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REVIEW OF TIRZEPATIDE AND CHROMIUM PICOLINATE FOR GLYCEMIC CONTROL AND WEIGHT LOSS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS (T2DM)

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ABSTRACT

Objectives: Tirzepatide and chromium picolinate have been found in Type 2 Diabetes Mellitus patients to improve glycemic management by slowing weight gain and improving lipid profiles. The aim of this paper is a mini comparative investigation of these two drugs in Type 2 Diabetes for their effectiveness in weight control and weight loss. This paper will scientifically assess the effects of tirzepatide and dietary adjuvant therapy on a range of metabolic health markers through a thorough assessment of clinical data. The results of this study will help to make educated and practical treatment choices for the condition. The data was abstracted from various databases available such as PubMed, Science Direct, and Google Scholar, utilizing keywords such as tirzepatide, chromium picolinate, glycemic control, and weight loss. The effect of Tirzepatide and Chromium picolinate for glycemic control and weight control was studied. Additionally, their common interactions and side effects were listed, various clinical trial study data on both drugs was summarized and interpretations were made accordingly.

KEYWORDS: Tirzepatide, Chromium picolinate, GLP-1, GIP, Glycemic control, Dietary adjuvant.

1. INTRODUCTION

According to studies in the year 2021, there were 529 million persons worldwide with diabetes, with a 6.1% global age-standardized rate of prevalence. The highest rates of incidence were found in regions like North Africa and, the Middle East at 9.3%, and in Oceania at 12.3%. Type 2 Diabetes Mellitus (T2DM) made up 95.4% of diabetes disability-adjusted life years (DALYs) across the globe in 2021, accounting for 52.2% of the world's T2DM DALYs.[1] The prevalence rate of T2DM is increasing globally, emerging as a significant contributor to both morbidity and mortality.

Certain regions, such as Western Europe and the Pacific islands, are experiencing a particularly high burden of this condition. Even with efforts to curb bad eating habits, sedentary lives, fast urbanization, and other economic development-related variables, the prevalence of diabetes is predicted to increase further. By 2030, it is expected that the global prevalence of T2DM will increase by 7079 per 100,000 people, indicating a continuous climb across all parts of the world.[2] The United States (US) and other developed nations have the highest diabetes-related life-year costs (DALYs). Asia's advanced economies—including Taiwan and South Korea—are joining the ranks of these nations. By 2050, more than 43.6% of the 204 countries and territories are projected to have an age-standardized rate exceeding 10%.[3] Diabetes and obesity are commonly known as the dual epidemics of the 21st century. According to predictions, it is expected that BMI will account for more than 50% of all DALYs globally in 2021 and emerge as a leading risk factor for T2DM. Indicating a higher correlation between high body mass index (BMI) and the disease, the percentage of T2DM DALYs globally associated with high BMI increased by more than 25% between 1990 and 2021.

Our forecasts suggest that the prevalence of T2DM will rise by over 60% worldwide by 2050, with increases of over 70% seen in six specific regions: central Latin America, east Asia north and northeast Africa, central sub- Saharan Africa, Middle East, and sub-Saharan and southern Africa.[1,2] Weight gain and obesity are highly prevalent, and they are intimately linked to the rising incidence of type 2 diabetes. Shedding excess weight is widely recognized as a crucial aspect of managing T2DM.[4] Substantial evidence supports the notion that even moderate weight loss can effectively prevent the progression from prediabetes to T2DM in individuals.[5] Furthermore, there is a dearth of thorough data about how weight loss affects the microvascular complications of diabetes. All things considered; weight loss has definite benefits for managing T2DM.[6]

Tirzepatide, a newly developed drug, acts as a dual agonist targeting the Gastric inhibitory polypeptide (GIP) and Glucagon-like peptide-1 (GLP-1) receptors. Initially used at Eli Lilly and Company for a glycemic control strategy in early 2016, it was later introduced as a medication called MAUNJARO on May 13, 2022, and received approval for treating adults with type 2 diabetes from the Food and Drug Administration (FDA).[7,8] It also received approval from the European Commission on September 15, 2022.[9] Finally, on November 8, 2023, it was authorized for chronic weight management under the brand name ZEPBOUND. It has garnered approval from regulatory bodies for treating T2DM and aiding in chronic weight management.[10] In contrast, chromium picolinate (CrPic) functions by enhancing insulin sensitivity and glucose metabolism, thus offering potential benefits for individuals with T2DM.[11] While Tirzepatide is administered as a pharmaceutical medication,[12] chromium picolinate is commonly consumed as a dietary supplement.[13,14] Both interventions have distinct mechanisms of action and methods of administration, yet their common goal is to enhance metabolic outcomes in individuals diagnosed with T2DM.[14]

2. MECHANISM OF ACTION

2.1. Tirzepatide

Despite having equal plasma concentrations, the insulinotropic peptide caused the "in-cretin effect," defined as an increase in the glucose secretory response when glucose is administered orally instead of intravenously.[11] In reaction to the intake of nutrients, the enteroendocrine cells in the intestine release the peptide hormones GLP-1 and GIP.[15] [Fig -2 shows the role of GIP and GLP- 1]. The pancreas glucose-stimulated release of insulin is enhanced by the incretin action.[16] When taken together, they have a synergistic impact.

Through alpha cells, GLP-1 receptors inhibit the pancreas production of glucagon, which shortens the time it takes for the stomach to empty, decreases hunger, and lowers nutrient intake. This causes weight reduction in a different way than glucose-dependent stimulation.[17] The medications provide efficient management of blood sugar levels, assist in shedding pounds, and reduce the chances of experiencing low blood sugar. GLP-1 receptors are in the beta-cells of the pancreas and gastrointestinal tract. By increasing insulin production in response to glucose, slowing the passage of food through the stomach, lowering blood levels of glucagon, and triggering brain circuits that inhibit appetite, they control blood glucose. As a result, GLP-1R signaling helps in maintaining glucose levels and promoting weight loss.[18] A hormone involved in maintaining glucose homeostasis is GLP-1.[19] The pancreatic beta-cell release of insulin is attributed to both hormones. Insulinotropic actions of the GIP hormone are triggered by meal ingestion.[20] Research and many clinical trials revealed that when GIP and a GLP-1R agonist were given together, the insulin response was greatly enhanced, and glucagon release was inhibited more than when either hormone was given separately.[21] Fig. 1 shows the mechanism of tirzepatide working.

