Created by PDF Combine Unregistered Version

If you want to remove the watermark, Please register

A COMPARATIVE STUDY OF TENELIGLIPTIN VERSUS OTHER STANDARD GLIPTINS USED IN TYPE II DIABETES MELLITUS PATIENTS

A Dissertation Submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI-600032

In partial fulfillment of the requirement for the award of the Degree of

MASTER OF PHARMACY

in

PHARMACY PRACTICE

OCTOBER-2017

DEPARTMENT OF PHARNACY PRACTICE,

KMCH COLLEGE OF PHARMACY,

KOVAI ESTATE, KALAPATTI ROAD,

COIMBATORE-641048.

A COMPARATIVE STUDY OF TENELIGLIPTIN VERSUS OTHER STANDARD GLIPTINS USED IN TYPE II DIABETES MELLITUS PATIENTS

A Dissertation Submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI-600032

In partial fulfillment of the requirement for the award of the Degree of

MASTER OF PHARMACY

in

PHARMACY PRACTICE

OCTOBER-2017

Submitted by

Tintu Chacko

(Reg. No. 261540604)

Under the Guidance of

Mr. C .Dhandapani, M.Pharm, (Ph.D)

Asst. Professor, Department of Pharmacy Practice

DEPARTMENT OF PHARMACY PRACTICE,

KMCH COLLEGE OF PHARMACY,

KOVAI ESTATE, KALAPATTI ROAD,

COIMBATORE-641048.

Prof. Dr. A.Rajasekaran, M. Pharm., Ph.D.,
Principal,
KMCH College of Pharmacy,
Kovai Estate, Kalapatti Road,
Coimbatore - 641 048.
Tamil Nadu

CERTIFICATE

This is to certify that the dissertation work entitled **"A COMPARATIVE STUDY OF TENELIGLIPTIN VERSUS OTHER STANDARD GLIPTINS USED IN TYPE II DIABETES MELLITUS PATIENTS"** was carried out by **(Reg. No. 261540604).** The work mentioned in the dissertation was carried out at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, Tamilnadu for the partial fulfillment for the degree of **Master of Pharmacy** during the academic year 2016-2017 and is forwarded to the Tamilnadu Dr.M.G.R.Medical University, Chennai.

Date: Signature

Place: Coimbatore **Prof. Dr. A. Rajasekaran, M.Pharm., Ph.D.**

Mr. C. Dhandapani, M.Pharm, (Ph.D)
Asst. Professor, Dept. of Pharmacy Practice,
KMCH College of Pharmacy,
Kovai Estate, Kalapatti Road,
Coimbatore -641 048.
Tamil Nadu

CERTIFICATE

This is to certify that the dissertation work entitled **"A COMPARATIVE STUDY OF TENELIGLIPTIN VERSUS OTHER STANDARD GLIPTINS USED IN TYPE II DIABETES MELLITUS PATIENTS"** is a bonafide work carried out by **Ms. Tintu Chacko (Reg. No. 261540604).** The work mentioned in the dissertation was carried out at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, Tamil Nadu, under my supervision and guidance during the academic year 2016-2017.This research work either in part or full does not constitute any of any thesis/dissertation.

Date: Signature

Place: Coimbatore **Mr. C. Dhandapani,M.Pharm, (Ph.D)**

DECLARATION

I do here by declare that to the best of my knowledge and belief ,the dissertation work entitled **"A COMPARATIVE STUDY OF TENELIGLIPTIN VERSUS OTHER STANDARD GLIPTINS USED IN TYPE II DIABETES MELLITUS PATIENTS"** submitted to the Tamil Nadu Dr. M.G.R. Medical university , Chennai, in the partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmacy practice,** was carried out at Department of pharmacy practice , KMCH College of Pharmacy, Coimbatore under the guidance of **Mr. C. Dhandapani,M.Pharm, (Ph.D)** during the academic year 2016-2017.

Date: Signature

Place: Coimbatore **Ms. Tintu Chacko**

(Reg. No. 261540604)

EVALUATION CERTIFICATE

This is to certify that the work embodied in the thesis entitled **"A COMPARATIVE STUDY OF TENELIGLIPTIN VERSUS OTHER STANDARD GLIPTINS USED IN TYPE II DIABETES MELLITUS PATIENTS"** submitted by **Ms. Tintu Chacko (Reg. No. 261540604).** to the Tamil Nadu Dr. M.G.R. Medical university, Chennai, in the partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmacy Practice,** is a bonafide research work carried out by the candidate during the academic year 2016-2017 at KMCH College of Pharmacy, Coimbatore, Tamilnadu and the same was evaluated by us.

Examination Center: K.M.C.H College of Pharmacy, Coimbatore

Date:

Internal Examiner **External Examiner**

Convener of Examination

ACKNOWLEDGEMENT

First and foremost I pay obeisance to the **Almighty** for blessing me with all the confidence, courage, inspiration and curiosity to complete this project.

I take this opportunity to express my deep sense of gratitude and faithfulness to my esteemed teacher and guide, **Mr. C .Dhandapani, M.Pharm.,(Ph.D) Assistant Professor**, Department of Pharmacy Practice, for this remarkable guidance, patience, constant encouragement, constructive comments and painstaking efforts for the successful completion of this work.

I put across my honest thanks and gratitude to my clinical guide, **Dr. Irania S.V, MD., D.A.A**, Kovai Medical Center and Hospital, for this guidance, valuable directions and interest shown towards the research work.

I would also like to express my sincere and heartfelt gratitude to **Dr. P. Velayutham MD., DM** and **Dr. T.R Sivananam MBBS. D. Diac** for their contributions and support which helped me to successfully proceed with my work.

I extend my sincere thanks and gratitude to my Principal**, Dr. A. Rajasekaran**, **M.Pharm., Ph.D.,** for providing me with co-operative and creative environment which enabled me to work assiduously.

I extend my sincere thanks to **Dr. Nalla G. Palanisamy, M.D., AB (USA),** Chairman of Kovai Medical Center and Hospital and Madam Trustee, **Dr. Thavamani D. Planiswamy, M.D., AB (USA),** for providing me with outstanding infrastructure, resources and the opportunity to work in a clinical setting.

I expressed my sincere thanks to all my teachers, **Dr. Suchandra Sen, Dr. Sankar, Dr. K. T.Manisenthil Kumar, Mrs. Sathyaprabha, Mr. A. Vijjayakumar, Dr. K.S.G Arulkumaran, Mrs.Aparna, Ms.Sreedevi, Ms.Geethu Grace, Mrs.Vennila** and all the other teaching and non-teaching staffs of KMCH college of Pharmacy for their encouragement and judicious help.

My special thanks to the Library Staff of KMCH college of Pharmacy, for proving the library facilities which contribute to the successful completion of my project work.

I also take this opportunity to acknowledge the help extended to me by **Mrs. Indrani Rajendran, Staff Nurse of General Medicine Department** for their immense help and co-operation. Without her timely assistance, the data collection would not have been possible.

I take this opportunity to thank my father **Mr. K.S Chacko** and my mother **Mrs. Lilamma Chacko** who shower their blessings always, and also my sister **Mrs. Tinu Chacko** and my brother **Master Akhil Chacko** who supported me through all stages. It also gives me great pleasure to dedicate my work to such adorable and affectionate parents, sister and brother without whom I wouldn't have been able to reach this stage. For their invaluable affection, concern, encouragement and for the prayers they have offered for the successful completion of my project.

Last but not the least, I owe my thanks and gratefulness to my ever loving friends for their memorable support, help and encouragement, and my heartfelt sincere thanks to all those who directly and indirectly contributed to the successful completion of my work.

Above all, I bow my work in feet of **Almighty** who let me to the actualization of this research work.

ABBREVIATIONS

AACE	:	American Association of Clinical Endocrinology
ACE	:	American College of Endocrinology
ADA	:	American Diabetes Association
DPP-4 inhibitor	:	Dipeptidyl Peptidase 4 inhibitor
FPG	:	Fasting Plasma Glucose
FBS	:	Fasting Blood Sugar
GIP	:	Gastric Inhibitory Polypeptide
GLP	:	Glucagon like peptide 1
HbA1C	:	Glycated Hemoglobin
IDF	:	International Diabetes Federation
PPG	:	Postprandial Plasma glucose
PPBS	:	Postprandial Blood Sugar
SrCr	:	Serum Creatinine
SGPT	:	Serum glutamic pyruvic transaminase
SUs	:	Sulfonyl ureas
T2DM	:	Type II Diabetes Mellitus
TZD	:	Thiazolidinediones

INDEX

1. INTRODUCTION

Diabetes mellitus was first reported in Egyptian manuscript about 3000 years ago. In 1936, the distinction between type 1 and type II DM was clearly made. Type II DM was first described as a component of metabolic syndrome in 1988.[1]

Type II diabetes (formerly known as non-insulin dependent DM) is due to insufficient insulin production from beta cells in the setting of insulin resistance.[2] Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver, and fat tissue. In the liver, insulin normally suppresses glucose release.[3]

The prevalence of Type II Diabetes Mellitus (DM) is increasing all over the world, especially in South Asia. India has largest population of diabetic patients. The International Diabetes Federation (IDF) estimates the number of people with diabetes in India will reach 80 million by the year 2025.[4]

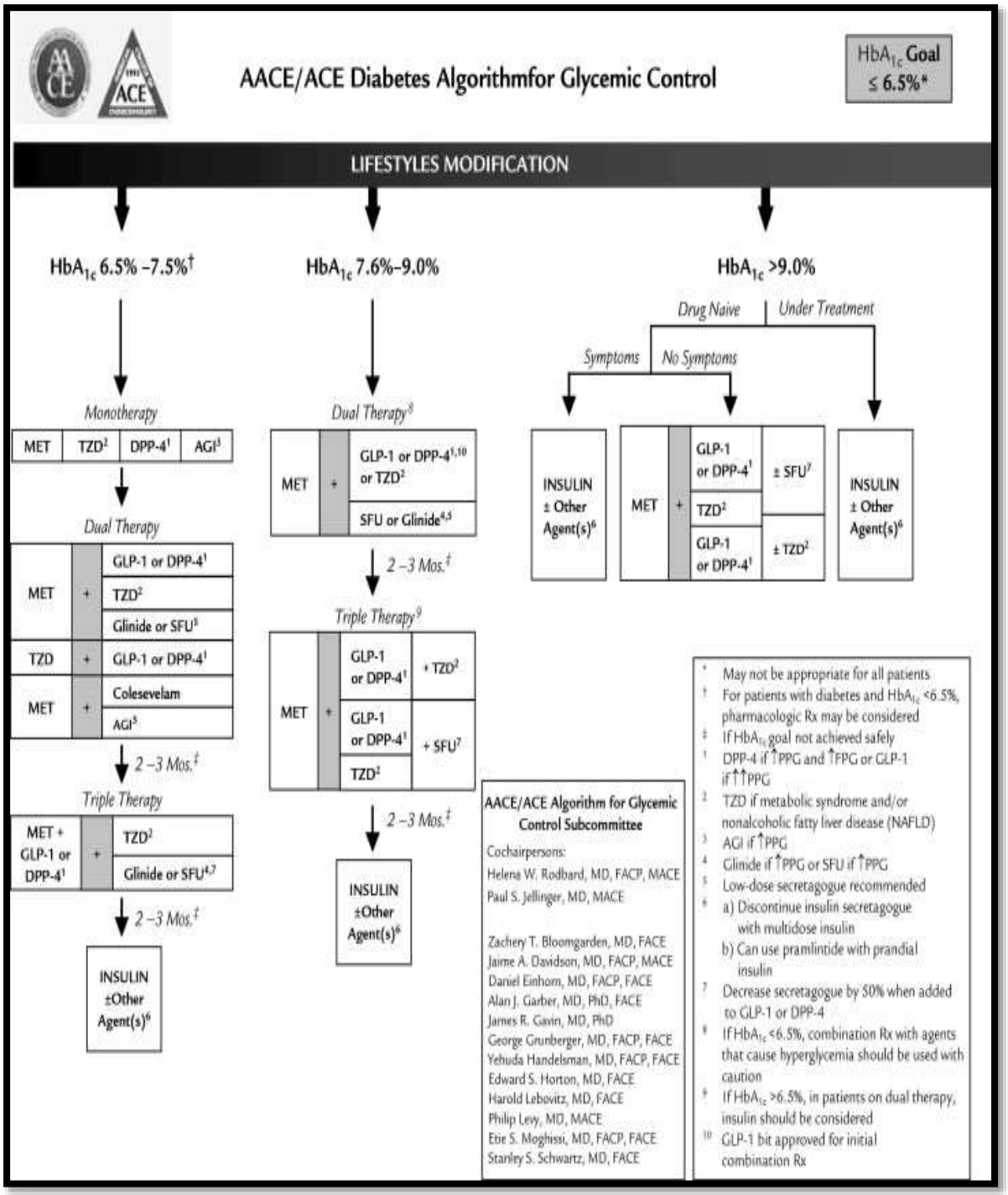
MANAGEMENT OF TYPE II DIABETES MELLITUS

Pharmacological agents:

There are at least seven different classes of agents used as monotherapy, or in combinations for the treatment of diabetes mellitus. Treatment include Metformin, Sulphonylureas,Meglitinides, Alpha-glucosidase inhibitors, Thiazolidinediones (TZD), DPP-4 inhibitors and insulin. Many conventional agents frequently exhibit reduced efficacy over time, leading to inadequate glycaemic control.

Metformin was recommended by most guidelines as first line therapy for T2DM. However, due to the progressive nature of T2DM, inevitable combination therapies are often required if glycemic targets not to be maintained by metformin monotherapy. Insulin resistance and pancreatic cell dysfunction are the two main pathophysiological reasons of T2DM, hence, proper treatment for such disease should target both these defects.

Figure 1: Treatment Algorithm for Type II Diabetes Mellitus



GLIPTIN: DPP-4 INHIBITORS

Dipeptidyl peptidase 4 (DPP-4) inhibitor is a relatively new class of antihyperglycemic agents that are now recommended as first or second-line agents in treatment of diabetes by guidelines like American Diabetes Association (ADA) 2016 and American Association of Clinical Endocrinologists and American College of Endocrinology 2016.

DPP-4 inhibitors control fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels through selective inhibition of DPP-4, resulting in increased plasma concentrations of active glucagon-like peptide-1.

DPP-4 inhibitors unlike Sulfonylureas, Meglitinides, or insulin are weight neutral and no risk of hypoglycemia. DPP-4 inhibitors, selectively inhibit the DPP-4 enzyme that degrades two major incretin hormones: GIP (gastric inhibitory polypeptide) and GLP-1(glucagon -like peptide1).

They are reported to have glucose lowering efficacy, without the risk of hypoglycemia, when added to the treatment regimen of patients in whom metformin monotherapy is no longer sufficient or when initial dual therapy metformin is required. DPP-4 inhibitors are reported to be well tolerated and efficacious in diverse population with type II DM including the elderly patient with renal impairment.[5]

There are 11 different compounds of DPP‑4Is have been made available worldwide, of which mostly available in Japan. In India, 4 DPP‑4Is are already available and marketed that includes Sitagliptin, Vildagliptin, Saxagliptin, and Linagliptin. Recently, two newer molecule Teneligliptin and Gemigliptin have been added to this segment.

Importantly, teneligliptin has been already approved and marketed product in Japan since 2012 and in Korea since 2014.

However, teneligliptin is neither approved in the USA or in Europe although it was registered in the US Food and Drug Administration (FDA) for Phase 1 clinical development in 2007 and Phase II clinical developments in European Medicines Agency in 2009, without any further progress.

Although various DPP-4 inhibitors have different pharmacokinetic and Pharmacodynamic profiles, they are remarkably similar with regards anti-hyperglycemic properties with a very safe adverse effect profile (weight neutral without causing hypoglycemia).

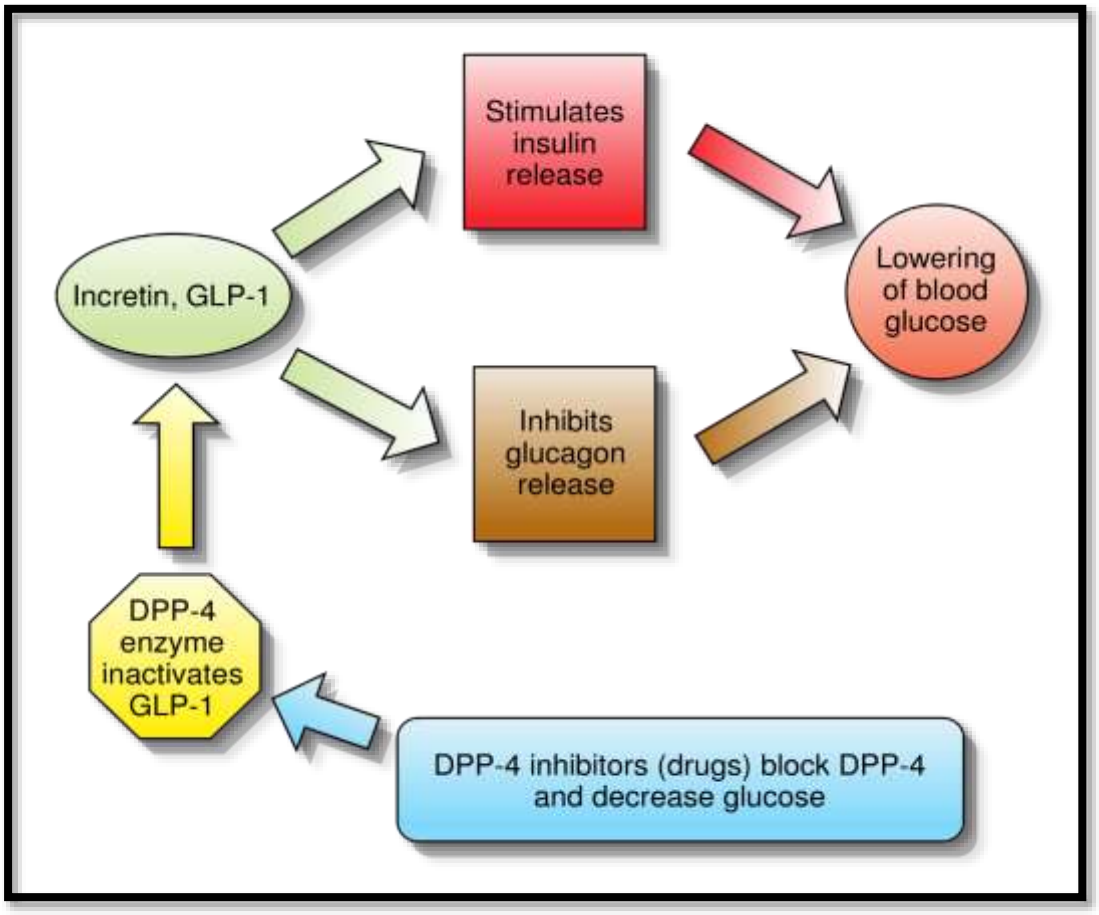
The DPP-4 inhibitors based on their structure can be divided into those that mimic the DPP-4 molecule (peptidomimetics, vildagliptin and saxagliptin) and those that do not (non-peptidomimetics, sitagliptin, alogliptin, linagliptin).

