Association of lipoprotein subfraction characteristics and metabolically healthy and unhealthy overweight individuals in Korea

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Association of lipoprotein subfraction characteristics and metabolically healthy and unhealthy overweight individuals in Korea

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This certifies that the Master's Thesis of
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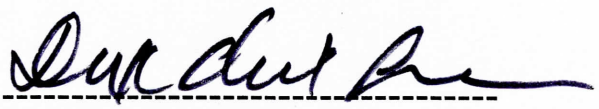

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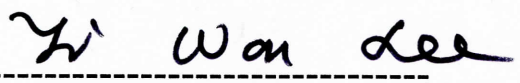

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ABSTRACT

Association of lipoprotein subfraction characteristics and metabolically healthy and unhealthy overweight individuals in Korea

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Objective

The purposes of this study were (1) to determine the association between lipoprotein subfraction profiles and metabolically healthy overweight (MHO) phenotype, as defined by visceral adiposity; and (2) to identify the strongest associated parameter with metabolic health among the lipoprotein measurements.

Materials and Methods

This cross-sectional study was comprised of 462 overweight patients, who were classified as MHO or non-MHO based on their visceral adipose tissue (VAT) area to subcutaneous adipose tissue area (SAT) ratio (VAT/SAT ratio). Serum lipoprotein subfraction analyses and other metabolic parameters were measured.

Results

Among the overweight participants, two hundred fifty-five individuals (53.7%) had the MHO phenotype. After adjusting for age, sex, medication status, lifestyle factors, and confounding metabolic characteristics, the non-MHO group showed significantly higher lipid levels and a greater prevalence of unfavorable lipid profiles. LDL subclass pattern type B was the most significantly strongest associated parameter with the non-MHO phenotype (odds ratio 2.70; 95% CI 1.55-4.69), while serum LDL cholesterol level was not significantly associated with the non-MHO phenotype.

Conclusions

Lipoprotein subfraction particle measurements were significantly associated with the non-MHO phenotype and a higher VAT/SAT ratio, with small dense LDL predominance being the most significantly strongest associated parameter with MHO phenotype. These findings will help identify MHO and non-MHO phenotypes and perhaps lead to a development of cost-effective individualized treatments.

Key words: overweight, small dense low-density lipoprotein (LDL), lipoprotein subfraction, visceral to subcutaneous adipose tissue ratio (VAT/SAT ratio)

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I. INTRODUCTION

Obesity is a major public health concern that leads to increased cardiovascular disease and mortality.[1] About 1.7 billion people worldwide are currently classified as overweight, and the health care costs associated with obesity and related diseases have increased.[1,2] Therefore, identifying overweight patients with an unhealthy metabolic profile may help develop cost-effective individualized prevention and treatment of obesity-related metabolic consequences.[3]

Evidence suggests that not all overweight or obese individuals show the metabolic dysfunction associated with an increased risk of metabolic comorbidities.[4-6] Overweight or obese people who do not have metabolic abnormalities such as diabetes (DM), hypertension (HTN), or other cardiovascular risks have a metabolically healthy overweight (MHO) phenotype.[7] Prevalence of MHO worldwide is surprisingly high as shown in recent studies, accounting for as much as 50% of the overweight and 30-47%

of the obese population.[8,9] MHO is associated with less visceral adiposity, as recent studies show that abdominal visceral fat is a critical variable in determining metabolic disturbance.[10,11] Moreover, the visceral adipose tissue (VAT) to subcutaneous adipose tissue (SAT) ratio, a reflection of the relative distribution of VAT and SAT accumulation and a strong correlate of cardiovascular disease risk, should be accounted for in overweight or obese populations.[12-14]

Lipid metabolism dysregulation is closely related to the cluster of metabolic profile abnormalities in patients with visceral obesity.[15] Moreover, atherogenic dyslipidemia, a group of lipoprotein abnormalities assessed through lipoprotein subfraction particle profile analyses, is an important predictor of cardiovascular disease and may be more clinically significant than traditional plasma lipid parameters, such as hypercholesterolemia or elevated LDL cholesterol levels.[16] To date, few studies have used lipoprotein subfraction profiles of atherogenic dyslipidemia to determine the metabolic health of overweight patients.[17,18]

The purpose of this study was to determine the association between lipoprotein subfraction parameters and MHO versus non-MHO phenotypes, as defined by visceral adipose tissue (VAT) area, and to identify which lipoprotein was the most significantly strongest associated with MHO phenotypes.

