

## Relation of Absolute or Relative Adiposity to Insulin Resistance, Retinol Binding Protein-4, Leptin, and Adiponectin in Type 2 Diabetes

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**Background:** Central fat mass (CFM) correlates with insulin resistance and increases the risk of type 2 diabetes and cardiovascular complications; however, peripheral fat mass (PFM) is associated with insulin sensitivity. The aim of this study was to investigate the relation of absolute and relative regional adiposity to insulin resistance index and adipokines in type 2 diabetes.

**Methods:** Total of 83 overweighted-Korean women with type 2 diabetes were enrolled, and rate constants for plasma glucose disappearance ( $K_{ITT}$ ) and serum adipokines, such as retinol binding protein-4 (RBP4), leptin, and adiponectin, were measured. Using dual X-ray absorptiometry, trunk fat mass (in kilograms) was defined as CFM, sum of fat mass on the lower extremities (in kilograms) as PFM, and sum of CFM and PFM as total fat mass (TFM). PFM/TFM ratio, CFM/TFM ratio, and PFM/CFM ratio were defined as relative adiposity.

**Results:** Median age was 55.9 years, mean body mass index 27.2 kg/m<sup>2</sup>, and mean HbA1c level 7.12 ± 0.84%.  $K_{ITT}$  was positively associated with PMF/TFM ratio, PMF/CFM ratio, and negatively with CFM/TFM ratio, but was not associated with TFM, PFM, or CFM. RBP4 levels also had a significant relationship with PMF/TFM ratio and PMF/CFM ratio. Adiponectin, leptin, and apolipoprotein A levels were related to absolute adiposity, while only adiponectin to relative adiposity. In correlation analysis,  $K_{ITT}$  in type 2 diabetes was positively related with HbA1c, fasting glucose, RBP4, and free fatty acid.

**Conclusion:** These results suggest that increased relative amount of peripheral fat mass may aggravate insulin resistance in type 2 diabetes.

**Keywords:** Adiponectin; Adiposity; Insulin resistance; Leptin; Retinol binding protein-4

### INTRODUCTION

Fat accumulation in the human body releases several adipokines from adipocytes, some of which are known to lead to elevate insulin resistance and to cause metabolic syndrome [1] as well as type 2 diabetes [2]. Ford et al. [3] have reported that for 1 kilogram of weight gain, the risk of diabetes increases by 4.5% to 9%. Obesity due to a proliferation of fat tissue not only increases insulin resistance, but is also closely related to abnor-

mal glucose metabolism [4]. Previous studies have reported that a higher body mass index (BMI) results in a higher risk of type 2 diabetes [4]; however, the general pattern of obesity in diabetic subjects involves fat accumulation in the abdomen regardless of sex [5], and such central fat accumulation leads to peripheral insulin resistance and increases the risk of cardiovascular complications. Free fatty acids released from abdominal fat are known to play a major role in the development of such insulin resistance [6].

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Several studies have analyzed the association among insulin resistance, body fat distribution, and race. In a study by Boutcher et al. [7], a greater amount of trunk fat was associated with severity of insulin resistance in Austrian women, while in Chinese women, insulin resistance was associated with a smaller amount of fat in the lower extremities. Trunk fat and fat located in the lower extremities cause separate effects on the metabolism of the body. Generally, the former causes metabolic diseases, such as cardiovascular diseases and diabetes, while according to previous studies, the latter may exert a preventive effect on such metabolic diseases [8,9].

Studies on fat distribution and their effects on the body have been performed in obese subjects; however, few researches have existed about obese subjects with diabetes. Studies by Kelley et al. [10] and Kotronen et al. [11] have reported more hepatic, intestinal, and intramuscular fat and less subcutaneous fat in diabetic subjects compared to obese, non-diabetic subjects. In other words, fat distribution in diabetic subjects is different from that of subjects without diabetes [12].

