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A PROSPECTIVE OBSERVATIONAL STUDY ON THE ANALYSIS OF UTILISATION PATTERN, SAFETY AND EFFECTIVENESS OF TENELIGLIPTIN IN TYPE 2 DIABETIC PATIENTS WITH CARDIOVASCULAR DISEASE

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ABSTRACT

Diabetes mellitus is a group of metabolic disorders characterised by hyperglycaemia and abnormalities in carbohydrate, fat and protein metabolism. It may result in chronic microvascular and macrovascular complications. The objectives of the study were to determine the utilization pattern, safety and effectiveness of Teneligliptin in type 2 diabetic patients with cardiovascular disease. This Prospective observational study was carried out at the cardiology department of a tertiary care teaching hospital for a period of six months. Patients were recruited as per the inclusion criteria. Predesigned structured proforma was used to collect information from the prescribing physicians regarding the effectiveness of Teneligliptin in T2DM patients. Information on the glycemic parameters at baseline prior to starting Teneligliptin and at the end of 3 months therapy was collected. The effectiveness was assessed by analyzing the mean change in 3-month values of HbA1c, FBS and PPBS. The eGFR can be calculated using MDRD equation. QTc interval prolongation checked through evaluation of ECG. The medication adherence was estimated using the MORISKY MEDICATION ADHERENCE SCALE - 8. Safety was assessed using NARANJO'S CAUSALITY SCALE. This study shows that Teneligliptin provided statistically significant and clinically meaningful reductions in the HbA1c, FBS and PPBS in cardiac patients with T2DM.

1. INTRODUCTION

1.1 DIABETES MELLITUS

Diabetes mellitus is a group of metabolic disorders characterised by hyperglycaemia and abnormalities in carbohydrate, fat and protein metabolism. It may result in chronic microvascular and macrovascular complications.[1]

Diabetes mellitus is the most common of the endocrine disorders.T2DM is a chronic condition, characterised by hyperglycaemia due to impaired insulin secretion with or without insulin resistance, which is inability of cells to respond adequately to normal levels of insulin.[2]

Cardiovascular disease remains the key comorbid condition and main contributor to mortality in the setting of diabetics – commonly in the form of coronary heart disease but also in the incremental risk associated with diabetes for cardiovascular disease, peripheral vascular disease and heart failure. It is recommended that screening for potential T2DM in people with cardiovascular disease is initiated with HbA1c and FBS. Patients with diabetes have 2- 4 times increased risk for development of death from CHD. Diabetes is associated with increased risk for MI.

1.1.1 EPIDEMIOLOGY

The prevalence of T2DM varies widely between population reflecting difference in both environment influences and genetic susceptibility. The diabetic epidemic is mainly driven by an explosive increase in the prevalence of type 2 diabetes which accounts for more than 90% of all diabetes cases. Type 2 diabetes now affects 6.6% of the world's adult population. More than 80% of global burden to T2DM is borne by developing countries.

Diabetes mellitus is one of the major chronic non communicable diseases that affect millions globally. The number of people with diabetes has risen from 108 million in 1980 to 425 million in 2017. The global prevalence of diabetes among adults over 18 years of age had risen from 4.7% in 1980 to 8.5% in 2014.[3]

Diabetes in India

India is facing an epidemic of diabetes, with high prevalence in urban area. Over the past 30 years, the prevalence of diabetes has increased to 12 – 18% in urban India and 3 – 6% in rural India with significant regional variation.

Significant determinants of diabetes are age, BMI, obesity, low physical activities and family history of diabetes. India's develop diabetes a younger age and those younger than 45 years accounts for 36% of all diabetes in India. Longer duration of diabetes lead to greater complication and this could threaten the national economy.

Diabetes in Kerala

Kerala is the diabetes capital of India with a prevalence of diabetes as high as 20% - double the national average of 8%. Several studies from different parts of Kerala support the high prevalence of diabetes. One study from central Kerala reported a prevalence of diabetes at 20% and prediabetes at 11%.[4]

Epidemiology of cardiovascular complications of T2DM

Macrovascular disease, especially CVD accounts for most of the mortality in patients with T2DM who have a much greater age related risk for CVD than non diabetics. The higher risk is due to the greater prevalence of cardiovascular risk factors among diabetics, including an abnormal lipoprotein profile, prothrombotic tendency, hypertension and obesity. Additionally the altered metaboilitic environment (i.e., hyperglycemia, hyperinsulinimia and insulin resistance) resulting from the diabetic state directly impacts on the cardiovascular status.[5-7] Cardiovascular events such as MI are associated with a greater case fatality rate, and this has been attributed to altered myocardial energy metabolism, impaired cardiac remodelling after infarction and a higher incidence of CHF in the first year after infarction.[8-10]

1.1.2 ETIOLOGY

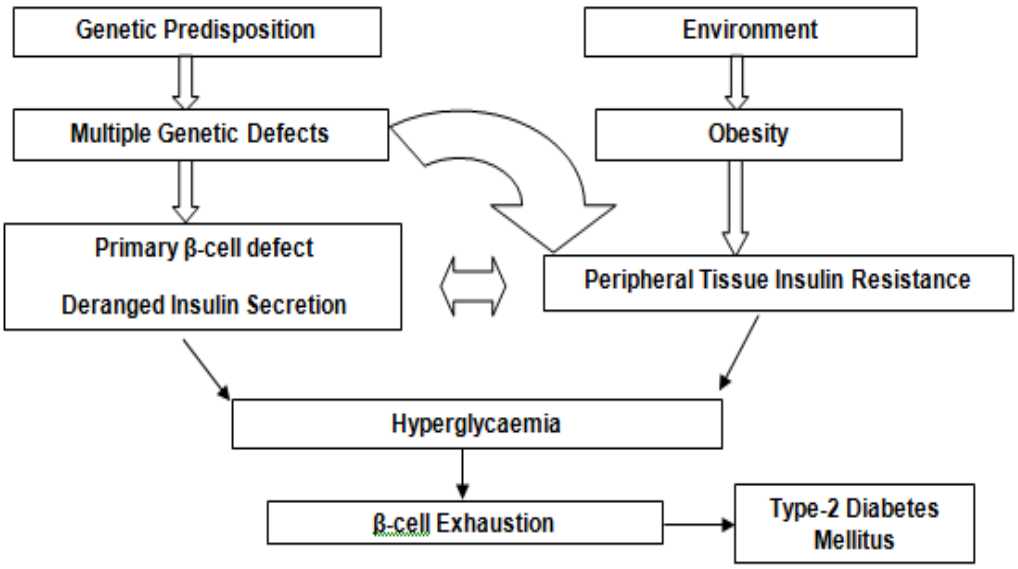

Fig no. 1: Etiology Of Diabetes.

1.1.3. RISK FACTORS FOR TYPE 2 DIABETES MELLITUS

- Overweight (≥25kg/m^2)
- Family history of diabetes (first- degree relative)
- Physical inactivity
- Ethnic predisposition
- History of PCOS, GDM or macrosomia
- Clinical conditions associated with insulin resistance(eg: severe obesity)
- Hypertension (≥ 140/90mmHg or on antihypertensive therapy)
- Dyslipidemia
- Cardiovascular disease.[11]

1.1.4 PATHOPHYSIOLOGY

Type -1 diabetes

The major factor responsible for type-1 diabetes is autoimmune attack by T-antigen result in destruction of β cell, which in turn result in insulin deficiency and less production of insulin. Various factors are there which triggered the autoimmune destruction of beta cell, such as environmental factor, genetic factor. Type-1 diabetes is generally occurring before age of 30 years. Individual suffering from type -1 diabetes has to take insulin from outside of body because his/her body is no longer able to produce insulin.[12] Type -1 diabetes also result in increase in ketone level because due to less insulin glucose could not enter into cell and thus remain in the blood vessel due to which body fat is broken and release glycerol and free fatty acid through biolysis, this free fatty acid can be converted into ketone and which ultimately decrease concentration of hydrogen ion and also decrease level of electrolyte thus cause dehydration and frequent urination which are common symptom of type-1 diabetes, untreated ketoacidosis may result in death.[13]

Type-2 diabetes

- ✓ Impaired insulin secretion is a hallmark finding; β-cell mass and function are both reduced, and β-cell failure is progressive.
- ✓ Normally, the gut incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are released and stimulate insulin secretion when nutrients enter the stomach and intestines. Patients with type 2 DM have a reduced incretin effect due to decreased concentrations of or resistance to the effects of these incretin hormones.

- ✓ Insulin resistance is manifested by excessive hepatic glucose production, decreased skeletal muscle uptake of glucose, and increased lipolysis and free fatty acid production.
- ✓ Excess glucagon secretion occurs because T2DM patients fail to suppress glucagon in response to meals because of GLP-1 resistance/deficiency and insulin resistance/deficiency, which directly suppress glucagon.

1.1.5 TYPES OF DIABETES

Diabetes is mainly classified in three types.

Type1

When the β cell of pancreas is unable to produce sufficient amount of insulin which leads to insulin deficiency. Destruction of β-cell by autoimmune attack by T cell is the primary cause of type1 diabetes it is also called insulin dependent diabetes mellitus.[14]

Type2

When insulin produced by β cell is resist by cell, it is also called non-insulin dependent diabetes mellitus in type 2 diabetes cells not responded to the insulin produced by β cell.[15]

Type3

Gestational diabetes occurs when pregnant women developed high blood sugar level without previous history.[16]

Etiologic classification of diabetes mellitus

Type 1 diabetes

- ❖ Immune mediated
- ❖ Idiopathic

Type 2 diabetes

Other specific types

- ❖ Genetic defects of β-cell function

1. Chromosome 20, HNF-4α (MODY1)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 12, HNF-1α (MODY3)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-1β (MODY5)
6. Chromosome 2, *NeuroD1* (MODY6)

7. Mitochondrial DNA
8. Others

❖ Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others

❖ Diseases of the exocrine pancreas

1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others

❖ Endocrinopathies

1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others

❖ Drug or chemical induced

1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone

6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. γ-Interferon
11. Others

❖ Infections

1. Congenital rubella
2. Cytomegalovirus
3. Others

❖ Uncommon forms of immune-mediated diabetes

1. "Stiff-man" syndrome
2. Anti-insulin receptor antibodies
3. Others

❖ Other genetic syndromes sometimes associated with diabetes

1. Down syndrome
2. Klinefelter syndrome
3. Turner syndrome
4. Wolfram syndrome
5. Friedreich ataxia
6. Huntington chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader-Willi syndrome
11. Others

Gestational diabetes mellitus.[17]

1.1.6 SYMPTOMS

Symptoms of diabetes include

- Frequent infections

- Glycosuria (presence of glucose in the urine)
- Hunger
- Increased urination (polyuria) and nocturia (excessive urination at night)
- Numbness and tingling
- Slow wound healing (hyperglycemia inhibits activity of neutrophils, a type of white blood cell)
- Thirst
- Visual changes
- Vomiting
- Weight loss, easy fatigability, irritability, nausea, and ketoacidosis (ketonuria).[18]

1.1.7 DIAGNOSIS

- Criteria for diagnosis of DM include any one of the following

a) A1C of 6.5% or more

b) Fasting (no caloric intake for at least 8 hours) plasma glucose of 126mg/dl (7mmol/L) or more

c) Two-hour plasma glucose of 200mg/dl (11.1mmol/L) or more during an oral glucose tolerance test (OGTT) using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

d) Random plasma glucose concentration of 200mg/dl (11.1 mmol/L) or more with classic symptoms of hyperglycemia or hyperglycemic crisis.

