

# Correlation Between Midhigh Low-Density Muscle and Insulin Resistance in Obese Nondiabetic Patients in Korea

DOLMI KIM, MD  
SUYOUN NAM, MD, PHD  
CHULWOO AHN, MD, PHD  
KYUNGWOOK KIM, MD  
SOOJEE YOON, MD  
JUNUH KIM, MD

BONGSOO CHA, MD, PHD  
SUNGKIL LIM, MD, PHD  
KYUNGRAE KIM, MD, PHD  
HYUNCHUL LEE, MD, PHD  
KAPBUM HUH, MD, PHD

sity and diabetes is relatively low. Therefore, the current study was undertaken to investigate the potential link between low-density muscle and insulin resistance in the Korean population.

## RESEARCH DESIGN AND METHODS

### Subjects

A total of 75 subjects (23 men, 52 women; mean age  $\pm$  SD,  $41.9 \pm 14.1$  years) with sedentary lifestyle were enrolled in this cross-sectional study. Of these, 69 patients were obese (BMI  $>25$  kg/m<sup>2</sup>) and the remainder were overweight (BMI 23–25 kg/m<sup>2</sup>), according to the revised definition of adult obesity in the Asian-Pacific race proposed at the Hong Kong meeting (9). A total of 33 premenopausal women and 19 women with natural menopause (mean age  $\pm$  SD,  $31.2 \pm 7.8$  and  $54.8 \pm 7.9$  years, respectively) were included. Subjects were divided into a normal glucose tolerance group ( $n = 46$ ) and an impaired glucose tolerance group ( $n = 29$ ), according to the results of an oral glucose tolerance test (OGTT). Individuals with a history of or evidence of hypertension, any type of diabetes, or cardiovascular disease were excluded. Individuals with hyperlipidemia (concentration of plasma total cholesterol  $>350$  mmol/l or concentration of triacylglycerol  $>300$  mmol/l) were excluded. Those taking any kind of oral or parenteral medications were excluded, and none of our subjects engaged in any regular exercise. The clinical and biochemical characteristics of the subjects are described in detail in Table 1. The study protocol was approved by the Yonsei University College of Medicine ethical committee, and informed consent was obtained from each subject.

### Anthropometric parameters

Body weight and height were measured in the morning, without clothing and shoes. BMI was calculated as body weight in ki-

**OBJECTIVE** — We investigated the link between lipid-rich skeletal muscle, namely low-density muscle, and insulin resistance in Korea.

**RESEARCH DESIGN AND METHODS** — Abdominal adipose tissue areas and midhigh skeletal muscle areas of 75 obese nondiabetic subjects (23 men, 52 women; mean age  $\pm$  SD,  $41.9 \pm 14.1$  years) were measured by computed tomography (CT). The midhigh skeletal muscle areas were subdivided into low-density muscle (0 to +30 Hounsfield units) and normal-density muscle (+31 to +100 Hounsfield units). The homeostasis model assessment (HOMA) score was calculated to assess whole-body insulin sensitivity.

**RESULTS** — The abdominal visceral fat area and the midhigh low-density muscle area were found to be well correlated with the HOMA score ( $r = 0.471$ ,  $P < 0.01$  and  $r = 0.513$ ,  $P < 0.01$ , respectively). The correlation between low-density muscle area and insulin resistance persisted after adjusting for BMI or total body fat mass ( $r = 0.451$ ,  $P < 0.01$  and  $r = 0.522$ ,  $P < 0.01$ , respectively) and even after adjusting for abdominal visceral fat area ( $r = 0.399$ ,  $P < 0.01$ ).

**CONCLUSIONS** — The midhigh low-density muscle area seems to be a reliable determinant of insulin resistance in Korean obese nondiabetic patients.

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The close relationship between abdominal adiposity and insulin resistance has been described in previous studies (1–3). Moreover, visceral adipose tissue is well recognized to be significantly related to insulin resistance of obese type 2 diabetic patients and even patients with normal weight (4,5).

Recently, the role of intramuscular lipid components in insulin resistance be-

came the subject of attention (6–8). Low-density muscle represents lipid-rich skeletal muscle, which includes fat components between and inside the muscle fibers. Many other studies have already shown that low-density muscle is significantly related to insulin resistance in obese type 2 diabetic patients. However, this relation has not been investigated in Korea, where the prevalence of both obe-

From the Division of Endocrinology and Metabolism, Department of Internal Medicine, Yonsei University, College of Medicine, Seoul, Korea.