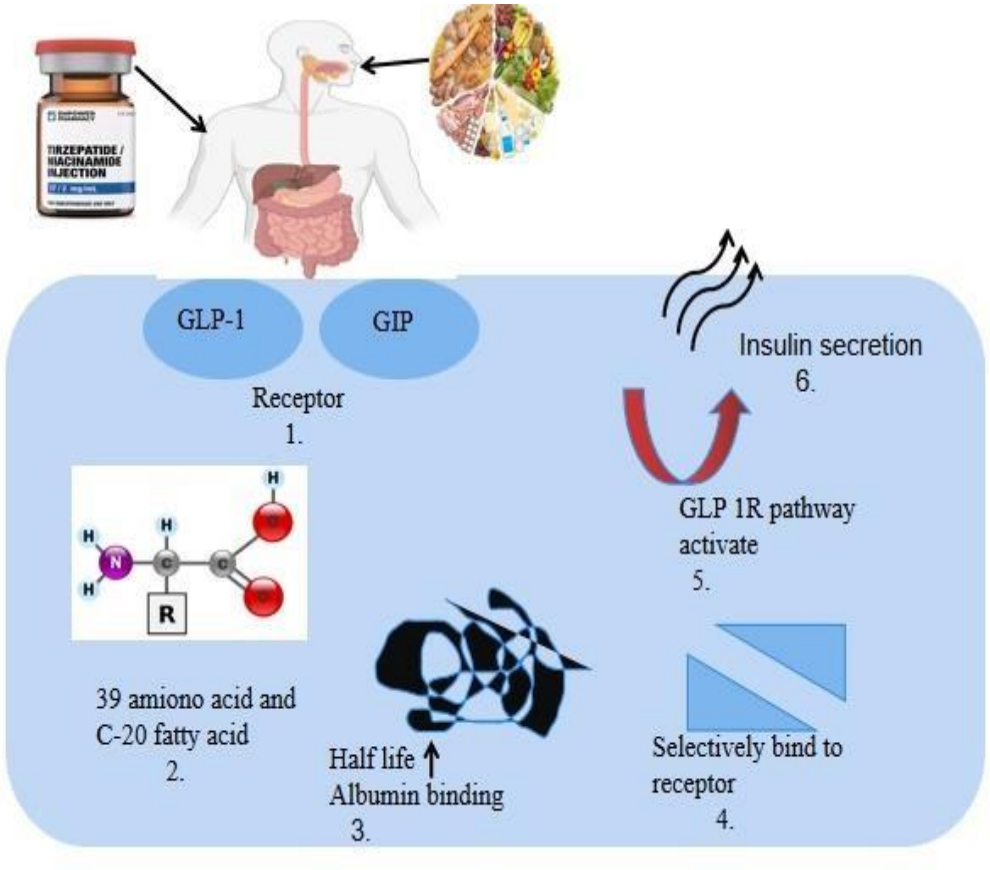

Figure 1: Mechanism of action of Tirzepatide.

Note- Tirzepatide is a peptide altered to function as a dual agonist for the GLP-1 and GIP receptors, designed to influence both. It has a C20 fatty acid moiety and a 39-amino acid sequence that help bind albumin and prolong its half-life in the body. Native GIP and GLP-1 are bound to and activated by this medication specifically, and GIP and GLP-1 receptors are their natural targets. Tirzepatide increases insulin secretion in both the first and second phases in a glucose-dependent manner. It also lowers glucagon levels, which improves glucose regulation even more. Tirzepatide primarily acts in reaction to elevated glucose levels, its glucose-dependent mode of action is important because it reduces the risk of hypoglycemia.

