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Review

Does teneligliptin reverse the metabolic syndrome components among non-diabetic obesity subjects? – A hypothesis

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Abstract

Obesity and its related metabolic syndrome complications are highly remarkable and need to be addressed. There are a limited number of anti-obesity drugs available, and there is a need for more safe and effective therapeutic options for treating obesity. Currently, drug repurposing is an alternative to novel drug development for the treatment of obesity patients. Teneligliptin is an oral anti-diabetic agent, and it was well tolerated. In addition to anti-diabetic activity, teneligliptin conserves endogenous incretins by inhibiting the dipeptidyl peptidase -4 enzyme. Incretins play a vital role in obesity and its related complications. Several pre-clinical studies with teneligliptin support ameliorated the metabolic syndrome in obesity without diabetes in Zucker fatty rats. Till now, there have been no studies on the obese population without diabetes. Hence, we hypothesize that teneligliptin 20 mg twice daily with a low carbohydrate diet and adequate physical activity may be more effective in reversing metabolic syndrome and obesity.

Keywords: teneligliptin, obesity, non-diabetics, metabolic syndrome, GLP-1.

Introduction

Obesity has reached epidemic proportions in most countries worldwide and is still rising [1]. Obesity is a major public health concern around the world, with serious medical and societal consequences [2–4]. Obesity raises the risk of several comorbidities, impacts physical and mental health, and reduces health-related quality of life. Pharmacotherapy may be a valuable adjunct to lifestyle intervention for individuals with obesity in order to achieve and maintain clinically relevant weight loss, improve comorbid conditions, and encourage a healthier lifestyle. There are currently a limited number of anti-obesity medications available, and there is a need for more safe and effective therapeutic options for treating obesity, particularly treatments that also target weight maintenance, prevention, and treatment of comorbidities [5]. Weight loss or weight neutrality is associated with incretin-based therapies such as glucagon-like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase (DPP)-4 inhibitors [6]. GLP-1 receptor agonists have already succeeded in diabetes treatment and, owing to their attractive body-weight-lowering effects in humans, may pave the

way for other anti-obesity agents [7, 8]. Currently, the novel class 3 DPP-4 inhibitors (increase GLP-1 and GIP) are developed to treat type 2 diabetes. DPP-4 is a novel adipokinetic and has potentially linked obesity to metabolic syndrome [9] and there are a good number of pre-clinical studies that evaluated the non-glycemic effects of teneligliptin.

Impact statement

- Obesity and overweight are the leading causes of diabetes and other metabolic disorders.
- Teneligliptin is an oral anti-diabetic agent with a good safety profile and no hypoglycaemic effects.
- Teneligliptin inhibits the DPP-4 enzyme by improving the role of GLP-1.
- Increased levels of GLP-1 can reverse the glycemic and non-glycemic effects.

Background to hypothesis

Teneligliptin is a class 3 Dipeptidyl peptidase (DPP)-4 inhibitor of oral anti-hyperglycaemic drug approved for managing T2DM in adults along with diet and exercise. Their mechanism of action is to increase levels of the active forms of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP) in response to meal intake, which in turn results in insulin secretion and reduces glucagon secretion [10]. GLP-1 has a very short half-life of 1–2 min, and eventually it was degraded by DPP-4 enzyme. Inhibition of DPP-4 could enhance the active form of GLP-1. GLP-I has a vital role in the control of glucose levels and it may also have the capacity to reduce body weight and manage some micro and macro-vascular complications [11, 12].

On the other hand, DPP-4 is linked with the intestinal secretion of triglycerides and the elevated triglycerides are associated with insulin resistance [13]. Similarly, a meta-analysis suggests that DPP-4 inhibitors may benefit cholesterol, which may contribute to a reduction in cardiovascular risk [14]. The relationship between the efficacy of DPP-4 inhibitors and BMI has been reported, but it needs to be more concise and understudied. Furthermore, no studies were conducted with only obese or overweight subjects who did not have diabetes. A clinical benefit of oral Teneligliptin's non-glycemic benefits ameliorating metabolic components could be a favorable option. Teneligliptin is a highly selective S2 subsite of the DPP-4 enzyme and has a longer plasma half-life as compared to other DPP-4 inhibitors [15, 16]. Based on this supporting evidence, we believe that teneligliptin can increase endogenous GLP-1 concentrations by suppressing the appetite glucagon release, delaying gastric emptying and increasing satiety and reducing body weight in overweight and obese subjects [17].