Therefore, we have attempted to investigate the specific type of body fat distribution related to insulin resistance and compute relative adiposity for comparison with body fat distribution. We have also investigated the association between body fat distribution and adipokines, such as adiponectin, leptin, and retinol binding protein-4 (RBP4).

## METHODS

### Subjects

A total of 83 female subjects with type 2 diabetes who were visiting the Diabetes Mellitus Center of Eulji General Hospital in Seoul, Korea were recruited for this study. The diagnosis of type 2 diabetes was made in accordance with the diagnostic criteria set by the World Health Organization (WHO), and among the diabetic subjects, overweight subjects with BMIs greater than 23 kg/m<sup>2</sup> and glycosylated hemoglobin (HbA1c) between 5.5% and 10.0% were included. Exclusion criteria included type 1 diabetes and heart diseases, including congestive heart failure, uncontrolled arrhythmia, and uncontrolled valvular diseases. Subjects with diseases contraindicating mild exercise necessary for glycemic control were also excluded.

### Methods

#### *Anthropometric and biochemical measurements*

The height, weight, waist circumference, and hip circumfer-

ence of the subjects were measured at the start of the study. Height and weight were measured in light clothing, and BMI was calculated by dividing weight (in kilograms) by the square of height (in meters).

For biochemical measurements, venous blood was sampled after a minimum of 10 hours of fasting, and the serum was separated by centrifuging at 3,000 rpm for 15 minutes. The serum was stored at -70°C until the time of analysis. Fasting glucose was measured with the glucose oxidase method, and glycosylated albumin was measured using high-performance liquid chromatography (HPLC). The maximum value of serum adipokines was measured with an enzyme-linked immunosorption assay (ELISA) (R&D Systems Inc., Minneapolis, MN, USA): the intra- and inter-assay coefficients of variability (CV) values were 8.3% and 8.3%, respectively. Serum leptin (intra- and inter-assay values of 5.8% and 12.8%, respectively) [13] and apolipoprotein A (ApoA) levels were also measured with ELISA (American Laboratory Products Company, Windham, NH, USA).

RBP4, a biochemical index used in conjunction with insulin resistance, was measured by amplifying the subjects' serum samples, which were stored at -70°C, with a radioimmunoassay (RIA) (Phoenix, Belmont, CA, USA): the intra-assay CV value was 8% [14].

#### *Insulin resistance*

The rate constant for plasma glucose disappearance ( $K_{ITT}$ ) was employed to assess insulin resistance. An insulin tolerance test was performed on the subjects after 10 hours of fasting. A 20-gauge catheter was inserted into a vein in each hand: one to sample blood and the other to infuse glucose. The subjects rested for 20 to 30 minutes after catheter insertion, and a heating pad was used to maintain the temperature of the sampling site between 60°C to 70°C. The sample was used to obtain arterialized venous blood. Insulin (Humulin, RI 100 U/mL), diluted by a factor of 100, was administered to the subjects via the antebial vein, with 1 kg of body weight calculated as 0.1 U at rest. Arterialized venous blood was sampled at baseline, 3, 6, 12, and 15 minutes after insulin administration. To prevent hypoglycemic events, 100 mL of 20% glucose solution was infused intravenously immediately after venous sampling at 15 minutes, and the sampled blood was immediately centrifuged to measure plasma glucose. The plasma glucose level measured during the insulin tolerance test was input to a computer program converting the values into natural log form,

and the slope of the regression curve constructed from the values measured at 3 and 15 minutes of the insulin tolerance test was obtained using SPSS software for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). The half-life of plasma glucose, or the time required for reducing baseline plasma glucose by half ( $t_{1/2}$ ) was calculated from the slope of the regression curve, and  $K_{ITT}$  was obtained by the following equation:

$$K_{ITT} = [0.693/t_{1/2} \times 100 (\%/min)]$$

### **Fat distribution measurement and calculation of total fat mass and relative adiposity**

Body fat mass and muscle mass were measured with dual-energy X-ray absorptiometry (DXA) (GE Lunar Prodigy; General Electric Medical Systems, Milwaukee, WI, USA) to assess the obesity type of the subjects. The subjects were lightly clothed and were scanned from head to toe while comfortably lying on the examination bed-the test required approximately 10 to 20 minutes to complete. Body composition was divided into body fat and body muscle mass, and the values of the whole body, arms, legs, and trunk were evaluated.

