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Association of daily carbohydrate intake with intermuscular adipose tissue in Korean individuals with obesity: a cross-sectional study

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ABSTRACT

BACKGROUND/OBJECTIVES: The prevalence of obesity, a worldwide pandemic, has been increasing steadily in Korea. Reports have shown that increased intermuscular adipose tissue (IMAT) is associated with an increased risk of cardiovascular disease, independent of body mass index. However, the relationship between dietary intake and IMAT accumulation in the Korean population remains undetermined. The objective of this study was to evaluate regional fat compartments using advanced magnetic resonance imaging (MRI) techniques. We also aimed to investigate the association between IMAT amounts and dietary intake, including carbohydrate intake, among Korean individuals with obesity.
SUBJECTS/METHODS: This cross-sectional study, performed at a medical center in South Korea, recruited 35 individuals with obesity (15 men and 20 women) and classified them into 2 groups according to sex. Anthropometry was performed, and body fat distribution was measured using MRI. Blood parameters, including glucose and lipid profiles, were analyzed using commercial kits. Linear regression analysis was used to test whether the IMAT was associated with daily carbohydrate intake.
RESULTS: Carbohydrate intake was positively associated with IMAT in all individuals, with adjustments for age, sex, height, and weight. No significant differences in blood indicators were found between the sexes.
CONCLUSIONS: Regardless of sex and age, higher carbohydrate intake was strongly correlated with greater IMAT accumulation. This suggests the need to better understand sex differences and high carbohydrate diet patterns in relation to the association between obesity and metabolic risk, which may help reduce obesity prevalence.

Keywords: Carbohydrates; dietary intake; adipose tissue; magnetic resonance imaging; obesity

INTRODUCTION

The prevalence of obesity is steadily increasing worldwide, including in Korea, and has been labeled a pandemic [1]. In many parts of the world, including Western countries, a body mass index (BMI) ≥ 30 kg/m^2 is commonly used as the threshold to define obesity. However,

Conflict of Interest
The authors declare no potential conflicts of interests.

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obesity was classified as a BMI of ≥ 25 kg/m^2 in Asia, based on the World Health Organization Asia-Pacific standards, because Asians have a higher risk of cardiovascular disease (CVD) than Caucasians [2]. In Korea, 36.3% and 23.9% of the total population have obesity and abdominal obesity, respectively, which is higher than the global prevalence of obesity (13% of adults worldwide) [1]. Additionally, the prevalence of class III obesity, which is defined as a BMI of ≥ 35 kg/m^2, increased by nearly 3-fold in 2019 compared with the 2009 levels in Korea [1]. Excess adipose tissue (AT), linked to hypertrophied adipocytes, can cause inflammation and the accumulation of triglycerides (TG) within organs [3]. Accumulation of TG within organs can accelerate the progression of sarcopenia, insulin resistance, nonalcoholic fatty liver disease, type 2 diabetes (T2DM), and heart failure [3]. Individuals with obesity have a 3.5 times greater risk of hypertension than healthy individuals [4]. A previous meta-analysis also reported that obesity was positively correlated with increased mortality (hazard ratio, 1.18) [5].

AT can be stored in subcutaneous tissue but accumulate in and around organs such as the heart, liver, and skeletal muscle through ectopic fat infiltration [6]. Ectopic fat in the intermuscular AT (IMAT) can affect skeletal muscle metabolism [7]. IMAT secretion of extracellular matrix proteins and pro-inflammatory cytokines such as interleukins and chemokines, including monocyte chemoattractant protein-1, is significantly higher than in the subcutaneous AT (SAT) and visceral AT (VAT) compartments [7,8]. Therefore, IMAT could promote muscle weakness and insulin resistance via extracellular matrix proteins and pro-inflammatory cytokines; however, evidence of the relationship between IMAT and cytokine secretion is still lacking [8]. Multiple studies have also revealed that IMAT is positively associated with impaired insulin resistance and increased risk of CVD, independent of VAT [8,9]. Therefore, IMAT accumulation may play a key role in increased metabolic risk than other regional AT depots observed in obesity. Accurately evaluating IMAT levels is difficult because this tissue is within skeletal muscle and is < 5% of total body fat [10]. For this reason, studies on this subject are still being conducted in Korea.