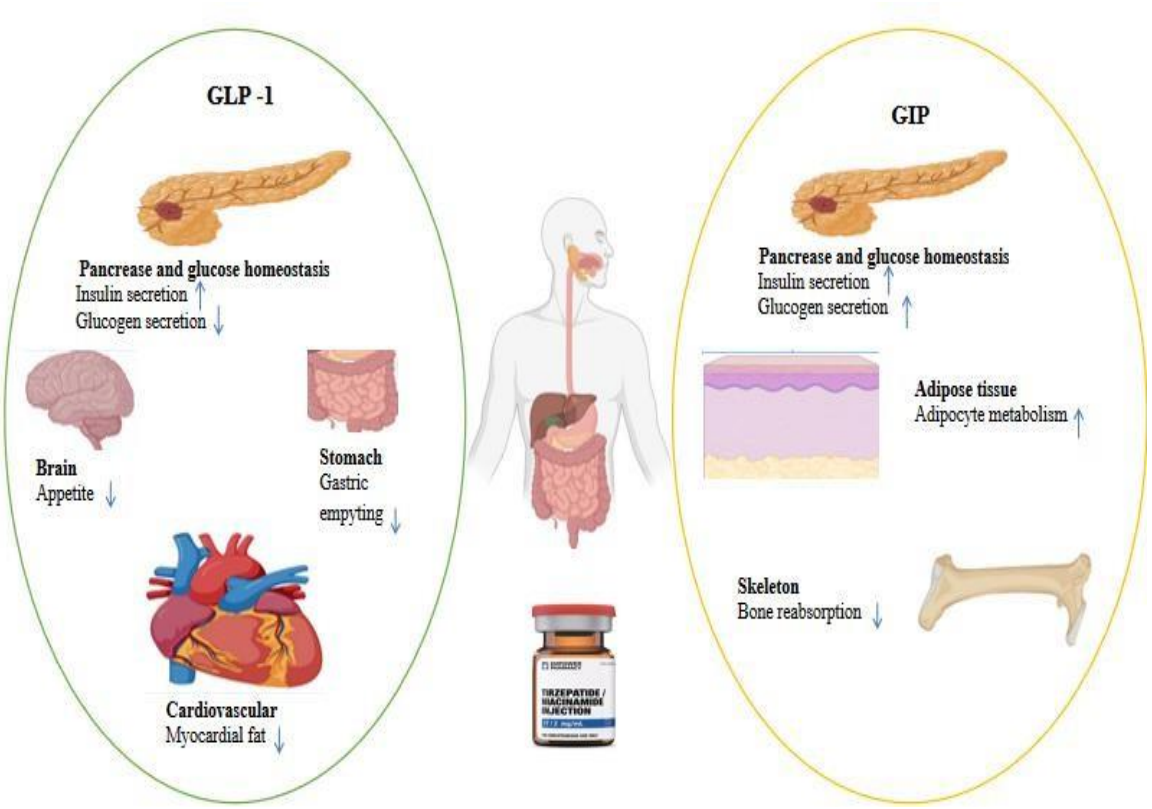

Figure 2: GLP-1 and GIP role inside the body.

2.1.1. The role of In-cretins in the pathogenesis of T2DM

The importance of incretins, such as GLP-1 and GIP, in the progression of T2DM is critical. The "incretin effect" plays a vital role in stimulating insulin release following meals.[22] For those with type 2 diabetes, tirzepatide, a dual-acting agonist that activates both GIP and GLP-1 receptors, has shown promise in helping them lose weight and control their blood sugar levels.[21] After a meal, the incretin hormones GIP and GLP-1 are generated, causing the pancreatic cells to begin an insulin-dependent insulin-dependent response.[23,24] Reduced insulinotropic action on pancreatic beta cells and decreased hormone production after meals are the two factors thought to contribute to the reduced in-cretin function in T2DM.[25,26]

2.2. Chromium picolinate

It is suggested that chromium functions as an insulin sensitizer and glucose tolerance factor, which may have an impact on T2DM.[27] Numerous investigations on both humans and animals have conclusively demonstrated its role in appropriate insulin action as well as the metabolism of fat and carbohydrates.[28] Furthermore, chromium not only enhances insulin activity but also reduces insulin levels, thereby enhancing glycemic control, particularly in individuals with T2DM who are obese. Because of its dual effects on insulin function and glycemic homeostasis, chromium may have therapeutic implications in the management of diabetes.[29] Chromium picolinate (CrPic), is positioned as an insulin sensitizer because several studies show that it can reduce blood glucose levels without increasing insulin production.[30] It is worth noting that CrPic has demonstrated several advantageous outcomes for individuals diagnosed with T2DM.[31] These include mitigating the pace of weight gain, enhancing lipid profiles, and improving endothelial function. This implies that CrPic might have broader advantages than glycemic control, which could make it an important part of the treatment of Type 2.[32,33]

Through a variety of processes, chromium plays a significant part in the intricate network of insulin and glucose metabolism.[34] It enhances insulin- stimulated signal transduction beyond the insulin receptor (IR), hence intensifying insulin signaling cascades, which makes it noteworthy.

Furthermore, chromium not only boosts the kinase activity of IR but also augments the activity of downstream effectors such as protein kinase B (Akt) and phosphatidylinositol 2-kinase (PI3K).[29]

It is worth mentioning that chromium showcases its versatility in insulin-resistant scenarios by promoting the movement of the GLUT-4 transporter without relying on crucial signaling molecules such as Akt, IRS-1, PI3-kinase, or IR.[29] This mechanism includes increased membrane fluidity, sterol regulatory element-binding protein 3 upregulation, and chromium-mediated cholesterol efflux. Additionally, chromium functions as a negative feedback regulator, reducing the activity of PTP-1B, an insulin-signaling negative regulator. Additionally, it lessens the serine phosphorylation of insulin receptor substrate (IRS) and c-Jun N-terminal kinase (JNK), which are linked to endoplasmic reticulum (ER) stress and insulin signaling control. Crucially, chromium stimulates AMP-activated protein kinase (AMPK) activation transiently, increasing the absorption of glucose. All things considered, chromium appears to be a complex nutrient that is essential for glucose absorption, insulin sensitivity, and the reduction of ER stress and insulin resistance.[29,35]

2.2.1. Insulin receptor phosphorylation and kinase activity

Early research showed that in rat adipocytes, a low-molecular-mass chromium-binding oligopeptide (LMWCr) improved insulin-mediated glucose metabolism.[36] The significance of chromium was highlighted by its connection to this impact. This potency was absent from other metal ion complexes. LMWCr, also known as chromodulin, is an amino acid complex that must bind to chromium to activate insulin kinase.[37] It improves insulin signaling by attaching to the insulin receptor and increasing its kinase activity, according to study. Chromium picolinate treatment increased the tyrosine phosphorylation and kinase activity of insulin receptors in cells.[29]

2.2.2. Glucose transporter

The impact of chromium on insulin signaling molecules in proximity also influences distant functional occurrences, including the movement of Glucose transporter type 4[Glut4] vesicles towards the cell membrane in reaction to insulin.[38] Insulin-induced Glut4 levels on the cell membrane of skeletal muscle were significantly reduced in animals fed a high-sucrose diet; nevertheless, normal levels were restored following Cr treatment. Chromium picolinate enhanced Glut4 presence on the plasma membrane, enhancing insulin-triggered glucose transportation through the cell membrane, as indicated by mechanistic findings from cultured adipocytes. Interestingly, laboratory studies demonstrated that insulin signaling proteins like IR, IRS-1, PI3-kinase, or Akt might not be essential for chromium to control Glut4 translocation.[38] Rather, by lowering membrane cholesterol, chromium improved membrane fluidity. Chromium also raised the expression of sterol regulatory element-binding protein, a membrane-bound transcription factor that controls cellular cholesterol homeostasis, and decreased the expression of the cholesterol efflux protein ATP binding cassette transporter 1 [ABCA1].[39,40] This complex interaction highlights chromium's function in regulating cholesterol homeostasis and insulin-regulated glucose transport.[29] [fig -3 shows the mechanism of action of chromium picolinate].

