# A COMPARATIVE PROSPECTIVE STUDY OF THE SAFETY OF TENELIGLIPTIN AND SITAGLIPTIN TO EVALUATE QTC PROLONGATION IN INDIAN TYPE 2 DIABETES PATIENTS

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# CERTIFICATION OF APPROVAL

This is to certify that Miss Chandrima Sarkar bearing examination CLASS ROLL NO:- 001711403005 ,REGISTRATION NO:- 140859 OF 2017-18,a candidate of Masters of Pharmacy in Clinical Pharmacy and Pharmacy Practise, has submitted the thesis project entitled "A Comparative Prospective Study of the Safety of Teneligliptin and Sitagliptin to Evaluate QTc Prolongation in Indian Type 2 Diabetes Patients" under our supervision at AMRI Hospitals, Dhakuria , Kolkata for fulfilment of requirement for the completion of M.Pharm.in Clinical Pharmacy and Pharmacy Practice".

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# DECLARATION OF ORIGINALITY

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# COMPLIANCE OF ACADEMIC ETHICS

I hereby declare that this thesis contains original research work by me (**Chandrima Sarkar**), as part of my post graduate programme in Clinical Pharmacy and Pharmacy Practice.

All information in the document have been obtained and presented in accordancewith academic rules and ethical conduct.

.I also declare that, as required by these rules and conduct, I have fully cited andreferred to all literature survey which i needed for the purpose of my study .

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# ABSTRACT

In this Project , the prevalence of patients with ECG changes with respect to QT prolongation in the Teneligliptin group versus the Sitagliptin group was studied . A comparison of the safety and tolerability of Teneligliptin with sitagliptin in patients with type 2 diabetes was determined .

Teneligliptin, a novel DPP-4 inhibitor, exhibits a unique structure characterized by five consecutive rings, which produce a potent and long-lasting effect. Teneligliptin is currently used in T2DM patients who fail to achieve adequate glycemic control even after diet control and exercise or a combination of diet control, exercise, and metformin sulfonylurea- or thiazolidine-class drugs. The metabolites of this drug are eliminated via renal and hepatic excretion, so no dose adjustment is necessary in patients with renal impairment.

Sitagliptin is the 1$^{st}$ in class gliptin to be introduced in India. A randomized, double-blind, placebo-controlled, crossover study was performed with a single oral dose of sitagliptin (100 mg, 800 mg), moxifloxacin (400 mg), and placebo in order to provide a rigorous assessment of the effect of sitagliptin on ventricular repolarization based on the ICH E14 guidance.

According to a strict QT/QTc evaluation study and clinical studies for type 2 diabetes conducted in Japan and other countries, no AEs related to QT prolongation were detected with 40 mg/day of teneligliptin, which is the maximal dosage used in clinical practice. The clinical dose of sitagliptin 100 mg was not associated with an increase in QTc interval, corrected using the Fridericia correction (QTcf), at any time point .

# -:CONTENTS:-

# INTRODUCTION

**Type 2 diabetes mellitus (T2DM)** is a complex chronic illness associated with a state of high blood glucose level, or hyperglycemia, occurring from deficiencies in insulin secretion, action, or both[1]. The chronic metabolic imbalance associated with this disease puts patients at high risk for long-term macro- and microvascular complications, which if not provided with high quality care, lead to frequent hospitalization and complications, including elevated risk for cardiovascular diseases (CVDs) [1]

T2DM may be identified in low-risk individuals who have spontaneous glucose testing during routine primary clinical care, in individuals examined for diabetes risk assessment, and in frankly symptomatic patients.[2] Early diagnosis of T2DM can be accomplished through blood tests that measure plasma glucose (PG) levels. Fasting plasma glucose (FPG) is the most common test to detect diabetes: a level of ≥126 mg/dl or 7.0 mmol/L confirmed by repeating the test on another clinic visit effectively diagnoses the disease. This test requires fasting for at least the previous 8 hours and generates enhanced reliability when blood is drawn in the morning. Another criterion is the 2 hour PG of ≥200 mg/dL or 11.1 mmol/L in a patient presenting with the traditional symptoms of diabetes such as polyuria, polydipsia, and/or unexplained weight loss. A positive 2-houroral glucose tolerance test (OGTT) will show a PG level of ≥200 mg/dL or 11.1 mmol/L after a glucose load containing 75 g of glucose solution in water. 2 hour PG OGTT is not commonly used in the clinic because, although it is more sensitive than FPG test, it is less convenient and more expensive for patients. Additionally, this test holds less relevance in routine follow-ups after confirmed diagnosis of diabetes is obtained.[2]

## PREVALENCE OF T2DM

T2DM is a disease that affects more than 400 million people around the world. Currently the disease affects approximately 171 million people worldwide, and the World Health Organization estimates 366 million people will have diabetes by 2030.[3] .The prevalence of T2DM is expected to double within the next 20 years, due to the increase of the age, sedentary lifestyle, obesity and the number of ethnic groups of high risk in the population [4].

### *T2DM in India*

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease [5][6]. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively [7]. According to Wild et al. [8] the prevalence of diabetes is predicted to double globally from 171 million in 2000, to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India [8]. The overall prevalence of diabetes in all 15 states of India was 7·3% (95% CI 7·0–7·5). There are large differences in diabetes prevalence between states in India. The prevalence of diabetes varied from 4·3% in Bihar (95% CI 3·7–5·0) to 10·0% (8·7–11·2) in Punjab and was higher in urban areas (11·2%, 10·6–11·8) than in rural areas (5·2%, 4·9–5·4; $p<0·0001$) and higher in mainland states (8·3%, 7·9–8·7) than in the northeast (5·9%, 5·5–6·2; $p<0·0001$). Overall, 1862 (47·3%) of 3938 individuals identified as having diabetes had not been diagnosed previously [9]. Figure 1 shows the diabetic presence of India globally [10].

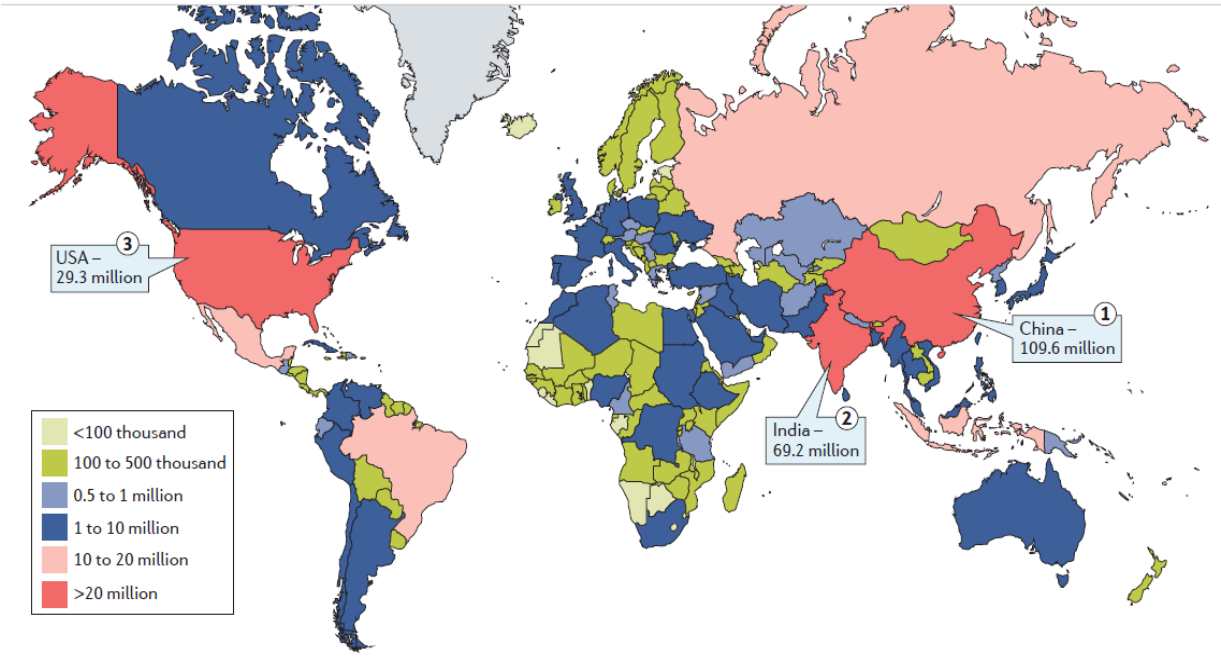



Figure 1 | **Estimated total number of adults (20–79 years) living with diabetes mellitus, highlighting the top three countries or territories for number of adults with diabetes mellitus (20–79 years) in 2015.** It was estimated that in 2015, 415 million adults aged 20–79 years had diabetes mellitus worldwide, and about 46.5% of them lived in three countries: China, India and the USA. The colour of the country or territory in the map relates to the total number of adults aged 20–79 years living with diabetes mellitus in the area. Figure adapted with permission from REF. 1, International Diabetes Federation Diabetes Atlas. IDF Diabetes Atlas, 7th edn Brussels, Belgium: International Diabetes Federation,

**Figure 1 showing the diabetic presence of India globally [10].**

The health care costs of T2DM are considerable, for example in 2002 the United States spent ~$132 billion on the treatment of diabetes. The primary cause of mortality and morbidity in patients with diabetes is cardiovascular disease (CVD), including stroke and heart disease. In patients with diabetes, the risk of CVD is 2- to 4-fold higher than in individuals who do not have diabetes. T2DM is also associated with neuropathic disease, and microvascular complications including renal disease and retinal disease, resulting in T2DM being the foremost cause of end-stage renal disease and blindness, it is also a leading cause of lower extremity amputation. [11]

The complications of T2DM have traditionally been divided into macrovascular complications (for example, cardiovascular disease (CVD) and microvascular complications (for example, complications affecting the kidney, the retina and the nervous system). Complications of T2DM are very common, with half of patients with T2DM presenting with microvascular complications and 27% with macrovascular complications in an observational study of 28 countries in Asia, Africa, South America and Europe. On the basis of cohort studies from developed countries, the relative risk of microvascular disorders and macrovascular disorders among patients with T2DM was estimated to be at least 10–20 times higher and 2–4 times higher, respectively, than in people without T2DM. In most developing countries, patients with T2DM are at a particularly increased risk of developing kidney complications and stroke (but have a reduced risk of coronary heart disease) compared with patients in developed countries.[10]

**THERAPEUTIC MANAGEMENT OF DIABETES**

Currently available glucose-lowering therapies target one or more of these key pathways. It is important that a patient-centered approach should be used to guide the choice of pharmacological agents. The factors to be considered include efficacy, cost, potential side effects, weight gain, comorbidities, hypoglycemia risk, and patient preferences.

Pharmacological treatment of T2DM should be initiated when glycemic control is not achieved or if HbA1C rises to 6.5% after2–3 months of lifestyle intervention. Not delaying treatment and motivating patients to initiate pharmacotherapy can considerably prevent the risk of the irreversible microvascular complications such as retinopathy and glomerular damage .Monotherapy with an oral medication should be started concomitantly with intensive lifestyle management.[12]

The major classes of oral pharmacological agents for treatment of T2DM include biguanides, sulfonylureas, meglitinide, thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucosecotransporter (SGLT2) inhibitors, and α-glucosidase inhibitors. If the HbA1C level rises to 7.5% while on medication or if the initial HbA1C is ≥9%, combination therapy with two oral agents,or with insulin, may be considered . [2]

**Biguanides**

Metformin is a biguanide that is the main first-line oral Drug of choice in the management of T2DM across all age groups. Metformin activates adenosine monophosphate-activated protein kinase in the liver,causing hepatic uptake of glucose and inhibiting gluconeogenesis through complex effects on the mitochondrial enzymes . Metformin is highly tolerated and has only mild side effects, low risk of hypoglycemia and low chances of weight gain. Metformin is shown to delay the progression of T2DM, reduce the risk of complications, and reduce mortality rates in patients by decreasing hepatic glucose synthesis (gluconeogenesis) and sensitizing peripheral tissues to insulin. Metformin is contraindicated in patients with advanced stages of renal
insufficiency.[13]

**Sulfonylureas**

Sulfonylureas lower blood glucose level by increasing insulin secretion in the pancreas by blocking the KATP channels. They also limit gluconeogenesis in the liver. Sulfonylureas decrease breakdown of lipids to fatty acids and reduce clearance of insulin in the liver . [14]Sulfonylureas are currently prescribed as second-line or add-on treatment options for management of T2DM. They are divided into two groups: first-generation agents, which includes chlorpropamide, tolazamide, and tolbutamide, and second-generation agents,

which includes glipizide, glimepiride, and glyburide. The first-generation sulfonylureas are known to have longer half-lives, higher risk of hypoglycemia, and slower onset of action, as compared to second-generation sulfonylureas. Currently, in clinical practice, second-generation sulfonylureas are prescribed and more preferred over first-generation agents because they are proven to be more potent (given to patients at lower doses with less frequency), with the safest profile being that of glimepiride. Hypoglycemia is the major side effect of all sulfonylureas, while minor side effects such as headache, dizziness, nausea, hypersensitivity reactions, and weight gain are also common. Sulfonylureas are contraindicated in patients with hepatic and renal diseases and are also contraindicated in pregnant patients due to the possible prolonged hypoglycemic effect to infants. [2]

**Meglitinide**

Meglitinides (repaglinide and nateglinide) are non-sulfonylurea secretagogues, which was approved as treatment for T2DM in 1997. [2] Meglitinide shares the same mechanism as that of sulfonylureas; it also binds to the sulfonylurea receptor in β-cells of the pancreas. However, the binding of meglitinide to the receptor is weaker than sulfonylurea, and thus considered short-acting insulin secretagogues, which gives flexibility in its administration. Also, a higher blood sugar level is needed before it can stimulate β-cells' insulin secretion, making it less effective than sulfonylurea. Rapid-acting secretagogues (meglitinides) may be used in lieu of sulfonylureas in patients with irregular meal schedules or those who develop late postprandial hypoglycemia while using a sulfonylurea.[2]

**Thiazolidinedione**

Like biguanides, TZDs improve insulin action. Rosiglitazone and pioglitazone are representative agents. TZDs are agonists of PPAR and facilitate increased glucose uptake in

numerous tissues including adipose, muscle, and liver. Mechanisms of action include diminution of free fatty acid accumulation, reduction in inflammatory cytokines, rising adiponectin levels, and preservationof β-cell integrity and function, all leading to improvement of insulin resistance and β-cell exhaustion. However, there are high concerns of risks overcoming the benefits. Namely, combined insulin-TZD therapy causes heart failure. Thus, TZDs are notpreferred as first-line or even step-up therapy. [2]

**Other Glucose-Lowering Pharmacologic Agents**

Pramlintide, an amylin analog, is an agent that delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety. It is a Food and Drug Administration (FDA)-approved therapy for use in adults with T1DM. Pramlintide induces weight loss and lowers insulin dose. Concurrent reduction of prandial insulin dosing is required to reduce the risk of severe hypoglycemia.[2]

**Other medications that may lower blood sugar**

Bromocriptine, alpha-glucosidase inhibitors like voglibose and acarbose, and bile acid sequestrants like colesevelam. It may be noted that metformin sequesters bile acids in intestinal lumen andthus has a lipid-lowering effect, also the same mechanism may contribute to gas production and gastrointestinal disturbances.[2]