The accumulation of ectopic fat and metabolic syndrome is positively correlated with the high consumption of carbohydrates by modulating lipogenic enzymes, leading to energy storage [11]. Some studies have focused on the high consumption of carbohydrates and IMAT accumulation [12-14]. A low-carbohydrate diet reduced IMAT in patients with polycystic ovary syndrome (PCOS), T2DM, and older adults with obesity [12-14]. The Korean diet mainly consists of rice-based foods and several plant foods high in carbohydrates [15]. Therefore, a study on the accumulation of IMAT as a function of carbohydrate intake may be particularly relevant in Korea. However, no study to date has investigated the association between dietary nutrient intake and IMAT accumulation in Korean individuals with obesity. Thus, in this study, we aimed to evaluate regional fat compartments using advanced magnetic resonance imaging (MRI) techniques and the association between IMAT amounts and dietary intake, including carbohydrate intake, among Korean individuals with obesity.

SUBJECTS AND METHODS

Participants and study design

This cross-sectional study was conducted from April 2013 to December 2013 and from April 2015 to December 2015 at the Kyung Hee Medical Centre in Seoul, Korea. Thirty-five patients, 19–60 yrs old, with obesity (BMI ≥ 25 kg/m^2), including 15 men and 20 women, were recruited. Participants were classified into 2 groups according to sex. The exclusion

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criteria were as follows: patients with diabetes, heart, kidney, liver, thyroid, cerebrovascular, or gallbladder disease, as well as those with a gastrointestinal disorder, gout, porphyria, a psychiatric disorder, depression, schizophrenia, alcoholism, and drug addiction, pregnant or lactating women, use of anti-obesity drugs, or participation in a diet program within the preceding month. All participants provided written informed consent and fully understood the goals of the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Kyung Hee Medical Centre (KMC IRB 1304-03 and KMC IRB 1509-01).

Anthropometric measurements and body composition

Anthropometric measurements were performed in the morning, with all participants wearing light clothing. An electronic scale measured height (cm) and body weight (kg) to the closest 0.1 cm and 0.1 kg. BMI (kg/m^2) was calculated using these measurements. Waist circumference (WC; cm) and hip circumference (HC; cm) were measured using plastic tape. WC was measured midway between the lowest rib edge and the iliac crest at the level of the umbilicus. HC was measured at the widest point of the buttocks. The waist-to-hip circumference ratio (WHR) was calculated from these measurements. Percentage of body fat (PBF; %), body fat mass (BFM; kg), and fat-free mass (FFM; kg) were measured using bioelectrical impedance analysis (BIA) with Inbody 3.0 (Biospace, Seoul, Korea).

Analysis of fat compartments based on MRI

We adopted the process for MRI measurement of fat distribution, including IMAT, previously described by Choi *et al.* [16] and Gallagher *et al.* [17]. Clinically trained investigators measured total SAT, VAT, IMAT, and lean body mass (LBM) using a 1.5T whole-body MRI scanner (63 Horizon; General Electric, Milwaukee, WI, USA) at 10 mm thickness and 40 mm intervals. Estimates of MRI volume were converted to mass using a presumed density of 1.0 kg/L for muscle and 0.9 kg/L for AT. Images were processed using SliceOmatic software (TomoVision, Magog, QC, Canada).

Biochemical analyses

All individuals fasted overnight. Their blood specimens were collected the next morning using a 10 mL syringe and centrifuged at 3,000 ×g for 15 min at 4°C (Eppendorf centrifuge 5415R; Eppendorf Hamburg, Germany) before use. Serum glucose and dyslipidemia parameters, including TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) levels, and high-density lipoprotein cholesterol (HDL-C) levels, were analyzed using commercial kits via an enzymatic method (Asan Pharmaceutical, Seoul, Korea). All kits were used according to the manufacturers' instructions.

