Does teneligliptin reverse the non-glycemic effects among the non-diabetic obesity subjects?

Ranakishor Pelluri
Department of Pharmacy Practice, Vignan Pharmacy College, Guntur, 522213
Srikanth Kongara
Department of Endocrinology and Metabolism, Endo-life Speciality Hospital, Guntur-522001
Vanitha Rani Nagasubramanian (drnvanitharani2020@gmail.com)
Department of Pharmacy Practice, Sri Ramachandra Institute of Higher Education Research, Deemed to be University, Porur, Chennai-600116
Shriraam Mahadevan
Department of Endocrinology and Metabolism, Sri Ramachandra Institute of Higher Education and Research, Deemed to be University, Porur, Chennai-600116
Jithendra Chimakurthy
Department of Pharmaceutical Sciences, Vignan's Foundation for Science Technology and Research, Deemed to be University, Guntur, 522213

Research Article

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Abstract

Incretins (GLP-1, GIP, DPP-4) are secreted in response to meal. The GLP-1 has very shorter half-life (1–2 min), meanwhile it was degraded by DPP-4 enzyme. The present novel, Teneligliptin which has greatest receptor selectivity and has longer half-life compared to other gliptins. The promising dipp-4 inhibition which can enhance the GLP-1 concentration in the blood. Augmentation of GLP-1 levels are helpful to reduce the weight loss in obesity subjects along with reversing metabolic syndrome components. GLP-1 analogues are gold mine and are succeeded in subjects with obesity. Apart from pharmacotherapy, lifestyle modification in the form of strict diet restrictions and physical exercise are the corner stone intervention for obesity, but subjects are filed to achieve it. Furthermore, there are currently few anti-obesity drugs available, and additional safe and effective therapeutic options for the treatment of obesity are needed. Teneligliptin is developed to treat diabetes, and which do not produce hypoglycaemic effect alone. Hence, considering its safety we are aimed evaluate the non-glycemic effects in non-diabetic obese 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].

Background To Hypothesis

Obesity has reached epidemic proportions in most countries around the world, and it is still increasing at an alarming rate [1]. Obesity is one of the world's most major public health concerns, with significant medical and societal consequences [2–4]. Obesity increases the risk of a number of comorbidities, has an impact on physical and mental health, and lowers health-related quality of life. For the individuals with obesity, pharmacotherapy may be a valuable adjunct to lifestyle intervention in order to achieve and maintain clinically relevant weight loss, improve comorbid conditions, and encourage a healthier lifestyle. There are currently few 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]. Incretin-based therapies, including glucagon like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase (DPP)-4 inhibitors, are associated with weight loss or weight neutrality [6].

GLP-1 receptor agonists have already succeeded in diabetes treatment and, owing to their attractive body-weight-lowering effects in humans, will perhaps also 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, but DPP-4 is a novel adipokinetic and has potentially linking obesity to the metabolic syndrome [9]. The relationship between the efficacy of DPP-4 inhibitors and the BMI has been reported, and this relationship is controversial and not explored well. Moreover, there were no studies were conducted only with obesity or over weight subjects without diabetes. A clinical benefit of oral Teneligliptin's non-glycemic benefits ameliorate metabolic components could be a favourable option. Teneligliptin is highly selective S2 subsite of the DPP-4 enzyme and longer plasma half-life as compared to other DPP-4 inhibitors [10, 11]. Based on this support evidence we believed that the teneligliptin has the capability to

increase endogenous GLP-1 concentrations there by it will suppress the appetite, glucagon release, delays gastric emptying and increase satiety and reduces body weight in over weight and obesity subjects [12].

Statement Of Hypothesis

Teneligliptin is a class 3 Dipeptidyl peptidase (DPP)-4 inhibitor of oral anti-hyperglycemic drug approved in the management of 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 [13]. GLP-1 has vey shorter half-life 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 vital role in control of glucose levels and it may also have capacity reduce body weight and it can manage some micro and macro-vascular complications [14, 15]. On another hand, DPP-4 is linked with the intestinal secretion of triglycerides and the elevated triglycerides are associated to insulin resistance [16]. Similarly, a meta-analysis suggests that DPP-4 inhibitors may have a beneficial effect on cholesterol, which may contribute to a reduction in cardiovascular risk [17].

