After being refilled with antiseptic gel (the active ingredient ethyl is alcohol 70%), those bottles were left two days before being tested.

Subjects of the study

These subjects were nurses selected by random sampling technique who met the inclusion criteria. Inclusion criteria were Dr. Yap Eye Hospital, Yogyakarta nurses doing WHO standardized hand hygiene and directly contacting patients. Hand hygiene was conducted in 8 steps for about 20-30 sec and supervised by an Infection Prevention Control Nurse (IPCN).[11,12] Exclusion criteria were nurses performing hand hygiene less than 1 h before and not correctly doing their profession accordingly.

Sterility testing

Sterility tests of those antiseptic ingredients were conducted by smearing those ingredients on 2 blood agar plates every 2 wk up to 2 mo. This research was conducted for 2 mo because the most prolonged use of a hand-rub bottle at Dr. Yap Eye Hospital, Yogyakarta was 2 mo. The agar plate was later incubated at 37^0 C for 24 h. Microbe counts were reckoned based on colonization growth on brown agar plate after 24 h incubation. An efficacy test was performed when the antiseptic gel inside the bottle was sterile.[9]

Efficacy testing

Efficacy of the hand-rub was calculated by the number of viable microbes by comparing pre-and post-handrub colonization. Efficacy testing was performed with total sample and subject determination based on consecutive sampling to 2 refilled bottles, plasma and detergent bottles. Each bottle had seven opportunities for hand hygiene. Therefore, there would have been a total of 56 opportunities for hand hygiene in nurses while comparing pre- and post-handrub colonization using a refilled bottle that had been sterilized by the plasma device (plasma bottle) vs washes by detergent (detergent bottle) before being refilled.

The pre- and post-hand hygiene colonization evaluation was done consecutively and was considered an efficacy test. Palm smears with size dimension 5x5 cm were performed entirely before and after undergoing hand rub. The smear of hands that had been planted on blood agar plate was incubated at 37^0 C for 24 h, growing colonizations were counted, and the results were later divided to 25 cm^2.[13]

Statistical analysis

The statistical analysis used to analyze these research's results was STATA version 14 (Stata Corp., College Station, TX) with a p value < 0.05 regarded as statistically significant. Ultimately, Mann-Whitney test was used to assess differences in colonization pre- vs post-handrub plasma bottle, pre- vs post-handrub detergent bottle, delta colonization between plasma bottle vs. detergent bottle. All colonization data were expressed as median (min – max).

Ethical clearance

This study has been approved by the Law and Ethics Committee of Dr. Yap Eye Hospital, Yogyakarta (Number 02/KEH/EC/II/ 2022).

RESULTS

The study was conducted for two months, considered the most prolonged antiseptic use since it was opened at Dr. Yap Eye Hospital, Yogyakarta. Before the efficacy test, a sterility test was

performed. Sterility test results are presented in TABLE 1 and showed that antiseptic inside plasma bottle (8 wk) were more sterilized than antiseptic inside detergent bottle (6 wk). If the sterility test had shown that the antiseptic ingredient was sterile, an efficacy test would have been performed.

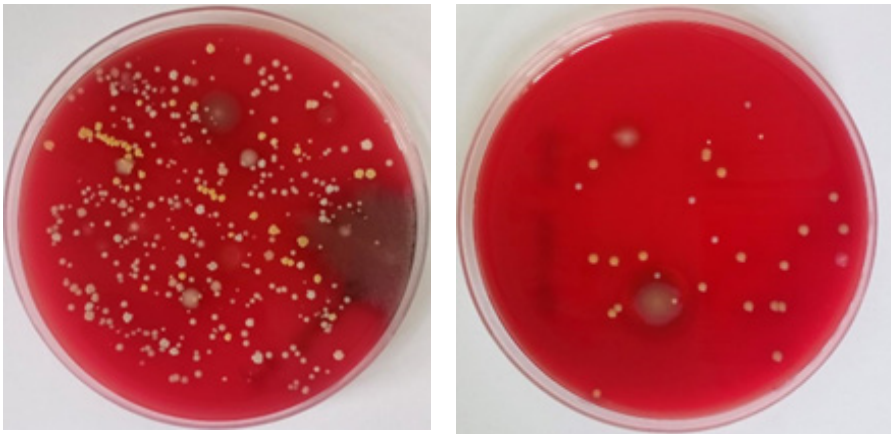
TABLE 1. Sterility test results between antiseptic in plasma and detergent bottle

Week	Plasma bottle (n=1)	Detergent bottle (n=1)
0	Sterile	Sterile
2	Sterile	Sterile
4	Sterile	Sterile
6	Sterile	Sterile
8	Sterile	Non-sterile

TABLE 2. Efficacy test results of comparison between decreasing of colonization

Week [median (min-max)]	Plasma bottle			Detergent bottle		
	Pre-	Post-	Δ	Pre-	Post-	Δ
0	n = 7			n = 7		
	2.40 (0.24-10.20)	0.40 (0.08-1.28)	1.12 (0.04-9.16)	2.60 (0.44-16.00)	0.20 (0.04-10.48)	2.04 (0.20-7.00)
2	n = 7			n = 7		
	4.4 (0.40-11.20)	0.76 (0.04-2.40)	3.64 (0.20-8.80)	0.76 (0.04-7.40)	0.12 (0.00-1.72)	0.24 (0.04-5.68)
4	n = 7			n = 7		
	0.96 (0.32-11.44)	0.52 (0.08-3.08)	0.44 (0.00-8.36)	1.68 (0.64-12.52)	0.52 (0.04 – 3.24)	1.16 (0.2-11.96)
6	n = 7			n = 7		
	2.08 (0.04-7.52)	0.48 (0.00-2.44)	1.52 (0.04-5.08)	9.48 (0.08-31.04)	0.40 (0.00-5.00)	5.80 (0.08-30.92)
8	n = 7					
	3.76 (0.48-16.92)	0.40 (0.12-1.68)	2.08 (0.4-15.76)		Not performed	
Total	n = 35			n = 28		
	2.08 (0.04-16.92)	0.48 (0.00-3.08)	1.12 (0.4-15.76)	1.78 (0.04-31.04)	0.32 (0.00-10.48)	1.08 (0.04-30.92)

Mann Whitney test: Pre- vs post-handrub plasma bottle ($p < 0.0001$); Pre- vs post-handrub detergent bottle ($p = 0.0007$); Δ colonization plasma bottle vs. detergent bottle ($p = 0.8790$).
n= handrub practice; Pre-: pre-handrub colonization; Post- : post-handrub colonization; Δ: different colonization between pre and post handrub.



A B

FIGURE 1 A. Pre hand-rubbed colonization; B. Post hand-rubbed colonization. Subject used plasma bottle in week 8th.

There were 56 nurses who fulfilled the inclusion and exclusion criteria. Pre-, post-, and Δ colonization of hand hygiene practice results are displayed in TABLE 2 and FIGURE 1. The result of pre-handrub colonization on 56 nurses was in the range of 0.04-16.92 CFU/cm^2 and significantly declined on post-handrub and became 0.00-3.08 CFU/cm^2 ($p<0.0001$). The significant decline of pre- vs. post-handrub colonization also occurred in using detergent bottle antiseptic (0.04-31.04 vs. 0.00-10.48 CFU/cm^2, $p=0.0007$). There was no significant difference in declining delta colonization between the two bottles (0.40-15.76 vs 0.04-30.92 CFU/cm^2, $p=0.8790$).

DISCUSSION

Antiseptic ingredients were common antiseptic substances containing alcohol, isopropanol, n-propanol, or a combination of both products. Antimicrobial activities of alcohol derived from its ability to denature protein, and its most efficacious concentration was 60 – 80%. Unfortunately, the higher its concentration, it did not become any more potent. Chlorhexidine decreased microbe counts despite lower concentrations by deteriorating the cytoplasmic membrane and causing precipitation of what was inside the microbe cells. The antimicrobial activity of chlorhexidine was relatively slower. However, chlorhexidine had a residual activity that was more significant than alcohol.[14]

According to WHO, average bacterial counts on medical officers were 3.9-4.6x10^4 CFU/cm^2. WHO recommended that alcohol-based handrub as the gold standard in performing hand hygiene to visually or seemingly clean handwashing with soap was recommended to visually dirty hands. The majority of alcohol-based antiseptics contained isopropanol and ethanol. Both agents could have killed most bacteria fast for about 10-20 seconds, including multidrug-resistant organism (MDRO), for instances methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), *Mycobacterium tuberculosis*, a few fungi, and is also capable of inactivating a few viruses such as herpes groups.[14]

Human skin surfaces consisted of varied bacterial colonization. Pre-handrub colonization on the 5x5 cm^2 size of hands was varied. The usage of antiseptic in plasma and detergent bottles significantly decreased colonization. This finding was similar

to a previous study that confirmed alcohol had the most delicate germicidal activity toward bacterial vegetation and various fungi. Moreover, another study of antiseptic activity had shown that 70% ethanol and 70% isopropanol could decrease enveloped bacteriophage titer more effectively than antimicrobial soup containing chlorhexidine 4%.[3,14]

In this study, handrub was leftover for two days after being refilled in a bottle, which is one day faster than homemade antiseptic production. According to WHO, it must be left over 72 h after being refilled.[9] The bottle that was disinfected using plasma was more sterile than the one washed with detergent (8 wk vs 6 wk). Based on this research, it was suggested that a refilled bottle washed by a detergent could be used for up to 1.5 mo until refilled numbers could be readjusted. The WHO hand sanitizer formula for local production has a 2-year expiration date from production. There is no FDA guidance to set expiration dates. Meanwhile, the Center for Disease Control and Prevention (CDC) recommended minimum 60% alcohol content well beyond the affixed expiration date.[15] Commercial hand-rub will expire depending on the bottle type. Alcohol-based hand disinfectant in a dispenser expires in 12 mo after opening. The expiration date is shorter in a dispenser without closing system to cover the neck of the bottle.[16] Hand-rub expires because of the alcohol content which dissolves over time to less than 60% as it evaporates.[17] However, there is no clear explanation why a detergent bottle is not sterile anymore in 8 wk from the refill process.

CONCLUSION

Antiseptic in the plasma bottle remained sterile longer than detergent bottle since refilled. Both of them are equally effective in reducing colonization after hand-rub activity. However, there is no significant difference in Δ colonization for the two bottles. This study does not identified growing microbes in pre-hand-rub compared to post-hand-rub. Therefore, follow-up study will be essential, particularly by examining microbe identification and using a larger sample at each efficacy test.

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Vitamin D levels of obesity and non-obesity health workers: a cross-sectional study in Dr. Sardjito General Hospital/Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada, Yogyakarta

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ABSTRACT

Obesity is one of the causes of chronic diseases, such as diabetes, hypertension, stroke, cancer, dyslipidemia, and heart disease. It is considered a financial burden on national health insurance since it drains the largest health fund. The study aimed to determine the difference in vitamin D levels in obese and non-obese health workers and analyze the factors that influence it. This was a cross-sectional study of the obese and non-obese health workers at Dr. Sardjito General Hospital, Yogyakarta. A total of 50 subjects, including 25 obese and 25 non-obese subjects were involved. Serum vitamin D levels was determined by ELISA. There was no significant difference between the obese and non-obese groups on vitamin D status (p<0.365). Vitamin D deficiency was found in 10% of subjects, whereas insufficient vitamin D levels were found in 46 and 44% of subjects, respectively. Vitamin D deficiency was more common in the obese (12%) than non-obese (8%) group. Contrarily, vitamin D insufficiency was more common in the non-obese (56%) than obese (36%) group. The serum vitamin D levels in the obese [30.08 (14.67-101.71) ng/mL] was not significantly different compare to those non-obese [28.54 (14.38-54.41) ng/mL] (p = 0.691). The multivariate analysis significantly showed that outdoor activities <30 min had a 7.061 times greater risk of having vitamin D deficiency/insufficiency compared to outdoor activities >30 min (OR 7.061; 95% CI: 1.064-46.872; p=0.043). In conclusion, there is no significant difference in vitamin D levels between the obese and non-obese groups. Vitamin D deficiency/insufficiency is more common in non-obese subjects than in obese subjects. Outdoor activity <30 min is a risk factor for vitamin D insufficiency/deficiency despite living in a tropical country with abundant sunlight throughout the year.

Keywords:
vitamin D;
serum 25(OH)D;
obesity;
deficiency;
health workers

ABSTRAK

Obesitas merupakan salah satu penyebab penyakit kronis, seperti diabetes, hipertensi, stroke, kanker, dislipidemia, dan penyakit jantung. Obesitas dikhawatirkan menjadi beban jaminan kesehatan nasional karena menyedot dana kesehatan terbesar. Penelitian ini bertujuan untuk mengetahui perbedaan kadar vitamin D pada tenaga kesehatan dengan obesitas dan non obesitas serta menganalisis faktor-faktor yang mempengaruhinya. Penelitian potong lintang yang dilakukan pada tenaga kesehatan dengan obesitas dan non obesitas di RSUP Dr. Sardjito Yogyakarta. Total sampel penelitian ini adalah 50 subjek, meliputi 25 subjek obesitas dan 25 subjek non-obesitas. Kadar vitamin D serum diukur dengan metode ELISA. Tidak ada perbedaan nyata kadar vitamin D pada kelompok obesitas dan non obesitas (p<0,365). Defisiensi vitamin D ditemukan pada 10% subjek, sedangkan insufisiensi dan kecukupan vitamin D ditemukan pada 46% dan 44% subjek. Defisiensi vitamin D lebih

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sering terjadi pada obesitas (12%) daripada non-obesitas (8%). Sebaliknya, insufisiensi vitamin D lebih sering terjadi pada kelompok non-obesitas (56%) daripada obesitas (36%). Rerata kadar vitamin D pada kelompok obesitas [30,08 (14,67-101,71) ng/mL] tidak berbeda nyata denga kelompok non-obesitas [28,54 (14,38-54,41) ng/mL] (p=0,691). Analisis multivariat menunjukkan bahwa aktivitas di luar ruangan <30 min secara nyata memiliki risiko 7.061 kali lebih besar mengalami kekurangan vitamin D dibandingkan dengan aktivitas di luar ruangan >30 min (OR 7,061; 95% CI:1,064-46,872; p=0,043). Kesimpulan, tidak ada perbedaan nyata kadar vitamin D pada kelompok obesitas dan non obesitas (p<0,365). Defisiensi/insufisiensi vitamin D lebih sering terjadi pada subjek non-obesitas daripada subjek obesitas. Berbagai faktor mempengaruhi perbedaan kadar vitamin D pada kedua kelompok. Aktivitas luar ruangan <30 min terbukti nyata sebagai faktor risiko defisiensi/insufisiensi vitamin D meskipun tinggal di negara tropis dengan sinar matahari yang melimpah hampir sepanjang tahun.

INTRODUCTION

Obesity is one of the contributing causes of chronic diseases, such as diabetes, hypertension, stroke, cancer, dyslipidemia, and heart disease. Obesity is considered a financial burden on national health insurance since it is the largest drain on the health fund. Accordingly, as a risk factor for various diseases, obesity needs to be addressed and treated properly. The global prevalence of obesity in 2017-2018 was 42.4%.[1,2] Data in Indonesia showed as many as 13.5% of adults aged 18 years and over are overweight, while 28.7% are obese with a body mass index (BMI) 25. In 2016, the National Health Indicators Survey (*Survei Indikator Kesehatan Nasional*/SIRKERNAS) reported that the obesity rate of BMI 27 rises to 20.7%, while obesity with BMI 25 became 33.5% (P2PTM, 2018).[3]

Obesity can be multifactorial caused included genetic, environmental (diet, and physical activity), chemical (steroids), and hormonal (leptin, ghrelin, thyroid, insulin, and estrogen) factors.[4] People have been advised to do activities at home and limit activities outside the home during the COVID-19 pandemic, increasing the community's sedentary lifestyle, and thereby increasing the risk of obesity and vitamin D deficiency due to lack of sun exposure.[5] Obesity is a systemic disease with excessive and abnormal body fat accumulation. Obesity will negatively impact individual health. Obesity is associated with higher comorbidity such as type 2 diabetes mellitus, dyslipidemia, hypertension, obstructive sleep apnea, certain types of cancer, steatohepatitis, obesity-related glomerulopathy, chronic kidney disease, gastroesophageal reflux, arthritis, polycystic ovarian syndrome, and also infertility. The severely obese patient also has a limitation in daily activities such as walking, climbing stairs, and bathing, which can lead to mental distress. Inheritable factors also account for a 70% difference in BMI in adult life.[6]

A bidirectional genetic study showed that the higher the BMI, the lower the 25(OH)D level. The basis for low vitamin D concentrations in obesity is still under debate.[7,8] Several causes of vitamin D deficiency include lack of vitamin supplementation, poor dietary habits, low sun exposure, and changes in activity and expression of enzymatic pathways in vitamin D metabolism. Indoor activity and the use of sunscreen will cause a decrease in the formation of endogenous vitamin D in the body.[8,9]

Vitamin D deficiency often occurs not only in countries with four seasons with limited sun exposure, but currently, vitamin D deficiency is also reported to occur in tropical countries with excellent, year-round sun exposure, including Indonesia.[10-12] Based on the literature search, no study has examined the comparison of vitamin D levels in obese

and non-obese subjects in Indonesia's population of health workers. Vitamin D deficiency in health workers increases the risk of being infected with COVID-19, so they need special attention. This study compared serum vitamin D levels in obese and non-obese participants to evaluate the factors influencing the obese and non-obese health workers' vitamin D levels.

MATERIAL AND METHODS

Research subjects

This cross-sectional study used purposive sampling until the total number of samples reached 25 obese and 25 non-obese subjects. The research subjects were health workers over 18 years old at Dr. Sardjito General Hospital and the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta. The study was conducted in the dry season between August and September 2021 to ensure abundant sunlight during sampling.

Exclusion criteria were patients with endocrine disorders other than diabetes mellitus (including thyroid disorders, and hypopituitary gland disorders), uncontrolled hypertension, chronic inflammatory diseases, kidney disorders, liver disorders, angina pectoris, myocardial infarction, heart failure, genetic heart disease, stroke, psychiatric disorders, underwent intestinal and gastric surgery, pregnancy, vitamin D and omega-3 supplementation in the last three months. Subjects who met the inclusion and exclusion criteria were followed to participate in the study and receive a consent letter. The protocol of the study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia (reference number KE/FK/0586/EC/2021).

Anthropometric data

Anthropometric data collection included measurements of height (m), weight (kg), and waist circumference (cm). The BMI criteria used were based on the World Health Organization (WHO) western pacific region (2000) for the Asia Pacific population.[13] The subjects were grouped into two categories: the obese group (BMI >25) and the non-obese group (BMI 18.5 - 22.9). Central obesity criteria were based on the WHO (2008) for South Asian ethnicity, Chinese, Malay and Asian-Indian populations. Metabolic syndrome criteria were based on the International Diabetes Federation (IDF) criteria in 2005 and the National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATP III) criteria in 2005.

Assessment of sun exposure, physical activity, and nutritional intake

The risk factors for sun exposure were assessed using a sun exposure questionnaire that had previously been tested for validity and reliability. Validity test with product-moment correlation obtained r count of 0.521 - 0.683, which means it is valid as a measuring tool. A reliability test with a Cronbach alpha value of 0.750 (>0.70) indicates good reliability.

Physical activity assessment was analyzed using the International Physical Activity Questionnaire-Short Form (IPAQ short form) questionnaire with validity and reliability that has been used internationally. Physical activity was categorized into three levels, namely category 1 (low physical activity) with <600 MET-minutes/week, category 2 (moderate physical activity) with 600-<3,000 MET-minutes/week, and category 3 (high physical activity) with ≥3,000 MET-minutes/week.

Food intake data were obtained through interviewing subjects using a

diet intake recall form of vitamin D with the Semi-Quantitative Food Frequency Questionnaire (SQ-FFQ). The amount of vitamin D intake was determined based on the converted household size into grams (g), then analyzed using a nutrition software program and compared with the 2013 Recommended Dietary Allowances (RDA), then categorized into the inadequate intake (<15 g/d) or adequate (≥15 g/d). In addition to dietary intake of vitamin D, dietary intake of calcium (mg), magnesium (mg), and phosphorus (mg) were also assessed.

Laboratory analysis

Laboratory examinations included 25(OH)D levels, fasting blood sugar, lipid profile (triglycerides, and high-density lipoprotein (HDL) cholesterol), urea, creatinine uric acid, and routine blood. Examination of serum 25(OH)D levels was conducted with the enzyme-linked immunoassay (ELISA) method using the vitamin D kit (Calbiotech, A Life Science Co., USA; Catalog No. VD220B). Plasma glucose levels were measured by the glucose oxidase method, while cholesterol (triglycerides, and HDL) by the automatic colorimetric method. Vitamin D levels in this study used the following criteria for deficiency (<20 ng/mL), insufficiency (21-29 ng/ml), sufficiency (>30 ng/mL), toxicity (>50 ng/mL), according to the cut-off value recommended by the United States Endocrine Society.[14]

Statistical analysis

The sample characteristic data are displayed as a mean with a standard deviation (SD) or a median (minimum-maximum) if not normally distributed. Independent t-tests (t) were used for continuous variables or Mann-Whitney tests if not normally distributed. Data were analyzed with bivariate statistical tests using chi-square test or Fisher's exact test, while logistic regression was used for the multivariate test. A p value <0.05 was considered to be statistically significant. Statistical analysis used the Statistical Package for Social Sciences (SPSS) version 22.0 application (SPSS Inc., College Station, TX).

RESULTS

Baseline characteristics of obese and non-obese groups

TABLE 1 shows some parameters had significant differences (p<0.05) between the obese and non-obese groups. The working duration of more than 8 h in the obese group was significantly more (56%) than in the non-obese group. Systolic and diastolic blood pressure were significantly higher in the obese group, following the criteria for hypertension, which was higher in the obese group than in the non-obese group (p<0.05). The mean weight of the obese group (73.93±9.39 kg) was significantly higher than that of the non-obese group (51.82±5.24 kg) (p = 0.001). The mean BMI in the obese group was 28.68 (25.19-37.20), while the BMI in the non-obese group was 20.83 (18.51-23) (p=0.001). Laboratory parameters such as fasting blood glucose (FBG), hemoglobin (Hb), and platelets were significantly higher in the obese group than in the non-obese group (p<0.05).

Metabolic syndrome, according to NCEP ATP III (48%) and IDF (44%), was significantly more prevalent in the obese group than in the non-obese group (p<0.05). The components of the metabolic syndrome parameters also had a statistically significant value (p<0.05). Subjects with hypertension (40%) and central obesity (96%) were more common in the obese group than in the non-obese group. The mean abdominal circumference in the obese group (94.98±9.24 cm) was higher than the non-obese group (75.56±6.53 cm) (p =

0.001). In obesity, FBG levels were higher than in the non-obese group, 95 (69-185) mg/dL in obese and 87 (58-103) mg/dL in non-obese. Meanwhile, triglyceride levels in the obese group were 92 (63-289) mg/dL, which were higher than the non-obese group with 79 (59-135) mg/dL.

Dietary intake of foods containing vitamin D in the obese group was slightly higher than in the non-obese group. The mean dietary vitamin D intake levels in the obese and non-obese groups were 6.80 (1.5-28.9) µg and 5.40 (2.70-28.30) µg (TABLE 1). The dietary needs target of vitamin D based on the RDA is 15 µg.[24] Based on this targeted recommendation, the percentages of vitamin D intake in the obese and non-obese groups were only 45.33% and 36%, respectively. Dietary intakes of calcium-containing foods in the obese and non-obese groups were 359.6 (124-791) mg and 289 (99.7-1375.3) mg from the target based on the RDA of 1,000 mg. Dietary intake of magnesium in the obese and non-obese groups was 139.4 (46.9-431.7) mg and 144.4 (52.2-453.9) mg, respectively, far from the target of 340-360 mg. Meanwhile, the average dietary intake of phosphorus-containing foods in the obese and non-obese groups was 658.3 (246.5-1433) mg and 607.5 (289.3-1930.1) mg, still lower than the target of 700 mg.

The average total physical activity in the obese group was higher than in the non-obese group (p=0.497). The proportion of strenuous activity (>3,000 met-min/wk) was found to be the same in the obese and non-obese groups. Most of the obese group (36%) did a strenuous activity with >3,000 met-min/wk, while in the non-obese group, most (44%) did a light activity that was <600 met-min/wk (TABLE 1).

TABLE 1. Basic demographic, anthropometric, and laboratory parameters of research subjects with obesity and non-obesity

Variable	Obese (n=25)	Non obese (n=25)	p
Gender [n (%)]			
• Man	4 (16.0)	4 (16.0)	1.000
• Woman	21 (84.0)	21 (84.0)	
Gender (mean ± SD years)	39.12±8.22	36.00±8.25	0.187
Hypertension [n (%)]			
• Yes	10 (40.0)	3 (12.0)	0.024
• No	15 (60.0)	22 (88.0)	
Central obesity [n (%)]			
• Yes	24 (96.0)	4 (16.0)	0.001
• No	1 (4.0)	21 (84.0)	
Metabolic syndrome (NCEP ATP III) [n (%)]			
• Yes	12 (48.0)	1 (4.0)	0.001
• No	13 (52.0)	24 (96.0)	
Metabolic syndrome (IDF) [n (%)]			
• Yes	11 (44.0)	1 (4.0)	0.001
• No			
Outdoor activity (min)			
• <30	14 (56.0)	14 (56.0)	0.231
• >30-60	4 (16.0)	8 (32.0)	
• >60	7 (28.0)	3 (12.0)	
Working duration (h)			
• >8 h	14 (56.0)	7 (28.0)	0.045
• 4-8 h	11 (44.0)	18 (72.0)	
Physical activity category (IPAQ) [n (%)]			
• Light	8 (32.0)	11 (44.0)	0.558
• Currently	8 (32.0)	5 (20.0)	
• Heavy	9 (36.0)	9 (36.0)	

Variable	Obese (n=25)	Non obese (n=25)	p
SBP (mmHg)	120 (100-160)	108 (86-140)	0.002
DBP (mmHg)	80 (61-130)	70 (58-100)	0.001
Waist circumference (cm)	94.98 ± 9.24	75.56 ± 6.53	0.001
Body height (cm)	158 (150-170)	157 (149-176)	0.891
Body weight (cm)	75.93 ± 9.39	51.82 ± 5.24	0.001
BMI	28.68 (25.19-37.20)	20.83 (18.51-23)	0.001
FBG (mg/dL)	95 (69-185)	87 (58-103)	0.001
HDL cholesterol (mg/dL)	47.84 ± 9.19	50.80 ± 7.95	0.229
Triglycerides (mg/dL)	92 (63-289)	79 (59-135)	0.060
Hemoglobin (g/dL)	13.47 ± 1.56	12.42 ± 1.86	0.036
Leucocyte count (x10^3/uL)	6.96 (4.75-13.99)	6.47 (4.19-10.10)	0.060
Thrombocyte count (x10^3/uL)	302.90 ± 57.60	261.80 ± 80.68	0.044
Vitamin D intake (µg)	6.80 (1.50-28.90)	5.40 (2.70-28.30)	0.720
Total physical activity (MET-min/wk)	1668 (148.5-8130)	631(99-8370)	0.497

NCEP ATP III: National Cholesterol Education Program Third Adult Treatment Panel III; IDF: International Diabetes Federation; IPAQ: International Physical Activity Questionnaire; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; FBG: fasting blood glucose; HDL: high-density lipoprotein; MET: metabolic equivalent of task.

Analysis of serum vitamin D levels in the obese and non-obese groups

Results showed that most subjects (46%) had vitamin D insufficiency (TABLE 2). As many as 22 (44%) subjects had sufficient vitamin D levels, and 5 (10%) subjects had vitamin D deficiency. The prevalence of vitamin D deficiency was higher in the obese (12%) than in the non-obese (8%) group. In comparison, vitamin D insufficiency was more common in the non-obese (56%) than the obese (36%) group, but it was not statistically significant (p=0.365). Remarkably, this study found that more subjects with sufficient vitamin D were obese (52%) than non-obese (36%) (p>0.005). It is suspected that several factors can affect vitamin D insufficiency, which was found in the obese group more than in the non-obese group in this study.

