

Telomere Length in Young Patients: Relationship With Metabolic Syndrome and Its Components

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Abstract

Background: Previous studies have reported inconsistent findings on the relationship between telomere length and metabolic syndrome (MS). The aim of the work was to study leukocyte telomere length in young patients without cardiovascular diseases and its relationship with MS and its components.

Methods: This study included 450 Caucasian patients with a median age of 30 (21 - 42) years. Glycemic parameters and lipid profile components were determined using the CardioChek PA (USA, 2017). Integral metabolic indices were calculated in all patients. To investigate leukocyte telomere length, 45 were randomly selected from the total cohort of 450 participants.

Results: The selected patients were divided into two groups according to the presence of MS. The median telomere length in MS patients (7.36 (6.96 - 8.67) pn) was significantly lower than in the comparison group (8.72 (8.37 - 8.96) pn) ($P = 0.016$). Correlation analysis was performed to assess the relationship between telomere length and various traditional cardiovascular risk factors (sex, age, smoking, and blood pressure levels), MS components, and integral metabolic indices. Several linear regression analysis models were constructed to assess the independent associations between various factors and telomere length. Age, smoking, neck circumference, triglycerides, high-density lipoprotein levels, LAP index, and the presence of dyslipidemia were significantly associated with telomere length.

Conclusion: Our results are consistent with the notion of shorter leukocyte telomere length in individuals with MS and support an association with dyslipidemia in premature shortening of telomere length. The causal relationship between these changes requires further study.

Keywords: Metabolic syndrome; Telomere; Metabolic parameters; Dyslipidemia; Hyperglycemia; Obesity

Introduction

Obesity increases the risk of developing various chronic diseases through a wide range of mechanisms, including metabolic disorders and inflammation. Obesity combined with dyslipidemia, carbohydrate metabolism disorders, and arterial hypertension constitutes metabolic syndrome (MS) [1], which contributes to accelerated vascular aging and cardiovascular diseases (CVDs) [2].

The aging process along with genetic instability, stem cell depletion, epigenetic damage, and mitochondrial dysfunction is characterized by telomere shortening [3, 4]. Telomeres are the terminal regions of linear eukaryotic chromosomes. They are composed of a protein-DNA complex, which contains repetitive nucleotide sequences “TTAGGG”. Telomeres maintain genomic stability and integrity, but with each successive cell division, their gradual shortening occurs [5]. Excessive telomere attrition can occur under the influence of oxidative stress and systemic inflammation, both of which are important factors in biological aging. Critical telomere shortening activates replicative senescence leading to genomic instability and apoptosis [4, 5]. This, in turn, leads to abnormalities and depletion of tissue stem and progenitor cells, as well as disruption of their structural integrity and functional activity [6].

In a study by Demanelis et al [3], telomere length measurements across 24 tissue types revealed different rates of telomere shortening depending on the tissue type. Thus, in cerebellar and testicular tissues, unlike all other tissue types, telomere length does not shorten with age. These differences, apparently, are caused not only by genetic factors, but also by specific tissue sensitivity to the influence of various factors. There is now a consensus that the most accessible and representative method is the measurement of leukocyte telomere

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length [3, 7, 8], which correlates with the telomere lengths in most studied tissues [3].

Data on the association of telomere length with various diseases remain contradictory. In 2023, Chen et al published a systematic review and meta-analysis of Mendelian randomization studies of the relationship between leukocyte telomere length and various diseases in humans [9]. In 62 studies included in the meta-analysis, 396 correlations of varying direction, strength, and reliability with 310 outcomes were identified. Significantly lower telomere length was found in elderly patients, as well as in ischemic heart disease, chronic kidney disease, and several systemic diseases. The study showed a shortening of telomere length against the background of systemic inflammation and intestinal dysbacteriosis [10]. The most significant direct associations were between leukocyte telomere length and the risk of 24 types of neoplasms, with less significant direct associations with the presence of multiple sclerosis, genitourinary and digestive system abnormalities, and essential hypertension (EH). Data on the relationship between telomere length and MS are also variable. Some studies have found mildly positive relationships [6] and others mildly negative relationships [8] between MS and telomere length [6]. This determines the significance of further studies to elucidate the nature and basic mechanisms of these relationships.

The aim of the work was to study leukocyte telomere length in young patients without CVD and its relationship with MS and its components.