They are competitive reversible inhibitors of the DPP-4 substrate acting extra-cellularly. The molecules have varying affinities toward the DPP-4 substrate [5].

A list of available gliptins are follows

- Sitagliptin (Merck Sharp and Dohme Corp, approved as Januvia by US FDA in year 2006)
- Vildagliptin (Novartis, approved as Galvus by EU in year 2007)
- Saxagliptin (Bristol-Myers Squibb, approved as Onglyza by US FDA in 2010)
- Linagliptin (Boerhinger Ingelheim, approved as Tradjenta by US FDA in year 2011)
- Alogliptin (developed by Takeda Pharmaceutical Company Limited, approved for use in Japan)
- Teneligliptin (approved and marketed product in Japan since 2012 and in Korea since 2014)

Figure 2: Mechanism action of gliptins[7]



EFFICACY OF DPP-4 INHIBITORS AND RECOMMENDATION FOR USE

1. As monotherapy

DPP-4 inhibitors have demonstrated a modest and comparable glycated hemoglobin lowering effect. Current guidance from the American Diabetes Association recommends an HbA1c goal of <7% for the most patient and stringent goal of <6.5 if this can be attained without significant hypoglycemia and side effects.[5]

2. As initial dual therapy with other anti-diabetic agents

DPP-4 inhibitors along with other anti-diabetic agents, significantly improved glycated hemoglobin when compared with monotherapy arms.

In patients with T2DM inadequately controlled with metformin, SUs, or thiazolidinedione monotherapy, the addition of DPP-4 inhibitor was associated with significant improvements in HbA1c outcomes, as compared to placebo control.[5]

3. In triple combinations

DPP-4 inhibitors consistently provided additive glycemic benefits. As add-on to metformin and SU or a TZD, individual DPP-4 inhibitors have each been observed to significantly reduce HbA1c from baseline as compared to dual therapy; and significantly increase the proportion of patients achieving A1C <7%.[5]

SAFETY AND TOLERABILITY OF DPP-4 INHIBITORS

1. Low risk for hypoglycemia

A low risk of hypoglycemia was consistently observed in studies in treatment-native patient receiving DPP-4 inhibitor monotherapy during 18 to 13 week therapy. Hypoglycemia was also low with DPP-4 inhibitor therapy administrated in dual and triple combination with metformin, an SGLT2 or a TZA.

2. Weight gain

A neutral or mildly beneficial effect on weight was observed when DPP-4 inhibitors was used in combination regimens including metformin or an SGLT2.

EFFICACY AND SAFETY IN PATIENTS WITH RENAL INSUFFICIENCY

In patients with T2DM and moderate-to-severe chronic kidney disease, DPP-4 inhibitors effectively improved glycemic outcomes, with an A1c-lowering effect ranging from -0.8% at 52 weeks, with two respective DPP-4 inhibitors. For patients with mild renal impairment, no dose adjustment is needed for the currently available DPP-4 inhibitors.[5]

EFFICACY AND SAFETY OF DPP-4 INHIBITORS IN ELDERLY PATIENTS

1. Efficacy profile

- Available data in older patients demonstrate that DPP-4 inhibitors administered alone or in combination with other antidiabetic medications, effectively improve glycemic outcome in this patient population.

2. Safety profile

- Studies including elderly population showed that the incidence of adverse events are generally similar between the DPP-4 inhibitor group and comparator groups, and no notable safety issues were observed.

- There was a low risk of hypoglycemia DPP-4 inhibitor treatment groups.
- A neutral or mildly beneficial effect on weight was observed in DPP-4 inhibitor treatment groups. [5]

TENELIGLIPTIN

Teneligliptin belongs to third generation DPP-4 inhibitor and it is approved for type 2 diabetes mellitus patients. It is a novel chemo type prolylthiazolidine based DPP-4 inhibitor, shows a unique chemical structure which is characterized by five consecutive rings (J-shaped), thereby potentially producing unique characteristics including its glucose lowering efficacy and half-time.

It is administered with 20- 40 mg once daily. Since the metabolites of this drug are excreted through hepatic (approximately35%) and renal (about 65%) route, no dose adjustment is necessary in patients with renal impairment. The efficacy and safety profiles of teneligliptin are similar to those of other DPP-4 inhibitors. It because of its long half-life (approximately 26 hr.), this drug is shown to stabilize the glucose fluctuations throughout the day.

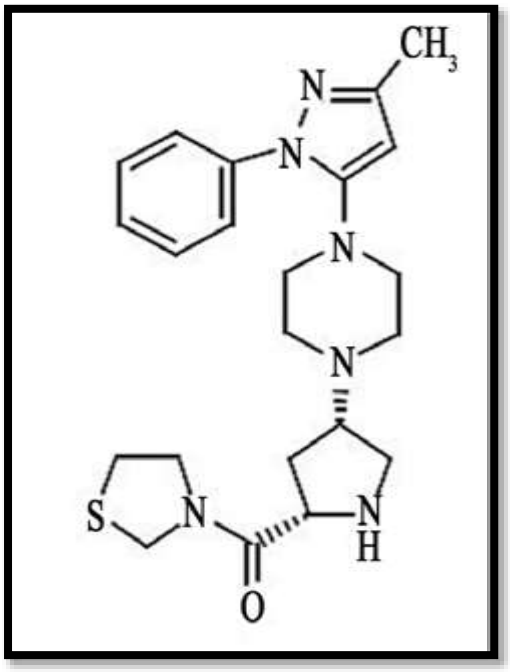
Teneligliptin is a third generation DPP-4 inhibitor approved for treatment of type II diabetes. It is currently available in Japan, South Korea, Argentina and India. Teneligliptin is under pre-registration in Indonesia & under Phase I trials in US & Phase II trials in Denmark, Germany, Hungary, Lithuania, Poland, Romania & UK.[5]

Chemistry of teneligliptin

Teneligliptin, {(2S, 4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl) piperazin-1-yl] pyrrolidin-2-yl} (1, 3-thiazolidin-3-yl) methanone hemipentahydrobromide hydrate exhibits a unique structure that is characterized by five consecutive rings and is peptidomimetic.

An X-ray co-crystal structure of teneligliptin with DPP-4 demonstrates that the key interaction occurs between the phenyl ring on the pyrazole and the S2 extensive subsite of DPP-4, which not only enhances the potency of the drug but also increases its selectivity.[1]

Figure 3: Chemical structure of Teneligliptin[6]



Metabolism and excretion

CYP3A4, a cytochrome P450 isozyme and flavin-containing monooxygenases (FMO1 and FMO3) play major roles in the metabolism of teneligliptin. In vitro, teneligliptin exhibits a weak inhibitory effect for CYP2D6, CYP3A4, and FMO; however, it demonstrates no inhibitory effect for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1. In addition, teneligliptin does not induce the expression of CYP1A2 or CYP3A4.

About 34.4% of teneligliptin is excreted unchanged via the kidney and the remaining 65.6% teneligliptin is metabolized and eliminated via renal and hepatic excretion; 216 hours after the administration of 14C-labeled teneligliptin (20 mg), the cumulative excretion percentages of radioactive teneligliptin in urine and feces were 45.4% and 46.5%, respectively.[5]

Dosage & Administration

The recommended dosage of Teneligliptin is 20 mg once daily. Teneligliptin can be administered irrespective of food, preferably before breakfast. It is also advisable to up titrate the dosage to 40 mg once daily in patients who do not achieve adequate

glycemic control as required. No dosage adjustment is required in patients with mild/moderate/severe renal impairment & mild/moderate hepatic impairment.

No dosage adjustment is required in elderly patients. Efficacy & safety of Teneligliptin is not studied in children. Teneligliptin should be used with caution in patients with severe hepatic impairment &those with heart failure (NYHA Class III - IV), because of a lack of clinical experience in these populations.[5]

Pharmacodynamic Advantage of Teneligliptin[5]

- Unique Structural Advantage
- Sustained DPP-4 Inhibition & High GLP-1 Concentration
- Insulin/Glucagon Modulator
- 24 Hours Glucose Control
- β-Cell Preservation
- Reduction in Short-Term Glycemic Fluctuations

Pharmacokinetic Advantage of Teneligliptin

Teneligliptin is rapidly absorbed in healthy volunteers 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. In humans, Teneligliptin is primarily metabolized by cytochrome P450 (CYP) 3A4 & flavin monooxygenases (FMO) 1 and 3 to several metabolites of unknown biological activity.

Pleiotropic Benefits of Teneligliptin

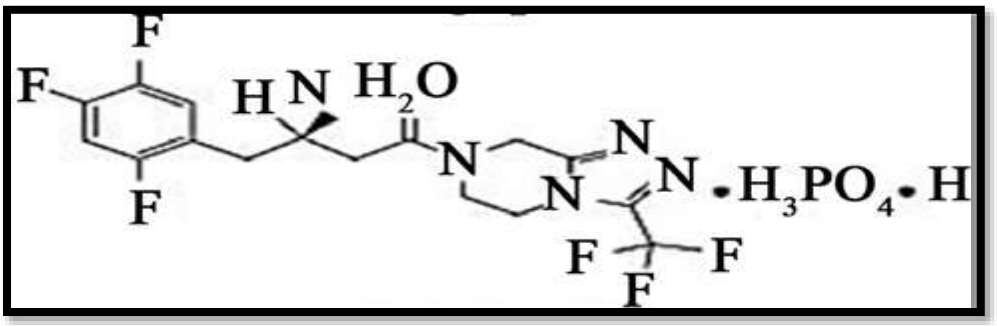
- Improvement in Endothelial Function
- Improvement in Lipid Profile
- Natriuretic & Diuretic Effects of Teneligliptin
- Weight Neutral

SITAGLIPTIN

This is the first gliptin to be US FDA approved. The recommended dose is 100 mg once a day. Its absorption is unaffected by food. For patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) the recommended dose is 50 mg/day and for severe renal impairment (creatinine clearance is <30 mL/min) the

recommended dose is 25 mg/day. In a meta-analysis it was shown to be more effective at reducing fasting blood sugar compared to vildagliptin, but overall efficacy was similar.

Figure 4: Chemical structure of Sitagliptin

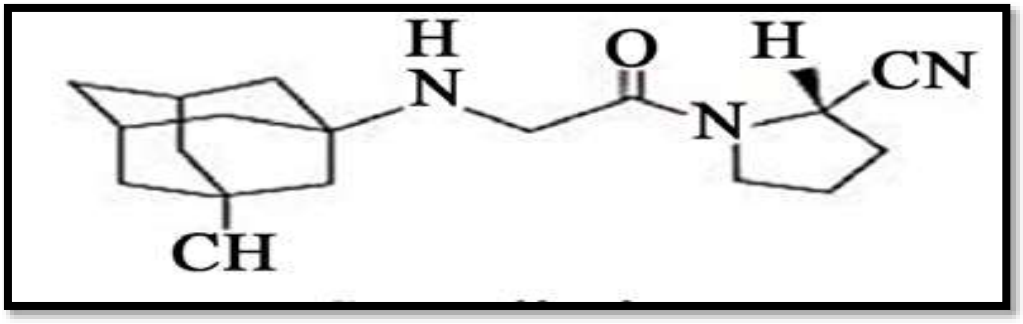


The Asian study (China India Korea study) suggested that sitagliptin was more effective in the Indian population with greater HbA1c reductions of approximately 1.3% compared to placebo.[6]

VILDAGLIPTIN

This is the second gliptin to be approved for commercial use although still not US FDA approved. The recommended dose is 50 mg twice a day. Its absorption is unaffected by food. It is extensively metabolized by the liver and has >90% bioavailability following a single oral dose.

Figure 5: Chemical structure of Vildagliptin



No dosage adjustment is required for liver disease although a greater amount of inactive metabolites (30% greater) are retained in patients with severe liver disease (Childs grade C). In patients with renal impairment no dose adjustment is required for mild renal insufficiency however for moderate renal insufficiency half the recommended dose of 50 mg is suggested.[7]

CURRENT POSITION OF GLIPTINS IN DIABETES MANAGEMENT GUIDELINES

The American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), European Society, and NICE (UK) guidelines suggest that gliptins should be considered over other anti-diabetic therapies especially if the patient is experiencing an increased incidence of hypoglycemia and/or weight gain.

It is clear that even major guidelines appreciate their usefulness with the only apprehension being that they have not withstood the test of time and therefore classified under less well-validated therapies. As data emerges suggesting sustained anit-hyperglycenic benefits they should replace current practices that include popular use of SU +/– insulin as second and third line agents to metformin.[8]

Current indications for use of gliptins are:

1. First line in T2DM with HbA1c <7%
2. Second line as add-on therapy in T2DM patients already on 1 out of the following {metfromin, SU, TZD, alfa-glucosidase inhibitor, miglitinide})for uncontrolled T2DM with HbA1c >7%
3. Third line as add-on therapy in T2DM patients already on combination therapy (2 out of the following {metfromin, SU, TZD, alfa-glucosidase inhibitor, miglitinide)

Contraindications or indication for stopping gliptin therapy includes previous or current adverse reaction to gliptins (hypersensitivity) or failure to achieve an HbA1c reduction of greater than 0.5% over a 6 month period.

Gliptins have revolutionized the concept of diabetes management and have provided a breath of fresh air to healthcare professionals dealing with diabetes. They provide an effective and safe alternative to the management of diabetes. Shown to reduced HbA1c from 0.5 to up to 2% effectively and safely (weight neutral without any if at all hypoglycemia) this new class of drugs is here to stay.

Even major diabetes management guidelines have acknowledged them for their safe adverse effect profile and urge healthcare professionals to use gliptins should they be struggling with regards weight or hypoglycemias with their patients. Recently, plagued with issues such as pancreatitis and cancer, these drugs need to stand the test of time and should they emerge victorious they will represent the only class of drugs that help improve beta-cell health, addressing the original triumvirate pathogenetic theory proposed for T2DM.[8]

2. REVIEW OF LITERATURE

1. **Manish Maladkar, [5] et al.,** conducted a study on 194 patients with type II diabetes mellitus, were treated for 120 days with teneligliptin (20 mg/day) alone teneligliptin add on Glimepiride. Result shows that 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, and hence can be administered safely in patients with renal impairment.
2. **Wakaba Tsuchimoch, [9] et al.,** conducted study on ten patients with type 2 diabetes mellitus, were treated for 3 days with teneligliptin (20 mg/day). Postprandial profiles for glucose, insulin, glucagon, active glucagon-like peptide-1, active glucose-dependent insulinotropic polypeptide (GIP), and 24 h glycemic fluctuations were measured via continuous glucose monitoring for 4 days. The result show that teneligliptin improved 24hours blood glucose levels by increasing active incretin levels and early-phase insulin secretion, reducing the postprandial insulin requirement, and reducing glucagon secretion. Even short-term teneligliptin treatment may offer benefits for patients with T2DM.
3. **Abhijeet Jain, [10] et al.,** The study was conducted as patients were randomly allotted into two groups. 50 patients were started with teneligliptin 20 mg/day along with metformin 1000 mg/day.Both group subjects had high FBS, PPBS and HbA1c at the start of study. After 24 weeks of treatment with teneligliptin and metformin, subjects had significant decrease in FBS, PPBS and HbA1c.This study showed that teneligliptin can be an effective alternative to other drugs for add on therapy to the patients who are inadequately controlled with metformin alone.
4. **Merlin C. Thomas, [11] et al.,** conducted study on 12-week, randomized, placebo-controlled trials on DPP-4 inhibitors in C50 patients with T2DM and RI. Outcomes assessed by change in HbA1c, overall safety, and incidence of hypoglycemic events (HEs).The result which shows that HbA1c reductions were similar at weeks 12 and 52. In the 12-week, placebo-controlled phase, sitagliptin and vildagliptin reduced HbA1c levels by 0.6–0.7. So that DPP-4 inhibitors have

the potential to improve glycemic control in patients with RI without increasing the risk of overall AEs.

5. **Fuyuhiko Marubayashi, [12] et al.,** conducted post-hoc pooled analysis used data from two Phase III clinical studies involving 702 Japanese patients. Evaluated teneligliptin as monotherapy and combined with a sulfonylurea, glinide, biguanide, or a-glucosidase inhibitor. Safety measures included adverse events (AEs), adverse reactions and hypoglycemia. .Which shows that Hypoglycemia was more frequent in the sulfonylurea combination therapy group than in other groups. Teneligliptin administered once daily as monotherapy or combination therapy resulted in a decrease in HbA1c, which was maintained for 52 weeks.
6. **Hamamoto.Y, [13] et al.,** study conducted a 12- or 16-week, placebo-controlled phase 2 and 3 trials, oral teneligliptin 20 or 40 mg once daily, as monotherapy or in combination with metformin, glimepiride or pioglitazone improved glycaemic control, including in patients with end-stage renal disease, and was generally well tolerated. This result shows that teneligliptin is a useful treatment option for adults with T2DM who have not responded adequately to diet and exercise regimens, or the addition of antidiabetic drugs.
7. **Takashi Kadowaki, [14] et al.,** conducted a teneligliptin as monotherapy and combined with a sulfonylurea, glinide, biguanide, or a-glucosidase inhibitor. Safety measures included adverse events (AEs), adverse reactions and hypoglycemia. The main efficacy measure was the change in glycated hemoglobin (HbA1c) from baseline. And 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.
8. **Takehiro Hashikata, [15] et al.,** conducted a study on 29 patients who had insufficiently controlled diabetes and consented to the study protocol were enrolled. All participants were evaluated at baseline and at 3 months after the additional treatment with teneligliptin. The study shows that the Teneligliptin treatment was associated with improvements in LV function and endothelial functions, and an increase in serum adiponectin levels. These results support the cardio-protective effects of teneligliptin in T2DM patients and increase in serum adiponectin levels.

9. **Rika Ito, [16] et al.,** an open-label, prospective clinical study was conducted. Thirteen patients (mean age 55.5 ± 3.9 years) with T2D underwent OGTT before and after teneligliptin 20 mg/day monotherapy. Plasma levels of glucose (PG), insulin, and C-peptide were measured at 0, 30, 60, 90, and 120 min after glucose loading in the OGTT. The result shows that twelve weeks of teneligliptin treatment improved IGI30min, AUC120min, and the SUIT index in Japanese patients with T2D.
10. **Enrique Z. Fismanet, [17] et al.,** the study conducted in 3 years of treatment, approximately 50 % of diabetic patients could achieve acceptable glucose levels with monotherapy. And monitored about the HbA1c, PPBS, FBS and also lipid profile .Study results shows that a definite relationship between gliptins treatment in hyperglycemia and improved cardiovascular outcomes remains uncertain and needs yet to be proven.
11. **Yuya Nakamura, [18] et al.,** the effects of dipeptidase-4 (DPP-4) inhibitors in diabetic hemodialysis (HD) patients, the findings have yet to be reviewed comprehensively. Eyesight failure caused by diabetic retinopathy and aging-related dementia make multiple daily insulin injections difficult for HD patients. The result shows that treating HD patients with DPP-4 inhibitors does not result in an increased incidence of adverse events. Furthermore, DPP-4 inhibitors are strongly anticipated to be effective in HD patients with diabetes.
12. **Valentina Lukashevich, [19] et al.,** conducted a study compared the safety and efficacy of vildagliptin and sitagliptin in patients with type 2 diabetes and severe renal impairment (RI). This study was a parallel-arm, randomized, multicenter, double-blind, 24 week study. In each group glycemic parameters are meauserd. Results shows that compared with sitagliptin demonstrated similar efficacy and both drugs were well tolerated.
13. **Jun-ichiro Mera, [20] et al.,** conducted a study with Vildagliptin 50 mg once daily was administered for 2 years. Various glycemic parameters are measured.The study concluded that Vildagliptin is a promising therapeutic option for safe, effective glycemic control in type 2 diabetic patients with ESRD
14. **Hirotoshi Ohmura, [21] et al.,** conducted study on 3,247 subjects treated with sitagliptin were retrospectively recruited. Glucose parameters were collected at

baseline, and 1, 3 and 6 months after initiation of sitagliptin. And also check whether about the sitagliptin-induced reduction in HbA1c using linear mixed effect model. The result shows that reduced HbA1c level from 7.44±1.20% at baseline to 6.73±0.99% at 6 months. So the sitagliptin is effective for diabetic management and generally well tolerated in Japanese patients with type 2 diabetes.

