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Empagliflozin Reduces Body Weight And Indices of Adipose Distribution In Patients With Type 2 Diabetes Mellitus

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ABSTRACT

The escalating prevalence of diabetes has triggered a global health crisis, leading to substantial mortality, increased medical costs, and reduced quality of life. In 2021 alone, diabetes claimed 6.7 million lives worldwide and affected 537 million individuals, a number projected to surge to 643 million by 2030. India, with 74.9 million diabetic patients, ranks second worldwide, poised to reach 124.9 million by 2045. Obesity, a pivotal risk factor for type 2 diabetes (T2DM), accounts for 90% of cases. Visceral adipose tissue (VAT), linked to insulin resistance, plays a vital role in obesity-related T2DM development. Despite advancements, many risk factors remain inadequately managed. Sodium-glucose cotransporter (SGLT2) inhibitors have emerged as a novel class of anti-diabetic drugs, effectively lowering blood glucose and weight.

This comprehensive review explores the influence of VAT on obesity-mediated diabetes mellitus. It emphasizes the intricate connections between obesity, insulin resistance, and beta-cell dysfunction, particularly highlighting the role of VAT in insulin resistance. Studies indicate VAT's correlation with metabolic risk factors, especially in women. Strategies like very low-calorie diets, exercise, and bariatric surgery effectively reduce VAT and improve glycemic control. Notably, SGLT2 inhibitors exhibit promise in reducing both body weight and adiposity indices, thereby mitigating cardiometabolic risk in T2DM patients.

A study by Ridderstrale et al. demonstrates the substantial contribution of empagliflozin, an SGLT-2 inhibitor, to weight loss and fat reduction, indicating its potential to lower cardiovascular risks. Another investigation by Neeland et al. highlights empagliflozin's efficacy in reducing weight and adiposity indices across various subgroups, irrespective of age, gender, or abdominal obesity levels. These findings underscore the significance of SGLT2 inhibitors in curbing visceral adiposity-related cardiometabolic complications, warranting further exploration.

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Consequently, strategies targeting VAT reduction, particularly employing SGLT2 inhibitors, hold promise for addressing the escalating burden of obesity-mediated diabetes and its associated morbidities.

Keywords: Diabetes, Obesity, Visceral Adipose Tissue, SGLT2 Inhibitors, Cardiometabolic Risk

Background

Diabetes, a chronic disease, has become increasingly widespread. It is the main cause of death and morbidity, resulting in higher treatment expenses around the world. Diabetes was responsible for nearly 6.7 million fatalities worldwide in 2021 alone. According to the International Diabetes Federation (IDF), 537 million people worldwide had diabetes in 2021; this figure is expected to rise to 643 million by 2030 if no effective preventive measures are implemented. Over 541 million individuals are at high risk of developing diabetes.[1,2] India has the second greatest number of patients with diabetes in the world. India has 74.9 million patients with diabetes between the ages of 20 and 79 in 2021, with a projected increase to 124.9 million by 2045. According to the IDF, India has one out of every seven patient with diabetes adults worldwide, and one in every third home has patients with diabetes.[1,2]

Obesity is a major modifiable risk factor for the development of diabetes, accounting for 90% of persons with type 2 diabetes mellitus (T2DM). Being overweight is connected with a threefold increase in the development of diabetes, and obesity is associated with a sevenfold increase.[3] Overweight, obesity, and associated comorbidities all increase the morbidity and mortality of cardiovascular disease, regardless of age or gender.[4] Despite advancements in (T2DM) risk factors during the previous decade, several risk variables remain under-controlled or under-recognized. Data suggest that intra-abdominal (visceral) adipose tissue (VAT) may be a main cause of obesity-related cardiometabolic problems, including T2DM.[5] A meta-analysis showed that sodium-glucose cotransporter (SGLT2) inhibitors significantly reduced body weight in T2DM patients as compared to placebo.[6]