Materials and Methods

This single-stage cross-sectional study was conducted at the 2nd Internal Medicine (2nd Faculty Therapy) Department of Sechenov University in accordance with the principles of the Declaration of Helsinki. The study was approved by the local ethics committee (protocol No. 25-22, dated 08.12.2022). Inclusion criterion for the main group was age between 18 and 45 years.

Exclusion criteria were as follows: presence of secondary hypertension, clinical signs of atherosclerosis-related diseases, clinical and laboratory signs of chronic liver disease, decreased glomerular filtration rate (GFR) < 60 mL/min/1.73 m², proteinuria ≥ 300 mg/day, type 1 and type 2 diabetes mellitus, any inflammatory diseases, and pregnancy at the time of study enrollment.

This study included 450 Caucasian patients with a median age of 30 (21 - 42) years. All patients underwent a questionnaire to assess risk factors and potential exclusion criteria, followed by comprehensive anthropometric examination, assessing traditional obesity markers: waist circumference (WC), hip circumference (HC), neck circumference (NC), and body mass index (BMI) [11]. Glycemic parameters and lipid profile components - total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG) - were determined using the CardioChek PA (USA, 2017). Integral metabolic indices were calculated in all patients: visceral adiposity index (VAI) [12], body fat percentage (BFP) [13],

body adiposity index (BAI) [14], and lipid accumulation product (LAP) index [15]. The presence of MS was determined according to the diagnostic criteria proposed in national clinical guidelines for the diagnosis, treatment, prevention of obesity and associated diseases (2017) [11, 16].

To investigate leukocyte telomere length, 45 patients (19 males (43%) and 26 females (57%)) were randomly selected from the total cohort of 450 participants using the random envelope method. In accordance with this method, a blinded researcher took out 45 sealed opaque envelopes out of 450 containing the patient's identification number. The age median was 26 (21 - 39) years.

Leukocyte DNA was isolated from whole blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Germany, 2022), following the manufacturer's instructions. DNA concentration was measured using a Qubit 4 fluorometer (Singapore, 2020). Two pairs of primers were used for RT-PCR: for telomeres (teloF and teloR) and single-copy gene (36B4F and 36B4R), as well as standard oligomers for telo and 36B4.

Statistical analysis

The results of the study were processed by Statistica 12.0 program (StatSoft Inc., USA). For variables with non-normal distribution, the median and interquartile range (25th and 75th percentiles) were calculated and presented as Me (25th - 75th). The significance of differences in mean values was assessed using the Mann-Whitney U test ($p(U)$) for variables with a non-normal distribution. When comparing categorical variables, Pearson's χ^2 test ($p(\chi^2)$) was used to assess statistical significance. The Spearman's rank correlation coefficient (ρ) was used to identify and evaluate the associations between the studied variables in cases of non-normal distribution. Multivariate linear regression analysis was conducted to assess the independent effect of each variable included in the model on the outcome, with all other variables held constant at their mean values.

Results

The 45 patients selected using the random envelope method were comparable to the main group ($n = 450$) in terms of age, sex, anthropometric parameters, and prevalence of hypertension, obesity, and smoking ($P > 0.05$) (Table 1).

The selected patients ($n = 45$) were divided into two groups according to the presence of MS. The MS group included 10 patients (22.2%), while the non-MS group included 35 patients (77.8%). The groups did not differ significantly by sex, age, and the proportion of smokers (Table 2). In the MS group, levels of anthropometric (BMI, WC, HC, and NC) and laboratory (TC and TG) metabolic markers, the proportion of patients with obesity, hypertension, dyslipidemia, and hyperglycemia were significantly higher compared to the non-MS group.

In the MS group, the levels of integral metabolic indices such as LAP, BFP, and BAI were significantly higher than in

Table 1. Clinical Characteristics of the Main and Randomized Groups

	Main group (n = 450)	Patients with telomere length assessment (n = 45)	P-value
Sex, male/female, %	48.7/51.3	44.4/55.6	0.25
Age, years	30 (21 - 42)	26 (21 - 39)	0.09
BMI, kg/m ²	24.01 (20.2 - 31.8)	23 (22 - 29.7)	0.44
Obesity by BMI, %	19.7	24.4	0.09
EH, %	34	24.4	0.06
MS, %	26	22.2	0.13
SBP, mm Hg	121 (111 - 136)	124 (114 - 135)	0.09
DBP, mm Hg	71 (64 - 81)	78 (71 - 85)	0.07
Smoking, %	40.6	42.2	0.39