15. **Yun‐Zhao Tang, [22] et al.,** conducted a study on randomized study on oral hypoglycemic agents such that vildagliptin and sitagliptin used in 535 T2DM patients. Body mass index, HbA1c, FPG and PPG, insulin dose, and adverse events were evaluated during the study. The result shows that the baseline HbA1c was reduced by vildagliptin is 66.27 % and 52.73 % sitagliptin.so that the study concluded that 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.
16. **Eiji Kutoh, [8] et al.,** newly diagnosed, drug naive Japanese subjects with type 2 diabetes (T2DM) were assigned to 20 mg/day teneligliptin monotherapy (n = 31). At 3 months, levels of glycemic and other parameters were compared with those at baseline. Result shows that 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.
17. **Atef Halabi, [23] et al.,** teneligliptin was compared in 3 groups of 8 subjects assigned according to their degree of hepatic impairment (mild, moderate, or matched healthy subjects). Hepatic impairment was associated with an increase in maximal plasma concentration and overall exposure to teneligliptin. Study shows that teneligliptin was well tolerated by subjects with hepatic impairment. These results may indicate that caution will be needed when administering teneligliptin to subjects with hepatic impairment.
18. **Seiichi Tanaka, [24] et al.,** conducted Twenty-six patients with type 2 diabetes were admitted for glycemic control. After admission, patients continued to be treated with optimal dietary therapy plus insulin therapy, with or without other

anti-diabetes drugs, until they achieved stable glycemic control. The result shows that Add-on treatment with teneligliptin led to significant improvements in 24-h mean glucose levels, the proportion of time in normo glycemia, mean amplitude of glycemic excursions, and total area under the curve within 2 h after each meal.

19. **Wakaba Tsuchimochi, [25] et al.,** conducted a Ten patients with T2DM were treated for 3 days with teneligliptin (20 mg/day). Postprandial profiles for glucose, insulin, glucagon, active glucagon-like peptide-1 (GLP-1), active glucose-dependent, fluctuations were measured via continuous glucose monitoring for 4 days. Once daily teneligliptin administration for 3 days significantly lowered postprandial and fasting glucose levels. The result shows that 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. Even short-term teneligliptin treatment may offer benefits for patients with T2DM.
20. **Brian Green, [26] et al.,** conducted 70 patients with type 2 diabetes were admitted for glycemic control. After admission, patients continued to be treated with optimal dietary therapy plus insulin therapy, with or without other antidiabetic drugs, until they achieved stable glycemic control .the result shows that Gliptins increase nutrient-stimulated insulin secretion in type 2 diabetes with low-risk of hypoglycemia and without weight gain.
21. **Line P. Malha, [27] et al.,** conducted a study randomized open-label clinical trial that recruited 69 patients with previously treated with a combination therapy of metformin and sulphonylurea. Patients in the control group were maintained on their usual metformin and sulphonylurea regimen with dose adjustment for the fasting period. Patients in the study group were given vildagliptin 50 mg twice daily. Result shows that calculated change in hemoglobin A1C from baseline to last visit was similar for both groups.
22. **Fatemeh Hayati, [28] et al.,** study conducted in 24-week, non-randomized, open-labeled trial study, T2DM patients (n=93) who were on optimum dosage of metformin and sulphonylurea were additionally treated with 100 mg sitagliptin daily. The end point was assessed by investigating the changes in HbA1c and also FPG. Safety was assessed by recording of hypoglycemia, change in body

mass index, blood pressure, lipid profiles HDL, LDL, total cholesterol (Tc) and triglycerides, AST, ALT, ALP, urea, uric acid and creatinine level. And the result shows that mean HbA1c was reduced by 0.41%, and overall, 18.27% of patients achieved an HbA1c goal of <7%. After 6 months study concluded that Sitagliptin is effective and safe to be used in combination with metformin and sulphonylurea therapies.

23. **Chun-Jun Li, [29] et al.,** conducted study on randomized, open-label, parallel clinical trial, enrolled inadequately controlled [HbA1c] ≥7.5% to ≤10%) patients with type 2 diabetes, who were treated by dual combination oral hypoglycemic agents and patients had been randomized to add-on 5 mg saxagliptin group or 100 mg sitagliptin once daily group, or 50 mg vildagliptin twice daily group for 24 weeks. HbA1c, FBG and P2hBG, body weight, BMI, episodes of hypoglycemia and adverse events were evaluated. And the result shows that After 24 weeks, HbA1c, FBG, and P2hBG of each group were significantly decreased.
24. **Dongsheng Cheng, [30] et al.,** study conducted on randomized-controlled trials that assessed the efficacy and safety of DDP-4 inhibitors compared with placebo, no treatment, or active drugs were identified using PubMed, and EMBASE. The result which shows that DPP-4 inhibitors reduced HbA1c significantly and had no increased risk of hypoglycemia or weight gain. So that DPP-4 inhibitors are effective at lowering HbA1c in T2DM patients with moderate to severe renal impairment. DPP-4 inhibitors also have a potential advantage in lowering the risk of adverse events.
25. **Paul Craddy, [31] et al.,** study conducted on Systematic review of randomized controlled trials, health economic evaluation studies, systematic reviews, and meta-analyses, followed by primary Bayesian Mixed treatment comparison meta-analyses (MTCs), and secondary frequents direct comparison a Meta-analyses using a random effects model. And which shows that this systematic review and MTC showed similar efficacy and safety for DPP-4 inhibitors as treatment for type 2 diabetes, either as monotherapy or combination therapy.
26. **Yoshinobu Nabikaru, [32] et al.,** the absorption, metabolism and excretion of teneligliptin were investigated in healthy male subjects after a single oral dose

of 20 mg teneligliptin. This study indicates the involvement of renal excretion and multiple metabolic pathways in the elimination of teneligliptin from the human body. Teneligliptin is unlikely to cause conspicuous drug interactions or changes in its pharmacokinetics patients with renal or hepatic impairment, due to a balance in the elimination pathways.

27. **Kazuoki Kondo, [33] et al.,** In an initial 12-week, double-blind, placebo controlled, parallel-group study, patients (n = 204) were randomized to teneligliptin 20 mg or placebo once daily added to their stable pioglitazone therapy. This was followed by a 40-week, open-label period during which all patients received teneligliptin once daily. The end point HbA_{1c} from baseline to week 12. Patients in the teneligliptin group showed significantly greater reductions in HbA_{1c} compared with the placebo group at week. The change in fasting plasma glucose from baseline to week 12 was greater in the teneligliptin group than in the placebo group ($P < 0.001$).
28. **Miyako Kishimoto, [34] et al.,** assess blood glucose control over 24 hours and the safety of teneligliptin at 10 and 20 mg doses, a randomized, double-blind, placebo-controlled, parallel-group study was conducted at four locations in Japan. Among the 99 patients who participated, 32 were treated with a placebo, 34 were treated with teneligliptin at a dose of 10 mg, and 33 were treated with teneligliptin at a dose of 20 mg before breakfast for 4 weeks. These results indicate that the once-daily administration of teneligliptin before breakfast improved blood glucose control, even at dinnertime.
29. **Sandhu-Minhas, [35] et al.,** study conducted as Retrospective population based cohort study. The cohort included 72 738 new users of oral antidiabetic drugs (8032 (11%) used sitagliptin; 7293 (91%) were taking it in combination with other agents) followed for a total of 182 409 patient years. Based on this study the result shows that Sitagliptin use was not associated with an excess risk of all cause hospital admission or death compared with other glucose lowering agents among newly treated patients with type 2 diabetes.

30. **Masaya Sakamoto, [36] et al.,** conducted a study on Twenty patients with type 2 diabetes mellitus were randomly allocated to groups who received vildagliptin then sitagliptin, or vice versa. Patients were hospitalized at 1 month after starting each drug, and CGM was used to determine that 24-hour blood glucose level, fasting blood glucose level, highest postprandial blood glucose level and time, increase in blood glucose level after each meal, were measured. The study which shows that showed that mean 24-h blood glucose, highest blood glucose level after supper, and hyperglycemia after breakfast were significantly lower in patients with type 2 diabetes mellitus taking vildagliptin than those taking sitagliptin.
31. **Hyun Jeong Jeon, Tae Keun Oh, [37]** conducted in a randomized, open-label, comparative study, and 106 patients with type 2 diabetes were enrolled. And HbA1c FPG, 2h-PPG reduction from baseline are monitored. Result shows that the comparable HbA1c reduction was observed with a mean±standard deviation change from baseline to the 32-week endpoint of -0.94±1.15% in the vildagliptin group and -1.00±1.32% in the glimepiride group. So that the gliptins are much better than the other oral hypoglycemic agents.
32. **Chahal. H, [38] et al.,** conducted 50 patients with type 2 diabetes were admitted for glycemic control under gliptins .the result shows that gliptins cause a modest reduction in glycated hemoglobin when used as monotherapy or combination therapy, of around 0.7–1%. They appear to be more potent when baseline glycated hemoglobin is higher. They appear to be well-tolerated, and are taken orally once daily. So these are useful in treating obese patients with type 2 diabetes, in combination with metformin, or a glitazone, or both.

3. AIM AND OBJECTIVES

AIM

To determine the therapeutic efficacy and safety of Teneligliptin when compared with other standard gliptin molecules such as sitagliptin and vildagliptin.

OBJECTIVES

- Whether this drug used as primary, secondary or add on therapy as third molecule.
- To find out whether it could be used as a monotherapy in special patients with metformin side effect.
- Find out the usefulness of the teneligliptin and since it is low cost therapy to be recommended more than the other standard gliptins since it may quite useful in developing country like India.

4. METHODOLOGY

STUDY SITE:

This study was performed in the Department of General medicine (Diabetology), Kovai Medical Center and Hospital (KMCH) at Coimbatore, Tamil Nadu India. The proposed protocol for the study was presented and approved by the Hospital Ethical Committee (Annexure 1).

STUDY DURATION:

The study period was from 25th February 2017 – 30th July 2017 (6 months).

SOURCE OF DATA:

Patient medical record - Patient medical record is observed and the required data such as age, op number, height, weight, FBS, PPBS, HbA1c, Serum creatinine, and SGPT was recorded. Other data such as educational status, material status, social habits, family history, employment status, duration of diabetes mellitus and adverse drug reactions were collected by directly interviewing the patient.

STUDY DESIGN:

The study is a hospital based prospective and retrospective observational study in which all the patients presented with type II diabetes mellitus to the General medicine department were considered. The study included describing data collected in terms of their level of measurement and summarizing them in forms of tables, graphs, and numerical values. Mainly the Paired Students *'t'* test and One-way ANOVA test was used to finalize the result.

STUDY POPULATION:

A total 155 patients who came to the General medicine department with type II diabetes mellitus were included in the study.

STUDY CRITERIA:

Inclusion criteria:

- Patients with type II diabetes with an HbA1C level ≥ 6.5%.
- FBS level ≥ 126 mg/dl.
- PPBS level ≥ 200 mg/dl.

Exclusion criteria:

- Patients with Type 1 diabetes.
- Patients with Gestational diabetes.
- Patients having more than 10% HbA1C

METHODS OF DATA COLLECTION:

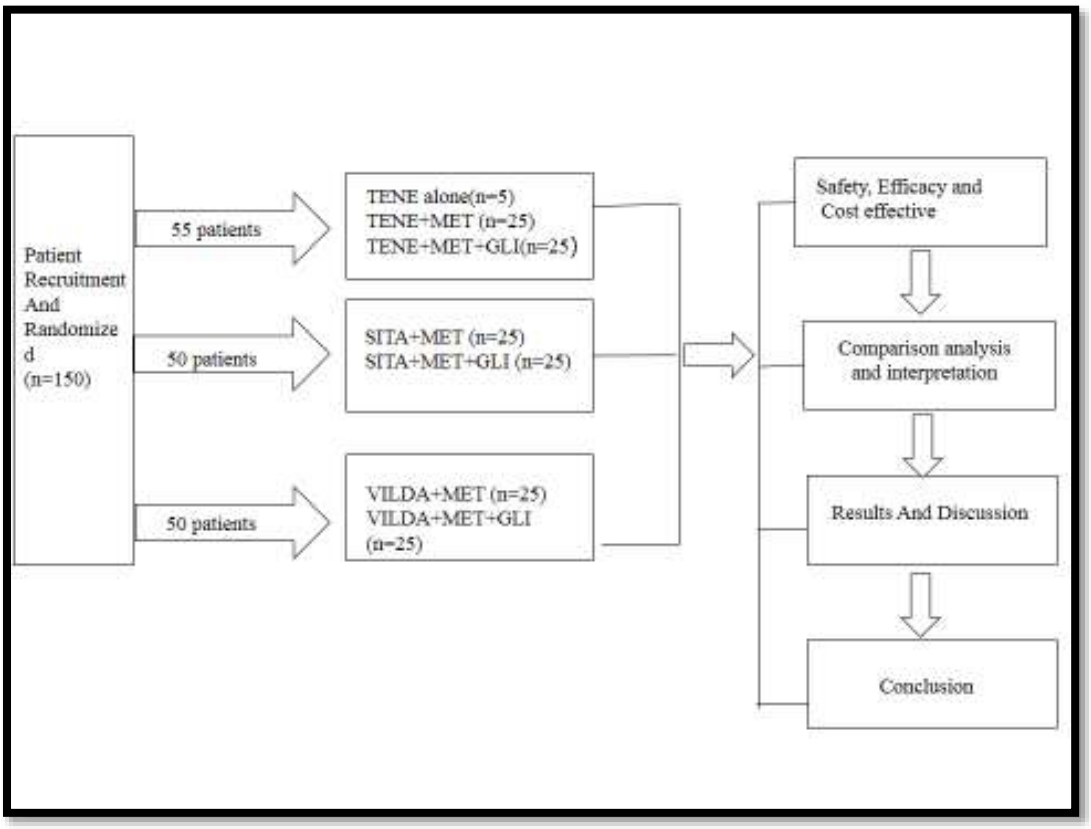
- Patient case notes.
- Medication/ treatment chart.
- Laboratory data report & other relevant source.
- Communication with the patients.

STUDY PROTOCOL:

Procedure:

The study was carried out after an approval from the ethical committee of the hospital on 25th February 2016. According to the inclusion criteria the patient who had type II diabetes were included in the study.155 patients were studied by the time period of 6 months. Patients were divided in to three groups namely, Group-A teneligliptin (55 patients), Group-B sitagliptin (50 patients) and Group-C vildagliptin (50 patients).

Figure 6: Patient Recruitment and Randomization



Group-A was further divided in to 3 subgroups, 5 patients were on teneligliptin 20mg as monotherapy, 25 patients on Teneligliptin add on Metformin as dual therapy. And 25 patients were on Teneligliptin add on Metformin plus Sulfonylurea as combination therapy.

Group–B was further divided into two sub groups, containing each 25 patients Sitagliptin add on metformin as dual therapy, and Sitagliptin add on metformin plus sulfonylurea as combination therapy. Group-C was also divided into two sub groups containing each 25 patients vildagliptin add on metformin as a dual therapy, and vildagliptin add on metformin plus sulfonylurea as combination therapy.

The patients were followed monthly during the study registration period. At the time of entry, complete medical history, and laboratory evaluation were obtained. Patient demographics were also considered and recorded. The following procedures are

were performed before and after 3 months of teneligliptin, vildagliptin, sitagliptin treatment. HbA1C, FBS, PPBS, Serum Creatinine, SGPT were measured. These essential data were collected using data collection form. After 3 months treatment, these patients interviewed again to assess if there any adverse drug reactions.

Literature Review: An extensive literature survey was done on safety, efficacy of gliptin molecule in type II diabetes mellitus patients. The literature supporting the study was gathered from various journal like Diabetes technology and therapeutics, International Journal of Pharma and Bio sciences, Scholar Journal of Applied Medical Sciences (SJAMS), International Journal of Research in Medical Sciences, Informa Health care, Journal of Diabetes Mellitus, Journal of Diabetes Ther, Endocrine Journal and Advanced Publication, International Journal of Medical Sciences and Public Health, Journal Of Diabetes Research and Clinical Metabolism, Indian Journal of Endocrinology and Metabolism, Diabetes and Metabolism Journal.

STATISTICAL ANALYSIS:

Statistical analysis was performed using the IBM SPSS (statistical package for the social services) software version 20. The baseline characteristics were studied by percentage. Difference between the before and after treatment were examined for statistical significance using the student′s Paired *t*-test. ANOVA were performed to determine overall difference between before and after treatment groups. The result were presented as mean ± SD or %. In all cases p-value ≤ 0.005 was considered as statistically significant.

