



Glycemic and Non-Glycemic Effects of Tenebigliptin

**Ranakishor Pelluri¹, Kongara Srikanth², Jithendra Chimakurthy³,
Rashed Ahemed Shaik⁴, R. Lavanya⁵ and N. Vanitha Rani^{5*}**

¹Department of Pharmacy Practice, Vignan Pharmacy College, Vadlamudi, Guntur-522213, Andhra Pradesh, India.

²Department of Endocrinology, Endo-Life Hospital, Kothapeta, Guntur- 522001, Andhra Pradesh, India.

³Department of Pharmaceutical Sciences, Vignan's Foundation for Science, Technology and Research (DU), Vadlamudi, Guntur-522213, India.

⁴Department of Pharmacology and Toxicology, Faculty of Pharmacy, King Abdul Aziz University, Jeddah, Saudi Arabia.

⁵Department of Pharmacy Practice, Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (DU), Porur, Chennai-600116, Tamilnadu, India.

Authors' contributions

All authors equally contributed for preparing this review article. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i630446

Editor(s):

(1) Dr. Wenbin Zeng, Xiangya School of Pharmaceutical Sciences, Central South University, China.

(2) Dr. R. Deveswaran, M. S. Ramaiah University of Applied Sciences, India.

Reviewers:

(1) Filip Nina, Universitatea de Medicină și Farmacie "Grigore T. Popa", Romania.

(2) Stalin, India.

(3) Adeyeye, Samuel Ayofemi Olalekan, Ton Duc Thang University, Vietnam.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/56381>

Received 24 February 2020

Accepted 29 April 2020

Published 09 May 2020

Review Article

ABSTRACT

The gut enzymes are released in response to intake of meal, those are GLP-I (glucagon link peptide-I) & GIP (glucose-dependent insulin tropic polypeptide) along with DPP-4(Dipeptidyl peptidase-4). GLP-I has vital role in control of glucose levels and it may also has capacity reduce body weight and it can manage some micro & macro-vascular complications. Unfortunately it has very shorter half-life 1-2 min, and eventually it was degraded by DPP-4 enzyme. Therefore GLP-I has ineffective to perform its tasks. To overcome this incidence essential to inhibit DPP-4 enzyme is benefited in diabetics and in non diabetics suffering with micro, macro vascular complications. Ubiquitous Dipeptidyl peptidase (DPP) - 4 has pleiotropic effects because it is widely distributed other than intestine. DPP-4 enzyme inhibition has a promising effect on glycemic control. DPP-4

*Corresponding author: E-mail: vanithak9@rediffmail.com

inhibition is also involved in the improvement of non-glycemic effects as directly or indirectly the DPP-4 enzyme is linked with some pathological conditions of particular organs, such as DPP-4 is linked with the intestinal secretion of triglycerides, and DPP-4 is expressed in the glomerulus in uncontrolled diabetics which in turn leads to nephritis. 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- γ . All these anti-inflammatory agents are inhibited by the DPP-4 enzyme which can lead to pathogenesis of cardiovascular diseases and provokes atherosclerosis & psoriasis. Serum sodium and brain natriuretic peptide (BNP) levels are also regulated by inhibition of the DPP-4 enzyme and which can produce vascular protection & regulates blood pressure. Tenzeligliptin is a recently developed oral DPP-4 inhibitor indicated for the management of T2DM in adults along with diet and exercise. Tenzeligliptin is recently available in India and is also available in combination with other oral hypoglycemic agents at affordable prices. This review is aimed at exploring the status of teneligliptin with emphasis on its glycemic effects and non-glycemic clinical benefits associated with increasing GLP-1 & GIP.

Keywords: *Tenzeligliptin; dipeptidyl peptidase-4; pleiotropic effects.*

1. INTRODUCTION

Inhibition of DPP-4 enzyme is essential and GLP-1 should be reached to systemic circulation and distribute to various organs from small intestine. Through this mechanism could be succeeded by a novel DPP-4 inhibitor teneligliptin. A PubMed search was made on Tenzeligliptin using MeSH word "TNG", "glycemic effects", "non-glycemic effects" and DPP-4 inhibitors. All the clinical trials on Tenzeligliptin published till the date was retrieved. Dipeptidyl peptidase – 4 (DPP-4) is a widely distributed enzyme and highly expressed transmembrane protein that removes NH₂ – terminal peptide from various substrate hormones, Chemokines, neuropeptides and growth factors. The two known substrates of DPP-4 are incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). These incretins are secreted by entero-endocrine cells in response to the ingestion of meal and which produce 60% - 70% of postprandial insulin secretion. Incretin hormones (GLP-1 & GIP) have a very shorter half-life (1 to 2 minutes) in plasma and are rapidly degraded by ubiquitous enzyme DPP-4 [1]. Therefore incretins are unable to produce insulin and hence DPP-4 inhibitors are developed to increase the GLP-1 levels in plasma and improve glycemic control. Tenzeligliptin (Tenelia) is chemically 3-[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl]carbonyl]. Tenzeligliptin (Tenelia) is chemically thiazolidine, which was developed by Mitsubishi Tanabe Pharma (Osaka, Japan) and was approved by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan on 10th September

2012. Tenzeligliptin and other oral hypoglycemic agent combinations came into the market in Japan, Argentina, and India in 2017. DPP-4 enzyme is structurally diverse among different gliptins based on the binding (Fig. 1) sites of the DPP-4 enzyme. Vildagliptin and saxagliptin are Class-1, Alogliptin and Linagliptin are Class-2 and Sitagliptin and Tenzeligliptin are Class-3 DPP-4 inhibitors. Structurally Tenzeligliptin and sitagliptin are Class-3 DPP-4 inhibitors with triazole piperidine and piperidine moiety having high affinity and inhibitory activity on DPP-4 enzyme (Fig. 2). The X-Ray co-crystallographic studies show that Tenzeligliptin has 5 fold higher activity than sitagliptin, it tightly binds to S2 extensive subsite of DPP-4 enzyme (Fig. 1), because it has an anchor (Fig. 3) like structure (J-shaped) and it consists of consecutive cyclic rings which can lead to small loss of energy during binding with hydrogen bonding. Tenzeligliptin has higher lipophilicity and greater distribution to the kidney than the other DPP-4 inhibitors, sitagliptin, alogliptin, saxagliptin, anagliptin, and vildagliptin. The reduction of HbA1C is 0.8%-0.9% following 12 weeks of therapy with Tenzeligliptin [2].

1.1 Pharmacodynamics

Tenzeligliptin suppresses the enzymatic activity of DPP-4, leading to an increase in the incretin levels (GLP-1 and GIP), which subsequently inhibit glucagon release and glucose production in the liver (Fig. 5) and increase insulin secretion and glucose uptake in skeletal muscle. Consequently, it leads to a decrease in blood glucose level [3] and can improve beta cell function and proliferation [4].