TABLE 2. Comparative distribution of serum vitamin D levels in the obese and non-obese groups

Variable	Deficient (< 20 ng/mL)	Insufficiency (20-3 ng/mL)	Sufficient (>30 ng/mL)	
Obesity [n (%)]	3 (12)	9 (36)	13 (52)	0.365
Non-obesity (n (%)]	2 (8)	14 (56)	9 (36)	
Total	5 (10)	23 (46)	22 (44)	

Analysis of the factors that affect the sufficiency of vitamin D

TABLE 3 describes the factors influencing vitamin D deficiency/ insufficiency (<30 ng/mL) in the obese and non-obese groups. It was found that hypertension, metabolic syndrome, and wearing sunscreen significantly affected vitamin D levels < 30 ng/mL in the obese and non-obese groups (p<0.005). The average vitamin D levels in subjects with

vitamin D deficiency/insufficiency (<30 ng/mL) and sufficient vitamin D (>30 ng/mL) were 25.72 and 33.93, respectively (p <0.001) (TABLE 4).

All variables in the bivariate analysis (TABLEs 3 and 4) that met the criteria of p < 0.25 were then continued to multivariate logistic regression analysis to determine the most powerful factor influencing the adequacy of vitamin D levels in the obese and non-obese groups. The multivariate analysis (TABLE 5) found that only outdoor activity factors significantly affected the adequacy of vitamin D levels with p<0.05. Obese and non-obese subjects with outdoor activities <30 min had an increased risk of vitamin D deficiency/insufficiency, as much as 7.061 higher than subjects with outdoor activities >30 min (OR=7.061; 95% CI: 1.064-46.872; p=0.043).

TABLE 3. Bivariate analysis of demographic variables, sun exposure, and physical activity that affect vitamin D deficiency/insufficiency in all subjects

Variable	Vitamin D level < 30 ng/mL	Vitamin D level < 30 ng/mL	p
Gender [n (%)]			
• Man	2 (25)	6 (75.0)	0.116
• Woman	26 (61.9)	16 (38.1)	
Age (mean ± SD years)	36.82 ± 8.28	38.50 ± 8.42	0.484
Smoking [n (%)]			
• Yes	0 (0)	1 (100.0)	0.440
• No	28 (57.1)	21 (42.9)	
Exercise min/wk [n (%)]			
• <60	26 (61.9)	16 (38.1)	0.116
• >60	2 (25.0)	6 (75.0)	
Income (million/mo)/[n (%)]			
• <5	4 (36.4)	7 (63.6)	0.178
• >5	24 (61.5)	15 (38.5)	
Comorbid [n (%)]			
• Yes	2 (33.3)	4 (66.7)	0.385
• No	26 (59.1)	18 (40.90)	
Hypertension [n (%)]			
• Yes	4 (30.8)	9 (69.2)	0.033*
• No	24 (64.9)	13 (35.1)	
Central obesity [n (%)]			
• Yes	13 (46.4)	15 (53.6)	0.124
• No	15 (68.2)	7 (31.8)	
Metabolic syndrome (IDF) [n (%)]			
• Yes	2 (16.7)	10 (83.3)	0.002*
• No	26 (68.4)	12 (31.6)	

Variable	Vitamin D level < 30 ng/mL	Vitamin D level < 30 ng/mL	p
Outdoor activity (min)/[n (%)]			
• <30	19 (67.9)	9 (32.1)	0.057
• >30	9 (40.9)	13 (59.1)	
Hours exposed to the sun [n (%)]			
• Uncertain	5 (83.3)	1 (16.7)	0.211
• 07.00-16.00	23 (52.3)	21 (47.7)	
Working hours [n (%)]			
• Non-shift/morning	6 (75.0)	2 (25.0)	0.439
• Alternating shifts	22 (52.4)	20 (47.6)	
Working duration (hr)/ [n (%)]			
• >8	10 (47.6)	11 (52.4)	0.310
• 4-8	18 (62.1)	11 (37.9)	
The work environment is exposed to light [n (%)]			
• Yes	4 (50.0)	4 (50.0)	0.718
• No	24 (57.1)	18 (42.9)	
Body parts covered with clothes [n (%)]			
• >4	24 (61.5)	15 (38.5)	0.178
• 1-4	4 (36.4)	7 (63.6)	
Clothing material [n (%)]			
• Difficult to absorb sunlight	17 (51.5)	16 (48.5)	0.373
• Easy to absorb sunlight	11 (64.7)	6 (35.3)	
Wear a hat [n (%)]			
• Yes	0 (0.0)	3 (100.0)	0.079
• No	28 (59.6)	19 (40.4)	
Wear sunscreen [n (%)]			
• Yes	19 (70.4)	8 (29.6)	0.027*
• No	9 (39.1)	14 (60.9)	
MET category [n (%)]			
• Light	10 (52.6)	9 (47.4)	
• Currently	10 (76.9)	3 (23.1)	0.185
• Heavy	8 (44.4)	10 (56.6)	

TABLE 4. Bivariate analysis of anthropometric variables, dietary intake, and biochemical parameters that affect vitamin D deficiency/insufficiency in all subjects

Variable	Vitamin D level < 30 ng/mL	Vitamin D level < 30 ng/mL	p
SBP [median (min-max mmHg)]	116.5 (90-151)	120 (86-160)	0.430
DBP [median (min-max mmHg)]	74 (58-95)	76 (60-130)	0.562
Waist circumference (mean ± SD cm)	82.8 ± 12.7	88.41 ± 12.05	0.120
Body height [median (min-max cm)]	157 (149-166)	158 (150-176)	0.346
Bodyweight (mean ± SD kg)	61.37 ± 14.57	64.80 ± 11.97	0.377
BMI [median (min-max mmHg)]	22.81 (18.51-37.2)	26.37 (18.61-33.83)	0.374
Vitamin D levels [median (min-max ng/mL)	25.72 (14.38-29.97)	33.93 (30.08-101.71)	<0.001
FBG [median (min-max mg/dL)]	91 (67-146)	93 (58-185)	0.379
HDL cholesterol (mean ± SD mg/dL)	49.68 ± 7.52	48.86 ± 10.04	0.744
Triglycerides [median (min-max mg/dL)]	84.5 (59-289)	90.50 (64-228)	0.384
Hb (mean ± SD g/dL)	12.55 ± 1.78	13.45 ± 1.69	0.075
Leucocyte count [median (min-max $x10^3$/uL)]	6.86 (4.75-11.10)	6.52 (4.19-13.99)	0.611
Thrombocyte count (mean ± SD $x10^3$/uL)	287 ± 86.2	276 ± 51.5	0.562
NLR [mean (min-max)]	1.99 1.20-3.87)	1.72 (0.98-5.10)	0.197
BUN [(median (min-max mg/dL)]	8.55 (4.50-12.20)	8.80 (7.30-13.60)	0.120
Creatinine (mean ± SD mg/dL)	0.68 ± 0.16	0.76 ± 0.14	0.066
Uric acid [median (min-max mg/dL)]	4.50 (2.40-9.40)	4.70 (3.30-8.40)	0.423
Vitamin D intake [median (min-max µg)]	5.85 (2.40-24.60)	6.80 (1.50-28.90)	0.369
Calcium intake [median (min-max mg)]	343.9 (126-791)	299.5 (99.7-1375.3)	0.907
Magnesium intake [median (min-max mg)]	143.2 (52.2-321.6)	143.4 (46.9-453.9)	0.961
Phosphorus intake [median (min-max mg)]	630.3 (252.5-1433)	706.1 (246.5-1930.1)	0.333

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; FBG: fasting blood glucose; HDL: high-density lipoprotein; Hb: hemoglobin; NLR: neutrophil-lymphocyte ratio; BUN: blood urea nitrogen

TABLE 5. Multivariate logistic regression analysis of various factors that affect vitamin D deficiency/insufficiency in all subjects

	p	OR	95% CI
Outdoor activities • <30 min • >30 min	0.043*	7.061	1.064-46,872
Constant	0.715	6.550	

*p-value < 0.05: statistically significant; CI: confidence interval; OR: odds ratio

DISCUSSION

Baseline characteristics of obese and non-obese groups

In this study, there was no significant difference between the physical activity of the obese and non-obese groups (p>0.05). This finding follows the research conducted by Gupta *et al.*[14] that found there was no significant difference in physical activity between obese and non-obese children (p=0.139).[14] Although exposure to ultraviolet (UV)-B light can

increase serum 25(OH)D levels, excessive UV radiation is not recommended to maintain adequate vitamin D production. The skin needs sun exposure to convert previtamin D3 to vitamin D. Physical activity can increase skin temperature. In contrast, high skin temperature can help produce vitamin D in the body.[12,15]

There was no significant difference in dietary intake of vitamin D, calcium, phosphorus, and magnesium between the obese and non-obese groups. This finding is consistent with the results of other studies, which showed no significant difference between dietary intake of vitamin D in the obese and non-obese groups.[14] Low dietary vitamin D intake [p=0.369; 5.85(2.40-24.60)] was associated with vitamin D deficiency and insufficiency, although this study did not prove statistical significance. Some of the reasons were the analysis of food diets in this study using a semi-quantitative Food Frequency Questionnaire which assesses the frequency of consuming foods containing vitamin D and only conducted one interview which should be done with more than one measurement. In addition, in this study, no daily diet recall was conducted, so the food intake analysis results were less than optimal. Another study conducted in North Sumatra, Indonesia demonstrated that vitamin D deficiency was significantly associated with low dietary vitamin D intake (p=0.046).[12] According to research by Masood and Iqbal *et al.*[16] the inability to buy food sources containing vitamin D causes vitamin deficiency, such as salmon and fish oil which are still considered expensive food sources in the market.[16]

There was a significant difference between SBP and DBP between the obese and non-obese groups in this study (p=0.002 and 0.001, respectively). This finding is similar with the research results by Alfawaz *et al.*,[17] that found there is a significant difference between SBP and DBP.[17] Research by Bugaz *et al.*,[18] reported a significant inverse relationship between hypertension and vitamin D levels, while in this study, a significant difference was found between hypertension and vitamin D (p=0.033). However, subjects with hypertension have higher levels of vitamin D sufficiency than those without hypertension. The difference in this relationship may be influenced by the fewer number of samples with comorbid hypertension, which was 26% of the total study sample. Several other studies found no significant difference between hypertension and vitamin D deficiency/ insufficiency.[14,19]

This study showed a significant difference between metabolic syndrome and vitamin D levels (p = 0.001). The study by Karatas *et al.*[19] showed that vitamin D deficiency not only occurred in overweight/obese subjects with metabolic syndrome (72%) and without metabolic syndrome (69%) but also occurred in healthy subjects (49%).[19] Another study stated that inadequate vitamin D status will increase the risk of developing metabolic syndrome by 2.5 times (OR 2.5).[20] Previous studies have also shown that low levels of 25(OH)D are significantly associated with components of the metabolic syndrome such as increased blood pressure, increased triglycerides, decreased HDL, and increased abdominal circumference.[19-21] On the other hand, several studies have failed to demonstrate any significant association between vitamin D and metabolic syndrome.[22-24] The difference in results may be due to the studies were conducted in different populations, namely in the low-risk or high-risk groups.[20] Therefore, larger samples are needed for further research to assess the relationship between vitamin D status and metabolic syndrome, especially in Yogyakarta, Indonesia.

Analysis of vitamin D levels in the obese and non-obese groups

In this study, the prevalence of vitamin D deficiency was slightly higher in the obese than in the non-obese group. In contrast, vitamin D insufficiency was more common in the non-obese than the obese group, although it was not statistically significant (p=0.365). This result follows a study by Gupta *et al.*[14] which showed that the prevalence of vitamin D deficiency was significantly more common in obese children than in non-obese children. However, there was no significant relationship between serum levels of 25(OH) vitamin D3 with comorbid obesity. Research by South East Asian Nutrition Surveys (SEANUTS) revealed that there was no vitamin D deficiency (levels <25 nmol/L) in children in Indonesia.[10]

1.25(OH)2-D in human cells will stimulate adipogenesis by upregulating the gene expression such as fatty acid synthase (FASN), fatty acid-binding protein (FABP), and peroxisome proliferator activator receptor (PPAR)-γ, which play a role in the adipocyte differentiation. 1.25(OH)2-D also stimulates the translocation of glucose transporter 4 (GLUT4) that induces adiponectin secretion. 1.25(OH)2-D also induces leptin that promotes adiponectin secretion. Vitamin D regulates the adipokine secretion in adipocytes, such as adiponectin (an anti-inflammatory and insulin-sensitizing hormone), leptin, and resistin. Obesity is also associated with low-grade inflammation. Vitamin D also promotes lower chemokine and cytokine release by adipocytes and the chemotaxis of monocytes. Vitamin D deficiency will decrease mRNA levels of oxidation-related genes, resulting in an alternation of adipocyte metabolic metabolism and obesity progression. miR-146a, miR-150, and miR-155 have been identified as related to vitamin D.[25]

Several studies have found a significant inverse relationship between vitamin D and BMI.[14,26] However, in this study, there was no significant difference between BMI and vitamin D levels (p=0.374) (TABLE 4). Vitamin D insufficiency/deficiency occurred in normal BMI (mean BMI 22.81), while vitamin D sufficiency occurred in obese BMI (mean BMI 26.37). Following a study conducted on women in North Sumatra, Indonesia, BMI did not significantly affect the concentration of 25-hydroxyvitamin D. Vitamin D deficiency was detected in obese women in Indonesia and was also found in subjects with normal adiposity (subjects with normal adiposity) or non-obese.[27]

Another study conducted on men in Yogyakarta, Indonesia, also showed that the proportion of vitamin D deficiency and insufficiency was relatively high but was not significantly associated with obesity, lipid profile, and physical activity.[11] Several studies have found low 25(OH)D levels in women with high body fatness and normal and low body fatness subjects.[27,28] This shows that several other factors, apart from body fat composition, can cause subjects with high or normal body fat to experience vitamin D deficiency. BMI and body weight do not represent the body fat percentage; for example, athletes and other well-trained people may have a relatively high BMI (overweight or obese) but have a low total fat mass.[29] The BMI parameter is a method used to measure obesity, but BMI itself is not a good indicator of the amount or distribution of body fat. Body fat distribution influences metabolic health since central obesity or visceral fat accumulation is associated with cardiometabolic risk, while femoral-gluteal subcutaneous fat may protect against cardiovascular risk.[6]

Based on research conducted by SEANUTS in 2016, it was found that there is a relationship between BMI and level 25(OH)D in Malaysia, Thailand, and Indonesia.[10] A negative relationship

between vitamin D and BMI or body fatness has also been reported in several studies, including in Indonesia.[30] Meanwhile, the positive correlation between 25(OH)D and BMI in Vietnam may be because children with obesity in Vietnam belong to a high socio-economic class, so their nutritional intake is better than non-obese subjects.[10] This is consistent with the results of our study, where dietary vitamin D intake in the obese group [6.80 (1.50-28.90)] was higher than in the non-obese group [5.40(2.7-28.30)], although it was not statistically significant. The high dietary vitamin D in the obese group is influenced by the higher educational status and income level in the obese group compared to the non-obese group (TABLE 1). This finding matches research conducted on the elderly in Indonesia, which also could not find significant evidence that the elderly who are obese are more at risk of malnutrition or vitamin D deficiency due to the social background of the subjects living in big cities where most of the subjects have a high level of education and economic status.[30]

Analysis of the factors that affect the sufficiency of vitamin D in all subjects

The high prevalence of vitamin D insufficiency in (sub)tropical countries requires a multifactorial approach, including promoting a lifestyle of outdoor activities with safe and adequate sun exposure and strategies to increase intake of foods containing high vitamin D.[10] Factors associated with vitamin D deficiency include the complexity of skin color, low sun exposure, vegetarian eating habits and low intake of fortified foods containing vitamin D.[14] This is following the results of the multivariate analysis (TABLE 5) which show that outdoor activities <30 min have a significantly higher risk by 7,061 times of having vitamin D deficiency/ insufficiency (vitamin D levels <30 ng/ mL) compared to outdoor activities > 30 min (p = 0.043). Outdoor activities with the most prolonged duration (> 1 h) were found more in obese subjects than non-obese (TABLE 1), so many non-obese subjects in this study experienced vitamin D insufficiency. This result aligns with a study that found vitamin D deficiency in women in tropical countries is associated with exposure to sunlight for less than 1 h/d and having an indoor job.[27] Despite living in a tropical country rich in sunlight throughout the year, many subjects still do not get enough sun exposure. Most subjects only did physical activity for 15 min daily while wearing sunscreen, hijab, or hat.[30] A study showed that Indonesians should get a minimum of 25 min of direct sun exposure at 9-10 AM to obtain a blood concentration of 2,700 IU of vitamin D per exposure and at least 3 times a week to prevent vitamin D deficiency.[31]

There was no significant difference between hours exposed to the sun and body parts covered with vitamin D deficiency/insufficiency ($p<0.05$). This is due to the typical behavior in tropical countries to avoid direct sun exposure, for example, by walking on the edges of buildings to avoid direct sunlight and wearing sunscreen, hats, or umbrellas when doing outdoor activities.[10,27] Most of the population of Malaysia and Indonesia are Muslim. Most of the female Muslim population wears closed clothes covering the whole body except the face and palms. Research in Malaysia found a relationship between wearing closed clothes (Muslim wear) and low levels of vitamin D.[32,33] The non-obese group experienced more vitamin D insufficiency because they wore clothes that covered almost their entire body (>4 body parts) and wore hats more when doing outdoor activities, but this was not statistically significant ($p>0.05$). Research by Hidayat *et al*.[30] on the elderly population in Indonesia proved that sunscreen was significantly correlated

with vitamin D deficiency (p=0.016). The finding is consistent with the results of this study, where subjects who used sunscreen (70.4%) had significantly more vitamin D deficiency/insufficiency than those who did not use sunscreen (39.1%) (p=0.027).[30]

Regional differences are the most significant source of variation in 25(OH) D levels across countries. Differences in 25(OH)D levels per region contributed to the significant difference in the prevalence of vitamin D insufficiency. The results showed that the population of Java island had a nine times higher risk for vitamin D deficiency compared to Sulawesi island, although still within the same country. These regional differences within a country have been observed previously in Thailand.[10,34]

Vitamin D deficiency in women in north Sumatra, Indonesia, is not associated with obesity but is more likely to be caused by a single nucleotide polymorphism.[12] Moreover, according to a trusted source study, people on the island of Java have a nine times higher risk of vitamin D deficiency than other islands in Indonesia.[34] Therefore, further research is needed to evaluate the relationship of vitamin D with obesity with a better method, such as a prospective cohort by considering vitamin D receptors' gene polymorphism, especially for Yogyakarta, Java Island. Genetic factors play a role in determining the concentration of 25(OH)-D in serum. Some research showed an association between Hydroxyvitamin D-1-α hydroxylase (CYP27B1), vitamin D 25-hydroxylase (CYP2R1), vitamin D binding protein (DBP/GC), vitamin D receptor (VDR), vitamin D 24-hydroxylase (CYP24A1), 7-dehydrocholesterol reductase (DHCR7), retinoid X receptors (RXR), calcium-sensing receptor (CASR), NPY, FOXA2, SSTR4, and IVL genes and serum 25(OH)-D Concentration.[25]

Remarkably, the differences between regions did not show a statistically significant relationship between the average hours of sun exposure and sun exposure per day. Some of the reasons include that the actual number of hours of sunshine in the area may differ from the annual mean value according to the meteorological department. In addition, hours of sunshine vary significantly throughout the year, and hours do not mean direct exposure to sunlight. People often like to stay indoors or in the shade or avoid direct sunlight by wearing clothes or an umbrella. The effectiveness of sun exposure may differ depending on factors such as air pollution, smog, and altitude. Additionally, Southeast Asians (including in Indonesia), especially women, tend to avoid sun exposure to maintain a fair skin tone because, culturally, white skin is a sign of beauty.[10,35]

Study limitations

This study has several limitations, including 1) the subjects were taken from health workers at a Central General Hospital in Yogyakarta, Indonesia, with a small number of samples so that the results cannot be generalized to the Indonesian population; 2) serum 25(OH) D levels were measured by the method ELISA, which is not the gold standard for measurement of vitamin D levels, but the technique of ELISA is currently the most widely used for research purposes since it is simpler and cheaper,[29] and 3) serum calcium and parathyroid hormone levels were not measured in this study. However, the strength of this study is that it analyzed various factors related to vitamin D levels, including demographic and anthropometric factors, lifestyle, dietary intake of food, physical activity, and factors of sun exposure which were relatively complete.

Despite the limitations of this study, the results of this study can be used as a preliminary study for further research to assess genomic studies of vitamin D (vitamin D receptor polymorphism),

obesity, and metabolic syndrome in the population in Yogyakarta, Indonesia, as one of the developing countries in Southeast Asia. With the present results, it is recommended that metabolic disease prevention programs can be done, which will decrease the prevalence of metabolic diseases in the next decade.

CONCLUSIONS

The results found that there is no significant difference in vitamin D status among the obese and non-obese groups. Vitamin D deficiency/insufficiency (vitamin D levels < 30 ng/mL) is more common in non-obese subjects than obese subjects although it is not statistically significant. Various factors influence the difference in vitamin D levels in subjects. Outdoor activity <30 min is found to be a significant risk factor for vitamin D insufficiency/deficiency, despite living in a tropical country with abundant sunshine throughout the year.

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Effect of *Citrullus lanatus* seed oil on xerosis in leprosy patients

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ABSTRACT

Xerosis in leprosy patients may result from defects in sweat gland function. Red watermelon (*Citrullus lanatus*) seed oil a lot of contains linoleic acid, which can hydrate the skin and reduce trans-epidermal water loss (TEWL). This study aimed to evaluate the effect of *C. lanatus* seed oil administration in leprosy patients with xerosis. It was a clinical study with one group pretest posttest control group design involving 30 leprosy patients with xerosis at the Department of Dermatology and Venereology, Dr. Pirngadi Medan Hospital, the Polyclinic of Dermatology and Venerology, Universitas Sumatera Utara Hospital and the Department of Dermatology and Venerology, H. Adam Malik General Hospital, Medan, Indonesia. Patients were asked to topically administration of 2 mL *C. lanatus* seed oil to the right and left legs for two times daily for 4 weeks. Specified symptom sum score (SRRC) and skin capacitance (SCap) were then measured before the intervention at the first visit (week 0), week 2, and week 4. A significantly different on SRRC and SCap of the leprosy patients was observed on the 2nd and 4th week after *C. lanatus* oil administration compared to week 0 ($p<0.001$). No side effects of erythema, blistering, and burning were observed. However, a mild degree itching was observed in 2 (6.7%) patients. Majority of leprosy patients feel good satisfaction (83.4%), followed by a moderate (13.3%) and a low satisfaction (3.3%). In conclusion, topically administration of red watermelon (*C. lanatus*) seed oil can reduce the xerosis degree in leprosy patients as indicated by the decrease of SRRC and the increase of SCap. The seed oil is well tolerated and gives a good satisfaction on the patients.

ABSTRAK

Xerosis pada pasien kusta kemungkinan terjadi akibat gangguan fungsi kelenjar keringat. Minyak biji semangka merah (*C. lanatus*) mengandung banyk asam linoleat yang dapat mempertahan kulit lembap dan menurunkan kehilangan air trans epidermal. Penelitian ini bertujuan mengkaji pengaruh pemberian minyak biji semangka merah (*C. lanatus*) terhadap xerosis pada pasien kusta. Penelitian ini merupakan penelitian klinik menggunakan rancangan *one group pretest posttest control group* yang melibatkan 30 pasien kusta dengan xerosis dari Departemen Dermatologi dan Venereologi, Rumah Sakit Dr. Pirngadi Medan, Poliklinik Dermatologi dan Venerologi, Rumah Sakit Universitas Sumatera Utara dan Departemen Dermatologi dan Venerologi, Rumah Sakit Umum Pusat H. Adam Malik, Medan, Indonesia. Pasien diminta memberikan secara topikal 2 mL minyak biji semangka merah (*C. lanatus*) pada tungkai bawah kanan dan kiri sebanyak 2 kali sehari selama 4 minggu. *Specified symptom sum score* (SRRC) dan *skin capacitance* (SCap) kemudian diukur sebelum perlakuan pada kunjungan pertama (minggu 0), minggu ke 2 dan ke 4. Perbedaan nyata pada SRRC dan SCap pasien kusta teramati pada minggu ke 2 dan ke 4 setelah pemberian minyak biji semangka merah (*C. lanatus*) dibandingkan dengan minggu ke 0 ($p<0.001$). Tidak dijumpai efek samping berupa eritema, lepuh dan rasa terbakar. Namun demikian rasa gatal derajat sedang dijumpai pada 2 pasien. Sebagian besar pasien merasakan tingkat kepuasan yang baik (83,4%), diikuti sedang (13.3%), dan rendah (3,3%). Dapat disimpulkan, pemberian secara topikal minyak biji semangka merah (*C. lanatus*) dapat menurunkan derajat xerosis pasien kusta sebagaimana ditunjukkan dengan penurunan SRRC dan kenaikan SCap. Minyak biji ini ditoleris dengan baik dan memberikan kepuasan yang baik pada penderita.

Keywords:
C. lanatus;
leprosy;
watermelon seed oil;
xerosis;
side effects

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INTRODUCTION

Leprosy, caused by *Mycobacterium leprae*, has been known for a long time, even years before Christ. Indonesia is the third in the world after India and Brazil regarding leprosy patients. The prevalence rate of leprosy in Indonesia in 2017 was 0.70 cases/10,000 population with a new case finding rate of 6.08 cases per 100,000 population.[1]

Xerosis is a common skin disorder in the general population. This condition has clinical characteristics of rough skin, scaly, and sometimes itchy. In leprosy lesions, there is a decrease in epidermal proliferative activity, and a reduction of sphingolipids in stratum corneum (SC), which can further change epidermal function.[2] The mechanism contributing to decreased SC hydration is defect in sweat gland function and decrease active osmotic components that contribute to the development of xerosis. The sphingolipid content in leprosy patients with and without lesions is lower than that in normal people. Lipid changes in SC, especially sphingolipids, are caused by cornification and loss of sweat gland function due to nerve damage in leprosy.[3] Studies found that patients with xerosis cutis showed higher psychosocial burden than participants without xerosis cutis which could lead to reduced quality of life of the patients.[4]

Red watermelon (*C. lanatus*) seed oil has been used to treat skin disease since ancient Egyptian times. Komane *et al*.[5] reported that *C. lanatus* seed oil contains linoleic acid as the primary fatty acid that can hydrate and soften the skin and reduce transepidermal water loss (TEWL). Visual moisture efficacy examination showed that *C. lanatus* seed oil increased the skin's water content, thereby improving skin barrier function. This oil can also increase the natural moisturizing factor because it has a low viscosity and low molecular weight to retain moisture in the skin.[5] This study aimed to investigate the effect of red watermelon (*C. lanatus*) seed oil on skin capacitance in leprosy patients with xerosis.

MATERIALS AND METHODS

Study design

It was a clinical study with pre experimental design using one group pretest and posttest design. The pre-test was conducted before applying the red watermelon (*C. lanatus*) seed oil and the post-test was performed after administration of the red watermelon (*C. lanatus*) seed oil for 2 and 4 wk.

Extraction preparation

The extract of the red watermelon seed oil was produced by the Association of Indonesian Traditional Herb Medicine (ASPETRI/*Asosiasi Pengobat Tradisonal Ramuan Indonesia*).