- Normal fasting glucose(FPG) less than 100mg/dl
- Impaired fasting glucose (IFG) is FPG 100-125mg/dl
- Impaired glucose tolerance (IGT) is diagnosed when the 2 hour postload sample of OGTT is 140-199mg/dl
- Pregnant woman should undergo risk assessment for GDM at first prenatal visit and have glucose testing if at high risk(eg. positive family history of GDM, marked obesity).[1]

1.1.8 MANAGEMENT

Non pharmacologic therapy

Patients with T2DM often require caloric restriction to promote weight loss. Rather than a set diabetic diet, advocate a diet using foods that are within the financial reach and cultural milieu of the patient. As most patients with T2DM are overweight or obese, bedtime and

between meal snacks are not needed if pharmacologic management is appropriate.[17]

Activity

In general, most patients with DM can benefit from increased activity. Aerobic exercise improves insulin resistance and glycemic control in majority of individuals reduces cardiovascular risk factors, contributes to weight loss or maintenance and improves well being. In addition, several complications (autonomic neuropathy, insensate feet, and retinopathy) can require restrictions on the activities recommended. Physical activity goals include at least 150 minutes per week of moderate (50-70% maximal hear rate) intensity exercise.[17]

Pharmacological therapy

CLASSIFICATION

1. **Enhance insulin secretion**

❖ Sulfonylureas (K^+-ATP channel blockers)

First generation: Tolbutamide

Second generation: Glibenclamide, Glipizide, Glimiperide

❖ Meglitinide/Phenylamine Analouges

Repaglinide, Nateglinide

❖ Glucagon like peptide receptor agonist

Exenatide. Liraglutide

❖ Dipeptidyl peptidase 4 inhibitors

Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, Teneligliptin

2. **Overcome insulin resistance**

❖ Biguanide : Metformin

❖ Thiazolidinediones : Pioglitazone

❖ α Glucosidase Inhibitor : Acarbose, Voglibose, Migliptol

❖ Amylin analogue : Pramlintide

❖ Dopamine D2 Receptor agonist : Bromocriptin

❖ Sodium glucose co-transport 2 inhibitor : Dapagliflozine

❖ Miscellaneous anti-diabetic drugs

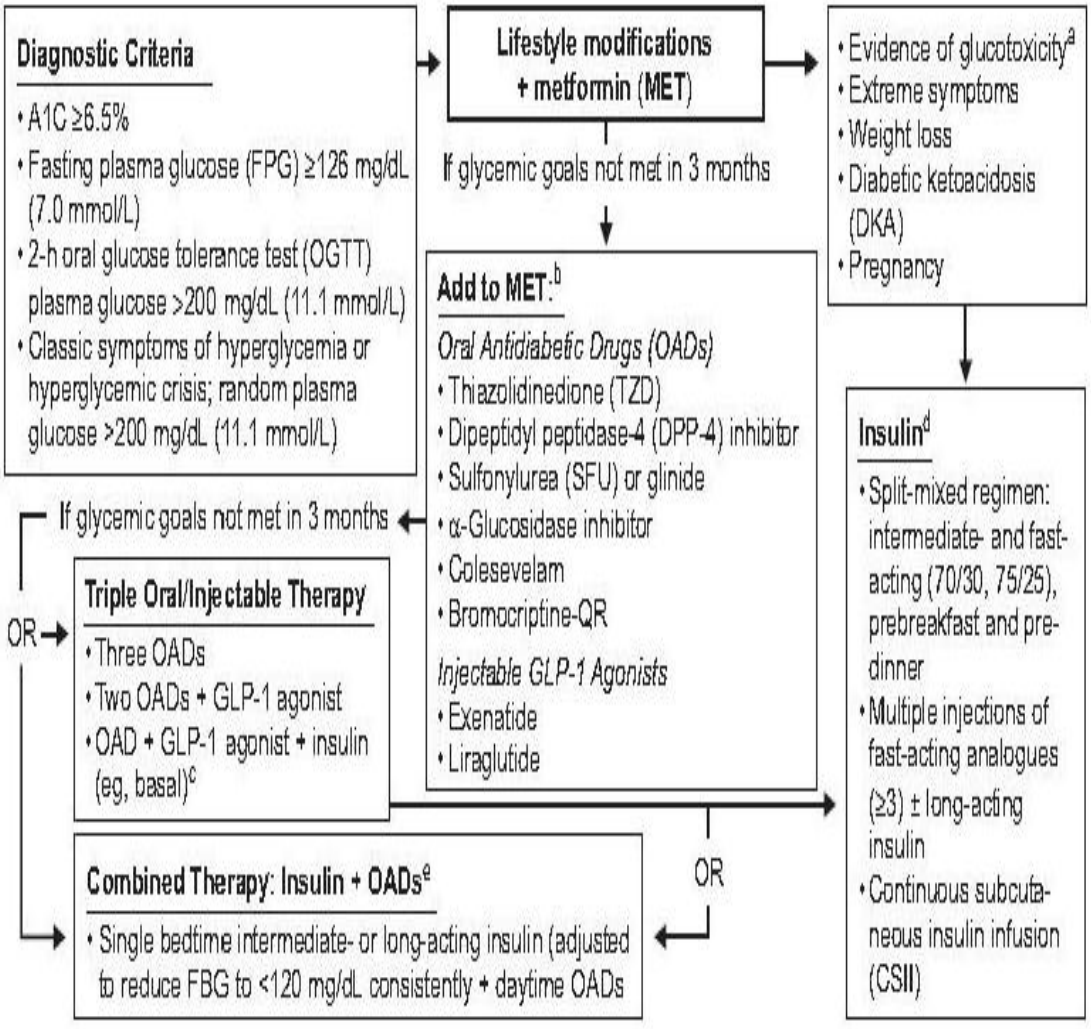

Fig No. 2: Algorithm Of Treatment T2DM.

1.1.9 COMPLICATIONS

Diabetes related complications can be broadly classified as

1) Microvascular complications

a) Diabetic retinopathy

b) Diabetic nephropathy

c) Diabetic neuropathy

2) Macrovascular complications

a) Cardiovascular disease

b) Cerebrovascular disease

c) Peripheral vascular disease

1.2 DIPEPTIDYLPEPTIDASE-4INHIBITORS

The DPP- 4 inhibitors are a new class of drugs that work on the incretin system. They are also commonly referred to as the 'gliptins'. They are now recommended as second or first line agents in treatment of diabetes by guidelines like American Diabetes Association 2016 and American association of clinical endocrinologist and American college of endocrinology 2016.[19,20]

A list of gliptins are given

- Sitagliptin (approved as Januvia by US FDA in year 2006)
- Vildagliptin (approved as Galvus by EU in year 2007)
- Saxagliptin (approved as Onglyza by US FDA in 2010)
- Linagliptin (approved as Tradjenta by US FDA in year 2011)
- Alogliptin (approved for use in Japan)
- Teneligliptin (approved and marketed product in Japan since 2012 and in Korea since 2014)

1.2.1 MODE OF ACTION.

DPP- 4 finds its major role in inactive action of the incretin hormones glucagon like peptide-1 (GLP-1) and glucose inhibitory peptide (GIP) involved in initiation of the insulin secretion cascade following a meal. The enzyme is a serine protease which reduces GLP-1 resulting in small half-life of the hormones. Thus, inhibition of DPP-IV results in an increase in half-life of incretin hormones and eventually in augmentation of insulin secretion.[21, 22]

1.2.2 PHARMACOKINETICS

DPP- 4 inhibitors are predominantly renally excreted. Sitagliptin is mainly excreted as unchanged drug in the urine, with a small metabolic contribution from the liver via the cytochrome P450 system. The kidney is thought to be mainly responsible for metabolic hydrolysis of vildagliptin to an inactive compound. Although saxagliptin is mainly eliminated renally, some hepatic biotransformation does occur via the cytochrome P450 system (CYP3A4/5), which results in a metabolite with half the potency of the parent compound.[10] Teneligliptin is metabolized by CYP3A4 and flavin containing oxygenases.

1.2.3 BIOCHEMISTRY

Dipeptidyl peptidases are a family of several complex proteases with similar chemical structure, the biological roles and identity of their endogenous substrates remains poorly

understood for majority of them.[23] Therefore, a cautious evaluation of the selectivity and specificity of any pharmacological compound used to inhibit DPP - 4 activity is required.[24] For the time being, DPP - 4 is the best known member of the family and acts as a membrane-anchored cell surface peptidase transmitting intracellular signals through a short intracellular tail. In humans, the DPP - 4 gene is located on chromosome 2 locus 2q24.3 and composed of 26 exons that encode a protein of 766 amino acids.[25] DPP - 4 is widely expressed in several cell types, particularly in exocrine glands and absorptive epithelia. It is mainly found in the brush borders of epithelial cells of the proximal convoluted tubules in the kidney, in the small and large intestine, prostate tissue, hepatocytes, fibroblasts and in activated leukocytes,[26-29] preferentially cleaving peptide hormones containing a position two alanine or proline.[23]

The incretins are gut-derived hormones, constituents of the glucagon super family, released in response to nutrient ingestion, mainly sugars and fat. They put forth a wide range of effects, including stimulation of pancreatic insulin secretion in a glucose-dependent manner and play a central role in local gastrointestinal and whole-body physiology. The principal incretins are the glucose-dependent insulinotropic polypeptide (GIP) and the glucagon-like peptide-1 (GLP-1), representing the endogenous physiological substrates for DPP - 4 activity.[30, 31] GIP is secreted from the L-cells of the distal ileum and colon and GLP-1 from the K-cells in the duodenum and jejunum.[32] GLP-1 is stronger than GIP regarding insulinotropic activity, and their biological activity is cumulative. GIP has a half life of approximately 7 min, much longer than the 2 min documented for GLP-1.[23, 33, 35] Therefore, taking into consideration the DPP - 4 mechanism of action, its pharmacological inhibition by gliptins will avoid interaction with its substrates, increasing plasmatic GIP and GLP-1 concentrations and stimulating insulin biosynthesis.[35]

Efficacy as glucose lowering agent

❖ **Monotherapy**

All approved DPP – 4, lower HbA1c when studied in new patients or at least when used in monotherapy. The approximate effectiveness is an HbA1c reduction by 0.6 – 0.9%. Accordingly DPP – 4 can be used as initial drug therapy, however only in patients who do not tolerate or have contraindication for the use of Metformin.

❖ **Add on to oral anti-diabetic agents**

All approved DPP – 4 have been studied as add on to previously existing treatment with oral anti-diabetic agents like Metformin, Sulfonylureas, Thiazolidinediones, if the previous treatment alone did not provide glycemic control with HbA1c in the target range.

❖ **Inability to provoke hypoglycaemia**

DPP – 4 exert their antidiabetic effects mainly through augmenting GLP-1 concentrations in response to nutrient intake, with some effect also in the basal state. GLP-1 or GLP-1 receptor agonist, even at high doses do not themselves provoke hypoglycaemic episodes. The biologic explanation is that they don't have the ability to close ATP dependent potassium channel, which would lead to the depolarisation of β- cells and subsequent release of insulin. In line with these cell biologic considerations, in clinical trials, DPP – 4 treatment did not raise the risk of hypoglycaemic episodes when used in monotherapy or on top of Metformin, an example for a agents which themselves do not have the potential to provoke hypoglycaemic episodes.

Rather there appears to be a potential that endocrine pancreatic α- cell responsiveness to hypoglycaemia maybe improved by DPP - 4.