# NEWER ORAL PHARMACOLOGICAL AGENTS FOR T2DM MANAGEMENT

**Sodium-glucose cotransporter (SGLT2) Inhibitors**

SGLT2 Inhibitors are new classes of glucosuric agents: canagliflozin, dapagliflozin, and empagliflozin.SGLT2 inhibitors provide insulin-independent glucose loweringby blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2 .Because of glucose-independent mechanism of action, these Drugs may be effective in advanced stages of T2DM when pancreatic β-cell reserves are permanently lost. These Drugs provide modest weight loss and blood pressure reduction. Urinary tract infections leading to urosepsis and pyelonephritis, as well as genital mycosis, may occur with SGLT2 inhibitors. SGLT2 inhibitors may rarely cause ketoacidosis. Patients should stop taking their SGLT2 inhibitor and seek medical attention immediately if they have symptoms of ketoacidosis (frank nausea or vomiting, or even non-specific features like tiredness or abdominal discomfort).[2]

**GLP-1 Receptor Agonists**

The currently GLP-1 receptor agonists available are exenatide and liraglutide. These Drugs exhibit increased resistance to enzymatic degradation by DPP4. In young patients with recent diagnosis of T2DM, central obesity, and abnormal metabolic profile, one should consider treatment with GLP-1 analogs that would have a beneficial effect on weight loss and improve the metabolic dysfunction. GLP-1 analogs are contraindicated in renal failure.[2]

**DPP-4 Inhibitors**

Dipeptidyl peptidase 4 inhibitors include sitagliptin, saxagliptin,vidagliptin, linagliptin, and alogliptin. These medications may be used as single therapy, or in addition with metformin,sulfonylurea, or TZD. This treatment is similar to the other oral antidiabetic Drugs. The gliptins have not been reported to cause higher incidence of hypoglycemic events compared with controls.Dipeptidyl peptidase 4 inhibitors impact postprandial lipid levels.[2]

Treatment with vidagliptin for 4 weeks decreases postprandial plasma triglyceride and apolipoprotein B-48-containing triglyceride-rich lipoprotein particle metabolism after a fat-rich meal in T2DM patients who have previously not been exposed to these medications. In diabetic patients with coronary heart disease, it was demonstrated that treatment with sitagliptin improved cardiac function and coronary artery perfusion. The three most commonly reported adverse reactions in clinical trials with gliptins were nasopharyngitis, upper respiratory tract infection, and headache. Acute pancreatitis was reported in a fraction of subjects taking sitagliptin or metformin and sitagliptin.[2].

# Commonly used DPP4 inhibitors - Sitagliptin and Teneligliptin

## Sitagliptin:

Sitagliptin was the first oral dipeptidyl peptidase-4 (DPP-4) inhibitor approved by the FDA as a trade name Januvia(Merck) in October 2006 [15] It is used in conjunction with diet and exercise to improve glycemic control in adults withT2DM[16] . It has been used as a monotherapy or in combination with other diabetic agents such as metformin, sulfonylureas, and pioglitazone. A sitagliptin/metformin combination was approved by the FDA in Apr. 2007 and is available under the trade name Janumet (Merck) in doses of 50/500 mg or 50/1000 mg.[17]

**Dosage:** Sitagliptin is available in 25-50, and 100-mg tablets.The recommended dose is 100 mg once daily. It can be taken with or without food.For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥50 mL/min, approximately corresponding to serum creatinine levels of ≤1.7 mg/dL in men and ≤1.5 mg/dL in women), no dosage adjustment for Sitagliptin is required.[16]

For patients with moderate renal insufficiency (CrCl ≥30 to <50 mL/min, approximately corresponding to serum creatinine levels of >1.7 to ≤3.0 mg/dL in men and >1.5 to ≤2.5 mg/dL in women), the dose of Sitagliptin is 50 mg once daily.[16]

For patients with severe renal insufficiency (CrCl<30 mL/min, approximately corresponding to serum creatinine levels of >3.0 mg/dL in men and >2.5 mg/dL in women) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of Sitagliptin is 25 mg once daily. Sitagliptin may be administered without regard to the timing of hemodialysis.[16]

Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of Sitagliptin and periodically thereafter. Creatinine clearance can be estimated from serum creatinine using the Cockcroft-Gault formula-

CrCl = [140 - age (years)] x weight (kg)/ [72 x serum creatinine (mg/dL)]

{x 0.85 for female patients} [16]

**Structure of Sitagliptin** figure1

IUPACname: (3R)-3-amino-1-[3-(trifluoromethyl)-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one.

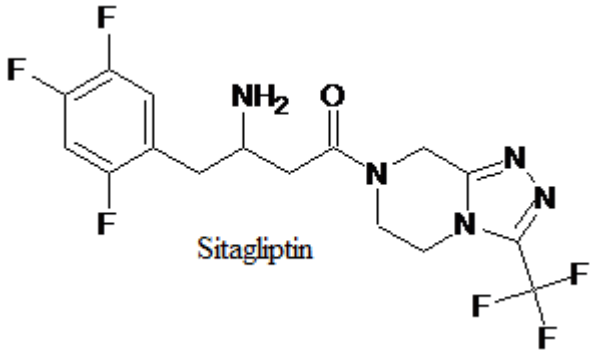



**Figure 1. Showing structure of Sitagliptin**

**Mechanism of Action:**

Sitagliptin exert its actions in patients with T2DM by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging action of these hormones. Incretinhormones,including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. Incretins are part of an endogenous system involved in physiologic regulation of glucose homeostasis.[16] When

blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.[16]

**Absorption** :Sitagliptin is 87% orally bioavailable and taking it with or without food does not affect its pharmacokinetics. Sitagliptin reaches maximum plasma concentration in 2 hours.[18]

**Metabolism**: In vitro assays indicated that at clinically relevant concentrations, sitagliptin did not inhibit cytochrome P450s or Pgp, nor did it induce human CYP3A4. Sitagliptin metabolites, which were present at low to trace levels in plasma, were formed by N-sulfation, N-carbamoylglucuronidation, hydroxylation of the triazolopiperazine ring, and by oxidative desaturation of the piperazine ring followed by cyclization via the primary amine. All metabolites detected in human plasma were observed in rat and dog, however, not all observed metabolites were present in the same matrix as observed in humans. Due to the minor metabolism of this compound, consequences of the differences in metabolism between human, rat and dog on the observed pharmacokinetics are not expected. The observed in vitro metabolism was similar to in vivo metabolism. Only metabolite M1 was not observed in vitro.[18]

**Route of elimination:** Approximately 79% of sitagliptin is excreted in the urine as the unchanged parent compound. 87% of the dose is eliminated in the urine and 13% in the feces[18]

**Half life** : A single oral 100 mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM. hr, Cmax was 950 nM, and apparent terminal half-life (t½) was 12.4 hours [18]

**Pharmacodynamics:**In patients with type 2 diabetes, administration of Sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.[16]
In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1concentrations,whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear how these findings relate to changes in glycemic control in patients with type 2 diabetes.[16]

**Pharmacokinetics:** The pharmacokinetics of sitagliptin has been extensively characterized in healthy subjectsandpatients with type 2 diabetes. After oral administration of a 100 mg dose to healthy subjects, sitagliptinwas rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours postdose.Plasma AUC of sitagliptin increased in a dose-

proportional manner. Following a single oral 100 mg doseto healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, Cmax was 950 nM, and apparentterminal half-life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following
100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.[16]

**Cardiac Electrophysiology:**

An electrophysiology (EP) study is a test performed to assess a subject's heart's electrical system or activity and is used to diagnose abnormal heartbeats or arrhythmia. Electrical signals usually travel through the heart in a regular pattern. Heart attacks, aging and high blood pressure may cause scarring of the heart. This may cause the heart to beat in an irregular (uneven) pattern. Extra abnormal electrical pathways found in certain congenital heart defects can also cause arrhythmias such as QTc prolongation. [19] In some study it is been reported sitagliptin prolong QTc interval so,determine the fact,
In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of Sitagliptin 100 mg, 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increasein the placebo-corrected mean change in QTc from baseline was observed at 3 hours postdose and was 8.0 msec [16]. This increase is not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100 mg dose. In patients with type 2 diabetes administered Sitagliptin 100 mg or 200 mg

daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.[16]

## Teneligliptin:

Teneligliptin is another common oral DPP4 inhibitor used for the treatment of T2DM teneligliptin has been approved by USFDA in Japan in 2012 marketed product and is less expensive than sitagliptin .[20]

**Dosages:** The recommended dosage of Teneligliptin is 20 mg once daily[21]. Teneligliptin may be administered irrespective of food, preferably before breakfast. It is advisable to uptitrate the dosage to 40 sitagliptin,as a newer DPP-4 inhibitor mg once daily in patients who do not achieve adequate glycemic control as required.[22]

**The structure of Teneligliptin** is shown in Figure2.

IUPAC name:1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-4-[(3S,5S)-5-(1,3-thiazolidine-3-carbonyl)pyrrolidin-3-yl]piperazine .

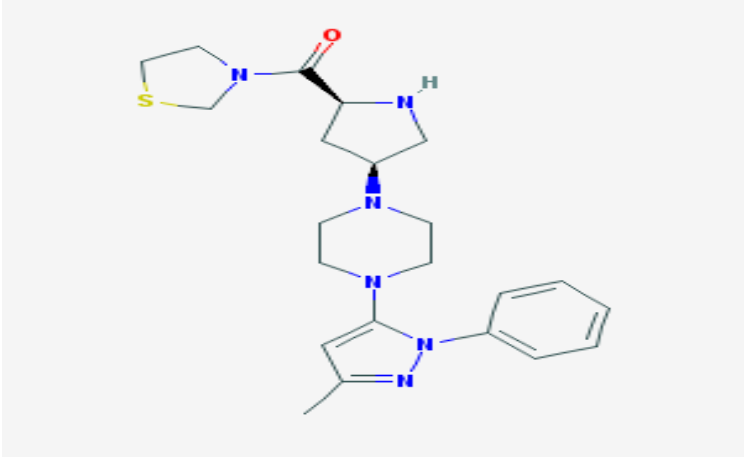



**Figure 2.showing structure of Teneligliptin**

**Mechanism of Action**: Teneligliptin increases incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels.[23]

**Absorption**: Teneligliptin is rapidly absorbed in patients after a single radiolabeled 20 mg dose, with maximum plasma concentrations attained in 1.33 hr . The Drug is 78% - 80% bound to plasma proteins.[24]

**Metabolism:**Teneligliptin is priorly metabolized by cytochrome P450 (CYP) 3A4 &flavinmonooxygenases (FMO) . Teneligliptin does not induce CYP3A4 or CYP1A2.[24]

**Route of elimination:** Teneligliptin has dual mode of elimination –renal and hepatic .It implies that the Drug can be provided to a patient who is already suffering from renal diseases ,like renal impairment .At least 90% of the radiolabeled dose of Teneligliptin is excreted within 216 h, with 45.4% excreted in the urine and 46.5% excreted in the faeces.[23]

**Half life:**Teneligliptin has long half-life of 26.9 hours with once daily dose irrespective of food. It does not require dosage adjustment in mild to moderate hepatic impairment. [25]

**Pharmacodynamics:**Teneligliptin inhibits concentration-dependent human plasma DPP-4 activity. In the glucose tolerance test using Zucker Fatty rat, an obesity model showing insulin resistance and abnormal glucose tolerance, teneligliptin increased plasma active form GLP-1 concentration and plasma insulin concentration by its single-dose administration. In patients having type 2 diabetes mellitus, the administration of 20 mg teneligliptin once daily

inhibited the plasma DPP-4 activity and increased the plasma active form GLP-1 concentration.[26]

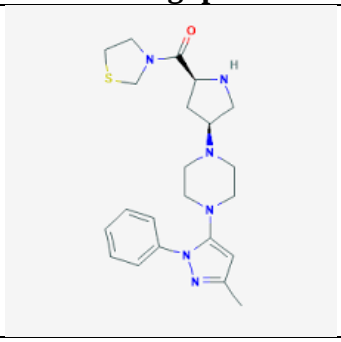
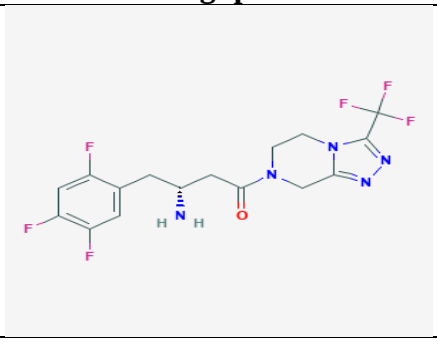
**Pharmacokinetics**:The plasma concentrations of teneligliptin after the administration of teneligliptin at dosages of 10 or 20 mg once daily for 4 weeks revealed a median time to maximum concentration (Cmax) of 1.0 hour in both groups and a mean t1/2 of 20.8 and 18.9 hours, respectivelyWhenteneligliptin was co-administered with Ketoconazole (a potent CYP3A4 and P-glycoprotein inhibitor), Metformin or Canagliflozin in healthy volunteers. No clinically relevant effects on the pharmacokinetics of Teneligliptin were observed when it was co-administered with Glimepiride or Pioglitazone . [27]

**Cardiac Electrophysiology:**

Published randomized controlled trial, do not report any serious cardiac events attributable to teneligliptin .A thorough QT/QTc evaluation study of teneligliptin 40 and 160 mg actively compared to moxifloxacin found a significant increase QTc in latter dose. Teneligliptin 40 mg/day which is currently the maximal recommended dose prolonged the placebo-corrected QTcF (QTc corrected for heart rate) by 4.9 ms after 3 h. The 160 mg/day of teneligliptin significantly increased the QTcF by 11.2 ms after 1.5 h of the Drug was administered, almost similar to 12.1 ms of QTcF prolongation as observed 2 h after moxifloxacin.[21]Regarding the cardiovascular effects, a mild QTc transient prolongation was documented while using supraclinical dosages. Hence, one needs to be cautiousif the Drug is used for a long period or in co-administration with medications known to cause QT prolongation on their own. Teneligliptin treatment is associated with improvements in left ventricular function—particularly diastolic—and endothelial functions, as well as with an increase in serum adiponectin levels.[28]