Role of VAT in obesity mediated diabetes mellitus

Obesity and T2DM are linked by a complex set of mechanisms that include: adipose tissue release of excess circulating fatty acids, glycerol, hormones, and pro-inflammatory cytokines, impairing cellular insulin signaling and increasing insulin

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resistance, and chronically elevated lipid levels, which lead to impaired islet beta-cell function and lower insulin production.[7,8]

Insulin resistance and β-cell dysfunction are crucial in obesity and obesity-related metabolic disorders; VAT, in particular, is connected to insulin resistance. Several studies have found that VAT, rather than subcutaneous adipose tissue, is connected with the frequency of insulin resistance and obesity-related comorbidities. Furthermore, VAT is connected with metabolic risk variables more strongly in women than in males. As a result, VAT measurement is essential to determine the risk of T2DM and other obesity-related illnesses in women.[9]

VAT_{volume} and VAT/SAT_{volume} ratio are associated with impaired glucose metabolism, independent of cardiovascular risk factors or MRI-based quantification technique, with a decreasing effect of VAT/SAT_{volume} ratio in obese subjects.[10]

Strategies to Reduce VAT

Multiple factors, including very low calorie diets, exercise, and bariatric surgery, result in considerable VAT reductions, which may explain some of the improvements in glycemic control and T2DM resolution found with lifestyle and surgical therapies. Unfortunately, some of the existing T2DM medications, particularly sulphonylureas, thiazolidinediones, and insulin therapy, cause weight gain and may increase the negative effects of VAT in T2DM patients.[5]

As a novel class of anti-diabetic medicines, SGLT-2 inhibitors have been developed. These medicines lower blood glucose concentrations by increasing urine glucose excretion (UGE), lowering hyperglycemia and weight with pleiotropic effects.[11]

Dual-energy X-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA) studies indicated that the SGLT2 inhibitor-associated weight loss was due to a decrease in (viscera and subcutaneous) adipose tissue mass, rather than an increase in lean tissue mass.[12,13] It has been proposed that SGLT2 inhibitors dramatically reduced weight and adiposity indices, potentially improving cardiometabolic risk in T2DM patients.[5]

Effect of Empagliflozin on Body Weight And Indices of Adipose

Empagliflozin is a strong and selective SGLT-2i used to treat T2DM that has been found in clinical trials to enhance glycemic control while also lowering blood pressure and body weight.[5]

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Ridderstrale *et al.* conducted a substudy in which changes in trunk fat, limb fat, total fat mass, fat-free mass, abdominal visceral adipose tissue, and subcutaneous adipose tissue were measured using dual energy X-ray absorptiometry and MRI scans. Bodyweight reductions with empagliflozin were significant and maintained, whereas glimepiride caused an increase. Figure 1 depicts the changes in bodyweight during the course of the 104-week treatment. Dual energy X-ray absorptiometry scans in the body composition substudy revealed that over 90% of the weight loss with empagliflozin was related to a reduction in fat mass, and empagliflozin reduced total fat mass by 1.9% points at week 104. MRI scans revealed that empagliflozin reduced both abdominal visceral fat tissue and abdominal subcutaneous adipose tissue.[14]