5. TABLES AND FIGURES

Table 1: Distribution of overall study population based on gender (n=155)

Gender	Frequency	Percentage (%)
Male	92	59
Female	63	41

Figure 7: Plot of overall study population based on gender (n=155)

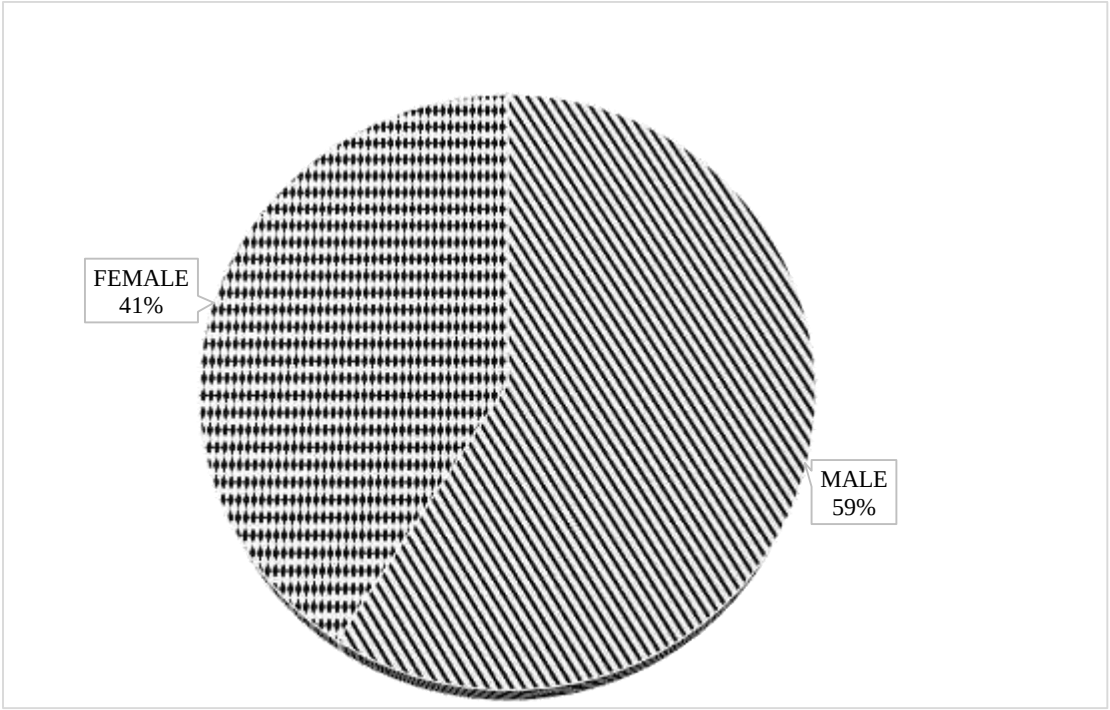


Table 2: Distribution of study population based on gender (n=150)

Gender	Teneligliptin (n=50)		Sitagliptin (n=50)		Vildagliptin(n=50)	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
Male	31	21	29	19	29	19
Female	19	13	21	14	21	14

Figure 8: Plot of study population based on gender (n=150)

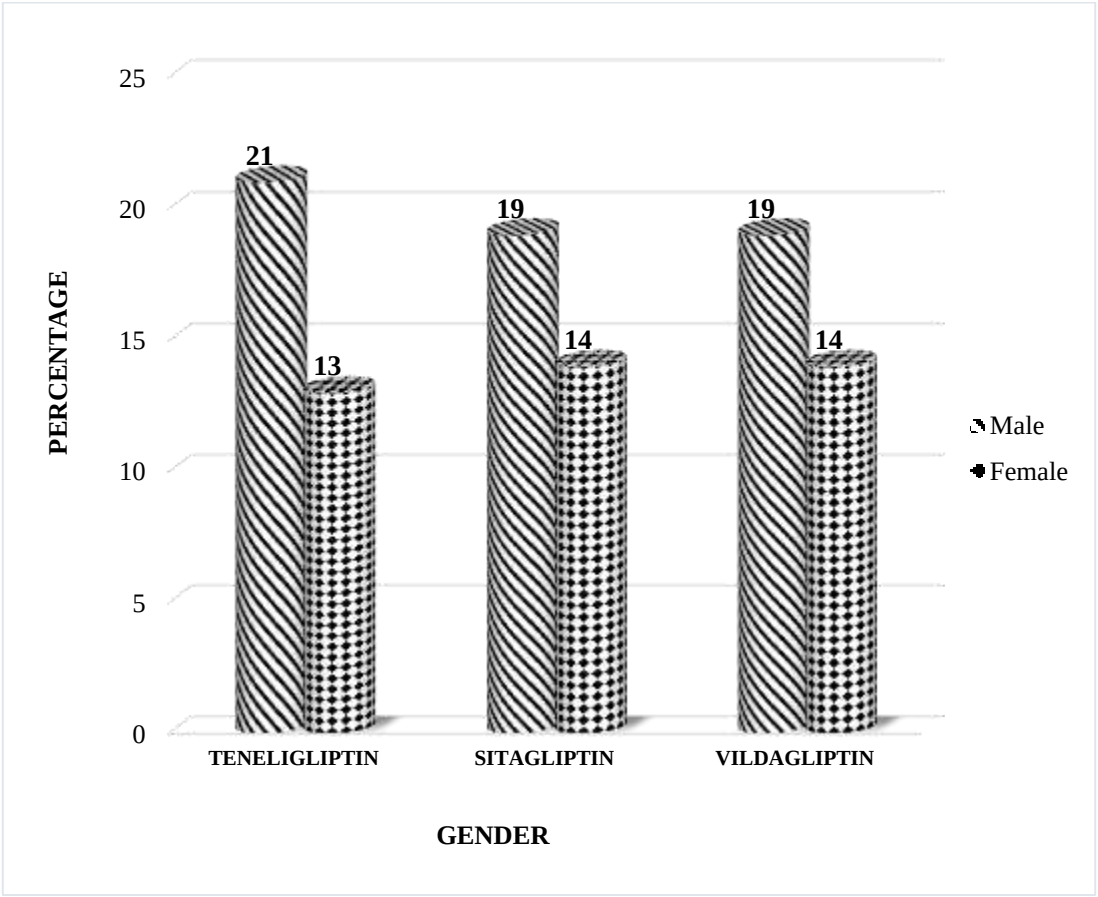


Table 3: Distribution of overall study population based on age (n=155)

Age	Frequency	Percentage (%)
30-40	20	13
41-50	35	23
51-60	67	43
61-70	21	13
71-80	12	8

Figure 9: Plot of overall study population based on age (n=155)

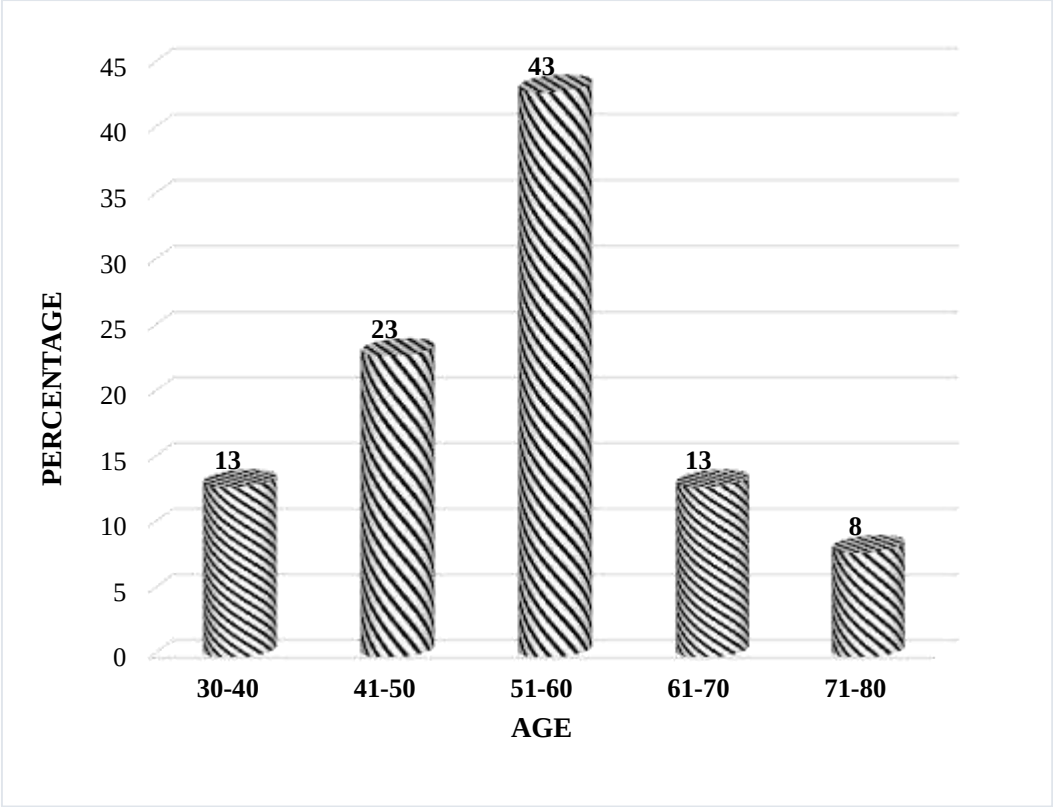


Table 4: Distribution of patients based on Age Group (n=150)

Age	Teneligliptin (n=50)		Sitagliptin (n=50)		Vildagliptin (n=50)	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
30-40	7	5	7	5	6	4
41-50	12	8	11	8	11	8
51-60	22	14	20	13	22	14
61-70	6	4	7	4	7	5
71-80	3	2	5	3	4	3

Figure 10: Plot of patients based on Age Group (n=150)

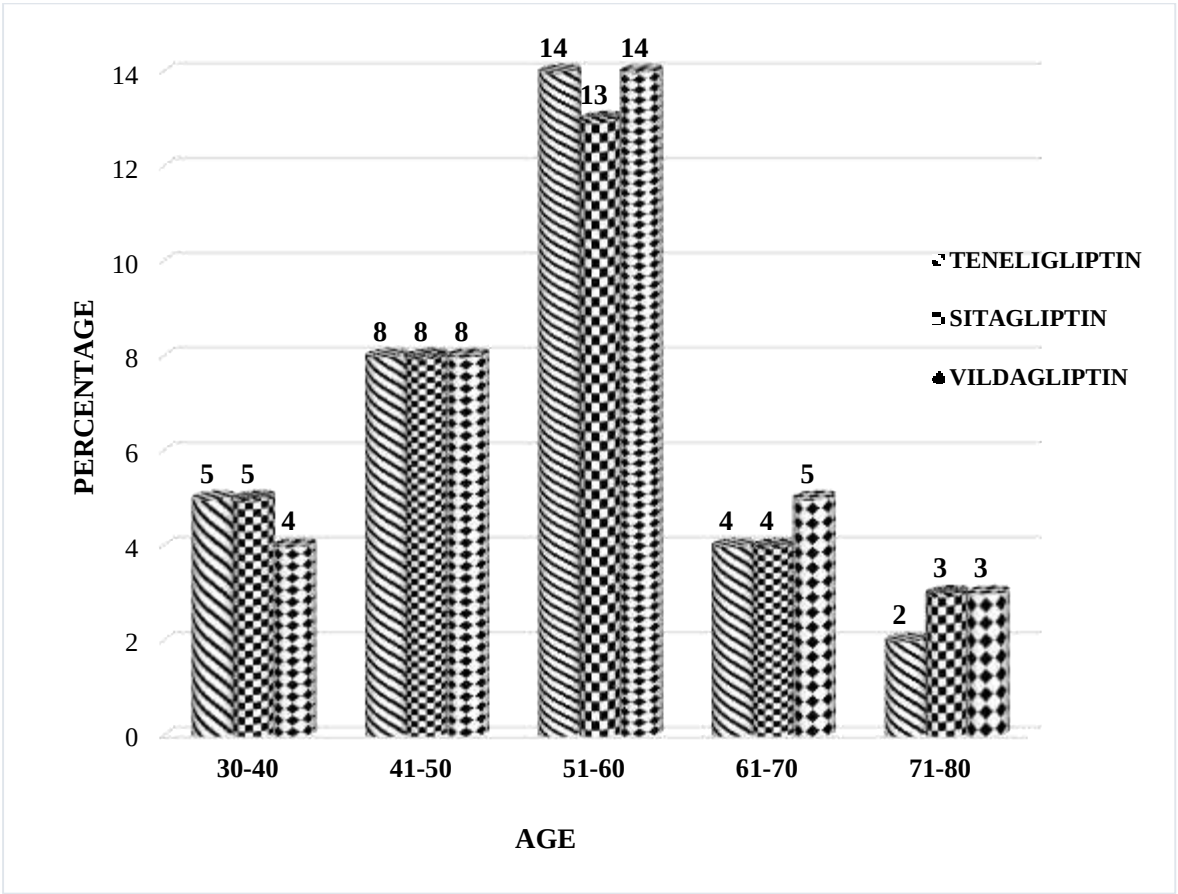


Table 5: Distribution of overall study population based on family-history (n=155)

Family-history	Frequency	Percentage (%)
Yes	69	45
No	86	55

Figure 11: Plot of overall study population based on family-history (n=155)

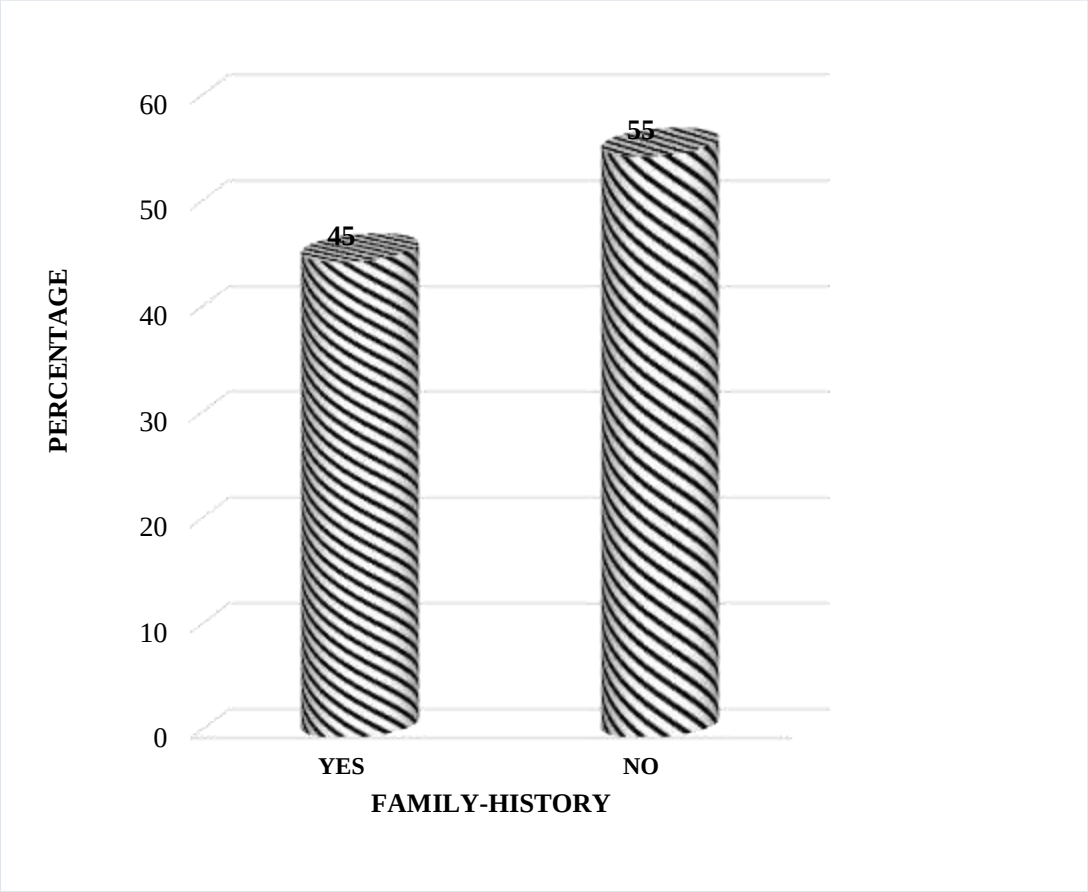


Table 6: Distribution of patients based on Family History (n=150)

Family-history	Teneligliptin (n=50)		Sitagliptin (n=50)		Vildagliptin (n=50)	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
Yes	23	15	23	15	21	14
No	27	18	27	18	29	20

Figure 12: Plot of patients based on Family History (n=150)

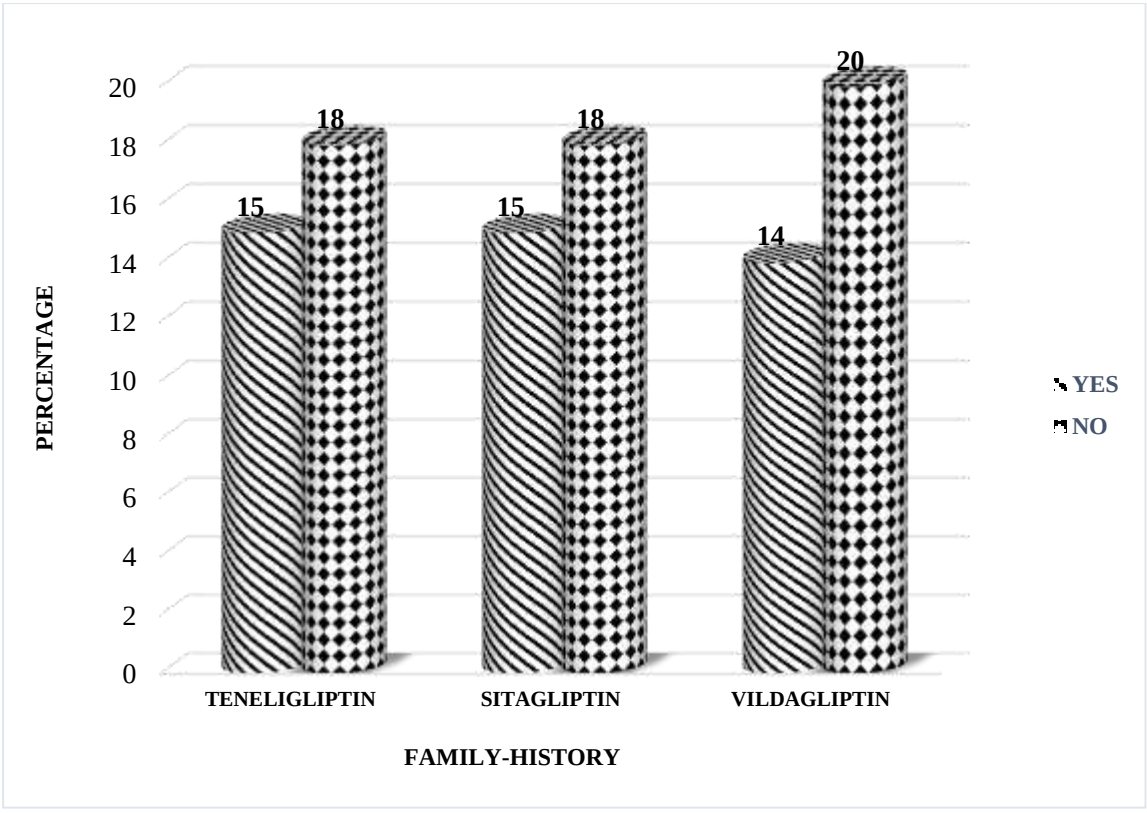


Table 7: Distribution of overall study population based on duration of diabetes mellitus (n=155)

Duration	Frequency	Percentage (%)
0-5	98	63
6-10	57	37

Figure 13: Plot of overall study population based on duration of diabetes mellitus (n=155)