Nevertheless DPP - 4 donot prevent hypoglycaemic episodes provoked by sulfonyl ureas. Thus in combination with sulfonyl ureas, DPP – 4 lose one of their typical advantages. Therefore before using DPP – 4 together with sulfonyl ureas, one should carefully weigh potential advantage of such a combination against this obvious disadvantage of allowing for hypoglycaemic episodes.[36]

1.3 TENELIGLIPTIN

Teneligliptin is a prolylthiazolidine[37] approved for the treatment of T2DM in Japan in 2012 and in South Korea in 2014.[38,39] A 4-week, randomized, double-blind, placebo-controlled trial showed a significantly improved 24-h blood glucose control,[40] and a subsequent pooled post hoc analysis including more than 700 patients provides evidence of the safety and efficacy of a 52 weeks mean follow-up of use of teneligliptin 20 mg daily as monotherapy or in combination with sulfonylurea, glinide, biguanide or α-glucosidase inhibitor in Japanese patients with T2DM.[37] The dose can be increased up to 40 mg per day.[41] Teneligliptin was also used as an initial monotherapy for drug-naive newly diagnosed T2DM subjects. It

activated beta-cell function and decreased insulin resistance, being rather effective in reducing both fasting blood glucose levels and HbA1C.[42]

Regarding the cardiovascular effects, it should be pinpointed that QT/QTc evaluations were performed for this compound.[41] No QT prolongations were detected with 40 mg daily of teneligliptin, which is the maximal dose in usual clinical practice. Anyway, a mild QTc transient prolongation was documented while using supraclinical dosages. Therefore, caution is needed if the drug is used for a long period or in co-administration with medications known to cause QT prolongation on their own.[41] On the other hand, teneligliptin treatment was associated with improvements in left ventricular function—particularly diastolic—and endothelial functions, as well as with an increase in serum adiponectin levels.[43]

Teneligliptin is a novel DPP- 4, having a unique chemical structure which is characterized by five consecutive rings (J-shaped), which might account for its unique potency and half-life time.[42,44] Teneligliptin was introduced in India in May 2015 and is available at almost one quarter to one fifth of the cost of other DPP-4 inhibitors (namely Sitagliptin, Vildagliptin, Saxagliptin, and Linagliptin). In a very short span of time (8–9 months) Teneligliptin has become the most widely prescribed DPP-4 inhibitor in India.[45]

Teneligliptin appears to possess a different chemical structure when compared to other DPP-4Is. An X-ray co-crystallography study of Teneligliptin found that the key interaction between the phenyl ring on the pyrazole and binding to “anchor lock domain” of S2 extensive subsite, boosts its potency, duration of action *in vivo*, and enhances selectivity.[47]

An X-ray crystallography study[46] revealed that DPP-4 can be categorized into three classes on the basis of their binding subsites of the DPP-4 molecule.

i) Vildagliptin and Saxagliptin (Class 1) form interactions with the core S_1 and S_2subsites and a covalent bond with Ser630 in the catalytic triad.
ii) Alogliptin and Linagliptin (Class 2) form interactions with the S_1 and/or S_2 subsites in addition to the S_1 and S_2subsites.
iii) Sitagliptin and Teneligliptin (Class 3) form interactions with the S_1, S_2, and S_2 extensive subsites.

Teneligliptin binds to the S_2 extensive subsites via an 'anchor lock domain', and this interaction may be related to the potency of inhibition, the residence time for binding to DPP-4, and the long duration of action *in vivo*.[46]

Teneligliptin has a half-life of 24.2 h, with resulting DPP-4 inhibition throughout the day, and suppression of postprandial hyperglycemia after all three daily meals.[30, 40]

1.4 DRUG UTILIZTION STUDIES

Drug utilization research was defined by the WHO in 1977 as the "Marketing, distribution, prescription and use of drugs in a society, with special emphasis on resulting social, medical and economic consequences. A drug utilization study is an essential part of pharmacoepidemiology. Drug utilization research may be divided into.

i) Descriptive studies
ii) Analytical studies

The principle aim of drug utilization studies is to facilitate rational use of drug which means prescription of a well documented drug at an optimal dose and affordable price.

1.5 MORISKY MEDICATION ADHERENCE SCALE (MMAS-8)

Non-adherence to medications is considered as one of the largest drug related issues. WHO states that non-adherence to medications is a "worldwide problem of striking magnitude."[48] Poor medication adherence can cause negative health outcomes such as worsening disease or even death and studies showed that there was an association between poor adherences to medications indicated for chronic diseases with health resources utilization.[49] Poor medication adherence also may result in increased health care cost. There are 33%-69% of drug-related hospital admissions in US are because of poor medication adherence, along with a cost of about $100 billion a year.[50]

This questionnaire may contain 8 questions; the score will be given according to the answer specified by the patient. For each first 7 questions, there were two possible answers: YES/ NO. Adherence for these two answers were set a score as YES =1, NO = 0 and the 8th question contain five possible answers. Medication adherence is calculated on the basis of total score of medication adherence questionnaire.

SCORE

> 2 = low adherence

1or 2 = medium adherence

0 = high adherence

1.6 ESTIMATING GLOMERULAR FILTRATION RATE

The normal serum creatinine reference interval does not necessarily reflect a normal GFR for a patient. An estimated GFR (eGFR) calculated from serum creatinine using an isotope dilution mass spectrometry (IDMS) traceable equation is a simple and effective way in which laboratories can help health care providers detect CKD among those with risk factors- Diabetes, Hypertension, Cardiovascular disease, or family history of kidney disease. Assessment of kidney function through eGFR is essential once albuminuria is discovered. Providers also may use eGFR to monitor patients already diagnosed with CKD.

1.6.1 MDRD EQUATION

The following is MDRD Study equation

GFR (ml/min/1.73 m2) = 175 × (Ser.cr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American).

The equation does not require weight or height variables because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.[51]

Fig No. 3 Naranjo's Interpretation Scale.

Score	Interpretation of Scores
Total Score > 9	**Definite.** The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.
Total Score 5 to 8	**Probable.** The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	**Possible.** The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤ 0	**Doubtful.** The reaction was likely related to factors other than a drug.

2. REVIEW OF LITERATURE

2.1 Priti singh,[57] ***et al.*, (2017);** Conducted a study on topic "Glycemic effect of fixed dose combination o teneligliptin and metformin in T2DM patients". The main objective of present

study was to evaluate the effect of teneligliptin and metformin fixed dose combination on glycemic parameters in the treatment of T2DM in India. In this prospective observational study total 70 patients were screened and among them 40 patients were eligible to be enrolled in the study. Teneligliptin (20mg/day), Metformin (500 mg/day) fixed dose combination was prescribed in patients with type 2 diabetes and changes in the glycemic parameters were observed at every 4 weeks for 16 weeks treatment whch were compared with baseline. there was statistically significant improvement in mean HbA1c, FBS and PPBS with teneligliptin and metformin fixed dose therapy.

2.2 Sharma SK,[53] ***et al.*, (2016);** Conducted a study on topic "Teneligliptin in management of type 2 diabetes mellitus." This review evaluates the efficacy and safety of Teneligliptin in the management of T2DM. Teneligliptin has been systematically evaluated in T2DM as monotherapy with diet and exercise and in combination with Metformin, Glimepiride, Pioglitazone, and Insulin in short-term (12 weeks) and long-term (52 weeks) studies. These studies have reported a reduction in HbA1c of 0.8%-0.9% within 12 weeks of therapy. Two 52-week studies reported sustained improvement in glycemic control with Teneligliptin. Teneligliptin has been found to be well tolerated, and the safety profile is similar to other dipeptidyl peptidase 4 inhibitors. Concluded that Teneligliptin provides clinically significant glycemic control within 12 weeks, which was maintained upto 52 weeks. It is useful both as monotherapy and in combination with other antidiabetic drugs. It can be also used in patients with the renal impairment and mild to moderate hepatic impairment.

2.3 Riyaz Mohammed,[54] ***et al.*, (2016);** Conducted a study on topic "Efficacy of Teneligliptin in T2DM." Patients with HbA1c of 7.0–10.0% and on Metformin upto 1000 mg/day were selected for the study. 130 Known diabetic patients were selected, out of which only 56 patients were eligible. These patients were randomly divided into two groups both of whose baseline FBS, PPBS, HbA1c was determined, group A comprises 28 patients the patients were put on Teneligliptin 20 mg per day apart from Metformin 1gm /day, Group B comprises of 28 patients and these patients were already on Metformin 500mg-1gm per day but there glycemic control was poor, all these patients in group B received an escalation of Metformin dose upto 2.5gm/day, to achieve glycemic control. It was observed that the mean HbA1c for Teneligliptin group after 30 weeks was 7.21% versus 7.63% in metformin group. HbA1c was significantly reduced in the Group A patients. Conclusion, the addition of

Teneligliptin to metformin treatment was effective and well tolerated in patients with type 2 diabetes.

2.4 Sujoy Ghosh,[52] ***et al.*, (2016);** Conducted a study on topic "Teneligliptin real-world efficacy assessment of T2DM patients in India." Information were collected about the glycemic parameter prior to starting teneligliptin and at the end of 3 months therapy was collected. Efficacy was analyzed by mean change in the 3 month values of HbA1C, FPG and PPG. Data of 4305 patients was available for analysis. At the end of the therapy, there was significant improvement in mean HbA1C, FPG and PPG with Teneligliptin therapy. So data suggest that Teneligliptin significantly improves glycemic control in Indian patients with T2DM prescribed either as monotherapy or combination therapy.

2.5 Manish Maladkar,[55] ***et al.*, (2016);** Conducted a study on topic "Teneligliptin: Heralding Change in Type 2 Diabetes." The objective of this study is to provide a comprehensive datum analysis of Teneligliptin in the management of type 2 diabetes. 194 patients with type II diabetes mellitus, were treated for 120 days with Teneligliptin (20 mg/day) alone, Teneligliptin add on Glimepiride. It summarizes the unique pharmacodynamic & pharmacokinetic advantages of Teneligliptin and additionally its pleiotropic benefit of cardio protection. It provides a comprehensive comparison of Teneligliptin and other gliptins in the class & provides a concise summary of all clinical trials till the date with Teneligliptin monotherapy & combination with other antidiabetic drugs. This study concludes saying Teneligliptin, a third generation gliptin offers unique pharmacodynamic advantage with unique "J-shaped anchor-lock domain" which provides potent & long duration of action. Teneligliptin offers unique pharmacokinetic advantage with long half-life of 26.9 hours allowing convenient once daily administration irrespective of food. It has unique dual mode of elimination via renal & hepatic, adherence can be administered safely in patients with renal impairment. Current review of all clinical trials on Teneligliptin reports no major cardiac concerns observed with Teneligliptin treatment.

2.6 Takashi Kadowak,[37] ***et al.*, (2015);** Conducted a study on topic "Safety and efficacy of Teneligliptin in Japanese patients with type 2 diabetes mellitus: a pooled analysis of two Phase III clinical studies." This post-hoc pooled analysis used data from two Phase III clinical studies involving 702 Japanese patients. Teneligliptin was evaluated as monotherapy and in combination with anti-diabetic agents. Safety measures included adverse events, adverse reactions and hypoglycaemia. The main efficacy measure was the change in glycated

hemoglobin (HbA1c) from baseline. Teneligliptin administered once daily as monotherapy or combination therapy resulted in a decrease in HbA1c, which was maintained for 52 weeks. This pooled analysis provides evidence for the safety and efficacy of long-term use of Teneligliptin as monotherapy or combination therapy in Japanese T2DM patients.

2.7 Wakaba Tsuchimoch,[56] ***et al.*, (2015);** Conducted a study on topic "Teneligliptin improves glycemic control with the reduction of postprandial insulin requirement in Japanese diabetic patients." The aim of this study was to evaluate the effects of Teneligliptin on 24 h blood glucose control and gastrointestinal hormone responses to a meal tolerance test, and to investigate the glucose-lowering mechanisms of Teneligliptin. Ten patients with T2DM were treated for 3 days with teneligliptin (20 mg/day). Postprandial profiles for glucose, insulin, glucagon, active GLP-1, active GIP, ghrelin, des-acyl ghrelin, and 24 h glycemic fluctuations were measured via continuous glucose monitoring for 4 days. Once daily teneligliptin administration for 3 days significantly lowered postprandial and fasting glucose levels. Significant elevations of fasting and postprandial active GLP-1 and postprandial active GIP levels were observed. Teneligliptin lowered postprandial glucose elevations; 24 h mean blood glucose levels, standard deviation of 24 h glucose levels and mean amplitude of glycemic excursions (MAGE) without hypoglycemia. Serum insulin levels in the fasting state and 30 min after a meal were similar before and after Teneligliptin treatment; however significant reductions at 60 to 180 min after treatment were observed. A significant elevation in early-phase insulin secretion estimated by insulinogenic and oral disposition indices, and a significant reduction in postprandial glucagon AUC were observed. Both plasma ghrelin and des-acyl ghrelin levels were unaltered following Teneligliptin treatment. Teneligliptin improved 24 h blood glucose levels by increasing active incretin levels and early-phase insulin secretion, reducing the postprandial insulin requirement, and reducing glucagon secretion.

2.8 Surendra Kumar Sharma,[57] ***et al.*, (2015);** Conducted a study on topic "Teneligliptin in management of type 2 diabetes mellitus. This review evaluates the effiacy and safety of teneligliptin in the management of T2DM. Teneligliptin has been systematically evaluated in T2DM as monotherapy with diet and exercise and in combination with metformin, glimepiride, pioglitazone, and insulin in short-term (12 weeks) and long-term (52 weeks) studies. These studies have reported a reduction in HbA1c of 0.8%–0.9% within 12 weeks of therapy. Two 52-week studies reported sustained improvement in glycemic control with

teneligliptin. Teneligliptin has been found to be well tolerated, and the safety profie is similar to other dipeptidyl peptidase 4 inhibitors. Hypoglycemia and constipation are the main adverse events. Teneligliptin can be administered safely to patients with mild, moderate, or severe renal impairment or end-stage renal disease without dose adjustment. Similarly, it can be used in patients with mild-to-moderate hepatic impairment. Teneligliptin is effective and well tolerated and may have an important role in the management of T2DM.