Address correspondence and reprint requests to Prof. Dr. Chul-Woo Ahn, Division of Endocrinology and Metabolism, Department for Internal Medicine, Yong-dong Severance Hospital, Yonsei University, College of Medicine, 146-92, Dogok-dong, Kangnam-ku, P.O. Box 135-720, Seoul, Korea. E-mail: acw@yumc.yonsei.ac.kr.

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**Abbreviations:** CT, computed tomography; HOMA, homeostasis model assessment; HU, Hounsfield units; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Clinical characteristics

	Men:women	Men	Women
Sex	23:52	23	52
Age (years)	41.9 ± 14.1	46.6 ± 13.6	39.8 ± 13.9
Body weight (kg)	78.6 ± 14.6	87.9 ± 19.1	74.5 ± 9.8†
BMI (kg/m <sup>2</sup> )	29.4 ± 3.9	29.6 ± 4.7	29.4 ± 3.6
Total body fat (kg)	27.8 ± 8.8	25.1 ± 11.6	29.0 ± 7.0
Total body fat (%)	36.0 ± 8.4	28.5 ± 8.2	39.3 ± 6.0†
Total cholesterol (mg/dl)	207.3 ± 33.5	215.7 ± 27.8	203.6 ± 35.4
Triglyceride (mg/dl)	158.6 ± 56.8	163.0 ± 55.6	156.7 ± 57.7
HDL cholesterol (mg/dl)	44.4 ± 9.9	40.4 ± 10.1	46.1 ± 9.3*
LDL cholesterol (mg/dl)	131.2 ± 27.9	142.7 ± 17.4	126.7 ± 30.2*
Fasting glucose (mmol/l)	5.3 ± 0.7	5.5 ± 0.6	5.3 ± 0.7
Fasting insulin (μU/ml)	9.8 ± 7.8	11.4 ± 8.9	9.2 ± 7.3
HOMA score	2.4 ± 1.9	2.8 ± 2.2	2.1 ± 1.7

Data are means ± SD. \**P* < 0.05; †*P* < 0.01.

lograms divided by height in meters squared (kg/m<sup>2</sup>).

### Biochemical profiles

The plasma glucose concentrations were measured immediately with an autoanalyzer using the hexokinase method (Hitachi 747; Roche, Montclair, NJ). Serum insulin and C-peptide concentrations were determined by an enzyme chemiluminescence immunoassay (ECIA, DPC, Immulite DPC). The serum total cholesterol, HDL cholesterol, and LDL cholesterol levels were measured by using a direct enzymatic method (Hitachi 747; Daiichi, Tokyo, Japan), serum triglyceride levels were measured by an enzymatic colorimetric method (Hitachi 747; Roche), and serum free fatty acid levels were measured by an enzymatic colorimetric method (Olympus AU640; Daiichi).

### OGTT

OGTT was performed after a 12-h overnight fast on the baseline plasma glucose and serum insulin samples. A glucose solution (75 g) was administered orally and samples were then collected at 30, 60, 90, and 120 min. Impaired glucose tolerance was defined as 2-h plasma glucose ≥140 and <200 mg/dl.

### Insulin sensitivity

To assess whole-body insulin sensitivity, we calculated the HOMA score in all 75 subjects. On the day before blood sampling, subjects were instructed not to consume any food after midnight and to avoid strenuous exercise. The HOMA

score was determined using the formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5), as described by Matthews et al. (10 and Bonora et al (11).

### Body composition

**Dual-energy x-ray absorptiometry.** After an initial bed rest of 30 min, whole-body fat mass and fat-free mass were determined by dual-energy X-ray absorptiometry (Hologic QDR 1500; Delphi). BMI was calculated by dividing the body weight by height squared (kg/m<sup>2</sup>).