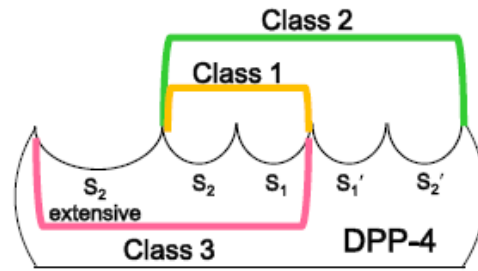


Fig. 1. Gliptins binding sites at DPP-4 Substrate [2]

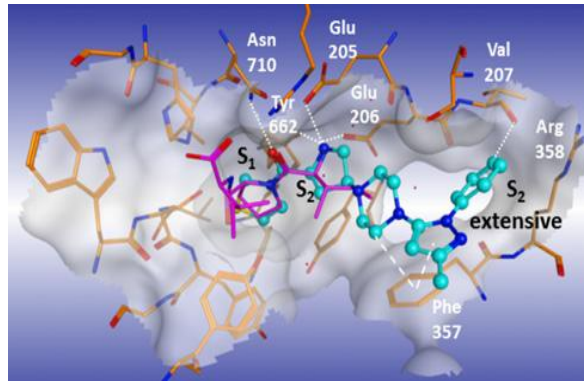


Fig. 2. X-Ray Co-Crystal structure of Teneligliptin [2]

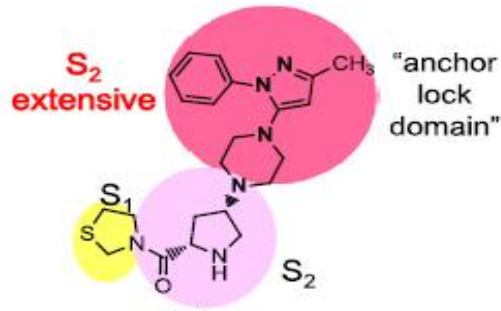


Fig. 3. Structure of Teneligliptin [2]

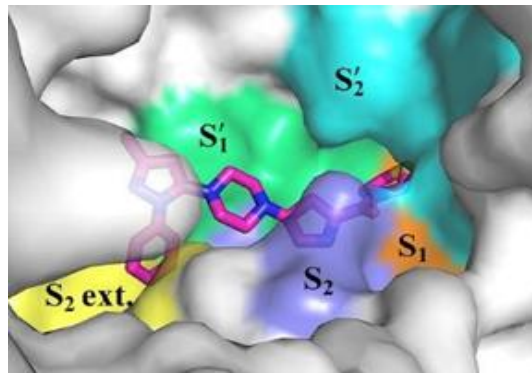


Fig. 4. Extensive sites of DPP-4 substrate [2]

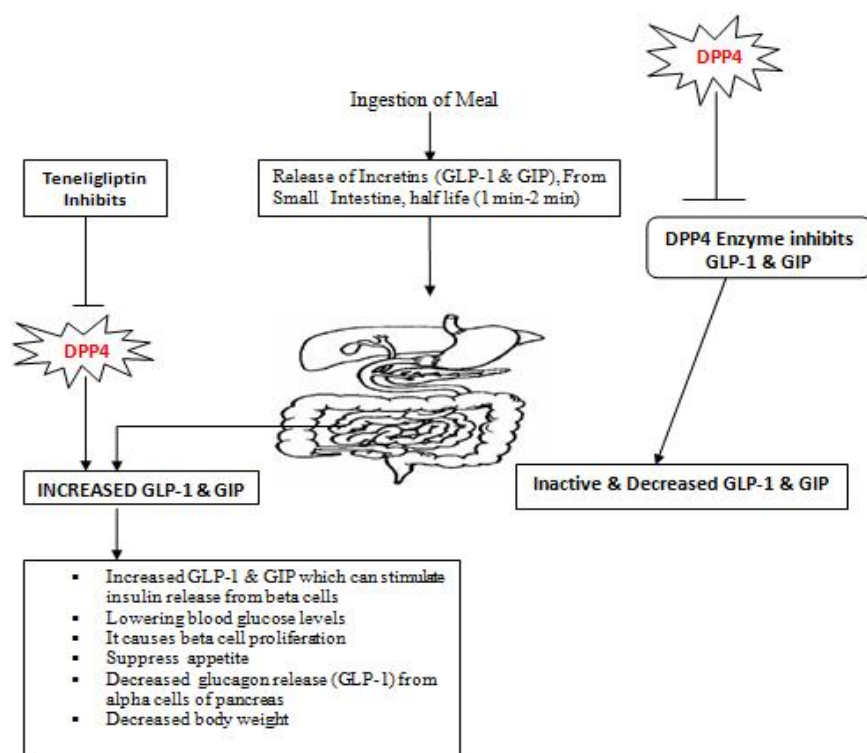


Fig. 5. Mechanism of action of Teneeligliptin

1.2 Pharmacokinetics

Orally administered teneligliptin's absorption takes place in the gastrointestinal tract and distributed throughout the body. Oral administration of 10 mg or 20 mg of teneligliptin once daily for 4 weeks shows the maximum concentration (C_{max}) in one hour in both groups and the mean t_{1/2} was found to be 20.8 and 18.9 hours and the IC₅₀ value of 0.37 mol/Lt. [5]. The maximum percentage of the inhibition in plasma DPP-4 activity was achieved within 2 hours after administration and was 81.3% and 89.7% in the 10 and 20 mg teneligliptin groups, respectively. About 34.4% of teneligliptin is excreted unchanged via kidney and the remaining 65.5% is metabolized and eliminated via renal and hepatic excretion. CYP3A4, a cytochrome P450 isozyme and flavin-containing monooxygenases (FMO1 and FMO3) play a major role in the metabolism of teneligliptin. In vitro, teneligliptin exhibits a weak inhibitory effect for CYP2D6, CYP3A4, and FMO; however, it demonstrates no inhibitory effect for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1. Besides, teneligliptin does not induce the expression of CYP1A2 or CYP3A4. Therefore it does not require dosage adjustment in renal

failures, but it should be cautiously administered in subjects with hepatic impairment. The major metabolite of teneligliptin is thiazolidine-1-oxide [6,7]. The plasma concentrations of teneligliptin after the administration at dosages of 10 or 20 mg once daily for 4 weeks, in two groups revealed a median time to maximum concentration (C_{max}) of 1.0 hour in both groups and a mean t_{1/2} of 20.8 and 18.9 hours, respectively. The maximum percentage of inhibition of plasma DPP-4 activity was achieved within 2 hours after administration and was 81.3% and 89.7% in the 10 and 20 mg teneligliptin groups, respectively. The active GLP-1 concentration in the plasma in the 10 mg and 20 mg teneligliptin groups was higher than that in the placebo group throughout the day, even at 24 hours after administration. Nabeno et al. [2] demonstrated that the percentage inhibition of plasma DPP-4 activity 24 h after administration of 20 and 40 mg dose of teneligliptin was varying between 53.9-66.9% and 59.8% respectively. Besides, only 80 mg doses of teneligliptin exhibited >80% (72-85%) plasma DPP-4 inhibition at 24h after administration. The AUC_{0-2h} values for the active GLP-1 concentration after breakfast, lunch, and dinner were 8.0, 8.4, and 7.8 pmol