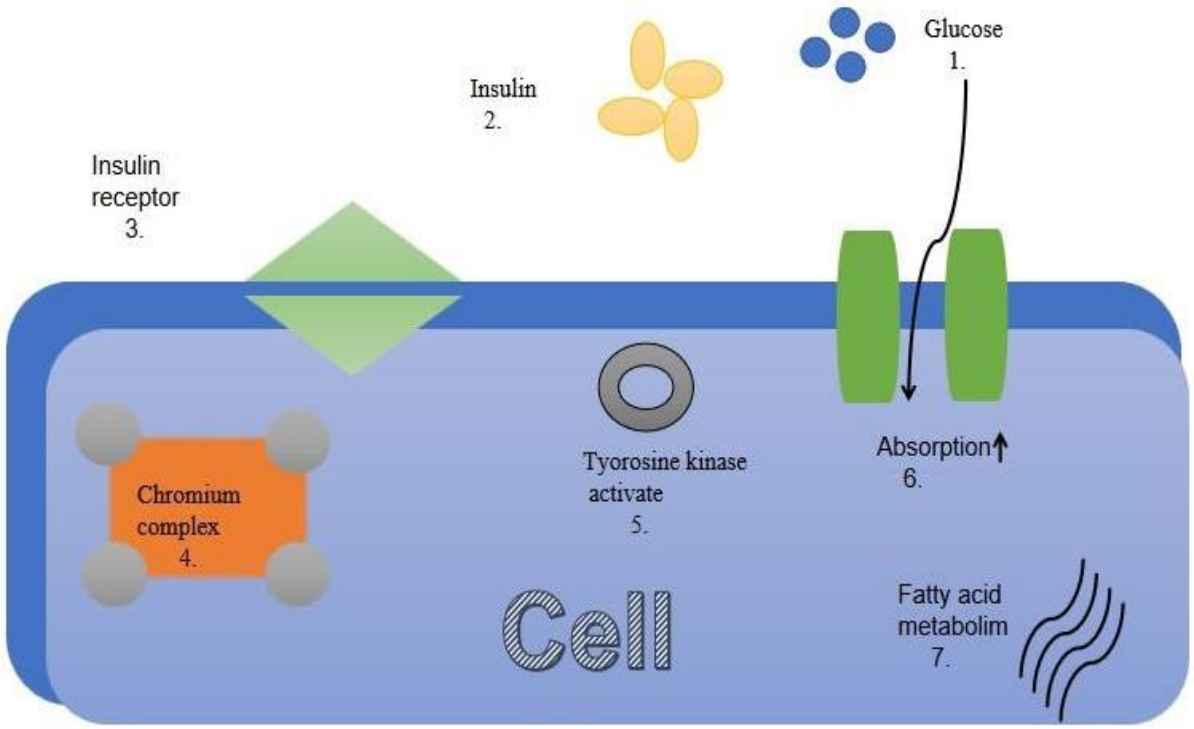

Figure 3: Mechanism of chromium picolinate.

Note - When insulin binds to insulin-sensitive cells, chromium is absorbed. This complex forms with chromodulin, activating the insulin receptor tyrosine kinase. This activation encourages the metabolism of fatty acids and improves the absorption of glucose. Insulin resistance is caused by a chromium shortage, which also impairs the absorption of glucose and the passage of amino acids. Supplementing with chromium is thought to counteract these effects and encourage weight loss, muscular growth, and fat burning.

3. Pharmacokinetics and Safety Profiles

3.1. Tirzepatide

Tirzepatide, a peptide, functions by stimulating the GLP-1 and GIP receptors to address HbA1c and body weight. It exhibits a strong binding affinity towards both receptors. This peptide stimulates insulin secretion and lowers glucagon levels by acting on glucose. Moreover, Tirzepatide initially delays stomach emptying, although this effect fades over time.[41] Tirzepatide has similar pharmacokinetics when delivered to people with T2DM and those who are healthy. After four weeks of once-weekly treatment, steady-state plasma concentrations are achieved, and Tirzepatide exposure increases in direct proportion to the dose. When injected subcutaneously, the maximal plasma concentration can be obtained between 8 to 72 hours, with an average absolute bioavailability of 80%. Consistent exposure is observed when Tirzepatide is injected into the abdomen, thigh, or upper arm.[42,43,44] With a 99% affinity for plasma albumin, the drug has a steady-state volume of distribution of about 10.3 liters. One dose can be taken once a week because of its elimination half-life of roughly five days and typical clearance of 0.061 L/h. The metabolism of Tirzepatide involves the breakdown of amides, the beta-oxidation of the C20 fatty acid component, and the proteolytic cleavage of the peptide backbone.[43,45] Urine and feces are the main ways that tirzepatide metabolites are eliminated, and neither excretion pathway exhibits complete tirzepatide. In general, the pharmacokinetic characteristics of Tirzepatide underscore its potential as a viable treatment choice for individuals diagnosed with T2DM. Furthermore, these characteristics provide strong support for its dosage regimen of once-weekly administration.[44,45]