Subjects

Leprosy patients with xerosis from the Department of Dermatology and Venereology, Dr. Pirngadi Medan Hospital, the Polyclinic of Dermatology and Venerology, Universitas Sumatera Utara Hospital and the Department of Dermatology and Venerology, H. Adam Malik General Hospital, Medan, Indonesia were involved in this study. The diagnosis of leprosy was performed by a dermatologist based on anamnesis, physical and microscopic examinations. Patients who were hypersensitive to *C. lanatus* seed oil, who had previously other skin conditions (such as psoriasis, ichthyosis, or atopic dermatitis), who had comorbidities (such as chronic kidney disease, diabetes, chronic liver disease, hypothyroid, malignancy, AIDS/HIV), who had already used other topical preparation on the skin two weeks before, and who had to consume hormonal

therapy, retinoid, antihistamine, antidiuretic, and antihypertension treatment for the last one month were all excluded from the study.

The application of watermelon seed oil (*C. lanatus*)

Red watermelon (*C. lanatus*) seed oil at dose of approximately 0.1 mL was administered to cover an area of 5.7 cm x 3.7 cm of the right and left legs. The seed oil applied topically by using fingers on the xerotic area, twice daily immediately after the morning bath (08.00 AM) and in the afternoon (04.00 PM). The subjects were asked to apply the seed oil for four wk. The evaluation of specified symptom sum score (SRRC) and skin capacitance (SCap) was conducted at the first visit (week 0), week-2, and week-4.

The subjective examination of xerosis using SRRC

Xerosis is a dry skin condition of the patient that consists of dull, rough, fissured, and scaly skin appearance. Clinical evaluation of xerosis on both lower limbs of the patients was performed visually and tactilely to calculate SRRC. The score ranges from 0 to 16.

The objective examination of xerosis using corneometer

SCap is the ability of the stratum corneum to bind water, and its value describes the water content in the stratum corneum. The CM825 corneometer (C&K, Courage-Khazaka, Köln, J Germany) was used to measure skin capacity. The measurements were conducted three times on mid-point of both lower limbs, and then the mean value was taken. The average result of three measurements was expressed in arbitrary units (AU) which was divided into three degrees of dryness i.e. <30AU (very dry), 30-45AU (dry), >45AU (normal).

The measurement technique of corneometer

The capacitance of a dielectric medium, in this case, the stratum corneum, the top layer of the skin, was used to make the measurement. As hydration increases, its dielectric properties change. The dielectric constant of water is higher than that of most other substances (mostly 7). An electric field with the alternating attraction between the tracks created by gold tracks on top of the probe head, separated from the skin by a glass lamina. One track accumulates electrons in excess (minus charge), whereas the other accumulates electrons in deficit (plus charge). When applied to the skin, the scattered field penetrates the very first layer. The Corneometer® CM825 detects the change in dielectric constant caused by the capacitance of a precision capacitor changing owing to skin surface moisture. The device can detect even the tiniest variations in hydration levels.[6]

The evaluation of side effect

Side effects are unwanted events during the use of the substance being tested in the experimental study. They were assessed and documented based on anamnesis and dermatological examination to seek any erythema, blisters, burning, and itching sensation during the study period. The side effects that appeared were classified into 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The evaluation of side effects was conducted after the 2nd and 4th weeks of use.

The evaluation of patient satisfactory

Patient satisfaction regarding their xerotic skin changes after using the red watermelon seed oil was asked after the end of the study. Patients were asked to classify their level of satisfaction on

a scale of 0 (dissatisfied), 1 (slightly), 2 (moderate), 3 (good), 4 (very satisfied).

Ethic committee

This clinical trial did not conflict with any human values and the research code of ethics. This study has been approved by the Research Ethics Committee, Universitas Sumatra Utara, Medan (reff. number 323/KEP/USU/2021 dated 23 April 2021).

Statistical analysis

Shapiro Wilk test was performed to evaluate the normality of the data. The data was normally distributed if $p > 0.05$. Repeated analysis of variance or the Friedman alternative test was applied to evaluate the effect of red watermelon (*C. lanatus*) seed oil on the degree of xerosis based on SRRC or on SCap in leprosy patients at the first visit (week 0), week 2, and week 4. Wilcoxon post hoc test was applied to evaluate the effect of red watermelon (*C. lanatus*) seed oil on the degree of xerosis based on SRRC or on SCap in leprosy patients at each measurement time.

RESULTS

This study involved 30 leprosy patients with xerosis with mean age of 36 yo and males majority (70%). All patients underwent anamnesis and physical examination to establish the diagnosis of leprosy with xerosis. All patients could finish their involvement in this study without drop out.

Effect of red watermelon (*C. lanatus*) seed oil on SRRC

The effect of red watermelon (*C. lanatus*) seed oil topically administration to the skin of the right and left legs on the degree of xerosis based on SRRC was observed in three different measurement times (TABLE 1). On the week 0, the median degree of xerosis was 10.75 (min-max: 4.00-16.00). After two weeks of administration, there was a decrease in the degree of xerosis to 8.5 (4.00-16.00). On the week 4, the median degree of xerosis decreased to 6.75 (2.00-15.00). A significantly decrease on SRRC of xerosis in leprosy patients after watermelon (*C. lanatus*) seed oil topically administration was observed ($p<0.001$).

TABLE 1. Effect of red watermelon (*C. lanatus*) seed oil administration on SRRC in leprosy patients

Time of assessment	n	Median	Min-Max	p[a]
Week-0	30	10.75	4.00-16.00	
Week-2	30	8.50[b,c]	4.00-16.00	<0.001
Week-4	30	6.75[d]	2.00-15.00	

[a]Friedman test was applied

The statistical analysis of SRRC was continued by using the post-hoc Wilcoxon test, a significantly different of SRRC in leprosy patients between week 0 and week 2, week 0 and week 4 as well as week 2 and week 4 were observed ($p<0.001$).

Effect of red watermelon (*C. lanatus*) seed oil on SCap in leprosy patients

The effect of red watermelon (*C. lanatus*) seed oil topically administration on SCap of the right and left legs based was observed in three different

measurement times (TABLE 2). On the week 0, the median SCap was 36.25AU (19.00-42.250AU). After two weeks of red watermelon (*C. lanatus*) seed oil topically administration, an increase in SCap to 40.67AU (22.50 – 44.85 AU) was observed. On week 4, the median SCap increased to 43.83AU (26.65-50.15AU). A significantly increase on SCap of xerosis in leprosy patients after watermelon (*C. lanatus*) seed oil topically administration was observed ($p<0.001$). The hydration status of the right lower leg of the leprosy patients was still classified as dry (30-45 AU).

The statistical analysis of SCap was continued by using the post-hoc Wilcoxon test, a significantly different of SCap in leprosy patients between week 0 and week 2, week 0 and week 4 as well as week 2 and week 4 were observed ($p<0.001$).

Side effects of red watermelon (*C. lanatus*) seed oil after topically administration

No side effect related to erythema, blistering, and burning was observed after red watermelon (*C. lanatus*) seed oil topically administration. Meanwhile, the incidence of itchy were found in 2 patients (6.7%) as shown in TABLE 3.

TABLE 2. The effect of red watermelon seed oil (*C. lanatus*) administration on SCap) in leprosy patients

Time of assessment	n	Median	Min-Max	p[a]
Week-0	30	36.25	19.00-42.50	
Week-2	30	40.67[b,c]	22.50-44.85	<0.001
Week-4	30	43.83[d]	22.65-50.15	

[a]Friedman test was applied

TABLE 3. Side effects of red watermelon (*C. lanatus*) seed oil after topically administration in leprosy patients

Side effects	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Erythema	30 (100)	0 (0)	0 (0)	0 (0)
Blister	30 (100)	0 (0)	0 (0)	0 (0)
Burning	30 (100)	0 (0)	0 (0)	0 (0)
Itching	28 (93.3)	2 (6.7)	0 (0)	0 (0)

Patient's satisfaction after red watermelon (*C. lanatus*) seed oil topically administration

All subjects were asked to give their opinion regarding their satisfaction related to changes on their skin. The majority of patients (25 or 83.4%) stated that they had a good level of satisfaction, followed by a moderate level of satisfaction in 4 (13.3%) and low level of satisfaction in 1 (3.3%) (FIGURE 1).

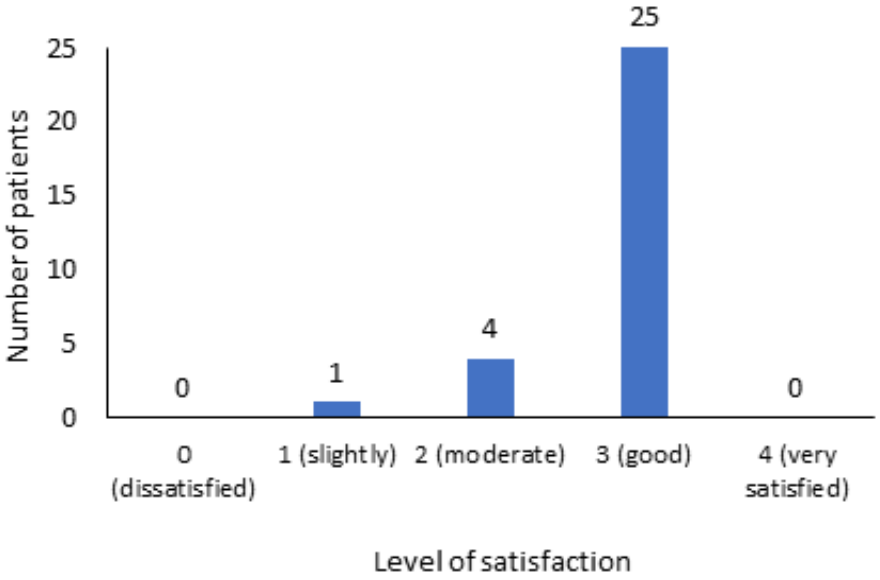

FIGURE 1. The level of leprosy patients' satisfaction after red watermelon (*C. lanatus*) seed oil topically administration

DISCUSSION

This study was dominated by male leprosy patients (70%). Oliveira and Romanelli reported that the incidence of leprosy is higher in men than women in Brazil.[7] In most Asian countries, leprosy is more common in men than women, while in Africa, the number of women affected by leprosy is more than men. However, men are diagnosed with multibacillary (MB) more often than women.[8] This condition could be affected by social, cultural, and educational factors. In certain cultures, women's access to health services is minimal. The higher incidence of leprosy in men could also be associated with the fact that man had greater mobility and chance of contact with leprosy patients. In addition, men are also more active in seeking treatment and get diagnosed.[9]

Dry skin, or xerosis, has the potential to become a more severe condition due to its tendency to break and the possibility of inflammation.[10] In leprosy, chronic fissures in dry skin could be a significant problem. This study showed that red watermelon (*C. lanatus*) seed oil is effective in treating xerosis in leprosy proved by improvement in xerosis level measured by SRRC method and corneometer. It is in line with study conducted by Ekayanti *et al.*[11] who found that moisturizing cream preparation containing watermelon (*C. lanatus*) water extract can maintain skin hydration as assessed using AUC value. Increasing the concentration of the extract in the preparation decreases the total AUC value.[11]

Komane *et al.*[5] also investigated the efficacy and safety of *C. lanatus* seed extract on the skin. The participants were asked to wash the calf area 2-4 times a day using a soap bar and apply moisturizer of 0.1 mL twice daily at five random locations tested (with an area of 5.7 cm x 3.7 cm) in a circular motion for seven days straight. Skin examinations were conducted on day 1, 2, 3, 4, 5, 8, 10, and 12. It was found that all products caused a significant decline in dryness from day one compared to day 12 (mean value of 2.4 vs 1.6, respectively).[5] These findings confirm the ability of *C. lanatus* seed extract oil to enrich the water content in the skin, which allows for an increase in

the skin barrier function by increasing the natural moisture factor due to its low viscosity and low molecular weight.[12,13]

Yusuf *et al.*,[14] also assessed the efficacy of oil extracts as a therapy for dryness in leprosy patients using virgin coconut oil. This study found a significant effect of virgin coconut oil on the skin of leprosy patients based on the overall dry skin score (ODS). This moisturizing effect of coconut oil was obtained from the high content of lauric acid. Komane *et al.*[5] reported that red watermelon seed extract oil also contains many acids that help increase skin moisture and prevent TEWL. One of the highest is the linoleic acid content of 41.5%.

In cosmetics and dermatology, skin moisture is an essential parameter. It has led to the development of tools for measuring skin moisture. Corneometer is one of the most commonly used tools to measure skin moisture. This technique determines the skin capacitance due to its behavior as a dielectric medium which can detect water content as deep as 10–20 μm in the stratum corneum layer. Although this tool assesses the skin's water content, it can also indirectly evaluate the skin's barrier function. Higher values indicate higher moisture and better skin barrier function.[15]

A statistically significant difference effect of red watermelon (*C. lanatus*) seed oil on SCap based on the corneometer in leprosy patients during eight weeks administration. This result is supported by Komane *et al.*,[5] who reported that red watermelon (*C. lanatus*) seed oil extract reduced skin dryness significantly between the first and the 12th day (16.44 vs 18.74, respectively). The effect of increasing the moisture content is due to the presence of stearic acid (6.3%), which can prevent TEWL.[5]

No side effects related to erythema, blistering, and burning were observed among 30 leprosy patients in this study. However, 2 patients had experienced a mild degree of itching. Loden *et al.*[16] reported that a common side effect of using moisturizers is a subjective sensation of burning. Humectants such as lactic acid and urea could also cause a burning sensation. Piraccini *et al.*[17] reported that the allergic contact dermatitis, burning sensation, and itching could emerge from using urea. Purnamawati *et al.*,[18] also reported that petrolatum causes folliculitis. This study showed that red watermelon (*C. lanatus*) seed oil is considered safe and only caused a few side effects.

The itching side effect can be attributed to the high linoleic acid content in red watermelon (*C. lanatus*) seed oil. Rahman *et al.*[19] reported that linoleic acid has the potential to scavenge free radicals that can trigger an anti-inflammatory effect on the skin and reduce irritation.[19] Zielińska *et al.*[20] found that oils with a high linoleic acid content are considered excellent skin treatments. In addition, Lima *et al.*[12] also reported that linoleic acid has properties that can trigger emollient substances.

All subjects were asked to provide their opinion on satisfaction related to their skin changes. The majority of patients (83.4%) stated that they had a good level of satisfaction, followed by a moderate level of satisfaction of 13.3% and a low level of satisfaction of 3.3%. This result is in line with conducted by Dewi *et al.*[21] concerning the effect of pumpkin (*Cucurbita moschata*) seed extract on xerosis in geriatrics. It was reported that participants claimed to be satisfied with a good satisfaction level of 85.7%; a moderate level of 11.4% and a mildt level of 2.8%. This showed that the use of plant seed extract oil generally has a good satisfaction level.

CONCLUSION

Red watermelon (*C. lanatus*) seed oil can improve xerosis degree in leprosy patients as indicated by the decrease in the degree of xerosis measured

subjectively by SRRC and objectively by the SCap. The topically administration of red watermelon (*C. lanatus*) seed may cause mild temporary itching. However, majority of leprosy patients feel good satisfaction.

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Comparison of neutrophil lymphocyte ratio (NLR), mean platelet volume (MPV) and platelet lymphocyte ratio (PLR) in preeclampsia and normotensive pregnancies

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ABSTRACT

The study aimed to compare the NLR (neutrophil lymphocyte ratio), MPV (mean platelet volume), and PLR (platelet lymphocyte ratio) values in preeclampsia and normotensive pregnancies. This was a retrospective case-control study using medical records of pregnancies between January 1, – December 31, 2019. A total 31 pregnancies with preeclampsia who met the inclusion and exclusion criteria were involved in the study. As control, 31 normotensive pregnancies recruited by simple random sampling were used. The data were presented as mean ± standard deviation (SD) and analyzed by using SPSS program. Receiver operating characteristic (ROC) curve were used to determine the optimal cut-off point for predicting preeclampsia. The NLR and MPV values of patients with preeclampsia were significantly higher compare to normotensive pregnancy ($p<0.001$). Whereas, the PLR value of both groups was not significantly different ($p>0.245$). The result of AUC analysis showed that the NLR and MPV have AUC values of 0.758 (95%CI:0.637-0.878; $p=0.000$) and 0.903 (95%CI:0.816-0.989; $p=0.000$), respectively. Further analysis showed that the optimal cut-off point for NLR was 4.0 (sensitivity of 64.5% and a specificity of 71.0%) and for MPV was 7.55 (sensitivity of 87.1% and specificity of 80.0%). In conclusion, the NLR and MPV values are significantly higher in preeclampsia. However, the MPV value has a better predictive value than NLR for preeclampsia.

ABSTRAK

Penelitian ini bertujuan membandingkan nilai NLR (*neutrophil lymphocyte ratio*), MPV (*mean platelet volume*), and PLR (*platelet lymphocyte ratio*) pada preeklampsia dan kehamilan normal. Penelitian kasus-kontrol retropektif ini menggunakan data rekam medis kehamilan antara 1 Januari – 31 Desember 2019. Total 31 kehamilan dengan preeklampsia yang memenuhi kriteria inklusi dan eksklusi terlibat dalam penelitian. Sebagai kontrol adalah 31 kehamilan normal yang direkrut secara sampel acak sederhana. Data disajikan sebagai rerata ± deviasi standar (SD) dan dianalisis dengan program SPSS. Kurva ROC digunakan untuk menentukan nilai *cut-off* optimal untuk memprediksi preeklampsia. Nilai NLR dan MPV pasien preeklampsia lebih tinggi secara nyata dibandingkan dengan kehamilan normal ($p<0,005$). Sedangkan nilai PLR kedua kelompok tidak berbeda secara nyata ($p>0,005$). Hasil perhitungan AUC menunjukkan NLR dan MPV berturut-turut mempunyai nilai AUC 0,758 (95%CI:0,637-0,878; $p=0,000$) dan 0,903 (95%CI:0,816-0,989; $p=0,000$). Analisis lanjutan menunjukkan nilai *cut-off* optimal untuk NLR adalah 4,0 (sensitivitas 64,5% dan spesifisitas 71,0%) dan untuk MPV adalah 7,55 (sensitivitas 87,1% dan spesifisitas 80,0%). Dapat disimpulkan, nilai NLR dan MPV secara nyata lebih tinggi pada preeklampsia. Namun demikian, nilai MPV mempunyai nilai prediksi lebih baik dibandingkan NLR untuk memprediksi preeklampsia.

Keywords:
preeclampsia;
normotensive pregnancy;
NLR;
MPV;
PLR

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INTRODUCTION

Maternal mortality rate (MMR) is the quality indicator of health services in a region. World Health Organization (WHO) reported that MMR in developing countries reached 462 compared to developed countries 11 per 100,000 live births.[1] Haemorrhage, hypertension in pregnancy, and sepsis are the causes of more than 50% of maternal deaths worldwide. In Indonesia MMR is still not successful yet to reach the MDG's target.[2,3] Meanwhile, MMR in North Maluku 2019 reached 47 per 29,195 live births, and based on the health profile in Central Halmahera Regency, the MMR reached 118/100,000 live births.[3,4]

Preeclampsia is a term of hypertension in pregnancy that remains a serious problem due to its high level of complexity. It is not only affecting the mother during pregnancy and childbirth, but also causing postpartum problems due to endothelial dysfunction in various organs, and affecting the survival of neonatal outcome. In Indonesia, the incidence of preeclampsia is 128,273/ year (5.3%).[5-7] A meta-analysis reported that the risk of hypertension (RR, 3.7; 95% CI 2.70-5.05), ischemic heart disease (RR, 2.16; 95% CI 1.86-2.52), stroke (RR, 1.81; 95% CI 1.45-2.27) and venous thromboembolism (RR, 1.79; 95% CI 1.37-2.33) of women with preeclampsia increase.[6] Furthermore, WHO reported that proportions of stillbirths (6.4% vs 1.9%), low birth weight (34.2% vs 10.6%), low Apgar score at birth (7.9% vs 2.6%), neonatal complications (20.6% vs 5.3%), and pre-term birth (30.89 vs 7.10%) of the preeclamptic women are more frequent compared to those without preeclampsia/ eclampsia. Whereas, neonates with low birth weight are at risk for metabolic diseases in adults. [5,8]

The cause of preeclampsia has not been fully understood, yet. One of the factors associated with preeclampsia is the inflammatory process. Placental dysfunction and hypoxia that occurred in preeclampsia lead to activation of immunological responses, including increased neutrophil counts, thrombocyte activation, and systemic inflammation process. Hyper-reactivation of inflammatory cells, immunological responses of neutrophils, and lymphocytes are taking place by releasing inflammatory cytokines and autoantibodies which impacting an endothelial dysfunction.[11-14] The changes in the hematological parameters level including, NLR, MPV, and PLR are known as a marker of the systemic inflammatory response in preeclampsia.[9-11] However, some studies showed the different results.

Cintesun *et al.*[9] reported that there is no significantly difference in NLR and PLR levels between healthy pregnancy and preeclampsia ($p > 0.05$), but MPV level is lower in the preeclampsia group ($p<0.001$). Mannaerts *et al.*[10] reported that MPV level significantly elevated in the preeclampsia compared to the control groups ($p<0.006$). Further analysis revealed an optimal cut-off point of 8.15 (sensitivity 66.7%, specificity 56.3%) for predicting preeclampsia. In contrast, NLR and PLR could not be used as marker for predicting preeclampsia. In another study by Syahputra *et al.*[11] reported that the NLR level is significantly higher in preeclampsia compared to normal pregnancy ($p=0.001$). However, there is no a significant difference in MPV and PLR levels values of both preeclampsia and normal pregnancy ($p>0.05$). Although some of those markers have been carried out in many previous research studies in preeclampsia patients, the results is not conclusive.[9,11]

Comprehensive management of preeclampsia requires advance laboratory equipment's and intensive care facilities which are still two major obstacles in Indonesia.[11] A simpler and easier examination method to predict preeclampsia therefore is needed. This

study aimed to compare the values of NLR, MPV, and PLR in preeclampsia and normotensive pregnancy at the Weda General Hospital, Central of Halmahera Regency, North Maluku.

MATERIALS AND METHODS

Subjects

It was a case-control study with a retrospective approach involving 31 patients with preeclampsia as cases group, and 31 normotensive pregnancies as the control group. Subjects was obtained by simple random sampling at the Weda General Hospital, Central of Halmahera Regency, North Maluku for the period of January 1 to December 31, 2019. The protocol of the study was approved by the Medical Research Ethic Committee, Faculty of Medicine, University of Trisakti, Jakarta.

Procedure

Preeclampsia was diagnosed in accordance with the National Guideline of Medical Care (*Pedoman Nasional Pelayanan Kedokteran*/PNPK) POGI 2016, as follow hypertension (SBP of ≥140 mmHg, or DBP of ≥90 mmHg, that occurs after 20-wk pregnancy in a woman with previously normal BP), and proteinuria (measured as 300mg/24-h urine specimen or >1+ with urine dipstick), if proteinuria cannot be obtained, one of the symptoms and signs can be used to diagnose preeclampsia i.e. thrombocytopenia (<100.000/mL), renal insufficiency (creatinine serum >1.1mg/dL or increase creatinine serum in the patient without any other renal diseases), impaired liver functions (elevated transaminases, right upper quadrant or epigastric abdominal pain), pulmonary edema, neurological complications (stroke, headache, visual disturbance), or signs of utero-placental dysfunction (oligohydramnios, fetal growth restriction (FGR), absent or reversed diastolic velocity). The distinction between the severe or mild preeclampsia was not made. Women with HELLP syndrome were also considered to have preeclampsia since HELLP syndrome was a more serious condition in the same spectrum of this disorder.

All demographic and laboratory data of subjects were obtained through a review of all available medical records for the period of 1 January - 31 December 2019 in Weda General Hospital, Central of Halmahera Regency, North Maluku. The maternal nutritional status of the subject was measured based on WHO BMI Classification-2020. The gestational age categories following ACOG-2017b. The NLR, MPV, and PLR levels were determined by manually counting from the CBC of blood laboratory levels of the subjects. The blood samples were taken at the time of admission before any medical treatment such as magnesium sulfate or induction/augmentation of labor. All blood samples were processed using the same automatic blood cell analyzer.

The inclusion criteria of cases group were diagnosis of preeclampsia, singleton fetus, no comorbidities or history of other comorbidities (diabetes mellitus, chronic hypertension, kidney disease, infection during pregnancy), did not have premature rupture of membranes, and did not have a history of malignancy. The inclusion criteria of control group were normal pregnancy, >37 wk of gestational age, singleton fetus, have no comorbidities or history of other comorbidities (diabetes mellitus, chronic hypertension, kidney disease, infection during pregnancy), have no premature rupture of membranes, have no history of malignancy. The exclusion criteria both for cases and control group were incomplete medical records, medical records of subjects who have been referred out of Weda General Hospital, Central of Halmahera Regency, North Maluku.

Statistical analysis

Data analysis were conducted by using the SPSS program. Kolmogorov-Smirnov normality test, bivariate analysis using independent t-test, Mann-Whitney, and Fischer exact with CI; 95% were used. The ROC-curve model gets tested to find the AUC (area under curve) value in predicting the parameters of the maternal preeclampsia sample was used.

RESULTS

A total of 62 subjects consisted of 31 patients with preeclampsia as case group and 31 normotensive pregnancies as control group were involved in this study. No significantly different in the characteristics of subjects ($p>0.05$) was observed between case group and control group (TABLE 1).

TABLE 1. Characteristics of the subject and Chi-square test

Variable	Preeclampsia [n (%)]	Normotensive [n (%)]	p
Gravida			
• Primi-gravid	11 (17.7)	9 (14.5)	0.587
• Multi-gravid	20 (32.3)	22 (35.5)	
Gestational age			
• Pre-term	4 (6.5)	0 (0)	
• Aterm	20 (32.3)	26 (41.9)	0.077
• Post-term	7 (11.3)	5 (8.1)	
Maternal nutritional status			
• Overweight	22 (35.5)	22 (35.5)	1.000
• Normal	9 (14.5)	9 (14.5)	

TABLE 1 describes the characteristics subject of the preeclampsia and normotensive pregnancy groups based on the level of gravida i.e. primigravida preeclampsia 11 (17.7%), multi-gravida preeclampsia 20 (32.3%), primigravida normotensive 9 (14.5%), and multi-gravida normotensive 22 (35.5%). Based on gestational age i.e. pre-term preeclampsia 4 (6.5%), aterm preeclampsia 20 (32.3%), post-term preeclampsia 7 (11.3%), pre-term normotensive 0 (0%), aterm normotensive 26 (41.9%), and post-term normotensive 5 (8.1%). Normal nutrition status for preeclampsia 9 (14.5%), overweight preeclampsia 22 (35.5%), normal nutrition in normotensive 9 (14.5%), and overweight normotensive pregnancy 22 (35.5%). The Chi-square test found that it was not significantly associated between the variables of gravida level, gestational age, and maternal nutritional status with the incidence of preeclampsia ($p>0.05$).

A significantly different in NLR and MPV values between patients with preeclampsia and normotensive pregnancy groups ($p<0.01$) was observed, whereas no significantly different in PLR ($p=0.245$) was observed (TABLE 2).

TABLE 2. The laboratory parameters values between the normotensive and preeclampsia groups.

Variable	Normotensive (mean ± SD)	Preeclampsia (mean ± SD)	p
Maternal age (yrs)	28.83 ± 5.568	30.677 ± 7.444	0.245
NLR	3.403 ± 0.975	5.911 ± 3.663	<0.001
MPV (fL)	6.887 ± 0.902	8.225 ± 0.935	<0.001
PLR	126.19 ± 46.09	138.73 ± 48.62	0.245

No significant difference in the NLR (p=0.792), PLR (p=0.780) and MPV (p=0.964) values between normal nutritional status and overweight were observed (TABLE 3). No significant difference in NLR (p=0.792), PLR (p=0.780) and MPV (p=0.169) values based on gestational groups were also observed (TABLE 4).

TABLE 3. The laboratory parameters value between normal nutritional status and overweight groups.