II. MATERIALS AND METHODS

1. Study participants

Four hundred seventy-two patients who visited the obesity clinic at Severance Hospital in Seoul, Korea from January 2008 to July 2012 were enrolled in this study. The study was approved by the Institutional Review Board of Severance Hospital.

The study participants were overweight (body mass index (BMI) ≥23 kg/ m^2), according to Asia-Pacific criteria, and sedentary (defined as participating in structured exercise fewer than two times per week).[19] No participants had undergone dietary therapy before beginning this study. Patients with a history of dyslipidemia or those who had used lipid-lowering medications or hormone replacement therapy were excluded from the study. Patients with a history of malignancy; abnormal liver, renal, or thyroid function; acute or chronic inflammatory disease; or clinical or electrocardiographic evidence of cardiovascular disease were also excluded.

Among the overweight participants, the MHO group was defined as having an abdominal VAT/SAT ratio, of <0.4 and the non-MHO group as having a VAT/SAT ratio ≥0.4, as measured by computed tomography (CT) scan.[20,21]

2. Clinical and anthropometric evaluation

Data on past and current medical conditions and medications were collected from medical records. Body weight was measured to the nearest 0.1 kg using an electronic scale, and height was measured to the nearest 0.1 cm using a stadiometer to calculate BMI of each participant. Waist circumference was measured midway between the lowest rib and the iliac crest while standing. Blood pressure was measured two times using a mercury sphygmomanometer

after more than 10 minutes of seated rest, and the average of the two measurements was recorded. Intra-abdominal visceral and subcutaneous fat areas were measured via computed tomography (Tomoscan 350; Philips, Mahwah, NJ, USA) as described previously.[21] Participants provided information on lifestyle factors such as smoking status and alcohol consumption, through questionnaires. Smoking status was considered to be yes if the participant indicated that they were a current smoker. Alcohol consumption was defined as a positive factor if the participant consumed 72 g or more per week.

3. Biochemical analyses

Biochemical analyses were performed on blood samples collected after an overnight fast (>12 hrs. Serum levels of fasting glucose (Hitachi 7600; High-Technologies Corporation, Hitachi, Tokyo, Japan) and fasting insulin (Roche; Indianapolis, IN, USA) were measured. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) index [fasting insulin (mUI/L) × fasting glucose (mg/dl)/405].[22] Insulin sensitivity was calculated using the quantitative insulin sensitivity check index (QUICKI) [1/{log fasting insulin (μU/mL) + log fasting glucose (mg/dL)}].[23] Total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and high sensitive C-reactive protein (hsCRP) were measured using the Hitachi 7600 Automatic analyzer (High-Technologies Corporation, Hitachi, Tokyo, Japan). Non-HDL cholesterol was defined as the difference between total cholesterol and HDL cholesterol.

Metabolic syndrome was defined using the criteria proposed by the American Heart Association and the National Heart, Lung, and Blood Institute, with waist circumference criteria modification based on the following World Health Organization-Asian Pacific region criteria for abdominal obesity: (1) a

waist circumference ≥90 cm for men and ≥85 cm for women; (2) triglycerides ≥150 mg/dl; (3) serum HDL cholesterol <40 mg/dl for men and <50 mg/dl for women; (4) systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or use of anti-hypertensive medication; and (5) fasting glucose ≥100 mg/dl, or insulin or hypoglycemic medication use.[19,24]