h/L, respectively, in the 10 mg teneligliptin group, and 8.3, 7.9, and 8.6 pmol· h/L, respectively, in the 20 mg teneligliptin group. Thus, the increase in AUC_{0–2h} for the active GLP-1 concentration after dinner was slightly greater in the 20 mg teneligliptin group than in the 10 mg teneligliptin group. Differences in the AUC_{0–2h} for the active GLP-1 concentration between both the teneligliptin treated groups and the placebo group were statistically significant [6]. The main differences between the eight gliptins include their potency, target selectivity, oral bioavailability, elimination half-life, binding to plasma proteins, metabolic pathways, the formation of the active metabolite(s), excretion routes, dosage adjustment for renal and liver insufficiency, and potential drug-drug interactions [3].

1.3 Plasma DPP-4 Activity of Gliptins

A study stated that the treatment with sitagliptin 200 mg twice daily had led to a mean inhibition on day 28 from baseline (predose day 1) in plasma DPP-4 of approximately 90.0% throughout the 24-hour sampling period. The mean difference in the weighted average inhibition of plasma DPP-4 activity over 24 hours between sitagliptin and placebo was 90.0% (P < .001) with the 95% CI of (81.5%, 99.3%) [8]. The study also revealed that treatment with sitagliptin led to an approximately 2- to 3-fold increase in active GLP-1 levels following an OGTT at 2 hours post-dose on day 28 compared to placebo and compared to pretreatment baseline levels relative to placebo. The geometric mean ratio (GMR; sitagliptin/placebo) of the post-OGTT time-weighted average active GLP-1 level on day 28 was 2.74 (P < .001) with the 95% CI of (1.87, 4.00). There was also significant fold increase on day 28 over baseline to post-OGTT time-weighted average active GLP-1 levels in sitagliptin group relative to placebo, with the GMR of sitagliptin/placebo and corresponding 95% CI estimated to be 2.18 and (1.54, 3.10); (P < .001) [8].

2. GLYCEMIC EFFECTS OF TENELIGLIPTIN

2.1 Effects on Insulin

The area under the curve (AUC)_{0–2h} values for the postprandial insulin levels significantly increased after dinner in the teneligliptin 10 mg group (P < 0.05), in comparison with the corresponding values in the placebo group, but not at other times in either group. The relative

insulin concentrations were higher in the teneligliptin-treated groups because of the decreased blood glucose concentrations of the patients in these groups [9].

2.2 Effects on Glucagon

The postprandial glucagon levels significantly decreased after breakfast and lunch as well as after dinner in the 20 mg teneligliptin group compared to the corresponding values in the placebo group. Besides, there were no significant differences in the insulin or glucagon concentrations between the two teneligliptin-dosage groups, although glucagon secretion was lower with teneligliptin treatment at 20 mg, particularly after dinner. Thus, the study concluded that teneligliptin effectively suppressed postprandial glucagon secretion after meals and improved postprandial hyperglycemia [9].

2.3 Effect on Glycated Hemoglobin (HbA1C) Levels

A recent systematic review and meta-analysis from xiaouan Li et al., (2018) on different randomized control trials of teneligliptin revealed that effects of teneligliptin vs. placebo on the HbA1c change from baseline and had shown a significant reduction of HbA1c (weighted mean difference (WMD) -0.82%, 95% CI [-0.91 to -0.72], p < 0.00001) as monotherapy (WMD -0.86%, 95% CI [-0.95 to -0.76], p < 0.00001), or add-on treatment (WMD -0.79%, 95% CI [-0.93 to -0.66], p < 0.00001) when compared to placebo [9].

2.4 Effect on Fasting and Postprandial Blood Glucose (FBG & PPG) Levels

The study by xiaouan Li et al., also identified that Teneligliptin decreased the fasting blood glucose (FBG) level (vs. placebo, WMD-18.32%, 95% CI [-21.05 to -15.60] and p. value < 0.00001), and also a significant reduction of the 2 h postprandial plasma glucose (2 h PPG) (WMD -46.94%, 95% CI [-51.58 to -42.30], p < 0.00001) and area under the glucose plasma concentration-time curve from 0 to 2 h (AUC_{0–2h}) for PPG (WMD -71.50%, 95% CI [-78.09 to -64.91], p < 0.00001) compared with placebo [9,10].

2.5 Effect on (HOMA-β) and HOMA-IR

Homeostasis model assessment of β cell function (HOMA-β) was increased with 9.31

(WMD, 95% CI [7.78–10.85], $p < 0.00001$) with teneligliptin and there was no significant difference in overall adverse effects between teneligliptin and placebo group (0.96 risk ratio (RR), 95% CI [0.87, 1.06], $p = 0.06$). The risks of hypoglycemia was not significantly different between teneligliptin & placebo (1.16 RR, 95% CI [0.59, 2.26], $p = 0.66$) & only combined treatment showed statistical significance, with a decrease in HOMA-IR by -0.25 (WMD, 95% CI $[-0.47$ to $-0.03]$, $p = 0.03$) [7].

3. NON-GLYCEMIC EFFECTS OF TENELIGLIPTIN

3.1 Pleiotropic Effects

DPP-4 is a ubiquitous enzyme, which has widely distributed in the body and it contributes a pleiotropic effect. Therefore, there is a need for drugs that are effective not only for controlling, glycemia but also for improving CVD outcomes independently of glycemic control. Gross evidence suggests that the modulation of incretin signaling by glucagon-like peptide-1 (GLP-1) agonists is beneficial in both glycemic control, as well as CV protection. In this regard, dipeptidyl peptidase-4 (DPP-4) inhibitors (DPP-4i), which have been developed specifically as incretin-based oral antihyperglycemic therapies, are

now emerging as novel agents that have the potential to reduce the progression to CVD and CKD. DPP-4i exhibit multiple protective effects such as neuroprotection, nephroprotection, vasculoprotection, hepatoprotection, reduce overweight/obesity, which collectively contributes to improvement in vascular function which can reduce the risk for development of the vascular disease, heart failure (HF), and CKD (Fig. 6). The beneficial effects of these drugs, beyond glycemic control, occur by both GLP-1-dependent and -independent mechanisms [2-4].