2.9 Dixit K. Patel,[58] **et al., (2003);** Conducted a study on the topic "Teneligliptin: a review on cardio-renal safety." A randomized, double-blind, placebo and moxifloxacin controlled, parallel-group comparative study was conducted in 240 healthy adult male and female subjects to investigate the effect of multiple-dose administration of teneligliptin (40, 160 mg) on QTc intervals. Placebo, teneligliptin 40 mg, and 160 mg were administered orally once daily for 4 days (placebo group, 40 mg group and 160 mg group). In the moxifloxacin group (positive control group), placebo was administered orally once daily for 3 days and moxifloxacin 400 mg on day 4. QTc interval prolongation was observed only time points near t max after administration of teneligliptin 160 mg because few patients had comorbid arrhythmia or ischemic heart diseases. No clinically significant QTc interval prolongation was observed at 40 mg. The study suggested that teneligliptin was not associated with QT interval prolongation at clinically relevant dose (maximum recommended dose 40 mg) in healthy individuals.

3. AIM AND OBJECTIVES

3.1 AIM

To study the utilization pattern, safety and effectiveness of Teneligliptin in type 2 diabetic patients with cardiovascular disease.

OBJECTIVES

1. To determine the effectiveness of Teneligliptin.
2. To determine the drug utilisation pattern of Teneligliptin.
3. To monitor the Adverse Drug Reactions.
4. To determine the effect of Teneligliptin on eGFR value and QTc prolongation.
5. To evaluate the medication adherence of Teneligliptin.

4. METHODOLOGY

STUDY DESIGN

Prospective Observational studies with 3 months follow up,

STUDY POPULATION

Patients diagnosed with Type 2 Diabetes mellitus and cardiovascular disease.

STUDY SITE

Study was carried out in Cardiology OP and IP at Pushpagiri Medical College Hospital, Thiruvalla.

STUDY PERIOD

6 months

SAMPLE SIZE

N = 60

$$N = \frac{4PQ}{D^2}$$

Where, P = Prevelance

Q = 1 – P

D = Precision error

INCLUSION CRITERIA

- IP / OP patients in Cardiology department
- Both female and male patients with Type 2 diabetes mellitus along with cardiovascular disease.
- Patients of age >18 years.
- Those who give consent voluntarily to participate in the study.
- Patients receiving Teneligliptin as monotherapy or combination therapy.

EXCLUSION CRITERIA

- Patients who are not willing to give consent.
- Gestational diabetes mellitus.
- Type 1 diabetes mellitus.

4. BRIEF PROCEDURE OF THE STUDY

- A prospective observational study was conducted in the Department of Cardiology at Pushpagiri Medical College Hospital, Thiruvalla, on the topic "A Prospective Observational Study on the Analysis of Utilization Pattern, Safety and Effectiveness of Teneligliptin in Type 2 Diabetic Patients with Cardiovascular Disease."
- The selection of patients was based upon the inclusion and exclusion criteria.
- All patients was provided with a brief introduction regarding the study and confidentiality of the data. Informed consent of patients diagnosed with Type 2 Diabetes Mellitus (with cardiovascular disease) was taken before the study.
- It was a total of 6 month study, which included a three month follow up.
- Predesigned structured proforma was used to collect information from the prescribing physicians regarding the effectiveness of Teneligliptin in T2DM patients.
- Information on the glycemic parameters at baseline prior to starting Teneligliptin and at the end of 3 months therapy was collected.
- The effectiveness was assessed by analyzing the mean change in 3-month values of HbA1c, FBS and PPBS.
- The eGFR can be calculated using MDRD equation.
- QTc interval prolongation checked through evaluation of ECG.
- The medication adherence was estimated using the MORISKY MEDICATION ADHERENCE SCALE - 8.
- Safety was assessed using NARANJO'S CAUSALITY SCALE.

5. RESULTS

Table No. 1: Distribution Of Patients According To Age.

Age	Frequency	Percent	Mean	SD
40-60	13	21.7	66.48	10.01
61-80	41	68.3		
Above 80	6	10.0		
Total	60	100.0		

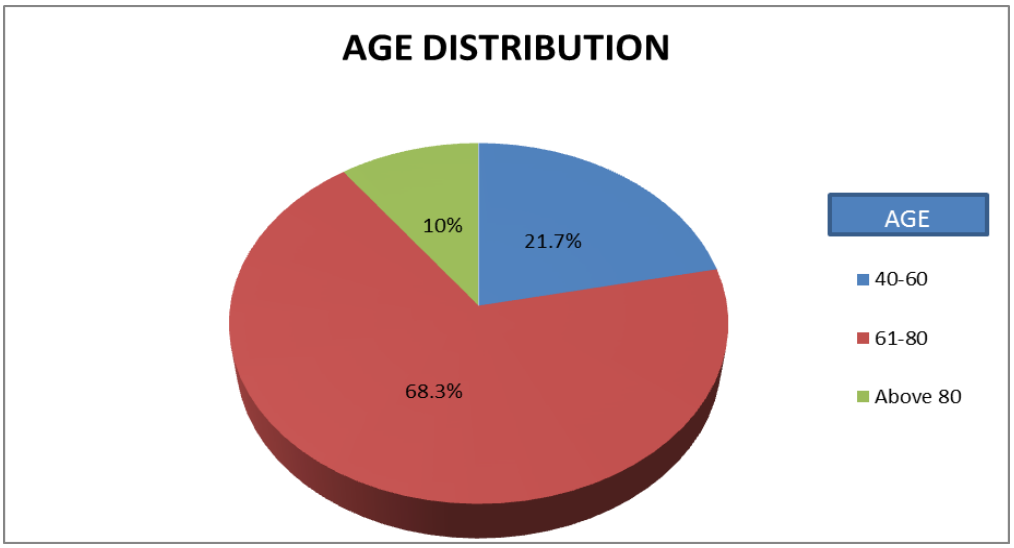

Fig No. 4: Distribution of patients according to age.

In this study, majority of patients belongs to the 60- 70 age group category.

Table No. 2: Distribution of Patient According to Age and Gender.

Age	Gender		Total
	Male	Female	
40-60	7	6	13
	53.8%	46.2%	100.0%
61-80	14	27	41
	34.1%	65.9%	100.0%
Above 80	2	4	6
	33.3%	66.7%	100.0%
Total	**23**	**37**	**60**
	38.3%	**61.7%**	**100.0%**

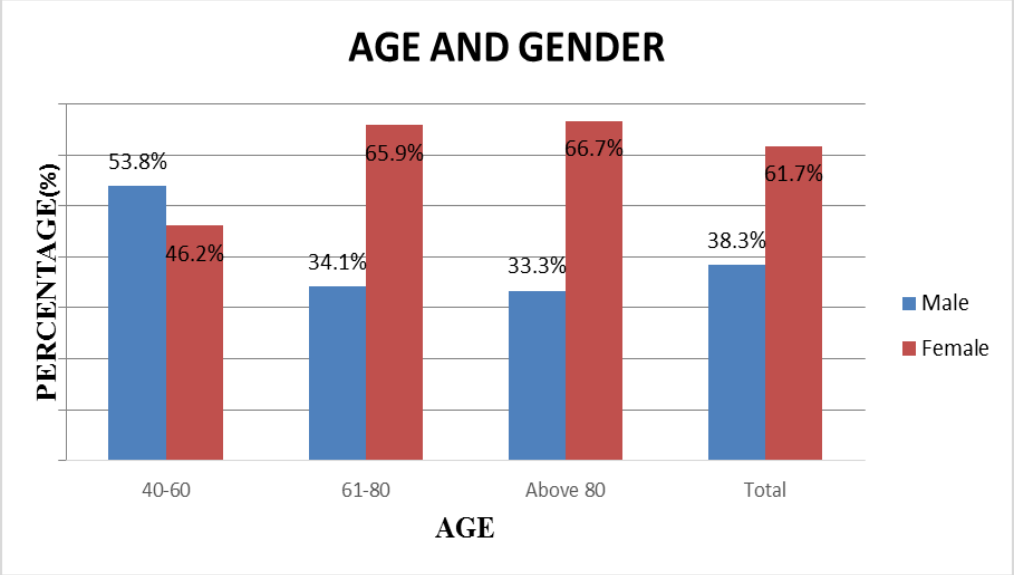

Fig No. 5: Distribution of patient according to age and gender.

In this study population 38.3% were male and 61.7% female. So the majority of patients were female.

Table No. 3: Distribution of Patient According to Family History.

Family History	Frequency (No.of patients)	Percent (%)
No	31	51.7
Yes	29	48.3
Total	**60**	**100.0**

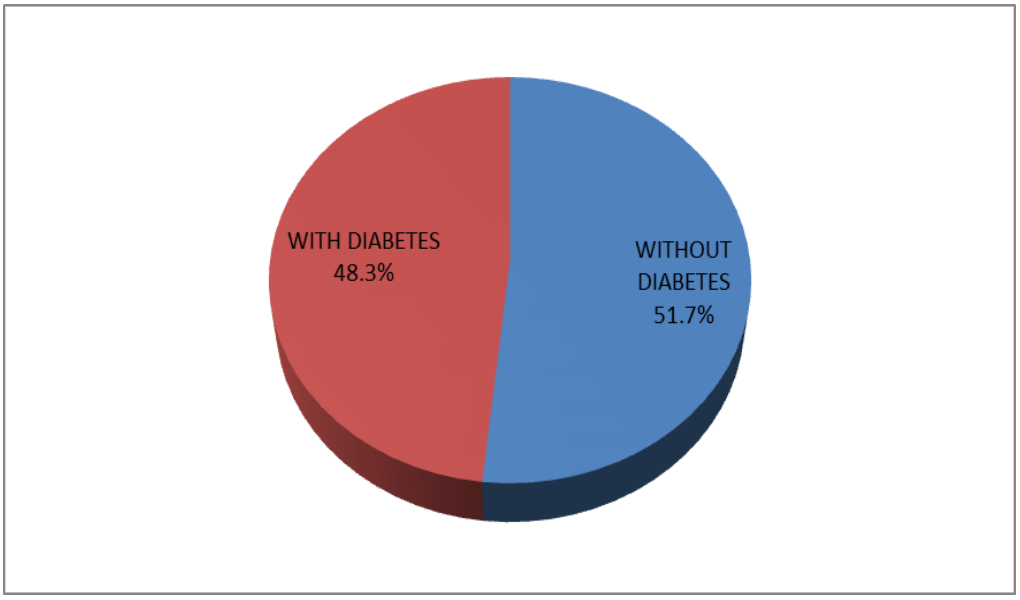

Fig No. 6: Distribution of patient according to family history.

In this study, 48.3% study population had significant family history of type 2 DM.

Table No. 4: Distribution of Patient According to Diabetic History.

