Regional Adiposity, Adipokines, and Insulin Resistance in Type 2 Diabetes

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The prevalence of obesity is rapidly increasing worldwide, and obesity is a well-known risk factor for type 2 diabetes involving insulin resistance. In recent decades, marked environmental and lifestyle changes have occurred and led to increased obesity and obesity-related cardiovascular diseases in Korea. Obesity is a heterogeneous condition, and body fat location may have a more important impact on the development of cardiovascular risk factors and related diseases than total excess adiposity [1]. Excessive accumulation of visceral adipose tissue causes low-grade chronic inflammation, dyslipidemia, insulin resistance, type 2 diabetes, and cardiovascular diseases. Recently, regional distribution of fat mass seems to correlate with risk level; fat mass in the lower extremities has a protective effect against insulin resistance and dyslipidemia [2,3]. Gluteofemoral fat, as measured by thigh circumference, hip circumference or leg adipose tissue mass, is independently associated with low total- and low-density lipoprotein triglyceride levels and high high-density lipoprotein cholesterol levels. A small amount of adiposity in the lower extremities is associated with higher insulin resistance and unfavorable glucose level [4].

Increased leg adipose tissue mass is associated with lower aortic calcification and arterial stiffness as well as with a decreased progression of aortic calcification [5,6]. Hip circumference was positively associated with plasma ascorbic acid level, an anti-oxidant marker, and might contribute to endothelial protection [7].

There are a few possible mechanisms to explain the protective role of lower extremity fat deposition. First, subcutaneous adipose tissue acts as a buffer for the daily influx of dietary lipids, protecting other tissues from a lipid overflow associated with lipotoxicity [8]. Second, there is differential secretion of adipose tissue-related proteins, called adipokines. Gluteofemoral adipose tissue could contribute to a protective adipokine profile by secreting more beneficial adipokines and fewer inflammatory molecules compared with abdominal fat.

However, even though the negative association between lower extremity fat mass and insulin resistance is established, it is still unclear whether the lower extremity fat mass per se exerts beneficial effects on glucose metabolism independent of the mere absence of trunk fat. Several metabolic characteristics of adipocyte size and location might influence their metabolic consequences. Adipocytes in the lower extremities are larger, less sensitive to lipolytic stimuli, and more sensitive to insulin compared with those in the abdomen [9,10]. Although increases in adipocyte number and size can occur with increasing obesity level, larger adipocytes are also associated with higher secretion of adipokines which favorably influence insulin resistance [11]. The large adipocytes in the femoral region can result in higher insulin sensitivity and increased secretion of metabolically beneficial adipokines. This combination of factors may partially “offset” the detrimental influence of abdominal adiposity and offer metabolic “defense” against additional glucose dysregulation [12].
Trunk to leg fat ratio may have a different impact according to age and gender. With aging, this ratio increased more markedly in women than men, because the women's lower extremity fat mass remained much the same at all ages. According to the literature, the relationship between leg and trunk fat mass is associated with the risk of insulin resistance and dyslipidemia in obese women, both before and after menopause [2].

Adipokines are biomarkers for fat mass, fat distribution, adipose tissue function, liver fat content, insulin sensitivity, and subclinical chronic inflammation associated with metabolic diseases. Circulating biomarkers for abdominal fat accumulation include adiponectin, retinol binding protein-4 (RBP4), vaspin, chemerin, progranulin, and fetuin-A and others [13]. RBP4 is predominantly secreted from the liver, but is also expressed in adipocytes. Increased RBP4 expression in visceral adipose induces the increased serum RBP4 levels in tissues of patients with insulin resistance [14]. Adiponectin and leptin are more likely to be associated with impaired insulin sensitivity or insulin secretion, while RBP4 is associated with adverse fat distribution and insulin resistance.

In a recent issue of Diabetes & Metabolism Journal, Kim et al. [15] presented an article regarding the relationship of absolute or relative adiposity to insulin resistance in obese women with type 2 diabetes. They measured the trunk fat mass and lower extremities fat mass and found that relative adiposity (defined by peripheral fat mass/trunk fat mass) was correlated with insulin resistance. They also observed the positive association of total, central, and peripheral fat mass with adiponectin and leptin levels, but not with RBP4 level. The regional adiposity was positively associated with serum adiponectin level and negatively associated with RBP4 level, suggesting the favorable effect of regional adiposity. However, regional adiposity was also positively associated with insulin resistance. Although the authors did not discuss these conflicting results, they may be due to the age distribution of the study subject's considering that peripheral fat mass does not change with age, while visceral adiposity is markedly increased after menopause. Additional studies in various conditions such as age, gender, obesity degree, and underlying disease condition will be helpful for understanding the metabolic effects of regional adiposity.

**CONFLICTS OF INTEREST**

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

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