Nutrient intake assessment

To assess the nutrient intake of the participants, 3-day estimated dietary records (2 random weekdays, one weekend), including breakfast, lunch, dinner, morning snack, afternoon snack, food name, main ingredients, and amount of food intake, were collected. Using these data, we analyzed dietary intake with reference to average energy requirements, major nutrients (carbohydrates, proteins, and fats), fibers, and cholesterol via the Can-pro 5.0 (Korean Nutrition Society, Seoul, Korea).

Statistical analyses

All continuous data are expressed as mean ± SD. Mann-Whitney *U* test was used to assess significant differences between sexes, and results were considered significantly different when $P < 0.05$. Correlations between daily carbohydrate intake and IMAT were assessed using linear regression and Pearson's correlation coefficient after adjusting for covariates, including age, sex, height, and weight. SPSS statistical software was used for statistical analysis (version 27.0 for Windows software package; IBM Corp., Armonk, NY, USA).

RESULTS

General characteristics and anthropometric data

Table 1 shows the general characteristics and anthropometric measurements of the participants. The height and body weight of men were significantly greater than those of women ($P < 0.001$ and $P = 0.002$, respectively). Men also had significantly greater WC and WHR than women ($P = 0.031$ and $P = 0.014$, respectively). BMI and HC of men and women were not significantly different.

Body composition and fat compartments

Table 2 summarizes the descriptive results of body composition using BIA and fat compartments by MRI, according to sex. PBF of women was considerably higher than that of men ($P < 0.001$). However, BFM did not differ significantly between the groups. Conversely, the FFM of men was shown to be significantly higher than that of women ($P < 0.001$). VAT and LBM of men were also significantly higher than those of women ($P = 0.033$ and $P < 0.001$, respectively), whereas the IMAT/LBM ratio was significantly greater in women ($P = 0.021$). Total AT mass, SAT, and IMAT did not show significant differences between the sexes.

Table 1. General characteristics and anthropometric data

Characteristics	Women (n = 20)	Men (n = 15)	*P*-value
Age (yrs)	42.7 ± 10.9	45.3 ± 8.6	0.479
Height (cm)	158.5 ± 7.0	173.2 ± 3.1	< 0.001
Weight (kg)	66.6 ± 13.1	83.0 ± 13.7	0.002
BMI (kg/m^2)	26.4 ± 5.0	27.6 ± 3.9	0.400
WC (cm)	88.8 ± 9.3	95.7 ± 8.5	0.031
HC (cm)	100.8 ± 8.7	103.0 ± 6.5	0.431
WHR	0.881 ± 0.051	0.928 ± 0.046	0.014

Values are presented as the mean ± SD.
BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-hip circumference ratio.

Table 2. Body composition and fat distribution

Characteristics	Women (n = 20)	Men (n = 15)	*P*-value
BIA body compositions			
PBF (%)	35.4 ± 6.3	26.2 ± 6.3	< 0.001
BFM (kg)	24.5 ± 8.6	22.4 ± 8.4	0.610
FFM (kg)	42.1 ± 6.2	60.5 ± 6.2	< 0.001
MRI body fat distributions			
TAT (kg)	25.9 ± 9.0	22.7 ± 7.6	0.347
SAT (kg)	22.5 ± 8.0	18.0 ± 6.3	0.114
VAT (kg)	2.4 ± 1.1	3.8 ± 2.1	0.033
IMAT (kg)	0.9 ± 0.4	0.9 ± 0.4	0.564
LBM (kg)	28.6 ± 3.7	42.3 ± 5.1	< 0.001
IMAT/LBM ratio	0.031 ± 0.011	0.023 ± 0.009	0.021

Values are presented as the mean ± SD.
BIA, bioelectrical impedance analysis; PBF, percentage body fat; BFM, body fat mass; FFM, fat-free mass; MRI, magnetic resonance imaging; TAT, total adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; IMAT, intermuscular adipose tissue; LBM, lean body mass.