3.2 Effect on Lipid Levels

Animal studies demonstrated that DPP-4i (sitagliptin and linagliptin) or GLP-1R agonism (exendin-4) significantly reduced intestinal secretion of Triglycerides (TG), cholesterol, and apolipoprotein B-48, suggesting that GLP-1 might directly regulate lipoprotein assembly and secretion in enterocytes.[11,12]. A recent study showed that the DPP-4i alogliptin ameliorates postprandial elevation of TG-rich lipoproteins (lipemia) and endothelial dysfunction in nondiabetic humans following an oral fat load [13], suggesting a potential antiatherogenic role for DPP-4i in humans. Recent clinical studies have reported that DPP-4i such as vildagliptin [14] and sitagliptin [15] improve postprandial

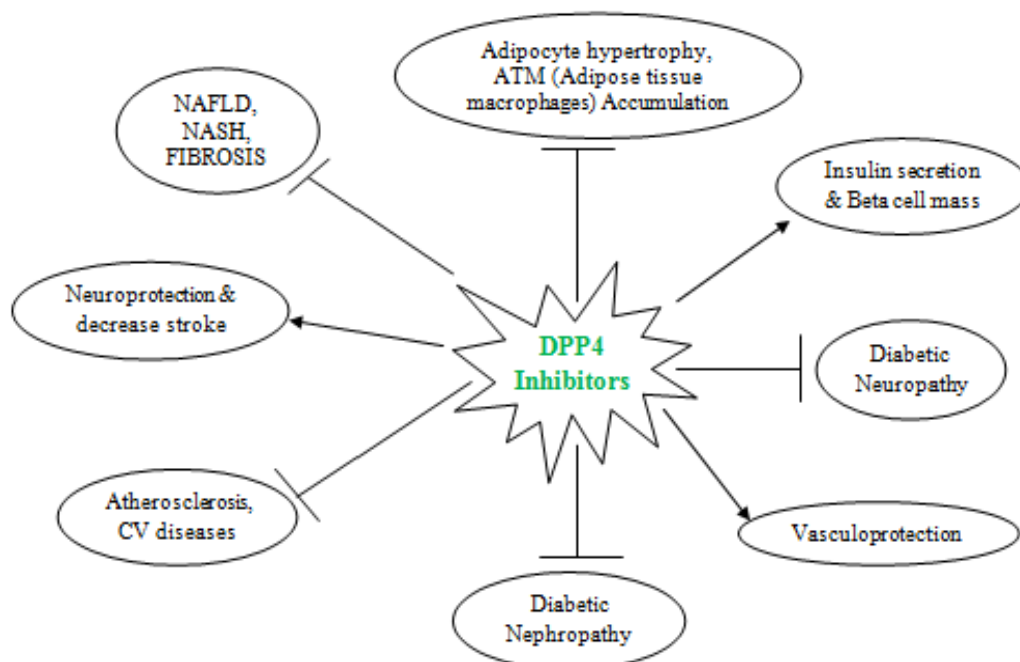


Fig. 6. Non glycemic effect of Teneligliptin

atherogenic TG-rich lipoprotein levels in patients with T2DM. Previous studies have shown that DPP-4i such as vildagliptin and sitagliptin decreased postprandial TG, remnant lipoprotein cholesterol and apolipoprotein B-48 levels after a fat loading test in patients with T2DM and non-obese subjects without diabetes [14]. However, the effects of other DPP-4i on postprandial lipid elevation-induced endothelial dysfunction have not been fully evaluated. Kusunoki M, et al. investigated the effect of 14-weeks treatment with teneligliptin (20 mg/day) on the homeostasis model assessment ratio (HOMA-R), an indicator of insulin resistance and serum lipid profile in 9 patients with type 2 diabetes. DPP4i produced a significant decrease of blood glucose, HbA1C & improved HOMA-R ($p=0.008$, $p=0.038$ and $p=0.039$). Furthermore, the patients showed elevation of the serum HDL-cholesterol level ($p=0.032$) and a tendency towards reduction of the serum triglyceride level. Teneligliptin not only improved glycemic effects but also improved serum lipid profile in Japanese type 2 diabetes patients [16]. Vyshnavi V, et al also conducted a comparative study of Teneligliptin and Atorvastatin on Lipid Profile in Patients with Type 2 Diabetes Mellitus and stated that Teneligliptin 20 mg and Atorvastatin 20 mg have proved to have similar efficacy on the lipid profiles. Hence, they concluded that Teneligliptin is an efficacious drug for T2 DM patients in the management of glycemic control and lowering lipid profiles [17].

3.3 Renoprotective Activity

In humans, histochemical analysis of DPP-4 expression and enzyme activity was observed primarily in glomerulus under pathological conditions (not in the healthy kidney). Tumor Necrosis Factor (TNF)- α is also responsible for the expression of DPP-4 in individuals with glomerular endothelial cells exposed to high glucose concentrations (hyperglycemia) [18,19] Gliptins involve alleviation of renal oxidative stress and inflammation by blocking advanced glycation end product (AGE) signaling pathways. Per-Henric Grop, et al. stated that the blocked AGE is responsible for the decrease of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-dependent reactive oxygen species generation. A recent pooled analysis of randomized double-blind, placebo-controlled clinical trials had demonstrated that linagliptin administered group showed enhanced RAAS inhibition, thereby significantly reduced albuminuria by 28% (95% CI -47 to -2; $p < 0.05$) after 24 weeks of treatment in T2DM patients

with hyper albuminuria, along with there is no risk of development or progression of microalbuminuria in follow-up period 2.1 years of trial with saxagliptin in the patients of T2DM with TIMI (thrombolysis in myocardial infarction) of the phase-4 clinical trial [20,21].

3.4 Effect on Heart

Kishimoto et al. evaluated the cardiovascular effects of Teneligliptin especially the QT/QTc evaluation. There was no QT prolongation with less than 40 mg daily dose of teneligliptin treated subjects but a mild QTC prolongation was observed with suprathreshold doses of more than 40 mg per day teneligliptin treated patients. Teneligliptin also improved the left ventricular function, particularly diastolic and endothelial functions, as well as an increase in serum adiponectin levels [1,22].

3.5 Effect on Body Weight, Adipoprotection, and Anti-Obesity Activity

Studies on the effect of DPP-4 inhibitors on body weight demonstrated variable results; however, these results were generally considered to be neutral [23,24]. The mean body weight change of the diabetic patients at week 52 (mean \pm SD) was $+0.18 \pm 2.14$ kg ($P = 0.3254$), which indicated that the effect of teneligliptin on body weight was neutral. However, no studies were conducted on obese and overweight subjects without diabetes and it needs to be addressed [25]. DPP4 is a novel adipokine that may impair insulin sensitivity in an autocrine and paracrine fashion. Furthermore, DPP4 release strongly correlates with adipocyte size, potentially representing an important source of DPP4 in obesity. Therefore DPP4 may be involved in linking adipose tissue and metabolic syndrome [26]. The elevated levels of DPP-4 reported in obesity/T2DM may be related to the consequences of insulin resistance (e.g., elevated insulin and/or glucose), hyperglycemia, and adipose tissue inflammation (elevated tumor necrosis factor- α), which promote DPP-4 shedding from adipose tissue. Insulin resistance is associated with increased expression and release of DPP-4 [27].