### Regional fat distribution

**Computed tomography.** The abdominal and midhigh adipose tissue areas and the midhigh muscle area were quantified by CT (Tomoscan 350; Philips, Mahway, NJ). With the subject in a supine position, a 10-mm CT slice scan was acquired at the L4–L5 level to measure the total abdominal and visceral fat areas. A cross-sectional scan of the same thickness was obtained for both legs at the midpoint be-

tween the anterior superior iliac crest and the patella, as described previously (12). Skeletal muscle attenuation was determined by measuring the mean value of all pixels within the range of 0 to 100 Hounsfield units (HU); adipose tissue areas fell in the range of –150 to –50 HU. The midhigh skeletal muscle area was compartmentalized into a normal density muscle area (+31 to +100 HU) and a low-density muscle area (0 to +30 HU).

### Statistical analysis

All values are expressed as means ± SD. Associations between anthropometric and biochemical parameters, body compositions, or regional fat distributions and the HOMA scores were identified using Pearson correlations. ANOVA was used to compare the mean values of these parameters between male and female subjects or between premenopausal and postmenopausal subjects. A *P* value of 0.05 was considered significant.

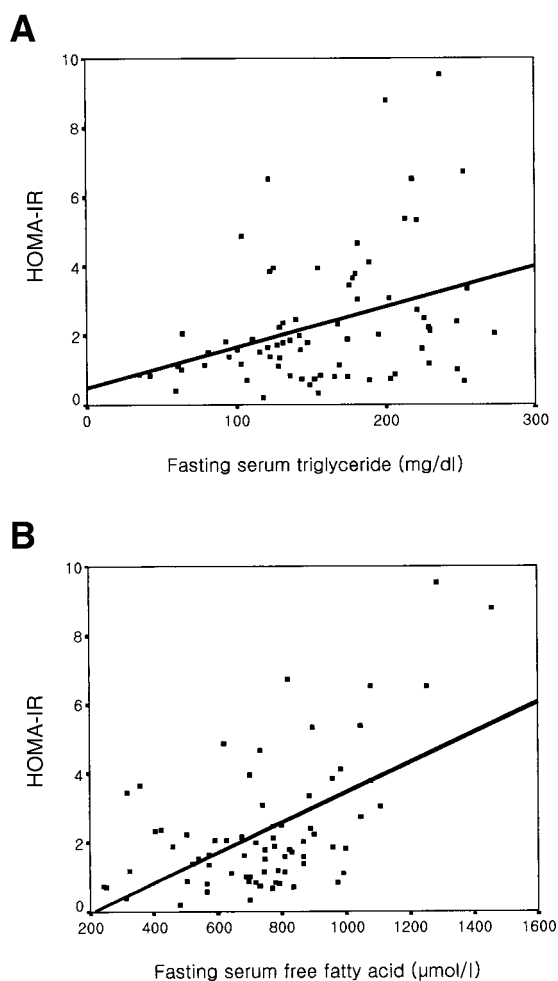
**RESULTS**— The mean values of abdominal visceral and subcutaneous adipose tissues were 120.9 ± 65.4 and 250.6 ± 97.4 cm<sup>2</sup>, respectively, and the mean midhigh muscle areas were 106.1 ± 28.6 cm<sup>2</sup> for normal density muscle and 17.3 ± 6.8 cm<sup>2</sup> for low density muscle, respectively (Table 2).

Fasting serum triglyceride levels and free fatty acid levels were found to be correlated with the HOMA scores (*r* = 0.354, *P* < 0.01 and *r* = 0.553, *P* < 0.01; Fig. 1). Fasting serum insulin levels were significantly related to BMI (*r* = 0.250, *P* < 0.05), the abdominal visceral fat area (*r* = 0.405, *P* < 0.01), and the midhigh low-density muscle area (*r* = 0.532, *P* < 0.01). Fasting serum free fatty acid levels were correlated with the midhigh low-density muscle area (*r* = 0.272, *P* < 0.05).

Table 2—Mean values of abdominal and mid-thigh area

Area (cm <sup>2</sup> )	Total subjects ( <i>n</i> = 75)	Men ( <i>n</i> = 23)	Women ( <i>n</i> = 52)
AVFA	120.9 ± 65.4	172.6 ± 83.5	98.0 ± 38.3*
ASFA	250.6 ± 97.4	194.2 ± 87.6	275.6 ± 91.6*
TLDMA	17.3 ± 6.8	18.5 ± 8.1	16.7 ± 6.2
TNDMA	106.1 ± 28.6	124.3 ± 35.9	98.0 ± 20.4*
TSFA	96.4 ± 43.6	69.4 ± 48.6	108.3 ± 35.7*

Data are means ± SD. \**P* < 0.01. ASFA, abdominal subcutaneous fat area; AVFA, abdominal visceral fat area; TLDMA, midhigh low-density muscle area; TNDMA, midhigh normal-density muscle area; TSFA, midhigh subcutaneous fat area.