**Comparative analysis between Sitagliptin and Teneligliptin**

A table showing comparison between sitagliptin and teneligliptin shown below-

| Parameters | Drugs | |
|---|---|---|
| | **Teneligliptin** | **Sitagliptin** |
| **Structure** |  |  |
| **Chemical Formula** | $C_{22}H_{30}N_6OS$ | $C_{16}H_{15}F_6N_5O$ |
| **CAS number** | 760937-92-6 | 486460-32-6 |
| **IUPAC Name** | 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-4-[(3S,5S)-5-(1,3-thiazolidine-3-carbonyl)pyrrolidin-3-yl]piperazine | (3R)-3-amino-1-[3-(trifluoromethyl)-5H,6H,7H,8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one |
| **Molecular weight** | 426.578 | 407.3136 |
| **Mechanism of action** | Bind additional site of S2 extensive and produce more extensive DPP-4 inhibition | By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). |
| **Advantages** | 1) Cost-effective molecule:<br><br>Cost of Teneligliptin is Rs. 10/tablet, whereas sitagliptin is Rs 45/tablet. This is the most common reason why many doctors prescribe teneligliptin.<br><br>2) Titration:<br><br>In kidney patients, the dose of Sitagliptin requires titration as follows:<br><br>• Mild renal insufficiency: No change in dosage (100mg of sitagliptin) | 1) It is a very well studied molecule.<br><br>2) Has a lot of clinical studies are published related to Sitagliptin,<br><br>3) Is available since past 10 years. |

| Parameters | Teneligliptin | Sitagliptin |
|---|---|---|
| | Moderate renal insufficiency: Reduced to 50mg of sitagliptin<br><br>• Severe renal insufficiency: Reduced to 25mg of sitagliptin<br><br>Whereas, the dosage of Teneligliptin (20mg) doesn't require titration in any stage of renal insufficiency. | |
| **Disadvantage** | The only disadvantages of Teneligliptin are published clinical studies related to its limited availability. | the cost and relative lack of long-term safety and efficacy studies. Impact, if any, on cardiovascular disease is also unknown at this point. |
| **Side effect** | • Hypoglycemia<br>• Constipation<br>• Nausea<br>• Loss of appetite<br>• Diarrhea<br>• Abdominal pain<br>• Abdominal discomfort | Severe and persistent pain in the abdomen (stomach area) which might reach through to your back with or without nausea and vomiting, as these could be signs of an inflamed pancreas (pancreatitis). |
| **Interaction** | Interaction with alcohol is unknown. It is advisable to consult your doctor before consumption.<br><br>Interaction with alcohol is unknown. It is advisable to consult your doctor before consumption.<br><br>**Interaction with Medicines**<br><br>**Beta blockers**<br><br>**Levo-Thyroxine**<br><br>**MAO inhibitors** | Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment. |

Despite the structural heterogeneity among DPP4 inhibitors, these Drugs prove to be effective for lowering glucose either as monotherapy or in combination with other Drugs. A composite endpoint including good HbA1C reduction and no hypoglycemia or weight gain adds on to the safety benefits of the Drug. The large number of studies documenting the use of DPP4 inhibitors in the treatment of T2DM are reported from the west. Also a definite relationship between gliptins treatment and improved cardiovascular outcomes remains uncertain and yet to be proven. Sitagliptin is most widely prescribed gliptin in India and there is no data regarding the safety of Teneligliptin, a relatively newer Gliptin in Indian type 2 diabetic patients with respect to QTc prolongation. The current study is therefore intended to evaluate the safety of Teneligliptin and Sitagliptin in T2DM patients with respect to QTc prolongation. [24]

## What is QT prolongation :-

As stated earlier a mild QTc transient prolongation was documented while using supraclinical dosages of Teneligliptin. AcquiredQT prolongation is the most important Drug-induced form of proarrhythmia, also called the long QT syndrome (LQTS). LQTS may result in potentially fatal polymorphic ventricular tachycardia termed torsades de pointes (TdP).

The QT interval represents the duration of ventricular depolarization and subsequent repolarization, and is measured from the beginning of the QRS complex to the end of the T wave. A delay in cardiac repolarization creates an electrophysiological environment that favors the development of cardiac arrhythmias, most clearly torsade de pointes (TdP), but possibly other ventricular tachyarrhythmias as well. TdP is a polymorphic ventricular tachyarrhythmia that appears on the ECG as continuous twisting of the vector of the QRS complex around the isoelectric baseline.[28]

A feature of TdP is pronounced prolongation of the QT interval in the supraventricular beat preceding the arrhythmia. TdP can degenerate into ventricular fibrillation, leading to sudden death.[28]Table 2 summarizes the gliptinsby approving authority , pharmacokinetics , chemistry , half life , dosage and catabolic pathway [20].

An ECG showing QT prolongation is shown in Figure 3

**QT Prolongation:**

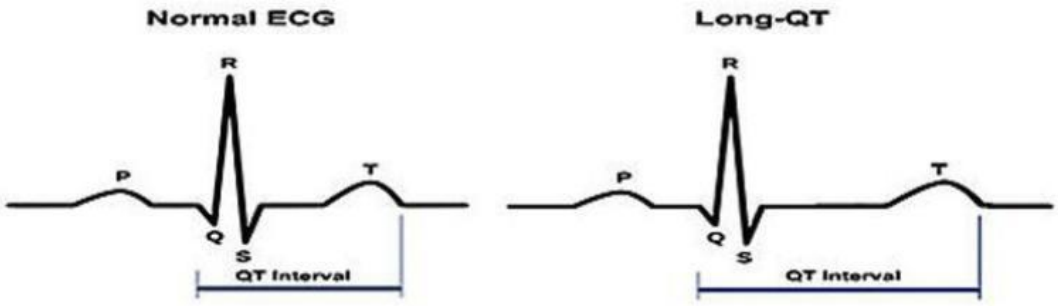



Figure 3: QT Prolongation

Evaluation of the effects of a Drug on the standard ECG intervals and waveforms is considered a fundamental component of the safety database of any new Drug application. Although increases from baseline in the QT/QTc interval constitute signals of interest, interpretation of these differences is complicated by the potential for changes not related to Drug therapy, including regression toward the mean and choice of extreme values.

There is no consensus concerning the choice of upper limit values for absolute QT/QTc interval and changes from baseline. While lower limits increase the false-positive rate, higher limits increase the risk of failing to detect a signal of concern. In clinical trials, a prolongation

of QTc> 500 ms during therapy has been a threshold of particular concern. Multiple analyses using different limits are a reasonable approach to this uncertainty, including:

- Absolute QTc interval prolongation: - QTc interval > 450 - QTc interval > 480 - QTc interval > 500
- Change from baseline in QTc interval: - QTc interval increases from baseline >30 - QTc interval increases from baseline >60

Because documented cases of TdP are relatively rare, even for Drugs that prolong the QT/QTc, they are often not reported until large populations of patients have received the agent in postmarketing settings. The available postmarketing adverse event data should be examined for evidence of QT/QTc interval prolongation and TdP and for adverse events possibly related to QT/QTc interval prolongation, such as cardiac arrest, sudden cardiac death and ventricular arrhythmias (e.g., ventricular tachycardia and ventricular fibrillation). A well-characterized episode of TdP has a high probability of being related to Drug use, whereas the other events that are reported more commonly would be of particular concern if reported in a population at low risk for them (e.g., young men experiencing sudden death).

The use of dosing adjustments following institution of therapy appears to gradually decrease the risk of TdP in hospitalized patients receiving an antiarrhythmic Drug; no similar data are available for Drugs of other therapeutic classes. For approved Drugs that prolong the QT/QTc interval, risk-management strategies aimed at minimizing the occurrence of arrhythmias associated with their use have focused on education of the health care providers and patients.[29]

# LITERATURE REVIEW

T2DM have concentrated on compensating for insulin deficiency and reducing insulin resistance. These approaches sequentially utilize diet and exercise, oral antidiabetic Drug therapy, and ultimately, exogenous insulin**.**Dipeptidyl peptidase-4 (DPP-4) inhibitors offer new options for the management of type 2 diabetes .this literature review summarizes the DPP 4 inhibitor currently used treatment of T2DM.

**1)** ***Modi et.al,2007***reported that Diabetes mellitus (DM) is a progressive disease characterized by insulin deficiency and insulin resistance or both. The fasting and post-prandial blood glucose is elevated, exposing the patient to acute and chronic complications (micro- and macro-vascular) leading to blindness, kidney failure, heart disease, stroke and amputations. Improving glycemic control has been demonstrated to lower the risk of these complications. Owing to the progressive nature of the disease, an evolving treatment strategy is necessary to maintain glycemic control.The prognosis of type-1 diabetes continues to improve with advances in home blood monitoring, basal insulins with modest peaks of action and insulin delivery systems exemplified by insulin pumps. Type-2 diabetes has emerged as the more serious form of diabetes, while prevention of it through attention to the predisposing factors is looming increasingly important to our public health. There will be an increase in the proportion of the population diagnosed with Type 2 diabetes and also a greater awareness of impaired glucose tolerance and dysmetabolic syndrome. Dysmetabolic syndrome is perhaps the single biggest health care issue in North America and individuals with this syndrome are at high risk of diabetes and heart disease. The US obesity epidemic continues unabated, with ever increasing numbers of the nation's obese children becoming irreversibly obese adults, replete with the insulin resistance in all of its' burgeoning complications, notably of progressive atherosclerotic disease, hypertension and type-2

diabetes. Patients will be diagnosed much earlier and treated more aggressively to stop these conditions from developing.[30]

**2)** ***Stonehouseet.al,in 2007***reported that Type 2 diabetes results from progressive -cell dysfunction and insulin resistance, leading to progressive worsening of glycemic control, and increased risk of microvascular and macrovascular complications. Traditionally, treatment strategies for type 2 diabetes have concentrated on compensating for insulin deficiency and reducing insulin resistance. These approaches sequentially utilize diet and exercise, oral antidiabetic Drug therapy, and ultimately, exogenous insulin. However, current therapies have little effect on the inexorable decline of -cell dysfunction, and in a group of patients already overweight or obese, treatment often comes with further weight gain. Consequently, patients often experience deterioration of glycemic control as their disease progresses while battling obesity. Several new therapies including new insulin platforms and new classes of pharmaceutical agents with unique modes of action have recently been introduced or are in clinical development for use in patients with type 2 diabetes. These include amylinomimetics, incretinmimetics, DPP-IV inhibitors, and glucagon antagonists. These new agents improve glycemia and in some instances can reduce body weight. Furthermore, anti-obesity agents, either currently available or in development, are being investigated for their potential to treat diabetes. This review focused primarily on these new therapeutic approaches, particularly those that improve glycemic control while improving control of body weight. It is clear that the pathophysiology of diabetes is complex and manifests multiple defects that are not addressed by historic therapies and begs the introduction of new treatment platforms. Recently available therapies and further approaches in late-clinical development raise the prospect of new treatment paradigms that may allow better glycemic control, improved treatment of the wider metabolic defects of diabetes, such as dyslipidemia, while also offering favorable effects on body weight. Treatments based on harnessing the pharmacologic effects of the incretin hormones, either by mimicking several

of the effects of GLP-1 (incretinmimetics) or by increasing endogenous GLP-1 concentrations (DPP-IV inhibitors), manifest with a robust improvement in glycemic control with, in the case of the incretinmimetics, favorable effects on body weight control.[31]

**3)** In the view of***Kishimotoet.al, in 2007***Dipeptidyl peptidase-4 (DPP-4) inhibitors have recently emerged as a new class of antidiabetic that show favorable results in improving glycemic control with a minimal risk of hypoglycemia and weight gain. Teneligliptin, a novel DPP-4 inhibitor, exhibit a unique structure characterized by five consecutive rings, which produce a potent and long-lasting effect. Teneligliptin is currently used in cases showing insufficient improvement in glycemic control even after diet control and exercise or a combination of diet control, exercise, and sulfonylurea- or thiazolidine-class Drugs. In adults, teneligliptin is orally administered at a dosage of 20 mg once daily, which can be increased up to 40 mg per day. Because the metabolites of this Drug are eliminated via renal and hepatic excretion, no dose adjustment is necessary in patients with renal impairment. The safety profile of teneligliptin is similar to those of other available DPP-4 inhibitors. However, the authors stated that caution needs to be exercised when administering teneligliptin to patients who are prone to QT prolongation. Thus, although clinical data for this new Drug are limited, this Drug shows promise in stabilizing glycemic fluctuations throughout the day and consequently suppressing the progression of diabetic complications. However, continued evaluation in long-term studies and clinical trials is required to evaluate the efficacy and safety of the Drug as well as to identify additional indications for its clinical use.[32]

**4)** ***Scheen et.al,2007***reported that Dipeptidyl peptidase-4 (DPP-4) inhibitors offer new options for the management of type 2 diabetes. Direct comparisons with active glucose lowering comparators in Drug-naive patients have demonstrated that DPP-4 inhibitors exert slightly less pronounced HbA1c reduction than metformin(with the advantage of better

gastrointestinal tolerability) and similar glucose-lowering effects as with a thiazolidinedione (TZD; with the advantage of no weight gain). In metformin-treated patients, gliptins were associated with similar HbA1c reductions compared with a sulphonylurea with the advantage of no weight gain, considerably fewer hypoglycaemic episodes and no need for titration) and a TZD (with the advantage of no weight gain and better overall tolerability). Despite the wide structural heterogeneity among gliptins and differences in their pharmacokinetic profiles, the data available so far indicate similar glucose-lowering efficacy with DPP-4 inhibitors as either monotherapy or in combination with other hypoglycaemic Drugs, similar weight-neutral effects, and comparable safety and tolerability profiles. A composite endpoint including HbA1c reduction, no hypoglycaemia and no weight gain could be used to combine both efficacy and Safety criteria, and so provide an integrated benefit/risk ratio for clinical use. Significantly more patients treated by a DPP- 4 inhibitor achieved an HbA1c level < 7% (53 mmol/mol) or an HbA1c reduction > 0.5%, with no hypoglycaemia and no increase in body weight compared with a SU, and with no weight gain compared with a TZD.. DPP-4 inhibitors also showed good efficacy as dual therapy in combination with SU orTZD and as oral triple therapy, and when added to basal insulin treatment in T2DM patients. Thus, combination therapy with a DPP-4 inhibitor offers the potential advantage of achieving glycaemic control with no additional tolerability concerns. Prospective long-term clinical trials are ongoing to confirm the safety/efficacy of DPP-4 inhibitors added to any type of glucose-lowering therapies as regards cardiovascular outcomes[33]

**5)** In a randomized, double-blind, placebo-controlled, 4-period crossover study performed by ***Bloomfield et.al,2 in 2009***patients received single oral dose of sitagliptin (100 mg, 800 mg), moxifloxacin (400 mg), and placebo for assessment of the effect of sitagliptinon ventricular repolarization based on the ICH E14 guidance. The clinical dose of sitagliptin 100 mg was not associated with an increase in QTc interval, corrected using the

Fridericia correction (QTcf), at any time point. The supratherapeutic 800-mg dose of sitagliptin was generally well tolerated and was associated with minimal, clinically insignificant prolongation of the QTcf interval at concentrations approximately 11-fold higher than maximal concentrations following the 100-mg clinical dose.The authors concluded that at clinically relevant concentrations, sitagliptin is not associated with clinically meaningful QTcf prolongation.[34]

**6)** According to***Waugh et.al, in 2010***the National Institute for Health and Clinical Excellence (NICE) issued an updated guideline [clinical guideline 66 (CG 66)] for the management of all aspects of type 2 diabetes. This technology assessment report (TAR) aimed to provide information to support the Short Guideline Development Group (GDG) which will produce a 'new Drugs update' to the 2008 guideline. In the authors' opinion, the long-acting insulin analogues, glargine and detemir, have only slight clinical advantages over NPH, but have much higher costs, and hence very high ICERs. They did not appear costeffective as first-line insulins compared with NPH insulin in type 2 diabetes.[35]