Statement of hypothesis

DPP-4 inhibition may increase the active form of GLP-1. GLP-I plays an important role in glucose control, and it may also have the ability to reduce body weight and manage metabolic syndrome, along with reversing some micro and macrovascular complications. DPP-4 inactivates incretins by hydrolyzing them; thus, DPP-4 inhibitors stimulate insulin secretion while inhibiting glucagon secretion, resulting in lower glucose levels without hypoglycemia [18]. Gliptins alone cannot produce hypoglycemia. The incidence of hypoglycemia is observed in combination with other oral hypoglycemic agents [19] and gliptin-induced postprandial rise in active GLP-1 concentrations does not produce hypoglycaemic effect [20]. Furthermore, high-dose teneligliptin (40 mg/day) [21] reduces hypoglycemia by increasing glucagon secretion during the hypoglycemic period [22] and may provide good "quality" glucose control, lowering the risk of diabetic complications and improving patients' quality of life.

Reduction of body weight, total cholesterol and triglycerides

Obesity and other metabolic problems are generally linked to decreased bile acid (BA) levels. BA synthesis was studied both *in vitro* and *in vivo* with teneligliptin. Ten weeks of Teneligliptin treatment on mice fed a high-fat diet showed that it reduced body weight, total cholesterol, triglycerides and adipocyte size by increasing the serum and ileal levels of bile acids [23]. Bile acids play a key role in maintaining whole-body homeostasis by facilitating the digestion, absorption, and transport of nutrients, lipids, and vitamins [24]. Teneligliptin suppressed the expression of factor Fgf15 (Fibroblast growth factor 15), which is responsible for the synthesis of bile acids [25]. Hence, increased synthesis of BAs can reduce total and LDL cholesterol levels, which is important in preventing diseases such as atherosclerosis and heart disease, which are closely

related to type II diabetes [26]. Visceral fat obesity increases serum DPP-4 levels in men with type 2 diabetes mellitus, and the serum DPP-4 level was positively and specifically associated with visceral fat accumulation and metabolic syndrome in men with T2DM [27].

Sayaka F. Tsuru *et al*. conducted extensive pre-clinical studies on Zucker fatty rats. Teneligliptin 60 mg/kg reversed adipocyte hypertrophy hepatic steatosis in high-fat diet-induced mice, resulting in a 22 percent reduction in body weight [28]. In Zucker fatty rats at 1 mg/kg improved the postprandial hyperglycemia and dyslipidemia after single and repeated administrations. Diet-induced adipose Tissue Inflammation and Liver Steatosis were also Prevented by DPP-4 Inhibition in Diabetic Mice [29].

Protection against atherosclerosis

Apart from glycaemic control with DPP-4 inhibitors, it also has a protective role in atherosclerosis [30–32]. DPP-4 inhibitors exert anti-atherosclerotic effects directly through multiple mechanisms, including improving endothelial cell dysfunction, increasing circulating endothelial progenitor cell (EPCs) levels, regulating mononuclear macrophages and smooth muscle cells, inhibiting inflammation and oxidative stress and improving plaque instability.

Anti-inflammatory effect

DPP-4 inhibition produces an anti-inflammatory activity because the activity of DPP-4 results in reduced production of cytokines, including interleukins and interferon-G. All these anti-inflammatory agents are inhibited by the DPP-4 enzyme, which can lead to the pathogenesis of cardiovascular diseases and provoke atherosclerosis and psoriasis. The beneficial effects of teneligliptin, beyond glycemic control, have non-glycemic benefits owned by both GLP-dependent and -independent [33–35].

Appetite suppression

GLP-1 promotes appetite suppression by stimulating GLP-1 receptors expressed in the hypothalamus and caudal brainstem [36]. Hansen HH colleagues demonstrated the status of appetite and body weight change in diet-induced obese rats. Linagliptin (1.5 mg/kg, p.o., or 0.5 mg/kg, s.c.) and GLP-1 (0.5 mg/kg) treatment evoked a marked anorectic response with both routes of linagliptin administration being equally effective on final body weight loss (7.5–8.0%). Interestingly, exogenous GLP-1 treatment causes inhibitory effects on food intake, implying that the anorectic effects of GLP-1 are unmasked when endogenous levels are raised above that attained by pharmacological DPP-IV inhibition alone. By inference, concurrent pharmacological inhibition of DPP-IV activity may thus further increase the capacity of exogenous GLP-1 to suppress food intake. In accordance with this notion, combined vildagliptin and GLP-1 treatment has recently been demonstrated to reduce acute food intake in lean mice and rats [37]. Hence, considering their pre-clinical support, we were proposed to test the effect of oral teneligliptin 20 mg twice daily with a low carbohydrate diet and physical exercise on non-diabetic obese individuals to reverse the metabolic syndrome component.