3.2 Summary of typical adverse effects from using tirzepatide and chromium picolinate

There are several possible adverse effects both serious and frequent, linked to tirzepatide and chromium picolinate use. It is important to be aware of these and if necessary, seek medical assistance. Common side effects seen with tirzepatide use are retching, diarrhea, diminished hunger, constipation, vomiting, dyspepsia, and stomach (abdominal) pain[46] and side effects associated with chromium picolinate use are headache, cognitive dysfunction, low blood sugar level, thrombocytopenia, anemia, sleep problems (insomnia), mood changes, and irritability.[47]

3.3. Overview of Serious Side Effects associated with the use of tirzepatide and Chromium Picolinate use

Tirzepatide, a medication for managing blood sugar levels, and chromium picolinate, a dietary supplement, both carry potential risks and side effects that users should be aware of. Pancreatitis and liver problems have been associated with chromium picolinate use, as documented in various studies,[48,49,50] Additionally, both medications can lead to hypoglycemia, manifesting as symptoms such as dizziness, perspiration, disorientation, and nausea, among others. Serious allergic reactions, including facial swelling and difficulty breathing, have been reported with both tirzepatide and chromium picolinate usage.[48,49,51] Moreover, kidney problems and stomach issues have been documented with the use of both medications.[49,51] Changes in eyesight and gall bladder problems, characterized by symptoms like abdominal pain and jaundice, are also potential concerns associated with chromium picolinate use.[49,52] For this reason, anyone thinking about using tirzepatide or chromium picolinate should carefully balance the possible advantages over these dangers and seek the advice of a healthcare provider.

3.4. Drug-drug interactions

The table lists possible pharmacological interactions between the dietary supplement chromium picolinate and the diabetic medicine tirzepatide. It explains how using tirzepatide along with glinides, sulfonylureas, or insulin may increase the risk of hypoglycaemia. It also highlights the possibility that chromium picolinate, when used with insulin or metformin, could increase the risk of hypoglycaemia and interfere with the absorption of medications such as levothyroxine and antacids.

Table 1: Drug-drug Interaction seen with Tirzepatide and Chromium Picolinate.

Tirzepatide					
S. no	**Drug Class**	**Interaction Mechanism**	**Interactions result**	**Symptoms**	**Reference**
1.	Insulin Aspart: An Example (Fiasp, NovoLog) insulin glargine (Basaglar, Lantus, Toujeo), insulin lispro (Admelog, Humalog, Lyumjev), insulin degludec (Tresiba), and insulin detemir (Levemir)	Tirzepatide and insulin can lower blood sugar levels	Tirzepatide and insulin can raise the risk of hypoglycemia	Dizziness, shaking, headache, and sweating	[53][54]
2.	Sulfonylureas Example- glipizide (Glucot rol XL) glyburide (Diabet es, Glynase) glimepiride (Ama ryl)	The concurrent use of sulfonylure a and tirzepatide can heighten the likelihood of experiencin g low blood sugar levels	Tirzepatide and sulfonylureas can raise the risk of hypoglycemia	Dizziness, shaking, headache, and sweating	[55]

3.	Glinides Example- Repaglinide Nateglinide	The concurrent use of tirzepatide and glinides can heighten the risk of low blood sugar levels	Tirzepatide and a glinide together can raise the risk of hypoglycemia	Hypoglycemia	[56]
4.	Birth control pills Example - Ethinyl estradiol/norg estimate (Tri- Sprintec) Ethinyl estradiol/norg estimate (TriNessa) Ethinyl estradiol/norg estimate (Estarylla)	Tirzepatide may affect how well oral contracepti ves are absorbed, potentially resulting in decreased levels of these contracepti ves in the body. Consequent ly, the efficacy of oral birth control medications may be compromis ed	Tirzepatide can make birth control pills less effective	Vomiting and diarrhea	[57]
Chromium picolinate					
1.	Antacid	Calcium carbonate-containing antacids can hinder the absorption of chromium in the body.	Chromium absorption reduce	Not available	[58]
2.	Insulin	Chromium and insulin can lower blood sugar levels	Hypoglycemia	Not available	[59]
3.	Levothyroxine	Chromium with levothyroxine reduces theamount of levothyroxine your body absorbs	Levothyroxine absorption reduce	Not available	[60]

3.5. Tips to use 3.5.1Tirzepatide

Tirzepatide usage guidelines emphasize strict adherence to the suggested schedule. Administer the subcutaneous injection weekly, with meal pairing and scheduling flexibility, in the upper arm, abdomen, or thigh utilizing a pre-filled single-dose pen. It is advised to rotate the injection site for every dose. Typically, patients initiate treatment with a low dose and escalate it slowly, but not more frequently than once every four weeks. Changing the weekly injection day is permissible if there is a minimum of three days between doses.[61,62] Tirzepatide controls T2DM without treating it, although it may take more than four weeks for all its advantages to become apparent. Even when feeling well, continued use is necessary, and stopping should only be done with a doctor's approval. Tirzepatide and insulin ought to be infused independently, even though they can be given close together. Tirzepatide has been designed to be used safely and effectively in the treatment of T2DM, according to these guidelines.[63] Tirzepatide usage instructions place a strong emphasis on following the recommended regimen precisely. Once a week, a pre-filled single-dose pen is used to inject it subcutaneously.[64] The injection can be administered during any time of day, paired with or without food, and it can go into the upper arm, abdomen, or thigh. It is advised to switch up the injection locations for each dosage. Patients usually begin on a low dose and increase it gradually, no more than once every four weeks. It is possible to switch the administration day of the week if there are three days or more between doses. Moreover, insulin and tirzepatide should be given as separate injections rather than combined ones, even though they can be given in the same approximate vicinity. Use 1 time each week, at any time of the day, with or without meals. Even if the patient feels well, it is important to take the medication as prescribed and not to quit without first talking to a doctor.[63,65] 3.5.2Chromium picolinate Chromium picolinate is imperative to rigorously follow the suggested usage

