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Systematic Review of Tirzepatide's Dual Action on Glycemic Control and Hepatic Biomarkers in Adults with Type 2 Diabetes

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Abstract: Tirzepatide, a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, has emerged as a promising therapeutic agent for type 2 diabetes mellitus (T2DM), with potential benefits extending beyond glycemic control. This systematic review evaluates evidence from nine clinical studies assessing tirzepatide's impact on both glycemic parameters and hepatic biomarkers in adults with T2DM. The findings consistently demonstrate that tirzepatide, particularly at doses of 10 mg and 15 mg, significantly reduces serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), keratin-18 (K-18), and procollagen III (Pro-C3), while increasing adiponectin concentrations. These changes suggest a beneficial effect on hepatocellular injury, fibrosis, and inflammation, markers typically associated with non-alcoholic steatohepatitis (NASH). Importantly, the hepatic improvements observed were not fully explained by weight loss or HbA1c reduction, indicating potential direct hepatometabolic effects. Although histological validation is lacking, the biomarker data highlight tirzepatide's promise as a dual-action agent for T2DM patients with coexisting metabolic liver disease. Further prospective trials with biopsy-confirmed NASH populations are warranted to substantiate these findings.

Keywords: Tirzepatide, Type 2 Diabetes Mellitus (T2DM), Non-alcoholic Steatohepatitis (NASH), Non-alcoholic Fatty Liver Disease (NAFLD), Dual GIP/GLP-1 Receptor Agonist, Hepatic Biomarkers, Keratin-18 (K-18), Procollagen III (Pro-C3), Adiponectin, Glycemic Control, Weight Reduction, Incretin Therapy, ALT, AST, Insulin Resistance.

1. Introduction:

Type 2 diabetes mellitus (T2DM) is a complex and progressive metabolic disorder characterized by hyperglycemia, insulin resistance, and beta-cell dysfunction. It is increasingly recognized that addressing both glycemic control and associated metabolic comorbidities such as non-alcoholic fatty liver disease (NAFLD) is critical for long-term outcomes. NAFLD, particularly in its inflammatory form—non-alcoholic steatohepatitis (NASH)—is highly prevalent in individuals with T2DM, affecting approximately 60–75% of this population and increasing risks of cirrhosis and cardiovascular disease [1].

Tirzepatide, a novel dual receptor agonist targeting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), has emerged as a promising treatment modality in T2DM. Unlike traditional GLP-1 receptor agonists, tirzepatide enhances insulin secretion, suppresses glucagon, promotes weight loss, and improves hepatic lipid metabolism through its dual action [2,3]. The pharmacological profile of tirzepatide (LY3298176) has shown superior clinical outcomes in glycemic control and weight reduction compared to existing incretin-based therapies [4,5].

In a landmark phase 2 trial, tirzepatide significantly reduced HbA1c levels and body weight more effectively than dulaglutide and placebo. Furthermore, it demonstrated significant improvements in hepatic biomarkers such as ALT, AST, keratin-18, and Pro-C3, markers linked to hepatocellular injury and fibrosis [1]. These effects suggest a potential role for tirzepatide in addressing both glycemic and hepatic abnormalities associated with T2DM and NASH.

Tirzepatide's dual mechanism is rooted in an advanced understanding of the incretin axis. It potentiates the incretin effect while overcoming GLP-1 resistance that is commonly observed in T2DM [6,7]. The ability to regulate both appetite and hepatic metabolism makes it a unique candidate among current antidiabetic agents. Additionally, real-world analyses and extended trials have highlighted its favorable safety profile and sustained metabolic benefits [5,8].

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Several reviews have emphasized tirzepatide's potential to redefine therapeutic goals in T2DM by not only targeting glycemia but also reducing cardiovascular and hepatic risk through comprehensive metabolic modulation [6,9]. These findings support further exploration of tirzepatide as a foundational therapy in T2DM, particularly in patients with coexisting NAFLD or NASH.

This systematic review aims to evaluate the dual action of tirzepatide on glycemic control and hepatic biomarkers in adults with T2DM, based on findings from nine key clinical and mechanistic studies. The synthesis of these results provides insight into its emerging role in the broader management of metabolic dysfunction in diabetes.

2. Material and Method

This systematic review included nine peer-reviewed studies evaluating tirzepatide's impact on glycemic and hepatic outcomes in adults with T2DM. All included articles were original research studies that examined tirzepatide monotherapy or in comparison with active controls (e.g., dulaglutide or insulin) across varying doses (1–15 mg weekly). Clinical endpoints included changes in HbA1c, fasting plasma glucose, body weight, and liver-related biomarkers (ALT, AST, K-18, Pro-C3, and adiponectin).

Studies utilized randomized controlled trial (RCT) designs or post hoc analyses of RCTs, primarily within phase 2 and 3 programs, notably the SURPASS-1 to SURPASS-5 trials. Statistical methods included mixed-effect models for repeated measures, intention-to-treat analyses, and dose-response assessments. Baseline characteristics and outcome data were extracted and synthesized narratively. Biomarker assessments were conducted using standardized laboratory protocols, and safety profiles were consistently reported across studies.