The fat mass of the whole body as evaluated by DXA was defined as total fat mass (TFM), and the fat distributed at the trunk was defined as central fat mass (CFM). In addition, the fat mass of the arms and the legs were combined and defined as peripheral fat mass (PFM). The indices representing relative adipose distribution were derived by obtaining the ratios of PFM to TFM, CFM to TFM, and PFM to CFM.

### **Data and statistical analysis**

Data were analyzed using SPSS software for Windows version 17.0 (SPSS Inc.). Data are presented as mean and standard deviation, and log-transformation was employed for variables with non-normal distribution. The association between abso-

lute and relative adiposity, adipokine levels, such as adiponectin and leptin, BMI, and insulin resistance was assessed with Pearson's correlation analysis. Statistical significance was defined as a  $P$  value less than 0.05.

## **RESULTS**

### **Clinical characteristics of study subjects**

A total of 83 subjects were enrolled in this study. The mean age of the subjects was  $55.93 \pm 6.85$  years, and their mean duration of diabetes was  $4.6 \pm 4.63$  years. The mean height and weight was  $156.89 \pm 4.48$  cm and  $66.93 \pm 7.23$  kg, respectively, with the mean BMI being  $27.20 \pm 2.88$  kg/m<sup>2</sup>. Mean fasting plasma glucose and HbA1c levels were  $132.11 \pm 23.41$  mg/dL and  $7.12 \pm 0.84\%$ , respectively. The mean and standard deviation values for adiponectin, leptin, and ApoA were  $5.68 \pm 2.62$   $\mu$ g/mL,  $11.57 \pm 6.37$  ng/dL,  $122.39 \pm 21.7$  mg/dL, respectively. Also, the mean high sensitivity C-reactive protein (hsCRP) level was  $0.24 \pm 0.59$  mg/L, and the mean RBP4 value was found to be  $74.24 \pm 28.41$   $\mu$ g/mL (Table 1).

### **Association between insulin sensitivity and absolute adiposity**

The statistical significance of the association between indices of insulin resistance ( $K_{ITT}$ , RBP4) and absolute adiposity indices (TFM, CFM, PFM) measured with DXA was examined. As shown in Table 2, neither RBP4 levels nor  $K_{ITT}$  were significantly associated with TFM, PFM, or CFM ( $P > 0.05$ ).

**Table 2.** Correlation between absolute regional adiposity, insulin sensitivity, and adipokines in type 2 diabetes (absolute regional and total fat mass)

	TFM		PFM		CFM	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
$K_{ITT}$	-0.075	0.492	-0.043	0.693	-0.154	0.157
RBP4	-0.151	0.176	-0.214	0.054	-0.088	0.431
Adiponectin	0.338	0.002	0.524	<0.001	0.165	0.135
Leptin	0.729	<0.001	0.681	<0.001	0.689	<0.001
ApoA	0.239	0.029	0.268	0.014	0.193	0.081
hsCRP	0.173	0.111	0.094	0.390	0.214	0.048

TFM, total fat mass; PFM, peripheral fat mass; CFM, central fat mass;  $K_{ITT}$ , rate constant for plasma glucose disappearance; RBP4, retinol binding protein-4; ApoA, apolipoprotein A; hsCRP, high sensitivity C-reactive protein.

**Table 1.** Baseline characteristics of the study subjects

	Mean	SD	Lower limit	Upper limit
Adiponectin	5.68	2.62	5.11	6.25
Leptin	11.57	6.37	10.18	12.96
ApoA	122.39	21.70	117.66	127.14
RBP4	74.24	28.41	67.99	80.48
hsCRP	0.24	0.59	0.11	0.37

SD, standard deviation; ApoA, apolipoprotein A; hsCRP, high sensitivity C-reactive protein; RBP4, retinol binding protein-4.