The LDL subfraction was analyzed using 3% polyacrylamide gel tube electrophoresis (Lipoprint TM LDL System; Quantimetrix, Redondo Beach, CA, USA) according to a previous procedure.[25,26] Electrophoretic mobility (Rf) was calculated qualitatively and quantitatively using the Lipoprint LDL system Template and the Lipoware software (property of Quantimetrix; Redondo Beach, CA), respectively. Rf of the LDL subfractions was estimated using the Rf between the very low-density lipoprotein (VLDL) fraction (Rf 0.0) and the HDL fraction (Rf 1.0). LDL is distributed as seven bands, with Rfs of 0.32, 0.38, 0.45, 0.51, 0.56, 0.60, and 0.64 corresponding to LDL subclasses 1-7, respectively. LDL subclasses 1-2 were defined as large, buoyant LDL subfractions and subclasses 3-7 were defined as small dense LDL subfractions.[27] The system also calculated the mean LDL particle diameter. LDL subclass pattern A defined a mean LDL particle size of same or greater than 26.80 nm (268.0 Angstrom), pattern I between 26.50 nm and 26.80 nm, and pattern B, indicating small dense LDL dominant, mean particle size ≤26.50 nm (265.0 Angstrom).[28]

4. Statistical analyses

Data is expressed as mean ± standard deviation (SD) or percentages. Kolmogorov-Smirnov tests were used to determine normality of the data. Fasting insulin and hsCRP were logarithmically transformed to adjust for skewed distributions. The clinical characteristics between the MHO and non-MHO groups were compared using independent-sample t-tests for continuous

variables and chi-square tests for categorical variables. After adjusting for age, sex, HTN and DM medication status, smoking and alcohol use, systolic and diastolic blood pressure, fasting serum glucose, HOMA-IR, hsCRP, which were all considered to be significant confounding variables between the two groups, lipid profiles were compared using an analysis of covariance (ANCOVA). Multiple logistic regression analyses were performed to measure the association between MHO phenotype and unfavorable lipid profiles and to determine the strongest lipoprotein predictor of non-MHO phenotype after adjusting for confounding variables. Unfavorable lipid profiles were classified according to the following criteria: (1) LDL subclass pattern B (2) high LDL cholesterol (≥100 mg/dl), (3) low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women), (4) high VLDL cholesterol (≥30 mg/dl), and (5) high triglycerides (≥150 mg/dl).[29,30] Additionally, to evaluate the association between the lipoprotein profile predictors and VAT/SAT ratio, univariate and multivariate regression analyses adjusted for the confounding variables were performed. Statistical analyses were performed using SPSS (version 20.0; SPSS Inc.; Chicago, IL, USA), and significance was set at $P<0.05$ for all analyses.

III. RESULTS

The clinical characteristics of the participants are shown in Table 1. Of the 631 visitors to the obesity clinic, 556 patients were overweight or obese. After the exclusion of patients with a history of a disease condition, 475 were eligible to participate in this study.

Among the overweight participants who had a mean BMI of 29.37, 255 individuals (53.7%) had the MHO phenotype. Non-MHO participants had significantly higher abdominal visceral fat area, lower abdominal subcutaneous fat area, and a higher VAT/SAT ratio than did MHO individuals. However, no between-group differences were seen in waist circumference and waist-to-hip ratio. Non-MHO participants were significantly older and had higher systolic and diastolic blood pressure, fasting glucose levels, and HOMA-IR, and had lower QUICKI measures. Additionally, a greater proportion of non-MHO participants had metabolic syndrome, smoked, consumed alcohol, and took HTN and/or DM medication.

Table 1. Clinical characteristics of metabolically healthy overweight (MHO) and metabolically unhealthy overweight (non-MHO) study participants

	MHO (n=255)	Non-MHO (n=220)	P-value
Age (years)	32.53±10.93	46.19±12.77	<0.001
Male, n (%)	46 (18.0)	85 (38.6)	<0.001
BMI (kg/m^2)	29.63±4.71	29.08±4.16	0.186
Waist (cm)	96.11±11.69	97.51±10.63	0.18
Waist-to-hip ratio	0.91±0.64	0.99±0.78	0.109
Systolic BP (mmHg)	125.1±15.41	129.62±15.54	0.002
Diastolic BP (mmHg)	73.63±9.48	78.76±9.97	<0.001
Visceral fat (cm^2)	92.06±38.69	162.33±70.14	<0.001
Subcutaneous fat (cm^2)	338.62±117.53	261.19±96.25	<0.001
VAT/SAT ratio	0.275±0.071	0.651±0.269	<0.001
Alcohol, n (%)	38 (15.0)	53 (11.2)	0.014
Smoking, n (%)	23 (9.1)	36 (16.4)	0.018
Medication for HTN, n (%)	8 (3.1)	36 (16.4)	<0.001
Medication for DM, n (%)	3 (1.2)	13 (5.9)	0.005
Fasting glucose (mg/dL)	92.28±12.43	99.36±19.72	<0.001
Fasting insulin (μU/mL)	11.99±8.34	13.08±11.06	0.224
HOMA-IR	2.77±2	3.29±3.19	0.03
QUICKI	0.34±0.03	0.33±0.04	0.038
hsCRP (mg/L)	3.45±8.76	2.77±5.35	0.325
Prevalence of MetS	65 (25.5)	114 (45.9)	<0.001