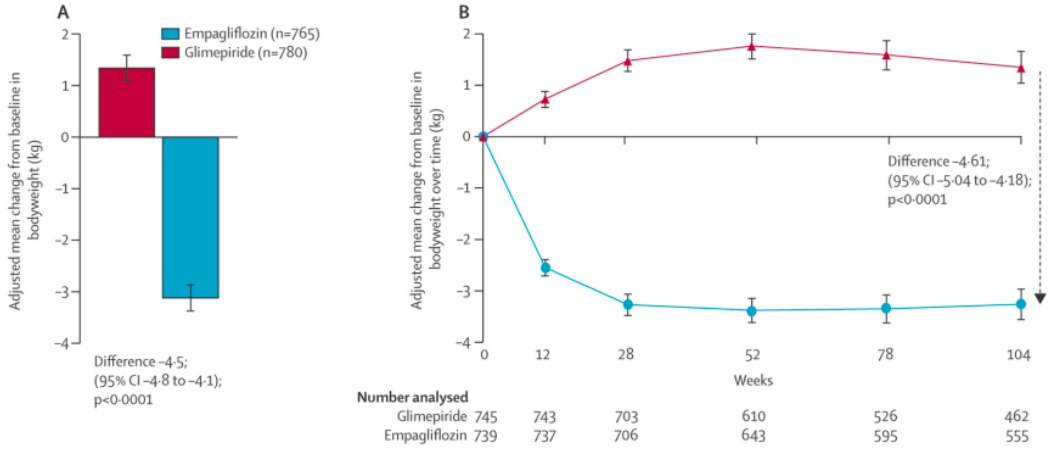

Figure 1: Changes in bodyweight in the full-analysis set (A) Adjusted mean change from baseline in bodyweight at week 104 (ANCOVA, last observation carried forward). (B) Adjusted mean change from baseline in bodyweight over 104 weeks (mixed model repeated measures, observed cases). Error bars show the 95% CIs.

Neeland *et al*, aimed to determine its effects compared with placebo on body weight, waist circumference (WC) and indices of total body fat and visceral adiposity over a short and intermediate treatment term among patients with T2DM enrolled in five clinical trials.

Data from two randomized trials were analyzed: one treated with double-blind empagliflozin versus placebo for 12 weeks (cohort 1) and one treated with double-blind empagliflozin versus placebo for 24 weeks (cohort 2). Cohort 1 consisted of EMPA-REG BP™ trial participants; the trial population and design were previously disclosed. Changes in weight, waist circumference, estimated total body fat, index of central obesity, and visceral adiposity index were assessed using analysis of

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covariance and treatment stratification for age, gender, and baseline waist circumference in patients with T2DM randomized to blinded treatment with empagliflozin versus placebo in 12-week (cohort 1: n = 823) or 24-week (cohort 2: n = 2477) clinical trials.

Empagliflozin reduced weight, waist circumference and adiposity indices versus placebo in both cohorts. Adjusted mean (95% confidence interval) change from baseline in empagliflozin versus placebo was:

- −1.7 kg (−2.1 to −1.4 kg) and −1.9 kg (−2.1 to −1.7 kg) for body weight ($p < 0.001$);
- −1.3 cm (−1.8 to −0.7 cm) and −1.3 cm (−1.7 to −1.0 cm) for waist circumference ($p < 0.001$);
- −0.2% (−0.7% to 0.3%; $p = 0.45$) and −0.3% (−0.7% to 0.0%; $p = 0.08$) for estimated total body fat;
- −0.007 (−0.011 to −0.004) and −0.008 (−0.010 to −0.006) for index of central obesity ($p < 0.001$);
- −0.3 (−0.5 to 0.0; $p = 0.07$) and −0.4 (−0.7 to −0.1; $p = 0.003$) for visceral adiposity index in cohorts 1 and 2, respectively.

Adipose reductions were seen across most age, sex and waist circumference subgroups.

Discussion

Empagliflozin significantly lowered weight and adiposity indices, potentially improving cardiometabolic risk in T2DM patients. Reductions in adiposity markers with empagliflozin were observed across all age, gender, and degree of abdominal obesity subgroups, with statistically significant heterogeneity of effects observed, such that the effects of empagliflozin on body weight, WC, and index of central obesity were greater with increasing age, and reductions in body weight were greater with more severe abdominal obesity in those patients treated for 24 weeks. There was no gender difference in the effects of empagliflozin on body weight, WC, or visceral adiposity markers. These findings imply that empagliflozin treatment may reduce VAT and result in changes in body composition associated with lower cardiometabolic risk.

Given that VAT is strongly associated with an increased risk of T2DM, atherosclerotic cardiovascular disease, and cardiac function, these findings may have

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important clinical implications for the prevention and treatment of visceral adiposity-related cardiometabolic complications and warrant further investigation.

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