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Biochemical parameters

Serum glucose levels and lipid profiles, including TG, TC, LDL-C, and HDL-C, are summarized in **Table 3**. Compared with men, women exhibited increased serum glucose and TC levels. Nevertheless, no significant differences were found between the 2 groups in terms of any of the blood indicators.

Dietary nutrient intake assessment

Table 4 summarizes the average daily intake of nutrients and intake proportion of carbohydrates, fat, and protein according to sex. **Table 4** also shows the percentages of the Dietary Reference Intake for Korean (KDRI) adults. Women consumed significantly fewer calories and protein than men ($P = 0.004$ and $P = 0.001$, respectively).

The percentages of calorie intake from carbohydrates, proteins, and fat were 60.5%, 12.2%, and 20.4%, respectively, in women, and 55.3%, 16.7%, and 24.5%, respectively, in men. The percentage of calorie intake from protein and fat was significantly higher in men than in women ($P < 0.001$ and $P = 0.039$, respectively). Conversely, the KDRI percentage of fiber in women was significantly higher than that in men ($P = 0.047$). The KDRI percentage of cholesterol did not differ significantly between men and women.

Linear regression models were used to assess the correlation between IMAT and carbohydrate intake with adjustments for age, sex, height, and weight (**Table 5**, **Fig. 1**). Carbohydrate intake ($\beta = 0.367$, $P = 0.029$) was positively correlated with IMAT accumulation.

Table 3. Blood parameters

Characteristics	Women (n = 20)	Men (n = 15)	*P*-value
Glucose (mg/dL)	135.8 ± 88.9	106.2 ± 24.9	0.949
TG (mg/dL)[1)]	2.2 ± 0.3	2.2 ± 0.3	0.799
TC (mg/dL)	209.0 ± 43.8	197.9 ± 42.6	0.317
LDL-C (mg/dL)	107.0 ± 57.6	102.6 ± 44.8	0.987
HDL-C (mg/dL)	48.2 ± 13.5	43.4 ± 9.6	0.306

Values are presented as the mean ± SD.
TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
[1)]Log-transformed values used TG.

Table 4. Dietary intake and intake ratio to KDRI

Characteristics	Women (n = 20)	Men (n = 15)	*P*-value
Dietary intake			
Calorie (kcal)	1,497.7 ± 391.6	1,963.8 ± 420.7	0.004
Carbohydrates (g)	225.4 ± 58.7	270.7 ± 70.8	0.097
Protein (g)	56.1 ± 16.4	77.1 ± 14.9	0.001
Fat (g)	41.9 ± 13.6	50.2 ± 9.4	0.077
Fiber (g)	18.1 ± 5.9	20.5 ± 7.1	0.323
Cholesterol (mg)	245.0 ± 117.4	312.8 ± 118.8	0.129
Energy distribution			
% Carbohydrates	60.5 ± 4.6	55.3 ± 8.6	0.065
% Protein	12.2 ± 3.6	16.7 ± 3.2	< 0.001
% Fat	20.4 ± 6.6	24.5 ± 4.6	0.039
Percentage of KDRIs			
% Energy	81.8 ± 22.4	81.5 ± 17.2	0.866
% Fiber	90.4 ± 29.3	68.2 ± 23.5	0.047
% Cholesterol	81.7 ± 39.1	104.3 ± 39.6	0.065

Values are presented as the mean ± SD.
KDRI, Dietary Reference Intake for Korean.