Variable	Normal (mean ± SD)	Overweight (mean ± SD)	p
NLR	4.801 ± 3.049	4.598 ± 2.933	0.792[a]
MPV (fL)	7.566 ± 1.142	7.552 ± 1.143	0.964[b]
PLR	129.29 ± 38.21	133.76 ± 51.04	0.780[a]

[a]: Mann-whitney; [b]: independent t-test

TABLE 4. The differences of mean laboratory parameters value between aterm and preterm / post-term groups.

Variable	Aterm (mean ± SD)	Preterm &/ post-term (mean ± SD)	p
NLR	4.63 ± 3.15	4.71 ± 2.33	0.792[a]
MPV (fL)	7.43 ± 1.10	7.89 ± 1.20	0.169[b]
PLR	131.14 ± 50.25	136.25 ± 39.31	0.780[a]

*a; Mann-Whitney, b; independent sample t-test

The area under ROC-curve model analysis of the NLR, MPV, and PLR was used to determine the predictive value of preeclampsia in pregnancy (FIGURE 1). The result showed that the AUC value of NLR, MPV and PLR were 0.758 (95%CI:0.637-0.878; p=0.000), 0.903 (95%CI:0.816-0.989; p=0.000) and 0.586 (95%CI: 0.441-0.731; p=0.245), respectively (TABLE 5). Further analysis showed that the optimal cut-off point for NLR was 4.0 with a sensitivity of 64.5% and a specificity of 71.0% (OR=3.8; 95% CI:1.33-10.94; p=0.011) and for MPV was 7.55 with a sensitivity of 87.1% and specificity of 80.0% (OR 28.1; 95% CI:7.09-111.47; p<0.001) (TABLE 6). These results indicate that the NLR-positive (>4.0) value and MPV-positive value (>7.6) are significantly associated with the preeclampsia incidence with the OR of 3.8 and 28.1, respectively.

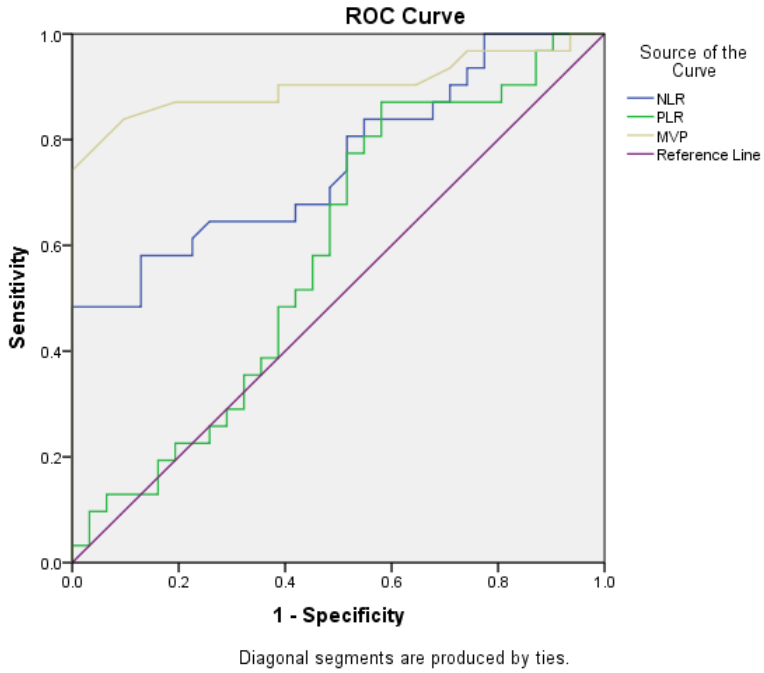

Figure 1. ROC-curve predictor preeclampsia.

TABLE 5. Area under curve (AUC) predictors for preeclampsia

Variable	Area	Standard Error	Sig	95% CI	
				Lower bound	Upper bound
NLR	0.758	0.061	0.000	0.637	0.878
MPV	0.903	0.044	0.000	0.816	0.989
PLR	0.586	0.074	0.245	0.441	0.731

TABLE 6. The result of the area under ROC-curve analysis, cut-off value, sensitivity, specificity and Chi-square test of NLR and MPV

Variable	AUC	p[a]	Cut-off value	Sensitivity (%)	Specificity (%)	p[b]
NLR	0.758	<0.001	4.00	64.5	71.0	0.011 [OR 3.8; 95% CI:1.33-10.94]
MPV	0.903	<0.001	7.55	87.1	80.0	<0.001 [OR 28.1; 95% CI:7.09-111.47]

*[a]; area under ROC-curve analysis, [b]; Chi-square

DISCUSSION

Preeclampsia occurs in 2-8% of pregnancies globally and causes disorder in several organ systems. However, the pathogenesis of preeclampsia is not clear yet.[10-12] The presence of activating factors from inflammatory cells (neutrophils, lymphocytes, platelets) that participate in the releasing of inflammatory cytokines and autoantibody reactions are associated with preeclampsia. Until now, termination of pregnancy is considered appropriate treatment.[11-14] It

makes predictive value and preventive measures essential to avoid maternal and fetal risks.[10,11] Changes in the value of hematological parameters, such as NLR, PLR, and MPV which are known as systemic inflammatory responses in preeclampsia have been studied. However, the results are still inconclusive.[12-16]

The NLR value is representing non-specific inflammatory mediators as the first-line defense and protective components of inflammation.[17,18] It has received more attention in providing predictive value in several diseases such as cancer and cardiovascular disease in recent years. Therefore, the NLR is considered as a provider of diagnostic and prognostic value in preeclampsia.[18-22]

Mannaerts *et al.*[10] reported that patients with preeclampsia have NLR value higher than normotensive pregnancies, although it is not significantly different. In contrast, some studies reported that the NLR value of patients with preeclampsia is significantly different compare with normotensive pregnancies.[18,21] Kang *et al.*[19] also reported that the NLR value is higher in patients with preeclampsia, especially in severe preeclampsia, compared to normotensive pregnancies. Therefore, NLR value might be a useful laboratory marker for clinical prediction and severity evaluation of preeclampsia.[19]

The cut-off value for NLR in predicting preeclampsia have been proposed by some authors. Singhal *et al.*[20] found that the NLR has a cutt-off value of ≥ 4.86 with a sensitivity of 68.6% and a specificity of 80.0% in predicting preeclampsia. Prasetyo *et al.*[22] found that the NLR is associated with preeclampsia with cut-off values between 3.5-5.6 in different sensitivity and specificity. In this study, it was found a cut-off value of 4.0 with a sensitivity of 64.5% and specificity of 71%.

In preeclampsia, neutrophil activation occurs while circulating in the intervillous space due to exposure with oxidized lipids secreted by the placenta.[11,13,14,18] Neutrophils from women with preeclampsia expressed more cyclooxygenase-2 than pregnancies without preeclampsia or in women who were not pregnant.[20,21] However, the mechanism behind this modulation of the immune system has not been elucidated. Another study showed that neutrophil activation occurs in the hypoxic placental circulation so that it infiltrates the systemic vascular tissue in women with preeclampsia which causes vascular inflammation.[11,20,21]

In a previous study, it was reported that all classes of leukocytes were activated in the maternal circulation of preeclampsia, but only neutrophil has significantly infiltrated the systemic vasculature. In the same study, it was found that the number of neutrophils in blood vessels was three times more than in lymphocytes. There are also research results that show an increase in the number of neutrophils up to 2.5 times at gestational age above 30 wk, and increases higher in patients with preeclampsia.[14,20,21]

A high MPV value indicates the number of young platelet cells in the circulation. The MPV value is an indicator of platelet activation, where platelet activity increases in pregnancy caused by the inflammatory process due to endothelial damage. The MPV in patients with preeclampsia was reported to be higher than in normotensive pregnancies.[10,11,16,18,23,25] The MPV was also reported increase as the severity of preeclampsia progressed.[25] The cut-off value for MPV in predicting preeclampsia have been also proposed by some authors. Mannaerts *et al.*[10] found that the MPV has a cutt-off value of 8.15 with a sensitivity of 66.7% and a specificity of 56.3% in predicting preeclampsia of pregnancies before 20 wk and 3rd trimester, whereas Yucel *et al.*[16] found a

cut-off value of 8.04 with a sensitivity of 74.39% and specificity of 33.33%.

Mean platelet volume is considered to reflect the inflammatory state. Its value is elevated in chronic inflammatory disease. In addition, a high MPV value is an independent risk factor for hypertension and a marker of poor prognosis for cardiovascular disease.[10,11,16,18] The high MPV in preeclampsia is caused by hypertension. The MPV increases or decreases depending on the severity of the inflammation. A higher MPV values in hypertensive patients with target organ damage compared to hypertension without target organ damage was observed. [16,21,23,24]

Platelet-lymphocyte ratio was obtained by dividing the number of platelets by the absolute lymphocyte value.[16] Several studies have been conducted to compare the PLR value between patients with preeclampsia and normal pregnancy with varied results. In this study, the PLR value in normotensive pregnancy was higher than patients with preeclampsia, although it was not significantly different (p=0.245). This result is similar with studies conducted by some authors.[11,21] In contrast, Yucel *et al.*[16] reported that the PLR value in patients with preeclampsia is significantly lower than in normal pregnancies. In addition, Kim *et al.*[21] also reported that the PLR values in patients with preeclampsia and severe preeclampsia are lower than in normal pregnancies. Whereas, Toptas *et al.*[26] reported that the PLR value in patients with severe preeclampsia is higher in the normal pregnancy and the patients with preeclampsia. Although, it was not significantly different.

The PLR value explains the correlation with platelet levels. It is associated with immune surveillance and major regulation of the cytokine-independent immune response. The interaction of endothelial cells and platelets in preeclampsia causes the release of inflammatory substances that induce leukocyte adhesion and migration. While platelet as a component of the PLR value decreased in preeclampsia due to the increased of clearance caused by the activation of the coagulation process that there is adhesion to the activated or damaged endothelium and the clearance of platelets through the reticuloendothelial system. In various diseases such as myocardial infarction, limb ischemia, kidney failure, and epithelial ovarian carcinoma, PLR value has correlation and prognostic values.[16,18,25,26] In this study, we have found that there was a slight difference in the mean PLR value, perhaps due to the small number of research samples.

Recent studies showed that systemic inflammatory response markers, such as NLR, PLR, and MPV have prognostic and predictive values in various benign and malignant diseases including coronary artery disease, inflammatory diseases, gynecologic or gastrointestinal malignancies, and preeclampsia. Mortality and morbidity in preeclampsia have significantly encouraged the examination which has a predictive value that could be conducted early in pregnancy to assess the development of preeclampsia, so the evaluation and preventive measures can be carried out.[9,10,16,26]

Cintesun *et al.*[9] reported that only the MPV has provided an higher predictive value for preeclampsia among the three hematological parameters i.e. NLR, MPV, and PLR. Mannaerts *et al.*[10] reported that MPV of pregnancies with preeclampsia before 20 wk and 3rd trimester is significantly higher than those normal pregnancies with optimal cut-off point of 8.15 (sensitivity 66.7% and specificity 56.3%) and 3.92 (sensitivity 84.4% and specificity 69.4%), respectively for predicting preeclampsia. Yucel *et al.*[16] also reported that MPV is significantly higher in patients with severe preeclampsia with cut-off point of 8.04 (sensitivity of 74.39% and specificity of 33.33%), whereas NLR

and PLR have no significantly value for predicting preeclampsia. A prospective case-control study in pregnancies more than 20 wk by Thalor *et al.*[23] concluded that MPV is reliable for predicting and early diagnosis of preeclampsia.

A meta-analysis conducted by Zeng *et al.*[18] reported that the diagnostic accuracy of NLR has unsatisfactory specificity but acceptable sensitivity for predicting preeclampsia. Whereas, another meta-analysis conducted by Kang *et al.*[19] concluded that NLR can be used as a laboratory marker for clinical prediction and severity of preeclampsia, with NLR values higher than in normal pregnancies. In addition, a systematic review conducted by Prasetyo *et al.*[22] concluded that there is a relationship between NLR and preeclampsia with a various cut-off point values between 3.5 – 5.6 in differences in sensitivity and specificity.

In this study, the AUC of NLR was 0.758 (95%CI:0.637-0.878; p=0.000) and the optimal cut-off point was 4.0 (sensitivity of 64.5% and specificity of 71.0%), whereas the AUC of MPV was 0.903 (95%CI: 0.816-0.989; p=0.000) and the optimal cut-off point was 7.55 (sensitivity of 87.1% and specificity of 80.0%). The AUC of PLR was 0.586 (95%CI: 0.441-0.731; p=0.245) (TABLE 5 and 6). The MPV had higher predictive value than NLR for predicting preeclampsia, meanwhile the PLR parameters were not significant in predicting preeclampsia.

CONCLUSION

In conclusion, the NLR and MPV are significantly higher in preeclampsia than in normotensive pregnancies. However, the PLR is not significantly difference in preeclampsia compared to that in normotensive pregnancies. In addition, the MPV has a better predictive value for preeclampsia than NLR. Further large-scale studies are required to validate the potential of MPV alone or in combination with NLR as predictor for preeclampsia.

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Effect of hormonal contraceptives on the ocular surface and the tear film

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ABSTRACT

Dry eye syndrome (DES) is a common multifactorial disease of the tears and ocular surface associated with sex hormones. Hormonal contraception is a risk factor for DES, but its relationship with DES exacerbations in women of childbearing age is still unclear. This study aimed to evaluate changes of the tear film and ocular surface of young women using the hormonal contraceptive agent. It was a case-control study involving 56 healthy women aged 20 to 45 y.o. Subjects was divided into two groups i.e. the hormonal contraceptives group and the control group without hormonal contraceptive. Subjects were interviewed with the ocular surface disease index (OSDI) questionnaire. Tear secretion and tear stability were measured using Schirmer's I test and fluorescein tear break-up time test (TBUT). Ocular surface impression cytology with cellulose acetate filter paper was taken from inferonasal bulbar conjunctiva and was stained with periodic acid- Schiff (PAS) and counterstained with hematoxylin and eosin (HE). No significantly decrease in tear secretion and tear stability in the hormonal contraceptives group compared with the control groups was observed ($p > 0.05$). However, a statistically significant decrease in goblet cell density and conjunctival epithelium metaplasia was observed, where 25% of the hormonal contraceptives group had an abnormal impression cytology result compared with the control group ($p<0.05$). The hormonal contraceptives group also had a higher OSDI score than the control group, although it was not statistically significant ($p> 0.05$). The hormonal contraceptives group had a significant effect on the ocular surface in which it induced squamous metaplasia and inflammation of conjunctival cells and the reduced number of goblet cells ($p<0.05$). The slightly decreased tear film volume and stability accompanied by an increase in OSDI score found in the hormonal contraceptives group support the possibility of hormonal contraceptive use as one of the risk factors in the occurrence of dry eye syndrome.

ABSTRAK

Sindrom mata kering (*dry eye syndrome*/DES) adalah penyakit multifaktorial umum dari air mata dan permukaan mata yang terkait dengan hormon seks. Kontrasepsi hormonal merupakan faktor risiko DES, tetapi hubungannya dengan kejadian eksaserbasi DES pada wanita usia subur belum jelas. Penelitian ini bertujuan mengkaji perubahan yang terjadi pada lapisan air mata dan permukaan mata pada remaja putri yang menggunakan kontrasepsi hormonal. Penelitian menggunakan kasus-kontrol yang melibatkan 56 wanita berusia 20 sampai 45 tahun. Subjek dibagi menjadi dua kelompok, kelompok kontrasepsi hormonal dan kelompok control tanpa kontrasepsi hormonal. Semua partisipan telah diwawancarai dengan kuesioner *ocular surface disease index* (OSDI). Sekresi air mata dan stabilitas air mata diukur menggunakan tes Schirmer I dan fluorescein *tear break-up time* (TBUT). Sitologi impresi permukaan okular dengan kertas saring selulosa asetat diambil dari konjungtiva bulbar inferonasal dan diwarnai dengan periodic acid-Schiff (PAS) dan hematoxylin dan eosin (HE). Terjadi penurunan sekresi air mata dan stabilitas air mata tidak signifikan pada kelompok kontrasepsi hormonal dibandingkan dengan kelompok kontrol ($p > 0,05$). Namun demikian, terdapat

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dry eye

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penurunan densitas sel goblet dan metaplasia epitel konjungtiva yang signifikan, yakni 25% kelompok kontrasepsi hormonal memiliki hasil sitologi impresi abnormal dibandingkan dengan kelompok kontrol (p<0,05). Kelompok kontrasepsi hormonal juga memiliki skor OSDI yang lebih tinggi dibandingkan kelompok control, meskipun tidak signifikan (p>0,05). Kontrasepsi hormonal memiliki efek yang signifikan pada permukaan okular yang menginduksi metaplasia skuamosa dan inflamasi sel konjungtiva dan penurunan jumlah sel goblet (p<0.05). Volume dan stabilitas lapisan air mata yang sedikit menurun disertai dengan peningkatan skor OSDI yang ditemukan pada pengguna kontrasepsi hormonal mendukung kemungkinan penggunaan kontrasepsi hormonal sebagai salah satu faktor risiko terjadinya sindrom mata kering.

INTRODUCTION

Dry eye syndrome (DES) is a common multifactorial disease of the tears and the ocular surface that can significantly diminish visual function and quality of life. Dry eye prevalence increases in both genders with age. However, the higher incidence among females after menopause suggested a role of sex hormones in its onset.[1,2] Sex hormones imbalance may be related to the onset and development of ocular surface disease and DES. The hormonal imbalance that influences tear physiology may be manifested with the use of hormonal contraceptives or menopause when significant changes from the normal hormonal state occur.[3-5]

Hormonal contraceptives are a known risk factor for DES. However, there is still an unclear association between hormonal contraceptive use and exacerbation of DES in women of childbearing age. Hormonal contraceptives are supposed to alter the androgen, estrogen, and progesterone serum level and exert a significant influence on the lacrimal gland, meibomian gland, and ocular surfaces. They may play an essential role in the pathogenesis of DES.[5,6] He *et al*.,[7] reported that women who use hormonal contraceptives regularly have two times risk to develop DES than women who irregularly use. However, other studies reported contradictory outcomes about hormonal contraceptive effects on the tear film. Several studies reported that hormonal contraceptives does not significantly affect tear physiology.[6,8-10] Another studies reported that women using oral contraceptives were more likely to experience DES than women not using it.[3,11,12] The effect of hormonal contraceptives on the ocular surface was still not apparent. Versura *et al*.[4] reported that the impairment of tear production and stability, ocular surface dryness, and inflammation are significantly related to hormonal fluctuations in the menstrual cycle, especially in patients with DES. It was also reported a significant decrease of goblet cell density in the follicular phase in women with and without dry eye but more pronounced in dry eye patients. Furthermore, it was suggested that the influence of estrogen in this finding since estrogen due to the dominant hormone in the follicular phase. These findings suggested that the hormonal imbalance due to other factors, such as hormonal contraceptives that could also affect the structural and functional changes in the cornea and conjunctiva cells. These structural and functional changes can be detected by impression cytology, which is a reliable and valuable tool for detecting structural and functional changes in ocular surface cells with a non-invasive and easy-to-perform procedure.[13,14] The inconclusive results from the previous study about hormonal contraceptives effects on the tear film need further study. The studies concerning the effect of hormonal contraceptives on the ocular surface, especially in goblet cells density and conjunctival cells metaplasia are limited. This study aimed to analyse the changes

of tear film regarding its secretion and stability, and the ocular surface, in terms of the goblet cells density and conjunctival cells metaplasia, in young women using hormonal contraceptive agents. This study will give new insight and information about the safety of hormonal contraceptive use on the ocular surface.

MATERIALS AND METHODS

Subjects

It was a case-control study done involving the outpatient clinic of the Andalas University Hospital, Padang, West Sumatra, Indonesia. The protocol of study was approved by the Research Ethic Committee, Faculty of Medicine, Andalas University with the reference number of ethical clearance: 594/KEP/FK/2019. Informed consent was obtained from each respondent before the study started. A total of 56 healthy women of childbearing ages, from age 20 until 45 y.o. were involved in this study. The sample size was calculated using the unpaired numerical, analytical study design formula. From the formula, the sample size for this study was 28 people for each group, i.e., the hormonal contraceptives group and the control group without the hormonal contraceptive.

Sample for the hormonal contraceptives group were women who regularly used hormonal contraceptives for at least one year, including combined oral contraceptives, injections, or subdermal implants. The participants were taken from the primary health facilities in the vicinity of the university hospital. Samples for the control group were women who had never used any hormonal contraceptive methods, and the participants were taken from the employee of the university hospital. The age inclusion criteria for both groups were from 20 until 45 y.o. Detailed history taken included personal data, the use of hormonal contraceptives and other forms of contraceptives, the type of hormonal contraceptive used, duration of use, visual complaint history, general health history, and systemic medication uses. A detailed ocular examination was done in the outpatient clinic to rule out any ocular surface and anterior segment abnormality.

Sample excluded in this study were women with ocular surface infection and inflammation, women with eyelid abnormalities (entropion, ectropion, and lagophthalmos), women with diabetes and autoimmune diseases, and current consuming oral â-blocker, antihistamines, and psychoactive drugs. Women with a history of ocular trauma or surgery, contact lenses wearers, pregnant women, women under topical eye drops, menopausal and post-menopausal women were also excluded.

Data collected include the severity of dry eye disease, measured by the ocular surface disease index (OSDI) questionnaire (OSDI; Allergan, Inc, Irvine, CA); the production of the tear film, measured by Schirmer's I test; the stability of tear film, measured by tear break-up time test; and goblet cell density and conjunctival cell morphology, measured by impression cytology procedure.

Data collection

Demographic information, history of using hormonal contraception, contact lens wear, ocular history, past medical and surgical history, current systemic and ophthalmic medications were obtained by patient self-report. In the first step, all participants were interviewed with the OSDI questionnaire (α: 0.92 (CI 95%: 0.89-0.94)).[15] The scores obtained were then calculated to determine dry eye disease severity as normal, mild, moderate, and severe. Then, all participants underwent a slit-lamp examination to rule out

eyelid and ocular surface abnormalities.

After slit-lamp examination, Schirmer's I test was performed to measure total tear secretion. Schirmer's strip (Whatman filter paper 41) was gently put at the junction of the middle and outer 2/3 of the lower lid, taking care not to touch the cornea or eyelashes. Participants were asked to close their eyes during the procedure. The strip was then removed 5 min after insertion. The wet portion of the strip measured in mm started from the bent strip.

The tear break-up time test (TBUT) was conducted after the Schirmer's I test was completed. The test used a fluorescein dye strip that gently swept over the conjunctival surface, and the participants were instructed to blink several times. Then, the participants were instructed to refrain from blinking, and fluorescein stained-tear film was observed on a slit lamp with cobalt blue light to notice the appearance of the dark spot or streak. The time elapsing between the eye-opening after the last blinking and the appearance of the first dark spot or streak was measured with a stopwatch. Three successive measurements were taken, and the mean value was calculated.

The final step was the conjunctival cells specimen collection for impression cytology, taken according to procedures described by Singh.[14] One drop of local anesthetic was instilled into the eye, and excessive tear fluid and medication were wiped away. Cellulose acetate filter paper was trimmed into a 5 mm strip with one square end and one tapering end. An eye speculum was inserted, and participants were asked to look up. The filter paper was applied to the conjunctiva on the inferonasal area. The filter paper was smoothed onto the ocular surface by applying gentle pressure with a glass rod. The paper was allowed to remain in contact with the ocular surface for approximately 5–10 sec and then peeled off with forceps. The filter paper was then fixed in a solution containing glacial acetic acid, formaldehyde, and ethyl alcohol in a 1:1:20 volume ratio for approximately 10 min. The specimen was then sent to the pathology laboratory for routine histological staining of impression cytology specimens with periodic acid Schiff with hematoxylin counterstain. The readings were then graded according to Scheffer and Tseng's classification.[16] Grade 2 or more is considered abnormal.

Statistical analysis

Differences in measurements between the two groups were assessed with t-tests for OSDI scores, Schirmer's I test, and TBUT results. Differences in impression cytology grades and dry eye grades based on the OSDI score were assessed with Fisher's exact test for categorical factors. A p value < 0.05 was considered as significant.

RESULTS

This study involved 56 females in the reproductive age group, divided into two groups; each group consisted of 28 females. The demographic profile is shown in TABLE 1, which demonstrates that the mean age for both groups is similar. However, the mean age of the control group is younger than the hormonal contraceptives group. Ethnicity in both groups was similar, with Minangkabau as the dominant ethnicity. Respondents in the control group had a higher level of education than the hormonal contraceptives group. Most respondents in the hormonal contraceptives group work as housewives, while most respondents in the control group work as employees. Only one person in the hormonal contraceptives group had a smoking history for 15 years, and she smokes one cigarette a day.

TABLE 1. Characteristics of respondents in both groups.

Characteristics	Group	
	Hormonal contraceptives	Control
Mean age (mean ± SD y.o.)	35.96 ± 6.563	31.57 ± 5.607
Ethnicity [n (%)]		
• Minangkabau	26 (92.85)	27 (96.43)
• Java	1 (3.575)	1 (3.57)
• Sunda	1 (3.575)	-
Education [n (%)]		
• Elementary school	1 (3.58)	-
• Junior high school	4 (14.28)	-
• Senior high school	23 (82.14)	3 (10.71)
• Diploma	-	15 (53.57)
• Bachelor	-	9 (32.14)
• Postgraduate	-	1 (3.58)
Employment [n (%)]		
• Employee	1 (3.57)	22 (78.57)
• Paramedic staff	-	6 (21.43)
• Housewife	21 (75.00)	-
• Microbusiness	6 (21.43)	-
Smoking history [n (%)]		
• Yes	1 (3.57)	
• No	27 (96.43)	28 (100)

TABLE 2 shows the type of hormonal contraceptives used. Injection hormonal contraceptive was the commonest hormonal contraceptive used. The injection used is three monthly hormonal contraceptives containing depot medroxyprogesterone acetate (DMPA), a progesterone hormone. Combined oral contraceptives were the second most commonly used hormonal contraceptive agent containing ethinylestradiol and levonorgestrel, a combination of estrogen and progestins. The subdermal implant was the less common method chosen for hormonal contraceptives, which contained levonorgestrel. Combined oral contraceptives had the most prolonged duration of use among other types of hormonal contraceptives.

TABLE 3 shows that 25% of the hormonal contraceptives group participants had an abnormal impression cytology result compared with none in the control group who had an abnormal result, which is statistically significant.

TABLE 2. The type of hormonal contraceptives used

Hormonal contraceptive agent	Frequency [n (%)]	Duration of use (mean ± SD years)
Combined oral contraceptives	7 (25)	9.14 ± 5.336
Injection	16 (57.1)	5.69 ± 4.922
Subdermal implant	5 (17.9)	2.40 ± 1.517

TABLE 3. Impression cytology grades between groups.

Impression cytology grade	Group		p
	Hormonal contraceptives [n (%)]	Control [n (%)]	
Grade 0	6 (21.4)	16 (57.1)	0.008
Grade 1	15 (53.6)	12 (42.9)	
Grade 2	4 (14.3)	0 (0.0)	
Grade 3	3 (10.7)	0 (0.0)	

TABLE 4 shows a slight decrease in the mean Schirmer value on the hormonal contraceptives group compared with the control group but not statistically significant. There is also a slight decrease in mean TBUT value in the hormonal contraceptives group compared with the control group but not statistically significant. TABLE 4 also shows that participants who used injection hormonal contraceptives had the lowest mean value of Schirmer test and TBUT compared to combined oral contraceptives and subdermal implant hormonal contraceptive users, but this was not statistically significant.

TABLE 4. Mean value of the Schirmer test and TBUT between groups.

