

**'Retatruiide' drug trial: A paradigm shift in Type 2 Diabetes management**

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Madam, Type 2 diabetes mellitus (T2DM) is a chronic medical condition characterised by persistent hyperglycaemia caused by insulin resistance and impaired beta cell function. Typically, it occurs in individuals aged 45 years and above, but due to the growing prevalence of obesity and sedentary lifestyle, it is increasingly being diagnosed in younger adults and adolescents. A positive family history of T2DM and specific genes such as TCF7L2 and PPARG also play an essential role.<sup>1</sup> Consequently, persistent hyperglycaemia in type 2 DM can give rise to a range of microvascular complications such as retinopathy, neuropathy and nephropathy and macrovascular complications such as coronary artery and cerebrovascular diseases.

T2DM accounts for 90% of the cases of diabetes, raising concern among the healthcare sector worldwide. In 2017, approximately 462 million individuals were affected by type 2 DM, accounting for 6.28% of the world's population. By 2030, it is estimated that the global prevalence will rise to 7079 individuals per 100,000.<sup>2</sup>

To prevent the complications caused by T2DM, it is essential to prioritize glycaemic control. First and foremost, effective dietary control is pivotal. It has been established that obesity in individuals with T2DM is closely associated with insulin resistance and defects in insulin secretions thus managing the calorie intake is mandatory. However, pharmacologic intervention with oral glucose-lowering agents or insulin therapy is necessary when the patient's blood glucose doesn't fall within normal limits despite weight reduction, exercise and dietary modifications.

The first line pharmacological agent used is Metformin, an oral medication that reduces glucose production in the liver. Additionally, insulin secretagogues such as sulfonylureas and glinides promote insulin release by stimulating beta cells. Thiazolidinediones is another example of an oral agent used to treat diabetes by enhancing glucose uptake by the muscle, liver and adipose

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tissue.<sup>3</sup>

Furthermore, it is crucial to understand that the Incretin effect, responsible for stimulating insulin secretion after meals, is primarily mediated by gut-derived incretin hormones known as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). However, patients with type 2 diabetes (T2DM) commonly exhibit defects in this process. To address this issue, in addition to oral medications, injectable drugs such as RA-GLP1 (Semaglutide, Dulaglutide) are administered to emulate the actions of human GLP-1 effectively. These injectable treatments are vital in reducing postprandial hyperglycaemia and have become indispensable in managing T2DM.

Additionally, a new class of drugs, dual GIP/GLP-1 receptor agonists, are more promising than the single GLP-1 agonists. Tirzepatide, with its once-weekly dosing and minimal side effects, remains superior.<sup>4</sup> Another dual agonist drug, Retatruiide, recently underwent a phase 2 trial, demonstrating remarkable efficacy in controlling blood glucose levels and body weight, with mild GI side effects, when injected once a week.<sup>5</sup> Moreover, in-depth studies have revealed that individuals using Retatruiide reported significantly lower HbA1C levels than individuals taking Dulaglutide or placebos. The study also reported no incidents of severe hypoglycaemia or any deaths, highlighting the drug's safety profile, which aligns with GLP-1 and GIP receptor agonists.<sup>5</sup>

The escalating statistics of Type 2 diabetes mellitus are concerning, emphasising the need for immediate implementation of preventive measures and novel treatments. The potential addition of the drug Retatruiide to the current treatment guidelines holds immense promise in significantly reducing the morbidity and mortality associated with this life-threatening chronic disease.

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ZA: Concept, literature search, drafting, analyzing, reviewing, final approval.

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