BMI: body mass index; DBP: diastolic blood pressure; EH: essential hypertension; MS: metabolic syndrome; SBP: systolic blood pressure.

the comparison group. The median VAI values did not differ between the groups ($P > 0.05$, Table 2). However, sex-specific analysis revealed a significant difference in VAI among men: in the presence of MS, VAI was 3.6 (1.7 - 5.1), compared to 1.37 (0.5 - 3.9) in those without MS ($P < 0.001$). Among wom-

en, no significant differences in VAI were observed: 0.72 (0.53 - 1.8) with MS and 0.63 (0.5 - 1.03) without MS ($P = 0.78$).

The median telomere length in MS patients (7.36 (6.96 - 8.67) pn) was significantly lower than in the comparison group (8.72 (8.37 - 8.96) pn) ($P = 0.02$) (Fig. 1).

Table 2. Clinical Characteristics of Groups With and Without MS

	MS group (n = 10)	Non-MS group (n = 35)	P
Sex, male/female, %	50/50	40/60	0.57
Age, years	28.5 (23 - 43)	26 (21 - 37)	0.35
Smoking, %	50	40	0.57
BMI, kg/m ²	30.95 (30 - 34.2)	22.6 (20.7 - 23.9)	< 0.001
WC, cm	119 (110 - 125)	79 (71 - 83)	< 0.001
HC, cm	117.5 (115 - 118)	95 (92 - 98)	< 0.001
NC, cm	39 (38 - 42)	33 (31 - 34)	< 0.001
Obesity (BMI > 30 kg/m ²), %	90	8.57	< 0.001
EH, %	50	17.14	0.03
SBP, mm Hg	157 (124 - 165)	120 (112 - 130)	0.01
DBP, mm Hg	90 (80 - 96)	77 (70 - 83)	0.005
Dyslipidemia, %	90	34.29	0.002
TC, mmol/L	6.01 (3.6 - 6.8)	4.7 (3.9 - 5.1)	0.04
TG, mmol/L	2.75 (1.9 - 3.0)	1.2 (0.7 - 1.9)	< 0.001
LDL, mmol/L	2.9 (2.8 - 3.5)	2.8 (2.1 - 3.1)	0.16
HDL, mmol/L	1.09 (0.9 - 1.54)	1.7 (1.08 - 1.8)	0.07
Hyperglycemia, %	20%	0%	0.007
Glucose, mmol/L	4.88 (4.1 - 5.5)	4.3 (3.9 - 4.9)	0.19
LAP	138.7 (90.6 - 156)	16.17 (9.7 - 38.2)	< 0.001
VAI	1.37 (0.5 - 5.01)	0.78 (0.56 - 0.9)	0.35
BFP, %	33.3 (28.7 - 43.9)	25.8 (17.6 - 29.2)	0.001
BAI	33.6 (29.7 - 38.5)	24.8 (21.5 - 27.4)	< 0.001
Telomere length, pn	7.36 (6.96 - 8.67)	8.72 (8.37 - 8.96)	0.02

BAI: body adiposity index; BFP: body fat percentage; BMI: body mass index; DBP: diastolic blood pressure; EH: essential hypertension; HC: hip circumference; HDL: high-density lipoprotein; LAP: lipid accumulation product index; LDL: low-density lipoprotein; MS: metabolic syndrome; NC: neck circumference; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; VAI: visceral adiposity index; WC: waist circumference.