Abbreviations: MHO, Metabolically healthy overweight; non-MHO,

metabolically unhealthy overweight; BMI, Body Mass Index; BP, Blood pressure; VAT/SAT ratio, visceral adipose tissue area to subcutaneous adipose tissue area ratio; HTN, Hypertension; DM, Diabetes Mellitus; HOMA-IR, Homeostasis model assessment of insulin resistance; QUICKI, Quantitative insulin sensitivity check index; hsCRP, high sensitive C-reactive protein; MetS, Metabolic Syndrome

The values are expressed as mean ± standard deviation or number (percentage).

The P values were derived from an independent-sample t-test for continuous data or Chi-square test for categorical data.

Insulin and hsCRP were logarithmically transformed due to skewed distribution.

After adjusting for age, sex, HTN and DM medication status, smoking and alcohol consumption, systolic and diastolic blood pressure, fasting glucose level, HOMA-IR, and hsCRP, both traditional lipid and LDL particle subfraction profiles were significantly different between the two groups (Table 2). Non-MHO participants had higher total cholesterol, LDL cholesterol, VLDL cholesterol, non-HDL cholesterol, and triglycerides, and had lower HDL cholesterol than the MHO participants. The non-MHO individuals also had a smaller mean LDL size, greater total amount and proportion of small dense LDL (LDL subclasses 3-7), smaller proportion of LDL type A, and greater proportion of LDL type B.

Table 2. Lipid profiles of metabolically healthy overweight (MHO) and metabolically unhealthy overweight (non-MHO) study participants

	MHO (n=255)	Non-MHO (n=220)	P-value
Total cholesterol (mg/dL)	185.52 (2.63)	196.69 (2.88)	0.009
LDL (mg/dL)	115.26 (2.29)	123.16 (2.49)	0.033
HDL (mg/dL)	50.82 (0.73)	47.17 (0.80)	0.002
VLDL (mg/dL)	26.81 (0.69)	32.81 (0.76)	<0.001
Non-HDL (mg/dL)	134.79 (2.56)	149.87 (2.80)	<0.001
Triglyceride (mg/dL)	109.86 (4.16)	141.67 (4.54)	<0.001
mean LDL size	268.48 (0.34)	265.95 (0.37)	<0.001
sdLDL (mg/dL)	6.75 (0.73)	12.06 (0.80)	<0.001
LDL 1-2 (large)(%)	32.79 (0.59)	30.33 (0.64)	0.010
LDL 3-7 (small)(%)	3.75 (0.38)	6.10 (0.42)	0.031
LDL, A type	62.1 (3.30)	49.4 (3.60)	0.016
LDL, B type	18.4 (2.90)	37.2 (3.20)	0.034

Abbreviations: MHO, Metabolically healthy overweight; non-MHO, metabolically unhealthy overweight; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; VLDL, Very low-density lipoprotein; sdLDL, small, dense Low-density lipoprotein.

The values are expressed as an estimated mean (standard error) for continuous variables or an estimated percentage (standard error) for categorical variables (LDL, A type, and LDL, B type).

The P-values were calculated using analysis of covariance (ANCOVA) after adjusting for age, sex, HTN and DM medication status, lifestyle factors (smoking, alcohol), systolic and diastolic blood pressure, fasting serum

glucose, HOMA-IR, and hsCRP.

After adjusting for the covariates, a greater proportion of the non-MHO group had an unfavorable lipid profile (Figure 1). The non-MHO group had greater odds of having an unfavorable lipid profile, such as LDL subclass pattern type B with a dominance of small dense LDL, high VLDL, low HDL cholesterol, and high triglycerides. However, non-MHO individuals did not show greater odds of having high total serum , a conventional lipid parameter (Table 3).