Tear film parameters	Hormonal contraceptives	Control	p	Combined oral contraceptives	Injection	Subdermal implant	p
Schirmer	22.71 ± 13.34	24.18 ± 10.06	0.645	31.29 ± 6.99	19.19 ± 13.27	22.00 ± 17.00	0.133
TBUT	10.76 ± 4.98	12.35 ± 5.79	0.274	12.68 ± 4.93	8.99 ± 4.46	13.73 ± 5.09	0.084

TABLE 5 shows that the hormonal contraceptives group had a higher OSDI score than the control group, but this was not statistically significant. It also shows that more participants with moderate and severe dry eyes in the hormonal contraceptives group than in the control group, but this was not statistically significant.

TABLE 5. OSDI scores and DES severity, based on the OSDI score.

Variable	Group		p
	Hormonal contraceptives	Control	
OSDI score	24.34±23.672	17.25±17.66	0.210
DES severity [n (%)]			
• Normal	12 (42.9)	14 (50.0)	0.229
• Mild	7 (25.0)	11 (39.3)	
• Moderate	8 (28.6)	3 (10.7)	
• Severe	1 (3.6)	0 (0.0)	

DISCUSSION

Tear physiology is affected by hormones from the hypothalamic-pituitary-gonadal axis, mainly due to the influence of sex steroids (androgens, estrogens, and progestins) and pituitary hormones. Hormonal influences on tear physiology may be manifested with the use of hormonal contraceptives or during menopause when significant changes from the normal hormonal state occur.[6,17] All type of hormonal contraceptives inhibit proliferation of ovarian follicles, resulting in anovulation and a decrease in circulating estrogen. Decreased serum oestradiol could have adverse effects on estrogen-sensitive tissues, including the conjunctiva. The conjunctival proliferation is disturbed and more susceptible to the development of squamous metaplasia and inflammation and exhibits a reduced number of goblet cells.[2,4,17,18]

The impression cytology results in this study (TABLE 3), graded according to Scheffer and Tseng's classification,[16] showed that women who used hormonal contraceptives had more abnormal results, which were 14.3% on Grade 2 (marked loss of goblet cells without keratinization (FIGURE. 1. A)) and 10.7% on Grade 3 (Marked loss of goblet cells with early and mild keratinization (FIGURE. 1. B)). Furthermore, this result differs significantly from the women in the control group, who all had normal results (Grade 0 (FIGURE. 1. C) and Grade 1 (FIGURE. 1.D)). Murube and Rivas[19] found a significantly decreased goblet cell density with an increase in dry eye severity. Shrestha *et al.*,[20] found similar results that 49.2% of dry eye cases showed decreased or absent gob,let cell density compared with only 26.3% of normal eyes showing decreased or absent goblet cells ($p<0.001$). This study found a higher prevalence of moderate and severe dry eye in the hormonal contraceptives group (32.2%) compared with the control group (10.7%) (TABLE 5). This finding also corresponded with the higher prevalence of abnormal grade of impression cytology results and decreased goblet cells in 25% of participants in the hormonal contraceptives group (TABLE 3). The loss of goblet cells and mild keratinization of conjunctiva found in these participants may correlate with the slight decrease of tear film parameters in the hormonal contraceptives group compared with the control group.

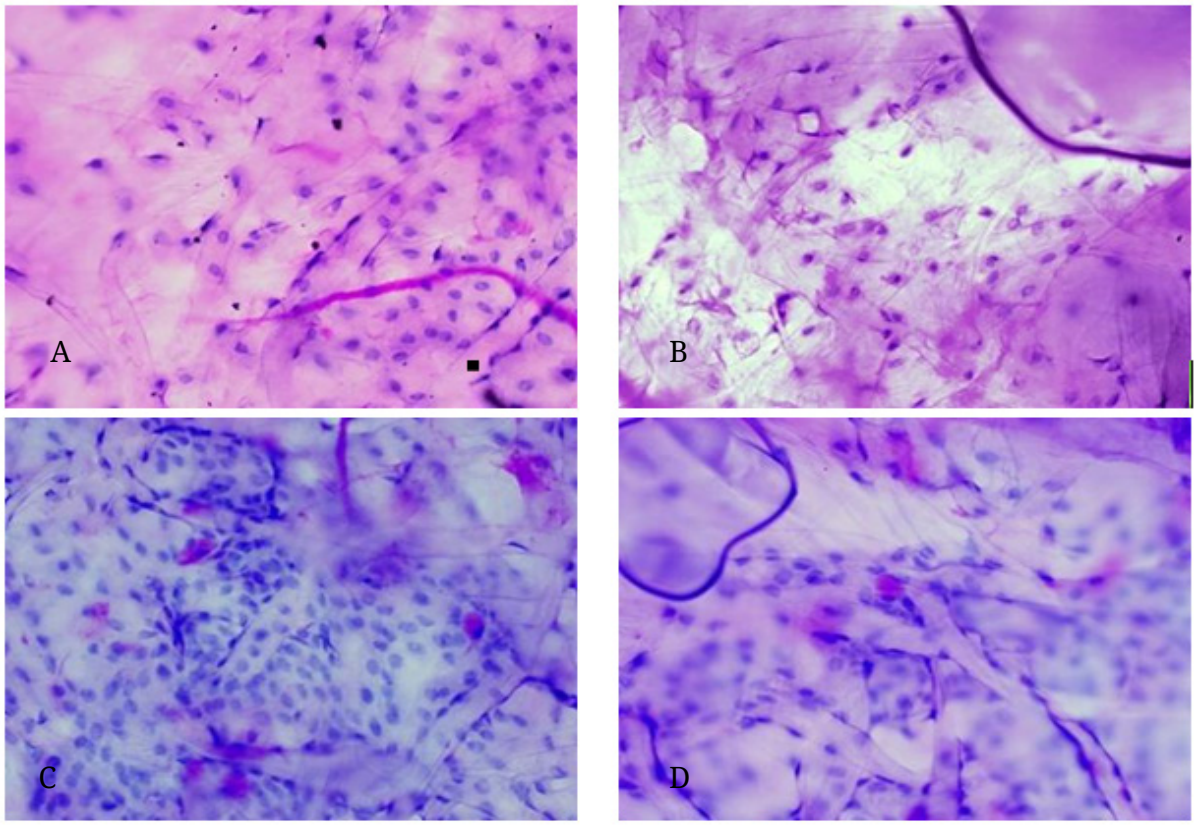

FIGURE 1. Conjunctiva impression cytology photomicrograph (magnification 40x, Scale bar, 10 µm). A. Grade 2 of impression cytology in the hormonal contraceptives group shows marked loss of goblet cells without keratinization. B. Grade 3 of impression cytology in the hormonal contraceptives group shows considerable loss of goblet cells with early and mild keratinization. C. Grade 0 of impression cytology in the control group shows normal conjunctival epithelium with a scattered moderate number of goblet cells. D. Grade 1 of impression cytology in the control group shows early loss of goblet cells without keratinization.

The results of this study (TABLE 4) also show a decrease in tear film production and stability in women who use hormonal contraceptives, based on the Schirmer test and TBUT, respectively, although statistically not significant (p=0.645 and p=0.274) compared with women who not use it. Another study by Tomlinson *et al.*,[6] who carried out a study on the effects of oral hormonal contraceptives on tear physiology, reported no significant difference in tear secretion and osmolarity between women on oral hormonal contraceptives and the control group. A similar result was also reported by Idu *et al.*,[10] which found no significant differences in tear secretion and tear stability between women on injectable hormonal contraceptives and women not using hormonal contraceptives. Sharma *et al.*,[3] reported different results that they found a significant decrease in tear secretion in women using oral hormonal contraceptives (13±3 mm) than in the control group (31±7 mm/5min) with p=0.00. Nevertheless, they do not find any significant difference in TBUT value between the two groups. Women in the hormonal contraceptives group, who used injection hormonal contraceptives had the lowest tears secretion and tears stability than women who used combined oral

contraceptives or subdermal implant hormonal contraceptives, but this was not statistically significant (TABLE 4). Women using combined oral contraceptives had better tear film parameters than women using other hormonal contraceptives, although theirs had the most prolonged duration of use. Other studies found that oral contraceptives did not affect Schirmer I test, tear break-up time (TBUT) test, and tear osmolarity value.[8,9,21] So, despite a decrease in serum androgen level, this does not correlate linearly with tear film parameters. We assumed that the serum level decrease was not too significant, so it did not cause an alteration in androgen bioactivity, which causes the androgen hormone to be unaffected in the lacrimal and meibomian glands.[22,23] This normal androgen bioactivity is seen in normal values of tears secretion and stability in women who used combined oral contraceptives, three monthly injections, and subdermal implant hormonal contraceptives. A study by Sharma *et al.*,[3] also found that the serum androgen level (testosterone and DHEA) was slightly decreased by 12% in the hormonal contraceptives group compared with the control, but the tear film parameters are still within normal limits. However, this study does not measure the androgen serum level of all participants, so the relationship between the type of hormonal contraceptives and androgen bioactivity on the lacrimal and meibomian gland is not yet confirmed. The mean OSDI score of both hormonal contraceptives and the control group belongs to the mild grade of dry eye severity. However, the mean OSDI score and dry eye severity are higher in the hormonal contraceptives group (TABLE 5), even not statistically significant. The OSDI is a validated questionnaire that only measures the frequency of dry eye symptoms, but its correlation with clinical signs and tear film parameters is still weak.[24-27] Garhöfer *et al.*,[28] and Song *et al.*,[29] found weak negative correlation between OSDI score and tear film parameters such as Schirmer and TBUT tests. The higher OSDI score in the hormonal contraceptives group corresponds to its Schirmer and TBUT tests value reduction. However, Chen *et al.*,[9] found that neither oral contraceptives use nor estrogen dose of oral contraceptives appeared to have a meaningful effect on tear osmolarity and dry eye symptoms measured by OSDI. Concerning the significant result of the abnormal grade of impression cytology in women using hormonal contraceptives in this study, accompanied by decreased tear film parameters and increased OSDI score, hormonal contraceptives could negatively impact tear film physiology and promote the occurrence of DES.

A small sample size is considered a limitation in this study, as a larger sample size could give more significant results. The lack of measurement of androgen and estrogen serum levels is another limitation because we can not do linear regression analysis between tear film parameters and androgen and estrogen serum levels to find its correlation. Further study with a large sample size, long-term follow-up, and hormonal serum level measurement should be done to establish hormonal contraceptives' impact on the tear film and ocular surface epithelium cells.

CONCLUSION

Hormonal contraceptives had a significant effect on the ocular surface in which they induced squamous metaplasia and inflammation of conjunctival cells and reduced the number of goblet cells. The slightly decreased tear film volume and stability accompanied by increased OSDI score found in hormonal contraceptives users support the possibility of contraceptive use as one of the risk factors in the occurrence of DES.

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Evaluation of clinical pathway implementation and clinical practice guidelines in the management of deep neck abscess (DNA) at Dr. Sardjito, General Hospital Yogyakarta, Indonesia

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ABSTRACT

Deep neck abscess (DNA) is an infectious condition categorized as an emergency case with high mortality and morbidity. The incidence decreases over time due to extensive use of antibiotics, operative intervention, and improved awareness of dental hygiene. Management of DNA must be carried out appropriately and efficiently to prevent complications that may occur, such as jugular vein thrombosis, pericarditis, and pneumonia. Patients with DNA are often categorized as high-cost patients, because of the long duration of hospitalization, the need for special examinations, and complicated management. Clinical practice guidelines (CPG) and clinical pathways (CP) are a standard created for management, quality, and cost control. The study aimed to evaluate the implementation of the CPG and CP in DNA patients at Dr. Sardjito General Hospital, Yogyakarta. The study used medical records data of DNA patients from January 2018 to December 2020 who met the inclusion and exclusion criteria. A total of 55 subjects were obtained, with compliance to complete CPG filling of 98.3% and CP filling of 96.2%. There was 100% completion in CPG filling categorized as good compliance, whilst the number of good compliances for CP was 92.7%. In conclusion, the diagnosis and management of DNA patients at Dr. Sardjito General Hospital has good compliance with CPG and CP available.

ABSTRAK

Abses leher dalam (ALD) merupakan salah satu kondisi infeksi yang dikategorikan dalam kasus emergensi yang bisa menimbulkan kecacatan hingga kematian pasien. Angka kejadian ALD dari waktu ke waktu menurun karena penggunaan antibiotik, intervensi operatif, dan meningkatnya kesadaran masyarakat akan kesehatan gigi. Penanganan ALD harus dilakukan secara tepat dan efisien untuk mencegah komplikasi yang mungkin terjadi dan berujung kematian seperti trombosis vena jugular, perikarditis, dan pneumonia. Pasien ALD sering dikelompokkan dalam pasien dengan biaya perawatan tinggi karena perawatannya yang lama di rumah sakit, memerlukan pemeriksaan khusus dan tata laksana yang rumit. *Clinical practice guidelines* (CPG) dan *clinical pathways* (CP) merupakan standar pelayanan yang dibuat untuk mengendalikan tata laksana, kualitas pelayanan dan biaya pengobatan. Penelitian ini bertujuan untuk mengevaluasi penerapan CPG dan CP pada tatakelola pasien ALD di RSUP Dr. Sardjito Yogyakarta. Penelitian menggunakan data rekam medis pasien dengan diagnosis ALB yang memenuhi kriteria inklusi dan eksklusi periode Januari 2018 hingga Desember 2020. Total 55 subyek penelitian diperoleh dengan kepatuhan dalam pengisian CPG secara lengkap sebanyak 98,3% dan pengisian CP sebanyak 96,2%. Terdapat 100% kelengkapan pengisian CPG dikategorikan dalam kepatuhan baik, sedangkan untuk CP sebanyak 92,7% dikategorikan baik. Sebagai kesimpulan, diagnosis dan tata laksana pasien ALD di RSUP Dr. Sardjito menunjukkan kepatuhan yang baik terhadap CPG dan CP yang tersedia.

Keywords:
deep neck abscess;
clinical practice guideline;
clinical pathway;
laryngology;
compliance

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INTRODUCTION

Standard of medical care is a guideline that must be followed by doctors or dentists in implementing the medical practice. There are many kinds of standard of medical care, one of them is standard operating procedure (SOP). Clinical practice guideline (CPG) and clinical pathway (CP) are part of lines in the SOP. It is a standard of medical care that must cover at least the definition, history taking, physical examination, diagnostic criteria, differential diagnosis, supporting examination, therapy, education, prognosis, and literature. The CPG and CP were determined by the health facility management. The arrangement of CPG is based on the most frequent or higher risk or high-cost disease or having wide variations in its management, whereas CP is a multidisciplinary integrated service planning concept that leads health care workers in giving medical services to patients.[1]

Every step of CP provided to patients is based on the standard of medical care and it is implemented while they are hospitalized. The goal of the CP are improving patient outcomes, encouraging patient safety, escalating patient satisfaction, and optimizing the utilization of resources. The principle of organizing CP must be focusing on patient care and continuing care, multidisciplinary service, recording the disease course in daily or in hourly form, a part of a medical record, aberration tread called as a variant, and variant happened because of disease course/ comorbidity/ complication/ medical error.[2-4]

Deep neck abscess (DNA) is one of the most dangerous infectious diseases that is categorized as an emergency case in the Otolaryngology Head and Neck Department. It can be a greater cause of disability and death in patients.[5,6] Literally, DNA can be defined as a collection of pus in the potential space between the deep cervical fascias induced by the spread of infection to the teeth, mouth, throat, paranasal sinuses, ears, neck, and other surrounding structures. Apart from being an abscess, infection in these organs can also manifest in the form of cellulitis or necrotizing fasciitis.[7-9] The incidence of this disease declines gradually over time due to the development of effective use of antibiotics, faster decision-making in intervention, and increasing public awareness to maintain dental hygiene, which is the most common etiology of DNA in adults. To prevent complications such as jugular vein thrombosis, pericarditis, and pneumonia the management of DNA must be performed appropriately and efficiently.[6,10]

The morbidity and mortality rate of DNA is arising. Saboo *et al.*,[11] reported that the mortality rate among 101 DNA patients is 0.99% due to cervical necrotizing fasciitis proceeded to myocardial infarct. The morbidity rate was approximately 9.9% with the presence of neck contracture, restricted mouth opening, and reoccurred DNA.[11] Furthermore Pineda-Alvarado *et al.*,[12] reported that there is an 8.33% mortality rate among 36 total patients and 13.88% of them were admitted to the intensive care unit. On the other hand, the costs of DNA management were particularly scarce. Hurley *et al.*,[13] reported that the incurred costs of DNA patients are £421,795.89 for 74 patients and the total cost per patient is £5,699.94 with a range of £332.06 to £46,700.24. This high burden cost was associated with the management of DNA patients because of the solemn nature of the condition.

The cost-effectiveness in the management of DNA for one night in Canadian Healthcare System was $4629.57.[14] It included hospital admission, surgical intervention, and postoperative ICU admission. In 2020 in Dr. Sardjito General Hospital, the average

burden costs for 6.8 days of inpatients were IDR20,077,172.00. These all studies could be concluded that the case of DNA is classified as high-risk and high-cost disease.

As a national center hospital, Dr. Sardjito General Hospital, Yogyakarta had become a referral destination from other hospitals. The CPG and CP for DNA management in Dr. Sardjito General Hospital, Yogyakarta was made by the Department of Otolaryngology Head and Neck Surgery and it had been approved by a board of management afterward. The DNA is a serious condition that needs hospitalization in management. The diagnosis and treatment of DNA patients require a lot of time and resources. Many supporting examinations were needed, as well as complicated and meticulous management. The complexity of the disease contributed to the high mortality and morbidity rate as well as the high cost of treatment. Therefore, it is necessary to control the quality and cost of DNA management based on evaluating CPG and CP. The study aimed to evaluate the compliance of the management of DNA to CPG and CP in the Dr. Sardjito General Hospital, Yogyakarta.

MATERIALS AND METHODS

Subjects

It was a descriptive study using data from the medical records of patients with DNA at Dr. Sardjito General Hospital, Yogyakarta in the period from January 2018 to December 2020 who met the inclusion and exclusion criteria. The research protocol was approved by the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta (ref. no. KE/FK/0236/EC/2021). The inclusion criteria of this study were all DNA patients treated at the Department of Otolaryngology Head and Neck Surgery, Dr. Sardjito General Hospital, Yogyakarta. The exclusion criteria in this study were DNA patients who does not follow treatment to completion.

Procedure

The points that we measured in CPG were history taking (localized pain, globus pharyngeus, halitosis, trismus, fever, fatigue, toothache, history of toothache or hypertrophy tonsils), clinical findings (swelling in the head / neck / submandibular / submental, skin hyperemic, tenderness), supporting examination (bacterial culture, multislice computed tomography, orthopantomography, laboratory examination), diagnosis and differential diagnosis, management (pharmacotherapy and surgery), education, prognosis, clinical indicator after surgery, and condition for being outpatient.

There were sixteen points measured in CP such as initial assessment, laboratory examination, imaging, consultation, further assessment, diagnosis and differential diagnosis, discharge planning, education, pharmacotherapy management, intervention, monitoring and evaluating, rehabilitation, outcome, criteria for being outpatient, and patient/family education. It must be fulfilled and done by health workers including doctors, nurses, pharmacists, and nutritionists.

Data analysis

Data from the medical records were collected, tabulated as frequency and then descriptively analyzed.

RESULTS

A total of 55 subjects who fulfilled inclusion and exclusion criteria were

involved in this study. The average compliance with the CPG and CP were 98.3% and 96.2%, respectively. From total 55 samples in CPG's, all considered having good compliance (100%), while on CP compliance, 51 samples (92.7 %) were categorized as good compliance, and 4 samples (7.84 %) were categorized as moderate compliance (TABLE 1).

TABLE 1. Compliance with CPG and CP

Compliance	CPG (n=55)	CP (n=55)
Compliance with CPG/CP (%)	98.3	96.2
Compliance category (%)		
• Good compliance (>85)	55	51
• Moderate compliance (51-84)	0	4
• Low compliance (10-50)	0	0

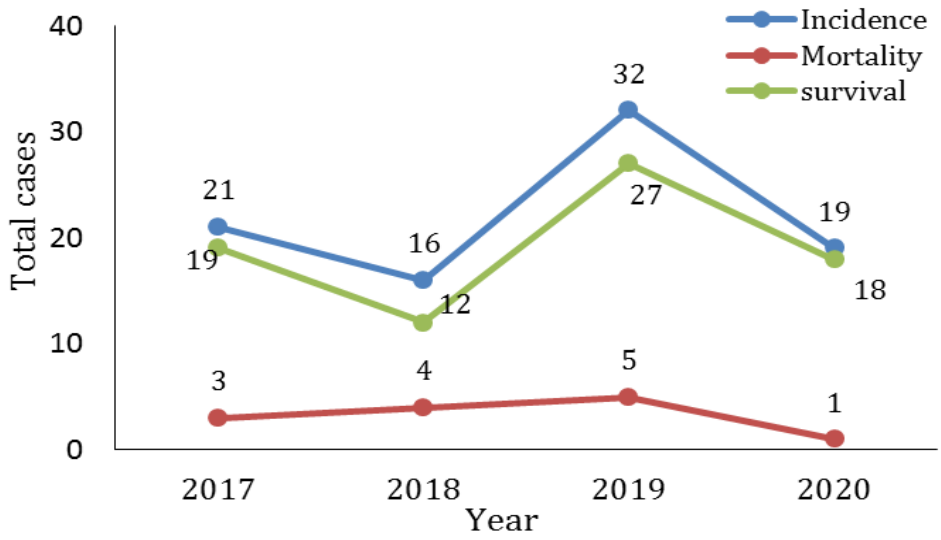

FIGURE 1. Incidence, mortality, and survival rate of DNA from 2017 to 2020

Incidence, mortality, and survival of DNA patients at Dr. Sardjito General Hospital, Yogyakarta treated at the Department of Otolaryngology Head and Neck Surgery from 2017 to 2020 was presented in FIGURE 1. In 2017, there were 21 new cases with a death rate of 3 subjects with a mortality percentage of 14.3%. In 2018, there was a decrease in the number of cases to 16 cases, with 4 death cases (25% mortality rate). In 2019, there was a rise in cases to 32 cases and 5 cases of death with a mortality percentage of 15%. In 2020, there were 19 new patients, and a mortality rate was one patient with a mortality percentage of 5%. Since DNA cases were not abundant, and often vary in severity and seasons, the lower the number of cases and the more severe the cases, the higher the mortality rate.

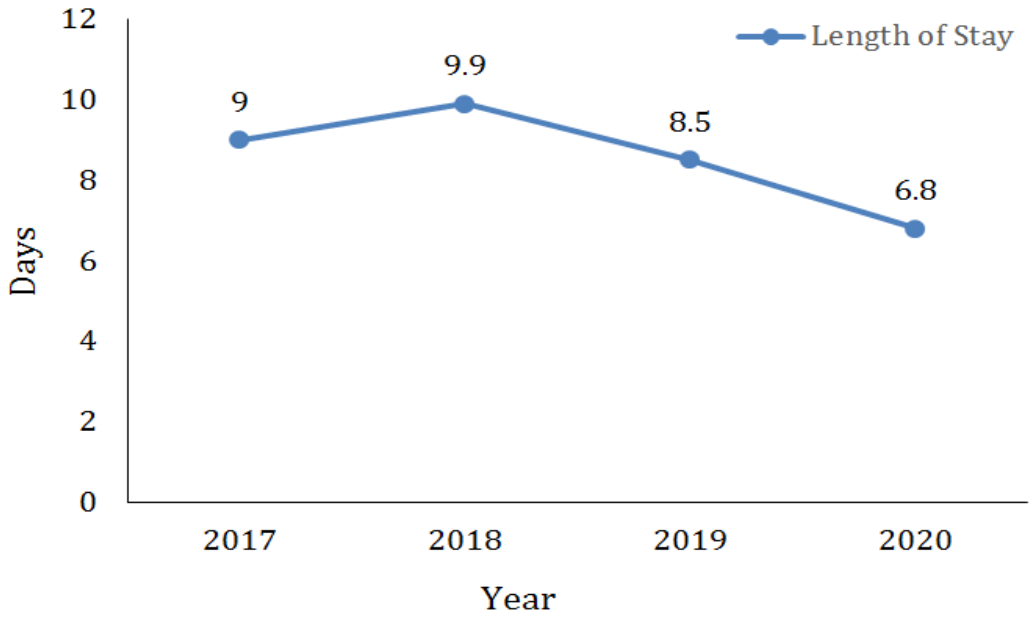

FIGURE 2. Average length of stay (LoS) patients with DNA from 2017 to 2020deep

FIGURE 2 illustrates the LoS of DNA patients each year from 2017 to 2020. In 2017, the average LoS for DNA patients was 9 days, in 2018 it was 9.1 days. In 2019, LoS of DNA patients are 8.5 days and in 2020 they are 6.8 days. This showed that the LoS had decreased in the last 4 years, which indicates the improvement of DNA management.

DISCUSSION

The compliance with the CPG and CP were 98.3% and 96.2%, respectively (TABLE 1). Based on the All-Wales Fundamentals of Care Audit, compliance with standard care is categorized into 3 categories, there were low compliance (10-50%), moderate compliance (51-84%), and good compliance (>85%).[15] In this study, the compliance to both CPG and CP in the management of DNA was considered good compliance in 55 (100%) and 51 (92.7%) from each of the total samples. In the CP group, 4 samples were included in the moderate compliance category (TABLE 1). It can be concluded that the service to patients based on CP and CPG in Dr. Sardjito General Hospital, Yogyakarta has shown good average compliance.[15] It showed that the implementation of services for DNA patients from diagnosis to treatment has been suitable with CP and CPG guidelines.

The investigation of the compliance with the CPG and CP in the management of DNA patients in medical services and practices in Indonesia is limited. Therefore, the data exhibiting the standard service for DNA patients is limited. Several studies to evaluate the compliance with CPG dan CP in the management of different diseases were reported. Mahmudin *et al.*[16] reported that the high compliance of CP in the management mastectomy is 39.5%, whereas the low compliance is 60.5%. Sari and Sundari[17] reported that the compliance with the CP in the management of hypertension is 28.57%. In other study, He *et al.*[18] reported the compliance with CP for five common diseases i.e. community-acquired pneumonia, acute myocardial infarction (AMI), heart failure, cesarean section, and type-2 diabetes at inpatients care in general hospital in China ranges from 61 to 89%.

In this study, the compliance with the CP in management of DNA patients were found 92.7% and considered

as a good category. It means that the diagnosis and management of DNA patients at the Dr. Sardjito General Hospital, Yogyakarta has been already in good compliance. Implementation of the CP for DNA patients at the Department of Otolaryngology Head and Neck Surgery, Dr. Sardjito General Hospital has begun since the end of 2018. This implementation could aid health workers to serve patients with applicable regulations or standards. Therefore, it is used to improve service quality and prevent unnecessary variations in treatment.[19]

The implementation of CP in DNA patients may contribute in the decrease of the mortality rate and the improvement of LoS. The mortality rate of DNA patients at Dr. Sardjito General Hospital, Yogyakarta shows a decrease in the last three years, with the percentage of death from 25% in 2018 to 15% of cases in 2019 and continuing to decline to 5% of cases in 2020 (FIGURE 1). Furthermore, the LoS decreased from 9.9 days in 2018 to 8.5 days in 2019, and continued to decline to 6.6 days in 2020. The decreases in mortality and LoS rates is in line to compliance with CP and CPG of DNA patients, which have good scores with 98.3% in CPG and 96.2% in CP.

CONCLUSION

The diagnosis and management of DNA patients at Dr. Sardjito General Hospital have good compliance with the CPG and CP. The decrease of mortality rate and LoS of the DNA patients are associated with the good compliance with CPG and CP.