**7)** ***Kalra et.al, 2011***reported that DPP-4 is an intrinsic membrane glycoprotein and a serine exopeptidase that cleaves X-proline dipeptides from the Nterminus of polypeptides. The Drugs indiscriminate antigenic enzyme expressed on the surface of most cell types and is associated with immune regulation, signal transduction and apoptosis . It catalyzes a diverse range of substrates of proline (or alanine)-containing peptides that includes growth factors, chemokines, neuropeptides, and vasoactive peptides . DPP4 inhibitorsare related to FAP (Fibroblast Activation Protein), DPP8 and DPP-9. Aside from its catalytic ability to regulate the effect of biological factors, data suggest that these glycoproteins also exert other functions, which contribute to tumor etiopathogenesis. Drug influences some signal transduction pathways that regulate cell-growth, migration, and apoptosis. Although DPP-4 has been shown to be capable of degrading a range of substrates in in vitro, however the

relevance of many of these in in vivo conditions is still uncertain. DPP-4 is also known as adenosine deaminasecomplexing protein or CD26 (cluster of differentiation). DPP-4 inhibitors are a relatively new class of Drugs used for the management of type 2 diabetes. The detailed mechanism of DPP4 inhibitors has been discussed earlier by others . They act by inhibiting the DPP-4 enzyme, which degrades glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, these are able to increase GLP-1 to high normal physiological levels, and thereby improve insulin secretion from the beta-cells of the pancreas in response to an increased blood sugar and simultaneously decrease glucagon output from the alpha- cells of the pancreas, which results in decreased hepatic glucose output.[36]

**8)** In the view of***Ringet.al,2011***the potential effects of therapeutic and supratherapeutic doses of linagliptin (BI 1356) on the QT/$QT_c$ interval in healthy subjects. Forty-four Caucasian subjects (26 male) entered the study and 43 subjects completed the study as planned in the protocol. Linagliptin was not associated with an increase in the baseline-adjusted mean $QT_cI$, at any time point. The placebo-corrected MCfB of $QT_cI$ was −1.1 (90% CI −2.7, 0.5) ms and −2.5 (–4.1, –0.9) ms for linagliptin 5 mg and 100 mg, respectively, thus within the non-inferiority margin of 10 ms according to ICH E14. Linagliptin was well tolerated; the assessment of ECGs and other safety parameters gave no clinically relevant findings at either dose tested. Maximum plasma concentrations after administration of 100-mg linagliptin were ∼24-fold higher than those observed previously for chronic treatment with the therapeutic 5-mg dose. Assay sensitivity was confirmed by a placebo-corrected MCfB of $QT_cI$ with moxifloxacin of 6.9 (90% CI 5.4, 8.5) ms. Therapeutic and significantly supratherapeutic exposure to linagliptin is not associated with QT interval prolongation.[37]

**9)** ***He YL et.al,2011***reported that This randomized, double-blind study evaluated the effects of vildagliptin, a dipeptidyl peptidase IV inhibitor for treating type 2 diabetes, on

cardiac repolarization and conduction. For time-matched analysis, mean changes in QTcF with vildagliptin were below predefined limits for QTc prolongation (mean increase <5 ms; upper 90% confidence interval [CI] < 10 ms), except for vildagliptin 100 mg at 1 and 8 hours post-dose (upper 90% CI > 10 ms). With moxifloxacin, significant QTcF prolongation occurred at most time-points, demonstrating assay sensitivity. No vildagliptin- or placebo-treated volunteer had QTcF> 450 ms. Incidences of QTcF increases ≥30 ms with vildagliptin (100 and 400 mg) and placebo were similar (4-8%) and were much lower than with moxifloxacin (39%). No QTcF increase ≥60 mswas observed with vildagliptin or placebo (versus one with moxifloxacin). Time-averaged, time-matched, and categorical analyses of QT/QTcF/QTcB showed similar results. Drug exposure analysis showed no correlation between vildagliptin plasma levels and QTc changes. Vildagliptin had no effect on PR or QRS intervals..[38]

**10)** ***Andrews et.al,in 2011***reported that Lifestyle changes soon after diagnosis might improve outcomes in patients with type 2 diabetes mellitus, but no large trials have compared interventions. Investigated the effects of diet and physical activity on blood pressure and glucose concentrations. Of 593 eligible individuals, 99 were assigned usual care, 248 the diet regimen, and 246 diet plus activity. Outcome data were available for 587 (99%) and 579 (98%) participants at 6 and 12 months, respectively. At 6 months, glycaemic control had worsened in the control group (mean baseline HbA(1c) percentage 6·72, SD 1·02, and at 6 months 6·86, 1·02) but improved in the diet group (baseline-adjusted difference in percentage of HbA(1c) -0·28%, 95% CI -0·46 to -0·10; p=0·005) and diet plus activity group (-0·33%, -0·51 to -0·14; p<0·001). These differences persisted to 12 months, despite less use of diabetes Drugs.[39]

**11)** According to ***Lee TIet.al, in 2013***hypertension induces cardiac dysfunction, calcium (Ca(2+)) dysregulation, and arrhythmogenesis. Dipeptidyl peptidase (DPP)-4 inhibitors, an

antidiabetic agent with anti-inflammation and anti-hypertension potential, may regulate peroxisome proliferator-activated receptors (PPARs)-α, -γ, and -δ and Ca(2+) homeostasis. The purpose of this study was to investigate whether DPP-4 inhibitor, sitagliptin, can modulate PPARs and Ca(2+) handling proteins in hypertensive hearts. Compared to the control group, SHR had lower cardiac PPAR-α and PPAR-δ protein expressions, but had greater cardiac PPAR-γ levels, and TNF-α, IL-6, RAGE, and AT1R protein expressions, which were ameliorated in the sitagliptin-treated SHR. SHR had prolonged QT interval and AP duration with less SERCA2a and RyR, and greater CaV1.2 expressions, which were also attenuated in sitagliptin-treated SHR. Sitagliptin significantly changed the cardiac electrophysiological characteristics and Ca(2+) regulation, which may have been caused by its effects on cardiac PPARs, proinflammatory cytokines, and AT1R.[40]

**12)** According to***Levibovitz.al,in 2013***Chronic treatment with currently available oral hypoglyemic medications may result in a differential effect on the clinical presentation of diabetic patients with acute coronary syndrome (ACS).

Patients in the DPP4i group displayed similar baseline clinical characteristics to the other 2 groups, with the exception of a younger age and a lower frequency of prior coronary heart disease and chronic renal failure. Medical therapy with DPP4i was associated with a significantly lower in-hospital complication rate (post MI angina, re-infarction, pulmonary edema, infections, acute renal failure and better KILLIP class) (9.7%), lower rates of 30-day MACE (12.9%) and a shorter hospital stay ($5.4 \pm 3.8$ days) as compared with patients treated with metformin (24.4%, 31.6% and $5.6 \pm 5.0$ days respectively) or other oral hypoglycemic Drugs (45.5%, 48.5% and $7.5 \pm 6.5$ days respectively).[41]

**13)** In the view of***Garget.al, in 2014***Canagliflozin belongs to a class of agents—the sodium–glucose co-transporter 2 (SGLT2) inhibitors—whose novel mechanism of action offers potential advantages over other antihyperglycemic agents , including a relatively

low hypoglycemia risk and weight-loss-promoting effects Subjects' mean age was 56 years, type 2 diabetes mellitus (T2DM) duration 6.3 years, and hemoglobin A1c (HbA1c). 7.5%. Treatment with placebo, dapagliflozin, or HCTZ resulted in changes from baseline in 24-hour ambulatory mean systolic blood pressure (SBP) of - 0.9 (95% CI - 4.2, + 2.4), - 3.3 (95% CI - 6.8, + 0.2), and - 6.6 (95% CI - 9.9, - 3.2)mmHg, respectively, at week 12, adjusted for baseline SBP.[42]

**14)** ***Kutoh et.al, in 2014***reported that Teneligliptin is a novel, highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor. The aim of this study is to explore the glycemic and non-glycemic efficacies of teneligliptin as an initial therapy. : Significant reductions of HbA1c (from 10.34 ± 2.06 to 8.38 ± 2.23%) and fasting blood glucose (FGB, from 211.3 ± 68.4 to 167.3 ± 70.2 mg/dL) levels were observed without any clinically significant adverse events. However, significant increases of uric acids (UA) levels were observed and two subjects reported mild hypoglycemic events. Homeostasis model assessment-B (HOMA-B) levels significantly increased, while high HOMA-R levels significantly decreased. Significant correlations were observed between the changes (Δ) of HbA1c and those of HOMA-B, and between ΔFBG and ΔHOMA-R. No changes in lipid and body weight were noted. Teneligliptin might be effectively and safely used as an initial therapy for newly diagnosed T2DM. Glycemic efficacy of teneligliptin is obtained through activating beta-cell function as well as decreasing insulin resistance.[43]

**15)** As per***Kaveeshwar et.al, in 2014***Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. 1,2 In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. According to Wild et al.3 the prevalence of

diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease. 3,4 India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country. Many influences affect the prevalence of disease throughout a country, and identification of those factors is necessary to facilitate change when facing health challenges.. Worryingly, diabetes is now being shown to be associated with a spectrum of complications and to be occurring at a relatively younger age within the country. The disease is now highly visible across all sections of society within India, there is now the demand for urgent research and intervention - at regional and national levels - to try to mitigate the potentially catastrophic increase in diabetes that is predicted for the upcoming years.[44]

**16)** In the view of***Helleret.al,in 2015***Thorough QT studies conducted according to the International Council on Harmonisation E14 guideline are required for new nonantiarrhythmic Drugs to assess the potential to prolong ventricular repolarization. Special considerations may be needed for conducting such studies with antidiabetes Drugs as changes in blood glucose and other physiologic parameters affected by antidiabetes Drugs may prolong the QT interval and thus confound QT/corrected QT assessments. This review discusses potential mechanisms for QT/corrected QT interval prolongation with antidiabetes Drugs and offers practical considerations for assessing antidiabetes Drugs in thorough QT studies. This article represents collaborative discussions among key stakeholders from academia, industry, and regulatory agencies participating in the Cardiac Safety Research Consortium. It does not represent regulatory policy.[45]

**17)** ***Hashikata et.al, in 2015***experienced that Incretin hormones have been reported to have cytoprotective actions in addition to their glucose-lowering effects. We evaluated whether teneligliptin, a novel dipeptidyl peptidase-4 (DPP-4) inhibitor, affects left ventricular (LV) function in patients with type 2 diabetes mellitus (T2DM). Twenty-nine T2DM patients not receiving any incretin-based Drugs were enrolled and prescribed with teneligliptin for 3 months. Compared to baseline levels, hemoglobin A1c levels decreased (7.6 ± 1.0 % to 6.9 ± 0.7 %, $p < 0.01$) and 1,5-anhydro-d-glucitol levels increased (9.6 ± 7.2 μg/mL to 13.5 ± 8.7 μg/mL, $p < 0.01$) after treatment.In this study, 29 patients were enrolled, and 2 patients were excluded because of a drop-out and a side effect of teneligliptin in this study. Finally, 27 patients were evaluated at baseline and at 3 months after additional treatment with teneligliptin. During the study registration period, no medication except teneligliptin was administered to the enrolled patients. The remaining therapy was continued unchanged and medications were not interrupted in any patient. In each patient, teneligliptin was administered at 20 or 40 mg/day according to the physician's decision. Patient clinical characteristics at baseline are shown in . LVEF was 63.7 ± 5.6 %, the E/A ratio was 0.94 ± 0.49, deceleration time was 229.4 ± 48.3 ms, and the E/e′ ratio was 13.3 ± 4.1. Of the patients, 83 % (24/29 patients) had asymptomatic moderate or severe LV diastolic dysfunction (moderate: E/A ratio 0.80–1.50, deceleration time 160– 200 ms, and E/e′ ratio 9–12; severe: E/A ratio ≥2, deceleration time <160 ms, E/e′ ratio ≥13) at baseline, including 22 with moderate and 2 with severe diastolic dysfunction. Approximately, 70 % of the patients (20/29 patients) had endothelial dysfunction at baseline. [46]

**18)** According to***Tang et.al, in 2015***the efficacy and safety of the three dipeptidyl peptidase 4 (DPP 4) inhibitors (vildagliptin, sitagliptin, and linagliptin) as add on therapy in Chinese patients with type 2 diabetes mellitus (T2DM) inadequately controlled on dual combination of insulin and metformin or acarbose. The baseline HbA1c was 9.59 ± 1.84 % (vildagliptin group), 9.22 ± 1.60 % (sitagliptin group), and 9.58 ± 1.80 % (linagliptin group).

At week 12 it was 8.16 ± 1.29 % (vildagliptin), 8.56 ± 1.96 % (linagliptin), and 8.26 ± 1.10 % (sitagliptin). The changes in HbA1c from baseline were −1.33 ± 0.11 % (vildagliptin), −0.84 ± 0.08 % (sitagliptin) and −0.81 ± 0.08 % (linagliptin), the vildagliptin group had the greatest reduction in HbA1c ($P < 0.05$). The proportions of patients that reached target HbA1c were 66.27 % (vildagliptin), 52.73 % (sitagliptin), and 55.49 % (linagliptin), the vildagliptin group had the highest one ($P < 0.05$). The baseline FPG and PPG values in the three groups were at the same level. The three DPP-4 inhibitors appear to be effective and safe as add on therapy for T2DM patients on dual combination of insulin and a traditional OHA. Vildagliptin was more effective in decreasing insulin requirement and achieving glycemic control when compared to the other two.[47]

**19)** ***Fismanet.al,in 2015***experienced that The traditional oral pharmacological therapy for type 2 diabetes mellitus (T2DM) has been based on the prescription of metformin, a biguanide, as first line antihyperglycemic agent world over. It has been demonstrated that after 3 years of treatment, approximately 50 % of diabetic patients could achieve acceptable glucose levels with monotherapy; but by 9 years this had declined to only 25 %. Therefore, the implementation of a combined pharmacological therapy acting via different pathways becomes necessary, and its combination with a compound of the sulfonylurea group was along decades the most frequently employed prescription in routine clinical practice. Meglitinides, glitazones and alpha-glucosidase inhibitors were subsequently developed, but the five mentioned groups of oral antihyperglycemic agents are associated with variable degrees of undesirable or even severe cardiovascular events. The gliptins—also called dipeptidyl peptidase 4 (DPP4) inhibitors—are an additional group of antidiabeticcompounds with increasing clinical use. We review the status of the gliptins with emphasis on their capabilities to positively or negatively affect the cardiovascular system, and their potential involvement in major adverse cardiovascular events (MACE). [48]

**20)** ***Juan José et.al,in 2016***reported that At present there are different treatments, both oral and injectable, available for the treatment of type 2 diabetes mellitus (T2DM). Treatment algorithms designed to reduce the development or progression of the complications of diabetes emphasizes the need for good glycaemic control. The aim of this review is to perform an update on the benefits and limitations of different Drugs, both current and future, for the treatment of T2DM.[49]

