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■ Original Article

Single point insulin sensitivity estimator index is associated with predominance of atherogenic small, dense low-density lipoprotein cholesterol particles in Korean obese adults: a retrospective study

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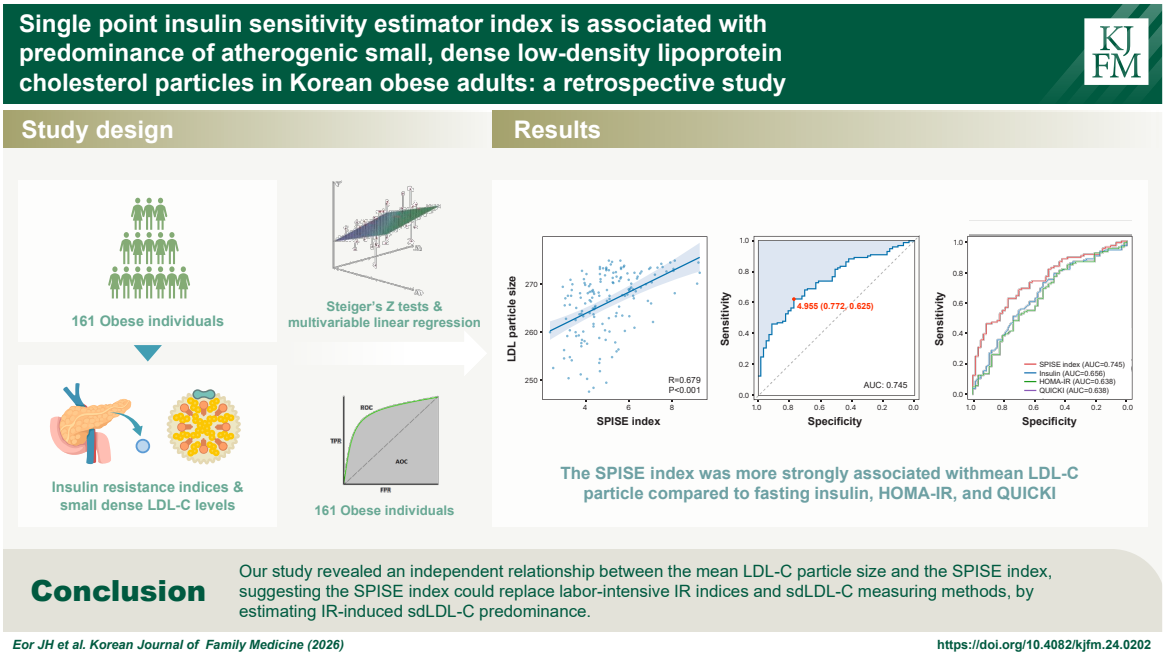

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ABSTRACT

Background: Insulin resistance (IR) influences lipid metabolism, particularly small dense low-density lipoprotein cholesterol (sdLDL-C), a key feature of diabetic dyslipidemia and a predictor of cardiovascular disease. The single-point insulin sensitivity estimator (SPISE) index is an effective tool for assessing IR. This study explored the relationship between the SPISE index and average low-density lipoprotein cholesterol (LDL-C) particle size in obese Korean adults.

Methods: Cardiovascular risk was assessed in 161 obese individuals. The participants were divided into three groups based on SPISE index tertiles. Steiger's Z test was used to assess the differences in correlation coefficients among various IR indices and average LDL-C particle size. Multivariate linear regression models were used to determine the independent association between the SPISE index and average LDL-C particle size. Receiver operating characteristic (ROC) curves established the SPISE index cut-off for sdLDL-C particle dominance.

Results: The SPISE index was positively correlated with mean LDL-C particle size after adjusting for confounders. It demonstrated a stronger independent association with average LDL-C particle size (r=0.679, P<0.001) than with fasting insulin, the homeostatic model assessment for IR, and the quantitative insulin sensitivity check index (P<0.001 for all). ROC analysis identified an optimal SPISE index cutoff for sdLDL-C predominance of 4.955, with an area under the curve of 0.745.

Conclusion: Our findings indicate a direct correlation between the SPISE index and average LDL-C particle size, suggesting that the SPISE index may complement labor-intensive IR indices and sdLDL-C measurement techniques for estimating IR-induced sdLDL-C predominance.