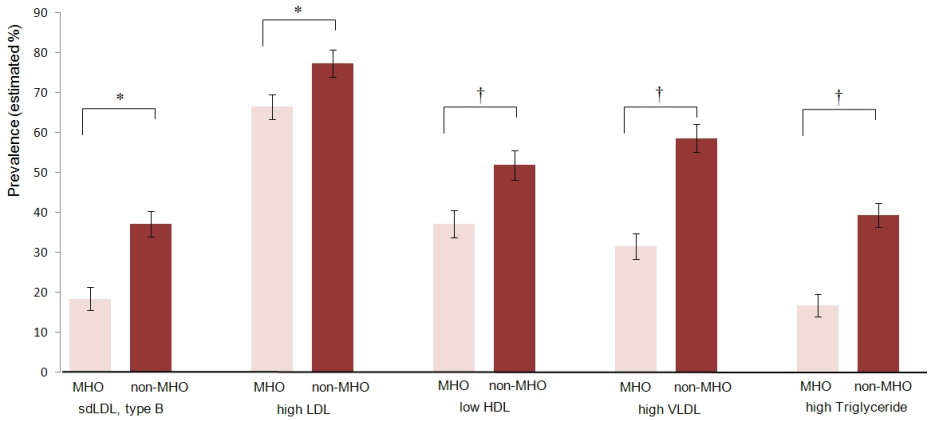

Figure 1. Prevalence of unfavorable lipid profile according to VAT/SAT ratio

Abbreviations: VAT/SAT ratio, visceral adipose tissue area to subcutaneous adipose tissue area ratio; MHO, metabolically healthy but overweight; non-MHO, metabolically unhealthy and overweight; sdLDL, small, dense Low-density lipoprotein; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; VLDL, Very low-density lipoprotein.

Cutoffs of unfavorable lipid profiles were defined as follows: (1) LDL subclass pattern B (2) high LDL (≥100 mg/dl), (3) low HDL (<40 mg/dl in men, <50 mg/dl in women), (4) high VLDL (≥30 mg/dl), and (5) high triglyceride (≥150 mg/dl).

Prevalence (estimated %) and standard error (indicated with error bars). *$p<0.05$ and †$p<0.01$ indicates significant differences between the two phenotypes. Differences were calculated using analysis of covariance (ANCOVA) after adjusting for age, sex, HTN and DM medication status, lifestyle factors (smoking, alcohol), systolic and diastolic blood pressure, fasting serum glucose, HOMA-IR, and hsCRP.

Table 3. Odds ratio for unfavorable lipid profiles in MHO and non-MHO participants

		Model 1	Model 2	Model 3
MHO		Ref	Ref	Ref
Non-MHO	sdLDL, type B	3.283 (2.132-5.055)†	2.827 (1.815-4.404)†	2.854 (1.808-4.505)†
	High LDL	1.457 (0.973-2.183)	1.596 (1.054-2.415)*	1.457 (0.951-2.231)
	Low HDL	1.367 (0.949-1.969)	1.955 (1.245-3.069)†	1.881 (1.177-3.006)†
	High VLDL	2.759 (1.891-4.026)†	3.466 (2.141-5.609)†	3.882 (2.368-6.364)†
	High Triglyceride	3.583 (2.326-5.520)†	4.174 (2.455-7.096)†	4.639 (2.615-8.229)†

Abbreviations: MHO, Metabolically healthy overweight; non-MHO, metabolically unhealthy overweight; VAT/SAT ratio, visceral adipose tissue area to subcutaneous adipose tissue area ratio; sdLDL, small, dense Low-density lipoprotein; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; VLDL, Very low-density lipoprotein.

Cutoffs of unfavorable lipid profiles were defined as follows: (1) LDL subclass pattern B (2) high LDL (≥100 mg/dl), (3) low HDL (<40 mg/dl in men, <50 mg/dl in women), (4) high VLDL (≥30 mg/dl), and (5) high triglycerides (≥150 mg/dl)

*p<0.05 and †p<0.01 for each model, calculated by multiple logistic regression analyses.

Model 1: unadjusted

Model 2: adjusted for age, sex, smoking, alcohol, DM, HTN medication

Model 3: adjusted for factors in model 2 plus systolic and diastolic blood pressure, fasting serum glucose, HOMA-IR, and hsCRP.