**Figure 1**—Correlation between biochemical parameters and insulin resistance. A: Fasting serum triglyceride and HOMA for insulin resistance (IR) ( $P < 0.01$ ). B: Fasting serum free fatty acid and HOMA-IR ( $P < 0.01$ ).

The abdominal subcutaneous fat area did not correlate with the HOMA score, but the abdominal visceral fat area was well correlated with the HOMA score ( $r = 0.471$ ,  $P < 0.01$ ; Fig. 2A). The ratio of visceral to subcutaneous abdominal fat area also correlated with the HOMA score ( $r = 0.434$ ,  $P < 0.01$ ; Fig. 2B). The midhigh low-density muscle area was found to be linearly correlated with the HOMA score ( $r = 0.513$ ,  $P < 0.01$ ; Fig. 2C). After adjusting for BMI and total body fat, the correlation between the low-density muscle area and the HOMA score remained valid ( $r = 0.451$ ,  $P < 0.01$  and  $r = 0.522$ ,  $P < 0.01$ , respectively). Even after controlling for abdominal visceral fat area, the low-density muscle area correlated with the HOMA score ( $r = 0.399$ ,  $P < 0.01$ ).

Total body weight, BMI, and total fat mass were shown to decline with age ( $r = -0.352$ ,  $P < 0.01$ ;  $r = -0.362$ ,  $P < 0.01$ ; and  $r = -0.402$ ,  $P < 0.01$ ; respectively). The abdominal subcutaneous fat area de-

creased with age ( $r = -0.438$ ,  $P < 0.01$ ), but the ratio of visceral to subcutaneous abdominal fat increased significantly with age ( $r = 0.369$ ,  $P < 0.01$ ), without a corresponding statistically significant increase in the abdominal visceral fat area. Midhigh subcutaneous fat areas decreased with age ( $r = -0.572$ ,  $P < 0.01$ ), but neither the low-density muscle area nor the normal-density muscle area was significantly correlated with age.

Although the BMI was identical in both sexes, the percentage of total body fat was higher in women ( $39.3 \pm 6.0$  vs.  $28.5 \pm 8.2\%$ ,  $P < 0.01$ ) and the percentage of fat-free mass was higher in men ( $P < 0.01$ ). Fasting serum insulin levels and the HOMA score in both sexes were identical. The abdominal visceral fat area was greater in men than in women ( $172.6 \pm 83.5$  vs.  $98.0 \pm 38.3$   $\text{cm}^2$ ,  $P < 0.01$ ), but the abdominal and midhigh subcutaneous fat area was greater in women ( $P < 0.01$ ). The midhigh low-density muscle area was similar in both