Keywords: Diabetes Mellitus; Dyslipidemia; Insulin Resistance; Low Density Lipoprotein; Cardiovascular Disease

Introduction

Insulin resistance (IR) is a physiological state where tissues that normally respond to insulin become less sensitive to its effects [1]. This condition precedes elevated plasma glucose levels and leads to chronic hyperinsulinemia, β-cell failure, and eventually type 2 diabetes mellitus (T2DM) [1]. IR is also linked to low levels of high-density lipoprotein cholesterol (HDL-C), T2DM, and hypertriglyceridemia, all of which increase the risk of cardiovascular disease (CVD) [2,3]. Multiple studies have confirmed that IR is a potent independent predictor of atherosclerotic CVD [3-5]. Several methods exist to measure IR, including the hyperinsulinemic-euglycemic clamp test and the oral glucose tolerance test. However, these methods are labor-intensive, time-consuming, and expensive [6]. To simplify IR assessment, various surrogate markers and indices, such as the homeostatic model assessment for IR (HOMA-IR) and the quantitative insulin-sensitivity check index (QUICKI), have been developed [7,8]. Despite their utility, their widespread clinical use is restricted by the need for insulin measurement [9]. Among non-insulin-derived indices, the single-point insulin sensitivity estimator (SPISE) index is a recent innovation that relies on body mass index (BMI) and the triglyceride (TG)/HDL-C ratio. This demonstrated robust predictive capabilities for the assessment of IR [10]. The SPISE index has been shown to predict nonalcoholic fatty liver disease, a metabolic disorder associated with IR. Moreover, a high SPISE index was independently associated with a reduced future cardiovascular risk in patients with type 2 diabetes [11].

IR affects lipid metabolism, with small dense low-density lipoprotein cholesterol (sdLDL-C) being a hallmark of diabetic dyslipidemia [12]. Recognized as an emerging biomarker and independent risk factor for CVD, sdLDL-C is considered a stronger predictor of CVD than traditional low-density lipoprotein cholesterol (LDL-C) [13]. Smaller LDL-C particles penetrate arterial walls, bind to proteoglycans, oxidize rapidly, and release pro-inflammatory cytokines, contributing to atherosclerosis and elevated ischemic heart disease risk [14]. A recent study highlighted sdLDL-C as having the highest atherogenic potential among lipoproteins [15]. However, correlations between sdLDL-C and various IR markers have been inconsistent, partly due to differences in the methods used to measure IR and LDL-C subfractions [2,16-18]. Additionally, these correlations are influenced by TG levels, which significantly impact sdLDL-C and its association with insulin sensitivity [19].

This study aims to explore the relationship between the SPISE index—derived from BMI and the TG/HDL-C ratio—and average LDL-C particle size, which decreases as sdLDL-C levels increase, in obese Korean adults.

Methods

Study population

This study included 161 outpatients who voluntarily visited the Obesity Clinic at Severance Hospital for cardiovascular risk evaluation between October 2016 and September 2021. Participants were recruited based on the Asia-Pacific criteria for obesity, defined as a BMI of 25.0 kg/m^2 or higher [20]. The inclusion criteria required participants to have no prior history of malignancy, thyroid disease, chronic liver disease (including cirrhosis, hepatitis B, or hepatitis C), kidney disease, chronic inflammatory disease, or CVD. The exclusion criteria were as follows: (1) diagnosis of dyslipidemia (n=38); (2) diagnosis of T2DM (n=38); (3) missing data on BMI, fasting serum triglycerides, and HDL-C levels (n=32); and (4) incomplete clinical data (n=8). Consequently,

161 patients were included in the final analysis (Figure 1). This study was approved by the Institutional Review Board (IRB) of Severance Hospital and adhered to the guidelines of the Declaration of Helsinki (IRB approval no., 4-2024-0883). The requirement for informed consent from individual patients was omitted because of the retrospective design of this study.

Clinical and anthropometric data

Information on medical and social history was gathered using self-administered questionnaires, and past and current medical conditions and health-related behaviors were verified using the patients' medical records. Smoking status was defined as any current smoking, and alcohol consumption was defined as consuming more than 72 g of alcohol per week [21]. Physical measurements were conducted by trained medical staff. Height was measured to the nearest 0.1 cm, and body weight were recorded to the nearest 0.1 kg. Body weight and composition were assessed using a bioelectrical impedance analyzer (InBody 720; Biospace), and BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference (WC) was measured at the midpoint between the lower costal margin and iliac crest while the participant was standing. Blood pressure (BP) was measured from the right arm of seated participants using an electronic manometer (BPBio 320; Biospace). Heart rate was monitored using a Polar FS3c heart rate monitor (Polar Electro Oy). Intra-abdominal visceral and subcutaneous fat areas were evaluated using computed tomography (TomoScan 350; Philips), following previously established protocols [11].