Among lipid profile parameters, LDL subclass pattern B was the most significantly strongest associated parameter with MHO phenotype, with an odds ratio of 2.70 (95% CI 1.60-4.53). Furthermore, small dense LDL showed a significantly higher odds ratio for the non-MHO phenotype, with an odds ratio of total small dense LDL (mg/dl) being 1.04, and that of small dense LDL (LDL subtype 3-7) percentage being 1.08, while that of other parameters were only below 1.010. However, total serum LDL cholesterol was not significantly associated with the non-MHO phenotype (Table 4).

Table 4. Odds ratio for lipid profiles associated with non-MHO phenotype

Lipid profile	OR for non-MHO	P value
Total cholesterol (mg/dl)	1.007 (1.001-1.014)	0.018
LDL (mg/dl)	1.007 (1.000-1.014)	0.069
HDL (mg/dl)	0.960 (0.938-0.983)	0.002
VLDL (mg/dl)	1.063 (1.037-1.090)	<0.001
Non-HDL(mg/dl)	1.010 (1.004-1.017)	0.001
Triglyceride (mg/dl)	1.010 (1.006-1.014)	<0.001
Mean LDL size	0.909 (0.866-0.954)	<0.001
sdLDL (mg/dl)	1.043 (1.019-1.067)	<0.001
LDL 1-2 (large)(%)	0.941 (0.905-0.979)	0.002
LDL 3-7 (small)(%)	1.069 (1.022-1.118)	0.004
LDL, type B	2.700 (1.553-4.694)	<0.001

Abbreviations: non-MHO, metabolically unhealthy overweight; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; VLDL, Very low-density lipoprotein; sdLDL, small, dense Low-density lipoprotein.

The P-values were calculated using multiple regression analyses after adjusting for age, sex, HTN and DM medication status, lifestyle factors (smoking, alcohol), systolic and diastolic blood pressure, fasting serum glucose, HOMA-IR, and hsCRP.

Additionally, LDL subclass pattern type B and the mean LDL size, which were the lipoprotein profile parameters found to be strongly associated with the non-MHO phenotype in the analyses, were shown to have significant association with the VAT/SAT ratio itself, before and after adjustment for the covariates (β=0.116, p=0.005, and β=-0.112, p=0.006, respectively) (Table 5).

Table 5. Association of lipoprotein subfraction characteristics and VAT/SAT ratio

1. Univariate and multivariate regression analyses of LDL subclass pattern and VAT/SAT ratio

	β	p
Univariate regression		
sdLDL, Type A	-0.208	<0.001
sdLDL, Type B	0.196	<0.001
Multivariate regression		
sdLDL, Type B	0.116	0.005

2. Univariate and multivariate regression analyses of mean LDL size and VAT/SAT ratio

	β	p
Univariate regression		
Mean LDL size	-0.233	<0.001
Multivariate regression		
Mean LDL size	-0.112	0.006

Abbreviations: LDL, Low-density lipoprotein; VAT/SAT ratio, Visceral adipose tissue area to Subcutaneous adipose tissue area ratio

The P-values were calculated using univariate or multivariate linear regression analyses. For multivariate analyses the following variables were adjusted; age, sex, HTN and DM medication status, lifestyle factors (smoking and alcohol comsumption), systolic and diastolic blood pressure, fasting serum glucose HOMA-IR, and hsCRP.

VI. DISCUSSION

Our results showed that a high proportion of atherogenic small dense LDL particles associated with LDL subclass pattern B was strongly associated with abnormal metabolic status in overweight adults. Total serum LDL cholesterol level, a conventional lipid parameter, was not significantly associated with metabolic status. These findings suggest lipoprotein subfraction particle profile analyses, beyond the conventional lipid profile, may help assess metabolic health more accurately in overweight Korean adults.