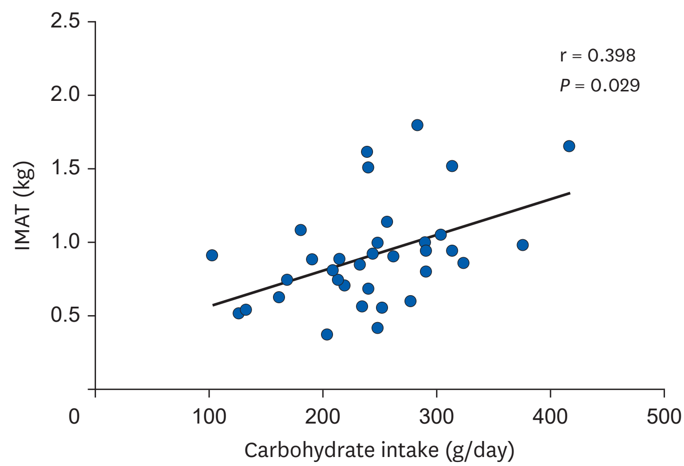

Fig. 1. Covariates-adjusted partial correlation coefficients between daily carbohydrate intake and IMAT.
IMAT, intermuscular adipose tissue.

Table 5. Multiple linear regression analyses of the correlation between carbohydrate intake and intermuscular adipose tissue

Characteristics	B	SE	β	t (p)
Constant	315.575	1,716.348		0.182 (0.857)
Carbohydrate intake (g/day)	1.931	0.841	0.367	2.296 (0.029)
Age (yrs)	9.872	6.291	0.282	1.569 (0.128)
Sex	−157.602	189.185	−0.224	−0.833 (0.412)
Height (cm)	−7.899	10.509	−0.210	−0.752 (0.459)
Weight (kg)	14.534	4.668	0.646	3.114 (0.004)
F(p)		3.255 (0.025)		
R^2		0.310		
Adjusted R^2		0.215		

Age, sex, height, and weight were adjusted as covariates.

DISCUSSION

In Korea, obesity criteria are generally used for BMI, according to the World Health Organization criteria for the Asian-Pacific classification [2]. Accordingly, "overweight" is classified as a BMI of ≥ 23 and obesity as a BMI of ≥ 25. Most national statistics and studies on non-communicable diseases are based on the BMI criteria. BMI has the advantage of quickly determining obesity and observing weight changes, but it cannot accurately evaluate BFM and muscle mass [18]. Regardless of BMI, changes in fat distribution patterns may be independent risk factors for various chronic diseases, including CVD and T2DM [19].

Multiple cross-sectional studies among individuals who were overweight, obese, and had T2DM report that a higher IMAT is correlated with poorer metabolic outcomes [20-23]. Among individuals who are overweight and have obesity, increased IMAT is associated with greater impairment of insulin sensitivity and fasting glucose levels [20,21]. Furthermore, despite similar thigh SAT, IMAT was significantly higher in T2DM patients than in older people with normal glucose tolerances [22]. Miljkovic-Gacic *et al.* [23] also observed that increased IMAT and lower SAT could be used as predictors for T2DM in middle-aged people with obesity. Some researchers have also focused on assessing the IMAT/muscle mass ratio in older individuals and individuals with obesity [24,25]. The IMAT/muscle mass ratio was significantly correlated with impaired fasting glucose and increased homeostasis model assessment of insulin resistance in middle-aged individuals with obesity [24]. Furthermore,

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the calf IMAT/muscle mass ratio was positively correlated with poor physical function and muscle quality in individuals with obesity and T2DM [25].

IMAT secretes more inflammatory cytokines, chemokines, hepatocyte growth factor, and resistin than SAT and VAT, resulting in muscle fat infiltration [7,8]. These studies suggest that IMAT is a unique AT with immunogenic and inflammatory secretions that can affect the metabolic dysfunction and insulin resistance of neighboring muscle tissue. IMAT has a higher rate of lipolysis than other ATs and increases the concentration of local free fatty acids in muscle, suggesting that IMAT can directly affect lipid accumulation and insulin resistance in muscle tissue [26]. Lipid signaling by IMAT may include the secretion of eicosanoids such as prostaglandins and thromboxanes [26]. These signaling pathways affect inflammation and insulin resistance in muscle tissue by promoting macrophage infiltration and inflammatory cytokine expression in AT and neutrophil, monocyte, and eosinophil chemotaxis, possibly contributing to skeletal muscle inflammation [8,16,26].