Biochemical analyses

Blood tests were conducted after a minimum of 12 hours of overnight fasting. The levels of total cholesterol, HDL-C, LDL-C, fasting plasma glucose, gamma-glutamyl transferase (GGT), aspartate transaminase (AST), alanine transaminase (ALT), uric acid, and high-sensitivity C-reactive protein (hsCRP) were analyzed using a chemical analyzer (Hitachi 7600; Hitachi). Fasting insulin levels were measured using an immunology analyzer (Elecsys 2010; Roche).

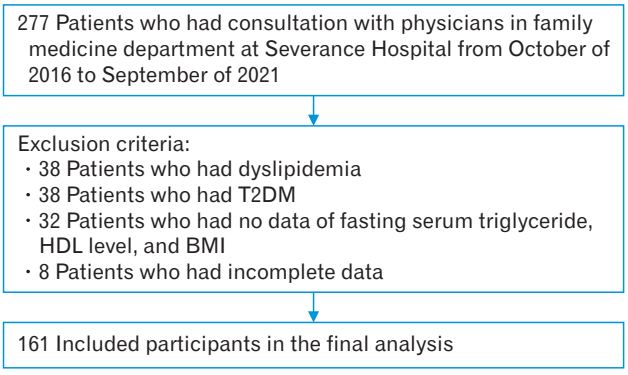

Figure 1. Flow chart for selecting participants. T2DM, type 2 diabetes mellitus; HDL, high-density lipoprotein; BMI, body mass index.

The Quantimetrix Lipoprint system categorizes LDL-C into seven subfractions (LDL-C1 to LDL-C7) based on electrophoretic mobility (Rf) ranging from very low-density lipoprotein (VLDL-C, Rf=0) to HDL-C (Rf=1). Large buoyant LDL-C encompasses subclasses LDL-C1 and LDL-C2, whereas sdLDL-C comprises subclasses LDL-C3–LDL-C7. The mean LDL-C particle size and percentage of sdLDL-C were computed and the ratio of sdLDL-C to large LDL-C was derived by dividing the sum of LDL-C3 and LDL-C7 by the sum of LDL-C1 and LDL-C2. This system also calculates the relative area of each lipoprotein band and determines VLDL-C and IDL concentrations by multiplying the area under the curve (AUC) for each fraction by the total cholesterol concentration, thus providing detailed insights into LDL-C particle size distribution and subfraction composition [22]. LDL-C particles are classified into three categories based on size: particles with a mean size of 268.0 Å or larger are classified as pattern A, those smaller than 265.0 Å as pattern B, and those between 265.0 Å and 268.0 Å as pattern I [23].

Insulin resistance index calculation

IR was assessed using three indices: HOMA-IR, QUICKI, and the SPISE index. HOMA-IR was calculated by multiplying the fasting serum insulin level (μU/mL) by the fasting plasma glucose level (mg/dL), and then dividing the result by 405 [7]. QUICKI was derived using the inverse of the sum of the logarithms of fasting insulin (μU/mL) and fasting glucose (mg/dL) [8]. SPISE index was calculated using the formula, $SPISE=600\times HDL\text{-}C^{0.185}/(TG^{0.2}\times BMI^{1.338})$ [10].

Statistical analysis

Continuous variables are presented as means±standard deviation for normally distributed data, and as medians and ranges for non-normally distributed data. Categorical variables are expressed as frequencies and percentages. To compare clinical characteristics across SPISE index tertiles, analysis of variance was used for normally distributed variables, whereas the Kruskal-Wallis test was employed for non-normally distributed variables. The proportions were compared using Pearson chi-square test. Spearman correlation coefficient was used to assess the relationship between the SPISE index and clinical variables.