restrictions, abstaining from using more than recommended amounts or for longer than indicated. It is advisable to seek advice from your doctor or a professional knowledgeable in herbal/health supplements before using herbal supplements.[66] Chromium picolinate should be used with careful blood sugar monitoring in mind if a patient has diabetes. Moreover, the suggested daily intake of chromium picolinate may change depending on age. It's important to realize that chromium picolinate is just one component of a comprehensive treatment strategy; regular exercise and weight control may also be necessary. Therefore, it is critical to stick to a consistent diet, take your medication, and work out regularly.[51,67] Utilize Chromium Picolinate exactly as recommended by your physician or as instructed on the label. Never use more, less, or any duration of time than is advised. If you are thinking about using herbal supplements, like chromium picolinate, consult your physician or a specialist in herbal/health supplements. As instructed by your healthcare professional or according to the dose guidelines on the packaging, follow these guidelines. Do not take more than the suggested amount. If you have diabetes, use Chromium Picolinate with caution and keep a close eye on your blood sugar levels. As people age, the recommended daily intake of chromium picolinate may rise. A therapy plan that involves nutrition, physical activity, and weight control may include chromium picolinate. Keep chromium picolinate at room temperature and out of the heat and moisture.[51,58]

4. Clinical Evidence

4.1. Clinical studies and tests performed on Tirzepatide and chromium picolinate for glycemic control

A comparison between clinical trials evaluating Tirzepatide, a medication used in the treatment of T2DM, and chromium supplementation for glycemic management in diabetic and non-diabetic adults is depicted in Table 2. Tirzepatide trials, including monotherapy and combination therapy with other antidiabetic agents like semaglutide and insulin, involved large cohorts of adult patients over various durations ranging from 40 to 48.1 weeks. These trials consistently demonstrated significant reductions in HbA1c levels, indicating improved glycemic control, along with notable decreases in body weight. However, adverse reactions such as nausea, diarrhea, and other gastrointestinal symptoms were observed, particularly in patients receiving Tirzepatide.

In contrast, chromium supplementation trials encompassed meta-analyses and controlled studies examining its effects on glycemic management in both diabetic and non-diabetic adults. While chromium supplementation showed promising results in improving glycemic control, particularly in individuals with T2DM, its impact on fasting glucose levels varied among diabetic and non- diabetic populations. Furthermore, chromium supplementation, both in combination and monotherapy form, was linked to modifications in lipid profiles, including increased HDL-C and decreased triglyceride levels. Overall, Tirzepatide appears to be effective in improving glycemic control and reducing body weight in patients with T2DM, although it may be accompanied by gastrointestinal side effects. Chromium supplementation also shows potential benefits for glycemic management, especially in individuals with T2DM, but further research is needed to elucidate its mechanisms of action and long-term effects.

Table 2: Clinical study on Tirzepatide and Chromium picolinate for glycemic control.

S.NO	CLINICAL TRIAL	NUMBER OF PARTICIPANTS	DURATION	DESCRIPTION	OUTCOME	REFERENCE
Tirzepatide						
1.	Seven Controlled Clinical Trials in One Pool	5119 adult patients [mean age 54 years]	An average of 48.1 weeks	Adverse effects were measured in adults with type 2 diabetes in combination trials (SURPASS-2, -3, -4) and placebo-controlled trials (SURPASS-1 and 5).	The tirzepatide group experienced increased rates of vomiting, dyspepsia, hypoglycaemia, nausea, diarrhoea, and decreased appetite.	[7]
2.	Monotherapy use of Tirzepatide	478 adult patients [mean age 54 years]	40-week double-blind study	SURPASS-1 trial: Tirzepatide (5 mg, 10 mg, 15 mg weekly) versus placebo for participants with uncontrolled glycemia despite diet/exercise, BMI 32 kg/m², average diabetes duration 4.7 years.	Tirzepatide monotherapy significantly reduced HbA1c levels, indicating its potential for enhancing glycemic control in patients.	[68]
3.	Tirzepatide combination with semaglutide	1879 individuals [mean age of 57 years]	40-week open-label SURPASS-2 clinical trial	In T2DM, semaglutide 1 mg weekly versus tirzepatide 5 mg, 10 mg, or 15 mg weekly as a metformin adjunct.	Tirzepatide significantly reduced HbA1c levels compared to semaglutide, indicating its potential for improving glycemic control in patients.	[69]
4.	Combination of tirzepatide and insulin, either with or without metformin	475 patients [mean age of 61 years]	40-week double-blind	SURPASS-5 trial: Weekly injections of Tirzepatide (5, 10, 15 mg) or placebo were given to patients who were not receiving enough insulin glargine, either with or without metformin.	The trial showed significant HbA1c reduction vs. placebo, with observed insulin glargine dosage adjustments, indicating potential glycemic control enhancement in patients.	[70]
5.	Monotherapy Tirzepatide	705 patients (54.1 years old on average)	40-week period	Tirzepatide doses (5 mg, 10 mg, 15 mg) and placebo were assigned randomly to patients with a mean diabetes duration of 4.7 years and, a BMI of 31.9 kg/m².	Tirzepatide patients achieved their HbA1c objectives and lost weight in the range of 7.0 to 9.5 kg, demonstrating the medication's effects on both weight and glycemic control.	[68]
Chromium picolinate						
1.	Randomized Controlled Clinical Trials[meta-analysis]	T1DM, T2DM adult patient	3-8 weeks	Included studies compared chromium mono or combination supplementation against placebo based on reported HbA1c or	Three studies on chromium supplementation demonstrated notable improvement in glycemic management, with	[71]