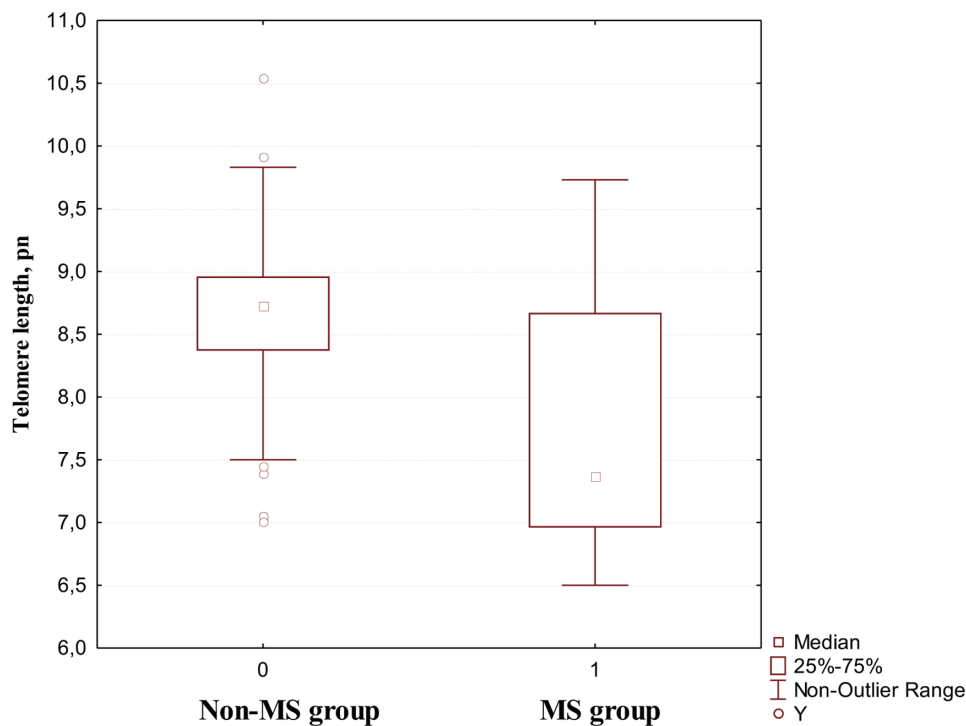


Figure 1. Median telomere length depending on the presence of metabolic syndrome.

Correlation analysis was performed to assess the relationship between telomere length and various traditional cardiovascular risk factors (sex, age, smoking, and blood pressure levels), MS components, and integral metabolic indices. Statistically significant correlations are summarized in Table 3.

Several linear regression analysis models were constructed to assess the independent associations between various factors and telomere length. The results of the regression analysis are presented in Table 4. Among the traditional risk factors (model 1), age and smoking were most significantly associated with telomere length (Table 4). Among the anthropometric markers of obesity (model 2), only NC was significantly associated with telomere length. When assessing the laboratory metabolic markers (model 3), TC and HDL levels were significantly associated with telomere length. Among the integral metabolic indices (model 4), LAP index in the general group (n = 45) and VAI among men (n = 20) demonstrated significant correlation (Table 4). When assessing the relationship between telomere length and the key component of MS - abdominal obesity - as well as its additional criteria (model 5), only the presence of dyslipidemia was significantly associated with telomere length.

Discussion

Original studies and meta-analyses have demonstrated that short leukocyte telomere length is associated with an increased risk of all-cause mortality (odds ratio (OR) 1.34; 95% confidence interval (CI): 1.21 - 1.47), cardiovascular mortality (OR 1.28; 95% CI: 1.08 - 1.52) [7], development of coronary heart

Table 3. Results of Correlation Analysis Between Telomere Length and Various Parameters in the Randomized Group (n = 45)

Parameter	Strength and reliability of the relationship, P < 0.05
Smoking	r = -0.35
presence of MS	r = -0.36
DBP	r = -0.31
Dyslipidemia	r = -0.76
WC	r = -0.3
HC	r = -0.35
NC	r = -0.53
TC	r = -0.64
HDL	r = 0.59
TG	r = -0.46
LDL	r = -0.52
Glucose	r = -0.33
LAP	r = -0.4
VAI (men)	r = -0.57
BAI	r = -0.32

BAI: body adiposity index; DBP: diastolic blood pressure; HC: hip circumference; HDL: high-density lipoprotein; LAP: lipid accumulation product; LDL: low-density lipoprotein; NC: neck circumference; MS: metabolic syndrome; TC: total cholesterol; TG: triglycerides; VAI: visceral adiposity index; WC: waist circumference.