To evaluate the differences in absolute correlation coefficients between the mean LDL-C particle size and various IR indices, Steiger's Z tests were applied. Multivariable linear regression models were constructed to analyze the risk factors associated with the SPISE index, with confounding variables (age, sex, mean arterial BP, mean LDL-C particle size, LDL-C and VLDL-C concentrations, alcohol consumption, smoking history, and fasting plasma glucose) were selected based on clinical relevance. The final model was selected using the backward elimination method, which involved sequentially removing predictors from the full model. Linear regression results were reported as beta coefficients, 95% confidence intervals (CIs), and P-values.

Receiver operating characteristic (ROC) curves were used to obtain the AUC and to determine the SPISE index cutoff value for sdLDL-C particle dominance. DeLong's method was used to calculate the stan-

dard error (SE) and 95% CI of the AUC. Using power calculations for the 161 participants in this study, the power to test the AUC was confirmed to be above 90%. Statistical significance was defined as a two-sided P-value of <0.05. All statistical analyses were performed using R ver. 4.3.0 (R Foundation).

Results

Clinical characteristics of the study participants

Table 1 presents the clinical characteristics of the study participants, categorized according to SPISE index tertiles. Among the 161 participants, 21.7% were male. The average BMI was 30.9 kg/m^2, and the average age was 39.2 years. Participants in the lowest SPISE tertile exhibited significantly higher mean BP (P<0.001), heart rate (P=0.031), WC (P<0.001), abdominal visceral fat area (P<0.001) and subcutaneous fat area (P<0.001), serum markers, including AST (P=0.001), ALT (P<0.001), GGT (P<0.001), hsCRP (P<0.001), uric acid (P<0.001), fasting insulin (P<0.001), HOMA-IR (P<0.001), and TG/HDL-C ratio (P<0.001). The QUICKI levels were notably lower (P<0.001).

The relationship between lipid profiles, LDL-C particle size and SPISE index

Lipid profiles and LDL-C particle sizes differed significantly among the SPISE tertile groups after adjusting for age, sex, BMI, smoking status, and alcohol consumption (Table 2). Participants in the lowest SPISE tertile exhibited significantly higher TG levels (P<0.001) and a greater proportion of small, dense LDL-C particles (P<0.001), which were associated with an increased cardiovascular risk. Conversely, the proportions of HDL-C, large buoyant LDL-C, and mean LDL-C particle size were significantly lower in this group (P<0.001 for all).

Figure 2 illustrates the associations between various lipid profiles and the SPISE index adjusted for age, sex, and BMI. The SPISE index was positively correlated with HDL-C levels (r=0.644, P<0.001) and LDL-C particle size (r=0.679, P<0.001). However, it was negatively correlated with non-HDL-C (r=–0.290, P<0.001) and VLDL-C levels (r=–0.584, P<0.001).

To determine the independent relationship between mean LDL-C particle size and the SPISE index, multiple linear regression analysis was conducted with adjustments for age, sex, mean BP, fasting glucose, VLDL-C, alcohol consumption, and smoking history. The analysis revealed a statistically significant independent association between mean LDL-C particle size and the SPISE index (P<0.001) (Table 3).