Our findings are in line with a few previous studies that assess the association between lipid profiles and MHO phenotypes. We are the first to present the relationship between lipoprotein subfraction analyses and obesity phenotypes that we defined as the relative distribution of abdominal adiposity quantified by a CT scan, in an overweight and obese Asian population. Manu et al.[17] investigates lipid profiles in MHO individuals, but only uses conventional lipoprotein analyses. Iacobellis et al.[18] also shows a relationship between larger LDL particle size and the MHO phenotype. However, the relationship between this phenotype and abdominal obesity is not significant in this study, likely due to relatively low number of participants and the small difference in the particle size. We found a significant relationship between small dense lipoprotein particles and obesity phenotypes in a large sample of overweight and obese individuals. Furthermore, we used a CT scan to measure precisely the relative distribution of excess fat as indicated by the VAT/SAT ratio, thus quantifying abdominal visceral obesity as a determinant of MHO phenotype.[12,20]

According to recent studies, not all overweight or obese individuals show an increased risk of cardiovascular disease or premature mortality.[5,11] According to one study, individuals with the MHO phenotype do not have higher rates of all-cause mortality, cancer, or cardiovascular disease compared to normal-

weight individuals.[5] Furthermore, Appleton et al. demonstrated that since the MHO phenotype is relatively unstable over time, intervention is necessary to maintain it.[11] Therefore, detecting the non-MHO phenotype should be emphasized to assess individualized therapeutic approaches.[3,31] High visceral fat storage is one of the most important determinants of a non-MHO phenotype in overweight or obese adults and is also a factor in whether the MHO phenotype is maintained.[10,32,33] Moreover, a high proportion of visceral fat and a relatively low proportion of subcutaneous fat is considered to be a form of partial lipodystrophy and may play a critical role in metabolic abnormalities, even if MHO individuals have a high proportion of total body fat, as we saw in our study.[34]

The VAT/SAT ratio can predict metabolic health because it is suggested to be a reflection of the relative distribution of abdominal fat and accounts for visceral adiposity associated with metabolic abnormalities.[12,20] SAT improves glucose metabolism and reduces fat mass in mice and humans.[35,36] SAT adipocytes may function as a buffer in taking up circulating free fatty acids and triglycerides. Dysfunction of SAT adipogenesis or lipid storage can lead to fat accumulation in ectopic areas, especially in VAT, resulting in unfavorable fat partitioning, leading to unfavorable metabolic profiles.[37,38] Previous studies show that having VAT/SAT ratio not less than 0.4 was thought to have a viscerally fat type and to have metabolic aberrations, which is related with metabolic obesity and to be used as its defnition.[20,21] A high VAT/SAT ratio is associated with increased cardiovascular risk factors, but its relationship with markers of glucose metabolism is unclear. Gastaldelli et al.[39] shows that similar to our findings, high VAT/SAT ratio is associated with a high fasting glucose level but not with fasting insulin level. More future studies are necessary to clarify this relationship.

Dyslipidemia with metabolic abnormalities, specifically an increased proportion of small dense LDL that is a characteristic of atherogenic

dyslipidemia, is frequently observed in individuals with visceral obesity.[15,40] The expanded visceral adipose tissue mass, together with abnormally functioning subcutaneous fat, results in reduced energy storage capacity and leads to excess non-esterified or free fatty acids (FFA) release.[39] The liver takes up a large proportion of circulating FFA entering the visceral splanchnic bed via portal vein drainage. Abnormally high levels of FFA present in the liver stimulate the hepatic TG synthesis in the form of VLDL, triglyceride-enriched LDL cholesterol, and HDL cholesterol.[41,42] These lipoproteins are a good substrate for hepatic triglyceride lipase, leading to the depletion of the lipoprotein lipid core and the formation of small dense LDL and HDL particles.[43] Small dense LDL particles are highly atherogenic because they can penetrate into the vascular wall and are susceptible to oxidation.[37,44] They also tend to bind less efficiently to LDL receptors, thereby reducing their clearance from the circulation.[45] Analyzing the characteristics of an atherogenic lipid profile will help identify non-MHO individuals and factors associated with increased cardiovascular disease risk.[42]

Although conventional lipid parameter such as total serum LDL cholesterol level was not associated with metabolic status, serum triglyceride was found to be highly correlated with metabolic obesity, and was also significantly associated in distinguishing non-MHO phenotype. As excess hepatic TG synthesis can lead to elevated small dense LDL production, previous studies show serum TG and small dense LDL levels to be positively associated in metabolic syndrome and cardiovascular disease patients.[46] But comparison of more efficient availabitily of TG versus small dense LDL level in association with metabolic abnormality to predict its risk has not been reported to this point. Further prospective large studies regarding this issue will be necessary to identify competent indicators of metabolic dysregulation for practice.