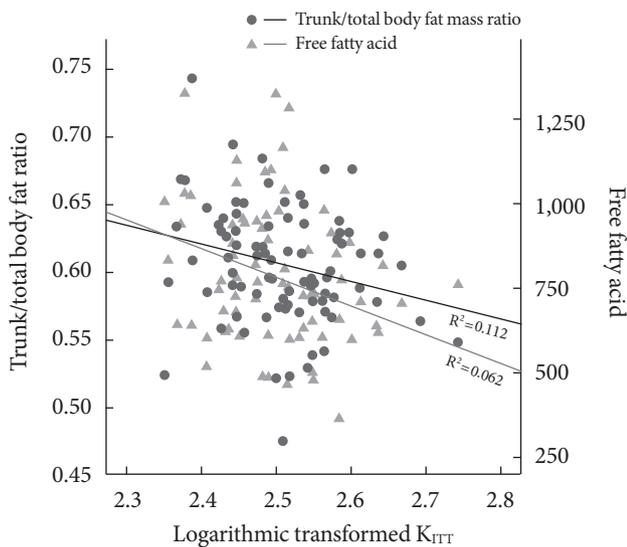
**Association between insulin sensitivity and relative adiposity**

The association between indices of insulin sensitivity and relative adiposity (PFM/TFM ratio, CFM/TFM ratio, PFM/CFM ratio) as measured and presented by DXA was also examined. RBP4 levels were positively associated with CFM/TFM ratio and negatively associated with PFM/TFM ratio and PMF/CFM ratio. However, an opposite finding was made with  $K_{ITT}$ , where we found a positive association with PFM/TFM ratio and PMF/CFM ratio, and a negative association with CFM/TFM ratio ( $P < 0.05$ ) (Table 3, Fig. 1).

**Table 3.** Correlation between relative regional adiposity, insulin sensitivity, and adipokines in type 2 diabetes

	PFM/TFM ratio		CFM/TFM ratio		PFM/CFM ratio	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
$K_{ITT}$	0.242	0.025	-0.246	0.022	0.224	0.038
RBP4	-0.220	0.047	0.217	0.050	-0.221	0.046
Adiponectin	0.548	<0.001	-0.566	<0.001	0.584	<0.001
Leptin	0.172	0.119	-0.122	0.273	0.144	0.194
ApoA	0.179	0.106	-0.161	0.146	0.150	0.176
hsCRP	-0.089	0.415	0.080	0.462	-0.095	0.385

PFM/TFM ratio, peripheral fat mass/total fat mass; CFM/TFM ratio, central fat mass/total fat mass; PFM/CFM ratio, peripheral ratio;  $K_{ITT}$ , rate constant for plasma glucose disappearance; RBP4, retinol binding protein-4; ApoA, apolipoprotein A; hsCRP, high sensitivity C-reactive protein.



**Fig. 1.** The relation of insulin resistance to relative adiposity and adiponectin.  $K_{ITT}$ , rate constant for plasma glucose disappearance.

**Association among adipokines, body fat distribution, and insulin sensitivity**

The association between adipocytokines and absolute and relative adiposity indices was investigated. As shown in Table 2, adiponectin, leptin, and ApoA levels demonstrated significant association with TFM, CFM, and PFM ( $P < 0.05$ ), but only adiponectin was significantly associated with indices of relative adiposity-PFM/TFM ratio, CFM/TFM ratio, and PFM/CFM ratio ( $P < 0.05$ ) (Table 3).

**Factors associated with insulin sensitivity in type 2 diabetes**

Table 4 presents an analysis of variables associated with insulin resistance in type 2 diabetes, in which  $K_{ITT}$ , a marker of insulin resistance, is significantly associated with fasting plasma glucose and HbA1c levels—both indices related to glycemia—as well as with free fatty acid and RBP4 levels ( $P < 0.05$ ) (Fig. 1). On the other hand, levels of other adipokines, such as adiponectin, leptin, and ApoA, were not significantly associated with  $K_{ITT}$  ( $P > 0.05$ ). Levels of hsCRP also were not associated with  $K_{ITT}$  ( $P = 0.158$ ) (Table 4).