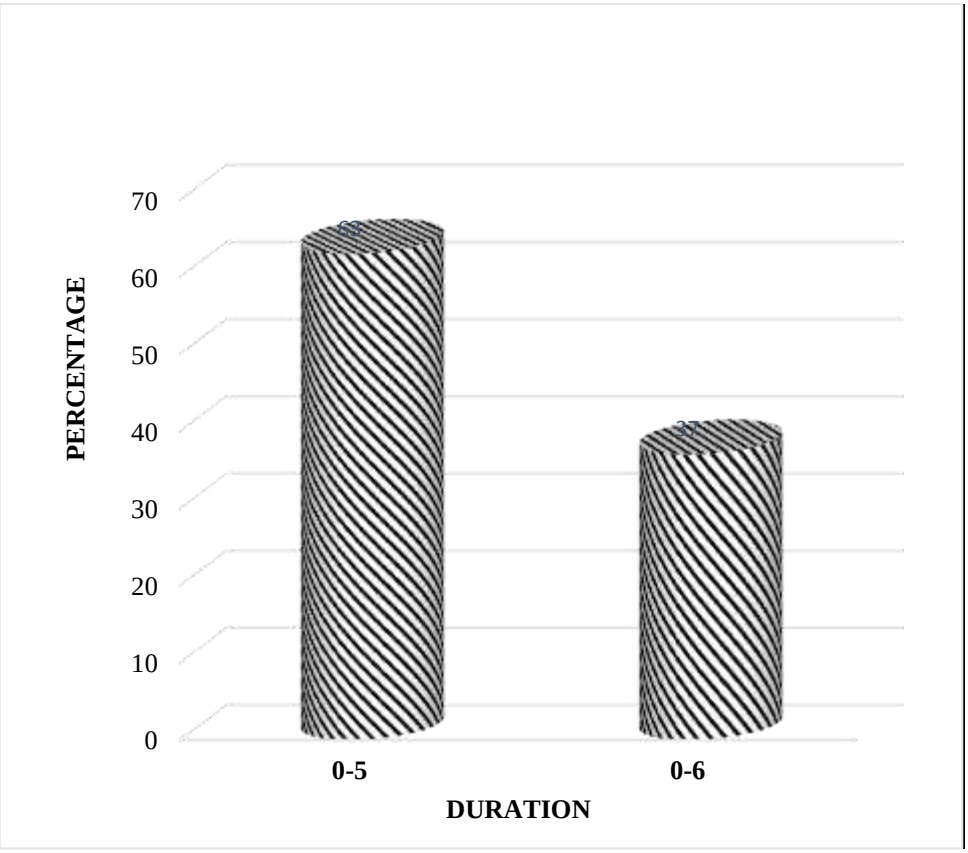


Table 8: Distribution of patients based on Duration of Diabetes (n=150)

Duration	Teneligliptin (n=50)		Sitagliptin (n=50)		Vildagliptin (n=50)	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
0-5	33	23	31	21	31	21
6-10	17	11	19	12	19	12

Figure 14: Plot of patients based on Duration of Diabetes (n=150)

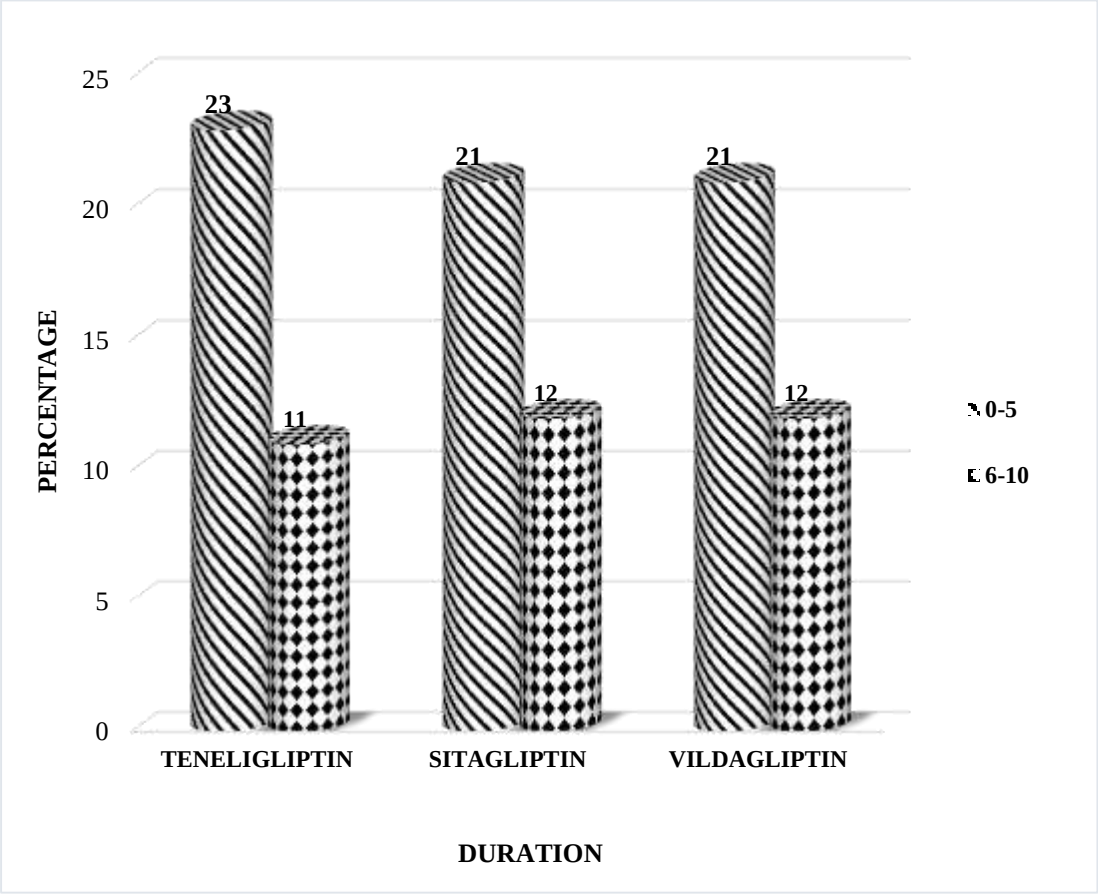


Table 9: Distribution of FBS (Dual therapy) levels in the study population (n=75)

FBS	Before Treatment	After Treatment
	Mean ± SD	Mean ± SD
Teneligliptin + Metformin	168.92±24.55	123.62±10.12
Sitagliptin + Metformin	168.68±24.13	123.64±10.45
Vildagliptin + Metformin	168.16±23.91	142.89±21.16

Figure 15: Plot FBS (Dual therapy) levels in the study population (n=75)

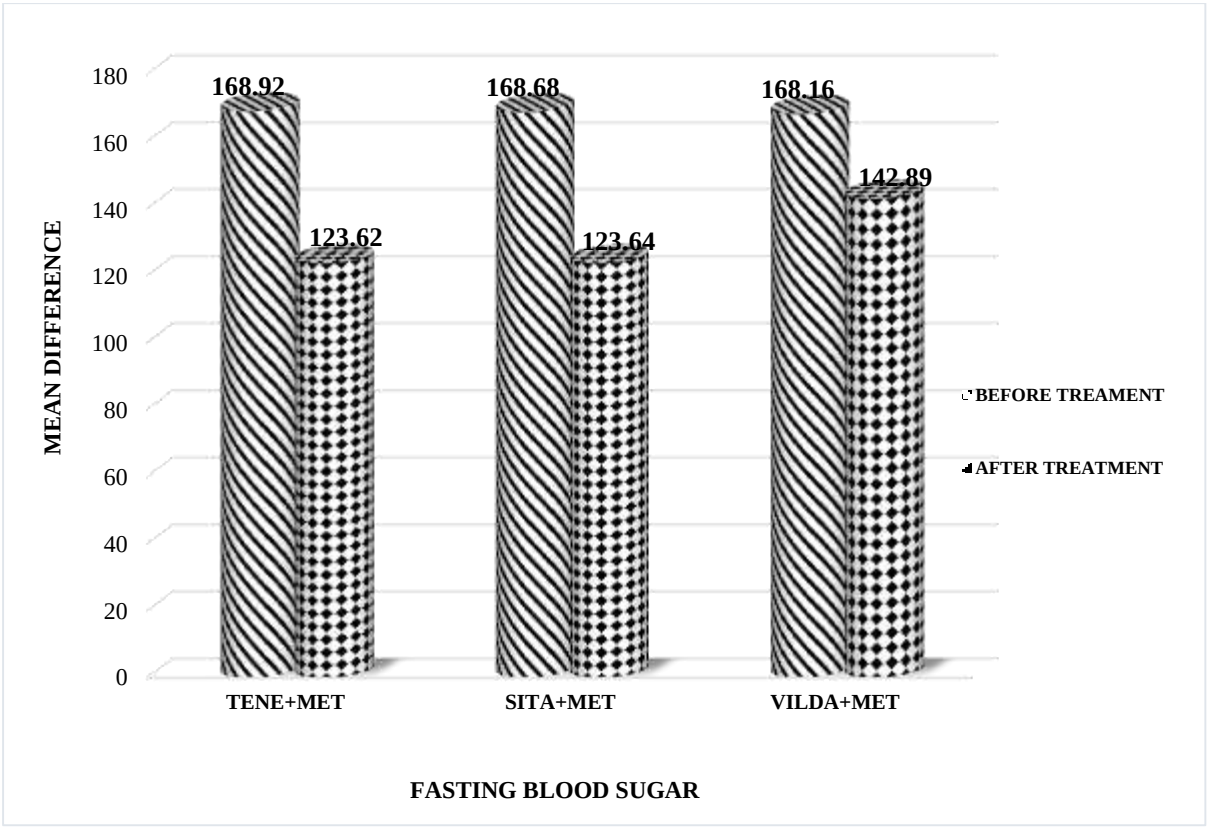


Table 10: Distribution of PPBS (Dual therapy) levels in the study population (n=75)

PPBS	Before Treatment Mean ± SD	After Treatment Mean ± SD
Teneligliptin + Metformin	274.56±37.62	165.10±35.15
Sitagliptin + Metformin	273.32±39.12	165.11±36.12
Vildagliptin + Metformin	275.88±36.27	190.44±44.29

Figure 16: Plot of PPBS (Dual therapy) levels in the study population (n=75)

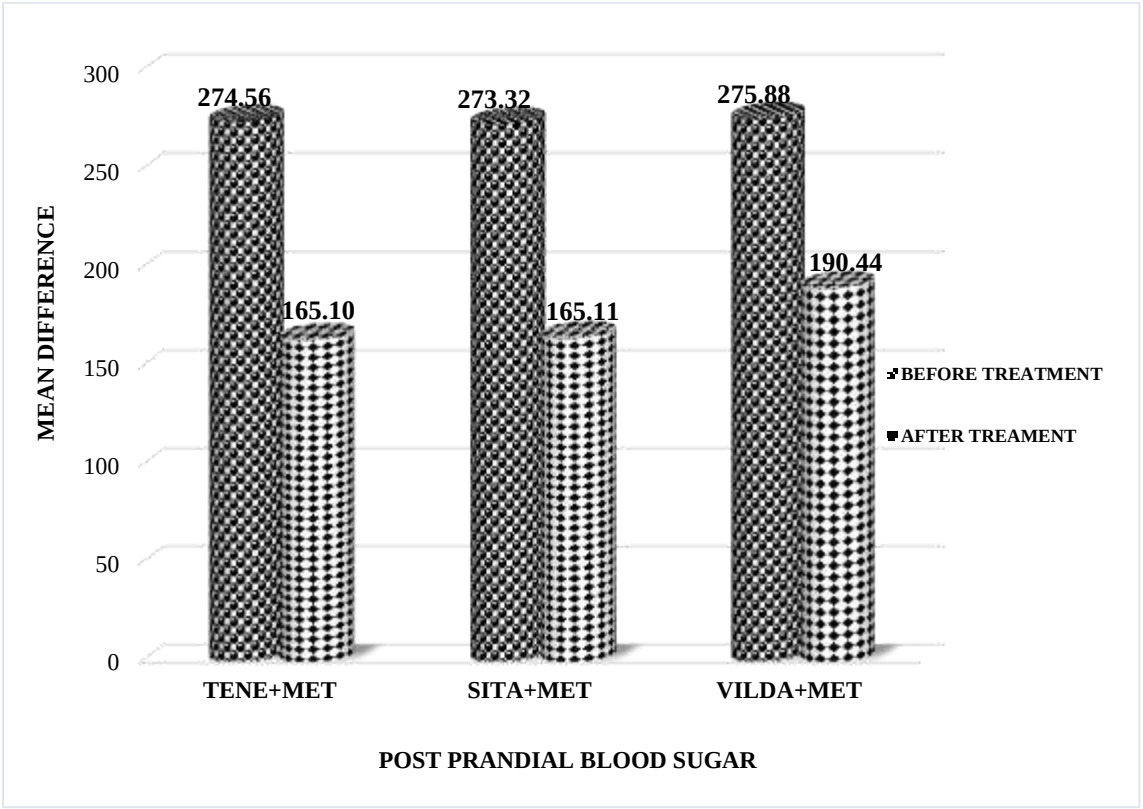


Table 11: Distribution of HbA1C (Dual therapy) levels in the study population (n=75)

HbA1C	Before treatment	After treatment
	Mean ± SD	Mean ± SD
Teneligliptin + Metformin	8.77±0.90	7.1±0.51
Sitagliptin + Metformin	8.81±0.91	7.1±0.56
Vildagliptin + Metformin	8.73±0.91	7.9±0.75

Figure 17: Plot of HbA1C (Dual therapy) levels in the study population (n=75)

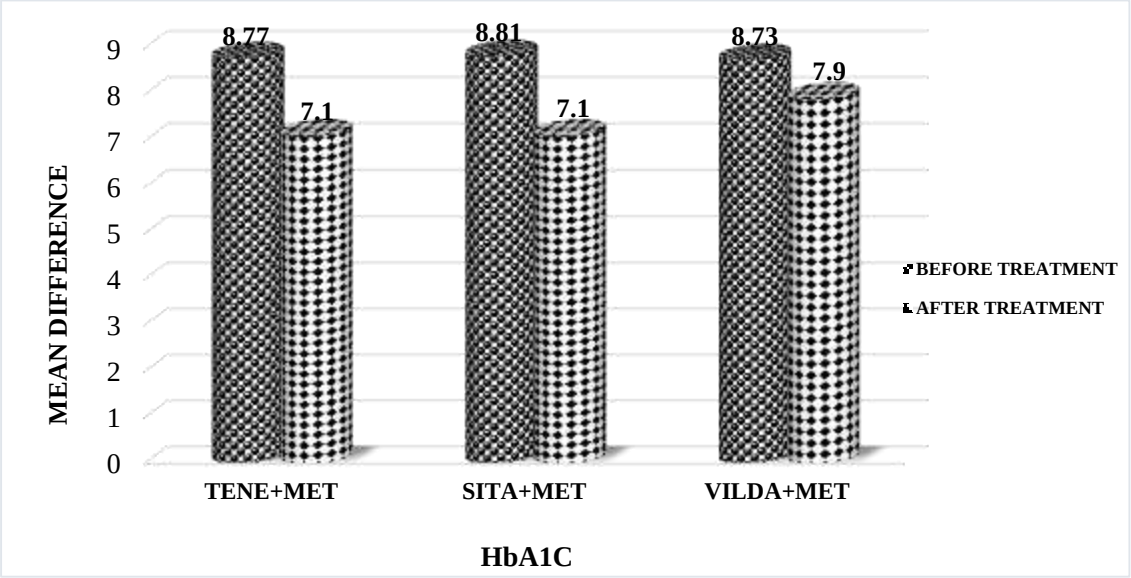


Table 12: Distribution of Serum Creatinine (Dual therapy) levels in the study population (n=75)

Serum Creatinine	Before Treatment Mean ± SD	After Treatment Mean ± SD
Teneligliptin + Metformin	0.83±0.33	0.83±0.33
Sitagliptin + Metformin	0.79±0.28	0.79±0.28
Vildagliptin + Metformin	0.78±0.25	0.78±0.25

Figure 18: Plot of Serum Creatinine (Dual therapy) levels in the study population (n=75)

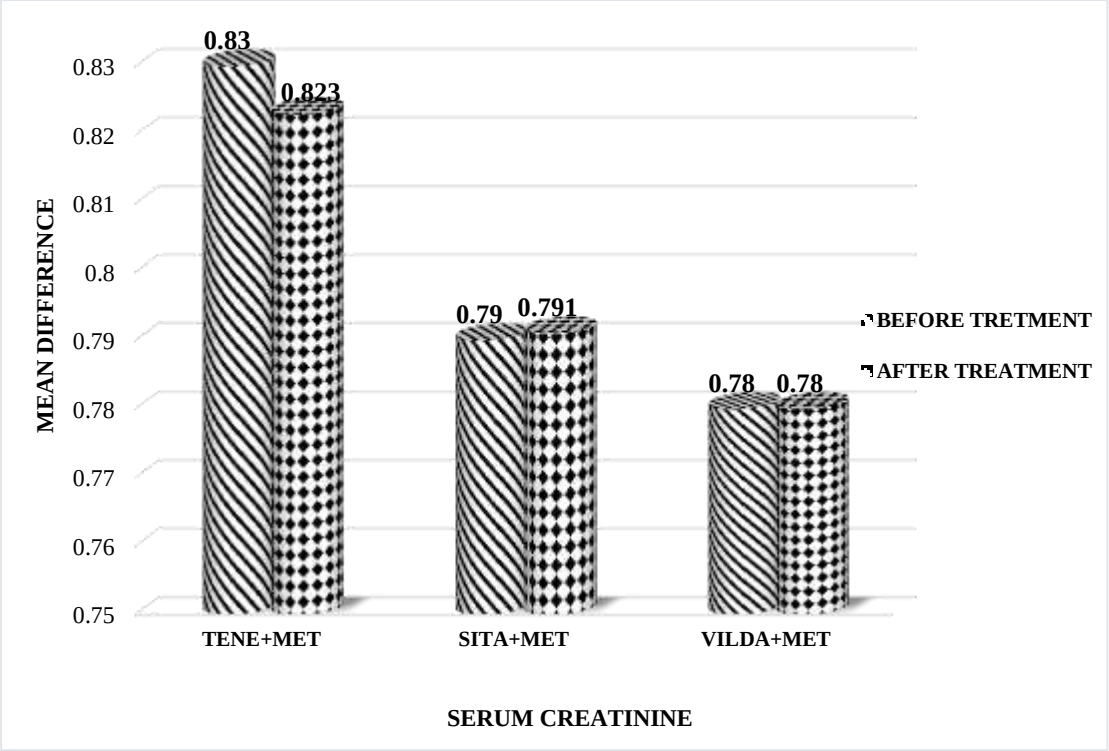


Table 13: Distribution of SGPT (Dual therapy) levels in the study population (n=75)

SGPT	Before Treatment Mean ± SD	After Treatment Mean ± SD
Teneligliptin + Metformin	33.84±3.72	33.91±3.50
Sitagliptin + Metformin	33.54±3.71	34.01±4.56
Vildagliptin + Metformin	33.91±3.83	39.96±5.61

Figure 19: Plot of SGPT (Dual therapy) levels in the study population (n=75)