Testing the hypothesis

In view of the above hypothesis, we proposed to amend the randomized controlled study to confirm the effectiveness of teneligliptin 20 mg twice daily for 48 weeks, in adjunct to low carbohydrate diet and physical activity in comparison with the low carbohydrate diet and physical activity alone in subjects with non-diabetic obesity. There are many randomized control trials with teneligliptin in T2DM patients [38]. There are no studies with teneligliptin on non-diabetic obesity patients. Carol's colleagues worked on omarigliptin once weekly on obese subjects with and without type 2 diabetes mellitus. Omarigliptin was well tolerated in both obese non-diabetic and obesity-alone population, and GLP-1 concentrations were significantly increased in obese non-diabetics [39]. DPP-4 inhibitors prevented weight regain in obese women with polycystic ovarian syndrome who had previously been treated with liraglutide [40]. The levels of DPP-4 are linked with adipokinetics and Sayuri Tanaka's colleagues proved it. They explored that serum DPP-4 level was positively and specifically associated with visceral fat accumulation and metabolic syndrome in men with T2DM [27].

Furthermore, Derosa G. *et al*. proved that DPP-4 inhibitors have prominent anti-inflammatory activity. They compared vildagliptin 50 mg thrice daily with glimepiride 2 mg twice daily in T2DM patients. They noticed blunting of inflammatory markers such as c-reactive protein (CRP), TNF-α and IL-6 in the vildagliptin-treated group [41]. A one-year monotherapy study was conducted on elderly patients with T2DM by Rosenstock *et al*. A significantly lower risk of hypoglycemia and without

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weight gain was observed with alogliptin as compared to glipizide [42]. Owing to clinical studies, some pre-clinical evidence also supported our hypothesis. Teneligliptin 60 mg/kg reduced body weight by 22% in mice with high-fat diet-induced adipocyte hypertrophy and hepatic steatosis [29]. Inhibition of DPP-4 can exhibit extra pancreatic protective effects against diet-induced adipose tissue inflammation and hepatic steatosis in diabetic mice [43]. Teneligliptin is a novel, long-lasting DPP-4 inhibitor that improves postprandial hyperglycemia and dyslipidemia after single and repeated administration at 1 mg/kg in Zucker fatty rats [44]. Noting the above scientific consensus, whether the teneligliptin produces relevant non-glycemic effects such as suppressed appetite, change of body weight, normalized lipid profile and improving insulin resistance associated with elevated protected active GLP-1 (7-36) amide levels in obese non-diabetics has to be confirmed.

Conclusion

The metabolic syndrome is the one that is strongly connected to cardio and cerebrovascular diseases. Among the metabolic syndrome components, obesity and dyslipidemia are substantial global public heath challenges that provoke insulin resistance and diabetes. Based on the pre-clinical and clinical evidence with teneligliptin, their possible pharmacological effects other than glycaemic benefits are reliable. Hence, this academic hypothesis is to hypothesize the effect of teneligliptin along with lifestyle interventions in non-diabetic obesity subjects. It could improve obesity-related comorbidities and body weight reduction to promote physical and mental health and improve health-related quality of life. Teneligliptin's safety, tolerability and efficacy (off-label use) may be an option or an adjunctive in ameliorating obesity and its related comorbidities in non-diabetics.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The study procedure was approved by the Institutional Ethics Committee, dated: 22.01.2022 (IEC/19/Nov/155/65) of Sri Ramachandra Institute of Higher Education and Research (Deemed to be University), Chennai, affiliated Endo-life Specialty Hospital, Guntur. The study has been conducted in accordance with the Declaration of Helsinki and in accordance with good clinical practice guidelines after obtaining informed consent from the eligible study subjects. The present prospective study was registered in the Clinical Trial Registry of India, Regd. ID: CTRI/2020/02/023329 (Registered on: 14/02/2020).

Consent to participate

Written informed consent was obtained from the participants.

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