Table 4. Multivariate Linear Regression Analysis Results of the Association Between Cardiovascular Risk Factors, MS Components, and Telomere Length

Model	Parameter	B	Standard error of B	P
Model 1	Overall significance	12.08	1.15	< 0.001
	Sex	-	-	> 0.05
	Age	-0.04	0.02	0.03
	Smoking	-0.87	0.26	0.001
	EH	-	-	> 0.05
	SBP	-	-	> 0.05
	DBP	-	-	> 0.05
Model 2	Overall significance	15.6	1.7	< 0.001
	Weight	-	-	> 0.05
	BMI	-	-	> 0.05
	WC	-	-	> 0.05
	HC	-	-	> 0.05
	NC	-0.23	0.07	0.001
	Overall significance	10.7	0.87	< 0.001
Model 3	Glucose	-	-	> 0.05
	TC	-0.37	0.87	< 0.001
	LDL	-	-	> 0.05
	HDL	0.59	0.24	0.02
	TG	-	-	> 0.05
	Overall significance	9.5	0.55	< 0.001
Model 4	LAP	-0.01	0.02	< 0.01
	VAI	-	-	> 0.05
	VAI (men)	-0.37	0.16	0.02
	VAI (women)	-	-	> 0.05
	BAI	-	-	> 0.05
	BFP	-	-	> 0.05
	Overall significance	9.06	0.14	< 0.001
Model 5	Presence of abdominal obesity	-	-	> 0.05
	EH	-	-	> 0.05
	Presence of dyslipidemia	-1.13	0.23	< 0.001
	Presence of hyperglycemia	-	-	> 0.05
	Overall significance	9.06	0.14	< 0.001

BAI: body adiposity index; BFP: body fat percentage; BMI: body mass index; DBP: diastolic blood pressure; EH: essential hypertension; HC: hip circumference; HDL: high-density lipoprotein; LAP: lipid accumulation product; LDL: low-density lipoprotein; NC: neck circumference; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; VAI: visceral adiposity index; WC: waist circumference.

disease (OR 1.54; 95% CI: 1.30 - 1.83) [7, 8], and type 2 diabetes mellitus [3, 7, 8]. However, uncertainty remains regarding the nature of these associations.

Our study included 450 young Caucasian patients without clinically manifested CVD but with various cardiovascular risk factors, the prevalence of which in our sample was comparable to that observed in the general population [17]. The comparable group (n = 45) was selected for the genetic analysis using randomization, which allowed extrapolation of the results from the leukocyte telomere length analysis to the total

sample. However, the study was conducted among Caucasian patients in a single-center setting, which limits the applicability of our results to other ethnic groups and is a limitation of this study.

In our study, patients with and without MS did not differ significantly by sex, age, and smoking prevalence; additionally, the median age in both did not exceed 30 years. This allows us to exclude the influence of age-related diseases known to contribute to telomere shortening [8]. All diagnostic components of MS - abdominal obesity, EH, dyslipidemia, and hyper-

glycemia - were significantly more frequent in the MS group. The absence of significant differences in glycemia, HDL, and LDL levels was due to the exclusion of individuals with diabetes, characterized by elevated blood glucose levels, and atherosclerotic diseases, typically associated with high LDL and low HDL values in this study [18]. Despite the higher prevalence of hypertension in the MS group, no significant differences in the SBP were obtained, which is probably due to effective blood pressure control achieved through antihypertensive therapy.

Among traditional risk factors, multivariate analysis revealed that age and smoking were significantly associated with telomere length. These relationships were negative, consistent with previous studies, and supporting the representativeness of our sample [9, 19]. The precise mechanisms through which smoking, environment, lifestyle factors, and dietary patterns influence telomere length remain unclear and require further investigation to clarify their roles.

In MS patients, the median telomere length was significantly shorter than in the control group. Univariate correlation analysis revealed significant negative correlations not only with the presence of MS, but also with its individual components: dyslipidemia, DBP, and glucose level. Among the markers of obesity, the strongest negative relationship was observed between telomere length and NC ($r = -0.53$; $P < 0.05$), reflecting the potential importance of this marker in identifying the metabolically unhealthy phenotype of obesity, consistent with previous studies [2].

Short telomere length may be either a cause or a consequence of MS [6]. There is no definite consensus in the literature on whether premature telomere shortening and the consequent aging of stem cells in subcutaneous adipose tissue lead to pathological redistribution of fat in the upper body and metabolic dysfunction with all its negative manifestations [18], or whether MS associated with a sharp increase in oxidative stress and systematic inflammation, impairs the activity of endogenous telomerase - the enzyme responsible for telomere length maintenance [6].