3.6 Anti-Inflammatory Effect

Feuerer M and Flegal KM et al. demonstrated the anti-inflammatory effects of DPP4 inhibition and the integral role of inflammation in the pathogenesis of the cardiovascular disease [28].

Molecules and cells of both innate and adaptive immune systems are involved in the development not only of atherosclerosis but also risk factors that facilitate atherosclerosis such as hypertension [29]. For example, in the development of atherosclerosis, TLRs and scavenger receptors on macrophages play a critical role in foam cell and atherosclerotic plaque formation. In addition to innate immunity, adaptive immune cells such as Th1 and Th17 cells have also been proposed to be implicated in the pathogenesis of atherosclerosis [30]. Therefore, anti-inflammatory therapy that targets either one or both of these pathways has been considered as promising therapeutic strategies for the prevention and treatment of cardiovascular disease [31,32]. Suppression of enzymatic activity of DPP4 results in reduced production of cytokines including interleukin (IL)-2, IL-10, IL-12, and interferon-gamma (IFN-gamma) by peripheral blood mononuclear cells and T cells. TGF-beta1, an immunosuppressive cytokine, was shown to be up-regulated by DPP4 inhibition [33,34]. DPP4 also exerts effects on numerous chemokines via enzymatic degradation. Cleavage of chemokines such as CXCL11, SDF-1, and eotaxin by DPP4 reduces the ability of these proteins to serve as chemoattractants to T cells and monocytes. N-terminal cleavage of CXCL11 has an 8-fold reduced potential to bind to its receptor, CXCR3 and competes with intact CXCL11 in preventing T-cell migration [35,36].

3.7 Dpp-4 and Hypertension

Approximately 70% of patients with diabetes have high BP, meaning they are twice as likely to have hypertension compared with individuals without diabetes [37]. BP responses to DPP-4i therapy have been reported to be either neutral with saxagliptin and linagliptin [38] or modestly reduced with sitagliptin [39-41]. Most relevant clinical trials were of a short and medium-term; results of long-term trials are not yet available, so it cannot be concluded definitively that DPP-4i therapy is BP neutral in hypertensive diabetic humans.

3.8 Natriuretic & Diuretic Effects of Teneligliptin

There is a significant association between diuretic effect & DPP-4 inhibition. GLP-1R & DPP-4 are expressed in the renal proximal tubular brush border, where they regulate Na⁺ reabsorption [42]. DPP-4 exists in physical

complexes with Na⁺-H⁺ exchanger isoform NHE3 in the brush border membranes of renal proximal tubule cells. The NHE3-DPP-4 complex exists predominantly in the microvilli of renal tubules [43]. DPP-4 inhibition reduces NHE3 activity and consequently induces natriuresis [44]. In addition to this, GLP-1 activation induces diuresis. DPP-4 inhibitors are antidiabetic agents that have diuretic & natriuretic effects, which might contribute to reducing blood pressure. A major proportion of diabetic patients are often diagnosed with hypertension. Furthermore, DPP-4 inhibitors have recently been shown to enhance nitric oxide release in hypertensive or diabetic models [45-47]. Thus, the action of DPP-4 inhibitors might be favorable for diabetic patients with hypertension. DPP-4 converts intact B-type natriuretic peptide [BNP (1 - 32)] into its des-SerPro form [BNP (3 - 32)] [48].

3.9 DPP-4 and Vasculoprotection

DPP-4 specifically cleaves dipeptides from incretin as well as some non-incretin peptide substrates containing a penultimate proline or alanine residue at the NH₂-terminus [49]. Importantly, some of these peptides, including stromal-cell derived factor-1α (SDF-1α), brain natriuretic peptide (BNP), neuropeptide Y (NPY), and peptide YY (PYY), have direct or indirect effects in the vasculature. The effects of these substrates add considerable complexity to the potential mechanisms by which DPP-4i mediate effects on vascular/endothelial function. However, most of these peptides mediate a wide range of beneficial pleiotropic effects in the vasculature that are not imparted by GLP-1 agonists alone, although some DPP-4 substrates, such as NPY, exert vasoconstrictor effects in the setting of hypertension [50]. Since DPP-4 activity is increased in obesity and T2DM, inhibition of DPP-4 may not only increase GLP-1 but also enhance the activities of several beneficial substrates.

3.10 DPP-4 and Hyperuricemia

Chihiro Moriya and Hiroaki Satoh demonstrated the effect of Teneligliptin on decreasing uric acid levels by reducing xanthine dehydrogenase expression in white adipose tissue of male Wistar rats. A central finding of their study is that teneligliptin, one of the DPP-4 inhibitors, reduced plasma uric acid levels in high-fat diet (HFD)-fed rats by downregulation of xanthine dehydrogenase (Xdh) expression in adipose tissue. This observation is strongly associated

with the up-regulation of DPP-4 expression and release in adipose tissue of obese subjects; hence teneligliptin decreases DPP-4-induced Xdh expression in 3T3-L1 adipocytes. DPP-4 stimulates Xdh expression, and then Xdh expression promotes the production of uric acid [51]. Elevation of serum uric acid levels is one of the culprit for the development of gout, renal dysfunction, hypertension, dyslipidemia, diabetes, and obesity. Till now there are no data on humans, therefore this preliminary evidence needs to be explored in humans with hyperuricemia.

3.11 DPP-4 linked to Psoriasis

The first report of anti-psoriatic effects of DPP-4 inhibitors was published in 2012 and showed remission of psoriatic lesions following sitagliptin therapy for 3 months [52]. Since then, several other reports have similarly described improvement in psoriasis after treatment with sitagliptin or teneligliptin [53,54]. A large-scale population-based retrospective study found that DPP-4 inhibitor therapy led to a reduced incidence of autoimmune disorders including psoriasis [55]. DPP-4 is a ubiquitously expressed transmembrane glycoprotein, also known as CD26, which has a multitude of functions besides GLP-1 degradation. DPP-4 is expressed in keratinocytes [56,57]. DPP-4 expression and activity are upregulated in psoriatic lesions compared to uninvolved skin and healthy volunteer skin. It was additionally shown that DPP-4 expression is elevated before the development of an overt psoriatic lesion and concentrated primarily towards the basal layers of a psoriatic lesion, suggesting its involvement in the pathogenesis of a psoriatic lesion [58]. DPP-4 inhibitor treatment decreased keratinocyte proliferation *in vitro* and partially restored keratinocyte differentiation *in vivo* [59]. Thus, DPP-4 inhibitors may alleviate psoriasis by inhibiting keratinocyte proliferation.