Table 1. Clinical characteristics of participants according to SPISE tertiles

Characteristic	SPISE index				
	Overall (n=161)	Tertile 1 (n=54)	Tertile 2 (n=53)	Tertile 3 (n=54)	P-value
Age (y)	39.2±13.4	36.7±11.6	39.4±13.8	41.4±14.6	0.192
Sex					0.002
Male	35.0 (21.7)	20.0 (37.0)	10.0 (18.8)	5.0 (9.3)	
Female	126.0 (78.3)	34.0 (63.0)	43.0 (81.1)	49.0 (90.7)	
Systolic blood pressure (mm Hg)	122.8±13.9	129.5±12.5	122.3±12.9	116.5±13.2	<0.001
Diastolic blood pressure (mm Hg)	72.7±10.0	76.4±9.8	72.0±9.8	69.5±9.4	0.001
Mean blood pressure (mm Hg)	89.4±10.8	94.1±10.1	88.8±10.4	85.1±10.2	<0.001
Heart rate (beat/min)	72.7±11.0	75.9±11.4	71.4±10.6	70.8±10.4	0.031
Body mass index (kg/m^2)	31.0±5.1	36.3±3.9	30.5±2.6	26.1±2.3	<0.001
Waist circumference (cm)	98.1±12.6	109.4±10.6	96.7±6.6	87.4±8.0	<0.001
Abdominal VAT area (cm^2)	60.5 (27.4–165.0)	73.4 (41.6–137.0)	56.6 (27.5–128.0)	52.3 (27.4–165.0)	<0.001
Abdominal SAT area (cm^2)	115.0 (49.0–311.0)	146.0 (65.3–311.0)	112.0 (53.2–297.0)	88.4 (49.0–154.0)	<0.001
AST (U/L)	23.0 (11.0–130.0)	26.5 (11.0–130.0)	25.0 (14.0–74.0)	21.0 (14.0–81.0)	0.001
ALT (U/L)	25.0 (4.0–280.0)	42.0 (4.0–274.0)	27.0 (6.0–280.0)	18.5 (8.0–178.0)	<0.001
GGT (IU/L)	22.0 (8.0–247.0)	27.0 (10.0–141.0)	23.0 (10.0–247.0)	15.5 (8.0–155.0)	<0.001
hsCRP (mg/dL)	1.3 (0.1–17.2)	3.3 (0.4–15.3)	1.4 (0.20–17.20)	0.7 (0.1–6.3)	<0.001
Uric acid (mg/dL)	5.8±1.4	6.5±1.3	5.7±1.3	5.2±1.1	<0.001
Fasting plasma glucose (mg/dL)	97.1±11.4	99.6±10.3	95.7±14.9	96.1±7.5	0.149
Insulin (mIU/L)	11.6 (1.1–61.4)	19.1 (6.1–47.8)	11.8 (4.1–61.4)	7.5 (1.1–26.8)	<0.001
HOMA-IR	51.4 (4.2–283.8)	82.9 (22.5–223.4)	51.4 (14.8–283.8)	30.5 (4.2–129.8)	<0.001
QUICKI	0.1±0.0	0.1±0.0	0.1±0.0	0.2±0.0	<0.001
TG/HDL-C ratio	3.0±2.0	4.1±2.1	3.1±2.0	1.8±0.9	<0.001
Smoking history (yes)	15.0 (9.3)	8.0 (14.8)	4.0 (7.6)	3.0 (5.6)	0.284
Alcohol consumption (yes)	33.0 (20.5)	11.0 (20.4)	10.0 (18.9)	12.0 (22.2)	0.911
Hypertension (yes)	25.0 (15.5)	12.0 (22.2)	6.0 (11.3)	7.0 (13.0)	0.243

Values are presented as means±standard deviation, number (%), or median (range).
SPISE, single-point insulin sensitivity estimator; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; hsCRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment-estimated insulin resistance; QUICKI, quantitative insulin sensitivity check index; TG, triglyceride; HDL-C, high density lipoprotein cholesterol.

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Table 2. Lipid and LDL-C subfractions profiles based on SPISE index tertiles

Variable	SPISE index				
	Overall (n=161)	Tertile 1 (n=54)	Tertile 2 (n=53)	Tertile 3 (n=54)	P-value
Total cholesterol	198.0 (116.0–335.0)	201.0 (116.0–274.0)	199.0 (143.0–335.0)	196.0 (147.0–295.0)	0.821
HDL-C	52.0 (33.0–94.0)	45.0 (33.0–75.0)	50.0 (34.0–91.0)	59.5 (36.0–94.0)	<0.001
Non-HDL-C	144.5 (74.0–279.0)	155.5 (74.0–228.0)	146.0 (94.0–279.0)	137.0 (82.0–222.0)	0.010
Triglyceride (mg/dL)	143.50±76.46	182.22±82.58	144.89±77.42	103.4±42.2	<0.001
LDL-C	126.0 (68.0–205.0)	128.0 (68.0–192.0)	130.0 (83.0–200.0)	122.0 (72.0–205.0)	0.843
VLDL-C	19.5 (5.5–31.1)	21.8 (5.5–31.0)	20.0 (12.2–27.3)	16.9 (8.8–31.1)	<0.001
lbLDL-C	28.3 (0.7–37.3)	26.3 (0.7–33.6)	28.7 (8.5–37.3)	29.3 (13.1–37.0)	0.012
sdLDL-C	2.5 (0.0–22.3)	5.5 (0.0–20.3)	2.5 (0.0–22.3)	1.25 (0.0–12.9)	<0.001
Percent sdLDL-C	7.7 (0.0–60.0)	16.8 (0.0–60.0)	7.7 (0.0–58.5)	3.9 (0.0–41.8)	<0.001
sdLDL-C : lbLDL-C ratio	0.1 (0.0–1.5)	0.2 (0.0–1.5)	0.1 (0.0–1.4)	0.0 (0.0–0.7)	<0.001
Mean LDL-C particle size	267.8 (247.5–274.8)	264.1 (247.5–272.7)	267.6 (248.4–274.8)	270.7 (256.3–274.8)	<0.001

