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Role of *TERT* Gene in Relationship between Body Fat Percentage with the Modifiable Risk Factors of Cardiometabolic Disease in Minangkabau Premenopausal

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Abstract

BACKGROUND: Cardiometabolic disease risk is increasing in the premenopausal phase of women life. The *telomerase reverse transcriptase (TERT)* gene is a gene that plays a role in protecting telomeres from progressive shortening. Telomere shortening is associated with the incidence of cardiometabolic disease.

AIM: This study aims to elucidate the relationship body fat percentage with the modifiable risk factors of cardiometabolic disease in Minangkabau premenopausal people.

METHODS: A cross-sectional study was conducted in 111 Minangkabau premenopausal people aged 40–55 years old at Padang City in West Sumatera, Indonesia. Body fat percentage analyzed by bioelectrical impedance analyzer. Fasting blood glucose and lipid profile were examined from venous blood. Polymorphism of the *TERT rs2736098* gene was analyzed by a polymerase chain reaction. Data were analyzed using Spearman's rank correlation test with significant levels $p < 0.05$.

RESULTS: Average body fat percentage of subjects was 36.23 ± 6.9, fasting blood glucose was 101.52 ± 12.3 mg/dL; total cholesterol was 193.99 ± 41.5 mg/dL; triglyceride was 113.76 ± 37.9 mg/dL; LDL-cholesterol was 120.59 ± 45.7 mg/dL and HDL-cholesterol was 53.52 ± 15.6 mg/dL. Body fat percentage has a significant correlation with triglyceride ($r = 0.368$; $p = 0.001$) and HDL-cholesterol levels ($r = −0.307$; $p = 0.006$) just in subject with polymorphism but does not have a significant correlation with another biomarker.

CONCLUSION: Body fat percentage correlates with triglyceride and HDL cholesterol in Minangkabau premenopausal women who have polymorphism of *TERT* gene.

Introduction

Obesity is a multifactorial disease that developed from an unbalanced energy and energy expenditure associated with cardiometabolic disorder. Obesity occurs as an effect of the interaction between genetic, environmental, and physiological factors. Body fat percentage has emerged as an essential indicator of cardiometabolic risk than body mass index. Body fat percentage is related to the biochemical marker of cardiometabolic risk factors such as blood glucose and lipid profile [1]. Cardiometabolic risk is increased in premenopausal women. Sen's study in India stated that cardiometabolic risk increased with age in women, including the premenopausal phase [2]. Another study also said that cardiometabolic risk in the premenopausal phase increased after 10-year follow-up [3]. Decreasing of estrogen levels in premenopausal women can lead the increased cardiometabolic risk in women, due to change in a hormonal milieu with declining estrogen and alteration of its ratio with testosterone [4]. The *telomerase reverse transcriptase (TERT) rs2736098* gene is a gene that plays a role in protecting telomeres from progressive shortening. Telomere shortening is associated with the incidence of cardiometabolic disease. The prevalence is a high in Europe and the world.

This study aims to elucidate the role of the *TERT rs2736098* gene in the relationship between body fat percentage with the modifiable risk factors of cardiometabolic disease in Minangkabau premenopausal people.

Methods

A cross-sectional study was conducted in Minangkabau premenopausal people at Padang City in West Sumatera, Indonesia. A total of 112 Minangkabau Premenopausal people aged 40-55 years were selected randomly. The research was conducted

from July to December 2017. Respondents have to sign an informed consent form. All subjects are the Minangkabau ethnicity (all of grandparent and parent are the original Minangkabau ethnicity, and there was no cross marriage) and women in the premenopausal phase (menorrhagia and/or metrorrhagia more than 3 months, but a menorrhagia <12 months). Body fat percentage analyzed by bioelectrical impedance analyzer. Fasting blood glucose and lipid profile were examined from venous blood after fasting for 8 to 10 h.