**DISCUSSION**

This study measured the absolute fat mass of various parts of the body with the aid of DXA in subjects with type 2 diabetes mellitus and calculated relative adiposity, which was defined as the ratio of fat mass between body regions. Furthermore, the association between these indices and insulin resistance and various adipokines was investigated. It was found that RBP4

**Table 4.** Correlation between glycemic indices, adipokines, and insulin sensitivity in type 2 diabetes

	$K_{ITT}$	
	<i>r</i>	<i>P</i> value
HbA1c	-0.280	<0.001
Fasting glucose	-0.227	0.003
Free fatty acids	-0.228	<0.001
RBP4	-0.164	0.027
Adiponectin	0.113	0.123
Leptin	-0.070	0.340
ApoA	-0.001	0.993
hsCRP	-0.103	0.158

$K_{ITT}$ , rate constant for plasma glucose disappearance; HbA1c, glycosylated hemoglobin; RBP4, retinol binding protein-4; ApoA, apolipoprotein A; hsCRP, high sensitivity C-reactive protein.

and  $K_{ITT}$  values, which are related to insulin resistance, show statistically significant associations with PFM/TFM ratio, CFM/TFM ratio, and PFM/CFM ratio, which were calculated to demonstrate the relative adiposity of the subjects. In addition, levels of adipokines, such as adiponectin, leptin, and ApoA, were found to be associated with the absolute fat mass of the body regions.

Previous studies have focused on total fat mass, and have argued that obesity resulting from an excessive accumulation of fat within the adipose tissue causes functional impairment of the adipose tissue, and that adipokines released from adipose tissue cause insulin resistance, leading to metabolic diseases, such as type 2 diabetes [15]. However, Yoon et al. [16] have compared the prevalence of chronic diseases related to insulin resistance, such as metabolic syndrome and type 2 diabetes mellitus, between Asians and Europeans with similar BMIs and have found that subjects with BMIs less than 25 kg/m<sup>2</sup> need to be considered as high-risk for type 2 diabetes or heart diseases. This study suggests that understanding metabolic syndrome, which causes insulin resistance, not only requires knowledge of absolute fat mass in an individual, but also insight into the relative distribution of fat within the body. In Asian countries, including South Korea, a high prevalence of metabolic diseases, such as diabetes and hyperlipidemia, has been noted in subjects with normal BMI, which strengthens the suggestion. Numerous researchers have devised and studied various indices to explain this phenomenon, and this study incorporated PFM/TFM ratio, CFM/TFM ratio, and PFM/CFM ratio to present relative adiposity.

In a study by Aasen et al. [17], total fat mass, trunk fat mass, and leg fat mass were obtained with DXA, from which leg/trunk fat mass ratio was calculated and an association between fat mass ratio and homeostasis model assessment of insulin resistance (HOMA-IR) was ultimately drawn. While this study is significant in that it used leg/trunk fat mass ratio to investigate relative adiposity and link it to insulin resistance, it included both pre- and post-menopausal women, overlooking the possibility that menopause-related hormonal changes may influence insulin resistance.

This study also analyzed the association between adipokines secreted from adipose tissue and absolute and relative adiposity. First, it was found that while adiponectin, leptin, and ApoA are associated with TFM, CFM, and PFM, they are not related to ratios of absolute fat mass, with the exception of adiponectin, which showed an association with both absolute fat mass

and fat mass ratios. Leptin and adiponectin, which are generally released from adipose tissue, tend to show an increasing or decreasing pattern depending on total body fat mass: the former is more strongly related to behavior of appetite, while adiponectin is more involved with insulin resistance or glucose metabolism [18]. These findings may explain the significant association between adiponectin and both total (TFM, CFM, PFM) and relative adiposity (fat mass ratios).