Diabetic history	Frequency(No.of patients)	Percent(%)
Below 5 years	13	21.7
5 - 10 years	24	40.0
11 - 15 years	12	20.0
Above 15 years	11	18.3
Total	**60**	**100.0**

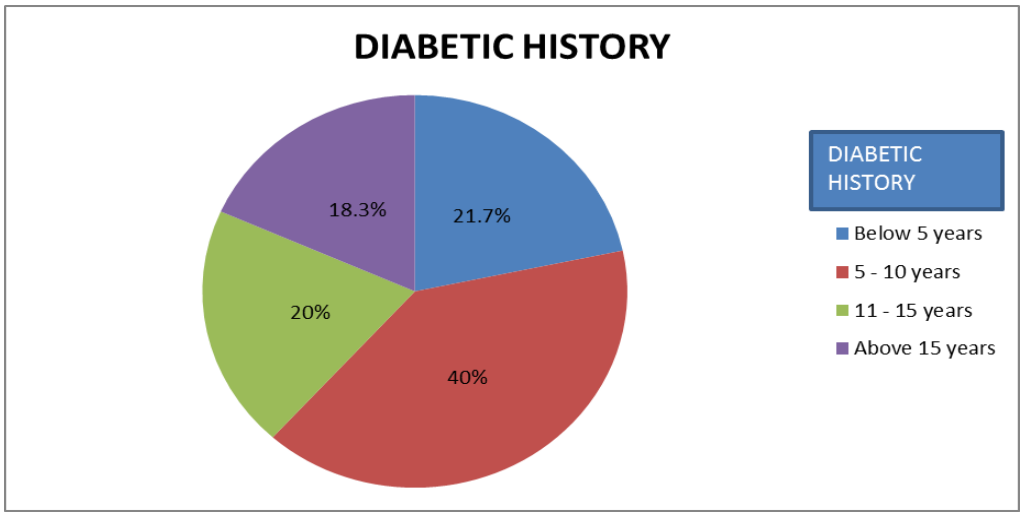

Fig No. 7: Distribution of Patient According To Diabetic History.

Upon analyzing the diabetic history, majority of patients had Diabetic history of 5-10 years (40%) followed by below 5 years (21.7%).

Table No. 5: Comparisons of Subjects With Respect to Fbs (On Consultation and After 3 Months).

FBS	Mean	S.D	M.D	Paired t value	P value
PRE	171.72	72.75	29.7	7.148	0.001
POST	142.02	69.08			

Since P value obtained is less than 0.01, the difference in FBS value is statistically highly significant. That is the FBS value is significantly reduced.

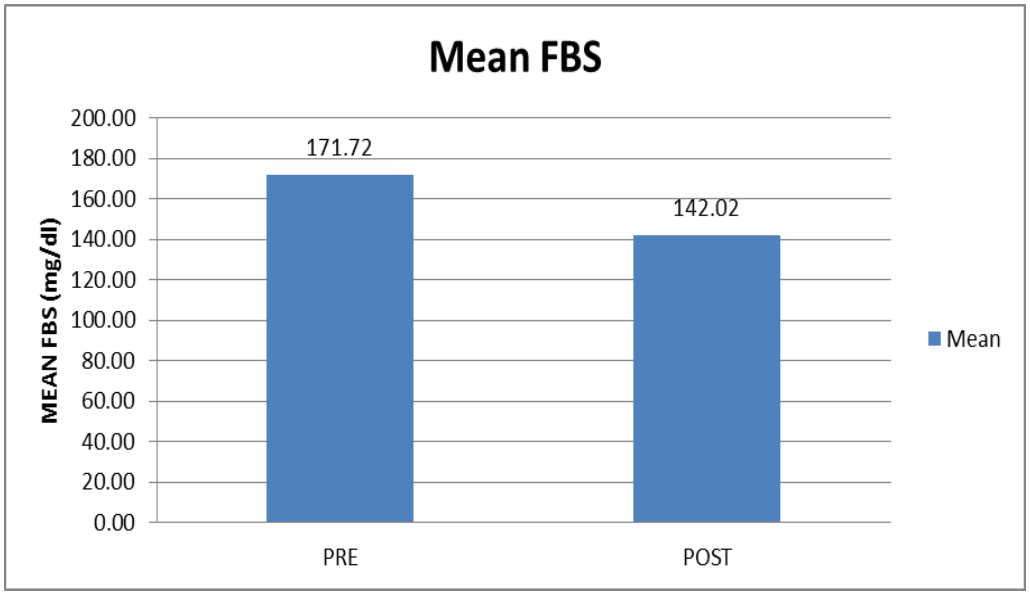

Fig No. 8: Comparison of FBS.

On consultation, mean of FBS value of patient's were 171.72mg/dl, which is significantly reduced to 142.02 mg/dl after 3months of treatment.

Table No. 6: Comparison of Subjects with Respect to Ppbs (on Consultation and After 3 Months).

PPBS	Mean	S.D	M.D	95% CI	Paired t value	P value
PRE	244.36	88.33	44.22	34.66-53.79	9.257	0.001
POST	200.14	79.19				

Since P value obtained is less than 0.01, the difference in PPBS value is statistically highly significant. That is the PPBS value is significantly reduced.

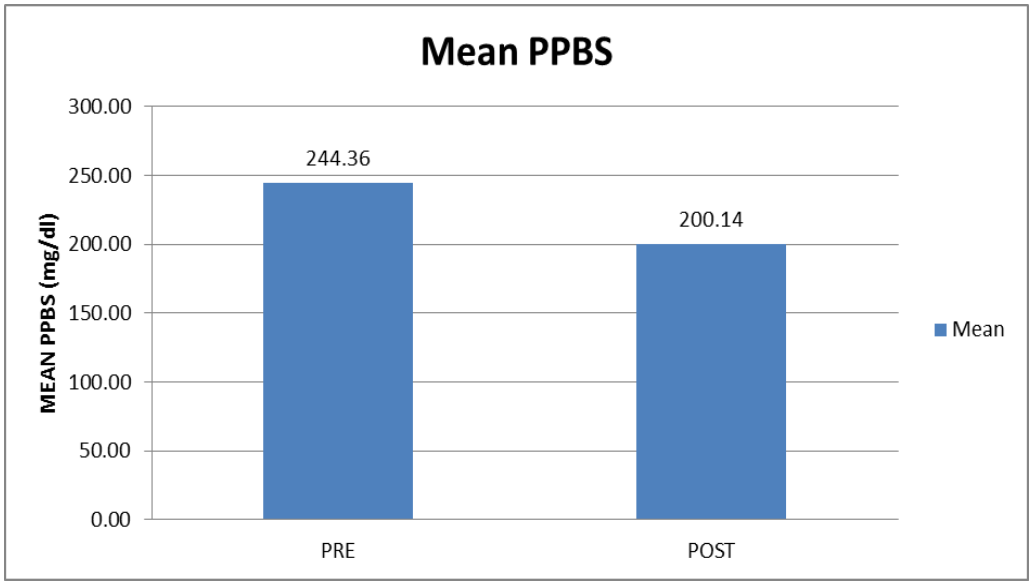

Fig No. 9: Comparison of mean PPBS.

The PPBS value should be reduced after 3months. In this study on consultation, mean PPBS value is 244.36 mg/dl and after3months it is 200.14 mg/dl.

Table No. 7: Comparison Of Subjects With Respect To Hba1c (On Consultation And After 3 Months).

HbA1c	Mean	S.D	M.D	95% CI	Paired t value	P value
PRE	8.47	0.88	0.76	0.68-0.85	17.929	0.001
POST	7.71	0.84				

Since P value obtained is less than 0.01, the difference in HbA1c value is statistically highly significant. That is the HbA1c value is significantly reduced.

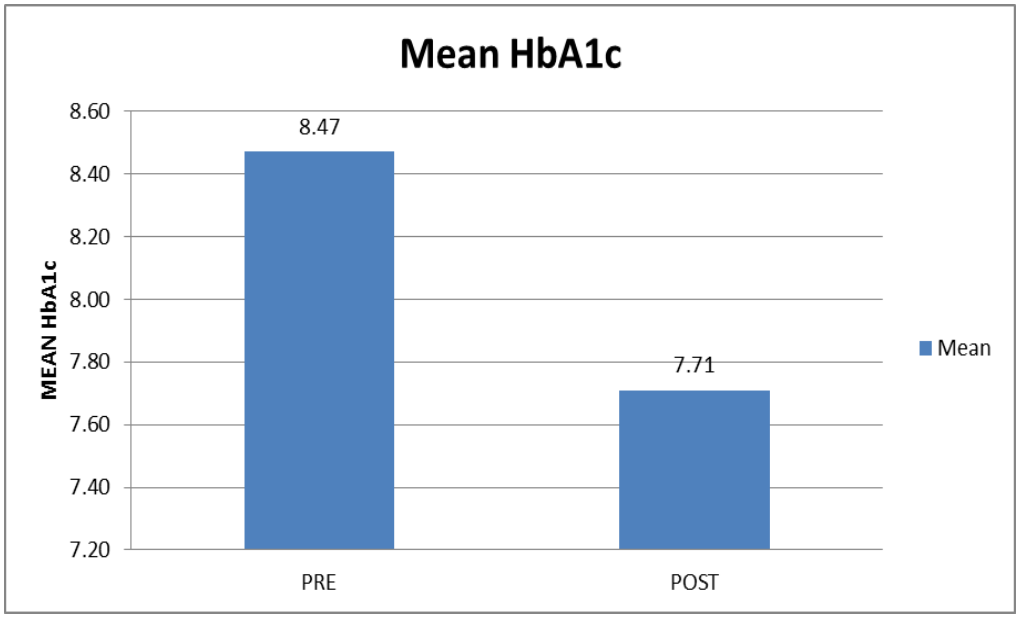

Fig No. 10: Comparison of mean HbA1C.

On consultation mean HbA1C value is 8.47% which is significantly reduced to 7.71% after 3months.

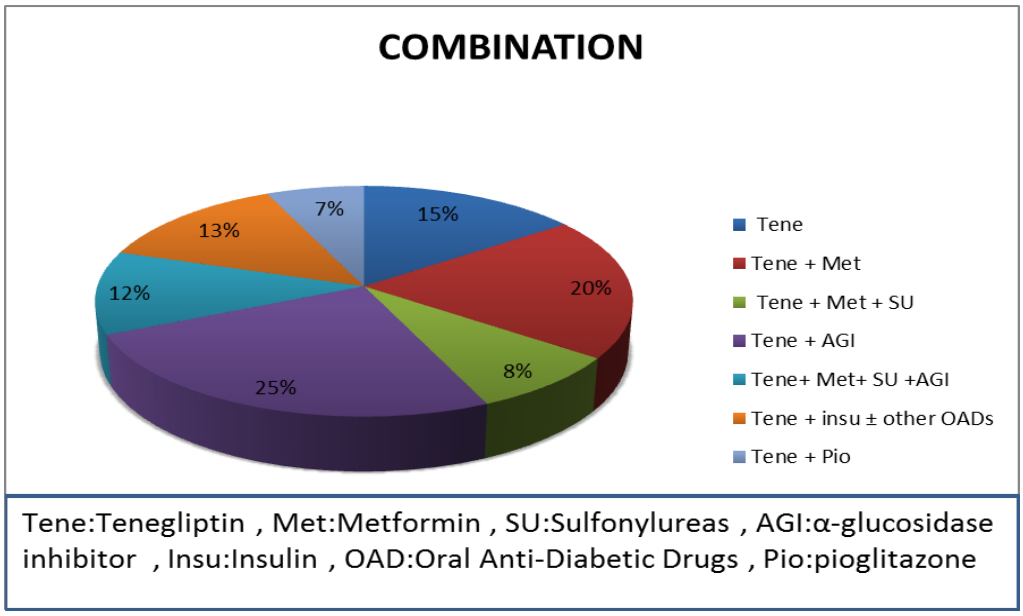

Fig No. 11: Commonly Prescribed Combination.

Teneligliptin was prescribed mostly as add on to α-glucosidase inhibitor (25%) followed by add on to Metformin (20%).

Table No. 8 Mean Reduction In Fbs Value At The End of 3 Months.