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Exercise-based cardiac rehabilitation adaptation protocol during Covid-19 pandemic achieved similar results as compared to non-pandemic usual practice: a single center experience

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ABSTRACT

During the Covid-19 pandemic, exercise-based cardiac rehabilitation (EBCR) faced challenges. Adaptation protocols were implemented to circumvent these challenges. The study aimed to investigate whether the adaptation protocols of EBCR during Covid-19 period influenced the result of cardiac rehabilitation. This was a retrospective cohort study. The subjects were patients who underwent an EBCR program in Dr. Sardjito General Hospital. Yogyakarta, Indonesia. The registry of cardiac rehabilitation was obtained and divided into two periods: non-Covid-19 period and Covid-19 period. During the non-Covid-19 period, 3 EBCR sessions per wk (10-12 total sessions) were performed. During the Covid-19 period, EBCR was reduced to 2 sessions per wk (10-12 total sessions). The functional capacities were evaluated as metabolic equivalents (METs) and exercise test time (min) by treadmill test. A total of 122 subjects completed the EBCR. There were no significant differences in METs and exercise minute-achieved between two time periods. Among subjects with different sessions per wk, namely 2, 3, and 4-5 sessions per wk, there were no significant differences in METs (7.01±1.89; 7.23±1.74; and 7.33±2.13, p=0.813) and minutes achieved (6.72±1.94; 6.96±1.96; and 6.81±1.84, p=0.848) in the end sessions. In conclusion, the adaptation of EBCR protocols during the Covid-19 period by reducing the number of sessions per wk has similar results as compared to the usual regular EBCR practice.

ABSTRAK

Selama pandemi Covid-19, rehabilitasi jantung berbasis latihan (*exercise-based cardiac rehabilitation*/EBCR) menghadapi tantangan. Protokol adaptasi diterapkan untuk menghindari tantangan ini. Penelitian ini bertujuan untuk mengetahui apakah protokol adaptasi EBCR selama periode Covid-19 mempengaruhi hasil rehabilitasi jantung. Ini adalah penelitian kohort retrospektif. Subjek adalah pasien yang menjalani program EBCR di RSUP Dr. Sardjito, Yogyakarta, Indonesia. Registrasi rehabilitasi jantung diperoleh dan dibagi menjadi dua periode yaitu periode non-Covid-19 dan periode Covid-19. Selama periode non-Covid-19, 3 sesi EBCR per minggu (total 10-12 sesi) dilakukan. Selama periode Covid-19, EBCR dikurangi menjadi 2 sesi per minggu (total 10-12 sesi). Kapasitas fungsional dievaluasi sebagai ekuivalen metabolik (MET) dan waktu uji latihan (menit) dengan uji *treadmill*. Sebanyak 122 subjek menyelesaikan EBCR. Tidak ada perbedaan signifikan dalam MET dan menit latihan yang dicapai antara dua periode waktu. Di antara subjek dengan sesi yang berbeda per minggu, yaitu 2, 3, dan 4-5 sesi per minggu, tidak ada perbedaan yang signifikan dalam MET (7,01±1,89; 7,23±1,74; dan 7,33±2,13; p=0,813) dan menit yang dicapai (6,72 ±1,94; 6,96±1,96; dan 6,81±1,84; p=0,848) di sesi akhir. Dapat disimpulkan bahwa adaptasi protokol EBCR selama periode Covid-19 dengan mengurangi jumlah sesi per minggu memiliki hasil yang sama dibandingkan dengan praktik EBCR reguler biasa.

Keywords:
cardiac rehabilitation;
exercise therapy;
Covid-19;
metabolic equivalent;
retrospective study

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INTRODUCTION

The movement restriction and physical distancing recommendations by government regulations during the Covid-19 pandemic are the exercise-based cardiac rehabilitation (EBCR) program in many countries. Cardiac rehabilitation facilities were not allowed to open or schedule many patients during exercise sessions. Patients could not freely attend these exercise sessions in the hospital. As a result, most countries suspended hospital- or center-based EBCR services and replaced them with virtual cardiac rehabilitation (VCR) or telerehabilitation.[1,2] However, the VCR and telerehabilitation are not feasible in several countries, especially in developing countries including Indonesia.

The hospital-based EBCR program in Indonesia is supported by national insurance, whereas the VCR and telerehabilitation are not, even during the Covid-19 pandemic. Therefore, the hospital or cardiac rehabilitation centers which rely on national insurance payment prefer performing hospital-based EBCR programs.[3] In most hospitals in Indonesia, the ECBR participation was reduced during the Covid-19 pandemic due to movement restriction, reduced cardiac surgery, hospital regulations to close or downsize EBCR programs, and the reluctance of patients and caregivers to come to the hospital during the pandemic.[4,5]

The cardiac rehabilitation service did not stop operating in Dr. Sarjito General Hospital, Yogyakarta which is a tertiary center for cardiovascular disease referral in the region but adapted with the pandemic condition. Dr. Sardjito General Hospital implemented an adaptive strategy to perform and sustain the participation of EBCR by reducing the number of EBCR sessions performed per wk and maintaining more than 70% of the total number of sessions completed. While VCR and telerehabilitation had not yet been implemented, these adaptation protocols in our hospital were well-received by patients who underwent EBCR and the nursing staffs who supervised the EBCR. However, the results of these EBCR adaptation protocols have not yet been compared with the results of the usual protocols given previously.

This study aimed to investigate whether the adaptation protocols of EBCR during Covid-19 period influenced the result of cardiac rehabilitation by comparing the functional capacity achieved at the end of the EBCR program among patients who underwent different EBCR sessions per wk. This study intends to provide some recommendations to perform the EBCR during the Covid-19 pandemic by adapting the EBCR protocols.

MATERIALS AND METHODS

Subjects

This study was a retrospective cohort study. The subjects were recruited from the patient's register who underwent EBCR in Integrated hearth center Dr. Sardjito General Hospital, Yogyakarta, Indonesia. The time of subjects' recruitment was divided into two periods i.e., the non-Covid-19 period (January 2019 – February 2020) and during the Covid-19 period (March 2020 – March 2021).

Procedure

Subjects admitted, performed, and evaluated in our cardiac rehabilitation center were included in this study. Demography data, pre-rehabilitation diagnosis, total number of sessions, and the evaluation results were collected. The subjects who did not completely perform the EBCR until evaluation, i.e., less than 8 out of a total number of sessions (70%

from 12 sessions), were excluded. The study protocol was approved by the Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Indonesia/Dr. Sardjito General Hospital, Yogyakarta.

The EBCR consisted of a hospital-based and supervised exercise program. Each exercise session consisted of a warming-up period (cycle ergometer for 5 min), main exercise (walking on the treadmill for 30 min with an optimal heart rate target), and cooling-down period (stretching for 10 min). Supervised by cardiac rehabilitation registered nurses, a total of 45-min of exercise each session was performed. During the non-Covid-19 pandemic period, 10-12 total sessions were performed, generally with 3 sessions per wk (every-other-day). Several patients performed 4-5 sessions per wk. During the Covid-19 pandemic, the sessions per wk were reduced to 2 sessions with 10-12 total sessions. The evaluation after the end of session was performed with graded treadmill test according to the Bruce or modified Bruce protocol. The functional capacities were calculated as predicted metabolic equivalents (METs) based on the treadmill test results, by standardized nomogram and as exercise test time, by minutes achieved during treadmill. The same registered nurses supervised the EBCR in both periods.

Statistical analysis

The comparison between two groups was conducted by Chi-square test for categorical data, or Fisher exact test where applicable, and by student t-test for continuous data, or Mann-Whitney test where applicable. The comparison among three groups were analyzed using a Chi-square test for categorical data and one-way Anova for continuous data.

RESULTS

The total subjects admitted for EBCR were 156 patients with 96 patients who performed EBCR in the non-Covid-19 period (January 2019-February 2020) and 60 patients in the Covid-19 period (March 2020-March 2021). Among them, 122 subjects completed more than 70% of the EBCR session (77 subjects of the non-Covid-19 period and 45 subjects of the Covid-19 period). The reduction of patients referred to the cardiac rehabilitation program during the Covid-19 period occurred due to the reduction of cardiac surgery to almost 50%.

There were no significant differences in sex, pre-rehabilitation diagnosis, the total number of sessions, evaluation protocol, and METs and minutes achieved in the evaluation between subjects performing EBCR in the non-Covid-19 and the Covid-19 periods (TABLE 1). However, there was a significant difference in the number of sessions per wk. Subjects in the Covid-19 period predominantly underwent 2 EBCR sessions per wk [n=22 (48.9%) vs. n=3 (3.9%), p<0.001], whereas in the non-Covid-19 period, EBCR was done predominantly in 3 sessions per-wk (every-other-day), [n=8 (17.8%) vs. n=59 (76.6%), p<0.001]. The most common protocol used for evaluation at the end of the sessions was the Bruce protocol in both periods. There was no significant difference in METs [median (interquartile range (IQR) : 7.37 (6.11-8.35) vs. 6.90 (5.40-8.10), p=0.075] and exercise minutes- achieved between two time periods respectively [median (IQR): 7.02 (6.10-8.14) vs. 6.36 (5.28-7.77), p=0.112].

TABLE 1. The comparison of parameters between subjects performing EBCR during the non Covid-19 period and Covid-19 period

Parameters	Non Covid-19 period (n=77)	Covid-19 period (n=45)	p
Sex [n (%)]			
• Male	30 (39.0)	11 (24.4)	0.101
• Female	47 (61.0)	34 (75.6)	
Age [mean±SD year]	40.6±12.3	37.4±12.4	0.174
Diagnosis [n (%)]			
• Post ASD/VSD closure	32 (41.6)	28 (60.9)	
• Post CABG	1 (1.3)	0	
• Post PCI	1 (1.3)	0	
• Post MVR	30 (39.0)	14 (31.1)	0.347
• Post AVR	6 (7.8)	1 (2.2)	
• Post DVR	5 (6.5)	1 (2.2)	
• Post myxoma surgery	2 (2.6)	1 (2.2)	
Total number of session [n (%)]			
• 8-9	15 (19.5)	6 (13.3)	0.385
• 10-12	62 (80.5)	39 (86.7)	
Session per wk [n (%)]			
• 2	3 (3.9)	22 (48.9)	
• 3	59 (76.6)	8 (17.8)	<0.001
• 4-5	15 (19.5)	15 (33.3)	
Treadmill protocol [n (%)]			
• Bruce	72 (93.5)	44 (97.8)	0.292
• Modified Bruce	5 (6.5)	1 (2.2)	
METs achieved [med (IQR)]	7.37 (6.11-8.35)	6.90 (5.40-8.10)	0.075*
Minute achieved [med (IQR)]	7.02 (6.10-8.14)	6.36 (5.28-7.77)	0.112*

*Mann Whitney test; SD: standard deviation; ASD: atrial septal defect; VSD: ventricle septal defect; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; MVR: mitral valve replacement; AVR: aortic valve replacement; DVR: double valves replacement; METs: metabolic equivalents; med: median; IQR: interquartile range; wk: week.

Among subjects with different sessions per wk, namely 2 sessions per wk, 3 sessions per wk, and 4-5 sessions per wk, there were no significant differences in METs (mean±SD: 7.01±1.89, 7.23±1.74 and 7.33±2.13, p=0.813) and minutes achieved (mean±SD: 6.72±1.94, 6.96±1.96 and 6.81±1.84, p=0.848) in the evaluation after the end-session of EBCR (TABLE 2).

TABLE 2. The comparison of parameters among subjects underwent EBCR based on sessions fulfilled per wk

Parameters	2 sessions per wk (n=25)	3 sessions per wk (n=67)	4-5 sessions per wk (n=30)	p
Sex [n (%)]				
• Male	8 (32)	26 (39)	7 (23)	0.323.
• Female	17 (68)	41 (61)	23 (77)	
Age (mean±SD year)	41.56±11.85	41.31±12.24	33.40±12.24	0.008
Diagnosis [n (%)]				
• Post ASD/VSD closure	15 (60)	29 (43)	16 (53)	
• Post CABG	0 (0)	1 (1.5)	0 (0)	
• Post PCI	0 (0)	1 (1.5)	0 (0)	
• Post MVR	7 (28)	27 (40)	10 (34)	0.345
• Post AVR	2 (8)	5 (7.5)	0 (0)	
• Post DVR	1 (4)	2 (3)	3 (10)	
• Post myxoma surgery	0 (0)	2 (3)	1 (3)	
Total number of session [n (%)]				
• 8-9	2 (8)	15 (22)	4 (13)	0.216
• 10-12	23 (92)	52 (78)	26 (87)	
Evaluation treadmill protocol [n (%)]				
• Bruce	25 (100)	63 (94)	28 (93)	0.439
• Modified Bruce	0 (0)	4 (6)	2 (7)	
METs achieved (mean±SD)	7.01±1.89	7.23±1.74	7.33±2.13	0.813
Minute achieved (mean±SD)	6.72±1.94	6.96±1.96	6.81±1.84	0.848

ASD: atrial septal defect; VSD: ventricular septal defect; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; MVR: mitral valve replacement; AVR: aortic valve replacement; DVR: double valve replacement; METs: metabolic equivalents; SD: standard deviation; wk: week

DISCUSSION

This study showed that the reduction of EBCR sessions per wk of outpatient cardiac rehabilitation program did not associate with the reduction of functional capacity achieved at the end-session of EBCR, which was comparable with previously conducted usual and regular EBCR. This result supports the current adaptive practice to reduce sessions of hospital-based EBCR practice during the Covid-19 pandemic where the VCR and telerehabilitation are not feasible.

The movement restriction during the Covid-19 pandemic affects hospital visits and load in the cardiac rehabilitation center. Therefore, a significant number of cardiac rehabilitation programs were temporarily halted during the Covid-19 pandemic.[6] An international survey indicated that most common cardiac rehabilitation program adaptations experienced a reduction in the program elements, postponement of the graduation until post-program assessments were finished, decreased program duration, while discharging patients more speedily, and adapting all program elements to maintain service

levels.[4,6] Program adaptation was made in Dr. Sardjito General Hospital, Yogyakarta as well by reducing the number of EBCR sessions per wk while maintaining at least 70% program completeness.

The patients who are scheduled to perform cardiac rehabilitation are reduced in order to circumvent overcapacity, as a solution if the VCR and telerehabilitation to perform EBCR are not feasible in several centers.[4,7] Current studies indicated that the VCR and telerehabilitation showed a significant benefit as an alternative to hospital-based cardiac rehabilitation during the Covid-19 pandemic for low-to-moderate risk patients.[2,8-11] However, in Indonesia, such technology has not been performed due to several limitations from healthcare providers, national insurance coverage, and patients' ability to access sites.[5,12] As a result, the practice of telemedicine in cardiac rehabilitation has not yet been performed during the current Covid-19 pandemic restrictions. The Covid-19 pandemic is predicted to make enduring impact on cardiac rehabilitation worldwide, therefore the sustainability of program and safe environments for exercise are important by performing adaptive protocols based on the respective policies of each center, region, or nation.[13-16]

Some limitations of this study were as follows (1) the retrospective method of the research may not be adequate to fully evaluate the results of different sessions among groups, (2) the limited sample size of subjects who participate in the study, (3) the single center analysis which needs more data from multicenter studies and (4) the potential bias by selecting subjects who motivated to perform EBCR in both periods and also performed unscheduled exercise at home. The best research method to evaluate the effectiveness of adaptation protocol is by performing randomized-control trials.

CONCLUSION

Based on our single center study experience, two EBCR sessions per wk with a complete evaluation of cardiac rehabilitation achieved a similar result to the previously usual number of sessions (3, 4 or 5 sessions per wk), but was accomplished with more safety for patients and staffs and in compliance to the government's movement restriction and physical distancing orders. Therefore, in countries which rely on hospital-based cardiac EBCR programs, this adaptation protocol is more feasible to sustain the participation of patients in the cardiac rehabilitation program.

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Maternal determinants of average weekly fetal weight gain in Yogyakarta, Indonesia

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ABSTRACT

Average fetal weight gain (AWG) is one of the important parameters usually used as an indicator to identify the fetal risk of poor outcomes of intrauterine growth restriction (IUGR) or macrosomia. This study aimed to investigate the association between AWG and maternal factors such as body weight (BW), body mass index (BMI), middle-upper arm circumference (MUAC), and economic status in Yogyakarta, Indonesia. This community-based cross-sectional study was conducted in one district in the Yogyakarta Special Province, Indonesia. The study included 50 mother-infant pairs who delivered at term (37-42 weeks of pregnancy). The mother's BW, height, BMI, and MUAC were recorded using a case-report form. Questionnaires were also completed to establish the respondents' economic status. Maternal factors associated with fetal birth weight were determined using univariate and multivariate analyses. The mothers registered in our study mostly had good nutritional status (74.0% had an optimal MUAC > 23cm). The mean AWG and birth weights were 172.6 ± 24.5g/wk and 3.08 ± 0.34kg, respectively. Univariable analysis models were used to assess the associations between each variable and AWG (with a cut-off value of 153.8 g/wk). Our study found no associations between higher MUAC and higher AWG (OR=1.03; 95% CI: 0.83-1.27; p=0.77) and energy intakes per day with AWG (OR=1.0; 95% CI: 1.00-1.001; p=0.21). Socioeconomic factors such as the mother's educational background also showed no association with AWG (OR=0.38; 95% CI: 0.92-1.57; p=0.18). In conclusion, this finding shows that there is no association between variables such as MUAC, mother's age, energy intake, and educational background with the average fetal weight gain achieved.

Keywords:
average fetal weight gain; middle-upper arm circumference; socioeconomic factors; low birth weight; intra uterine growth restriction

ABSTRACT

Rerata pertambahan berat badan janin (BBJ) adalah salah satu parameter penting yang dapat digunakan sebagai indikator untuk mengidentifikasi janin yang memiliki risiko luaran buruk seperti *intra uterine growth restriction* (IUGR) atau makrosomia. Penelitian ini bertujuan untuk melakukan studi menilai hubungan antara faktor maternal seperti berat badan, asupan energi harian, lingkar lengan atas (LILA), dan status ekonomi terhadap rerata pertambahan BBJ di populasi ibu hami di Yogyakarta, Indonesia. Penelitian ini merupakan penelitian potong lintang berbasis komunitas yang dilakukan di salah satu kabupaten di Daerah Istimewa Yogyakarta. Penelitian ini melibatkan 50 ibu hamil yang melahirkan secara aterm (37-42 minggu). Berat badan dan tinggi badan serta LILA ibu dicatat dalam form laporan. Kuesioner juga diberikan kepada partisipan untuk menilai status ekonomi dan pendidikan pasien. Faktor maternal yang berkaitan dengan berat badan janin dianalisis secara univariat dan multivariat. Sebagian besar ibu hamil memiliki status nutrisi yang cukup (74% memiliki LILA optimal > 23cm) pada saat proses rekrutmen partisipan penelitian. Rerata pertambahan BBJ dan berat badan lahir (BBL)

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secara berurutan adalah 172,6 ± 24,5g/minggu dan 3,08 ± 0,34kg. Analisis univariat untuk menganalisis hubungan antar variabel dan rerata BBJ (dengan nilai ambang 153,8g/minggu). Dalam penelitian ini didapatkan adanya hubungan namun secara statistik tidak signifikan antara besarnya LILA (OR=1,03; 95% CI: 0,83-1.27; p=0,77) dan asupan energi harian (OR=1,0; 95% CI: 1,00-1,001; p=0,21) dan besarnya rerata kenaikan BBJ. Faktor sosioekonomi dan latar belakang pendidikan juga tidak menunjukan hubungan yang signifikan terhadap rerata kenaikan BBJ (OR=0,38; 95% CI: 0,92-1,57; p=0,18). Dapat disimpulkan, tidak ada hubungan antara faktor maternal seperti LILA, usia maternal, asupan energi, dan latar belakang pendidikan terhadap rerata kenaikan BBJ.

INTRODUCTION

Low birth weight (LBW) is a major public health problem, especially in developing countries. Several studies confirmed that LBW is strongly associated with a higher risk of neonatal death, stunting, lower academic performance, mental health, and some non-communicable diseases (NCDs) including type 2 diabetes mellitus, hypertension, and cardiovascular diseases (CVDs) in later life.[1–5] The global prevalence of LBW is estimated at 14.6 to 20% of all live births, of which almost 95.6% are in developing countries. It is also associated with 60 to 80% of neonatal deaths worldwide.[6] The prevalence of LBW in Indonesia itself is relatively low. However, the number has been fluctuating between 2007-2018, from 5.4 to 6.2%.[7] Several risk factors are associated with LBW including lower pre-gestational weight, fewer antenatal care (ANC) visits, poor gestational weight gain, lower mother's educational status, mother's aged <18 and >35 years old, and presence of comorbidity during pregnancy.[8-10]

The measurement of average fetal weight gain (AWG) in association with maternal gestational weight gain (GWG) plays a significant role in the early identification of newborns who are at risk of adverse outcomes such as neonatal LBW, intrauterine growth restriction (IUGR), large for gestational age (LGA), and fetal macrosomia.[11] This measurement can be used to predict the occurrence of LBW.[12] However, the use of this method to facilitate antenatal screening for the IUGR or LGA fetus remains uncommon in clinical practice compared to other parameters such as GWG,[13,14] fundal height, and estimated fetal weight (EFW).[15] This is probably because AWG is relatively unpractical and several guidelines does not incorporate this parameter to be assessed routinely.[16,17] Regardless of the parameters that are being examined, it is important to detect abnormal growth patterns in the antenatal period, to predict and prevent adverse neonatal outcomes including LBW and stillbirth.

According to the National Institute of Child Health and Human Development (NICHD) fetal growth studies (n = 1,733) from 12 United States sites, the AWG calculated after 20wk of gestational age was in the range of 117 to 215g/wk with a mean of 175g/wk.[18] Data from the Australian population (n = 12,425) showed an almost similar range for the AWG from 130 to 225.6g/wk.[12] For the Asian population, the range is smaller than Caucasian infants. A study conducted by Uehara *et al.*,[19] in the Japanese population (n = 144,980) found the AWG was in the range of 133 to 175.7g/wk with a median value of 153.8g/wk.

The estimation of fetal growth using ultrasound parameters in combination with maternal anthropometric parameters (i.e. body mass index/ BMI, MUAC) has been shown to have promising and consistent results with neonatal outcomes.[18,20] This study aimed to calculate average fetal weight gain in the Javanese sub-population which

was derived from birth weight and gestational age at term.

MATERIALS AND METHODS

Design and subjects

This community-based cross-sectional study was conducted in one district in the Yogyakarta Special Province, Indonesia. The subjects were enrolled consecutively. We included subjects with a) the second trimester in gestational age; b) low- and middle-income economic status (regional minimum wage below standard <IDR 1,701,000/monthly); c) maternal age below 25 yo; and d) educational background below/equal to senior high school. We excluded subjects with concomitant diseases a) anemia; b) pre-eclampsia and eclampsia; and c) multiple gestations.

Procedure

The current study included 50 mother-infant pairs who delivered at term (37-42 weeks of pregnancy). The mother's BW, height, BMI, total energy intake/day, and MUAC were recorded using a case-report form. Questionnaires were also completed to establish the respondents' economic status. Maternal factors associated with fetal birth weight were determined using univariate and multivariate analyses.

Measurement of total energy intake/day was performed using the semi-quantitative food frequency questionnaire (SQ-FFQ) by direct interviews with the subjects. We calculated the AWG using the formula proposed by Mongelli *et al.*,[12] which divides the difference between fetal birth weight (BWT) and the 24-week median fetal weight by the difference between gestational age at birth and 24 weeks, as follows:

$$AWG = \frac{BWT - 670}{GA - 24}$$

The signed informed consent was acquired for each participant to be included in our study. The study protocol was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta (Ref No: KE/FK/0410/EC/2019).

Analytical statistics

For the statistical analysis, we performed a descriptive analysis of the data. The continuous data were presented in mean and standard deviation (SD) or median and interquartile range (IQR) depending on the results of the normality test of the data using the Shapiro-Wilk or Kolmogorov-Smirnov test. The categorical data were presented in percentages. The comparison between the two groups was performed using student t-test or Mann-Whitney and Chi-square or Fisher Exact tests according to the type of the data. In this comparison analysis, we decided to use a cut-off for the AWG using a study from Uehara *et al.*[19] with a median value of 153.8g/wk. This was due to the Japanese population's characteristics, which are almost similar to the Indonesian population. A multivariable logistic regression analysis was conducted to assess the independent association among covariables. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 50 mothers were included in this pilot study. The median age at the first registry was 20 ± 2.3 yo (median ± IQR). The majority of the women in this study with as many as 46 participants (92%) were aged >18yo, and only 4 participants were aged below 18yo.

TABLE 1. Baseline characteristics of study population at first registry

Characteristics	Total (n = 50)	<153.8g/wk (n = 10)	≥153.8g/wk (n = 40)	p
Demographic characteristics				
• Age at first registered (mean±SD yo)	20.7 ± 2.3	21.4 ± 2.4	20.6 ± 2.3	0.36
• Body weight (median±IQR kg)	57.0 ± 18.3	50.5 ± 21.9	57.0 ± 17.5	0.47
• Body height (median±SD cm)	154.0 ± 6.0	152.5 ± 11.3	154.0 ± 6.8	0.14
Gestational age at first registered (median±IQR wk)	30.5 ± 5.0	29.5 ± 5.0	31.0 ± 4.0	0.91
MUAC (mean±SD cm)	24.9 ± 3.37	24.7 ± 5.3	25.0 ± 3.34	0.90
Energy intakes/day (median±IQR kcal)	1775.9 ± 969	1656.2 ± 839	1775.9 ± 1161	0.32
Parity [n (%)]				
• Null	40 (80)	8 (80)	32 (80)	0.65
• ≥ 1	10 (20)	2 (20)	8 (20)	
Education background [n (%)]				
• Less than high school	16 (32)	5 (50)	11 (27.5)	0.17
• High school	34 (68)	5 (50)	29 (72.5)	

*p value < 0.05; MUAC: middle upper arm circumference; IQR: interquartile range; SD: standard deviation

In TABLE 1, we grouped the study population into two categories based on the cut-off value of AWG <153.8g/wk and ≥153.8g/wk. The median body weight of the subjects was 154.0 ± 18.3kg. Most subjects were recruited at a gestational age of 30.5 ± 5.0wk and there was no significant statistical difference between the groups (p=0.91). Most of the women had finished high school with as many as 68% while 32% had not finished high school.

The mean MUAC was 24.9±3.37cm among all subjects and there was also no significant difference between both groups (p=0.91). Overall, only 26% of all pregnant women in this study were found to have a MUAC <23.0cm. The mean birth weight was 3,086.6g, mean birth length was 48.5cm, with 80% nulliparas. Measurement of total energy intakes/day in our study was also performed using SQ-FFQ. Our study found that the median of total energy intake/day was 1,775.9 ± 969kcal. There was also a statistically insignificant association between total energy intake/day with average AWG in our study (p>0.05).

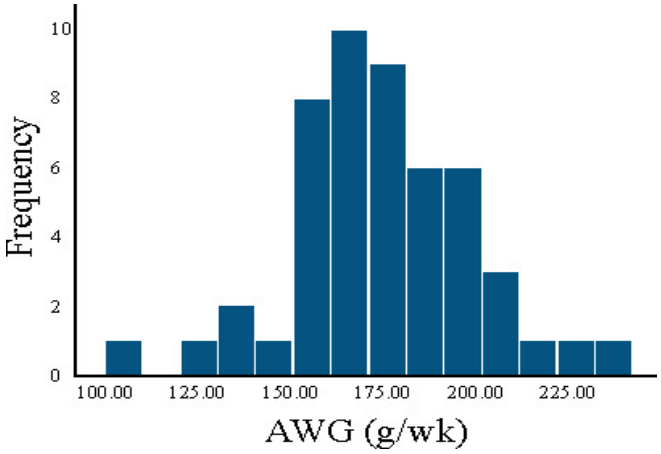

FIGURE 1. Histogram of the AWG showing its approximate normal distribution.