3.12 Safety and Tolerability

Teneligliptin as monotherapy or add-on therapy to other agents such as glimepiride, metformin, and pioglitazone, was generally well tolerated in patients with T2DM participating in clinical trials. In monotherapy study, adverse drug reactions (ADRs) and AEs occurred in $\geq 5\%$ of patients in any group were nasopharyngitis, a positive urine ketone body, urine glucose, and urinary protein [60]. The incidence of ADRs was not significantly different among the four groups although the

adverse rate tended to be higher in the teneligliptin 40 mg group. All ADRs were categorized as mild in intensity by the investigator. In Phase 3 add-on to glimepiride study, the incidence rates of serious AEs were similar in both groups at 12 weeks [61]. In Phase 3 add-on to pioglitazone, specific AEs occurred in $>5\%$ & included nasopharyngitis and peripheral edema [62]. Hypoglycemia was reported in two patients (1.9%) in the teneligliptin group at week twelve. In the pooled 52 weeks of safety analysis, treatment-related hypoglycemia occurred with an overall incidence of 3.4% in teneligliptin recipients, with all episodes of mild intensity. The incidence of hypoglycemia was numerically higher in the teneligliptin plus sulphonylurea (10.1%) and teneligliptin plus meglitinide (5.0%) groups than in the teneligliptin monotherapy (2.5%), teneligliptin plus biguanide (1.1%), or teneligliptin plus α -glucosidase inhibitor (1.3%) groups [63]. Thyroid cancer was observed in one patient in the teneligliptin monotherapy group [64]. Xiao Wu Chen et al, conducted a review on gliptins and stated that the safety profile of teneligliptin was similar to those of other available DPP-4 inhibitors [1]. The incidence of adverse drug reactions was $\sim 10\%$ in all clinical studies of patients ($n = 1183$) with T2DM. These mainly included abnormalities in clinical examination values such as levels of liver and kidney function, blood cell count, creatinine phosphokinase, and electrolytes. The main adverse effects included hypoglycaemia (35 patients: 3.0%) and constipation (11 patients: 0.9%). No adverse effects related to QT prolongation were detected with 40 mg/day of teneligliptin, which is the maximal dosage used in clinical practice. The pharmaceutical company warned of serious adverse effects such as hypoglycemia, which could occur when other antidiabetic drugs were co-administered. Also, they cautioned that intestinal obstruction could occur with an unknown frequency. GLP-1 is involved in gastrointestinal motility [65,66] and the patients with intestinal obstruction had a past medical history of intestinal obstruction or abdominal surgery. Therefore, it should be cautious when T2DM patients with a history of these conditions are treated with DPP-4 inhibitors. Continued evaluation of adverse effects and post-market monitoring is warranted to define the benefit/risk ratio.

4. CONCLUSION

The novel teneligliptin offers fruitful advantages along with controlling glycemic and non-glycemic

effects, because of inhibition of ubiquitous DPP-4 enzyme. Tenzeligliptin structure has a unique "J-shaped anchor-lock domain" which provides potent and long duration of action and hence it is most efficacious than other gliptins. Incretins (GLP-I & GIP) are released in response to a meal, which is responsible for reducing blood glucose levels and reduces insulin resistance. GLP-I & GIP have a very shorter half-life (1-2 min) in plasma, are rapidly degraded by ubiquitous enzyme DPP-4. Therefore incretins are unable to produce insulin and hence teneligliptin inhibits 78-90% of DPP-4 enzyme at the IC50 value 0.37 nmol/Lt to increase the GLP-I levels in plasma & improve glycemic control. The kinetic properties of teneligliptin have their maximum serum concentration (Cmax) of one hour, t_{1/2} nearly 19 hours & 65.5% of teneligliptin is metabolized & eliminated via renal and hepatic clearance. Therefore it does not require dosage adjustment. Teneligliptin has recently emerged as a new class of antidiabetic agents that shows the favorable result in improving postprandial insulin levels, reduction of postprandial glucagon levels & improvement of glycated hemoglobin levels (HbA1C) & decrease of fasting plasma glucose levels with minimal risk of hypoglycemia & weight gain. Apart from glycemic control, an improvement of non-glycemic effects is also observed with inhibition of the ubiquitous DPP-4 enzyme. Therefore, patients with T2DM may have some other co-morbidities such as hypertension, dyslipidemia, and inflammatory disorders. All these comorbidities are well controlled by inhibiting the ubiquitous enzyme DPP-4 with teneligliptin.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kishimoto M. Teneligliptin: A DPP-4 inhibitor for the treatment of type 2 diabetes. *Diabetes Metab Syndr Obes.* 2013;6:187-95.
2. Nabeno M, Akahoshi F, Kishida H, Miyaguchi I, Tanaka Y, Ishii S, Kadowaki T. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site. *Biochem Biophys Res Commun.* 2013; 434(2):191-6.
3. Xiao-Wu Chen, Zhi-Xu He, Zhi-Wei Zhou, Tianxin Yang, Xueji Zhang, Yin-Xue Yang, Wei Duan and Shu-Feng Zhou. Clinical pharmacology of dipeptidyl peptidase 4 inhibitors indicated for the treatment of type 2 diabetes mellitus. *Clinical and Experimental Pharmacology and Physiology.* 2015;42:999-1024.
4. Maladkar M, Sankar S, Kamat K. Teneligliptin: heralding change in type 2 diabetes. *Journal of Diabetes Mellitus.* 2016;6:113-31.
5. Röhrborn D, Wronkowitz N, Eckel J. DPP4 in Diabetes. *Frontiers in Immunology.* 2015;6:1-20.
6. Yoshinobu Nakamarua B, Chie Emotoa, Makiko Shimizua, Hiroshi Yamazakia. Human pharmacokinetic profiling of the dipeptidyl peptidase-IV inhibitor teneligliptin using physiologically based pharmacokinetic modeling. *Biopharm. Drug Dispos.* 2015;36:148– 162.
7. Eto T, Inoue S, Kadowaki T. Effects of once daily teneligliptin on 24h blood glucose control & safety in Japanese patients with Type-2 diabetes mellitus - a 4-week randomised double blind placebo controlled trial. *J Diabetes Obes Metab.* 2012;29:999.
8. Gary A. Herman, Arthur Bergman, Fang Liu, et al. Pharmacokinetics and pharmacodynamic effects of the oral DPP-4 inhibitor sitagliptin in middle-aged obese subjects. *J Clin Pharmacol.* 2006;46:876-86.
9. Xiaoxuan Li, Xuefei Huang, Chongfei Bai, Dalian Qin, Shousong Cao, Qibing Mei, Yun Ye, Jianming Wu. Efficacy and safety of teneligliptin in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *Front. Pharmacol.* 2018;9:449.
10. Annayya R. Aroor, James R. Sowers, Guanghong Jia, Vincent G. DeMarco. Pleiotropic effects of the dipeptidylpeptidase-4 inhibitors on the cardiovascular system. *Am J Physiol Heart Circ Physiol.* 2014;307:H477–H492.
11. Hsieh J, Longuet C, Baker CL, Qin B, Federico LM, Drucker DJ, Adeli K. The glucagon- like peptide 1 receptor is essential for postprandial lipoprotein

