

Waist Circumference and Body Mass Index Variability and Incident Diabetic Microvascular Complications: A *Post Hoc* Analysis of ACCORD Trial (*Diabetes Metab J* 2022;46:767-80)

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Epidemiological studies indicate that obesity is a global epidemic linked to an increased risk of macrovascular diseases. However, the association between obesity and microvascular complications in patients with type 2 diabetes mellitus (T2DM) remains controversial. Prior experimental studies suggest that obesity may result in endothelial dysfunction; however, limited epidemiological studies have examined the association between obesity and microvascular diseases, such as retinopathy, nephropathy, and neuropathy, in patients with T2DM [1]. Several post-hoc analyses of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study data have explored the role of obesity in microvascular complications in patients with T2DM. In 2021, Gao et al. [1] investigated the associations between obesity measured using body mass index (BMI), waist circumference (WC), and fat mass index (FMI) and risk of microvascular complications in individuals with T2DM who participated in the ACCORD study. Patients in the highest FMI quartile had a greater risk of nephropathy and neuropathy but not retinopathy compared to those in the lowest quartile [1]. Their discordant analyses revealed that FMI and WC are superior to BMI in identifying patients at risk of neuropathy related to obesity [1]. Yeboah et al. [2] observed a positive association between body weight variability and the composite outcome of neuropathy, nephropathy, and retinopathy in a previous inves-

tigation using the ACCORD cohort. However, that study did not delineate the association between obesity variability and each microvascular outcome.

Using annually collected anthropometric data from the ACCORD project, Hukportie et al. [3] examined the association between WC and BMI variability, assessed by variability independent of the mean (VIM) and the risk of microvascular events including neuropathy, nephropathy, and retinopathy. ACCORD was a randomized clinical trial that assessed the health effects of strict glycemic, lipid, and blood pressure control against conventional control in 10,251 individuals with T2DM [4]. In the present study using those data, participants were excluded if they had fewer than two recorded anthropometric measurements or several microvascular complications at baseline. After exclusion, the analytic samples for neuropathy, nephropathy, and retinopathy outcomes numbered 7,204, 8,720, and 6,217, respectively. The main variability measure was VIM, which was calculated as $100 \times \text{standard deviation (SD)}/\text{mean}^\beta$, where β is the regression coefficient, based on the natural logarithm of the SD with the natural logarithm of the mean. The corrected VIM was calculated using the following formula: $\text{VIM}_{\text{corrected}} = (\text{VIM}_{\text{uncorrected}} \times \text{mean of coefficient of variation})/\text{mean of VIM}_{\text{uncorrected}}$. The researchers discovered a higher risk of neuropathy with increased WC and BMI vari-

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ability, a high risk of nephropathy with increased BMI variability, and a null association of retinopathy with increased WC and BMI variability. Compared with the lowest quartiles, the highest quartiles of WC and BMI variability presented increased neuropathy risk, with a hazard ratio (HR) of 1.21 (95% confidence interval [CI], 1.05 to 1.40) and 1.16 (95% CI, 1.00 to 1.33), respectively, and the highest BMI variability quartile presented an increased nephropathy risk with an HR of 1.31 (95% CI, 1.18 to 1.46). The findings of this study suggest that patients with T2DM should be encouraged to maintain stable WC and BMI to avoid diabetic microvascular complications, particularly neuropathy. The primary strength of this study is that it is the first to investigate the impacts of BMI and WC variability on microvascular complications in patients with T2DM.

Previous studies have found increased incidence of microalbuminuria, macroalbuminuria, renal function impairment, and neuropathy in obese patients with T2DM [1,5,6]. The link between obesity and worsening renal function or neuropathy strengthened as obesity severity increased, indicating a dose-response relationship. These data imply that obesity is a substantial risk factor for several microvascular complications in people with T2DM. The study by Hukportie et al. [3] adds to our understanding of the relationship between obesity and microvascular problems; not only excess body weight at baseline, but also weight variability are associated with worse outcomes. This knowledge emphasizes the necessity of patients with T2DM to maintain an optimal body weight to minimize the risk of complications, both in the short and long terms.

While the specific pathophysiology underlying the increased complication risk with weight variability remains unknown, the following are possible explanations. First, unintended weight loss may be indicative of poor glycemic control or an underlying cachexic condition, such as infection or cancer. This may indicate sarcopenia rather than a lean healthy body. Second, weight gain in patients with T2DM who were already obese indicates that the patients progressed to a more obese state, which is definitely associated with a higher risk of complications. Finally, “weight cycling” may be responsible for the negative effects of weight change [7]. Short-term weight reduction accomplished through diet modification followed by gradual weight increase promotes preferential visceral fat accumulation. Changes in adipose tissue during weight regain may result in the release of pro-inflammatory adipocytokines, which can lead to negative health outcomes. However, addi-

tional studies with a randomized controlled design are needed to elucidate the effect of intentional weight loss or weight gain in T2DM populations with a varying baseline obesity status and the effect of weight variability on complication risk.

Based on the study findings, patients with T2DM should minimize body weight fluctuations and avoid the ‘yo-yo’ phenomenon. Intentional and healthy weight control through sustained lifestyle modifications, especially in overweight or obese patients with T2DM, should be encouraged. While definitive evidence is lacking, clinicians should advocate for weight loss in overweight or obese patients with T2DM, particularly given the additional benefits of weight reduction, such as improved mobility and better cardiometabolic outcomes.

CONFLICTS OF INTEREST

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

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