**21)** ***Reddy Kankanalaet.al, in 2016***experimented that cardiovascular safety of DPP4 inhibitors as a class, especially in regards to heart failure, has been questioned after the publication of first trials (SAVOR-TIMI 53 and EXAMINE) assessing the cardiovascular risks of DPP4 inhibitors alogliptin and sitagliptin in 2013. Although there were no increased risks in composite cardiovascular outcomes, the SAVOR-TIMI 53 trial reported a 27% increase in hospitalization for heart failure in diabetic patients who received the DPP4 inhibitor saxagliptin.The cardiovascular safety, especially in regards to heart failure, of DPP4 inhibitors has gained much attention since 2013. The heart failure assessments on three out of the four FDAapproved DPP4 inhibitors showed saxaglitpin, but not alogliptin and sitagliptin, may increase the risks of heart failure.[50]

**22)** ***Wiley & Sons Ltd et.al, in 2016***reported that Teneligliptin is a novel dipeptidyl peptidase-4 (DPP-4) inhibitor belonging to the relatively novel pharmacological class of antihyperglycaemica gents that are now recommended as second- or first-line agents in specific situations . In a phase II clinical trial, a 4-week course of teneligliptin (20mg) monotherapy produced significant least squares (LS) mean reductions of −2.78±0.43, −1.93±0.51, and −2.08±0.42mmol/l in 2-h postprandial glucose level after breakfast, lunch and dinner, respectively, in Japanese patients with type 2 diabetes (T2DM) . We therefore

conducted the present phase III, randomized, double-blind, placebo-controlled study to assess the clinical efficacy and safety of teneligliptin in Korean patients with T2DM that was in a dequately controlled with diet and exercise.[51]

**23)** As per as***Singh et.al, in 2016*** Incretin based therapies (IBT) including dipeptidyl peptidase 4 inhibitors (DPP4Is) and glucagon like peptide 1 receptor agonists (GLP1RAs) have been the cornerstone of therapy for type 2 diabetes mellitus (T2DM) since the evolution of incretin science. DPP4Inhibitor are particularly popular in the treatment of T2DM as they are oral Drugs, less costlier than GLPRAs, with modest to moderate glucose lowering similar to sulfonylureas (SU) depending on the baseline glycemic load. DPP4Is carries novel mechanism of action and also have additional potential to protect from hypoglycemia, through unique glucagon dynamics. Indeed, consensus statements from the American College of Endocrinology/American. In India, 4 DPP4Is are already available and marketed that includes sitagliptin, vildagliptin, saxagliptin, and linagliptin..[52]

**24)** In the view of***Krishna R et.al,in 2016***the pharmacokinetics (PK) and pharmacodynamics (PD) of omarigliptin, a novel once-weekly DPP-4 inhibitor, were assessed following single and multiple doses in healthy subjects. Absorption was rapid, and food did not influence single-dose PK. Accumulation was minimal, and steady state was reached after 2 to 3 weeks. Weekly (area under the curve) AUC and $C_{max}$ displayed dose proportionality within the dose range studied at steady state. The average renal clearance of omarigliptin was ~2 L/h. DPP-4 inhibition ranged from ~77% to 89% at 168 hours following the last of 3 once-weekly doses over the dose range studied. Omarigliptin resulted in ~2-fold increases in weighted average postprandial active GLP-1. Omarigliptin acts by stabilizing active GLP-1, which is consistent with its mechanism of action as a DPP-4 inhibitor. Administration of omarigliptin was generally well tolerated in healthy subjects, and both the PK and PD profiles support once-weekly

dosing. A model-based assessment of QTc interval risk from the single ascending dose study predicted a low risk of QTc prolongation within the likely clinical dose range, a finding later confirmed in a thorough QT trial.[53]

**25)** ***Chaudhuryet.al,in 2017***experienced that T2DM Diabetes mellitus is a chronic, progressive, incompletely understood metabolic condition chiefly characterized by hyperglycemia. Impaired insulin secretion, resistance to tissue actions of insulin, or a combination of both are thought to be the commonest reasons contributing to the pathophysiology of T2DM, a spectrum of disease originally arising from tissue insulin resistance and gradually progressing to a state characterized by complete loss of secretory activity of the beta cells of the pancreas. T2DM is a major contributor to the very large rise in the rate of non-communicable diseases affecting developed as well as developing nations. In this mini review, we endeavor to outline the current management principles, including the spectrum of medications that are currently used for pharmacologic management, for lowering the elevated blood glucose in T2DM..[54]

**26)** According to***Zhenget.al,in 2017***the number of people with diabetes mellitus has quadrupled in the past three decades, and diabetes mellitus is the ninth major cause of death. About 1 in 11 adults worldwide now have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (T2DM). Asia is a major area of the rapidly emerging T2DM global epidemic, with China and India the top two epicentres. Although genetic predisposition partly determines individual susceptibility to T2DM, an unhealthy diet and a sedentary lifestyle are important drivers of the current global epidemic; early developmental factors (such as intrauterine exposures) also have a role in susceptibility to T2DM later in life.The epidemic of diabetes mellitus and its complications poses a major global health threat. . This estimate is projected to rise to 642 million by 2040, and the largest increases will come from the regions experiencing economic transitions from low-income to middle-income levels1.

However, these estimates might have under-represented the true global burden of diabetes mellitus, especially in regions undergoing rapid epidemiological transitions.[55]

**27)** ***Keshavarzet.al,in 2017***experienced that T2DM is one of the most common chronic and costly diseases worldwide and type 2 diabetes is the most common type which accounts for about 90% of cases with diabetes. New medication-therapy regimens such as those containing linagliptin alone or in combination with other medications (within the category of DDP-4 inhibitors) must be evaluated in terms of efficacy and compared with other currently used Drugs and then enter the medication list of the country. Hence, this study aimed to compare the clinical efficacy of the two Drugs, i.e. linagliptin and sitagliptin, in patients with type 2 diabetes . This network meta-analysis included 32 studies (Linagliptinvs PLB: n = 8, Sitagliptinvs PLB: n = 13, Linagliptin + MET vs PLB + MET: n = 4, and Sitagliptin + MET vs PLB + MET:n = 7) and a total of 13,747 patients. The results showed no significant difference between linagliptin and sitagliptin in terms of key efficacy and safety outcomes such as HbA1c changes from baseline, body weight change from baseline, percentage of patients achieving HbA1c <7, and percentage of patients experiencing hypoglycemic events ($p > 0.05$). The results showed that the efficacy of the two Drug regimens was the same. Based on the results, there was no significant difference between the two Drugs, i.e. linagliptin and sitagliptin, in terms of efficacy; in other words, the efficacy of the two Drugs was the same. Therefore, the use of these two Drugs depends on their availability and cost.[56]

**28)** ***Karagianniset.al,in 2018***reported that dipeptidyl peptidase-4 (DPP-4) inhibitors for glycaemic control in type 2 diabetes. The authors concluded that DPP-4 inhibitors were similarly effective to sulphonylureas or pioglitazone, with neutral effects on body weight, and inferior to metformin. Uncertain trial quality and some unclear interpretation of the

results suggests the reliability of the review is uncertain.Twenty-six reports (19 studies, 7,136 participants) were included in the review. Risk of bias was considered to be low in three reports, high in 14 reports and unclear in nine reports. All except three studies were double-blind. DPP-4 inhibitors were associated with a smaller decline in HbA (WMD 0.20, 95% CI 0.08 to 0.32; seven trials, $I^2$=60%), and a lower proportion of patients who achieved HbA less than 7% (RR 1.18, 95% CI 1.07 to 1.29; seven trial, $I^2$=34%), which favoured metformin monotherapy. When combined with metformin, there was a statistically significant smaller decline in HbA when DPP-4 inhibitors (as a second-line treatment) were compared with other hypoglycaemic Drugs (overall WMD 0.12, 95% CI 0.04 to 0.20; 10 trials, $I^2$=70%). Removal of poorer quality trials did not alter these results. DPP-4 inhibitors were less effective than sulphonylurea (WMD 0.07, 95% CI 0.03 to 0.11; six trials, $I^2$=0%) and GLP-1 agonists (WMD 0.49, 95% CI 0.31 to 0.67; two trials, $I^2$=27%) in reducing HbA . There was no significant difference in the comparison with pioglitazone (three trials, $I^2$=40%). Achievement of the HbA target of less than 7% statistically favoured pioglitazone (RR 1.33, 95% CI 1.09 to 1.63; two trials, $I^2$=0%) and GLP-1 agonists (RR 1.82, 95% CI 1.50 to 2.21; two trials, $I^2$=0%; figures from forest plot, error in text). There was no significant difference for sulphonylureas (five trials, $I^2$=26%).When added to metformin, DPP-4 inhibitors can lower HbA in a similar way to sulphonylureas or pioglitazone, with neutral effects on body weight in patients with type 2 diabetes. DPP-4 inhibitors as monotherapy appeared to be inferior to metformin in terms of glycaemic efficacy and reduction in body weight.[57]

**29)** ***Baileyet.al,in 2019***reported thatreview examines recent randomized controlled cardiovascular (CV) outcome trials of glucose-lowering therapies in type 2 diabetes and their impact on the treatment of patients with type 2 diabetes. The trials were designed to comply with regulatory requirements to confirm that major adverse cardiac events (MACE) are not detrimentally affected by such therapies. Trials involving dipeptidyl

peptidase-4 (DPP-4) inhibitors did not alter a composite MACE outcome comprising CV deaths, non-fatal myocardial infarction and non-fatal stroke; however, the possibility that some members of this class might incur a small increased risk or worsening of heart failure cannot be excluded. Some studies on glucagon-like peptide-1 receptor agonists (liraglutide: LEADER trial; semaglutide: SUSTAIN-6 trial) found significant benefits for MACE, while treatment with sodium-glucose co-transporter-2 inhibitors (empagliflozin: EMPA-REG OUTCOME trial; canagliflozin: CANVAS trial) also significantly reduced MACE and reduced hospitalization for heart failure.[58]

# STUDY OBJECTIVES

**Primary Objective**

The primary study objective is to evaluate the prevalence of patients with ECG changes with respect to QT prolongation in the Teneligliptin group versus the Sitagliptingroup .

**Secondary Objective**

The secondary study objective is to evaluate and compare the safety and tolerability of Teneligliptin with sitagliptin in patients with type 2 diabetes.

# STUDY RATIONALE

Teneligliptin is orally administered at a dosage of 20 mg once daily, which can be increased up to 40 mg per day. The safety profile of teneligliptin is similar to those of other available DPP-4 inhibitors

According to a strict QT/QTc evaluation study and clinical studies for type 2 diabetes conducted in Japan and other countries, no AEs related to QT prolongation were detected with 40 mg/day of teneligliptin, which is the maximal dosage used in clinical practice.

There is no data regarding the safety of Teneligliptin in Indian type 2 diabetic patients with respect to QTc prolongation. Hence the current study is intended to evaluate the safety of Teneligliptin in type 2 diabetes patients with respect to QTc prolongation.

# METHODOLOGY

**Study Design**

This was a double blind, randomized, comparative, prospective, multi centric study. The end of the study was the date of the last study visit for the last subject in the study.

**Study period and study setting**

The study was conducted over a period of 09 months from July 2018 to March 2019 . The study was conducted in the Diabetic Clinic of AMRI Hospitals, Dhakuria and Dept of Endocrinology,IPGME&R and SSKM Hospital Kolkata-700020 .

**Study population**

All patients with type 2 diabetes was included in the study. The total number of included patients were randomized with 50% patients in each treatment group. The eligibility of a subject with respect to laboratory criteria were assessed according to the laboratory results.

**Inclusion Criteria**

Patients were only included if they fulfilled the following criteria:

1. Male or female subjects, age ≥ 18 to ≤ 65 years at the time of informed consent
2. Uncontrolled Type 2 diabetes uncontrolled with a haemoglobinA1c (HbA1c) ≥7.0 % - ≤ 10%
3. Type 2 Diabetic patients who are gliptins naïve
4. Provide written informed consent
5. Willing and able to comply with all aspects of the protocol

**Exclusion Criteria**

Subjects meeting any of the following criteria were excluded from the study.

1. Type 1 diabetes
2. Patients on insulin therapy
3. Severe diabetic complications such as ketoacidosis

4. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds (ms))

5. A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)

6. The use of concomitant medications that prolong the QT/QTc interval

7. Liver dysfunction

8. Pregnant or nursing women and those who might be pregnant

9. Patients with a history of seizures

10. A history of stroke and cardiovascular events, and

11. Any patient whom the investigator judged to be inappropriate for this study.

12. Patients with a history of alcohol or Drug abuse

13. Any patients with H/o cardiovascular diseases.

14. Thyroid Dysfunction

15. Calcium dysfunction

**Study procedure**

When the patient satisfies the inclusion criteria and was enrolled into the study. after providing the written informed consent, he/she was randomized for treatment with Drug A or Drug B as per the randomization chart. was added to the standard treatment.

**Screening: Visit 1**

A Screening visit is to occur 1 to 7 days before the Enrollment Visit.

Before performing any procedures or assessments, the nature of the study and the potential risks associated with the study was explained to all subjects and written informed consent was

obtained. Once informed consent had been obtained, the following procedures and evaluations was performed:

a) Recording of demographic details (Age, Height, Body Weight and BMI).

b) Examination of Vitals (Blood Pressure – Sitting position, Pulse rate, Respiratory rate, Body Temperature).

c) Physical Examination (General appearance, Alertness, Pallor, Icterus, Cyanosis, Clubbing and Pedal edema and Lymph nodes).

d) Systemic Examination (Cardiovascular system, Respiratory system, Gastrointestinal system, Neurological system, Musculoskeletal system).

e) Medical history, Past obstetric history and Prior medication.

f) History of allergy.

g) Laboratory assessment: Routine hematology (Hb, RBC, TLC, DLC), LFT (SGOT, SGPT, S. Bilirubin – Total), RFT (BUN, S. Creatinine), serum electrolytes, Urine analysis (Routine) Other assessment: ECG.

h) Serum electrolytes

i) Blood sugar fasting and postprandial

j) 12 lead ECG

k) HbA1c

l) UPT (Urine Pregnancy Test ) in women

• Determine inclusion/exclusion criteria

• Medical and surgical history

• Prior and concomitant medications

**Visit 2: Enrollment visit**

When the patient satisfies the inclusion criteria and was enrolled into the study, he/she had been treated with either Drug A or Drug B.

a) Examination of Vitals (Blood Pressure – Sitting position, Pulse rate, Respiratory rate, Body Temperature).

b) Physical Examination (General appearance, Alertness, Pallor, Icterus, Cyanosis, Clubbing and Pedal edema and Lymph nodes).

c) Systemic Examination (Cardiovascular system, Respiratory system, Gastrointestinal system, Neurological system, Musculoskeletal system).

d) Enrollment of subject based on Inclusion/Exclusion criteria

e) Dosing of IP(Teneligliptin/Sitagliptin)

f) 12 Lead ECG (post 2 hours of IP dosing)

g) Concomitant medication

h) Safety evaluation

**Visit 3**

At the subsequent visit (visit 3 –dosing after 7 days) Fasting blood glucose and postprandial blood glucose was estimated..

a) Examination of Vitals (Blood Pressure – Sitting position, Pulse rate,

b) Physical Examination (General appearance, Alertness, Pallor, Icterus, Cyanosis, Clubbing and Pedal edema and Lymph nodes).

c) Systemic Examination (Cardiovascular system, Respiratory system, Gastrointestinal system, Neurological system, Musculoskeletal system).

d) Serum Electrolytes, Fasting blood glucose and postprandial blood glucose

e) Dosing of IP(Teneligliptin/Sitagliptin)

f) 12 Lead ECG

g) Concomitant medication

h) Safety Evaluation

A comprehensive physical examination was include respiratory system, cardiovascular system, per abdomen examination and neurological examination. Documentation of the physical examination was included in the source documentation at the site. Any adverse event during study period was noted in the data sheet and the principal investigator was informed. The study was approved by the Institutional Ethics Committee of AMRI Hospitals, Kolkata.