CATEGORY	FBS
Overall (n=60)	29.7±32.18
Teneligliptin (n=9)	26.11±15.73
Teneligliptin + Metformin (n=15)	49.2±25.99
Teneligliptin + Metformin + SU (n=12)	36.67±36.83
Teneligliptin + AGI (n=5)	17.87±35.31
Teneligliptin + Metformin + SU +AGI (n=7)	44.57±16.38
Teneligliptin + insulin ± other OADs (n=8)	39.13±29.83
Teneligliptin + Pio (n=4)	8±34.48

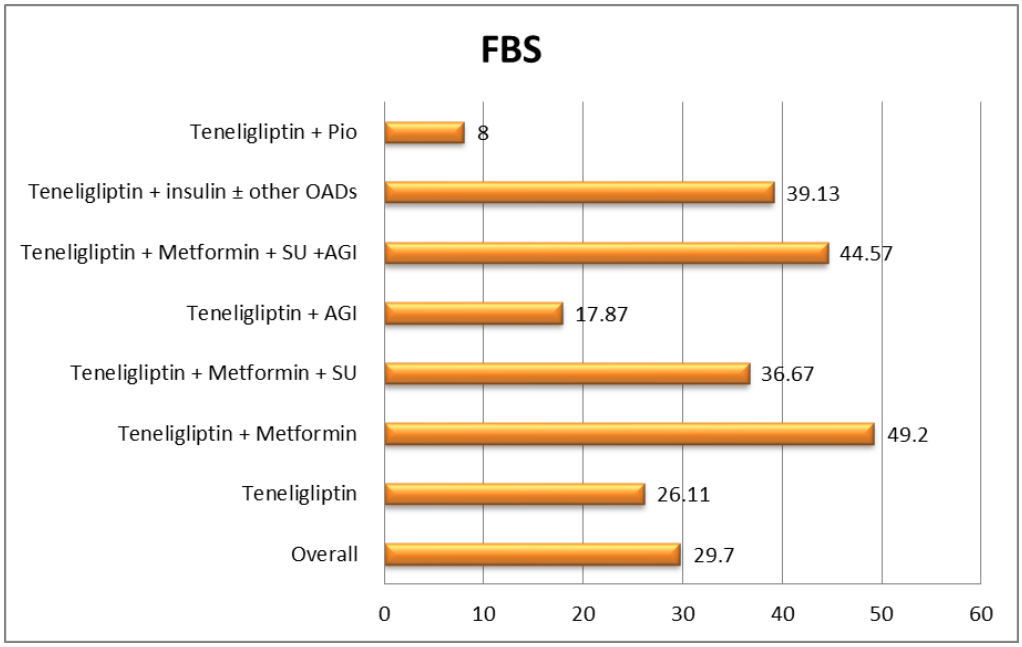

Fig No. 12: Mean reduction in FBS value at the end of 3 months.

Sub group analysis revealed that, mean FBS reduction was higher when Teneligliptin add on to Metformin (49.2 mg/dl) followed by when add on to Metformin + Sulfonylurea+ α-glucosidase inhibitor (44.57mg/dl).

Table No. 9: Mean Reduction In Ppbs At The End Of 3 Months

CATEGORY	PPBS
Overall (n=58)	44.22±36.38
Teneligliptin (n=9)	43.44±24.83
Teneligliptin + Metformin (n=14)	64.57±32.47
Teneligliptin + Metformin + SU (n=12)	53.83±25.89
Teneligliptin + AGI (n=5)	46.6±8.35
Teneligliptin + Metformin + SU +AGI (n=7)	42.43±19.56
Teneligliptin + insulin ± other OADs (n=7)	41.36±46.47
Teneligliptin + Pio (n=4)	8.25±60.49

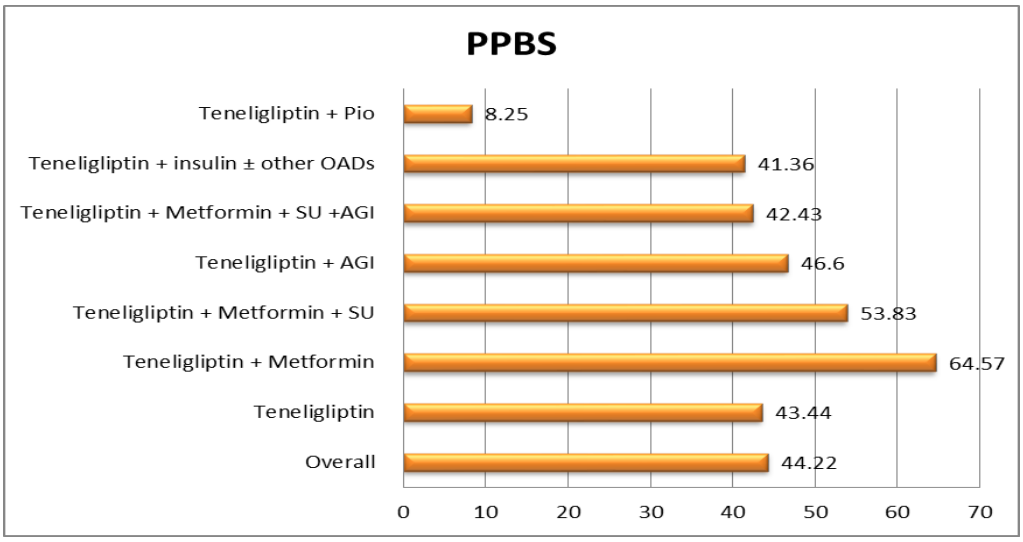

Fig No. 13: Mean reduction in PPBS at the end of 3 months.

In case of PPBS, mean reduction was higher when Teneligliptin add on to Metformin (64.57 mg/dl) followed by when add on to Metformin + Sulfonyl urea combination(53.83 mg/dl).

Table No. 10: Mean Reduction In Hba1c At The End of 3 Months.

Category	HbA1c
Overall (n=37)	0.76±0.26
Teneligliptin (n=6)	0.68±0.19
Teneligliptin + Metformin (n=8)	0.95±0.23
Teneligliptin + Metformin + SU (n=10)	0.68±0.29
Teneligliptin + AGI (n=3)	0.9±0.1
Teneligliptin + Metformin + SU +AGI (n=5)	0.78±0.37
Teneligliptin + insulin ± other OADs (n=4)	0.8±0.08
Teneligliptin + Pio (n=1)	0.5±0.0

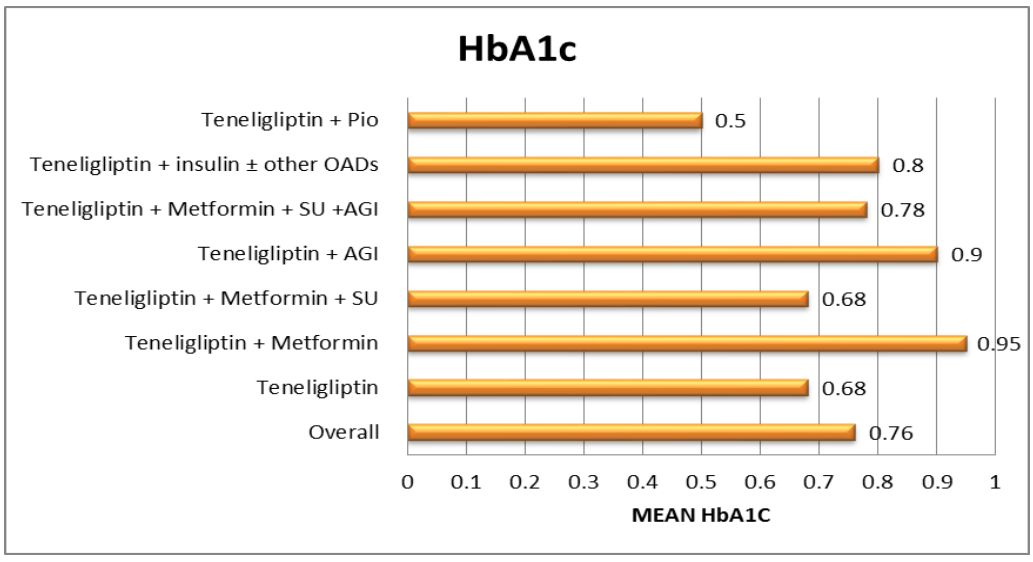

Fig No. 14 Mean reduction in HbA1c at the end of 3 months.

In case of HbA1C, mean reduction was higher with teneligliptin with Metformin (0.95%) followed by when add on to α-glucosidase inhibitor (0.9%).

Table No. 11: Comparisons of Subjects With Respect To Mean Serum Creatinine (On Consultation and After 3 Months).

SrCr	Mean	S.D	M.D	Paired t value	P value
PRE	1.09	0.59	0.01	1.011	0.316
POST	1.07	0.57			

Since P value is greater than 0.05, the difference in creatinine value is not statistically significant.

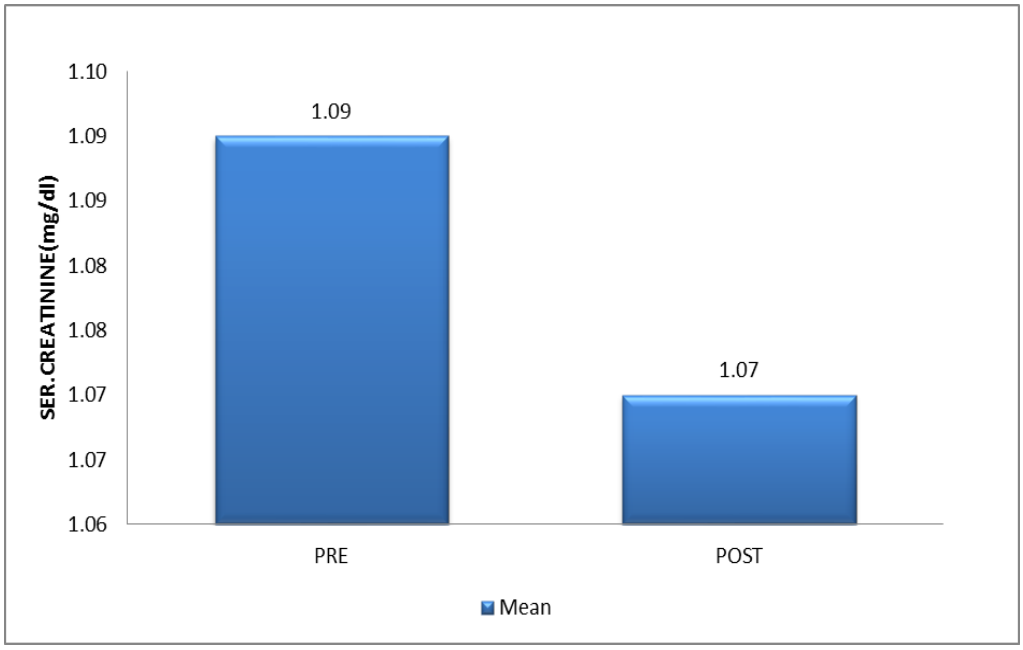

Fig No. 15 Comparison of mean creatinine.

Based on the serum creatinine, on consultation the Sr.cr of patients were 1.09mg/dl which is reduced into 1.07mg/dl.

Table No. 12: Comparisons Of Subjects With Respect To Mean Egfr (On Consultation And After 3 Months).

Egfr	Mean	S.D	M.D	95% CI	Paired t value	P value
PRE	80.94	42.34	1.31	0-4.19	0.909	0.367
POST	79.63	39.03				

Since P value is greater than 0.05, the difference in eGFR value is not statistically significant.

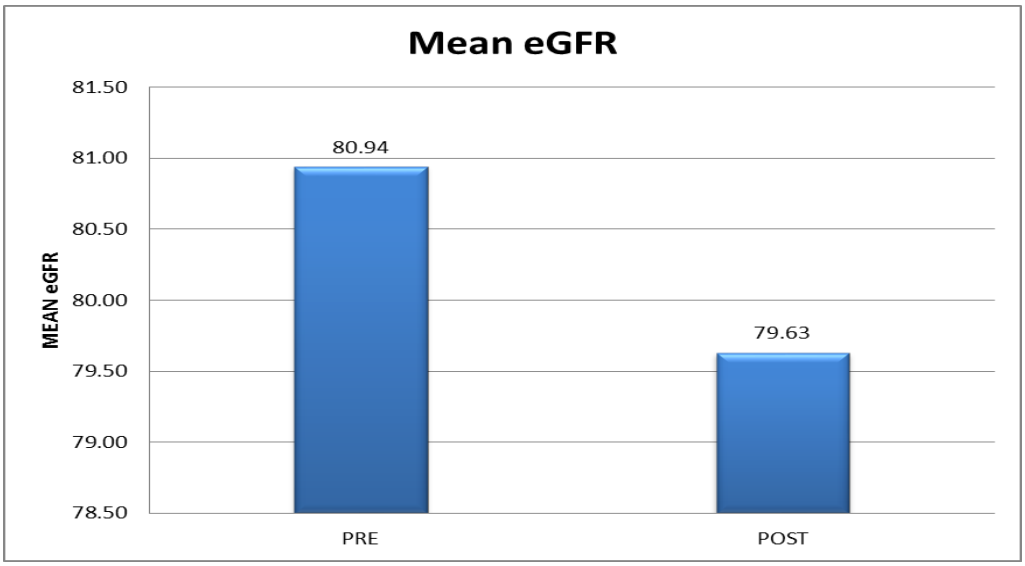

Fig No. 16: Comparison of mean eGFR.