Values are presented as median (range) or means±standard deviation after adjusting age, sex, body mass index, smoking history, and alcohol consumption.
LDL-C, low-density lipoprotein cholesterol; SPISE, single-point insulin sensitivity estimator; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; lbLDL-C, large buoyant low-density lipoprotein cholesterol; sdLDL-C, small dense low-density lipoprotein cholesterol.

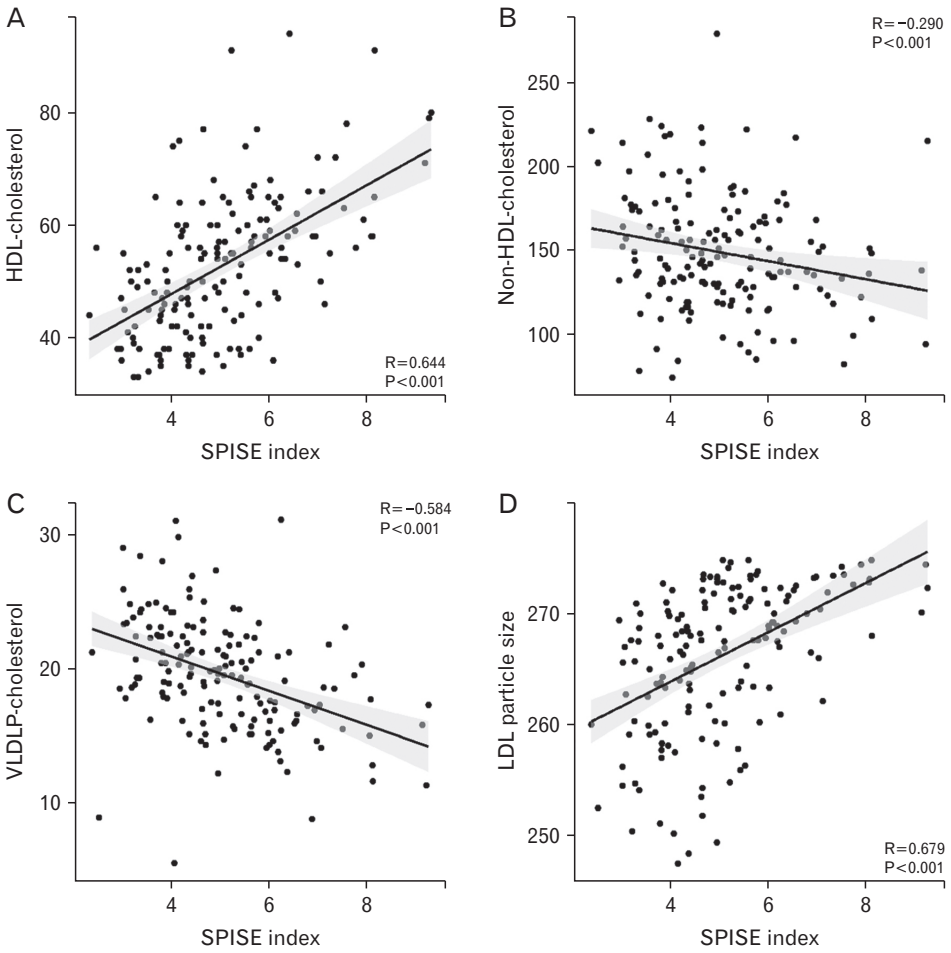

Figure 2. Relationship between single point insulin sensitivity estimator (SPISE) & lipid particles. To evaluate differences in absolute correlation coefficients with lipid profiles and the SPISE index, Steiger's Z tests were applied. Multivariable linear regression models were constructed to analyze the risk factors associated with the SPISE index. (A) SPISE & high-density lipoproteins (HDL), (B) SPISE & non-HDL, (C) SPISE & very-low-density lipoprotein particles (VLDL), and (D) SPISE & mean LDL particle size.