Polymorphism of the *TERT rs2736098* gene was analyzed by polymerase chain reaction (PCR) using a self-composed primer. We used TERT ex F primer (5'-GAACCATAGCGTCAGGGAG-3') and TERT ex R (5'-TCCCAAGCAGCTCCAGAAACA-3'). The PCR amplification products were analyzed using electrophoresis techniques in agarose 1.5% and electrophoresis at 120 volts for 50 minutes. The location of DNA contained in the gel can be observed by staining using red gel, then documented in the form of an electropherogram using the Doc Gel from Biorad. After it was confirmed that the DNA in the PCR product was good enough for sequencing, the PCR product was sent for sequencing.

This study has had ethical approval from the Ethical Committee Medical Faculty of Andalas University with registration number 279/KEP/FK/2017. Data were analyzed using non-parametric Spearman's rank correlation test with significant levels $p < 0.05$. All data analyzed using the SPSS software.

Results

The frequency distribution of *TERT* gene polymorphisms in the research subject is shown in Table 1.

Table 1: Frequency distribution of TERT rs2736098 gene polymorphisms in Minangkabau premenopausal people (n=111)

Variables	N	(%)
Wild type/polymorphism (−)	33	29.73
Polymorphism (+)	78	70.27

TERT: Telomerase reverse transcriptase.

This research got a research subject with characteristic, as shown in Table 2.

Table 2: Distribution of body fat percentage and biochemical marker of cardiometabolic disease based on polymorphism gen of TERT in Minangkabau premenopausal people (n=111)

Variable	Mean			p-value
	Total	Wild type/ polymorphism (−)	Polymorphism (+)	
Body fat percentage	36.23 ± 6.9	35.23	36.64	0.330
Blood glucose	101.52 ± 12.3	101.75	101.43	0.903
Total cholesterol	193.99 ± 41.5	194.10	193.95	0.986
Triglyceride	113.76 ± 37.9	193.95	193.95	0.825
LDL-cholesterol	120.59 ± 45.7	120.81	120.49	0.975
HDL-cholesterol	53.52 ± 15.6	53.33	53.59	0.935

TERT: Telomerase reverse transcriptase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein.

Average body fat percentage of subjects was 36.23 ± 6.9, blood glucose was 101.52 ± 12.3 mg/dL, total cholesterol was 193.99 ± 41.5 mg/dL, triglyceride was 113.76 ± 37.9 mg/dL, LDL-cholesterol was 120.59 ± 45.7 mg/dL, and HDL-cholesterol was 53.52 ± 15.6 mg/dL.

From Table 3, we can see that body fat percentage has a significant correlation with triglyceride ($r = 0.368$; $p = 0.001$) and high-density lipoprotein (HDL)-cholesterol levels ($r = -0.307$; $p = 0.006$) just in subject with polymorphism but does not have a significant correlation with another biomarker.

Table 3: Correlation between a biochemical marker of cardiometabolic disease with body fat percentage in Minangkabau premenopausal people

Variable	Polymorphism gene of TERT	Body fat percentage	
		r	p-value
Blood glucose	Wild type	0.027	0.884
	Polymorphism (+)	0.240	0.033
	Total	0.176	0.065
Total cholesterol	Wild type	−0.162	0.933
	Polymorphism (+)	0.095	0.405
	Total	0.063	0.514
Triglyceride	Wild type	0.113	0.538
	Polymorphism (+)	0.368	0.001*
	Total	0.297	0.002*
LDL-cholesterol	Wild type	−0.193	0.290
	Polymorphism (+)	0.113	0.323
	Total	0.028	0.772
HDL-cholesterol	Wild type	−0.120	0.513
	Polymorphism (+)	−0.307	0.006*
	Total	−0.243	0.010*

*Significant level at p<0.05. TERT: Telomerase reverse transcriptase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein.

Discussion

Average body fat of subjects was 36.23 ± 6.9. It means that the subject of this study was obese. This result is similar to the results of Flint *et al*. (2014) study of 4065 women aged 44 ± 12.9 years, who received a body fat percentage of 36 ± 8.4% [5]. Dos Anjos *et al*. (2013) research on 352 women in Brazil showed an average percentage of body fat that increased at an older age. The percentage of body fat with the age range of 40–50 years is 39.6 ± 0.59% and the age range of 50–60 years is 40.3 ± 0.65% [6]. The results of other studies in China also obtained a body fat percentage of 33.12 ± 5.85% in 154 women aged 40.46 ± 13.28 years. The results in the study also relate to the previous research which states that Indonesia is a country with a high percentage of body fat, besides China, Japan, Ethiopia, Thailand, and Mexico [7].