The AWG was normally distributed with a mean of 172.6g/wk (FIGURE 1). Authors categorized AWG using the previous cut-off value suggested by Uehara *et al.*with a median of six scans in each pregnancy. The average fetal growth rate was retrospectively calculated for the last 6 weeks to birth, and expressed as daily weight gain in grams per day. Adverse pregnancy outcome was defined as operative delivery for fetal distress, acidotic umbilical artery pH (< 7.15[19] Our study found that the mean of the AWG in our population was higher than the Japanese population with 172.6g/wk vs 153.8g/wk. However, in the univariate analysis, there were no associations found between higher MUAC and higher average fetal weight gain achieved (OR=1.03; 95% CI: 0.83-1.27; p=0.77) and energy intakes per day with AWG (OR= 1.0; 95% CI: 1.00-1.001; p=0.21). Socioeconomic factors such as the mother's educational background also showed no significant association with AWG (OR=0.38; 95% CI: 0.92-1.57; p=0.18).

DISCUSSION

In our population, we found a mean fetal weight gain of 172.6g/wk. This result was relatively higher than previous studies conducted by De Jong *et al.*[21] which found an average fetal weight gain of only 169.4g/wk using the Amsterdam population and Japanese population with a median value of the AWG was 153.8g/wk.[19]with a median of six scans in each pregnancy. The average fetal growth rate was retrospectively calculated for the last 6 weeks to birth, and expressed as daily weight gain in grams per day. Adverse pregnancy outcome was defined as operative delivery for fetal distress, acidotic umbilical artery pH (< 7.15 This previous study by De Jong *et al.*,[21] used a small sample of 200 high-risk pregnancies, and our study used only 50 participants with low-risk pregnancies. Several high-risk pregnancy-related conditions included in the study were a) previous history of IUGR; b) pregnancy-induced hypertension; c) pre-existing hypertension; d) smoked 15 or more cigarettes/day' and e) aged 35 yo or older. The above mentioned risk factors were significantly associated with adverse perinatal outcomes including LBW and stillbirths.[22,23]

Our finding of the AWG is still in the normal range as described earlier by Uehara *et al.*,[19] in the Japanese population (133 to 175.7g/wk). Our result was higher compared to the Japanese data, which is probably due to there was an increasing trend of prevalence of pre-pregnancy underweight mothers and poor weight gain during pregnancy which was correlated with an increased incidence of LBW infants in Japan (~9.4%) compared to the average of Organization for Economic Cooperation and Development (OECD) countries.[24] In our study, the authors also did not find any participants with an adverse neonatal outcome such as LBW.

Several factors which are thought to be associated with the occurrence of LBW such as maternal age, MUAC, and mother's educational background were not found in this study. It was possibly due to the relatively small sample size and also this study did not encompass low birth weight samples. In contrast to our study, Rahfiludin and Dharmawan in 2018Temanggung, Central Java, Indonesia. The sample size required for this study was 69 based on the Slovin formula. Data were collected using questionnaires and semi-quantitative Food Frequency Questionnaire forms. Data on infant birth weight was taken from midwives' delivery cohort records. Mid upper arm circumference (MUAC found that MUAC and mother's age were significantly associated with LBW.[8] The usefulness of MUAC for screening women at high risk of poor pregnancy outcomes is promising. Since MUAC reflects the

maternal fat composition and/or lean tissue stores, while the relationship between MUAC, BW and gestational age is independent.[25]

Remarkably, the authors found that the average energy intake/day of pregnant women in our study population was still below the WHO recommendation on energy requirement during pregnancy, which is approximately 2,140 kcal/d.[26] There was a deficit of as much as 370kcal/d according to our study. This problem should be confirmed with a larger-scale study.

CONCLUSION

In conclusion, our study showed that there is no association between maternal variables such as MUAC, mother's age, energy intake, and educational background with the average fetal weight gain achieved. Our study also found that the average energy intake/d of pregnant women in the study population is below the WHO guidelines.

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Family-centered rehabilitation in a high-risk infant: a case report

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ABSTRACT

Preterm infants are categorized as a high-risk group in neonatology. They are physiologically less mature and have limited compensatory responses to the extrauterine environment compared with term infants. Preterm infants need long-term evaluation, monitoring, and follow-up to optimize neonatal care and development through an extensive rehabilitation period. However, the COVID-19 pandemic restricted patient care and follow-up in the outpatient hospital setting. This case report discusses a high-risk infant treated with family-centered rehabilitation (FCR). The patient's rehabilitation issues included delays in gross motor, fine motor, and language development and preventing complications that may arise in a high-risk premature infant. Considering recent occurrences, our approach to rehabilitation programs for high-risk infants needs to be reevaluated and revised, focusing on home programs through family-centered treatment. These techniques may aid in delivering rehabilitation treatments to children with developmental delays during COVID-19.

ABSTRAK

Bayi prematur merupakan kelompok risiko tinggi di bidang neonatologi, karena secara fisiologis belum matur dan kemampuan kompensasi terhadap lingkungan ekstrauterin yang terbatas dibandingkan bayi cukup bulan. Bayi prematur biasanya memerlukan evaluasi, monitoring, dan ditindak lanjuti terus menerus untuk mengoptimalkan perawatan dan perkembangan neonatal melalui periode rehabilitasi jangka panjang. Namun, terjadinya pandemi COVID-19 menyebabkan terbatasnya pelayanan dan tindak lanjut pasien di poli rawat jalan. Di sini, kami melaporkan kasus bayi risiko tinggi dengan tatalaksana melalui *family-centered rehabilitation* (FCR). Masalah rehabilitasi yang didapatkan pada pasien meliputi keterlambatan perkembangan motorik kasar, motorik halus, bicara bahasa, dan mencegah komplikasi yang mungkin timbul pada bayi prematur risiko tinggi. Mengingat kondisi pandemi yang baru terjadi, pendekatan program rehabilitasi pada bayi risiko tinggi perlu dievaluasi dan direvisi kembali, dengan menitikberatkan pada tatalaksana di rumah yang berbasis pada keluarga. Teknik-teknik ini dapat membantu dalam memberikan layanan rehabilitasi medik kepada anak dengan keterlambatan perkembangan selama pandemi COVID-19.

Keywords:
high-risk infant;
family-centered rehabilitation;
COVID-19;
pandemic

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INTRODUCTION

Late preterm infants (LPIs) are born between 34 0/7 and 36 6/7 weeks gestational age. From 2014 to 2016, the LPI birth rate rose from 6.82% to 7.09%, accounting for approximately 72% of all preterm births in the United States. In Indonesia, more than 550,000 late preterm infant babies are born yearly.[1-3] Compared with term infants, preterm infants have an immature central nervous system. Between 34 and 40 weeks of gestational age, cortical volume increases by 50%, and 25% of cerebellar development occurs. These factors place preterm infants at an increased risk for altered brain development, which may influence long-term neurodevelopmental outcomes. Late preterm infants account for 72% of all preterm births, and even the smallest increases in adverse outcomes could causing a large public health burden.[4-6]

It has been suggested that congenital cytomegalovirus (CMV) infection is a risk factor for preterm delivery.[7] Infection by CMV is the most frequent cause of congenital infection globally, affecting 0.7-6.1% of newborns. Among symptomatic patients, 50% presented with sequelae. The most serious sequelae are neurocognitive impairment and sensorineural hearing loss. Symptoms at birth include low birth weight and microcephaly. Microcephaly at birth was the most specific predictor of poor cognitive outcome and major motor disability in children with symptomatic congenital CMV infection. A highly significant positive correlation was found between head size at birth and the intelligence/developmental quotient (IQ/DQ).[8-10]

A long-term evaluation, monitoring, and follow-up of high-risk infants are needed to optimize neonatal care, promote healthy growth and development, and improve human health status. However, the COVID-19 pandemic restricted the patient care and follow-up. Family-centered rehabilitation that provides home-based programs is considered useful in addition to or even replacing center-based therapy in this situation.

Home-based programs provide a unique opportunity to train continuously. These programs enable parents to incorporate training into their daily routine with their childs. Separated training is not needed. In addition, increased training may facilitate the retention of established intervention effects.[11,12]

When parents become therapy providers, the relationship between parents and the health professional changes: the health professional becomes the parents' coach. Depending on the role of parents and their specific needs, the way and amount of coaching can vary from limited instruction only at the beginning of the program to extensive demonstration, feedback, and coaching throughout the entire program. The coaching mode can vary from home visits by the therapist to remote coaching by e-mail or telephone consultation.[11]

Family-centeredness has been the cornerstone of service delivery for children with developmental difficulties in pediatric health care for decades. Services that provided family-centered care were associated with improved developmental outcomes and adjustment for the children, better family functioning, parental wellbeing, parental perceptions of competency and satisfaction, and more efficient use of services.[13] Here, we report a case of a high-risk premature infant treated with FCR.

Case

In October 2020, a male infant patient was referred from the Pediatric Outpatient Clinic, Dr. Sardjito General Hospital with a perinatal history of

congenital infection of cytomegalovirus (CMV), herpes simplex virus (HSV), respiratory distress, hypoglycemia after delivery, left parieto-temporal epidural hemorrhage, left temporal intracerebral hemorrhage, bilateral intraventricular hemorrhage, umbilical cord hemorrhage due to suspected vitamin K deficiency, neonatal anemia, and extrahepatic cholestasis due to sepsis.

Considering fetal distress, intrauterine growth restriction, and oligohydramnios, the patient was delivered late preterm (35 weeks of gestational age) via cesarean section at Dr. Sardjito General Hospital. The body weight at birth was 1270 g (extreme low), body length was 39 cm, and head circumference was 28 cm. The patient was admitted to the Neonatal Intensive Care Unit (NICU) for 35 days. Before being discharged home, the patient could breastfeed orally, and his body weight reached 1810 g.

The patient is the first child of his parents, live together daily. His mother is his primary caregiver, and his father earned 1.8 million rupiahs monthly as a private employee. The medical treatment for this patient was covered by national healthcare insurance. There was no history of developmental problems or serious sickness in the family. The patient's mother was pregnant at the age of 33 y.o. During her pregnancy course, she received regular antenatal care from a midwife. She consumed vitamins and iron supplements daily during her pregnancy.

When the patient arrived at the Medical Rehabilitation Outpatient Clinic, he was 6th months 16th d.o. (correction age 5th months 9th d.o.) and had a complete medical examination. His body weight was 6.4 kg, his height was 63.5 cm, his body mass index (BMI) was 15.87 kg/m^2, and his head circumference was 38.5 cm. Temperature, pulse, and blood pressure were all within normal limits. The respiratory system and other internal organs were all functioning normally. During the examination of the extremities, movements in both hands and feet were equally active, there was hypertonus on the trunk extensor and extremity, physiological reflexes (biceps, triceps, and patella) were increased +3/+3, and pathological reflexes (Hoffman-Trommer and Babinski) were positive. The patient could roll to prone, but it was still on rare occurrence, and he could not return. The patient could elevate his head in a prone position despite having poor neck control, turning his head left and right, and holding a toy that is touched to his hand (movement/physical development match to 3 mo.o. baby). Primitive reflex showed central nervous system maturation at the midbrain level (asymmetrical tonic neck reflex (ATNR) positive, neck righting reflex positive, foot placement reflex negative, and parachute reflex negative).

The patient made a sound (mumble) in a low voice, reacted to the sound of the bell, and did spontaneous cooing (language/communication match to a 2-3 mo.o. baby). He also could recognize his mother and smile spontaneously (a social/emotional match to 4 mo.o. baby). The patient received enough breast milk, could suck adequately, and had no previous choking or shortness of breath episodes during breastfeeding. The patient has also begun receiving supplementary food, organic baby porridge, given twice a day in amounts of up to 2 tablespoons; there have been no complaints of coughing or choking while swallowing. Oromotor function examination showed inadequate lip seal with drooling, good oral hygiene, and baby teeth have not grown yet.

The patient's rehabilitation issues included delays in gross motor with postural control abnormality, fine motor, language development, and preventing complications that may arise in a high-risk premature infant (growth failure, neurologic impairments, developmental

delay, and lower cognitive functioning). The rehabilitation management goals were for parents to understand the importance of the rehabilitation program provided for the patient, to be able to stimulate their child according to the child's developmental stages, to optimize the child's growth and development, and to prevent the risk of neurodevelopmental disabilities.

Because of the COVID-19 pandemic that has been impacted since May 2020, most non-emergent practices, including outpatient rehabilitation services, have been restricted by hospital regulations based on government regulations. For this patient, we applied family-centered rehabilitation combined with hospital-based rehabilitation treatment.

The patient visited the outpatient rehabilitation clinic every two weeks for physiotherapy treatments and evaluation by a physiatrist (including the application of the FCR program and achievement of the child's development). For a one-hour therapy session, parents were coached and guided on how to correctly position and stimulate their child at home to improve postural control development and facilitate normal movement patterns. Parents' training includes actions during which health care professionals guide parents and demonstrate how to apply intervention strategies clearly and strictly. During the treatment session, we also ensured whether parents could do the therapeutic technique correctly as a daily routine, i.e., motor stimulation in the prone position with hand support to assist neck and trunk control.

As a daily routine, parents applied a massage method for tactile and proprioceptive stimulation for 10-15 min. Play therapy for 10-15 min at least three times daily to develop reaching and grasping functions by employing colorful toys and appealing sounds. Parents were also advised to maximize engagement and communication with the child (for example: conduct a chit chat for every diaper change, dressing, and bathing, tell a tale while massaging the child, play peek-a-boo, sing, and play with appealing toys according to the child's developmental stage).

At four months follow-up after the rehabilitation program, when the patient was 11 months 3 d.o. (correction age 9 mo 26 d.o.), his body weight was 9.1 kg (weight to age -1<Z<0), body height 74.2 cm (height to age 0<Z<2), BMI 16.5 kg/m^2, and head circumference 41.7 cm (-3<Z<-2, microcephaly). The patient was able to sit independently and crawl. In terms of fine motor, the patient could reach and hold a toy before moving it from one hand to the other, but he couldn't pinch a small object. The patient could smile or laugh when playing peek-a-boo and show several facial expressions (happy, sad, and surprised). During playtime with the mother, the patient could make sounds or babble in a low voice, but it was uncommon. The patient turned toward the bell sound but didn't respond when his mother called his name. Brainstem evoked response audiometry (BERA) examination showed moderate-severe hearing loss in the right ear (60 dB) and moderate hearing loss in the left ear (42.5 dB). Movement/physical development and social-emotional milestones have reached his age's expectations, but we need more attention to language and speech development. The hearing aids and a new strategy would be provided to develop a wide range of listening skills and optimize speech/language development.

DISCUSSION

The patient, in this case, was born at 35 wk of gestation; hence he was categorized as a LPI. Although late preterm infants may be close to term, losing the last 6 weeks of gestation is vital to their physiologic and metabolic maturity. These LPIs have higher morbidity and mortality rates

than term infants. The most common morbidities experienced by LPIs include respiratory complications, feeding difficulty, hypoglycemia, temperature instability, hyperbilirubinemia, and neurodevelopmental delays.[1,3] The perinatal history of congenital infection of CMV and HSV that cause very low birth weight and microcephaly further add to the problems and place the patient at a high risk of developmental delay and cognitive impairment.

During the COVID-19 pandemic, the World Health Organization (WHO) urges individuals of all ages to take precautions against the virus. Current advice emphasizes the necessity of avoiding public areas and remaining at home.[14] The family-centered rehabilitation approach that provides a home-based program might be a good solution to solve this problem. Parents with adequate resources and support and physical and psychological health can provide positive caregiving environments for children with physical disabilities.[15,16]

For this patient, we gave daily programs at home and face-to-face training to parents to take on a therapeutic role as a co-therapist. The patient's mother is a housewife and has enough hours daily to perform the program next to her daily activities. A systematic review reported coaching parents is a key element of home-based programs. When parents are effectively coached and guided throughout the training period, parents become more confident in carrying out the home-based program, find it easier to implement the program in their daily routine, and enjoy seeing their children improve.[11,16]

After four months, the patient has reached the expected motor development of his age. It could be due to no upper motor neuron sign, such as spasticity or congenital deformity that could prevent normal motor development. High compliance of parents in implementing the rehabilitation program plays an important role. A systematic review has indicated that parental involvement in early intervention is associated with a better outcome for infants and families.[11,17]

But this patient has not yet reached his expected speech and language development age. Our patient's moderate-severe bilateral hearing loss may restrict access to speech and language input and significantly impact oral communication development. Unlike children with severe and profound loss, our patient still has some access to speech. However, this access will be highly dependent on the amplitude and spectrum of the speech signal and the presence of noise.[18,19]

Home-based programs have become the practice of choice in pediatric rehabilitation and early childhood intervention programs. Our fundamental goal in health service delivery is, and indeed must be, improved quality of life for the affected child and family. Family-centered care provides an evidence-based means to objectively achieve this goal. Evidence of the beneficial effects of this method on outcomes in varying domains exists, including better demonstrable child development, improved child psychological adjustment, enhanced parental psychological wellbeing (reduced stress, anxiety, depression), more robust parental perceptions of competency and control, and higher levels of actual satisfaction with the care provided.[20]

Even though parents are great importance in home-based programs, a survey among parents has shown that they do not have an unfavorable opinion concerning home programs because these programs may induce or enhance stress in parents. Parents may experience pressure to comply, especially when the program is demanding. Furthermore, the altered parent-child interaction during training may cause additional tension. As the role of parents changes to that of a therapy provider, this may

cause a conflict between their parenting style and their approach as a therapy provider. Consequently, the loss of motivation by parents and/or children to complete training activities may affect compliance and probably the effectiveness of the intervention. Because of the factors mentioned above, home-based interventions need to be carefully developed and implemented.[11,21]

Prior study in Turkey pioneered the development of emergency remote training programs for young children with Down syndrome, learning disabilities, and serious health issues.[22] They assessed the effectiveness of the "applied emergency remote training program" designed to meet the requirements of parents of children with Down syndrome and provide them with at-home care. It was an evaluative case study with 11 parents of Down syndrome children aged 11 to 35 mo. The findings showed that the program could be used in the home, enhanced parents' and children's interactional behavior, decreased the number of challenging routines, and could be used as an educational, instructional, and band-aid solution.

During the pandemic, some countries used telemedicine as their major method of providing chronic disease services, while others relied on Virtual Reality and Video Games. Low- and middle-income nations and distant places with limited access to rehabilitation treatments benefit from telemedicine.[23]

Family-centeredness has been the cornerstone of service delivery for children with developmental difficulties in pediatric care.[11,13] However, this approach needs parents and caregivers to be fully involved and adequately educated to attend to the children's needs. Clinicians must ensure the family is ready and can stimulate children according to prescribed treatment. The development of FCR in Indonesia, especially in remote places, may need a long way to go. This program may need further look to be incorporated into national healthcare insurance to include follow-up visits by healthcare providers to ensure optimal children's care at home.

CONCLUSION

Considering recent occurrences, our approach to physical therapy and rehabilitation management of infant with a high risk of developmental delay must be reevaluated and revised, focusing on family-centered programs. These techniques may aid in delivering rehabilitation programs to children with developmental delays during COVID-19.

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Practical tips to adopt active lifestyle for university students during pandemic life: a narrative review

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ABSTRACT

The Covid-19 pandemic worsened the physical inactivity pandemic and also increased sedentary behavior across the population, including university students. While physical inactivity and sedentary behavior are detrimental to health and academic performance, there is an urgent need to help university students to adopt an active lifestyle during post-pandemic life. This narrative review discussed current physical activity (PA) and sedentary behavior recommendations, practical tips for adopting an active lifestyle by applying PA doses using the frequency, intensity, time, and type (FITT) principle, and behavioral strategies to adopt and maintain an active lifestyle. Finally, several considerations related to the PA-related musculoskeletal injury and cardiovascular events risks were also discussed with examples from interventions during the pandemic in university settings.

ABSTRAK

Pandemi Covid-19 memperburuk prevalensi inaktivitas fisik dan juga meningkatkan perilaku sedenter semua populasi, termasuk mahasiswa. Oleh karena itu, ada kebutuhan mendesak untuk membantu mahasiswa mengadopsi gaya hidup aktif selama kehidupan pandemi untuk menurunkan dampak buruk akibat inaktivitas fisik maupun perilaku sedenter. Tinjauan naratif ini akan membahas rekomendasi terkini aktivitas fisik dan perilaku sedenter, tips praktis untuk mengadopsi gaya hidup aktif dengan menerapkan dosis aktivitas fisik menggunakan prinsip frekuensi, intensitas, waktu, dan tipe aktivitas fisik, serta strategi perilaku untuk mengadopsi dan mempertahankan gaya hidup aktif. Terakhir, beberapa pertimbangan terkait dengan cedera muskuloskeletal terkait aktivitas fisik dan risiko kejadian kardiovaskular juga dibahas dengan contoh intervensi selama pandemi di lingkungan universitas.

Keywords:
physical activity;
university students;
exercise;
academic performance;
Covid-19

INTRODUCTION

Physical activity (PA), defined as any bodily movement produced by skeletal muscles that require energy expenditure, is essential in preventing and managing cardiovascular diseases, metabolic diseases, certain cancers, mental health, and general well-being.[1] However, physical inactivity, defined as not meeting the global recommendation on PA for health, persists as a global pandemic that resulted in more than two-thirds of all-cause and cardiovascular disease mortality attributable to physical inactivity. Moreover, almost two-fourths of cardiovascular disease mortality attributable to physical inactivity occur in middle-income countries.[2]

In addition to the pandemic of physical inactivity, technological innovations contribute to increased sedentary behavior across the world. Sedentary behavior is defined as any

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waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents (METs) while in a sitting, reclining, or lying posture.[3] Sedentary behavior leads to detrimental health effects through distinct mechanisms than physical inactivity.[4] Thus, the World Health Organization (WHO) 2020 also released recommendations to increase PA and limit sedentary behavior.[5]

The Covid-19 pandemic led more than 100 countries to enforce containment measures resulting in increased physical inactivity and sedentary behavior across the population, including university students in Indonesia.[6,7] Reduction of PA during the pandemic could be detrimental to pandemic control since the evidence showed the benefits of regular physical activities in reducing infection mortality, enhancing the first-line defense of the immune system, and improving the potency of vaccination.[8,9] Since physical inactivity and sedentary behavior could also negatively affect students' learning achievement and mental health, which were also affected by the pandemic situations,[10-12] it is crucial to implement strategies for increasing PA and limiting sedentary behavior to improve university students' physical health, mood enhancement, and academic performance during post-pandemic life.[13,14] In addition, college-age is a crucial phase in which current lifestyle could be adopted into later life and could affect future health condition.[15] In this narrative article, we discussed current recommendations on PA and sedentary behavior for health, then practical tips for university students to adopt the recommendations. We also discussed several risks associated with PA, with the examples of PA intervention conducted in university settings during the pandemic.

MATERIALS AND METHODS

Three important topics following the Scale for the Assessment of Narrative Review (SANRA) guidelines were narratively reviewed.[16] 1). Current guidelines on PA and sedentary behavior; The two latest guidelines on PA and sedentary behavior were reviewed, the 2020 WHO guidelines[5] and the 11th of the American College of Sports Medicine (ACSM) guidelines.[17] 2). Practical tips for adopting an active lifestyle; The strongest evidence available related to the practical tips mentioned in the 11th edition of the ACSM guidelines was manually searched. The WHO 2020 Guidelines were not reviewed because they do not provide detailed implementation guidelines. 3). Benefits vs. risks associated with PA; Manual searching was conducted for the most robust evidence available related to the benefits and risks associated with PA from the 11th edition ACSM guidelines.[17] The evidence on benefits of PA was used from the 2020 WHO guidelines since they have already conducted umbrella reviews to search for the best available evidence.[5] To provide examples from interventions conducted during the pandemic, a database search was conducted on Pubmed on June 15, 2022 using the following search strategy: ((“physical activity” OR exercise) AND university students AND (2020/3:3000/12/12[pdat])) AND ((((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh]))) OR ((((nonequivalent or non equivalent) adj3 control$) or posttest$ or post test$ or pre test$ or pretest$ or quasi experiment$ or quasiexperiment$ or timeseries or time series).tw.)) OR ((nonequivalent control group or posttesting or pretesting or pretest posttest design or pretest posttest control group design or quasi experimental methods or quasi experimental study or time series or time series analysis).sh

AND (2020/3:3000/12/12[pdat]))

We only included randomized controlled trials examining the effects of either supervised exercise intervention or behavioral intervention on either health or cognitive-related outcomes or PA behavior or risks/harms associated with PA. We only included studies conducted during the pandemic. We extracted the health, academic, and behavioral outcomes of the interventions as well as the adverse events or injuries related to the intervention to provide an example of risk-benefits assessment of PA intervention during the pandemic in university settings.

RESULTS

Current recommendations on physical activity and sedentary behavior for health

Almost five decades since the early guideline on PA for health was released in the 1970s, WHO released "The 2020 guidelines on PA and sedentary behavior"[5]. Having systematically reviewed evidence to assess the effect of PA and sedentary behavior on health outcomes, the WHO Guideline Development Group released several conclusions including, but not limited, to the following recommendations (TABLE 1)

TABLE 1. WHO physical activity and sedentary behaviour guideline for adults (18-64 years)

Recommendations	Explanation
Doing any amount of physical activity is better than doing none	Adults (18-64 years) who are inactive should start by engaging in small amounts of PA, then gradually increase the frequency, intensity, and duration over time. Doing any amount of PA can provide health benefits that are better than doing none.
Amount of aerobic physical activity for substantial health benefits	For substantial health benefits, adults should make a goal to do at least 150-300 min per wk of moderate-intensity aerobic PA or at least 75-150 min per wk of vigorous-intensity aerobic PA or an equivalent combination of moderate and vigorous-intensity aerobic PA, which could be spread throughout the wk.
Amount of muscle-strengthening activities for additional health benefits	For additional health benefits, adults should also do at least two days a wk of muscle-strengthening activities at a moderate or greater intensity that involve all major muscle groups.
Amount of sedentary behaviour and the benefits of any intensity of physical activity	To reduce the detrimental effects of sedentary behavior, adults should limit the amount of time being sedentary by replacing them with any intensity PA.
Amount of aerobic physical activity exceeding the recommended amount for substantial health benefits	Adults could still gain additional health benefits and reduce the detrimental effects of sedentary behavior by doing more than the equivalent of 300 min/wk of moderate-intensity aerobic PA.

By aiming to do the recommended amount of PA, adults, including university students, could get several long-term benefits, such as reducing all-cause and cardiovascular mortality as well as the reducing incidence of hypertension, certain cancers, type-2 diabetes, and also short-term benefits, such as reducing anxiety and depressive symptoms, improving cognition, sleep, and body composition as well as improving academic achievement.[5,13,14]

Practical tips to adopt active lifestyle

Having known the recommended amount of PA for health is not yet sufficient to help individuals to adopt and maintain an active lifestyle. In addition to providing knowledge of PA doses, evidence suggests that providing practical tips based on behavioral strategies should be used to assist individuals in adopting and maintaining an active lifestyle.[17]

Physical activity doses

Physical activity recommendations allow for flexibility in the different combinations of frequency, intensity, time, and type (FITT) principles.[17] It is crucial to understand the impact of FITT variations to achieve an active lifestyle.