Our results showed that the body weight and WHR of men were higher than those of women, whereas the IMAT/LBM ratio was significantly higher in women than in men, regardless of BMI. Our study also revealed that the LBM and FFM of men were higher than those of women. FFM comprises bones, muscles, essential organs, and extracellular fluids. LBM differs from FFM because it contains lipids from cellular membranes, although it only accounts for a small portion of total body weight (up to 3% in men and 5% in women) [27]. This study showed no significant differences in blood parameters between the sexes, whereas the glucose and TC values were lower in men than in women. Serum glucose and TC values for all participants were also within the upper normal range or partly over the normal range in our results [28]. In women, HDL-C has a negative correlation with IMAT ($P = 0.048$, $r = -0.459$; data were not shown). Therefore, these results indicate that IMAT accumulation may be a marker of the risk of CVD in women with obesity.

Asians, including Koreans, traditionally consume a large amount of rice as a staple food, thus obtaining a large percentage of calorie intake from carbohydrates [29]. Daily carbohydrate intake is potentially associated with a risk of metabolic syndrome [30,31]. Korean people, who consume the highest quintile of carbohydrates, revealed metabolic abnormalities with increased TG and reduced HDL-C levels compared with those in the United States [32]. Therefore, continuous research on carbohydrate intake and metabolic risk is necessary in Korea. Dietary carbohydrates profoundly influence several aspects of weight gain, the endocrine system, and appetite [11,33], and can be used directly for energy via glycolysis. Alternatively, excess energy is stored through TG synthesis (lipogenesis) in the liver and AT. After high carbohydrate consumption, blood glucose levels increase, causing a rapid release of insulin in the blood [33]. Plasma glucose upregulates the carbohydrate response element-binding protein (*ChREBP*) gene, which activates glycolysis and lipogenesis by elevating acetyl-CoA carboxylase and fatty acid synthase (FAS) [34]. *ChREBP* also directly activates the expression of the sterol regulatory element-binding protein-1c (*SREBP-1c*) gene [35]. Insulin secreted in response to elevated blood glucose levels upregulates *SREBP-1c*, promoting the expression of lipogenic enzymes, such as acetyl-CoA synthetase and FAS [34,35]. Therefore, excess consumption of carbohydrates can modulate lipogenic enzymes, leading to energy storage in the form of TG. A reduced carbohydrate diet (41% energy from carbohydrates over 8 weeks) has beneficial effects on fat distribution, including IMAT, in individuals at risk of developing T2DM [14]. Similarly, another study reported that a reduced carbohydrate diet decreased SAT and thigh IMAT in women with PCOS [12]. Sjöholm *et al.* [36] demonstrated that the energy percentage of carbohydrates is negatively associated with IMAT in younger individuals (27–31 yrs) and men.

Our research has several strengths and limitations. This study is the first to investigate the association between carbohydrate intake and IMAT in Korean individuals with obesity. Some studies have suggested the importance of reducing carbohydrate intake to prevent IMAT accumulation. Given the high carbohydrate consumption patterns in Koreans, the findings indicate that the amount of IMAT varies by sex and can serve as a foundation for future obesity-related diet intervention research. However, the small sample size may limit the statistical power of the results. Moreover, the study did not measure gene expression or enzymes related to carbohydrate metabolism and IMAT, nor did it provide guidelines for preventing IMAT accumulation in Korean individuals with obesity. Additionally, as a cross-sectional study rather than an intervention study, this research provided a limited analysis of the correlation between carbohydrate intake and IMAT. Longitudinal studies are needed to consider obesity phenotypes and dietary patterns to distinguish the characteristics of separate fat depots.

Our findings showed that an increase in carbohydrate intake in Koreans with obesity was independently associated with IMAT accumulation. Therefore, nutritional counseling and education related to appropriate low-carbohydrate diet consumption for middle-aged people with obesity may be a possible solution to prevent IMAT accumulation and reduce metabolic risk. Larger longitudinal studies are required to confirm these results.

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