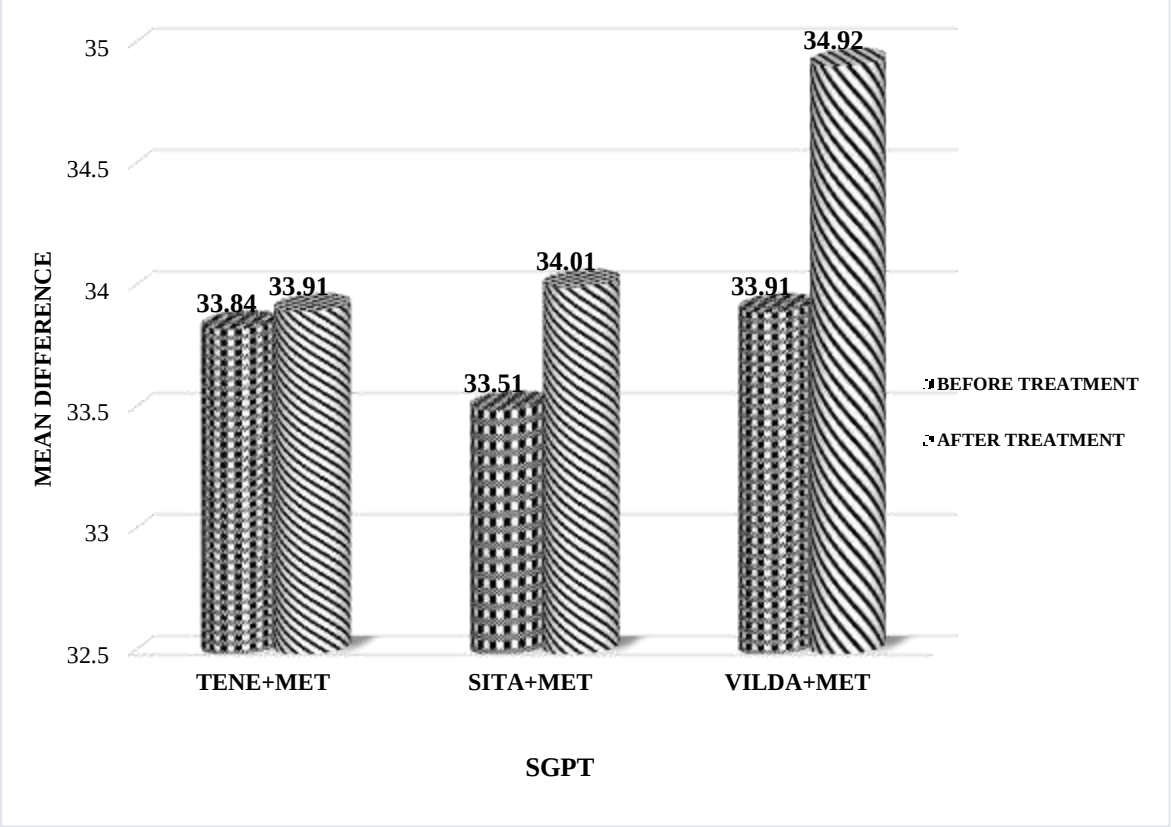


Table 14: Distribution of FBS (Combination therapy) levels in the study population (n=75)

FBS	Before Treatment	After Treatment
	Mean ± SD	Mean ± SD
Teneligliptin + Metformin + Glimepiride	193.8±34.30	121.5±22.69
Sitagliptin + Metformin + Glimepiride	195.3±34.05	121.4±19.96
Vildagliptin + Metformin + Glimepiride	193.4±28.66	132.9±25.07

Figure 20: Plot of FBS (Combination therapy) levels in the study population (n=75)

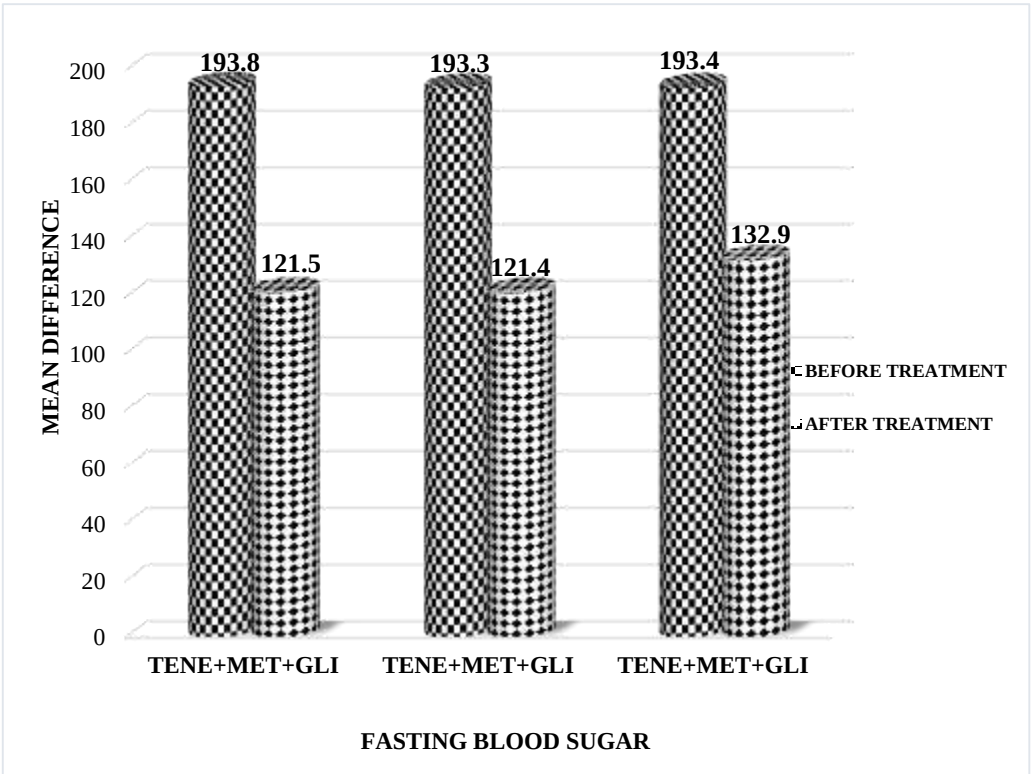


Table 15: Distribution of PPBS (Combination therapy) levels in the study population (n=75)

PPBS	Before Treatment	After Treatment
	Mean ± SD	Mean ± SD
Teneligliptin + Metformin + Glimepiride	294.7±43.80	183.44±19.84
Sitagliptin + Metformin + Glimepiride	294.9±44.12	183.9±20.65
Vildagliptin + Metformin + Glimepiride	294.5±41.89	199.4±23.25

Figure 21: Plot of PPBS (Combination therapy) levels in the study population (n=75)

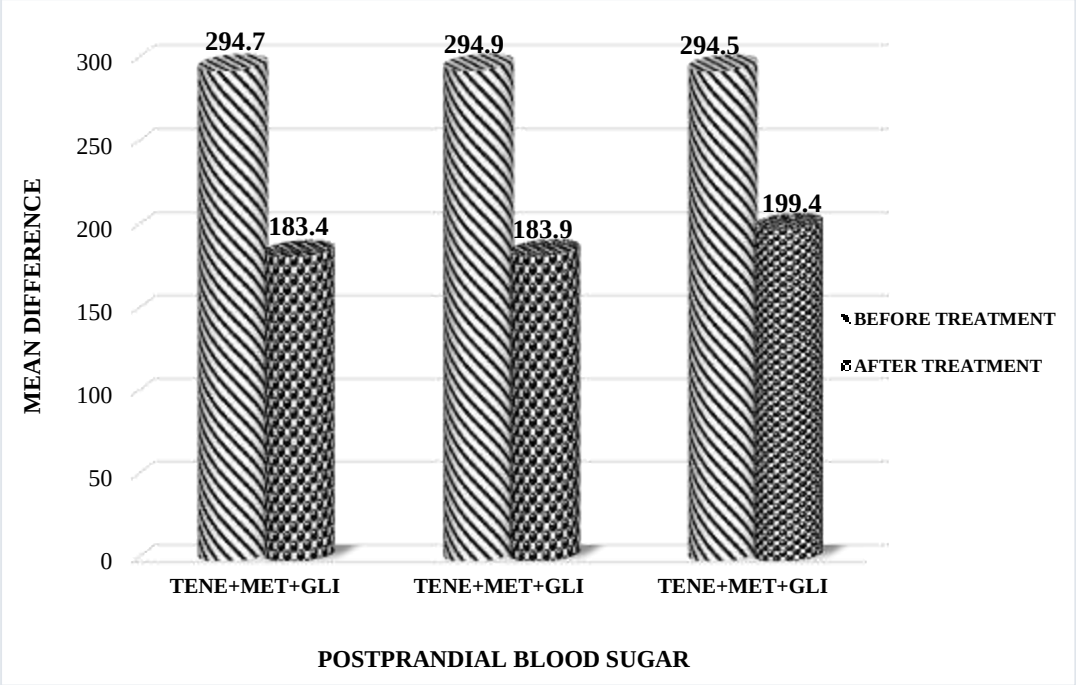


Table 16: Distribution HbA1C of (Combination therapy) levels in the study population (n=75)

HbA1C	Before Treatment	After Treatment
	Mean ± SD	Mean ± SD
Teneligliptin + Metformin + Glimepiride	0.93±0.94	7.49±0.48
Sitagliptin + Metformin + Glimepiride	9.47±0.91	7.51±0.54
Vildagliptin + Metformin + Glimepiride	9.48±0.93	8.60±0.79

Figure 22: Plot of HbA1C (Combination therapy) levels in the study population (n=75)

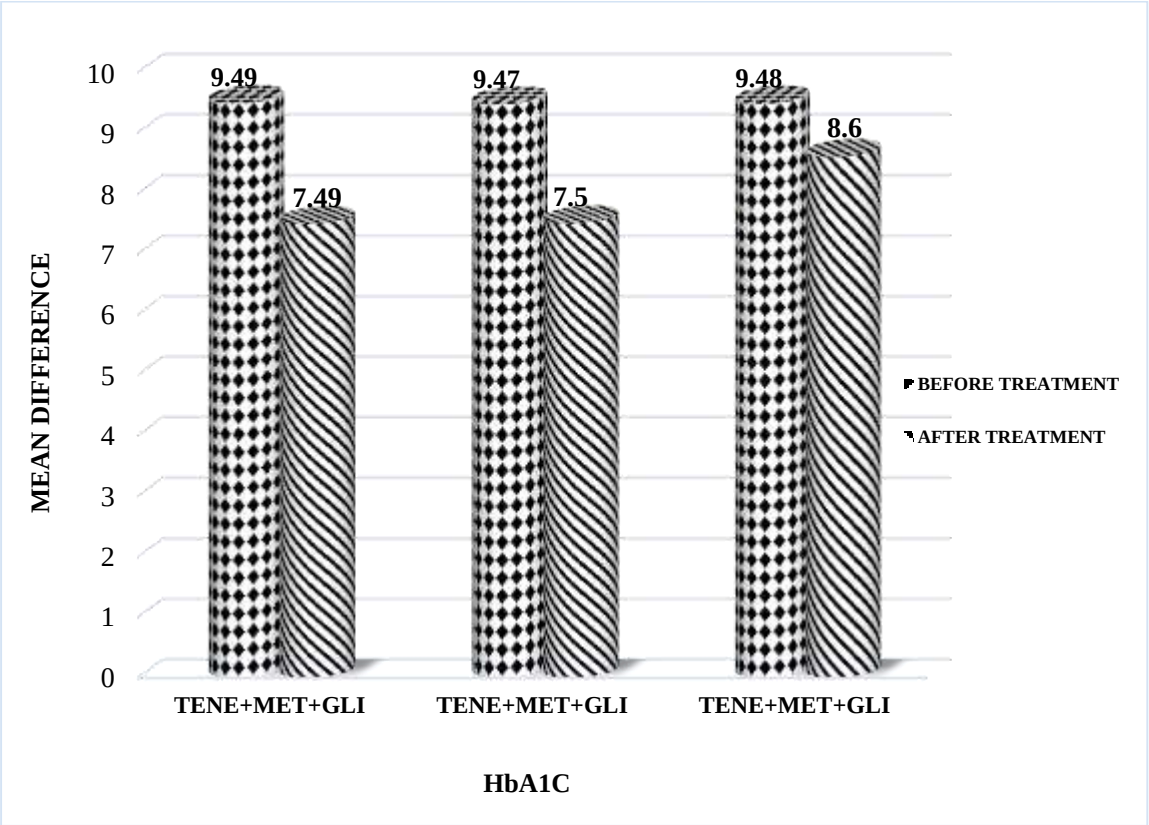


Table 17: Distribution of SrCr (Combination therapy) levels in the study population (n=75)

Serum Creatinine	Before Treatment	After Treatment
	Mean ± SD	Mean ± SD
Teneligliptin + Metformin + Glimepiride	0.83±0.34	0.83±0.34
Sitagliptin + Metformin + Glimepiride	0.79±0.24	0.79±0.24
Vildagliptin + Metformin + Glimepiride	0.82±0.31	0.82±0.31

Figure 23: Plot of SrCr (Combination therapy) levels in the study population (n=75)

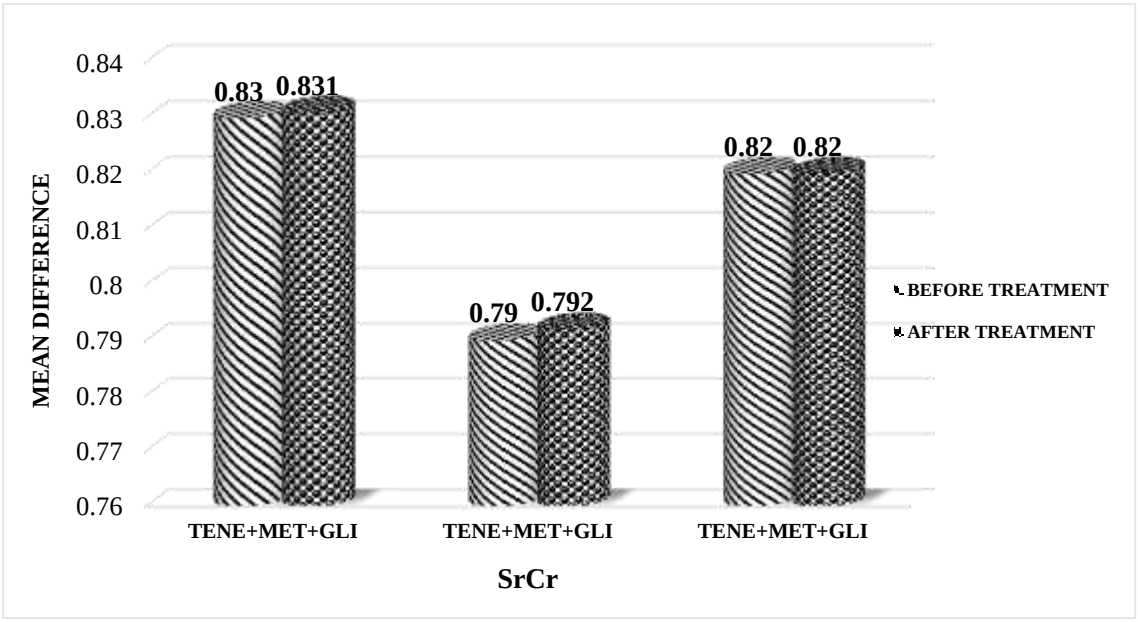


Table 18: Distribution of SGPT (Combination therapy) levels in the study population (n=75)

SGPT	Before Treatment	After Treatment
	Mean ± SD	Mean ± SD
Teneligliptin + Metformin + Glimepiride	28.68±5.59	28.76±6.12
Sitagliptin + Metformin + Glimepiride	30.64±6.31	31.44±6.92
Vildagliptin + Metformin + Glimepiride	28.36±5.32	30.19±5.61

Figure 24: Plot of SGPT (Combination therapy) levels in the study population (n=75)

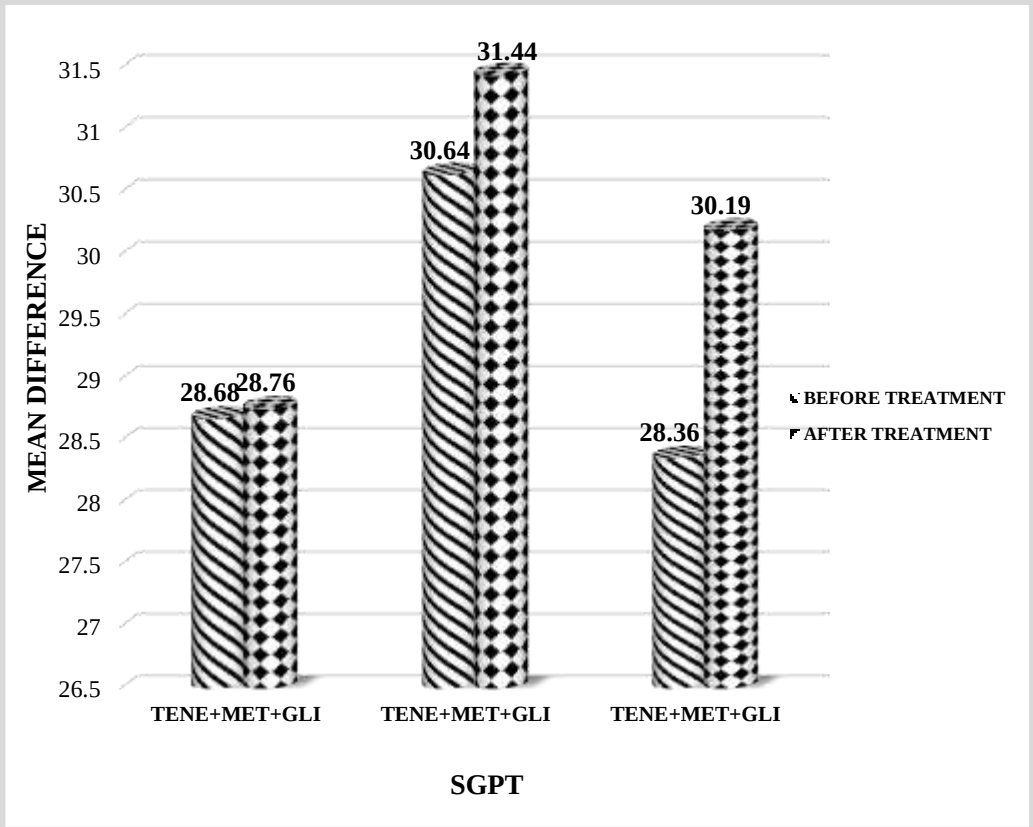


Table 19: Distribution of mean reduction in Glycemic parameters (Teneligliptin) in the study population (n=75)

Category	Mean reduction in HbA1C	Mean reduction in FBS	Mean reduction in PPG
Teneligliptin	0.92	41.33	65.83
Teneligliptin +Metformin	1.68	48.53	72.91
Teneligliptin + Metformin + Glimepiride	1.97	55.68	88.53

Figure 25: Plot of mean reduction in Glycemic parameters (Teneligliptin) in the study population (n=75)