DPP-4 release strongly correlates with adipocyte size, potentially representing an important source of DPP-4 in obesity. 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 pathogenesis of cardiovascular diseases and provokes atherosclerosis & psoriasis. The beneficial effects of teneligliptin, beyond glycemic control, which has non-glycaemic benefits owned by both GLP dependent and -independent mechanisms [18–20]. In safety concern, in normoglycemic healthy male subjects, inhibition of plasma DPP-4 activity with Sitagliptin induced postprandial rise in active GLP-1 concentrations does not produce hypoglycaemic effect [21]. Teneligliptin alone does not produce hypoglycemic effect. Hypoglycemia is observed in combination with other oral hypoglycemic agents [22]. Considering the above consensus, whether this teneligliptin produce relevant non glycaemic effects such as supress appetite, change of body weight, normalise the lipid profile and improving the insulin resistance associated with elevated protected active GLP-1 (7–36) amide levels in obese nondiabetics has to be confirmed.

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 [23]. There are no significant studies with teneligliptin on non-diabetic obesity patients. The another DPP-4 inhibitor omarigliptin once-weekly, was tested in 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 are significantly increased in obese non diabetics [24]. DPP-4 inhibitors prevented weight regain in obese women with polycystic ovarian syndrome who had previously been treated with liraglutide [25]. The levels of DPP-4 are linked with adipokinetic and it was proven by Sayuri Tanaka colleagues. They were explored that serum DPP-4 level was positively and specifically associated with accumulation of visceral fat and the presence of metabolic syndrome in men with T2DM [26]. 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 that blunting of inflammatory markers such as c-reactive protein (CRP), TNF-α and IL-6 in vildagliptin treated group [27]. A one-year monotherapy study was conducted in elderly patients with T2DM by Rosenstock et al. The significant lower risk of hypoglycaemia and without weight gain was observed with alogliptin as compared to glipizide [28]. Owing to clinical studies some preclinical evidence also supported with our hypothesis.

In a preclinical study with teneligliptin 60 mg/kg, a 22 percent reduction in body weight was observed. It was seen in mice with high-fat diet-induced adipocyte hypertrophy and hepatic steatosis [29]. The DPP-4 inhibition exhibits extra pancreatic protective effects against diet-induced adipose tissue inflammation and hepatic steatosis in diabetic mice [30]. As teneligliptin is a novel, long lasting DPP-4 inhibitor, which improves postprandial hyperglycemia and dyslipidemia after single and repeated administration at 1mg/kg in zucker fatty rats [31].

Conclusion

The metabolic syndrome is the one which is strongly connected to cardio and cerebrovascular diseases. Among the MetS components, obesity and dyslipidaemia are substantial public heath challenge globally and which provokes insulin resistance and diabetes. Based on the preclinical 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 co-morbidities and reduction of body weight to promote physical, mental health and improves 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 co-morbidities in non-diabetics.

Declarations

Funding/financial statement- Funding not received for the study. All authors declared that they have no known competing financial interests or personal relationships that could have appeared to influence the proposed work reported in this paper.

Conflict of interest- The authors does not have any conflicts of interest.

Data availability statement- All the proposed protocol related information is provided within the manuscript.

Authors contributions- Dr Srikanth Kongara and Dr Shrirram Mahadevan-Inception of conceptualization/Hypotheses; Dr Vanitha Rani Nagasubramanian-Design the work and methodology; Dr Ranakishor Pelluri and Dr Jithendra Chimakurthy-Literature review and developed protocol. Dr Ranakishor Pelluri had prepared the first draft of the protocol and all the authors have approved the revised version of the protocol.

Ethical considerations/ approvals- 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 to be conducted in accordance with the Declaration of Helsinki, 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 in the study- The informed consent was taken from the participants before enrolling in the study.

Consent for publication- All authors agreed to publish present version of the protocol.

Consent for publication regarding publishing an individual's data or image-No data or image had been used in the manuscript.

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