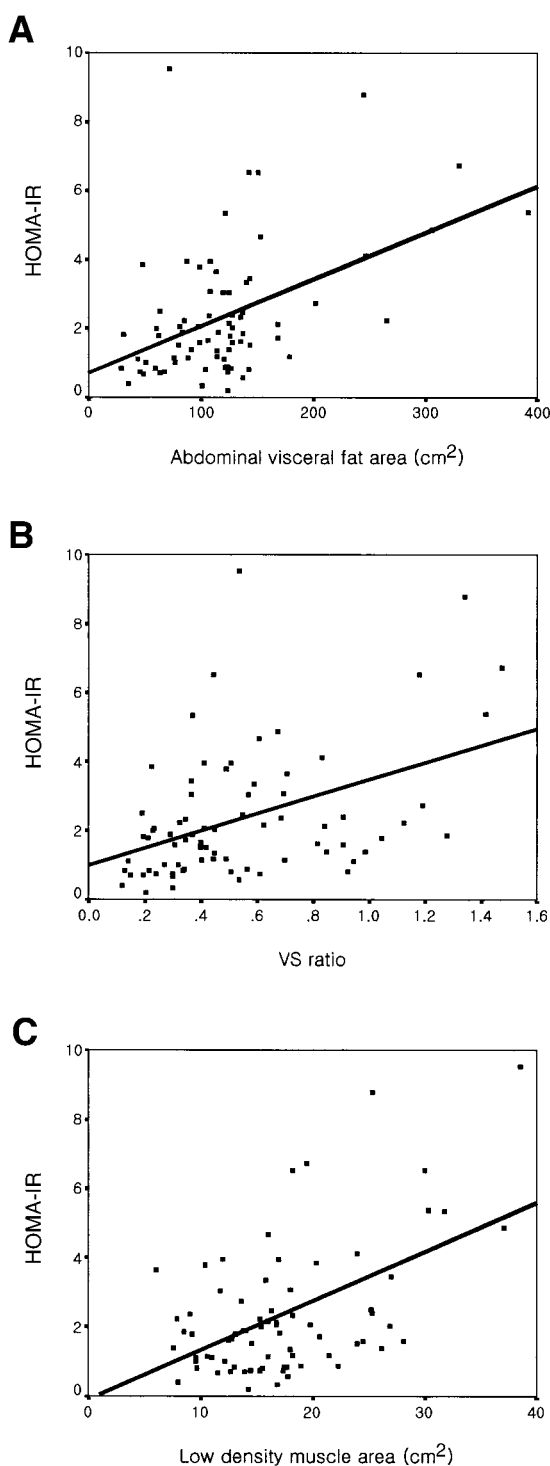
sexes ( $18.5 \pm 8.1$  vs.  $16.7 \pm 6.2$   $\text{cm}^2$ , NS), but the normal density muscle area was greater in men than in women ( $P < 0.01$ ). In men, the abdominal visceral fat area was related most closely to the HOMA score ( $r = 0.652$ ,  $P < 0.01$ ), and this correlation persisted after adjustment for BMI and total fat mass ( $r = 0.53$ ,  $P < 0.05$  and  $r = 0.67$ ,  $P < 0.01$ , respectively). In women, only the midhigh low-density muscle area was correlated with the HOMA score ( $r = 0.59$ ,  $P < 0.01$ ) independent of BMI, total fat mass, or abdominal visceral fat area.

Postmenopausal women had a greater abdominal visceral fat area than premenopausal women ( $113.0 \pm 35.0$  vs.  $89.5 \pm 38.0$   $\text{cm}^2$ ,  $P < 0.01$ ), but the abdominal and midhigh subcutaneous fat areas were greater in premenopausal women than in postmenopausal women ( $P < 0.05$ ). The midhigh low-density muscle area was identical in both groups, but the normal-density muscle area was greater in the premenopausal women than in the postmenopausal women ( $104.9 \pm 14.7$  vs.  $86.0 \pm 23.6$   $\text{cm}^2$ ,  $P < 0.01$ ).

Patients with impaired glucose tolerance had higher HOMA scores ( $3.3 \pm 2.4$  vs.  $1.7 \pm 1.2$ ,  $P < 0.01$ ) and greater abdominal visceral fat and midhigh low-density muscle areas ( $143.0 \pm 80.6$  vs.  $107.0 \pm 49.8$   $\text{cm}^2$ ,  $P < 0.05$  and  $19.1 \pm 6.9$  vs.  $16.1 \pm 6.5$   $\text{cm}^2$ ,  $P = 0.06$ , respectively) than those with normal glucose tolerance. Men and postmenopausal women showed a greater glycemic response to a 75-g oral glucose load than premenopausal women ( $7.9 \pm 1.1$  and  $7.8 \pm 0.9$  vs.  $7.2 \pm 1.0$   $\text{mmol/l}$ , respectively,  $P < 0.05$ ).

**CONCLUSIONS**—Recent evidence suggests that low-density muscle is closely linked to insulin resistance in obese Caucasian patients (6,13,14). The present study confirms that low-density muscle is strongly associated with insulin resistance in nondiabetic obese subjects in Korea.

To evaluate regional fat distribution, we used single-slice images from the mid-abdomen at L4–L5 and from the midhigh, which have been frequently used to measure the quantity and distribution of adipose tissue in the thigh in many other studies (6,12,15). Goodpaster et al. (16) showed that skeletal muscle attenuation by single-slice CT scans well demonstrate muscle fiber lipid content in



**Figure 2**—Correlation between regional adiposity and insulin resistance. A: Abdominal visceral fat area and HOMA-IR ( $P < 0.01$ ). B: VS ratio and HOMA-IR ( $P < 0.01$ ). C: Midhigh low density muscle and HOMA-IR ( $P < 0.01$ ). VS ratio = abdominal visceral fat area to abdominal subcutaneous fat area ratio.

percutaneous biopsy specimens. Therefore, skeletal muscle attenuation in vivo as determined by CT may provide valuable information about the association between muscle composition and muscle function.