While previous studies [19,20] have found an association between adiponectin and insulin resistance, adiponectin was found to be unrelated to insulin sensitivity in this study, as were other adipokines. The results of preceding studies were based on subject groups with simple obesity or metabolic syndrome. Such studies generally define obesity on the basis of total fat mass, as does WHO, which may be inadequate in perfectly explaining type 2 diabetes as a metabolic complication of obesity. Adiponectin alone does not sufficiently explain the problems resulting from diabetes, and new concepts are currently being created to overcome the incompleteness; for example, the incorporation of leptin/adiponectin ratio [1].

While RBP4 released from adipocytes is an adipokine released from adipocytes [21], it is more strongly associated with intestinal fat mass than with total fat mass, and is known to increase in an elevated insulin resistance setting [22]. Graham et al. [23] investigated the relationship between serum RBP4 concentration and insulin resistance in obese and diabetic subjects and found that RBP4 concentrations are strongly associated with insulin resistance in both type 2 diabetic and non-diabetic subjects, while also influencing metabolic syndrome and cardiovascular heart disease. Additionally, a study on a Chinese population by Jia et al. [14] reported that intestinal fat, especially in a subject group with abdominal obesity, is significantly associated with HOMA-IR regardless of diabetic state. In the same study, RBP4 levels were related to the distribution of fat and contributed to insulin resistance, causing it to become a risk factor for type 2 diabetes mellitus, as well as for cardiovascular diseases.

The aforementioned studies analyzed the relationship between RBP4 levels and  $K_{ITT}$  or HOMA-IR values, and were performed based on the hypothesis that fat accumulation at a specific site—especially at the abdomen—leads to insulin resistance due to secretion of RBP4 from the accumulated fat, ultimately resulting in metabolic syndrome and diabetes mellitus. This study also examined the association between RBP4 or  $K_{ITT}$  values and absolute adiposity (TFM, CFM, PFM) or

relative adiposity (PFM/TFM ratio, CFM/TFM ratio, PFM/CFM ratio), and found that significant associations are found more frequently in relative fat distribution than in absolute fat mass. This result may become the basis for explaining the high prevalence of chronic disease in Asian subjects, who usually have normal BMIs. This study further developed the idea of site-specific fat accumulation leading to metabolic disorders and measured PFM/TFM ratio, CFM/TFM ratio, and PFM/CFM ratio in an attempt to determine and assess relative adiposity. These ratios combine central fat, which is associated with insulin resistance, and peripheral fat, which is related to insulin sensitivity [24], in a single index, providing an understanding on the relative distribution of fat within the body. A study by Kang et al. [25] reported that fat accumulation around the pelvis, rather than abdominal or intestinal fat, is associated with metabolic diseases in older subjects. However, the indices suggested in this study are expected to be a useful in understanding a subject's relative adiposity regardless of his or her age.

Overall, this study examined whether fat accumulation at a certain site in the body is associated with insulin resistance, and incorporated the concept of a relative adiposity index to confirm the association. As in previous studies, the association between total fat mass and adipokines—especially adiponectin and leptin—has been reconfirmed. Furthermore, this study employed ratios of fat mass between different regions of the body, and demonstrated statistically significant relationships between those ratios and RBP4 or  $K_{ITT}$  values, providing evidence for predicting insulin resistance. Also, the results of this study found that when approaching metabolic diseases, such as type 2 diabetes, in Asian populations, which has received social and economic attention due to the recently increasing prevalence, focus needs to be made not on simple fat accumulation, but on the distribution of fat within the body, and as a result, relative adiposity indices should be taken into consideration. Therefore, when managing chronic patients—for example, patients with metabolic syndrome or type 2 diabetes—attention may also need to be paid to subjects with normal BMIs who demonstrate elevated relative adiposity, and indices such as PFM/TFM ratio, CFM/TFM ratio, and PFM/CFM ratio are expected to act as a reference for classification of these subject groups.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was re-

ported.

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