Editorial

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Implication of Sex Differences in Visceral Fat for the Assessment of Incidence Risk of Type 2 Diabetes Mellitus

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Prevalence of type 2 diabetes mellitus (T2DM) in South Korean adults steadily increased from 11.8% in 2012 to 13.8% in 2018 [1]. More than half of these patients were obese (53.2%) and had abdominal obesity (54.0%) determined by abdominal circumference [1]. Moreover, the incidence of T2DM in abdominal obesity is 2.14-fold higher than that in the control group [2]. The strong relationship between T2DM and abdominal obesity originates from visceral adipose tissue (VAT)-mediated insulin resistance [3]. Given that fat distribution is affected by sex hormones, aging, and genetic factors [4], the authors measured visceral fat area (VFA) and visceral-to-subcutaneous fat ratio (VSR) with computed tomography, which is a gold standard for fat mass quantification, and analyzed the sex difference in incidence risk of T2DM.

Body fat composition in humans is sexually dimorphic [4]. For instance, estrogen promotes fat accumulation in gluteofemoral subcutaneous adipose tissue (SAT) rather than in VAT. In a fatty acid kinetic study using radiolabeled triolein, premenopausal women stored a larger percentage of dietary fat in SAT than did men [5], while postmenopausal women store body fat in a more central location than premenopausal women [6,7]. Moreover, estrogen replacement in postmenopausal women reduced VAT and body mass index [8]. Mechanisms promoting estrogen-dependent fat distribution are estrogen-induced inhibition of lipid storage in VAT by suppression of lipoprotein lipase (LPL) activity and lipogenic gene expression [4], estrogen-mediated inhibition of lipolytic activity in gluteofemoral SAT [9], and estrogen-induced gene expression of anti-lipolytic α2A adrenergic receptors in gluteofemoral SAT [9]. The protective effect of estrogen is well documented [10]; the proportion of postmenopausal women who develop incident diabetes (71.0%) is higher than that in the no diabetes group (59.8%). Another sex hormone, testosterone is thought to suppress LPL activity and adipogenesis to inhibit VAT accumulation, though the mechanism is not fully understood, and age-dependent decline in testosterone level is associated with visceral obesity. Testosterone therapy upregulated lipolytic activity from VAT but not from gluteofemoral SAT [11]. Another study showed that short-term testosterone suppression increased postprandial fatty acid storage in gluteofemoral SAT and their LPL activity, implying that physiological testosterone level inhibits meal-derived fat storage in gluteofemoral SAT [4]. These findings indicate that imbalance of sex hormones in men and women respectively creates android- and gynoid-type body shapes. Based on this hypothesis, Kim et al. [10] proposed optimal cut-off values of VFA and VSR separately for men and women; as expected, the values were higher in men.

Another lesson from this study is that visceral fat accumulation in women increases susceptibility to diabetes mellitus compared to that in men. From subgroup analysis by VFA, the odds ratio for incident T2DM was 5- to 10-fold higher in women than in men. Based on this result, VFA in women is a more sensitive and specific measure for predicting T2DM than in men. Although there are differences in degree, previous

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studies support the susceptibility of women to T2DM related to visceral fat accumulation [12,13]. Thus, as emphasized in many papers, interventions such as exercise and hormone replacement for perimenopausal women should be considered to prevent unfavorable fat distribution [14-16].

The premise of this study is that VAT accumulation induces insulin resistance. The underlying mechanism of VAT-mediated insulin resistance is unclear, but a common pathway of proposed models is inflammation of VAT, possibly from hypoxia [17] or adipocyte cell death [18]. In addition, the immune cells in VAT, including macrophages, dendritic cells, natural killer cells, and T-cells, are dynamically regulated by obesity and participate in obesity-induced VAT inflammation [19,20]. On this basis, a new strategy for predicting T2DM should consider VAT inflammation status. Therefore, it could be helpful to evaluate VAT inflammation using a quantifiable measure of T2 relaxation time using magnetic resonance imaging and by measuring pro-inflammatory cytokines (interleukin 1β [IL-1β], TNF-α, IL-12, and IL-18) derived from M1 macrophages and T-cells.

CONFLICTS OF INTEREST

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

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