- synthesis and secretion in hamsters and mice. *Diabetologia*. 2010;53:552–561.
12. Masuda D, Koybayashi T, Okada T, Nakaoka H, Kawase R, Nakatani K, Ohama T, Nishida M, Matsuyama A, Komuro I, Yamashita S. Treatment with linagliptin can attenuate postprandial hyperlipidemia (abstract). In: Proceedings of the 73rd Annual Scientific Sessions of the American Diabetes Association. Chicago, IL. 2013;A77.
 13. Noda Y, Miyoshi T, Oe H, Ohno Y, Nakamura K, Toh N, Kohno K, Morita H, Kusano K, Ito H. Alogliptin ameliorates postprandial lipemia and postprandial endothelial dysfunction in non-diabetic subjects: A preliminary report. *Cardiovasc Diabetol*. 2013;12:8.
 14. Matikainen N, Manttari S, Schweizer A, Ulvestad A, Mills D, Dunning BE, Foley JE, Taskinen MR. Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes. *Diabetologia*. 2006;49:2049–57.
 15. Tremblay AJ, Lamarche B, Deacon CF, Weisnagel SJ, Couture P. Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes. *Diabetes Obes Metab*. 2011; 13:366–73.
 16. Kusunoki, M, Sato D, Nakamura T, Oshida Y, Tsutsui H, Natsume Y, Miyata T. DPP-4 inhibitor teneligliptin improves insulin resistance and serum lipid profile in Japanese patients with type 2 diabetes. *Drug Research*. 2014;65(10):532–34.
 17. Vyshnavi V. Supriya, Bandaru Siva Subrahmanyam T, Eggadi Venkateshwarlu, Bandaru Sheshagiri Sharvana Bhava. Comparison of teneligliptin and atorvastatin on lipid profile in patients with type 2 diabetes mellitus. *Curr Res Diabetes Obes J*. 2018;8(1). [CRDOJ.MS.ID.555735]
 18. Elleder M, Stejskal J. Induction of dipeptidyl peptidase IV activity in human renal glomeruli—A histochemical study. *Acta Histochem*. 1985;77:75–78.
 19. Stefanovic V, Ardaillou N, Vlahovic P, Placier S, Ronco P, Ardaillou R. Interferon-gamma induces dipeptidylpeptidase IV expression in human glomerular epithelial cells. *Immunology*. 1993;80(3):465–470.
 20. Per-Henric. Groop ME, Cooper V. Perkovic et al. Dipeptidyl peptidase-4 inhibition with linagliptin and effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: Rationale and design of the MARLINAT2D trial. *Diabetes and Vascular Disease Research*. 2015;12(6):455–462.
 21. Per-Henrik Groop, Mark E. Cooper, Vlado Perkovic, Angela Emser, Hans- Juergen Woerle, Maximilian von Eynatten, Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. *Diabetes Care*. 2013;36(11): 3460-8.
 22. Hashikata T, Yamaoka-Tojo M, Kakizaki R, Nemoto T, Fujiyoshi K, Namba S, Kitasato L, Hashimoto T, Kameda R, Maekawa E, Shimohama T, Tojo T, Ako J. Teneligliptin improves left ventricular diastolic function and endothelial function in patients with diabetes. *Heart Vessels*; 2015.
 23. Dicker D. DPP-4 inhibitors. Impact on glycemic control and cardiovascular risk factors. *Diabetes Care*. 2011;34(Suppl 2): S276–S278.
 24. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: Systematic review and meta-analysis. *JAMA*. 2007;298:194–206.
 25. Scheen AJ. A review of gliptins in 2011. *Expert Opin Pharmacother*. 2012;13:81–99.
 26. Daniela Lamers, Susanne Famulla, Nina Wronkowitz, Sonja Hartwig, et al. Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome. *Diabetes*. 2011;60(7):1917–25.
 27. Zhong J, Rao X, Rajagopalan S. An emerging role of dipeptidyl peptidase 4 (DPP4) beyond glucose control: Potential implications in cardiovascular disease. *Atherosclerosis*. 2013;226(2):305–314.
 28. Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, Lee J, Goldfine AB, Benoist C, Shoelson S, Mathis D. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat Med*. 2009;15: 930–39.
 29. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA*. 2012;307:491–7.
 30. Freemantle N. Commentary: What can we learn from the continuing regulatory focus