Comparisons of correlation coefficients of LDL-C particle size and insulin resistance indices

Correlation coefficients between mean LDL-C particle size and various IR indices were compared using Steiger's Z test (Table 4). Pearson correlation analysis showed that the SPISE index was more strongly associated with mean LDL-C particle size (r=0.679) than fasting insulin (r=–0.255), HOMA-IR (r=–0.224), and QUICKI (r=0.209), with Steiger's Z-test indicating P<0.001 for all comparisons.

Table 3. Multiple linear regression analysis to determine relationship between SPISE index and clinical metabolic variables

Variable	Enter		Stepwise	
	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Age (y)	0.03 (0.02 to 0.04)	<0.001	0.03 (0.02 to 0.04)	<0.001
Mean arterial pressure (mm Hg)	–0.05 (–0.07 to –0.03)	<0.001	–0.05 (–0.07 to –0.04)	<0.001
VLDL-C (mg/dL)	–0.06 (–0.11 to –0.02)	0.006	–0.07 (–0.11 to –0.03)	0.001
Mean LDL-C particle size (Å)	0.08 (0.05 to 0.11)	<0.001	0.08 (0.05 to 0.11)	<0.001
Alcohol consumption (yes)	0.47 (0.02 to 0.92)	0.041	0.42 (0.02 to 0.83)	0.041
Female sex	0.25 (–0.19 to 0.70)	0.258		
Fasting plasma glucose (mg/dL)	–0.01 (–0.02 to 0.01)	0.379		
Smoking history (yes)	–0.04 (–0.69 to 0.61)	0.896		
LDL-C (mg/dL)	0.00 (–0.01 to 0.01)	0.971		

SPISE, single-point insulin sensitivity estimator; CI, confidence interval; VLDL-C, very low-density lipoprotein cholesterol; LDC-C, low-density lipoprotein cholesterol.

Table 4. Comparisons of correlation coefficients of LDL-C particle size and insulin resistance indices

Variable	r	P-value[a]	P-value[b]
Mean LDL-C particle size			
Insulin	–0.251	0.001	<0.001
HOMA-IR	–0.224	0.004	<0.001
QUICKI	0.209	0.008	<0.001
SPISE index	0.679	<0.001	Ref[c]

Between the mean LDL-C particle size and insulin, HOMA-IR, QUICKI and SPISE index, partial correlation coefficients are defined as r values, adjusted for age, sex, and body mass index.
LDC-C, low-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; QUICKI, quantitative insulin-sensitivity check index; SPISE, single-point insulin sensitivity estimator.
[a]P-values for r between the mean LDL-C particle size and insulin, HOMA-IR, QUICKI, and SPISE index. [b]P-values for comparing absolute correlation coefficients via Steiger's Z test between the mean LDL-C particle size and insulin, HOMA-IR, QUICKI and SPISE index. [c]The reference value is defined as r between the SPISE index and mean LDL-C particle size.

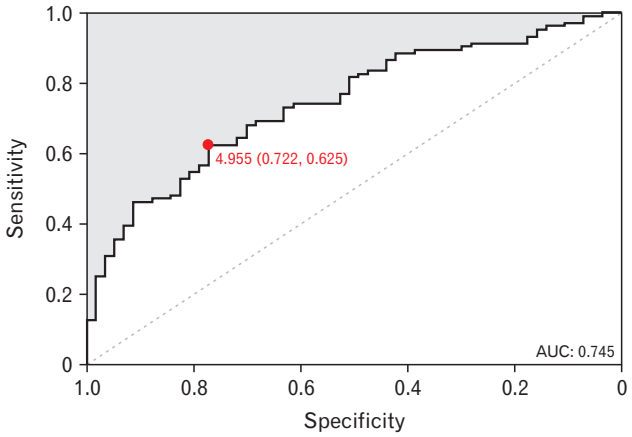

Figure 3. Receiver operating characteristic (ROC) curve analysis of single-point insulin sensitivity estimator (SPISE) and other insulin resistance (IR) indices. ROC curve was performed for diagnostic ability of SPISE, fasting insulin, homeostatic model assessment for IR, and quantitative insulin sensitivity check index, assuming null hypothesis of no difference in area under the curve (AUC) at 0.5. The red spot and number means the cut off value of SPISE index for small dense low-density lipoprotein predominance.