# RESULT

A total of 65 patients were included in the study during study period. 53.8 % were males. After randomization, 33 patients received Drug A and 32 patients received Drug B. There was no statistically significant difference between the mean age and mean BMI of patients receiving Drug A or B (Table 1).

1. Table for age and BMI

| Baseline characteristics | Drug A | Drug B | P |
|---|---|---|---|
| Age, mean±SD | 46±4.8 | 47.3±5.2 | 0.663 |
| BMI, mean±SD | 24.3±3.4 | 24.6±3.2 | 0.292 |

Among those who received Drug A, 45.5% were males and among those who recieved Drug B, 46.9% were males (Figures 2a and 2b)

Pi chart for sex(male female percentage) Drug A and Drug B.

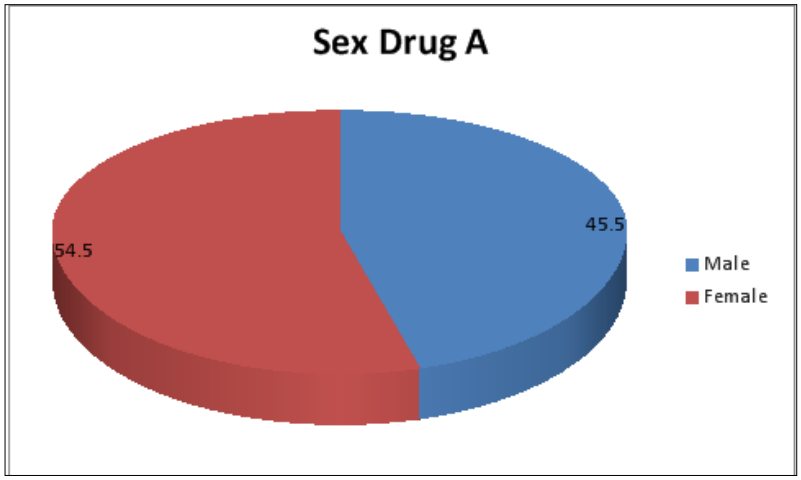



Figure 2a.

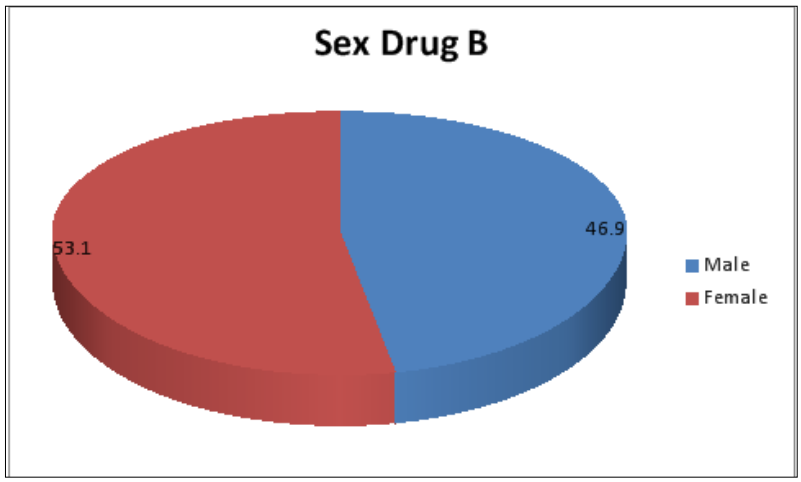



Figure 2b

We assessed the baseline laboratory parameters of patients in both groups prior to allocating them to the Drug A and Drug B group. The mean Hb for patients in Drug A group was 12.8±1.4 g/dl and those in Drug B group was 13±1.3gm/dl. The mean HbA1C levels were 8.3±0.7 and 8.0±0.7, mean SGPT levels were 31.8±23.3 and33.6±23.6 mean creatinine levels were 0.6±0.1 and 0.7±0.1 For Drug A and Drug B groups respectively. There was significant difference in the mean creatinine levels between the two groups (p=0.013). There was no difference in the mean baseline values for the other parameters in the two groups (Table 2).and Figure3.

2. Table for blood lab value ( Drug A Drug B and p value)

| **Baseline characteristics** | **Drug A** | **Drug B** | **P** |
|---|---|---|---|
| **Laboratory blood values, mean±SD** | | | |
| Hb, g/dl | 12.8±1.4 | 13±1.3 | 0.392 |
| SGOT, U/L | 23.8±12.3 | 26.8±13.4 | 0.292 |
| SGPT, U/L | 31.8±23.3 | 33.6±23.6 | 0.767 |
| Bilirubin | 0.6±0.3 | 0.6±0.3 | 0.306 |
| BUN | 9.8±2.4 | 10.3±2.3 | 0.554 |
| Creatinine | 0.6±0.1 | 0.7±0.1 | 0.013 |
| HbA1C | 8.3±0.7 | 8.0±0.7 | 0.248 |

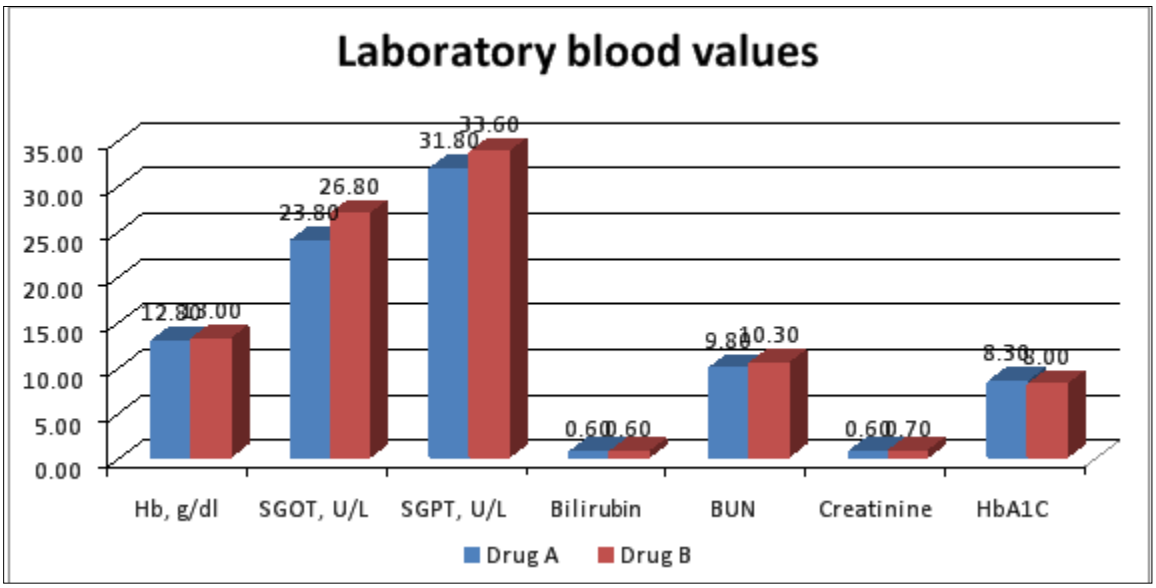



Figure 3.

We evaluated the urine for acetone, albumin and sugar at baseline. While 33.3% of those receiving Drug A showed presence of sugar in urine, 28% receiving Drug B showed urine sugar to be positive, but this

difference was not statistically significant (p=0.649). Urine acetone and albumin results for patients in both groups were negative. Figures: 4 Bar chart for urine analysis ( Drug A and Drug B)

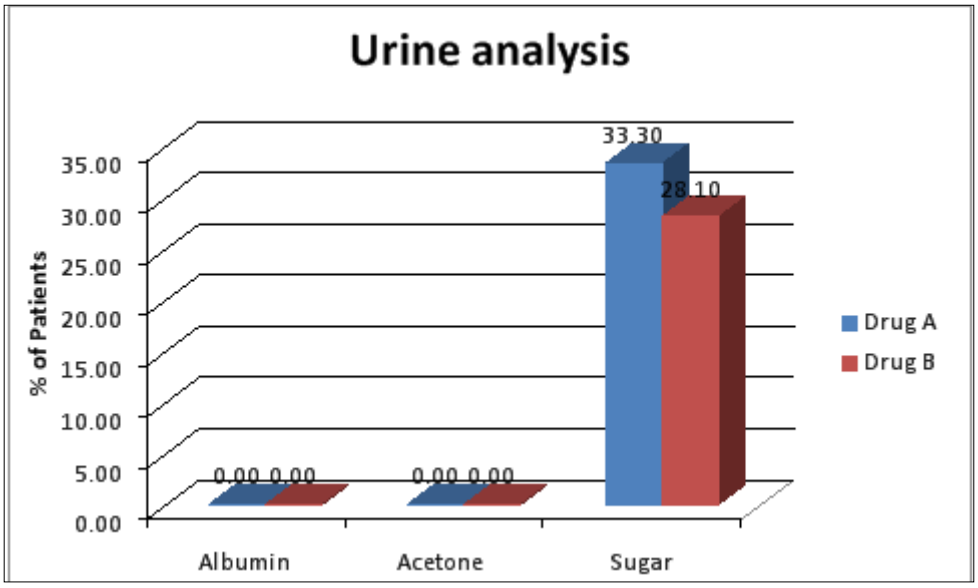



Figure 4.

Changes in physiological parameters were analyzed for both Drug A (Table 3a, Figure 5a) and Drug B (Table 3b, Figure 5b) to assess if there were any significant changes over time. The systolic blood pressure significantly differed between assessment days 0,1 and 7 (p=0.02) for Drug A . The respiratory rates and diastolic blood pressures differed significantly between visits ( p = 0.002 and p = 0.002 respectively). There was no significant difference in any other parameter over the visits.

3.a)Table for comparison of physiological parameter of Drug A over time.( 1day, day2, after7 day)

| Characteristics | Baseline, pre-Drug (Day0) | 1 day after Drug (Day1) | 7 days after Drug (Day 7) | P |
|---|---|---|---|---|
| **Physiological parameters, mean±SD** | | | | |
| Pulse rate | 80.4±10.4 | 79.8±10.8 | 79.4±11.2 | 0.368 |
| Respiraory rate | 80.4±10.4 | 14.8±1.3 | 14.6±1.9 | 0.211 |
| Systolic blood pressure | 121.0±13.1 | 124.1±10.3 | 121.9±10.3 | 0.024 |
| Diastolic blood pressure | 76.3±6.9 | 77.4±6.5 | 77.5±5.7 | 0.384 |
| Body temperature | 37.4±0.4 | 37±0.8 | 37.3±0.35 | 0.149 |

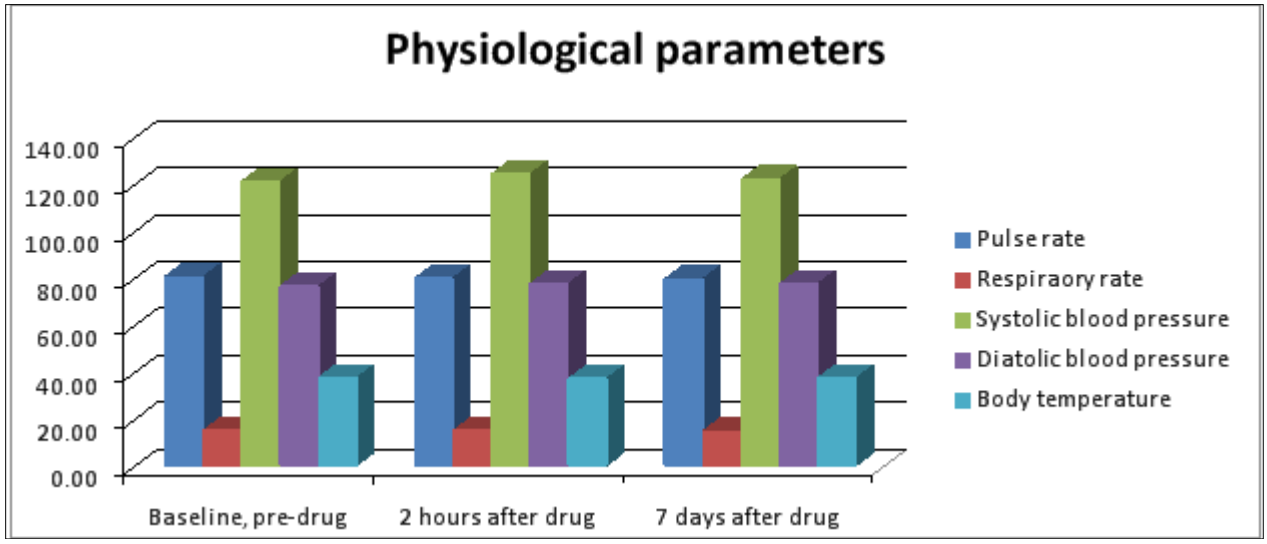



Figure 5a.

3 b) Table for comparison of physiological parameter of Drug B

| Characteristics | Baseline, pre-Drug (Day0) | 1 day after Drug (Day1) | 7 days after Drug (Day 7) | P |
|---|---|---|---|---|
| **Physiological parameters, mean±SD** | | | | |
| Pulse rate | 78.5±10.5 | 78.0±10.1 | 79.0±9.9 | 0.051 |
| Respiraory rate | 15.1±1.2 | 14.6±1.1 | 14±1.9 | 0.002 |
| Systolic blood pressure | 123.9±16.4 | 126.0±11.2 | 124.9±10.9 | 0.421 |
| Diastolic blood pressure | 78±7.5 | 77.7±8 | 79.1±6.7 | 0.002 |
| Body temperature | 37.4±0.3 | 37.2±0.5 | 37.3±0.4 | 0.768 |

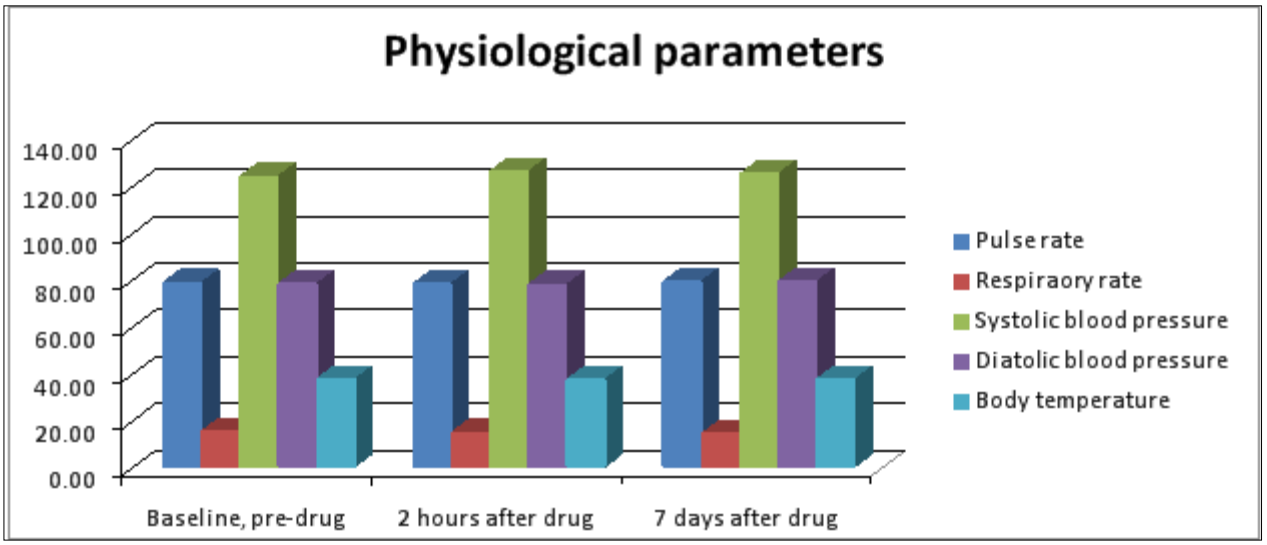



Figure 5b.

