Editorial

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Advent of tirzepatide: boon for diabetic and obese?

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Dear Editor,

Obesity is defined by WHO as 'an abnormal or excessive fat accumulation that may impair health'[1,2]. It is defined as the BMI over 30 kg/m^2 in adults[2]. Obesity affecting approximately 600 million people, is the most prevalent chronic disease worldwide[3]. Type 2 Diabetes Mellitus (T2 DM) is a chronic progressive disease associated with microvascular and macrovascular complications and increased cardiovascular mortality[4]. In the year 2021, 537 million adults across the globe were suffering from T2 DM and this number is estimated to rise to 783 million by the year 2045[2]. In this 21st century, DM and obesity are considered as twin epidemics causing significant morbidity and mortality by negative socioeconomic and environmental impacts by combination with genetic, epigenetic, and lifestyle factors[2].

Tirzepatide is a 39-amino acid linear synthetic peptide based on the sequence of native glucose-dependent insulinotropic polypeptide (GIP). It shares 19 amino acids with human GIP, conjugated to a C20 fatty diacid moiety through a hydrophilic linker at the lysine at position 20, allowing albumin binding, prolonging its half-life to approximately 5 days, thus allowing for once-weekly dosing. It is a single molecule with agonistic activity at both the GIP receptor and glucagon-like peptide-1(GLP-1) receptor[5].

GLP-1 agonism stimulates insulin secretion in hyperglycemic states, suppressing glucagon secretion in hyperglycemic or euglycemic states, delaying gastric emptying, decreasing appetite, and reducing body weight. GIP, the main incretin hormone in healthy individuals, is glucagonotropic in a glucose-dependent manner. Under hyperglycemic conditions, GIP stimulates the release of insulin, thereby lowering glucagon levels, and under euglycemic or hypoglycemic conditions, glucagon levels are increased. GIP receptors being abundant in adipose tissue, enhances both the postprandial lipid-buffering capacity of white adipose tissue and the sensitivity of adipose tissue to insulin, which may prevent ectopic fat deposition[5,6]. The GIP component of dual GIP–GLP-1 agonism is hypothesized to act centrally to potentiate a GLP-1–induced reduction in food intake[6]. Not only this, dual agonism has an additive effect in healthy individuals with a significantly increased insulin response compared with separate administration of each hormone and also significant glucagonostatic effect while separate administration of either GLP-1 or GIP did not suppress glucagon secretion more than glucose alone[4].

In a study to confirm the efficacy of tirzepatide compared to semaglutide, tirzepatide was found to be superior and noninferior to semaglutide with respect to weight reductions and dose-dependent reductions in glycated hemoglobin level[5]. A study of 12 weeks showed clinically significant reductions in glycated hemoglobin from the baseline as compared to placebo, suggesting that lower starting doses and smaller dose increments of tirzepatide are associated with a more favorable side effect[6]. In phase 1 and phase 2 trials, tirzepatide demonstrated dose-dependent reduction in HbA1c (up to 2.4%) and body weight (up to 11.3 kg) in patients with T2 DM, suggesting its superiority to dulaglutide[4]. In one of the studies, homeostatic model assessment 2-B significantly increased with dulaglutide and tirzepatide 5, 10, and 15 mg compared with placebo. Proinsulin/insulin and proinsulin/C-peptide ratios significantly decreased with tirzepatide 10 and 15 mg compared with placebo and dulaglutide and markers of improved insulin sensitivity adiponectin, insulin like growth factor binding protein-1 (IGFBP-1) and insulin like growth factor binding protein-2 (IGFBP-2) significantly increased by one or more doses of tirzepatide[7]. In phase 3 double-blind, randomized, controlled trial involving 2539 adults, which was done for 72 weeks where escalating doses (5, 10, and 15 mg) of tirzepatide was administered subcutaneously, including a 20 weeks dose escalation period showed significantly decreasing weight and improvement in glycated hemoglobin with the escalating doses of tirzepatide as compared to placebo[3]. Another study of 26 weeks to know about lipid profile change following the administration showed that tirzepatide dose-dependently decreased levels of apoprotein C-III (ApoC-III) and apoprotein B (ApoB) with escalating doses (10 and 15 mg) even reducing large triglyceride-rich lipoprotein particles, small low-density lipoprotein particles, suggesting a net improvement in atherogenic lipoprotein profile[8]. The most common side effects were related to the gastrointestinal system (nausea, vomiting, and diarrhea), with the second most common side effect being reduced appetite, with some rare ones including cholecystitis, pancreatitis, injection site reactions, and hypersensitivity reactions[4–10].

By taking all the above facts into consideration, it can be implied that tirzepatide could be a boon for obese patients and patients with T2 DM because of improvement in physical profile (weight reduction), sugar profile (reduction in glycated hemoglobin), and atherogenic profile (reduction in low-density lipoprotein particles and triglyceride-rich lipoprotein particles). Widespread access of tirzepatide could be a challenge for a socioeconomically deprived country like ours (Nepal). This can

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be well taken into control by the interplay of multiple factors like stakeholders including the manufacturer, healthcare policy, the health insurance industry and pharmaceutical benefit managers, and the WHO.

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