Based on the U.S., the National Institutes of Health Criteria standards for percent body fat and the American Dietetic Association/Canadian Dietetic Association, body fat percentage values defined as obesity when body fat percentage in men ≥25% and women ≥30%. Differences in the percentage values are found in the study of Zhao *et al*. (2013), which define obesity with a number >25% in men and >35% who rely on the previous studies [6], [7], [8].

From the biochemical marker of cardiometabolic disease, such as blood glucose and lipid profile, its

average is a normal value. Dyslipidemia is strongly associated with an increase in cardiovascular disease. However, only a small number of research subjects were enlarged prediabetes and dyslipidemia. Dyslipidemia plays a role in the pathogenesis of the cardiovascular disease, namely, in the formation of atherosclerosis. The management of dyslipidemia must be carried out comprehensively through pharmacological and non-pharmacologic aspects. Pharmacological management is using drugs, especially statins, while non-pharmacological control through lifestyle modification, low-fat and high-fiber diets, increase physical activity and stress management [9].

The TERT gene is located on chromosome 5p15.33 in base pairs to 1,253,167 to 1,295,047, having 16 exons with a length of about 35 kb [10], [11]. A total of 69.9% of subjects had *TERT* gene polymorphism rs2736098, where 50.4% heterozygotes and 19.5% were homozygous recessive.

In this study, we can see that there is no significant difference in body fat percentage, blood glucose, and lipid profile between wild type and mutation groups. Although as more than half of subjects have polymorphism of *TERT rs2736098* gene. The number of *TERT rs2736098* polymorphisms is higher than single-nucleotide polymorphism research in the Asian population in China which ranges from 42% to 66% [12], [13], [14], [15], [16], [17], in India 58.28% [18] and in Korea 54.16% [19]. The percentage of polymorphism in this study was lower than that in other Asian populations in Iran, which amounted to 74.05% and the Caucasian population in Turkey (83.26%), and Austria (76.03%) in Serbia at 76.11% [20], [21], [22], [23].

Spearman's rank correlation test showed that body fat percentage has a significant correlation with triglyceride ($r = 0.368$; $p = 0.001$) and HDL-cholesterol levels ($r = -0.307$; $p = 0.006$) just in subject with polymorphism of *TERT* gene, but does not have a significant correlation with another biomarker. A research conducted on 234 Thai adults found that body fat percentage is a good predictor of insulin resistance, hyperglycemia, hypertriglyceridemia, and hyperleptinemia, and also atherogenic lipoprotein particles [24]. Likewise, research in China suggests that body fat percentage cut off for predicting the risk of cardiac abnormalities to be 24% and 33% in Chinese men and women, respectively [25].

In this study, a significant relationship between the percentage of body fat and biomarkers of cardiometabolic disease only occurred in subjects who had polymorphisms. It has been caused by the reduced expression of the *TERT* gene which causes a change in the function of the *TERT* gene itself. *TERT's* function is to express telomerase which serves to keep telomeres from fast restriction. If there is a change in the function of the TERT gene that causes its expression to be disrupted, there will be a decrease in telomerase production. This will cause telomere shortening to occur faster which disrupts chromosomal stability. Chromosomal stability disorders will eventually lead to various health problems, including an increased risk of cardiometabolic disease [12], [26], [22], [27]. The research about the other mechanisms of relationship the *TERT* gene polymorphisms on the risk of cardiometabolic disease in Minangkabau ethnic is needed.

Conclusion

From this study, we can conclude that body fat percentage correlates with triglyceride and HDL cholesterol in Minangkabau premenopausal people who have *TERT* polymorphism. It is recommended for Minangkabau ethnicity who have *TERT rs2736098* gene polymorphism to maintain body weight and body fat percentage under normal conditions.

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