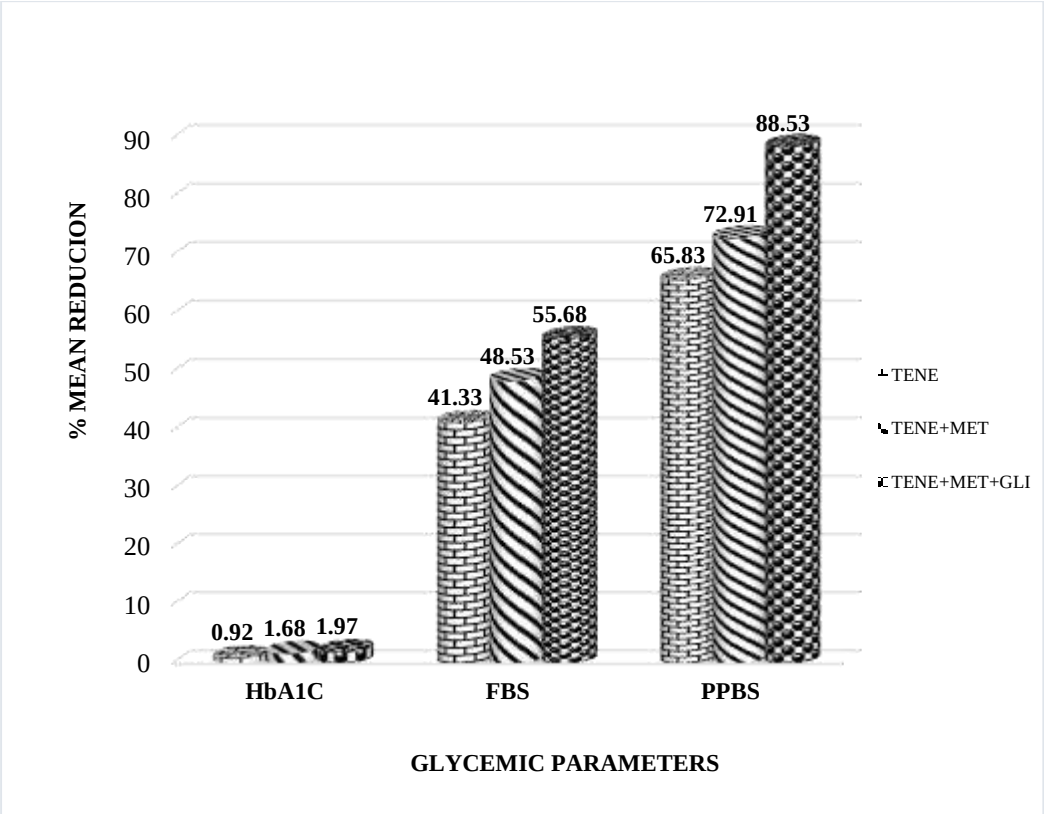


Table 20: Distribution of ADRs (Teneligliptin) in the study population (n=50)

ADRs	Frequency	Percentage (%)
GI irritation	4	8
Hypoglycemia	3	6
Diarrhea	1	2

Figure 26: Plot of ADRs (Teneligliptin) in the study population (n=50)

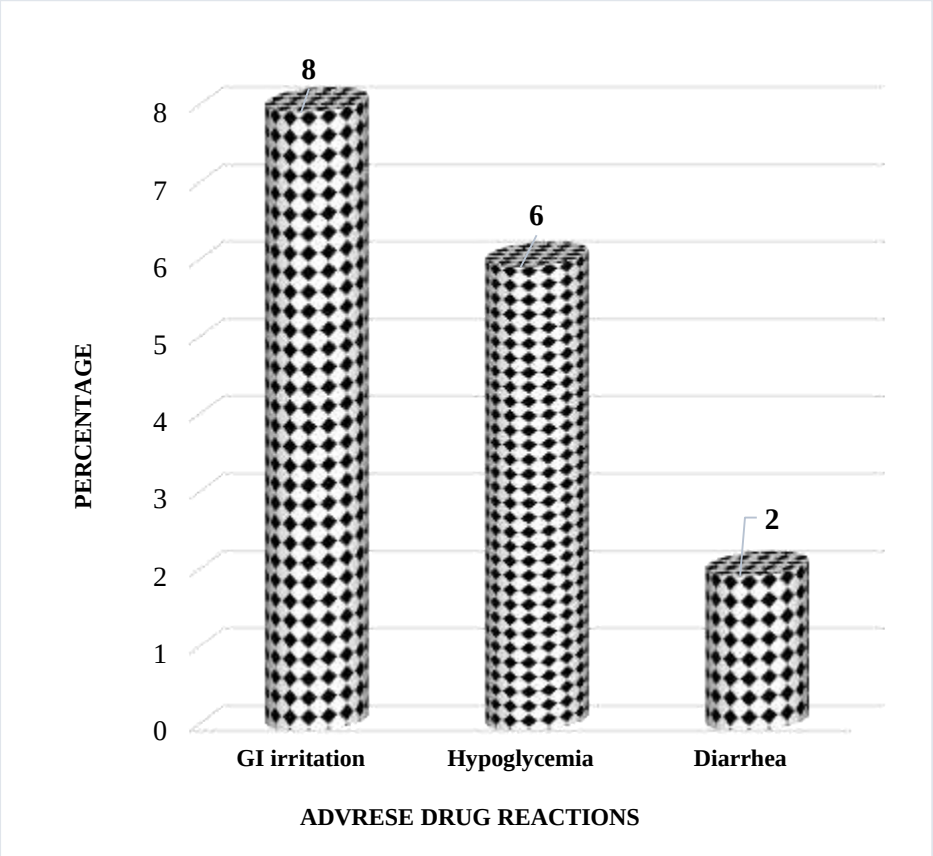


Table 21: Distribution of ADRs (Sitagliptin) in the study population (n=50)

ADRs	Frequency	Percentage (%)
GI irritation	6	12
Headache	1	2
Nausea	1	2
Diarrhea	2	4

Figure 27: Plot of ADRs (Sitagliptin) in the study population (n=50)

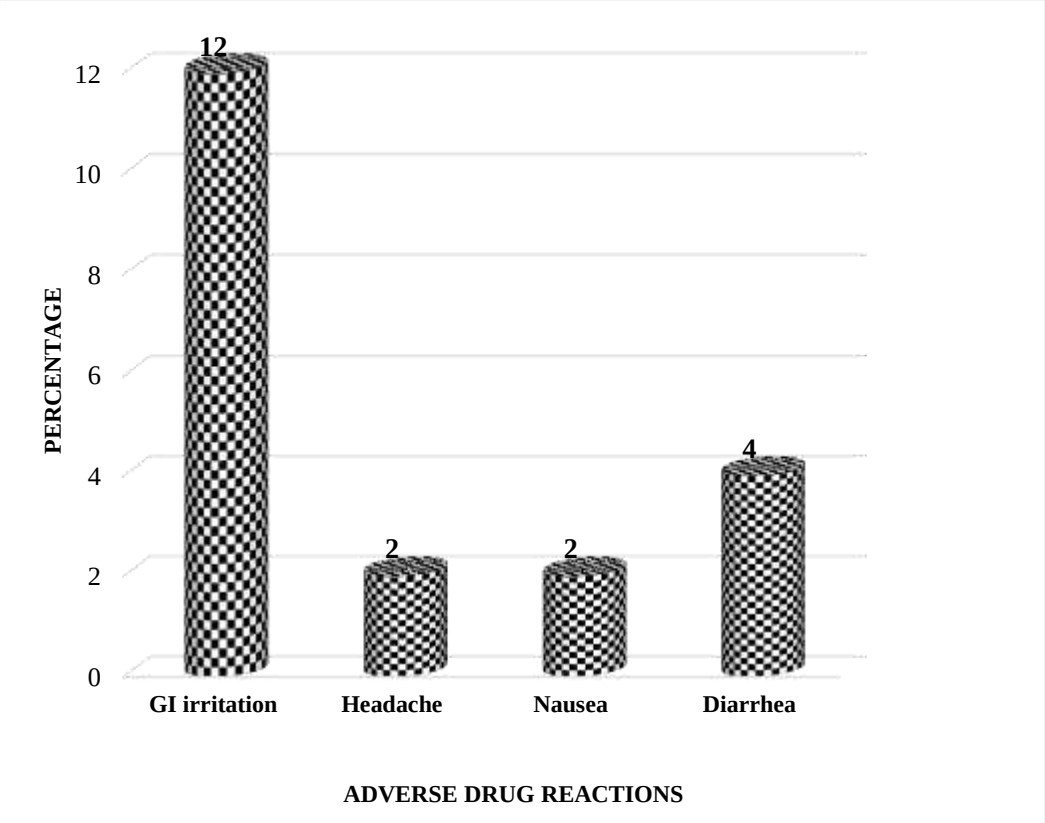


Table 22: Distribution of ADRs (Vildagliptin) in the study population (n=50)

ADRs	Frequency	Percentage (%)
Hypoglycemia	7	14
GI irritation	4	8
Headache	2	4
Dizziness	1	2
Diarrhea	1	2

Figure 28: Plot of ADRs (Vildagliptin) in the study population (n=50)

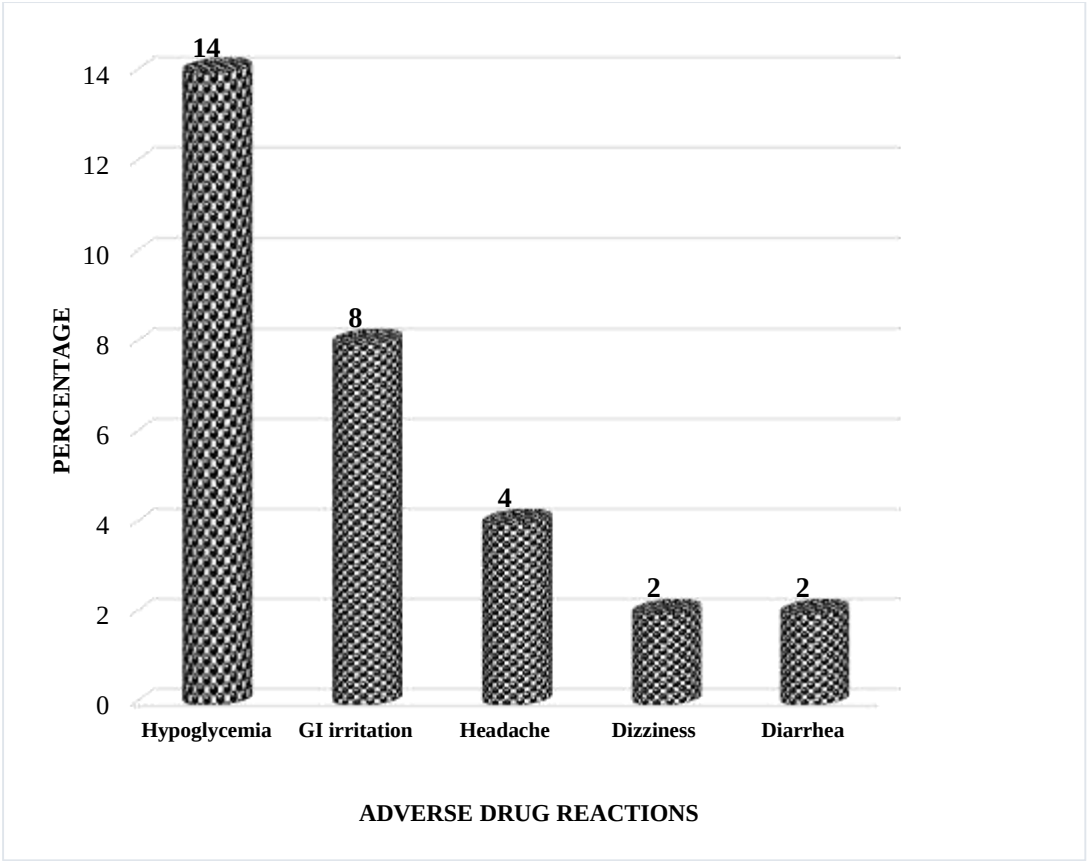


Table 23: Distribution of cost effectiveness in Monotherapy

Group	Drug	Price of a tablet	Price for 3 months	Difference
Monotherapy	Teneligliptin	7.69	692.1	
	Sitagliptin	38.4	1080	30.71
	Vildagliptin	25.7	2313	18.01

Table 24: Distribution of Cost effectiveness in Combination therapy

Group	Drug	Price of a tablet	Price for 3 months	Difference
Combination therapy	Teneligliptin + Metformin	12	1080	
	Sitagliptin + Metformin	23.2	2088	11.2
	Vildagliptin + Metformin	26.52	2386	14.52

Table 25: Student paired *t*-test for Dual therapy (n=75)

Parameter	Dual therapy	Before Treatment	After Treatment	*t-value*	*p- value*
		Mean ± SD	Mean ± SD		
FBS	Teneligliptin+ Metformin	168.92±24.55	123.62±10.12	10.04	**≤0.000*** **
	Sitagliptin + Metformin	168.68±24.13	123.64±10.45	5.807	**≤0.000*** **
	Vildagliptin + Metformin	168.16±23.91	142.89±21.16	12.03	**≤0.000*** **
PPBS	Teneligliptin +Metformin	274.56±37.62	164.16±35.15	16.47	**≤0.000*** **
	Sitagliptin+ Metformin	273.32±39.12	165.11±36.12	21.25	**≤0.000*** **
	Vildagliptin+ Metformin	275.88±36.27	190.44±44.29	10.41	**≤0.000*** **
HbA1C	Teneligliptin+ Metformin	8.77±0.90	7.1±0.51	9.49	**≤0.000*** **
	Sitagliptin+ Metformin	8.81±0.91	7.1±0.56	11.56	**≤0.000*** **
	Vildagliptin+ Metformin	8.73±0.91	7.9±0.75	18.2	**≤0.000*** **
SRCR	Teneligliptin+ Metformin	0.83±0.33	0.83±0.33	1.732	0.104
	Sitagliptin+ Metformin	0.79±0.28	0.79±0.28	1.693	0.103
	Vildagliptin+ Metformin	0.78±0.25	0.78±0.25	1.693	0.103
SGPT	Teneligliptin+ Metformin	33.84±3.72	33.91±3.50	-1.875	0.073
	Sitagliptin+ Metformin	33.54±3.71	34.01±4.56	-1.82	0.081
	Vildagliptin+ Metformin	33.91±3.83	39.96±5.61	-2.48	0.21

*** ≤ 0.005 is considered as statistically significant.**

Table 26: Student paired *t*-test for Combination therapy (n=75)

Parameter	Combination therapy	Before Treatment	After Treatment	*t-value*	*p-value*
		Mean ± SD	Mean ± SD		
FBS	TENE+MET+GLI	193.8±34.30	121.5±22.69	10.25	**≤0.000*** **
	SITA+MET+GLI	195.3±34.05	121.4±19.96	11.44	**≤0.000*** **
	VILA+MET+ GLI	193.4±28.66	132.9±25.07	9.27	**≤0.000*** **
PPBS	TENE+MET+ GLI	294.7±43.80	183.44±19.84	13.01	**≤0.000*** **
	SITA+MET+ GLI	294.9±44.12	183.9±20.65	15.37	**≤0.000*** **
	VILA+MET+ GLI	294.5±41.89	199.4±23.25	14.89	**≤0.000*** **
HbA1C	TENE+MET+ GLI	0.93±0.94	7.49±0.48	11.29	**≤0.000*** **
	SITA+MET+ GLI	9.47±0.91	7.51±0.54	10.64	**≤0.000*** **
	VILA+MET+ GLI	9.48±0.93	8.60±0.79	20.7	**≤0.000*** **
SRCR	TENE+MET+ GLI	0.83±0.34	0.83±0.34	0	1
	SITA+MET+ GLI	0.79±0.24	0.79±0.24	-450	0.657
	VILA+MET+ GLI	0.82±0.31	0.82±0.31	-157	0.877
SGPT	TENE+MET+ GLI	28.68±5.59	28.76±6.12	-0.097	0.927
	SITA+MET+ GLI	30.64±6.31	31.44±6.92	-0.525	0.605
	VILA+MET+ GLI	28.36±5.32	30.19±5.61	-5.07	0.621

*** ≤ 0.005 is considered as statistically significant.**

Table 27:One-Way ANOVA test for Dual therapy (n=75)

Parameter	Dual therapy	Before Treatment	Before Treatment	After Treatment	After Treatment
		f	***p-value***	***f***	***p-value***
FBS	Sitagliptin+ Metformin	1.619	0.179	0.215	1.86
	Vildagliptin+ Metformin	3.242	0.012	0.043	**≤0.000*** **
PPBS	Sitagliptin+ Metformin	2.431	0.539	0.214	0.635
	Vildagliptin+ Metformin	2.865	0.008	2.415	**≤0.000*** **
HbA1c	Sitagliptin+ Metformin	1.74	2.87	0.192	0.826
	Vildagliptin+ Metformin	2.184	0.12	2.905	**≤0.000*** **
SrCR	Sitagliptin+ Metformin	1.823	0.151	0.811	0.575
	Vildagliptin+ Metformin	1.823	0.151	0.811	0.575
SGPT	Sitagliptin+ Metformin	0.923	0.541	0.701	0.701
	Vildagliptin+ Metformin	_	_	13.901	0.141

*** ≤ 0.005 is considered as statistically significant.**

Table 28: One-Way ANOVA test for Combination therapy (n=75)

Parameter	Combination therapy	Before Treatment	Before Treatment	After Treatment	After Treatment
		f	***p-value***	***f***	***p-value***
FBS	SITA+MET+GLI	1.434	0.26	0.373	0.693
	VIDA+MET+ GLI	1.941	0.167	14.351	**≤0.000*** **
PPBS	SITA+MET+ GLI	1.873	0.155	1.488	0.248
	VIDA+MET+ GLI	0.113	0.976	9.375	**≤0.000*** **
HbA1c	SITA+MET+ GLI	0.821	0.497	0.892	0.424
	VIDA+MET+ GLI	0.594	0.626	9.24	**≤0.000*** **
SrCr	SITA+MET+ GLI	0.846	0.551	1.24	0.333
	VIDA+MET+ GLI	0.787	0.592	1.417	0.262
SGPT	SITA+MET+ GLI	0.885	0.594	1.528	0.25
	VIDA+MET+ GLI	_	_	3.366	0.03

*** ≤ 0.005 is considered as statistically significant.**

6. RESULTS AND ANALYSIS

A total 155 patients with type II diabetes mellitus was included in this study. They were divided into three groups namely Group A-Teneligliptin, Group B-Sitagliptin and Group C-Vildagliptin.

They were further divided into three sub-groups, teneligliptin 20 mg as monotherapy (5 patients), Teneligliptin and Metformin as dual therapy (25 patients) and Teneligliptin and Metformin with Glimepiride as combination therapy (25 patients).

Group B was divided into the two sub-groups, containing each 25 patients Sitagliptin with Metformin as dual therapy and Sitagliptin with Metformin plus Glimepiride as combination therapy.

Group C was divided into the two sub-groups, containing each 25 patients Vildagliptin with Metformin as a dual therapy and Vildagliptin with Metformin plus Glimepiride as combination therapy.

GENERAL BASE LINE CHARACTERISTICS OF STUDY POPULATION:

The patients were categorized based on their gender. There were 92 males and 62 females in overall study population, 31 males and 19 females in group A and 29 males and 21 females in Group B and Group C. The results shows the higher predominance in male for type II diabetes mellitus. (Table 1, 2 and Figure 7, 8)

Study population was categorized in to 5 groups on the basis of age. Among the 5 groups more number of patients were came under the category of 51-60 and less in 71-80 category. This indicates that incidence of type II diabetes mellitus is higher in 51-60 years and lower in 71-80 years. (Table 3, 4 and Figure 9, 10)

Among the study population, more number of patients (58%, 54% and54% in group A, B and C respectively) were known to have no family history of type II diabetes mellitus. (Table 5, 6and Figure 11, 12)

Study population was categorized into two groups on the basis of duration of the disease in years. More number of patients were came under category 0-5 years and less in 6-10 years. (Table 7, 8 and Figure 13, 14)

GLYCEMIC CONTROL:

The glycemic efficacy was assessed by analyzing the mean change in the value of Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), and Glycated hemoglobin (HbA1c) from the start of the therapy to the end of 3 months study period in each group.