There are some limitations to this study. Due to the cross-sectional design, the cause-and-effect relationship between lipid profile and MHO phenotype

cannot be determined with certainty. The study participants had a relatively high proportion of female participants in each group. Therefore, our results may not be applicable to the general population. Furthermore, although we included alcohol consumption and smoking status in our analysis, we did not account for other variables such as birth weight and physical activity that may influence the MHO phenotype.

Despite the limitations, our study is the first to introduce the clinical relevance of LDL subfraction data for identifying MHO and non-MHO phenotypes defined by the VAT/SAT ratio, which reflects the relative distribution of excess abdominal fat and is correlated to metabolic disease risk. Additionally,the relationship between lipoprotein subfraction particles and the MHO phenotype was reported in a large overweight and obese Asian population. Because excess obesity, particularly visceral adiposity, affects lipid metabolism, it is useful to study these findings in Asian overweight populations.[15,47] Finally, we used a CT scan and achieved accurate and quantifiable measures in the exact amount of abdominal visceral and subcutaneous adipose tissue.

V. CONCLUSION

Lipoprotein subfraction particle characteristics were significantly associated with the non-MHO phenotype. Predominance of small dense LDL was the most significantly strongest associated parameter with unhealthy metabolic status among lipoproteins, whereas the serum total LDL cholesterol, a conventional lipid parameter, was not significantly associated. Our findings imply the lipoprotein subfraction particle profiles can be strong determinants of obesity phenotypes and the VAT/SAT ratio, which may lead to further obesity studies in diverse ethnic populations. Because the metabolic characteristics of overweight and obese individuals vary widely, distinguishing MHO from non-MHO using lipoprotein subfraction measurements could help develop cost-effective individualized treatment approaches. Further prospective studies are needed to confirm that small dense LDL is relevant for identifying MHO and non-MHO phenotypes and determining visceral adiposity.

VI. REFERENCES

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ABSTRACT (IN KOREAN)

대사적으로 건강한 과체중 유형과 건강하지 않은 과체중 유형에서 혈청 지단백 소분획 분석 지표와의 관련성

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연구 목적

본 연구는 복부 비만 여부로 대사적으로 건강한 과체중 유형과 건강하지 않은 과체중 유형을 구분하여 건강하지 않은 과체중 유형과 혈청 지단백 소분획 분석 지표와의 연관성을 살펴보고자 하였다.

연구 방법

462명의 과체중 및 비만 환자를 복부 내장 지방/복부 피하 지방의 비율을 기준으로 대사적으로 건강하거나 건강하지 않은 과체중 군으로 나누고, 혈청 지질 및 혈청 지단백 소분획 분석 지표와 기타 대사적 지표들을 측정하여 분석하였다.

결과

과체중 및 비만 환자에서, 255명 (53.7%)가 대사적으로 건강한 과체중 군으로 분류되었다. 나이, 성별, 복약 과거력, 생활 습관, 대사적 지표들을 보정한 후 분석하였을 때, 대사적으로 건강하지 않은 과체중 군은 건강한 군에 비해 대사적으로 위험한 혈청 지질 수치를 보였다. 혈청 지단백 소분획 분석의 저밀도 지질 단백질 type B (작고 조밀한 저밀도 지단백이 양적으로 우세한 type)는 대사적으로 건강하지 않은 과체중 군과 가장 높은 연관성을 나타내는 인자였다.

결론

혈청 진단백 소분획 분석 중 작고 조밀한 작고 조밀한 저밀도 지단백이 양적으로 우세한 유형이 대사적으로 건강하지 않은 과체중 유형과 높은 연관성을 나타내었다. 이는 과체중 및 비만 환자에서 대사적으로 건강하거나 건강하지 않은 유형을 구분해내는데 도움을 줄 가능성이 있음을 의미한다.

핵심되는 말: 과체중 및 비만, 작고 조밀한 저밀도 지단백, 혈청 지단백 소분획 분석, 내장 복부 지방과 피하 복부 지방 비율

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