Optimal cutoff value of SPISE index for sdLDL-C particles predominance

The optimal cut-off value of the SPISE index for sdLDL-C particle predominance was determined using ROC curve analysis (Figure 3). The AUC was 0.745 (SE, 0.039; 95% CI, 0.668–0.821), and the cutoff value was 4.955. Additionally, we estimated the diagnostic performance of other IR indices by AUC values using ROC curve analysis (Supplements 1, 2).

Discussion

After adjusting for relevant confounders, we identified an independent association between the SPISE index and average LDL-C particle size. The SPISE index showed a stronger correlation with LDL-C particle size compared to other IR markers, highlighting its effectiveness as a practical predictor of sdLDL-C predominance.

The SPISE index is a non-invasive tool for evaluating IR based on fasting TG, HDL-C, and BMI. This tool facilitates easy diagnosis across age groups, from pediatric to adult populations [10,24]. Comparably sensitive and specific to the clamp-derived M-value, the SPISE index is a hepatic IR indicator and has shown superiority to insulin-based IR indices [25]. Additionally, sdLDL-C significantly contributes to atherosclerosis and CVDs through lipid metabolism, inflammation, oxidative stress, and fibrinolytic system activation [26].

The specific mechanisms underlying the close relationship between sdLDL-C predominance and the SPISE index remain unclear. However, this relationship may be explained by early alterations in lipid and lipoprotein metabolism in IR [27]. Elevated TG levels lead to TG-rich VLDL-C, which undergoes hydrolysis and exchanges with LDL-C and HDL-C, resulting in TG-rich LDL-Cs that are further processed into sdLDL-C by hepatic lipase [28]. Indeed, elevated TG levels and reduced HDL-C levels are significant risk factors for CVD, regardless of LDL-C levels [3]. In addition, the superior correlation of the SPISE index with LDL-C particle size to other IR indices in this study might be explained by the feature of the SPISE index. Because the SPISE index is a representative non-insulin-derived IR index that includes TG and HDL-C, which have a strong relationship with LDL-C concentration,

the SPISE index could overcome the limitations of other insulin-derived IR indices, such as HOMA-IR [24]. Further research is needed to elucidate the pathophysiological mechanisms underlying the relationship between IR and sdLDL-C.

Our results indicated that the SPISE index cutoff value for sdLDL-C particle predominance was 4.995, aligning with previous findings in obese Korean adolescents, where a SPISE index below 4.49 was associated with the onset of type 2 diabetes [29]. Furthermore, this aligns with a 2020 study suggesting that a low SPISE index (females, <6.0; males, <5.0) is associated with increased cardiometabolic risk [24]. However, due to the retrospective study design and the limited sample size, precise cutoff values could not be proposed, necessitating larger prospective studies for accurate determination.

Our study had several limitations. The cross-sectional design prevents the assessment of causality and limits conclusions regarding the longitudinal relationship between the SPISE index and sdLDL-C. Additionally, the sample size was relatively small, and the study participants were health examinees rather than a general population sample, which could have introduced an unintentional selection bias. Moreover, as this study was conducted at a single institution, the findings may not be generalizable to a broader population. The specific characteristics of the patients who sought care at our facility could have influenced the results, necessitating caution when generalizing these findings to other demographic groups or clinical settings. Future studies involving larger and more diverse populations across multiple centers are necessary to validate these findings and ensure their generalizability. Observational studies are also susceptible to confounding factors that cannot be fully accounted for in the analyses. Nevertheless, a strength of this study is that, to our knowledge, this is the first study to investigate and establish a connection between the SPISE index and the predominance of sdLDL-C. We also assessed the predictive ability of the SPISE index in identifying sdLDL-C dominance in obese patients in Korea.

In conclusion, our study established an independent relationship between the mean LDL-C particle size and the SPISE index, with the SPISE index exhibiting a stronger association than the other IR indices. This suggests that the SPISE has the potential to replace current labor-intensive and time-consuming IR indices and sdLDL-C measurement methods, thereby effectively estimating individual IR-induced sdLDL-C predominance and future CVD risks. However, given the limitations of this study, further research is required to validate this index.

Article Information

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Contact the corresponding author for data availability.

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Supplementary materials

Supplementary materials can be found via https://doi.org/10.4082/kjfm.24.0202. Supplement 1. Comparison of different insulin resistance markers' ROC curve analysis. Supplement 2. Comparison of different insulin resistance markers' receiver-operating-characteristic (ROC) curve analysis.

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