We also assessed the laboratory parameters of patients in Drug A and Drug B groups over the three visit days (Table 4a Figure 6a and Table 4b Figure 6b). The mean post prandial blood sugar was significantly lower in both groups after receiving the Drugs for 7 days ( Drug A: 265.6±67.6 to 220.7±87.7, p = 0.002; Drug B: 260.7±63.0 to 237.7±61.6, p=0.007). There was no significant difference in other parameters over time.

4.a)Table for comparison lab parameters Drug A.

| Characteristics | Baseline, pre-Drug (Day0) | 1 day after Drug (Day1) | 7 days after Drug (Day 7) | P |
|---|---|---|---|---|
| **Laboratory parameters** | | | | |
| Sodium | 136.6±1.5 | | 136.7±1.2 | 0.565 |
| Potassium | 4.3±0.5 | | 4.4±0.4 | 0.242 |
| Chloride | 94.6±21.9 | | 100.3±1.6 | 0.280 |
| Fasting blood sugar | 144.9±34.2 | | 142.7±35.2 | 0.084 |
| PP blood sugar | 265.6±67.6 | | 220.7±87.7 | 0.002 |
| QT interval | 420.6±14.4 | 421.7±16.9 | 425.0±17.9 | 0.492 |

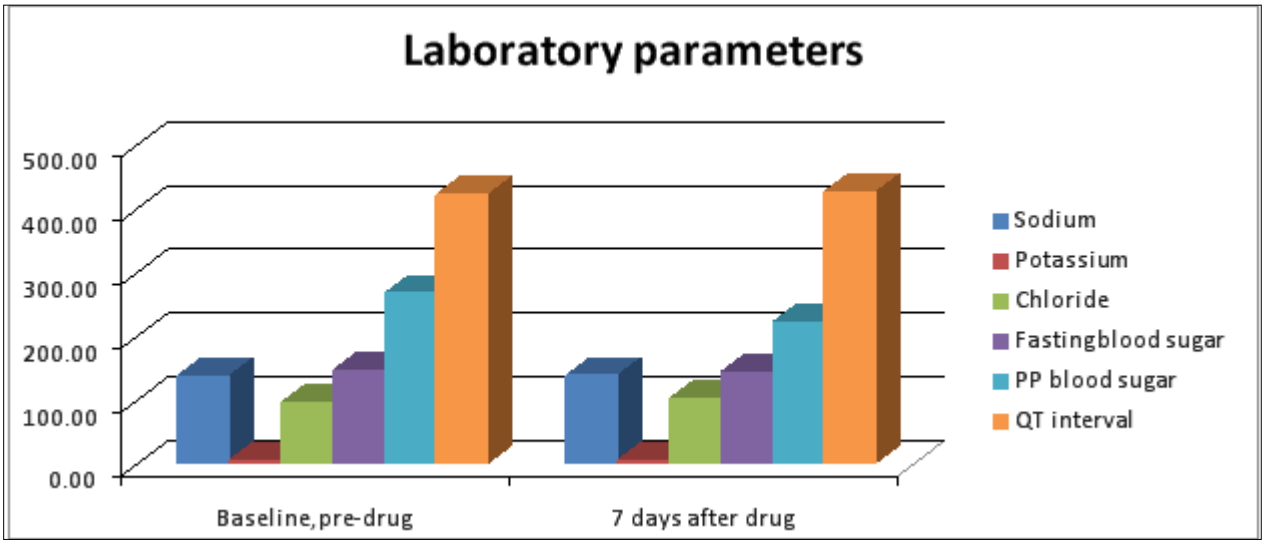



Figure 6a.

4 b) Table for comparison lab parameters Drug B.

| Characteristics | Baseline, pre-Drug (Day0) | 1 day after Drug (Day1) | 7 days after Drug (Day 7) | P |
|---|---|---|---|---|
| **Laboratory parameters** | | | | |
| Sodium | 136.9±1.9 | | 136.6±1.9 | 0.249 |
| Potassium | 4.3±0.5 | | 4.4±0.5 | 0.633 |
| Chloride | 92.1±26.9 | | 100.1±1.4 | 0.732 |
| Fasting blood sugar | 142.4±34.8 | | 141.3±26.9 | 0.410 |
| PP blood sugar | 260.7±63.0 | | 237.7±61.6 | 0.007 |
| QT interval | 422.8±17.9 | 420.7±19.1 | 422.03±18.0 | 0.679 |

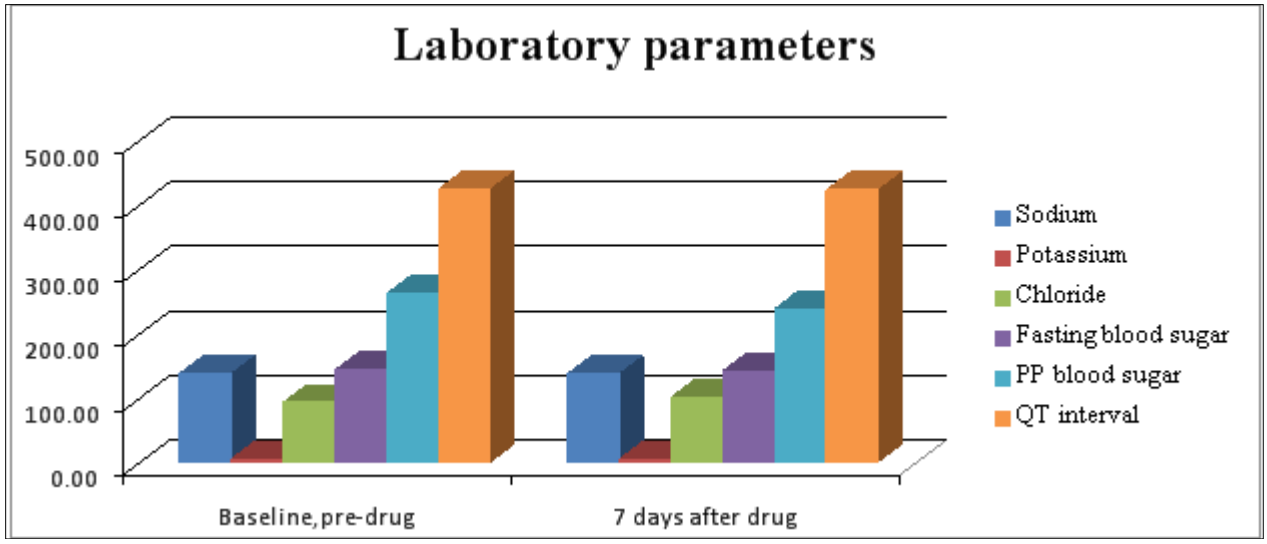



Figure 6b.

We assessed the laboratory and physical parameters of patients in Drug A and Drug B groups over the three visit days (Table 5a,5b,5c). There was no significant difference QT Interval..

5a) Table for comparison physiological parameters and lab parameters in between Drug A and Drug B in **Day0.**

| Characteristics | Drug A | Drug B | P |
|---|---|---|---|
| **Physiological Parameters** | | | |
| Pulse Rate | 79.8±10.8 | 78.0±10.1 | 0.619 |
| Respiratory Rate | 14.8±1.3 | 14.6±1.1 | 0.657 |
| Systolic Blood Pressure | 124.1±10.3 | 126.0±11.2 | 0.444 |
| Diastolic Blood Pressure | 77.4±6.5 | 77.7±8 | 1.000 |
| Body Temperature | 37±0.8 | 37.2±0.5 | 0.410 |
| **Laboratory parameters** | | | |
| QT Interval | 421.7±16.9 | 420.7±19.1 | 0.599 |

5b) Table for comparison physiological parameters and lab parameters in between Drug A and Drug B in **Day1**

| Characteristics | Drug A | Drug B | P |
|---|---|---|---|
| **Physiological Parameters** | | | |
| Pulse Rate | 80.4±10.4 | 78.5±10.5 | 0.868 |
| Respiratory Rate | 15.0±1.3 | 15.1±1.2 | 0.657 |
| Systolic Blood Pressure | 121.0±13.1 | 123.9±16.4 | 0.353 |
| Diastolic Blood Pressure | 76.3±6.9 | 78±7.5 | 0.220 |
| Body Temperature | 37.4±0.4 | 37.4±0.3 | 0.947 |
| **Laboratory parameters** | | | |
| Sodium | 136.6±1.5 | 136.9±1.9 | 0.540 |
| Potassium | 4.3±0.5 | 4.3±0.5 | 0.921 |
| Chloride | 94.6±21.9 | 92.1±26.9 | 0.425 |
| Fasting Blood Sugar | 144.9±34.2 | 142.4±34.8 | 0.844 |
| PP blood sugar | 265.6±67.6 | 260.7±63.0 | 1.000 |
| QT Interval | 420.6±14.4 | 422.8±17.9 | 0.574 |

5c) Table for comparison physiological parameters and lab parameters in between Drug A and Drug B in **Day7**

| Characteristics | Drug A | Drug B | P |
|---|---|---|---|
| **Physiological Parameters** | | | |
| Pulse Rate | 79.4±11.2 | 79.0±9.9 | 0.790 |
| Respiratory Rate | 14.6±1.9 | 14±1.9 | 0.249 |
| Systolic Blood Pressure | 121.9±10.3 | 124.9±10.9 | 0.230 |
| Diastolic Blood Pressure | 77.5±5.7 | 79.1±6.7 | 0.422 |
| Body Temperature | 37.3±0.35 | 37.3±0.4 | 0.786 |
| **Laboratory parameters** | | | |
| Sodium | 136.7±1.2 | 136.6±1.9 | 0.686 |
| Potassium | 4.4±0.4 | 4.4±0.5 | 0.740 |
| Chloride | 100.3±1.6 | 100.1±1.4 | 0.568 |
| Fasting Blood Sugar | 142.7±35.2 | 141.3±26.9 | 0.844 |
| PP blood sugar | 220.7±87.7 | 237.7±61.6 | 0.469 |
| QT Interval | 425.0±17.9 | 422.03±18.0 | 0.598 |

# DISCUSSION

This Study was carried out in West Bengal, India. There were no data regarding the safety of Teneligliptin in Indian type 2 diabetic patients with respect to QTc prolongation. The impact of Teneligliptin and Sitaglitpin on QTc was evaluated and compared as a double blind study. The total of 65 patients were included in this study during study to evaluate the QTc. After randomization,the total number of 65 patients were divided into two group ,in first group 33 patients received Drug A and second group 32 patients received Drug B.

As baseline parameters the mean HbA1C levels were 8.3±0.7 and 8.0±0.7, mean SGPT levels were 31.8±23.3 and33.6±23.6 mean creatinine levels were 0.6±0.1 and 0.7±0.1 for Drug A and Drug B groups respectively . There was significant difference in the mean creatinine levels between the two groups (p=0.013).. There was no difference in the mean baseline values for the other parameters in the two groups.The mean values of postprandial blood sugar of patients receiving Drug A , the values were found 265.6 mg/dl and 220.7 mg/dl respectively for baseline and 7days after Drug.,for Drug B the values were found 260.7 mg/dl and 237.7 mg/dl respectively for baseline and Day 7. Which showed statistically significantly lower postprandial blood sugar after receiving thei.e Drug A. p=0.002, Drug Bp=0.007.We were observed mean QTc interval for Drug A and Drug B value 420.6±14.4, 421.7±16.9, 425.0±17.9 and422.8±17.9, 420.7±19.1, 422.03±18.0 for baseline, day1,day7 and respectively.

Kutoh et al. in a 3-month study of 31 Drug naive Japanese T2DM patients, evaluated teneligliptin daily 20 mg as a monotherapy. This study found a significant reduction in HbA1c (from 10.34 ± 2.06 to 8.38 ± 2.23%, $P < 0.00001$) and fasting blood glucose (from 211.3 ± 68.4 to 167.3 ± 70.2 mg/dL, $P < 0.0002$) from the baseline. In my study meanbaseline HbA1C levels were 8.3±0.7 for Drug A and 8.0±0.7 Drug B we measured only baseline HbA1c value .And

fasting blood glucose for Drug A 144.9±34.2mg/dl to 142.7±35.2mg/dl P=0.084 and for DrugB142.4±34.8 mg/dl to 141.3±26.9 P=0.410. So in both Drug in this study fasting blood sugar level little bit lower.

Another study according to Japan pharmaceutical and medical device agency in 2012 a thorough QT/QTc evaluation study of teneligliptin 40 and 160 mg actively compared to moxifloxacin found a significant increase in latter dose. Teneligliptin 40 mg/day which is currently the maximal recommended dose prolonged the placebo-corrected QTcF (QTc corrected for heart rate) by 4.9 ms after 3 h. The 160 mg/day of teneligliptin significantly increased the QTcF by 11.2 ms after 1.5 h of the Drug was administered, almost similar to 12.1 ms of QTcF prolongation as observed 2 h after moxifloxacin. Comparison with this study we were observed mean QTc interval for Drug A and Drug B value 420.6±14.4, 421.7±16.9, 425.0±17.9, P=0.492 and 422.8±17.9, 420.7±19.1, 422.03±18.0 ,P=0.679 for baseline, day 1 after Drug , and 7days after respectively.There was no significant difference QT Interval both DrugA and Drug B. This is probably because our study used 20 mg of Teneligliptin dose for our patients.

The study has limitations. The study sample size was small. Larger studies with a bigger sample size may be helpful to provide a better estimation of difference in QT prolongation between the two Drugs. The study encountered significant number of patients who were lost to follow up. However this was the first study to assess QT prolongation between Sitagliptin and Teneligliptin in India.