Frequency and time

There is no difference in PA adherence between the different combinations of frequency and time to achieve the total amount of PA.[18] It could be suggested that individuals could self-select frequency and time/duration to fulfill their autonomy which could improve their adherence to PA.[19] Spreading the PA sessions across 3 to 5 days per week may suit most individuals.[17] Performing once or twice per week PA sessions could also be adopted since they also bring substantial health and fitness benefits.[5,17] Individuals may also select their preferred duration of each PA session since the accumulation of PA bouts provides health and fitness benefits regardless of the duration.[17]

Intensity

Individuals who are more active and have higher fitness levels will be more likely to adhere to higher intensity PA. In contrast, less active individuals will prefer to perform lower-intensity PA since they will feel an unpleasant affective response to higher intensity.[20] However, the evidence consistently showed that individuals who can self-select their preferable PA intensity would be more likely to adhere to the PA.[18,20] While the evidence showed that PA conducted in any intensity could provide health benefits, PA recommendations allow flexibility in selecting the range of moderate-vigorous intensity physical activities for the healthy adult population.[17] Talk test, a valid and reliable measure of PA intensity, is a recommended effective primary method for prescribing and monitoring PA intensity.[17] Using this test, individuals can determine that they are performing a light intensity PA if they still can sing during a session. Individuals who performing a moderate PA session cannot sing but are still able to talk. When the individuals can not talk anymore, they perform a vigorous PA session. Heart rate reserve (HRR) calculated from obtained or predicted maximal heart rate and resting heart rate and VO_2 reserve can also be used to prescribe PA intensity, especially in individuals with cardiovascular diseases.[17] While PA prescribed using a talk test could provide similar benefits to PA prescribed using HRR, a talk test could be suggested to be implemented in PA prescription since it is easier and simpler to be implemented.[21]

Type

Type of PA refers to mode or kind of PA and program/delivery type of PA.[17] There are several kinds of aerobic PA, such as walking, cycling, and swimming. The available evidence found trivial effects of the PA mode on adherence.[18] Self-preference, environmental and socioeconomic may have greater effects on adherence.[18] Thus, individuals could self-select aerobic activity based on their physical condition, preference, and environmental and socioeconomic factors.

The delivery of the PA program also influences adherence. For certain populations, such as patients in cardiac rehabilitation and older adults, home-based or lifestyle programs that include remotely delivered support resulted in a greater adherence than structured or center-based programs.[22,23] PA programs delivered through the web or app also hold promising results, especially for the populations who are already familiar with technology.[24] Individuals could select technology-delivered PA programs which contain self-monitoring with a combination of intention formation, goal-setting, providing feedback, or providing reviews of PA goals.[25]

Application of behavioral strategies

Enhancing self-efficacy

To successfully adopt and maintain an active lifestyle, individuals must be confident in their ability to perform their PA dose and goal.[26] It can be achieved by setting realistic goals, watching others with similar backgrounds performing the similar PA dose and reaching the similar goals, getting encouragement telling them can be successful in reaching their goals, and getting pleasurable physiological feedback by choosing the pleasurable type and intensity of PA or using music and scenery to make PA pleasurable.[17]

Adequate and positive perception

Accurate and broad knowledge and understanding regarding the benefits of physical activity, in particular, can further encourage awareness and the urge to be physically active.[27] Identifying misperceptions and reducing barriers will increase the motivation to make behavioral changes.[28] Consistent exposure to information and being involved in a community that actively shares information are needed to maintain positive perceptive growth.

Self-monitoring

Self-monitoring is one of the most important factors associated with a successful PA program when combined with other strategies such as goal setting.[25] Individuals can use a paper-and-pencil log or technology devices and apps to self-monitor their PA dose and goals.[17] Several apps that provide self-monitoring and goal setting could adopt and maintain an active lifestyle.[29] In addition to monitoring PA progress (e.g., amount of PA, distance traveled, step counts), individuals could also monitor the effect of increased PA, such as cardiorespiratory fitness, body composition, or other health-related outcomes.

Goal setting

Setting short- and long-term goals are essential for initiating and maintaining an active lifestyle. Individuals can use the specific, measurable, action-oriented, realistic, timely, and self-determined (SMARTS) principle to guide effective goal setting (TABLE 2).[17]

TABLE 2. SMARTS principle to guide effective goal setting

Principle	Explanation
Specific	Individuals should set precise amounts of PA based on the FITT principle as their goals
Measurable	Individuals should set quantifiable amounts of PA based on the FITT principle as their goals
Action-oriented	Individuals should determine what needs to be done to achieve the goals
Realistic	Individuals should set achievable goals
Timely	Individuals should set a specific and realistic time frame
Self-determined	Individuals should develop their goals primarily by themselves.

It is also crucial to regularly monitor the progress, get feedback, and review success and struggles while achieving the goals. Therefore, the goals can also be reviewed and revised consistently to provide some directions to individuals' efforts, enhance persistence, and learn new strategies for achieving them.

Rewards

Individuals should reward themselves for meeting their PA goals.[30] The rewards can be extrinsic rewards or intrinsic rewards. Extrinsic rewards, such as money, medal, new shirts, or praises, could be beneficial to initiate an active lifestyle.[30] However, intrinsic rewards are crucial for maintaining an active lifestyle over the long term.[19] Intrinsic rewards can be provided by building feelings of autonomy, competence, and relatedness.[19]

Social support

Social support, which can come from family members, friends, instructors, neighbors, or exercise and health professionals, is a powerful motivator to an active lifestyle for many individuals.[17] It can provide encouragement and figures for increasing self-efficacy. By having social support, individuals can also get feedback and discussion to help them achieve their goals. The feeling of being a part of a group also fulfills the needs of relatedness, which could provide intrinsic rewards.

Benefits versus risks associated with PA

There are concerns regarding the increasing risk for musculoskeletal injury and potential cardiovascular complications associated with PA.[17] However, the benefits of regular PA far outweigh the risks.[28] In addition to prevention of certain non-communicable diseases in later life, sufficient PA also provides benefits for improving mental health and academic performance among university students.[5,13,14] The risk of musculoskeletal injury is associated with the increasing PA intensity, the nature of the activity, and the previous level of PA.[17, 32]

The risk of musculoskeletal injury (MSI) is very low for walking and other low-moderate intensity physical activities. In contrast, high-intensity PAs such as running or competitive sports is associated with a higher risk

of injury.[17] The risk of MSI is also higher during direct contact PA between participants or with the ground (e.g., football, basketball, martial arts) than PA conducted without or with minimal direct contact (e.g., baseball, swimming, walking). Adults who were previously not met the recommended amount of PA have a higher risk of MSI than their more active counterparts.[33] Therefore, it is crucial for physically inactive adults to start by doing a small amount of PA and gradually increasing the frequency, intensity, and duration.

In general, PA does not elicit cardiovascular events in healthy individuals with a normal cardiovascular system.[33] The most concerning PA-related cardiovascular events are sudden cardiac death and acute myocardial infarction. The annual risk of PA-related sudden cardiac death among young adults is low (1 per 133.000 men athletes, 1 per 769.000 women athletes, 1 per 1.5 million episodes of vigorous physical exertion in men, 1 per 36.5 million hours of moderate to vigorous exertion in women) and indicated that it is caused by congenital and hereditary abnormalities. There is a transient increase in the risk of acute myocardial infarction while performing vigorous-intensity exercise in individuals with diagnosed or occult cardiovascular diseases. However, individuals who regularly performed vigorous exercise had 50 times higher protection from the risk of acute myocardial infarction (AMI) during or immediately following vigorous-intensity exercise compared to their habitually inactive counterparts. It reinforced the importance of initiating an active lifestyle by starting with a small amount of physical activities and gradually increasing the dose over time. To reduce excessive screening, which could result in unnecessary barriers to adopting an active lifestyle, pre-participation should only be conducted for individuals at risks, such as individuals with known cardiovascular, metabolic, or renal diseases who are going to engage in competitive sports or vigorous PA.[34-36]

From 1995 search results, we found seven published studies examining PA interventions in university settings (TABLE 1). Four of them examined exercise intervention[37-40] and the leftovers examined behavioral intervention.[41-43] All studies that examined health outcomes reported PA benefits, including improved cardiorespiratory fitness, body composition, lipid profile, mood, mental health, and sleep quality. Among 296 participants receiving supervised exercise intervention, only 1 participant reported tibial pain.[40] None of the participants receiving behavioral intervention reported any injury or adverse event. It can be concluded that the risk of musculoskeletal injury associated with PA intervention during the pandemic in university settings was also very low (less than 2 per 1000 participants). Health benefits resulting from the PA intervention conducted in university settings also outweighed the risk. It strengthens current recommendations and advocation on PA promotion in university settings.

TABLE 3. List of physical activity intervention studies in university settings during the pandemic

Author	Description of intervention	Intervention	Control	Outcome	Adverse event
Wu *et al.*[37]	3 times a week, 30 min of exercise in adventure mode using a Nintendo Switch game, 4-6 METs	40	40	Improved running speed, mood, and sleep quality	No injury was reported
Li *et al.*[38]	Supervised Baduanjin exercise, 5 times a week, 45 min for 1 week, and unsupervised >5 times a week 45 min/ session for 11 week, unmeasured intensity	195	192	Improved Covid-19 anxiety score, psychological well-being, and low back pain	No injury was reported
Hu *et al.*[39]	Supervised 5 times a week, 30 min interval training sessions (3 sets of 9 min circuit training at 90% maximum heart rate followed by 1 min rest), 4 week	17	13	Improved body composition and lipid profile, decreased resting heart rate	No injury was reported
Lan *et al.*[40]	Supervised 3 times a week, either low intensity with blood flow restriction, moderate-intensity continuous training, or high-intensity interval training, 8 week	44	12	Improved cardiorespiratory fitness and body composition	1 participant reported tibial pain
Muntaner-Mas *et al.*[41]	Behavioral intervention comprises self-monitoring of behavior, action planning, review of behavioral goals, providing feedback on performance, provide instruction, and demonstration on how to perform the behavior	35	31	Improved cardiorespiratory fitness	No injury was reported
Dost *et al.*[42]	Behavioral intervention using Pender's health promotion model	110 (total)	Unknown	Improved body composition and physical activity	No injury was reported
Blow *et al.*[43]	Behavioral intervention comprises self-monitoring of behavior, action planning, review of behavioral goals, providing feedback on performance, provide instruction and demonstration on how to perform the behavior, feedback, and goal setting	145	122	Improved perceived competence of PA and movement through the stage of change	No injury was reported

CONCLUSION

University students as adult populations should aim to initiate and maintain performing PA at least 150 min of moderate-intensity aerobic PA per week and limit their sedentary time, which is beneficial for their physical and mental health as well as cognitive performance. Physical activity doses and behavioral regulation could be implemented to initiate and maintain an active lifestyle. While the benefits of PA outweigh the risk, pre-participation health screening and exercise testing during PA interventions in university settings should only be considered for individuals at risk who are going to engage in competitive sports or vigorous PA to reduce excessive screening and unnecessary barriers to PA adoption.

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A report of two cases of type 2 diabetes mellitus (T2DM): happy and longevity

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ABSTRACT

Chronic hyperglycemia in patients with type 2 diabetes mellitus (T2DM) is associated with the development of complications and the increase of risk of mortality. Patients with T2DM have a shorter life expectancy than non-diabetic population. It is attributed to cardiovascular disease, stroke, renal disease, and infection. Depression secondary to T2DM worsens the quality of life. On the contrary, positive emotions correlated strongly with long life expectancy. A number of mechanisms might explain this correlation. We reported two geriatric patients over 80 y.o. with T2DM comorbidity for more than 20 years. Discussion point of these cases is the subject's longer life span compared to the average diabetic patient's life expectancy and great quality of life despite the disease burden of chronic hyperglycemia in T2DM and cardiovascular risk.

ABSTRAK

Hiperglikemia kronis pada pasien diabetes mellitus tipe 2 (DMT2) dikaitkan dengan perkembangan komplikasi dan peningkatan risiko kematian. Pasien diabetes memiliki harapan hidup yang lebih pendek daripada populasi non-diabetes. Hal ini dikaitkan dengan penyakit kardiovaskular, stroke, penyakit ginjal, dan infeksi. Depresi sekunder akibat DMT2 memperburuk kualitas hidup. Sebaliknya, emosi positif berhubungan kuat dengan harapan hidup yang panjang. Sejumlah mekanisme mungkin menjelaskan hubungan ini. Kami melaporkan dua pasien geriatri berusia di atas 80 tahun dengan komorbiditas DMT2 selama lebih dari 20 tahun. Poko diskusi dari kasus ini adalah rentang hidup subjek yang lebih lama dibandingkan dengan rerata harapan hidup pasien diabetes dan kualitas hidup yang baik meskipun mempunyai beban penyakit hiperglikemia kronis pada DMT2 dan risiko penyakit kardiovaskular.

Keywords:
chronic hyperglycemia;
type 2 diabetes;
life expectancy;
life quality;
risk factor

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a group of metabolic disease characterized by hyperglycemia that results from inadequate insulin secretion or defects in tissue response to insulin.[1] Untreated hyperglycemia in uncontrolled DM over time leads to various organ damage and dysfunctions.[2,3] Type 2 diabetes mellitus is a significant risk factor for cardiovascular disease, chronic kidney disease, peripheral nerve disease and, other complications.[4,5] Diabetes mellitus is associated with increased risk for mortality and morbidity in both men and women, especially from cardiovascular disease, in which nearly half of the cases are due to stroke. Mortality in T2DM adult patients is twice higher compared to adults without T2DM.[6,7]

Psychosocial factors such as disease burden, interpersonal relationships, social supports, and emotional disturbances contributes to quality of life in T2DM patients.[8] Constant behavior of

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diabetes self-care which revolves around medication adherence, blood glucose monitoring, diet intake, eating patterns, physical activity and prevention of disease progression are reported to be directly associated with DM-related distress.[9,10]

Emotional well-being is an important part of diabetes care and self-management. Integrating mental and physical health care can improve quality of life outcomes.[11,9] Happier people tend to maintain better physical health and longer life expectancy. Mortality risk is lower in happier adults than less happier adults and happiness may be associated with overall better health outcomes and longevity.[12,13]

Subjects in our cases are diabetic patients who exceeded the average of diabetic patient's life expectancy. Both subjects were diagnosed with T2DM for over 20 years, aged more than 80 y.o. and live normally. The subjects presented with uncontrolled high blood glucose level to achieve expected HbA1C target level. The patients were not distressed despite the emotional response of having been diagnosed with T2DM and carried out daily activities contently.

CASE 1

Mrs. SA, an 84 y.o woman diagnosed with T2DM in May 2000, was born on January 11, 1937. She was prescribed glibenclamide and metformin for three years. She did not comply with routine self-monitoring of blood glucose and on visits to the outpatient diabetes clinic even though her blood glucose level was always above 200 mg/dL. HbA1C level on this patient was not regularly evaluated due to lack of routine hospital visits. The patient obtained her medicine through her private provider. Patient's body weight ranges from 58 to 55 kg and her height is 150 cm. She put no limitations or restrictions to her diet and the amount of food that she included in her diet was sufficient. Her occupation is a college lecturer which serves as her daily physical activity.

She reported symptoms of cephalgia and her blood glucose level was over 300 mg/dL upon testing in May 2000. Glibenclamide and metformin prescription was permanently discontinued, substituted with insulin until recently and her blood glucose level improved, approaching 200 mg/dL on routine testing.

The patient was admitted to hospital in June 2016 due to severe hyperglycemia which was provoked by insulin injection noncompliance for 7 days prior to hospitalization. The patient was diagnosed with stroke due to slight paralysis in her right extremities on examination finding. Treatment for her neurological deficit lasted for a few months and the patient was able to recover completely with slight speech impairment sequelae. The patient was also prescribed amlodipine 5 mg on account of high blood pressure and later the blood pressure was successfully lowered.

The patient's visual acuity was normal and was not aided with glasses for daily activities. Complain of tingling sensation on her toes was recorded and her caregiver prescribed mecobalamin which effectively reduced the symptoms. Her sleep schedule is quite stable, which requires her to go to bed at 10 PM and then rise at 3 AM to conduct routine prayer. She always exudes a positive energy personality and is always kept company by family and friends.

The patient's recent treatment regimen includes insulin mix 30/70 with 14 unit doses on every meal and mecobalamin 500µg taken once a day. The patient's weight is 56 kg, height 155 cm and blood pressure is 120/70 mmHg.

Laboratory result

Laboratory results in 2020 and 2021 are presented in TABLE 1.

TABLE 1. Laboratory result of general check up

Components	Result per May 4th, 2020	Result per April 21st, 2021
HbA1 (%)	8.6	10.5
BUN (mg/dL)	25.3	34
Creatinine (mg/dL)	1.24	1.27
Cholesterol (mg/dL)	272	271
HDL-C (mg/dL)	52	45
LDL_C (mg/dL)	161	173
Triglyceride (mg/dL)	297	267

Geriatric depression Scale on May 18th, 2021

Total score of Geriatric Depression Scale on May 18th 2021, was 3. The score was obtained after ask question YES or NO answer from the following list of questions 1) Are you basically satisfied with your life? **YES**/NO; 2) Have you dropped many of your activities and interests? **YES**/NO; 3) Do you feel that your life is empty? YES/**NO**; 4) Do you often get bored? YES/**NO**; 5). Are you in good spirits most of the time? **YES**/NO; 6). Are you afraid that something bad is going to happen to you? **YES**/ NO; 7). Do you feel happy most of the time? **YES**/ NO; 8). Do you often feel helpless? **YES**/ NO; 9). Do you prefer to stay at home, rather than going out and doing new things? YES/**NO**; 10). Do you feel you have more problems with memory than most? YES/**NO**; 11). Do you think it is wonderful to be alive now? **YES**/NO; 12). Do you feel pretty worthless the way you are now? YES/**NO**; 13). Do you feel full of energy? **YES**/NO; 14). Do you feel that your situation is hopeless? YES/**NO**; 15). Do you think that most people are better off than you are? YES/**NO**.

CASE 2

Mrs. SD, an 81 y.o. woman born on May 10th, 1940, was diagnosed with T2DM in 1998. At the time of initial diagnosis, the patient had an ulcer in her feet that resisted for more than a month with a blood glucose level of 400 mg/dL. She possessed familial risk of T2DM as her sister was also diagnosed with T2DM. She was prescribed glibenclamide and metformin. The patient's blood glucose level was recorded over 200 mg/dL multiple times. She visited her doctor regularly once a month, but HbA1C level was not regularly evaluated. The patient did not limit her food consumption and did not do the recommended physical exercise, such as jogging and aerobic exercise. Her daily recorded activities include walking during work.

The patient's treatment regimen was changed to insulin therapy in 2001 because the patient's body weight decreased, and her blood glucose did not achieve targeted level. Her body weight was recorded 37 kg and her height was 148 cm. After being treated with insulin her body weight increased by 8 kg to 45 kg. She still included refined sugar and processed foods in her diets, hence the >200 mg/dL blood glucose level customarily.

The patient also had dyslipidemia and was treated with simvastatin. The treatment was discontinued after her cholesterol level decreased to normal cut-off. She had hypertension simultaneously with her initial diagnosis with T2DM

and was prescribed amlodipine 5 mg routinely.

In 2019, the patient was diagnosed with peripheral arterial disease upon presenting with symptoms of intermittent claudication and the result of ankle brachial index examination was <0.9 thus the doctor prescribed her clopidogrel 75 mg routinely. She also complained of blurred vision on her right eye and was diagnosed with cataract, yet she objected to undergo surgery and visual acuity in her left eye was not impaired.

She lived with her sons, grandchildren and she had a happy family. Sometimes her pupils visited her house as she was their former lecturer and they had missed her. Lately she started light physical activity by walking in the morning for approximately 500 m. She conducted religious practices every day and had a good quality of life with her family.

The patient's treatment regimen consisted of insulin mix aspart/glargine 50/50 14 unit doses on every meal, amlodipine 5mg once a day, CPG 75mg once a day, folic acid 1mg once a day and mecobalamin 500µg once a day. The patient's body weight is 46 kg, height is 145 cm, and blood pressure 130/80 mmHg.

Laboratory result

Laboratory results showed numbers of following components are presented in TABLE 2.

TABLE 2. Laboratory result of general check up

Components	Result per January 9th, 2020	Result per March 18st, 2021
FBG (mg/dL)	180	243
BUN (mg/dL)	-	16.9
Creatinine (mg/dL)	1.25	0.67
Uric acid (mg/dL)	7.3	4.9
Triglyceride (mg/dL)	135	171
Cholesterol (mg/dL)	-	239
LDL_C (mg/dL)	120	143

Geriatric depression scale on May 19th, 2021

Total score of Geriatric Depression Scale on May 19th, 2021 was 2. The score was obtained after ask question YES or NO answer from the following list of questions as performed in Case 1 1). Are you basically satisfied with your life? **YES**/NO; 2). Have you dropped many of your activities and interests? **YES**/NO; 3). Do you feel that your life is empty? YES/**NO**; 4). Do you often get bored? YES/**NO**; 5). Are you in good spirits most of the time? **YES**/NO; 6). Are you afraid that something bad is going to happen to you? YES/**NO**; 7). Do you feel happy most of the time? **YES**/NO; (8). Do you often feel helpless? YES/**NO**; 9). Do you prefer to stay at home, rather than going out and doing new things? **YES**/NO; 10). Do you feel you have more problems with memory than most? YES/**NO**; 11). Do you think it is wonderful to be alive now? **YES**/NO; 12). Do you feel pretty worthless the way you are now? YES/**NO**; 13). Do you feel full of energy? **YES**/NO; 14). Do you feel that your situation is

hopeless? YES/**NO**; 5). Do you think that most people are better off than you are? YES/**NO**.

DISCUSSION

Previous study conducted in 2012 reported that 43% T2DM-related mortality occurrs before the age of 70 y.o.[1] The study estimated T2DM patients' life expectancy decreases with age because organ dysfunction complication risk allows diabetic patients to have significantly lower health-related quality of life.[14-18]

Shorter life expectancy in diabetic population is largely attributed to cardiovascular complications. Patients with poor glucometabolic control are posed to 4-fold higher risk of dying from ischemic heart disease compared to non-diabetic population.[19,20] Life expectancy predictors for T2DM patients specifically attributed to cardiovascular risks are age, sex, body mass index (BMI), systolic blood pressure, HbA1C level, total:HDL cholesterol ratio, and smoking status. If all the combined risk factors are successfully reduced, life expectancy would increase.[21]

The study resulted in significant decrease of mortality after the age of 60 y.o. in diabetic population related to comorbidities and complications factor.[22] Mean age of death was significantly higher in women compared to men in diabetic population.[23] The 2019 World Health Organization's life expectancy reported the fact that men had a shorter life span than women which can be attributed to ischemic heart disease, traffic injuries, lung cancer, chronic obstructive pulmonary disease, and stroke.[24] In this case, the subject is an 80 y.o. diabetic female with T2DM for over 20 years. Tachkov *et al.*[22] reported a progressive increase in life expectancy and reduction in mortality in female diabetic population.

Patients with T2DM and elevated HbA1c levels of ≥6.5% are exposed to increasing microvascular and macrovascular complication and are associated with unfavorable outcomes.[3,25] Chronic or intermittent hyperglycemia activates diacylglycerol formation, protein kinase C, NADPH-oxidase, the production of reactive oxygen species (ROS), and oxidative stress. These inflammatory reactions are mediated by a pathological cellular death and may be aggravated by the action of advanced glycation end products, an interaction with the respective receptor for advanced glycation end products. These process leads to chronic low-grade inflammation that is mechanism of diabetes complications.[26] Achieving HbA1C targets of <7% are associated with reduced onset or progression of some microvascular complications lead to significantly decreased risk of macrovascular and death.[27] The subject in this study was presenting with neuropathy, retinopathy and PAD symptoms, but their quality of life and daily activities were not impaired. Blood glucose level and HbA1C level in these patients were not routinely controlled. The Case 1 HbA1C level recorded in May 2020 was 8.6% and in the Case 2 blood glucose levels were recorded for more than 200 mg/dL multiple times.

Other symptoms such as hypertension and dyslipidemia often coexist with T2DM as metabolic diseases add the risk factors for atherosclerotic cardiovascular disease. Some studies reported that <140/90 mmHg blood pressure reduces cardiovascular events as well as microvascular complications.[28-31] A meta-analysis showed that lowering LDL cholesterol possess beneficial effects on atherosclerotic cardiovascular disease outcomes and further persistent statin regimens reduced the incidence of these major vascular events.[32] The both subjects had hypertension and were prescribed amlodipine routinely hence the blood pressure steadiness. The

patients also had dyslipidemia but were not routinely treated with statin. These two patients have low cardiovascular risks based on the study conducted by Hedayatnia *et al.*[33] After adjusting for confounding factors (age, BMI, family history of cardiovascular disease, smoking status (non-smoker, ex-smoker and current smoker), lipid lowering drug treatment, antihypertensive drug treatment, hypertension, healthy eating index, total energy intake, and presence of DM, Hedayatnia *et al.*[33] reported that only triglyceride baseline level is significantly associated with the risk of infarct myocard on male patient but not on female patient.

The other significant cardiovascular predictor presented by our patients were BMI because both of the patients did not partake in smoking. Obesity is associated with abnormal endothelial function which decreased in nitric oxide level. It may be related to elevated oxidative stress or may result from proinflammatory cytokines. Decrease in the function of nitric oxide would result in vasoconstriction and increase in vascular resistance that may predispose to cardio vascular disease risk factors.[34] Obesity management had been proven beneficial in treatment of morbidly obese patients with T2DM along with modest and sustained weight loss to improve glycemic control and reducing medications needed to lower high blood glucose level.[34,35] The second subject's BMI was normal and the first subject's BMI was between 25.8 – 24.4 kg/m^2, interpreted as overweight and stage 1 obesity in Asian population. The first case maintained a normal BMI throughout her T2DM therapy, and the second case underwent weight increasing despite being in normal range.

The other factor attributing to improved outcome in T2DM patients is psychosocial factors namely social and emotional.[12,13] Happier people tend to have overall better physical health and longer survival. Happiness appears to be inversely related to perceived stress and may protect against illness through better immune response. An important indicator of overall happiness are people's cognitive and affective evaluations of their lives has been robustly linked to better physical health.[36-38] In these cases, the subjects are supported by accepting families and people with positive thoughts. The first case obtained a low geriatric depression scale as well as a second case.

Happiness as an emotion formed as a general interaction between internal and external factors. Biological factors as endogenic factors are significant predictors of happiness. Genetic, brain, neurotransmitters, endocrinology, hormones, physical health, morphology, and physical attractiveness are endogenic factors that influence happiness. Neurotransmitters are Dopamine, Serotonin, Norepinefrine, and Endorphin play a role in control of happiness.[38,39]

Studies indicate that up to 50% of the variance in happiness between individuals can be attributed to genetic influences.[37] There are two genes investigated directly on happiness: 5-HTTLPR and MAO-A. The 5- HTTLPR gene is coding serotonin distribution in brain cells and therefore leads to mood regulation. There are two different functional forms for this gene: Long one (L), Short one (S). Genetic factors significantly influence individual subjective well-being or happiness. A particular genotype— 5-HTTLPR 'long'—is identified as having a sizable positive association with self-reported life satisfaction. The long polymorphism thus results in increased gene expression and more serotonin transporters in the cell membrane. Individuals with long 5-HTTLPR alleles display a significant bias toward processing positive information and selectively avoiding negative information.[40]

Serotonin is a neurotransmitter that mediates satisfaction, happiness, and optimism. Serotonin levels decreased in depression, and increased serotonin level is related to positive mood.[41-44] Most serotonin is distributed outside of the central nervous system and influences a wide range of physiologic processes in many organs. Serotonin present in CNS is only 2% and plays a pivotal role in the etiology of many mental disorders. The serotonin receptors are expressed outside as well as within the brain. Serotonin regulates numerous biological processes including cardiovascular function, bowel motility, ejaculatory latency, and bladder control and regulate some processes, including platelet aggregation by receptor-independent, secretion of cytokines, transglutaminase-dependent covalent linkage to cellular proteins.[45-49]

This study did not cover internal contributing factors, genetic factors, and neurotransmitters that influence happiness and mood. The authors find it interesting to identify multifaceted factors that are associated with T2DM and longevity. Unveiling factors that influence the longevity in T2DM will improve the understanding of underlying biological processes in T2DM patients.

CONCLUSION

We reported two geriatric patients over 80 y.o. with T2DM comorbidity for more than 20 years. Discussion point of these cases is the subject's longer life span compared to the average diabetic patient's life expectancy and great quality of life despite the disease burden of chronic hyperglycemia in T2DM and cardiovascular risk. It is an appealing point of interest to conduct future research to study the relationship between T2DM and longevity risk factors.

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