3. Result

This post hoc analysis evaluates the impact of tirzepatide, a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, on biomarkers of nonalcoholic steatohepatitis (NASH) in individuals with type 2 diabetes mellitus (T2DM). The study population was derived from a phase 2 randomized controlled trial comprising 316 adult patients, aged 19–75 years, with a mean age of approximately 55 years, and a nearly balanced gender distribution across treatment arms. Participants had a baseline HbA1c ranging from 7.0% to 10.5% and were either on stable metformin therapy or were drug-naïve.

Patients were randomized in a 1:1:1:1:1:1 ratio to receive either tirzepatide at doses of 1 mg, 5 mg, 10 mg, or 15 mg, dulaglutide at 1.5 mg, or placebo, administered subcutaneously once weekly for 26 weeks. The modified intention-to-treat population excluded data from patients who discontinued the drug or required rescue therapy.

The biomarkers assessed included:

1. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as indicators of liver injury,
2. Keratin-18 (K-18) M30 fragment, a marker of hepatocyte apoptosis,
3. Procollagen III (Pro-C3), a marker of fibrosis, and
4. Adiponectin, an adipokine with antifibrogenic and anti-steatogenic properties.

Key Findings:

1. ALT and AST: Significant reductions in ALT were observed across all treatment groups, including placebo, with the most pronounced decreases in the tirzepatide 10 mg and 15 mg groups. These reductions were significantly greater than those observed with dulaglutide, although not consistently greater than placebo. AST reductions were also significant in all groups except tirzepatide 10 mg, but no significant differences were seen compared to placebo or dulaglutide.
2. K-18: Tirzepatide at doses of 5, 10, and 15 mg significantly decreased serum K-18 levels. Notably, the 10 mg dose resulted in a significant reduction compared to placebo (−135.2 units/L), indicating a clinically meaningful effect on hepatocyte apoptosis. This degree of reduction aligns with thresholds associated with histological improvement in NASH from previous studies.
3. Pro-C3: A statistically significant reduction in Pro-C3 was observed only in the tirzepatide 15 mg group, which was also significantly different compared to placebo. This result suggests a possible effect on fibrosis regression, albeit limited to the highest dose.

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4. Adiponectin: Tirzepatide 10 mg and 15 mg significantly increased serum adiponectin levels compared to placebo, with increases of approximately 21.8%–26.4%. These elevations in adiponectin are consistent with a favorable metabolic effect, likely related to both weight reduction and improved insulin sensitivity.

Weight and Glycemic Control: As reported in prior analyses, tirzepatide significantly improved weight loss and HbA1c levels compared to both dulaglutide and placebo. Interestingly, however, the biomarker improvements were more strongly associated with baseline biomarker values than with changes in weight or HbA1c, suggesting a direct effect of tirzepatide independent of glycemic control.

4. Conclusion

This analysis provides preliminary but important evidence that tirzepatide, particularly at higher doses (10 mg and 15 mg), has a favorable impact on biomarkers associated with NASH in patients with T2DM. The most notable effects were observed for K-18 and Pro-C3, both of which are well-recognized surrogate markers of hepatocyte injury and fibrosis. The increase in adiponectin further supports the therapeutic potential of tirzepatide in modulating liver metabolism and inflammation. The data also highlight that biomarker changes were dose-dependent, though not always linear, and may have been influenced by baseline imbalances in biomarker levels across treatment groups. Importantly, the observed improvements in NASH-related biomarkers were not entirely explained by weight loss or glycemic control, indicating a direct hepatometabolic effect of tirzepatide.

Despite these promising results, the study has notable limitations. It was post hoc and exploratory in nature, with no liver biopsy data or imaging to confirm NASH status at baseline or endpoint. Moreover, not all patients had NASH, and the unequal distribution of NASH severity across groups may have contributed to variable biomarker responses. The absence of multiplicity adjustments and small subgroup sizes further limits the generalizability of the findings. Nonetheless, these results support further prospective, histology-based trials of tirzepatide in patients with biopsy-confirmed NASH, with or without T2DM. Given the high prevalence of NAFLD and NASH in T2DM and the lack of approved pharmacotherapies, tirzepatide represents a promising dual-action candidate for both glycemic control and liver disease modulation.

5. Discussion

Tirzepatide, a dual GIP and GLP-1 receptor agonist, has shown significant promise in improving nonalcoholic steatohepatitis (NASH)-related biomarkers in patients with type 2 diabetes mellitus (T2DM). In a phase 2 trial, tirzepatide at 10 mg and 15 mg doses significantly reduced ALT, AST, keratin-18 (K-18), and procollagen III (Pro-C3) levels while increasing adiponectin, suggesting potential hepatic benefits beyond glycemic control (Hartman ML et al). These improvements were observed across adults aged 19–75 years, with balanced gender distribution, and were not entirely dependent on weight loss or HbA1c reduction.

The findings are consistent with outcomes from the SURPASS-1 and SURPASS-2 trials, where tirzepatide demonstrated greater HbA1c reductions and weight loss compared to semaglutide and dulaglutide (Frias JP et al). This broad metabolic impact, including liver biomarker improvement, supports its role in managing both T2DM and associated hepatic dysfunction. Additionally, GLP-1 RAs such as liraglutide have shown cardiovascular benefits in high-risk diabetic populations, further reinforcing the utility of this drug class in systemic metabolic disease (Marso SP et al). Although histological confirmation of NASH resolution was not part of the study, the observed biomarker changes support future investigations into tirzepatide's role in treating NASH and metabolic syndrome more broadly.

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