# CONCLUSION

A comparative prospective multi centric study was carried out in diabetic out patients clinic of AMRI Hospital, Dhakuria, and IPGME&R and SSKM Hospital Kolkata from July 2018 to March 2019

The study was conducted with male and female diabetic patients of the age group 34 to 61years were treated with anti-diabetic Drugs .This study proved Drug A and Drug B as a good anti-diabetic Drug and has no QTc prolongation .

The study was conducted as a double blind randomized study, so in the end of the study when the results and statistical analysis had proved no significant effect on QTc prolongation both group of patients ; the identity of Drug A and Drug B would be revealed at the end of the study .

Since Sitagliptin and Tenegliptin having equal safety profiles, it will be easier for physicians to choose a Drug particularly in resource constrained countries like India.

# BIBLIOGRAPHY

1.I. c. g. team, "Type 2 Diabetees in Adult: Management," London: National Institute for Health and care Excellence, 2015,p28.

2.Chaudhury A, Duvoor C, Dendi V, Kralet S. i, Chada A, Ravilla R, Marco A, Shekhawat N, Montales M. T., Kuriakose K, A., Sasapu A. Beebe, Patil N., C. K. Musham and Lohan G. P., "Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management," Frontiers in Endocrinology, 2017, P. 1-12.

3. "Prevalence of diabetes worldwide countery and regional data. world health organisation," : http://www.who.int/diabetes/facts/worldfigures/en/Accessed June 6,2018.

4. DeFronzo RA, Bonadonna RC and Ferrannini E, "Pathogenesis of NIDDM.A Balance Overview," Diabetes care, 1992, 15:318-268.

5. Joshi. SR and Parikh RM , "India-Diabetes Capital of The World:Now Heading Towards Hypertension," J ASSOC phhysicians India 2007;55: , p 323-4.

6. Kumar A, Goel MK, Khanna P. Jain RB and Chaudhury V, "India Towards Diabetes Control:Key Issues," Australes Med J 2013;6(10):524-31.

7. Kaveeshwar C. J. SA, "The current state of diabetes mellitus in India.," AMJ, 2014 7, 1, 45-48..

8. Wild S, Roglie G, Green A, Sicree R and King H, "Global prealence of diabetes estimates for the year 2000 and projections for 2030," Diabetes care ; 2004,27(3); 1047-53.

9. Anjana RM, Deepa M, PradeepaR, kumarNarainMJ,Das.HK,Adhikari .P, Sahoo.B"Prevelance of diabetes and prediabetes in 15 states of india:results from the ICMR-INDIAB population based cross sectional study"August2017,vol.5

10.Zheng .Y, Sylvia H. Ley and Frank B. Hu, "Global aetiology and epidemiology of type 2 diabetes mellitus and its complications," NATURE REVIEWS | ENDOCRINOLOGY, 2017.

11. "Whilepaper.National Diabetes Fact Sheet 2002.American Diabetes Association.," : http://www.diabetes.org/diabetes-statistics/national-diabetes-fact-sheet.gsp. [Accessed 7 June 2018].

12. . "National Diabetes Education Program(NDEP).Guiding Principles for the care of people with or at risk for diabetes," : http://www.niddk.nih.gov. [Accessed June2018].

13. Defronzo RA., "Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus.," Diabetes (2009)58(4):773–95.

14. Proks P, Reimann F, Green N, Gribble F, Ashcroft F., "Sulfonylurea stimulation of insulin secretion.," Diabetes (2002) 51(3):5368–76.

15. Kalra S,.Unnikrishnan A. G,.Agrawal N and Singh A. K., "Linagliptin and Newer DPP-4 Inhibitors: Newer Uses and Newer Indications," Recent Patents on Endocrine, Metabolic & Immune Drug Discovery 2011, 5, 197-202l

16. Viollet B, Guigas B, Garcia N, Leclerc J, Foretz M, Andreelli F., "Cellular and molecular mechanisms of metfromin: an overview.," ClinSci (Lond) (2012) 122(6):253–70

17. "Sitagliptin an overview,"[Online]. Available: https://www.sciencedirect.com>topics. [Accessed 2019].

18. “Review Of sitagliptinphosphate:a novel treatment for type 2 diabetes”, Online available:https://www.ncbi.nlm.gov>articles [Accessed2019].

19. “Electrophysiology Procedure_PatientEducation_UCSF," [Online]. Available: https://www.ucsfhealth.org> [Accessed 2019].

20. “JANUVIA,INN:Sitagliptin”,Online Available:http://www.ema.europe.eu>documents[Accessed 2019].

21. .Fisman E. Z and. Tenenbaum A, "Antidiabetic treatment with gliptins:focus on cardiovascular effects and outcomes," Fisman and TenenbaumCardiovascDiabetol (2015) 14:129

22. "Teneligliptin-DrugBank,"[Online].Available:https://www.Drugbank.ca.Drugs. [Accessed 2019]

23. K. Danao, M. Shende, R. Gupta, N. Dumore and U. Mahajan, "Teneligliptin: DPP-4 inhibitor in the treatment of type II Diabetes Mellitus," International Journal of Phytopharmacy, no. Volume 7 Issue 4, 2017

24.Kutoha, E., Hiratea, M. and Ikenoa, Y. (2014) Teneligliptin as an Initial Therapy for Newly Diagnosed, Drug Naïve subjects With Type 2 Diabetes. Journal of Clinical Medicine Research, 6, 287-294.

25. Suryawanshi SY, Bhargava A, Agarwal P, Chamle V. Evaluation of safety and efficacy of teneligliptin in newly diagnosed Indian type 2 diabetes mellitus patients.52nd Annual Congress of European Association of Study in Diabetes, Munich. 2016:753. PS067

26. "Teneligliptin:Heralding Change in Type 2 Diabetes,"Online Available: https://www.scirp.org/journal/paperinformation.aspx?paperid=65290 [Accessed 2019]

27. . Hashikata T, Yamaoka-Tojo M, Kakizaki R, Nemoto T, Fujiyoshi K, NambaS, 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.

28. . Singh A. K, "Efficacy and safety of teneligliptin," Indian Journal of Endocrinology and Metabolism | Published by Wolters Kluwer - Medknow 2014;18.

29. . US Food and Drug Administration (FDA). Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-AntiarrhythmicDrugsAvailable From:http://www.fda.gov/downloads/Drugs/guidancecomplianceregulatoryinformation/guidances/ucm073153.pdf .[Last accessed on 2019].

30. . Modi, P. "Diabetes Beyond Insulin: Review of New Drugs for Treatment of Diabetes Mellitus," Current Drug Discovery Technologies, 2007, 4, 39-47.

31. Stonehouse A. H and Maggs D. G., "Emerging Therapies for Type 2 Diabetes," Current Drug Therapy, 2007, 2, 151-160.

32. . "Teneligliptin a DPP-4 inhibitor for the treatment of type 2 diabetes.-PubMed-NCBI," :http://./Teneligliptin_+a+DPP-4+inhibitor+for+the+treatment+of+type+2+diabetes.+-+PubMed+-+NCBI_files/28977.

33. Scheen A., "DPP-4 inhibitors in the management of type 2 diabetes:A critical review of head-to-head trials," Diabetes & Metabolism 38 (2012) 89–101.

34. . "A thorough QTc study to assess the effect of sitagliptin,a DPP4 inhibitor on ventricular repolarization in healthy subjects.-PubMed-NCBI files," [Online]. Available

35.http://./A+thorough+QTc+study+to+assess+the+effect+of+sitagliptin,+a+DPP4+inhibitor,+on+ventricular+repolarization+in+healthy+subjects.+-+PubMed+-+NCBI_files/28977

36. Waugh N,. Cummins E,.Royle P, Clar C.,.Marien M,. Richter B and Philip S., "Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation," Health Technology Assessment 2010; Vol. 14: No. 36

37. . Tang Y, Wang G.,. Jiang Z, Yan T.,. Chen Y, Yang M., Meng L., Zhu Y.,. Li C,. Li Z, Yu P. and Ni C., "Efficacy and safety of vildagliptin,sitagliptin, and linagliptin as add-on therapy in Chinese patients with T2DM inadequately controlled with dual combination of insulinand traditional oral hypoglycemic agent," DiabetolMetabSyndr (2015) 7:91

38. . "The DPP-4 inhibitor linagliptin does not prolong the QT interval at therapeutic and supratherapeutic doses,"
: http://./The+DPP-4+inhibitor+linagliptin+does+not+prolong+the+QT+interval+at+therapeutic+and+suprathe Hashikata T., Yamaoka-Tojo M., KakizakR.i, Nemoto T., Fujiyoshi, K. Namba1 S.,.Kitasato L, Hashimoto T., Kameda R., Maekawa E., Shimohama T., Tojo T. andAko J., "Teneligliptin improves left ventricular diastolic function and endothelial function in patients with diabetes," Heart Vessels rapeutic+doses_files/28977.

39. "Considerations for assessing the potential effects of antidiabetesDrugs on cardiac ventricular repolarization_ A report from the Cardiac Safety Re...-PubMed-NCBI," http://./Considerations+for+assessing+the+potential+effects+of+antidiabetes+Drugs+on+cardiac+ventricular+repolarization_+A+report+from+the+Cardiac+Safety+Re...+-+PubMed+-+NCBI_files/28977

40. .Kankanala SR, Rafay Syed, Quan Gong, BoxuRen, XiaoquanRao, JixinZhong"Cardiovascular safety of dipeptidyl peptidase-4 inhibitor:recentevidance on heart failure"may30,2018

41.KrishnaR,AddyC,TatosianD,GlasgowXS,GendranoIiiIN,RobberechtsM,HaazenW,deHoonJN, Depre M,Martucci A, Peng JZ, Johnson LevonasAO,WagnerJA,StochSA"Pharmacokinetics and Pharmacodynamics of Omarigliptin, a Once-Weekly Dipeptidyl Peptidase-4+(DPP-4) Inhibitor, After Single and Multiple Doses-, : http://./Pharmacokinetics+and+Pharmacodynamics+of+Omarigliptin,+a+Once-

Weekly+Dipeptidyl+Peptidase-4+(DPP-4)+Inhibitor,+After+Single+and+Multiple+Doses+in+H...+-+PubMed+-+NCBI_files/28977

42. Wilay j &sons"Efficacy and safety of teneligliptin, a novel dipeptidyl peptidase-4 inhibitor, in Korean patients with type 2 diabetes mellitus: a 24-week multicentre, randomized, double-blind,placebo-controlled phase III trial," Diabetes, Obesity and Metabolism 18: 2016. 528–532

43. . Leibovitz E, Gottlieb S, Goldenberg I, Gevrielov-Yusim N, MatetzkyS,Gavish D., "Sitagliptin pretreatment in diabetes patients presenting with acute coronary syndrome: results from the Acute Coronary Syndrome Israeli Survey (ACSIS)," CardiovascDiabetol. 2013;12:53

44. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR,Sherwin R, Zinman B., "Medical management of hyperglycemia type 2 diabetes: a consensus algorithm for the initiation andadjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes," Diabetes Care 2009; 32: 193-203

45. Williamson DA, Rejeski J, Lang W, Van Dorsten B, Fabricatore AN, Toledo K., "Impact of a weight management program on healthrelated quality of life in overweight adults with type 2 diabetes," Arch Intern Med 2009; 169: 163-171

46. I. M.-T. Juan José Marín-Peñalver, C. Sevillano-Collantes and F. J. d. Cañizo-Gómez, "Update on the treatment of type 2 diabetes mellitus," World J Diabetes 2016 September 15; 7(17): ISSN 1948-9358 . p354-395

47. :. Franz MJ, Boucher JL, Green-Pastors J, Powers MA., "Evidencebased nutrition practice guidelines for diabetes and scope and standards of practice.," Am Diet Assoc 2008; 108: S52-S58

48. . Nguyen NT, Nguyen XM, Lane J, Wang P., "Relationship between obesity and diabetes in a US adult population: findings from the National Health and Nutrition Examination Survey, 1999-2006.," ObesSurg 2011; 21: 351-355

49. GargalloFernández Manuel M, Breton Lesmes I, BasultoMarset J, QuilesIzquierdo J, FormigueraSala X, Salas-Salvadó J., "Evidence-based nutritional recommendations for the prevention and treatment of overweight and obesity in adults (FESNAD-SEEDOconsensus document).The role of diet in obesity treatment (III/III).," NutrHosp 2012; 27: 833-864

50. "Thorough QT study of the effects of vildagliptin, a dipeptidyl peptidase IV inhibitor, on cardiac repolarization and conduction in healthy volunteers. - PubMed - NCBI," :http://./Thorough+QT+study+of+the+effects+of+vildagliptin,+a+dipeptidyl+peptidase+IV+inhibitor,+on+cardiac+repolarization+and+conduction+in+healthy+volunteers.+-+PubMed+-+NCBI_files/28977.

51. "The dipeptidyl peptidase-4 inhibitor-sitagliptin modulates calcium dysregulation,inflammation, and PPARs in hypertensive cardiomyocytes.-PubMed-NCBI,"http://./The+dipeptidyl+peptidase-4+inhibitor sitagliptin+modulates+calcium+dysregulation,+inflammation,+and+PPARs+in+hypertensive+cardiomyocytes.+-+PubMed+-+NCBI_files/28977.

52. .Garg S. K and. Shah V. N "Newer Therapies for Diabetes Management," DIABETES TECHNOLOGY & THERAPEUTICS 2014 Volume 16, Supplement 1, DOI: 10.1089/dia.2014.1514.

53. Hibuse T, Maeda N, Kishida K, Kimura T, Minami T, Takeshita E, Hirata A, Nakagawa Y, Kashine S, Oka A, Hayashi M, Nishizawa H, Funahashi T, Shimomura I., "pilot 3-month sitagliptin treatment increases serum adiponectin level in Japanese patients with type 2 diabetes mellitus—a randomized controlled trial START-J study.," Cardiovasc Diabetol.2014;13:96

54. E. Kutoh, M. Hirate and Y. Ikeno, "Teneligliptin As an Initial Therapy for Newly Diagnosed,Drug Naive Subjects With Type 2 Diabetes," J Clin Med Res. 2014;6(4):287-294.

55. Andrews RC, Cooper AR, Montgomery AA, Norcross AJ,Peters TJ, Sharp DJ, Jackson N, Fitzsimons K, Bright J, Coulman K, England CY, Gorton J, McLenaghan A, Paxton E, Polet A, Thompson C, Dayan CM., "Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial.," Lancet 2011; 378: 129-139

56. Keshavarz K, Lotfi F. ,Sanati E., Salesi, M. Hashemi-Meshkini A. ,Jafari M., Mojahedian M., Najafi B. andNikfar S., "Linagliptin versus sitagliptin in patients with type 2 diabetes mellitus: a network meta-analysis of randomized clinical trials," Keshavarz et al. DARU Journal of Pharmaceutical Sciences (2017) 25:23

57. Karagiannis T., Paschos P., Paletas K.,.Matthews D and Tsapas. A., "Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis," PubMed Health. A service of the National Library of Medicine, National Institutes of Health.Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. York (UK): Centre for Reviews and Dissemination (UK); 1995.

58. .BailleyCJ., "The current Drug treatment landscape for diabetes and perspectives for the future.," ClinPharmacolTher (2015) 98(2):170–84

# THANK YOU