- on the thiazolidinediones? *BMJ*. 2010; 341:c4812.
31. Friedrich C, Emser A, Woerle HJ, Graefe-Mody U. Renal impairment has no clinically relevant effect on the long-term exposure of linagliptin in patients with type 2 diabetes. *Am J Ther*. 2013;20:618–21.
 32. Fujisaka S, Usui I, Kanatani Y, Ikutani M, Takasaki I, Tsuneyama K, Tabuchi Y, Bukhari A, Yamazaki Y, Suzuki H, Senda S, Aminuddin A, Nagai Y, Takatsu K, Kobayashi M, Tobe K. Telmisartan improves insulin resistance and modulates adipose tissue macrophage polarization in high-fat-fed mice. *Endocrinology*. 2011; 152:1789–99.
 33. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008;358:580–51.
 34. Gallwitz B, Rosenstock J, Rauch T, Bhattacharya S, Patel S, von Eynatten M, Dugi KA, Woerle HJ. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: A randomised, double-blind, non-inferiority trial. *Lancet*. 2012;380:475–83.
 35. Giorda CB, Nada E, Tartaglino B, Marafetti L, Gnani R. A systematic review of acute pancreatitis as an adverse event of type 2 diabetes drugs: From hard facts to a balanced position. *Diabetes Obes Metab*. 2014;16(11):1041-7.
 36. Graefe-Mody U, Friedrich C, Port A, Ring A, Retlich S, Heise T, Halabi A, Woerle HJ. Effect of renal impairment on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor linagliptin. *Diabetes Obes Metab*. 2011;13:939–946.
 37. Lago RM, Singh PP, Nesto RW. Diabetes and hypertension. *Nat Clin Pract Endocrinol Metab*. 2007;3:667.
 38. Von Eynatten M, Gong Y, Emser A, Woerle HJ. Efficacy and safety of linagliptin in type 2 diabetes subjects at high risk for renal and cardiovascular disease: a pooled analysis of six phase III clinical trials. *Cardiovasc Diabetol*. 2013; 12:60.
 39. Mistry GC, Maes AL, Lasseter KC, Davies MJ, Gottesdiener KM, Wagner JA, Herman GA. Effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on blood pressure in nondiabetic patients with mild to moderate hypertension. *J Clin Pharmacol*. 2008;48: 592–8.
 40. Monami M, Ahren B, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: A meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2013;15:112–20.
 41. Ogawa S, Ishiki M, Nako K, Okamura M, Senda M, Mori T, Ito S. Sitagliptin, a dipeptidyl peptidase-4 inhibitor, decreases systolic blood pressure in Japanese hypertensive patients with type 2 diabetes. *Tohoku J Exp Med*. 2011;223:133–5.
 42. Von Websky K, Reichetzeder C, Hocher B. Physiology and pathophysiology of incretins in the kidney. *Current Opinion in Nephrology and Hypertension*. 2014;23: 54-60.
 43. Girardi AC, Degray BC, Nagy T, Biemesderfer, Aronson P. Association of Na⁺-H⁺ exchanger isoform NHE3 and dipeptidyl peptidase IV in the renal proximal tubule. *The Journal of Biological Chemistry*. 2001;276:46671-7.
 44. Girardi AC, Knauf F, Demuth HU, Aronson PS. Role of dipeptidyl peptidase IV in regulating activity of Na⁺/H⁺ exchanger isoform NHE3 in proximal tubule cells. *The American Journal of Physiology—Cell Physiology*. 2004;287:C1238-C1245.
 45. Mason RP, Jacob RF, Kubant R, Walter MF, Bellamine A, Jacoby A, Mizuno Y, Malinski T. Effect of enhanced glycemic control with saxagliptin on endothelial nitric oxide release and CD40 levels in obese rats. *Journal of Atherosclerosis and Thrombosis*. 2011;18:774-83.
 46. Ishii M, Shibata R, Kondo K, Kambara T, Shimizu Y, Tanigawa T, Bando YK, Nishimura M, Ouchi N, Murohara T. Vildagliptin stimulates endothelial cell network formation and ischemia-induced revascularization via an endothelial nitric oxide synthase-dependent mechanism. *The Journal of Biological Chemistry*. 2014; 289:27235-45.
 47. Shih CM, Chen YH, Lin YW, Tsao NW, Wu SC, Kao YT, Chiang KH, Li CY, Chang NC, Lin CY, Huang CY, Lin FY. MK-0626, a dipeptidyl peptidase-4 inhibitor, improves neovascularization by increasing both the number of circulating endothelial progenitor cells and endothelial nitric oxide synthetase expression. *Current Medicinal Chemistry*. 2014;21:2012-22.
 48. Brandt I, Lambeir AM, Ketelslegers JM, Vanderheyden M, Scharpé S, De Meester I. Dipeptidyl- peptidase IV converts intact B-type natriuretic peptide into its des-

- serpro form. *Clinical Chemistry*. 2006;52: 82-87.
49. Mentlein R, Gallwitz B, Schmidt WE. Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7–36) amide, peptide histidine methionine and is responsible for their degradation in human serum. *Eur J Biochem*. 1993;214:829–35.
50. Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev*. 2012;33:187–215.
51. Chihiro Moriya, Hiroaki Satoh. Tenziglipitin decreases uric acid levels by reducing xanthine dehydrogenase expression in white adipose tissue of male wistar rats. *J Diabetes Res*; 2016. Available:org/10.1155/2016/3201534.
52. Nishioka T, Shinohara M, Tanimoto N, Kumagai C, Hashimoto K. Sitagliptin, a dipeptidyl peptidase-IV inhibitor, improves psoriasis. *Dermatology*. 2012;224:20–21.
53. Lynch M, Tobin AM, Ahern T, O’Shea D, Kirby B. Sitagliptin for severe psoriasis. *Clin Exp Dermatol*. 2014;39:841–842.
54. Nagai H, Fujiwara S, Takahashi Y, Nishigori C. Ameliorating effect of the novel dipeptidyl peptidase-4 inhibitor teneligliptin on psoriasis: a report of two cases. *J Dermatol*. 2015;42:1094–97.
55. Kim SC, Schneeweiss S, Glynn RJ, Doherty M, Goldfine AB, Solomon DH. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes may reduce the risk of autoimmune diseases: A population-based cohort study. *Ann Rheum Dis*. 2015;74: 1968–1975.
56. Novelli M, Savoia P, Fierro MT, Verrone A, Quaglino P, Bernengo MG. Keratinocytes express dipeptidyl-peptidase IV (CD26) in benign and malignant skin diseases. *Br J Dermatol*. 1996;134:1052–56.
57. Van Lingen RG, van de Kerkhof PC, Seyger MM, de Jong EM, van Rens DW, Poll MK, et al. CD26/dipeptidyl-peptidase IV in psoriatic skin: Upregulation and topographical changes. *Br J Dermatol*. 2008;158:1264–72.
58. Van Lingen RG, Poll MK, Seyger MM, de Jong EM, van de Kerkhof PC, van Erp PE. Distribution of dipeptidyl-peptidase IV on keratinocytes in the margin zone of a psoriatic lesion: A comparison with hyperproliferation and aberrant differentiation markers. *Arch Dermatol Res*. 2008;300: 561–67.
59. Thielitz A, Reinhold D, Vetter R, Ute Bank, Martin Helmuth, Roland Hartig, et al. Inhibitors of dipeptidyl peptidase IV and aminopeptidase N target major pathogenetic steps in acne initiation. *J Invest Dermatol*. 2007;127:1042–51.
60. Kadowaki T, Kondo K. Efficacy, safety and dose-response relationship of teneligliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2013;15: 810-8.
61. Kadowaki T, Kondo K. Efficacy and safety of teneligliptin added to glimepiride in Japanese patients with type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled study with an open-label, long-term extension. *Diabetes Obes Metab*. 2014;16:418-25.
62. Kadowaki T, Kondo K. Efficacy and safety of teneligliptin in combination with pioglitazone in Japanese patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2013;4:576-84.
63. Kadowaki T, Marubayashi F, Yokota S, Katoh M, Iijima H. Safety and efficacy of teneligliptin in Japanese patients with type 2 diabetes mellitus: A pooled analysis of two phase III clinical studies. *Expert Opin Pharmacother*. 2015;16:971-81.
64. Singh AK. Efficacy and safety of teneligliptin, Indian. *J Endocr Metab*. 2017;21:11-7
65. Stonehouse AH, Darsow T, Maggs DG. Incretin-based therapies. *J Diabetes*. 2012;4:55–67.
66. Dailey MJ, Moran TH. Glucagon-like peptide 1 and appetite. *Trends Endocrinol. Metab*. 2013;24:85–91.

© 2020 Pelluri et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/56381>