				fasting plasma glucose levels.	chromium picolinate showing efficacy in affecting glucose levels.	
2.	Randomized Controlled Clinical Trials[meta-analysis]	Healthy nonpregnant adults with and without diabetes were 809 participants. (440 diabetics and 369 nondiabetics)	Not available	Meta-analyses show chromium lowers fasting glucose in diabetes but not in non-diabetic individuals; alternate effect size d(ppc2) considered variations.	According to the analysis, chromium supplementation had no discernible impact on either non-diabetics or diabetics.	[72]
3.	Single-center trial with parallel-arm design, randomization, blinding, and placebo control.	The study included 43 overweight/obese participants (18-65 years), male/female.	4 weeks	In a randomized experiment, 600 µg of chromium (chromium picolinate) and 2 mg of biotin were given to one group, and a placebo was given to the other.	Biotin and chromium picolinate combo may aid T2DM patients.	[73]
4.	Randomized Controlled Clinical Trials	T2DM adult patient [1,690 subjects]	Not available	Among 15 studies with 1,690 participants (1,505 in the CrPic group), 13 (including 11 RCTs) showed significant glycemic control improvement.	CrPic supplementation in T2DM leads to significant drops in hyperglycemia and hyperinsulinemia, reducing disease complication risks.	[74]
5.	A clinical trial that is randomized, double-blind, and placebo-controlled.	52 adult patients over 40-year-old [T2DM]	8 weeks	Two groups were assigned randomly, with one group receiving a daily dosage of 400 µg CrPic, while the other group was administered a placebo.	1,000 µg CrPic for 6 months improves insulin sensitivity, and glycemic control, and may aid T2DM-related disturbances in lipid profile.	[75][76]

4.2. Clinical studies and tests performed on Tirzepatide and chromium picolinate for weight reduction

The comparative analysis between trials (Table 3) evaluating Tirzepatide and chromium picolinate supplementation reveals distinct outcomes regarding their effectiveness in inducing weight loss. Trials investigating Tirzepatide, a medication targeting T2DM and obesity, consistently demonstrate significant weight reduction effects. In a phase 3 trial spanning 72 weeks, Tirzepatide administration led to substantial weight loss across varying doses, with participants experiencing reductions ranging from 16.1 kg to 23.6 kg compared to placebo. Similarly, in another trial focusing on obesity treatment over 72 weeks, Tirzepatide showed significant weight loss efficacy, with the high-dose group achieving a notable percentage reduction in initial weight compared to placebo.

In contrast, trials examining chromium picolinate supplementation present less robust findings regarding weight loss efficacy. Despite initial optimism, studies evaluating chromium picolinate's impact on weight loss reveal modest effects. Chromium picolinate supplementation, either by itself or in conjunction with exercise, produced only a slight reduction in body weight when compared to placebo in one research involving adult patients with a BMI of 30 kg/m^2; no appreciable dose-dependent impact was seen. In a similar vein, an 8-week randomized, double-blind, placebo-controlled trial found that 400 µg of chromium picolinate supplementation did not significantly alter body weight or BMI when compared to a placebo. A study evaluating diet instruction and chromium picolinate supplementation in overweight or obese individuals only marginally lowered weight over 24 weeks, according to a meta-analysis of 10 double-blind, placebo-controlled trials. Tirzepatide appears to be a more viable treatment choice for people trying to control their obesity because it consistently and significantly works better at promoting weight reduction than supplementing with chromium picolinate.

Table 3: Clinical study on Tirzepatide and Chromium picolinate for weight reduction.

S. No	Clinical trials	No of the subjects used	Duration and Description	Conclusion	Reference
Tirzepatide					
1.	Randomized controlled clinical trial	2539 adults who were at least 18 years old	Participants were randomly assigned 1:1:1:1 to take between 5 mg, 10 mg, or 15 mg of subcutaneous tirzepatide or a placebo for 72 weeks. The dose was increased by 2.5 mg every four weeks for a total of 20 weeks.	Patients who used tirzepatide (5 mg, 10 mg, and 15 mg dosage) dropped 16.1 kg, 22.2 kg, and 23.6 kg of weight, compared to 2.4 kg with placebo.	[77], [78]
2.	Randomized controlled clinical trials	938 T2D individuals (mean 8.5-year follow-up)	The mean age is 54.2 years. Ten milligrams (n = 312), fifteen milligrams (n = 311), and a placebo (n = 315) were assigned at random. For the treatment of obesity, SURMOUNT-2 randomized participants to receive tirzepatide 10 mg, 15 mg weekly, or a placebo during a 72-week period.	Subcutaneous 10 mg and 15 mg weekly doses were found to cause 14.7% weight reduction after 72 weeks, compared to 3.2% with the placebo, according to SURMOUNT-2.	[79], [80]
Chromium picolinate					
1.	Randomized Controlled Clinical Trials	622 adult patients [30 kg/m2 body mass index]	RCTs compared chromium picolinate (CrP) + resistance training or CrP alone with a placebo, assessing the efficacy of doses (200 µg - 1000 µg). The time duration for the trial was 8 to 24 weeks.	Combining findings from dosages (200 µg - 1000 µg) of chromium picolinate, weight decreased by 1 kg vs. placebo, and safety was unclear.	[81]
2.	A randomized, double-blind, placebo-controlled clinical study	52 adult patients over 40-year-old [T2DM]	Two groups: one received 400 µg CrPic daily, another placebo. The time duration of the trial was 8 weeks	400 µg CrPic supplementation showed no effect on body weight/BMI	[82]
3.	Randomized Controlled Clinical Trials	80 Adult men and women who are overweight or obese	Assesses nutritional education and 1000 µg chromium picolinate on overweight adults' weight loss over 24 weeks. The time duration for the trial was 24 weeks.	Meta-analysis: chromium picolinate led to ~1.1–1.2 kg weight drop.	[83]

5. Comprehensive T2DM management algorithm with tirzepatide and chromium picolinate

However, management typically involves lifestyle modifications and pharmacological interventions tailored to individual needs. Tirzepatide, a GLP- 1 receptor agonist, and chromium picolinate, an oral supplement, may be considered a second-line agent for improving glycemic control and promoting weight loss [74]. Healthcare providers should refer to the latest clinical guidelines and evidence-based practices fig 4 shows the use of tirzepatide and chromium picolinate in the management of T2DM.