The eGFR value on consultation is 80.94ml/min/1.73 m^2 and after 3 months it is 79.63ml/min/1.73m^2.

Table No. 13: Distribution Based On Qtc Prolongation Seen In Patients.

ECG		pre	post	P Value
QTc prolongation	PRESENT	0	0	<0.0001
	ABSENT	59	59	

Since P value obtained is less than 0.0001, No QTc prolongation seen in any of the patients, it was statistically significant.

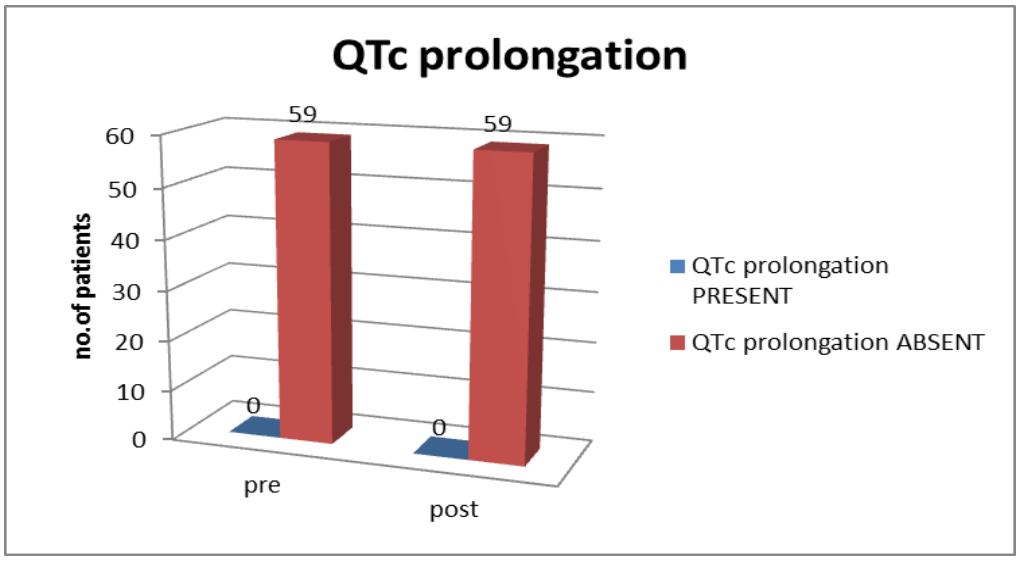

Figure No. 17: Distribution based on presence of QTc prolongation in patients.

In our study, no QTc prolongation seen at 20mg dose of Teneligliptin.

Table No. 14: Distribution Based On Adverse Drug Reaction Reported By Patients.

ADR	Frequency (no.of patients)	Percent(%)
NO	57	95.0
YES	3	5.0
TOTAL	60	100.0

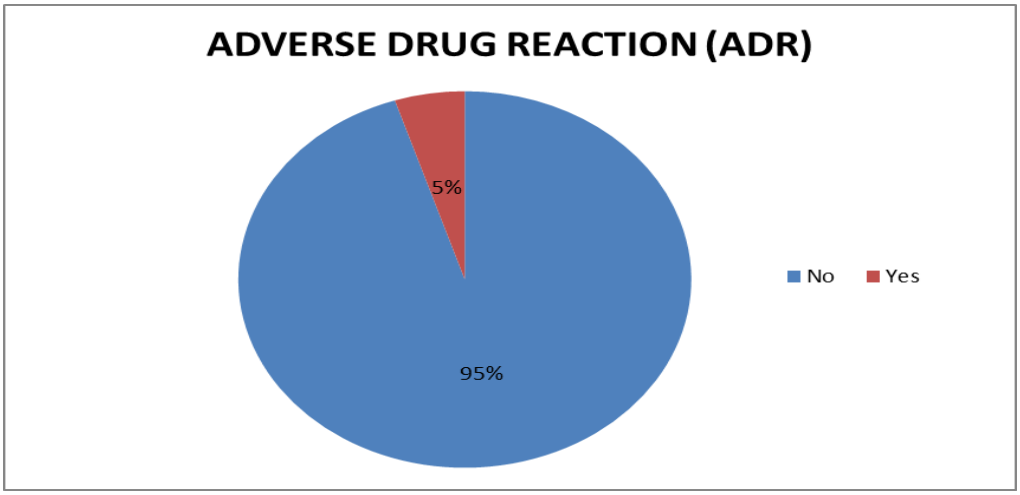

Fig No. 18: Adverse Drug Reaction reported by patients.

In this study only 3 patients show mild ADR on Teneligliptin administration.

Table No. 15: Distribution of Patient Based on Medication Adherence.

MMAS	Frequency(no.of patients)	Percent
HIGH ADHERENCE	9	15.0
MEDIUM ADHERENCE	33	55.0
LOW ADHERENCE	18	30.0
TOTAL	60	100.0

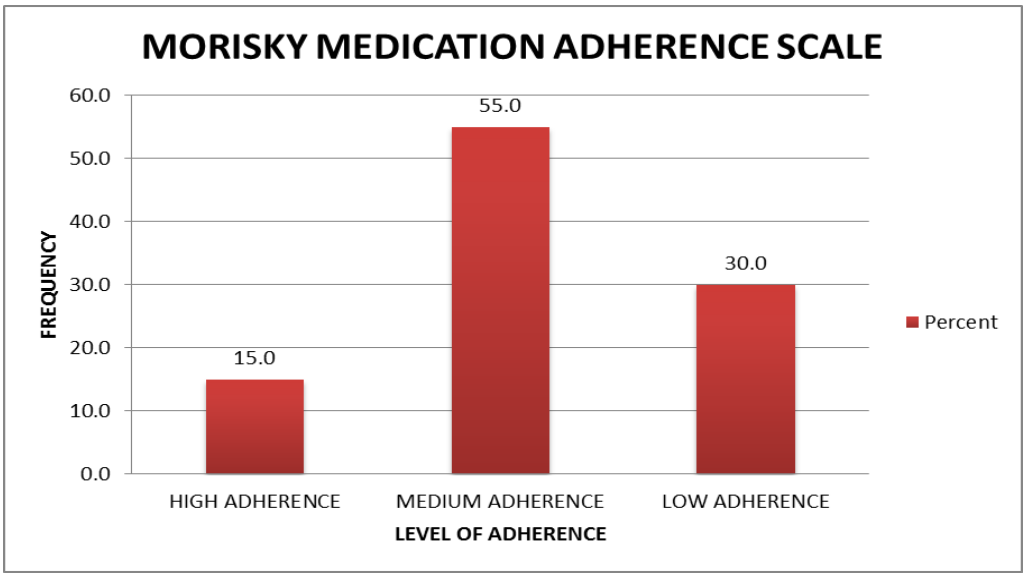

Fig No. 19: Distribution of patients based on medication adherence.

Medication Adherence was measured out by using Morisky Medication Adherence Scale 8. Among 60 patients, 15% (9) shows high adherence, 55% (33) shows medium adherence and 30% (18) patients show low adherence.

Table No. 16: Distribution Of Patient According To Dose.

DOSE(MG)	Frequency (no.of patients)	Percent
20	57	95.0
40	3	5.0
TOTAL	60	100.0

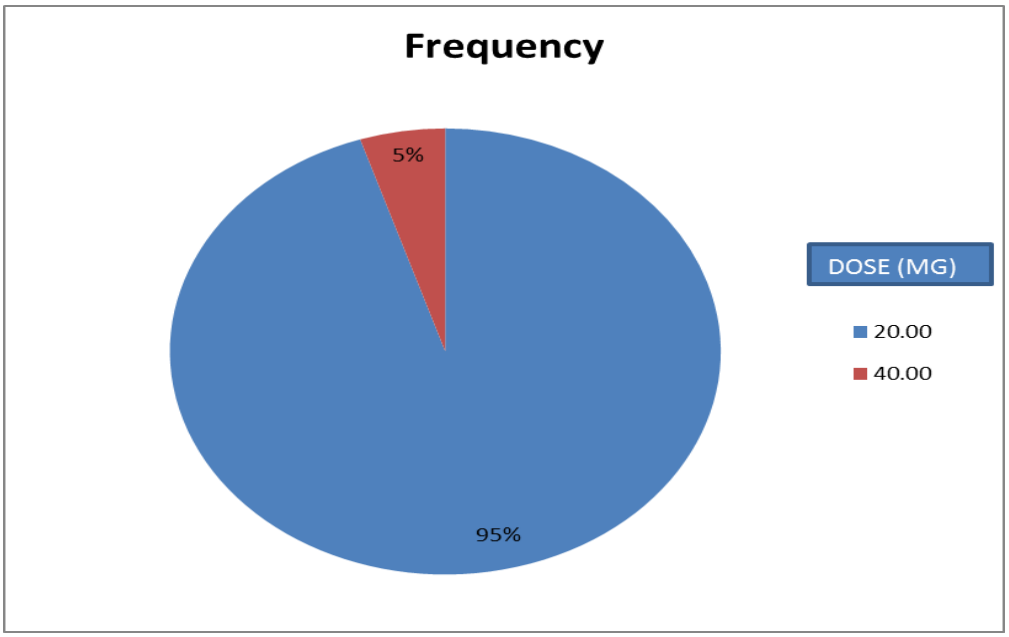

Fig no. 20: Distribution of patient according to dose.

In this study most commonly prescribed Teneligliptin dose was 20 mg.

Table No.17: Distribution of Patient According to Administration of Teneligliptin.

Frequency	Frequency(no.of patients)	Percent
ONCE DAILY	55	91.7
TWICE	4	6.7
THRICE	1	1.7
TOTAL	60	100.0

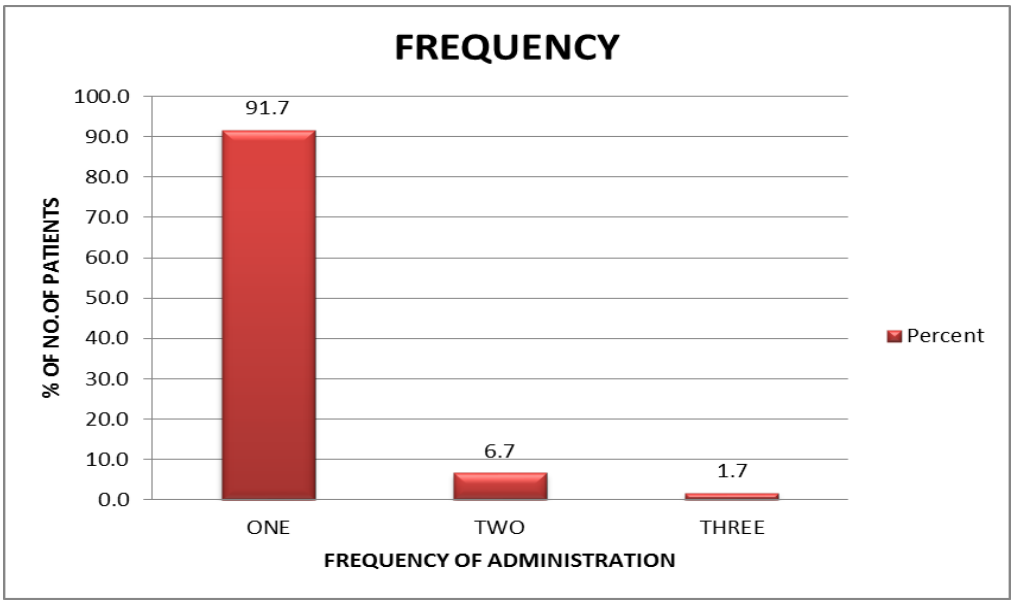

Fig no. 21: Distribution of patient according to administration of Teneligliptin.

Among the various frequency of dose prescribed, once daily category was found to be highest in this study population.

Table No. 18: Distribution Based on Comorbidity Associated With T2dm – Ckd.