The causal mechanisms underlying telomere shortening and MS may be diverse and depend on the combination or predominance of different components - obesity, dyslipidemia, hyperglycemia, and EH - each accelerating cellular aging through different mechanisms [20]. Regardless of the causal relationship and triggering mechanism, the accumulation of senescent cells in the vascular intima and atherosclerotic plaques reduces the regenerative potential of tissue and promotes apoptosis, which in turn enhances inflammatory reactions and endothelial dysfunction, forming a vicious circle [8]. In addition, cellular aging is characterized by a decrease in the proliferative potential of vascular smooth muscle cells, which contributes to fibrous cap thinning and atherosclerotic plaque instability, leading to cardiovascular complications [8].

Our study revealed negative association between leukocyte telomere length and the integral metabolic indices VAI (in men), LAP, and BAI. The LAP index in its calculation formula, in addition to anthropometric markers of obesity, contains triglyceride level, which also negatively correlated with telomere length. BAI index, an analog of BMI adjusted for age [21], was likewise negatively associated with telomere length. When evaluating the correlation between VAI and telomere length in

the total group, no significant associations were observed. However, sex-specific analysis revealed the negative correlation in men, whereas no correlation was found in women. A 2014 meta-analysis reported longer telomere length in women [21], but a 2017 study [22] failed to confirm these sex-related differences, and there is evidence that differences in leukocyte telomere length are less pronounced at younger ages [23]. In our study, it was not possible to evaluate sex-related differences in telomere length among patients with and without MS due to the small number of patients with MS ($n = 10$) and narrow age range. This limitation underscores the need for further investigation.

The results of multivariate regression analysis demonstrated significant negative associations of age and smoking with leukocyte telomere length. Among anthropometric markers of obesity, only NC was significantly associated with telomere length, emphasizing the importance of this marker [24]. Among the laboratory markers, TC level was negatively associated with telomere length, whereas HDL was positively associated with telomere length. The strongest negative association was observed in the LAP index. Thus, among the individual components of MS, only the presence of dyslipidemia was significantly negatively associated with telomere length. In the 2021 study by Loh et al, positive correlations between telomere length and MS were obtained. However, the authors emphasized the determining role of hypertension as a key component of MS, with the significant positive associations observed between telomere length and hypertension with its variables [6]. In our study, the contribution of hypertension to the formation of MS [25] was not so pronounced (24%), which can be explained by the young age of the participants and the widespread use of regular antihypertensive therapy with achievement of target blood pressure levels. There are data in the literature on changes in metabolic markers, in particular HDL, in patients with hypertension with controlled and uncontrolled course, thus the nature of the course of the disease is apparently of great importance [26]. In addition, the lack of significant statistical results for the relationship between MS and telomere length in multivariate regression analysis may be due to the small sample size, which is a limitation of this study.

Thus, our results are consistent with the notion of shorter leukocyte telomere length in individuals with MS [8] and confirm the importance of proatherogenic laboratory markers and dyslipidemia in systemic inflammation and oxidative stress - key contributors in premature shortening of telomere length [6]. The importance of integral metabolic indices, in particular the LAP index, significantly correlated with leukocyte telomere length, is also highlighted. However, many questions remain unresolved: the contribution of individual MS components and sex-related differences in the relationship between MS and telomere length, the influence of environmental factors, food culture and dietary habits on telomere length, as well as differences in leukocyte telomere length in patients with different ectopic variants of obesity.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

All individuals included in the study provided written informed consent.

Author Contributions

Conceptualization: AB, AT, VP, LV, and ND; methodology: AB, ND, YS, AT, and LV; software: KN, PM, and ES; validation: AB and ND; formal analysis: IL, KN, and ND; data collection and analysis: OA, YS, NV, and KN; interpretation of data: AB, ND, IL, and KN; data curation: AB, ND, and VP; writing - original draft preparation: ND, KN, and LV; writing - review and editing: AB, AT, ND, and VP; writing - literacy search: LV and ND; supervision: VP; project administration: VP. All authors approved the final version of the manuscript for submission.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

BAI: body adiposity index; BFP: body fat percentage; BMI: body mass index; DBP: diastolic blood pressure; EH: essential hypertension; HC: hip circumference; HDL: high-density lipoprotein; LAP: lipid accumulation product index; LDL: low-density lipoprotein; MS: metabolic syndrome; NC: neck circumference; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; VAI: visceral adiposity index; WC: waist circumference

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