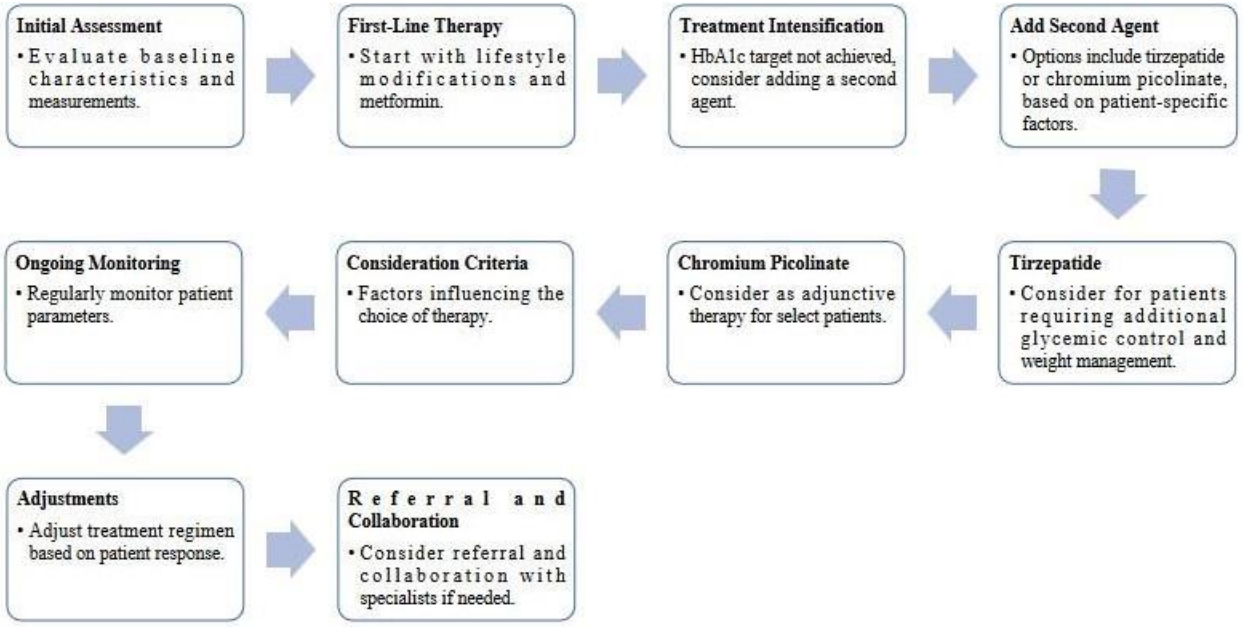

Figure 4: Tirzepatide and chromium picolinate into the treatment algorithm for T2DM (Broadhurst & Domenico, 2006).[74]

6. Future Directions

For individuals diagnosed with T2DM losing weight has long been seen to raise HbA1c levels and lower their risk of weight-related problems. Recent findings, however, indicate that many T2DM patients should have a primary therapeutic goal of 5–15% weight loss.[84] Maintaining a healthy weight is crucial to the overall care of individuals with type 2 diabetes because it greatly enhances metabolic control and reduces the risk of complications.[49] Research suggests that greater weight reduction amounts result in better results. Based on a consensus report released in 2021, shedding off 5-10% of body weight can bring about metabolic enhancements.[85] On the other hand, a more significant 10%– 15% drop in weight or beyond may have a disease-altering impact and potentially induce the remission of diabetes. Remission is characterized by the sustained maintenance of normal blood glucose levels for three months or more without the need for pharmaceutical intervention.[86]

Precision medicine, which customizes weight-management plans based on unique genetic, metabolic, and lifestyle characteristics is one fascinating field of study. In addition, new drugs that target neuroendocrine pathways—like GLP-1 receptor agonists—are being researched to determine whether they can help people with T2DM lose weight and improve their glycemic control.[87] Future diabetes clinical trial designs must take a calculated approach to close current data gaps and move the field closer to more individualized and successful management techniques.[88] To guarantee that results apply to a broad range of demographics and diabetes subtypes, trials should include a diversity of patient

populations. Additionally, extended follow-up periods are necessary to assess the durability of therapy benefits.[89] Head-to-head comparison trials and other comparative effectiveness research are crucial for determining which interventions work best for patient populations. Furthermore, the incorporation of digital health treatments and multidisciplinary care models has the potential to improve patient participation and enable comprehensive management strategies.[90] A thorough investigation of treatment effect heterogeneity and meta-analyses of current clinical trials utilizing individual-level data is crucial.

For individualized treatment methods, reanalysis of previous studies demonstrating differences in treatment responses across patient subgroups is essential. To test a priori ideas about treatment heterogeneity, fresh clinical trial designs should be created, particularly those that compare two or more active therapies to help with clinically relevant decision-making. To help with treatment strategy optimization and treatment response prediction, novel genetic and nonstandard biomarkers must be found and evaluated. Combining clinically observable traits, such as lifestyle variables, clinical traits, and biomarkers, shows potential for improving treatment response prediction.[91]

7. CONCLUSION

Despite the absence of a known cure for T2D or obesity, these conditions can be effectively managed through appropriate therapy, treatment, and lifestyle modifications. Clinical trials have demonstrated the excellent efficacy of tirzepatide, a dual GIP and GLP-1 receptor agonist, in enhancing glycemic control and reducing body weight in individuals with type 2 diabetes.

Research on chromium picolinate, a dietary supplement containing chromium, has shown conflicting findings regarding its impact on glucose metabolism.

While some studies suggest modest benefits, others fail to show any noticeable effects. As a result, the evidence supporting the use of chromium picolinate in managing T2DM is less conclusive than that of tirzepatide, a well-established pharmaceutical agent with proven efficacy in this field. Further studies with larger sample sizes could provide more clarity on the drug's effectiveness.

Conflict of Interest

NA

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