CKD	FREQUENCY (NO.OF PATIENTS)	PERCENT
NO	49	81.7
YES	11	18.3
TOTAL	60	100.0

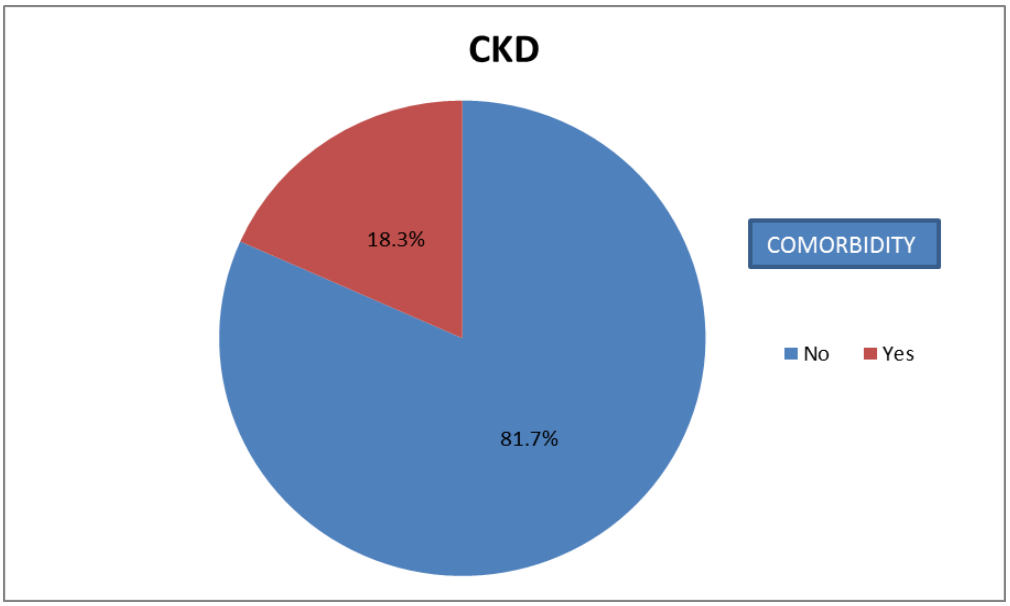

Fig No. 22: Distribution based on comorbidity associated with T2DM – CKD.

In this study population (18.3%) were presented with comorbidity CKD

Table No. 19: Distribution Based On Comorbidity Associated With T2dm – Dlp.

DLP	Frequency(no.of patients)	Percent
NO	38	63.3
YES	22	36.7
TOTAL	60	100.0

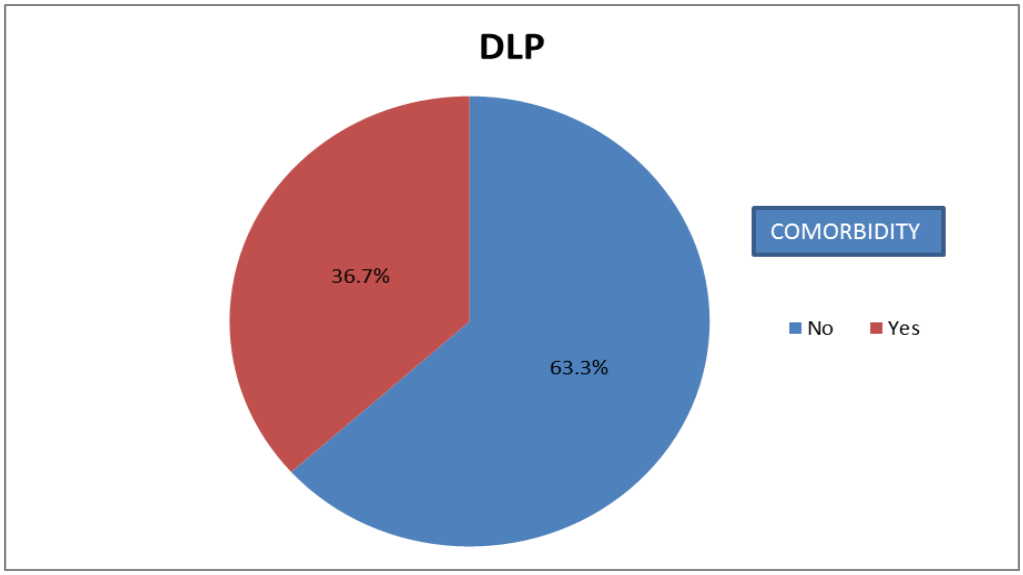

Fig No. 23: Distribution based on comorbidity associated with T2DM – DLP

In this study population (36.7) were presented with co-morbidity Dyslipidemia.

6. DISCUSSION

- This prospective observational study was conducted in the Department of Cardiology at Pushpagiri Medical College Hospital to find out Utilization Pattern, Safety and Effectiveness of Teneligliptin in Type 2 Diabetic Patients with Cardiovascular Disease. The selection of patients was based upon the inclusion and exclusion criteria. It was a total of 6 month study, which included a three month follow up. Information on the glycemic parameters at baseline prior to starting Teneligliptin and at the end of 3 months therapy was collected. The effectiveness was assessed by analyzing the mean change in 3-month values of HbA1c, FBS and PPBS. The eGFR can be calculated using MDRD equation. The medication adherence was estimated using the MORISKY SCALE 8.Safety was assessed using NARANJO'S CAUSALITY SCALE.

❖ Patient demographic data

- Age

  Majority of patients in the study belong to the age group 61-80 (68.3%) followed by 40-60 (21.7%).

- Gender

  In this study population 38.3% were male and 61.7% female. So the majority of patients were female.

- Family history

  Out of 60subjects considered, 48.3% had significant family history of type 2 DM.

- Diabetic history

  Upon analyzing the diabetic history, majority of patients showed history of 5-10 years of diabetes(40%).

❖ Biochemical profile of the patient

- On consultation mean of FBS value were171.72mg/dl, this was significantly reduced to 142.02 mg/dl after 3months of treatment. Since the P value is less than 0.01, the FBS value was significantly reduced after 3months.
- In this study on consultation, mean PPBS value was 244.36 mg/dl and after 3months it reduced to 200.14mg/dl. Since P value is less than 0.01, the PPBS value was significantly reduced.
- On consultation mean HbA1C value was 8.47% which was significantly reduced to 7.71% after 3months. Since P value obtained was less than 0.01, the HbA1C value was significantly reduced.
- Teneligliptin was prescribed mostly as an add on to α-glucosidase inhibitor (25%) and as an add on to Metformin (20%).
- Sub group analysis revealed that mean FBS reduction was higher when Teneligliptin was given as add on with Metformin (49.2 mg/dl) followed by add on with metformin + sulfonylurea + α-glucosidase inhibitor (44.57mg/dl).
- In case of PPBS, mean reduction was higher when Teneligliptin was given as an add on to Metformin (64.57 mg/dl) followed by, add on to metformin + sulfonyl urea combination (53.83 mg/dl).
- In case of HbA1C, mean reduction was higher with Teneligliptin add on to Metformin (0.95%) followed by, add on to α-glucosidase inhibitor (0.9%).
- No QTc prolongation was observed prior and post administration of Teneligliptin in the study, therefore it can be used in cardiac patients.

- Based on the serum creatinine, on consultation the mean ser.cr of patients were1.09mg/dl which was reduced to 1.07mg/dl. Since P value is greater than 0.01, the difference in Ser, cr value was not statistically significant.
- The eGFR value on consultation was 80.94ml/min/1.73 m^2 and after3months it was reduced to 79.63ml/min/1.73m^2. Since value was greater than 0.01, the difference in eGFR value was not statistically significant.
- In this study only 3 patients showed mild ADR on Teneligliptin administration.
- In this study most commonly prescribed teneligliptin dose was 20 mg.
- Among the various frequency of dose prescribed, once daily category was found to be highest in this study population.
- In this study population, 18.3% of population were presented with co-morbidity CKD.
- In this study population, 36.7% population were presented with co-morbidity DLP.
- Medication adherence was measured out by using Morisky medication adherence scale 8. Among 60 patients, 15% (9) shows high adherence, 55% (33) shows medium adherence and 30% (18) patients show low adherence.

7. SUMMARY

- This prospective observational study was conducted in the Department of Cardiology at Pushpagiri Medical College Hospital to find out Utilization Pattern, Safety and Effectiveness of Teneligliptin in Type 2 Diabetic Patients with Cardiovascular Disease. The selection of patients was based upon the inclusion and exclusion criteria. It was a total of 6 month study, which included a three month follow up.
- Majority of patients in the study belong to the age group 61-80 years.
- In this study population majority of patients were female.
- In this study, 48.3% of study population had significant family history of type 2 DM.
- Upon analyzing the diabetic history, majority of patients had diabetic history of 5-10 years.
- On consultation, the average FBS value of patient's were171.72mg/dl, which was significantly reduced to 142.02 mg/dl after 3months of treatment. The FBS value was significantly reduced after 3months.
- In this study on consultation, the mean PPBS value was 244.36 mg/dl and after 3 months it is 200.14mg/dl. The PPBS value was significantly reduced.
- On consultation, mean HbA1c value is 8.47% which was significantly reduced to 7.71% after 3months. The HbA1c value was significantly reduced.

- Teneligliptin was prescribed mostly as add on to α-glucosidase inhibitor (25%) and as an add on to Metformin (20%).
- Sub group analysis revealed that mean FBS reduction was higher when Teneligliptin was given as add on with Metformin (49.2 mg/dl) followed by add on with metformin + sulfonylurea + α-glucosidase inhibitor (44.57mg/dl).
- In case of PPBS, mean reduction was higher when Teneligliptin was given as an add on to Metformin (64.57 mg/dl) followed by, add on to metformin + sulfonyl urea combination (53.83 mg/dl).
- In case of HbA1C, mean reduction was higher with Teneligliptin with Metformin (0.95%) followed by, add on to α-glucosidase inhibitor (0.9%).
- Ser.cr and eGFR do not show any significant change on consultation and after 3 months. So the difference in Ser.cr value and eGFR is not statistically significant. So it is safer in CKD.
- No QTc prolongation was observed prior and post administration of Teneligliptin in the study, therefore it can be used in cardiac patients.
- In this study only 3 patients show mild ADR on Teneligliptin administration. 2 Patients with headache and 1 with dizziness.
- In this study, the most commonly prescribed Teneligliptin dose was 20 mg.
- Among the various frequency of dose prescribed once daily category was found to be highest in this study population.
- In this study population (18.3%) were presented with co-morbidity CKD.
- In this study population (36.7%) were presented with co-morbidity dyslipidemia.
- Medication adherence was measured out by using Morisky medication adherence scale 8. Among 60 patients, 55% shows medium medication adherence.

8. CONCLUSION

Diabetes mellitus is the most common of the endocrine disorder. Cardiovascular disease remains the key comorbid condition and main contributor to mortality in the setting of diabetics – commonly coronary heart disease. The study was conducted in the Department of Cardiology at Pushpagiri Medical College Hospital, Thiruvalla. 60 patients were selected for the study. This study was undertaken to determine the Utilization Pattern, Safety and Effectiveness of Teneligliptin in Type 2 Diabetic Patients with Cardiovascular Disease. This study shows that Teneligliptin provided statistically significant and clinically meaningful reductions in the HbA1c, FBS and PPBS in cardiac patients with T2DM. Teneligliptin has a

unique pharmacokinetic advantage which allows convenient once daily administration irrespective of food, superadded it has a dual mode of elimination via renal and hepatic hence can be administered safely in renal impairment patients.

The FBS, PPBS and HbA1C values were significantly reduced after 3 months of treatment. Sub group analysis showed that addition of Teneligliptin to Metformin causes more significant reduction in FBS, PPBS and HbA1C in comparison to other therapies. Teneligliptin was prescribed mostly as add on to α-glucosidase inhibitor (25%) followed by add on to Metformin (20%).

The obtained parameters were analysed and the results concluded that Teneligliptin 20mg is safe in cardiac and renal patients. Also teneligliptin add on to metformin is a much better therapy for maximum reduction of FBS, PPBS, HbA1C.

Our study suggest that, there was no significant QTc prolongation prior and post administration of 20mg Teneligliptin, which ensures cardiovascular safety in T2DM patients. The study showed that, there was no change in the eGFR value prior and post administration of Teneligliptin. Therefore, Teneligliptin 20mg is found to be safe, well- tolerated and efficacious in T2DM patients with CKD.

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