The abdominal visceral fat area increased with age in both sexes; a more marked fat redistribution was noted in

women ( $r = 0.382$ ,  $P < 0.01$ ). Both hormonal and body compositional changes occur with aging, primarily due to a decrease in lipolytic activity and the consequent prevalence of liposynthesis, resulting in visceral fat accumulation (17). Diminished leptin action or leptin resistance was proposed to explain the

metabolic decrease associated with aging. Previous investigators have asserted that age is an independent predictor of low-density muscle, which is associated with insulin resistance in obesity irrespective of sex or age (18,19). A recent study based on muscle biopsies of obese children demonstrated that skeletal muscle triglyceride stores are not a consequence of aging but occur early in the natural course of obesity (20).

Many differences in anthropometric and biochemical parameters, body composition, and regional fat distribution were observed in both sexes in our study, suggesting hormonal effects. Because circulating leptin levels are known to be strongly related to the percentage of body fat and because leptin values in women are twice those in men, higher estrogen levels in women might be responsible for the sexual dimorphism of leptin concentrations, but this hypothesis has not been confirmed.

Our results suggest that the menopause transition is associated with an accumulation of visceral adipose tissue. The menopause transition is associated with a reduction in resting metabolic rate, physical activity, and fat-free mass and an increase in fat mass and abdominal adipose tissue accumulation. Abdominal visceral adipose tissue was found to be a more important predictor of insulin resistance than low-density muscle in postmenopausal women in our study, which is consistent with the findings of previous studies (21,22), whereas low-density muscle seems to play a key role in premenopausal women.

Few studies have been conducted in the Asian populations with regard to racial differences in body composition, regional fat distribution, and insulin resistance (23–28). Our results show that abdominal visceral adiposity and low-density muscle are related to insulin resistance in mildly obese Korean subjects (under grade II). The prevalence and severity of obesity and related complications are reported to be relatively low in Korea compared with westernized countries. The prevalence of abdominal or visceral obesity may be much higher, although only preliminary data of a small population are currently available (29, 30). It is clear that the global issues of obesity per se and abdominal obesity are relevant in Korea and should not be overlooked. Moreover, the significance of in-

sulin resistance and its determinants should be emphasized in the Korean population, because Koreans are more susceptible to glucose intolerance and diabetes. The maximal secretory function of  $\beta$ -cells is relatively low, and consequently, even slight stresses on  $\beta$ -cells, including mild obesity, can substantially disrupt the metabolic balance and prematurely induce the overt failure of  $\beta$ -cells to meet the metabolic demands of insulin in obese patients (31,32). This hypothesis provides presumptive evidence that may explain recent data concerning the rapidly increasing prevalence of metabolic syndrome and type 2 diabetes in Korea. Further global epidemiologic studies are needed if we are to fully understand metabolic disparities with respect to the different ethnicities.

Previously, Greco et al. (33) emphasized the role of abnormal fat deposition within skeletal muscle on obesity-related insulin resistance. They found that lipid deprivation selectively depletes intramyocellular lipid stores and induces a normal metabolic state. Potential mechanisms for this association include apparent defects in fatty acid metabolism at the mitochondrial level in obese individuals with type 2 diabetes. Substantial evidence indicates that perturbations in fatty acid oxidation are involved in the accumulation of skeletal muscle triglyceride and the pathogenesis of insulin resistance. Moreover, recently acquired knowledge of insulin receptor signaling indicates that the accumulation of lipid products within skeletal muscle can interfere with insulin signaling and finally produce insulin resistance (6,34).

Although low-density muscle accounts for a relatively small portion of the total skeletal muscle, it seems to be a valuable marker of insulin resistance in the Korean population. From our data and previous epidemiologic data, we speculate that the significance of low-density muscle as well as visceral adipose tissues deserves much consideration with regard to genetically determined low  $\beta$ -cell capacity. The mechanisms whereby triglyceride contents within the skeletal muscle provoke insulin resistance should be investigated further.

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