Clinical efficacy of teneligliptin

At the end of 3 months of dual therapy mean HbA1c, FPG, and PPG were significantly (*p value*-≤0.0001) reduced by 7.1±0.5% 123.62±9.31mg/d L and 164.16±35.15mg/d L respectively. (Table 9, 10, 11 and Figure 15, 16, 17)

At the end of 3 months combination therapy the following results were noted (*p value*-≤0.0001) reduction in HbA1c, FPG, PPG by 7.49±0.48% 121.5±22.69mg/d L and 183.44±19.84mg/d L respectively. (Table 14, 15, 16 and Figure 20, 21, 22)

The mean reduction of HbA1c was found to be 0.92% in monotherapy, 1.68% in dual therapy and 1.79% in combinational therapy. (Table 19 and Figure 25)

The mean reduction of FBS was found to be 41.33 mg/d L. in monotherapy, 48.53 mg/d L in dual therapy and 55.68 mg/d L. in combinational therapy (Table 19 and Figure 25)

The mean reduction of PPBS was found to be 61.58mg/d L. in monotherapy, 72.71mg/d L in dual therapy and 88.53 mg/d L. in combinational therapy. (Table 19 and Figure25)

Clinical efficacy of Sitagliptin:

After the 3 months treatment with sitagliptin significant reduction of HbA1c, FPG, and PPG level were observed. Mean HbA1c, FPG, and PPG of dual therapy was

significantly *(p value*-≤0.0001) reduced by 7.16±0.56% 123.64±20.24mg/d L and 165.11±30.16mg/d L respectively. (Table 9, 10, 11 and Figure 15, 16, 17)

Combination therapy shown significant (*p value*-≤0.0001) reduction in HbA1c, FPG, PPG by 7.51±0.54% 121.41±19.96mg/d L and 183.9±20.65mg/d L respectively. (Table 14, 15, 16 and Figure 20, 21, 22)

Clinical efficacy of Vildagliptin:

After the 3 months treatment, dual therapy mean HbA1c, FPG, and PPG were significantly (*p value*-≤0.0001) reduced by 7.9±0.75%, 142.89±21.10mg/d L and 190.44±29.29mg/d L respectively. (Table 9, 10, 11 and Figure 15, 16, 17)

Combination therapy shown significant (*p value*-≤0.0001) reduction in HbA1c, FPG, PPG by 8.60±0.48% 132.9±25.07mg/d L and 199.49±21.80mg/d L respectively. (Table 14, 15, 16 and Figure 20, 21, 22)

COMPARITIVE ANALYSIS

GROUP A ((TENELIGLIPTIN AND ITS COMBINATIONS) VERSUS GROUP C (VILDAGLIPTIN AND ITS COMBINATIONS)

Effect on HbA1c

Post 3 months of treatment for the two groups are shown below. The mean HbA1c of the dual therapy for group -A (teneligliptin with metformin) was 7.1±0.5% and group C (Vildagliptin with metformin) therapy 7.9±0.75 %.(Table 11 and Figure17)

The mean HbA1c of combination therapy was found to be (teneligliptin with metformin plus glimepiride) 7.49±0.48%, which was significantly lower than the mean HbA1c in 8.60±0.48% in group C (Vildagliptin with metformin plus glimepiride) therapy. (Table 16 and Figure 22)

It is clearly evident that Group -A (dual and combination therapy) patients had greater reduction in HbA1c level when compared to Group C (dual and combination therapy).

Effect on FBS

In group A the mean FBS of dual therapy (teneligliptin with metformin) was123.62±9.31mg/d L which was significantly lower than the mean FBS in 142.89±21.10mg/d L in group C (Vildagliptin with metformin) therapy. (Table 9 and Figure 15)

In group A the mean FBS of combination therapy (teneligliptin with metformin plus glimepiride) was 121.5±22.69mg/d L, which was significantly lower than the mean FBS in 132.9±25.07mg/d L in group C (Vildagliptin with metformin plus glimepiride) therapy. (Table 14 and Figure 20)

It is shows Group A (dual and combination therapy) patient had greater reduction of FBS than compared to Group C (dual and combination therapy).

Effect on PPBS

In group A the mean PPBS of dual therapy (teneligliptin add on metformin) was 164.16±35.15mg/d L which was significantly lower than the mean PPBS in 190.44±29.29mg/d L mg/d L in group C (Vildagliptin add on metformin) therapy. (Table 10 and Figure 16)

In group A the mean PPBS of combination therapy (teneligliptin add on metformin plus glimepiride) was 183.44±19.84mg/d L which was significantly lower than the mean PPBS in 199.49±21.80mg/d L in group C (Vildagliptin add on metformin plus glimepiride) therapy. (Table 15 and Figure 21)

It is clearly evident that Group A (dual and combination therapy) patient had greater reduction of PPBS than compared to Group C (dual and combination therapy)

Effect on SrCr (Serum creatinine) and SGPT

There was no significance difference was seen in SrCr level following 3 months of therapy with teneligliptin and its combinations when compared to sitagliptin and its combinations and vildagliptin and its combinations. (Table 12, 17 and Figure 18, 23)

SGPT level showed a slightly significant increase in all the three groups, but it was in normal range. (Table 13, 18 and Figure 13, 18)

GROUP A (TENELIGLIPTIN AND ITS COMBINATIONS) VERSUS GROUP B (SITAGLIPTIN AND ITS COMBINATIONS)

Effect on HbA1c

A mean reduction in HbA1c of 7.1±0.5%, was seen with teneligliptin add on metformin therapy, while a same mean reduction in HbA1c of 7.1±0.5% was found with sitagliptin add on metformin therapy. Comparison both the groups demonstrated that there was no significant difference. (Table 11 and Figure17)

Mean reduction in HbA1c of 7.49±0.48% was seen with teneligliptin with metformin plus sulfonyl urea therapy, while a slight increase of HbA1c of 7.51±0.54% was found with sitagliptin add on metformin plus glimepiride therapy. (Table 16 and Figure 22)

Effect on FBS

A mean reduction in FBS of 123.6±9.31mg/d L was seen with teneligliptin with metformin therapy, while a same mean reduction in FBS of 123.64±20.24mg/d L was found with sitagliptin with metformin therapy. Comparison both the groups demonstrated that there was no significant difference. (Table 9 and Figure 15)

A mean reduction in FBS of 121.5±22.69mg/d L was seen with teneligliptin add on metformin plus glimepiride, while a slight decrease of FBS of 121.41±19.96mg/d L was found with sitagliptin add on metformin plus sulfonyl urea therapy. (Table 14 and Figure 20)

Effect on PPBS

Mean reduction in PPBS of 164.1±35.15mg/d L, was seen with teneligliptin add on metformin therapy, while a same mean reduction in PPBS of 164.1±30.16mg/d L was found with sitagliptin add on metformin therapy. (Table 10 and Figure 16). On the comparison both the group demonstrated no difference statistically.

A mean reduction in PPBS of 183.44±19.84mg/d L, was seen with teneligliptin add on metformin plus glimepiride, while a same mean reduction in PPBS of 183.9±20.65mg/d L was found with sitagliptin add on metformin plus glimepiride therapy. On the comparison both the group demonstrated no difference statistically. (Table 15 and Figure 21)

It shows that both the regimens on comparison reveled similar efficacy there by failing to prove the superiority over each other.

Effect on SrCr and SGPT

There was no significance difference between SrCr following 3 months of therapy with teneligliptin and its combinations when compared with sitagliptin and its combinations and vildagliptin and its combinations. (Table 12, 17 and Figure 18, 23)

SGPT level showed a slightly significant increase in three groups, but which was still in normal range. (Table 13, 18 and Figure 19, 24)

SAFETY ANALYSYS:

Group-A

Treatment with Teneligliptin and its combination was well tolerated over the 3 months treatment period. . In monotherapy there were no ADR reported. 8 patients experienced ADRs .Mild hypoglycemia reported in (6%) the cases, was mostly reported ADR followed by GI irritation (8%) and less in headache (2%). (Table 20 and Figure 26)

Group-B

There were no severe ADR is reported in Sitagliptin and its combination therapy .Mild GI irritation (12%) was occurred in the group. Other ADR including nausea (2%) and headache (2%) and diarrhea (4%) were happened among the group. No other frequently observed or serious ADR were observed in this study. And no hypoglycemia occurred in any of the patient taking vildagliptin and their combination. (Table 21 and Figure 27)

Group-C

The frequent ADR in the vildagliptin and their combination therapy were hypoglycemia (14%) GI irritation (8%), headache (4%), dizziness (2%) and diarrhea (2%). No severe ADR were reported in the 3 groups. All the ADR reported during the study were mild. (Table 22 and Figure 28)

There were no incidence of renal and hepatic toxicity. There was no significance difference between groups in terms of reported ADR.

COST EFFECTIVE ANALYSIS (CEA)

The cost effectiveness of teneligliptin, sitagliptin, and vildagliptin monotherapy and their combination with metformin was studied. It shows that teneligliptin and its combination with metformin was found to be more cost effective. (Table 22 and 23)

7. DISCUSSION

The study was designed to compare safety, efficacy and cost effectiveness of teneligliptin, sitagliptin and vildagliptin in type II diabetes mellitus patients. The study was started with 155 patients. Each gliptin were compared with metformin and add on therapy of metformin plus glimepiride.

In this study the patients were categorized based on their gender. There were 31 males and 19 females in teneligliptin group, 29 males and 21 females in sitagliptin group and vildagliptin group. The results shows the higher predominance in male for type II diabetes mellitus. This was similar to the previous studies conducted by **Bennett et al.,** and **Howteerakul et al.,** which showed higher prevalence of type II DM in men than women.

In this study population was categorized in to 5 groups on the basis of age. Among the 5 groups more number of patients were came under the category of 51-60 and less in 71-80 category. Type II DM is commonly seen in middle-aged individuals, especially after 50 years of age. The mean age in this study was 51-60 years, this fact is supported by the study conducted by **Miyako Kishimoto et al.,** .

Among the study population, more number of patients (58%, 54% and54% in group A, B and C respectively) were known to have no family history of type II diabetes mellitus. In this study, 40% patients had a positive family history indicating either one or both the parents had type II DM, which was at one stage or the other transferred from one generation to another. Also this was accordance with larger prospective study conducted by **Bennett et al.,** .

Study population was categorized into two groups on the basis of duration of the disease in years. More number of patients were came under category 0-5 years and less in 6-10 years. The average duration of DM in this study was found to be 0- 5 years, which was in line with a previous study conducted by **Jeon et al.,** where the mean duration was 5.89 years.

The glycemic efficacy was assessed by analyzing the mean change in the value of Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), and Glycated hemoglobin (HbA1C) from the start of the therapy to the end of 3 months study period in each group.

Teneligliptin has been demonstrated to improve glycemic control when monotherapy and added to glimepiride, metformin, in patients with type II diabetes. It is confirmed that the combination of Teneligliptin, metformin and glimepiride significantly improved glycemic control. However, in this study, the reduction in HbA1C with teneligliptin monotherapy was greater than those in teneligliptin metformin group and teneligliptin with metformin and glimepiride group.

In this study shows at the end of 3 months of dual therapy mean HbA1C, FPB, and PPBS were significantly (p value-≤0.0001) reduced by 7.1±0.5% 123.62±9.31mg/d L and 164.16±35.15mg/d L respectively. At the end of 3 months combination therapy the following results were noted (p value ≤ 0.0001) reduction in HbA1C, FPG, PPG by 7.49±0.48% 121.5±22.69mg/d L and 183.44±19.84mg/d L respectively. The result of this study perfectly complies with the former study conducted by, **Kim et al.,** studied in combination of teneligliptin with metformin in known type II diabetic Korean patients whose glycemic status were not under controlled with metformin monotherapy, this shows teneligliptin add on metformin plus glimepiride therapy shows the significant reduction of glycemic parameter.

Another study conducted by in **Ghosh et al.,** (TREAT-INDIA), there was statistically significant improvement in mean HbA1c, FPG, and PPG with teneligliptin therapy. Means changes in HbA1c, FPG, and PPG were 1.37%±1.15%, 51.29±35.41 mg/dL, and 80.89±54.27 mg/dL, respectively.

Subgroup analysis revealed that HbA1c (%) reduction with teneligliptin when used as monotherapy, add-on to metformin or add-on to metformin plus combination, was 0.98±0.53, 1.07±0.83, 1.46±1.33, respectively.

In this study the mean reduction of HbA1C was found to be 0.92% in monotherapy, 1.68% in dual therapy and 1.79% in combinational therapy and the mean reduction of FBS was found to be 41.33 mg/d L. in monotherapy, 48.53 mg/d L in dual therapy and 55.68 mg/d L. in combinational therapy. The mean reduction of PPBS was found to be 61.58mg/d L. in monotherapy72.71mg/d L in dual therapy and 88.53 mg/d L. in combinational therapy. The similar result were observed by, **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 and fasting blood glucose from the baseline.

Scott et al., in his study suggested that Teneligliptin, a DPP-4 inhibitor was added to the armamentarium for use in patients with type II diabetes in India. In different clinical trials conducted in Japan, Korea, and India, it has been shown to be safe and effective in T2DM patients when used either as monotherapy and combination antidiabetic therapy.

Recently an Indian study by **Suryawanshi et al.,** reported the results of a 16-week, multi centric, double-blind, placebo-controlled, Phase 3 studies of teneligliptin 20 mg daily in drug naive T2DM patients. This study (N =237) reported a significant −0.55% glycated hemoglobin (HbA1C) reduction (placebo-subtracted) in teneligliptin arm (P = 0.0043) compared to control. While a significant reduction in 2 hrs postprandial glucose (PPG) (−25.8 mg/dl, P = 0.0070) versus placebo was observed, an insignificant reduction in fasting plasma glucose (FPG) was seen (−8.8 mg/dl, P =0.18) in teneligliptin 20 mg arm. Similarly, higher percentage of patient achieved the target HbA1c of <7% in teneligliptin arm (43.4% vs. 27.3%, P = 0.026) compared to the control and "overall" the drug was well tolerated.

The similar results shows that **Kadowaki et al.,** and **Kondo et al.,** conducted a double-blind placebo-controlled parallel-group study in 324 Japanese patients with type 2 diabetes randomized to receive different doses of teneligliptin or placebo once daily before breakfast for 12 weeks. These results indicate that treatment with teneligliptin

for 12 weeks provided significant and clinically meaningful reduction in the levels of HbA1c and FPG across the dose range studied.

Wakaba et al., study was to evaluate the effects of teneligliptin on 24 hour blood glucose control and gastrointestinal hormone responses to a meal tolerance test, and to investigate the glucose-lowering mechanisms of teneligliptin. Teneligliptin was given once a day for 3 days significantly lowered fasting and postprandial glucose levels. Significant elevations of fasting and postprandial active GLP-1 and postprandial active GIP levels were observed.

In this study after the 3 months treatment with sitagliptin and its combination significant reduction of HbA1c, FPG, and PPG level were observed. Mean HbA1c, FPG, and PPG of dual therapy was significantly (p value≤0.0001) reduced by 7.16±0.56% 123.64±20.24mg/d L and 165.11±30.16mg/d L respectively. Combination therapy shown significant (p value≤ 0.0001) reduction in HbA1c, FPG, PPG by 7.51±0.54% 121.41±19.96mg/d L and 183.9±20.65mg/d L respectively.

This was in accordance with previous studies conducted by **Goldstein et al.,** and **Hermansen et al.,** where the effects of combination of sitagliptin + metformin with other oral hypoglycemics have been well documented. The improvement in HbA1c was highly significant in both the study groups ($p < 0.001$) at the end of 24 weeks.

Previous studies by **Hermansen et al.**, **Raz et al.,** and **Bennettet al.,** have proven the improvement in HbA1c by combination of metformin and sitagliptin and metformin and glimepiride. At the end of the study period, the intergroup comparison between groups I and II was done for FPG, PPG, and HbA1c. It was insignificant for FPG and HbA1C ($p > 0.05$) and significant for PPG ($p < 0.05$) indicating that the group where combination of sitagliptin and metformin was given had a better glycemic control in terms of PPG.

Previous studies conducted by **Reasner et al., Perez-Monteverde et al., and Wainstein et al.**, have proven that combination of sitagliptin and metformin produces significant improvement in glycemic parameters such as FPG, PPG, and HbA1c.

In this study after the 3 months treatment, dual therapy mean HbA1C, FPG, and PPG were significantly (p value ≤0.0001) reduced by 7.9±0.75%, 142.89±21.10mg/d L and 190.44±29.29mg/d L respectively. Combination therapy shown significant (p value ≤ 0.0001) reduction in HbA1C, FPG, PPG by 8.60±0.48% 132.9±25.07mg/d L and 199.49±21.80mg/d L respectively.

Recent studies have shown that**, Matthews et al.,** and **Filozof et al.,** as add-on therapy in patients with inadequately controlled T2DM treated with vildagliptin, metformin dual therapy and vildagliptin metformin and Sulphonylurea as combination therapy.

Masato Odawara et al., 12-week, randomized, double-blind study evaluated the efficacy and safety of vildagliptin 50 mg bid in Japanese patients with T2DM inadequately controlled on metformin monotherapy.

Vildagliptin produced a statistically significant and clinically meaningful change in HbA1c compared with placebo (-1.1% vs. -0.1%; P\0.001) as add-on to metformin (250 mg bid or 500 mg bid) after 12 weeks of treatment in Japanese patients with T2DM.

A similar result was obtained from **Pan et al.,** adding vildagliptin to metformin resulted in 1.05% reduction of HbA1C after 24 weeks treatment. In a recent Indian retrospective study **Chatterjee et al.,** the reduction in HbA1C was 1.9% which is compatible with another study **Bosi et al.,** where vildagliptin combined with metformin was given in treating T2DM naïve patients.

The similar results shows that **Ahren et al.,** combination of vildagliptin therapy with metformin have also been evaluated in three double-blind controlled studies and showed statistically meaningful reduction in Hba1c of 0.7 and 0.9%. A meta-analysis **Cail et al.,** of 30 randomized controlled trials showed that treatment with vildagliptin, metformin and sulfonylurea are decreased Hba1c by 0.77%.

Post 3 months of treatment for the two groups are shown below. The mean HbA1c of the dual therapy for group -A (teneligliptin with metformin) was 7.1±0.5%

and group C (Vildagliptin with metformin) therapy 7.9±0.75% .The mean HbA1c of combination therapy was found to be (teneligliptin with metformin plus sulfonylurea) 7.49±0.48%, which was significantly lower than the mean HbA1c in 8.60±0.48% in group C (Vildagliptin with metformin plus sulfonylurea) therapy. In this study it is clearly evident that Group -A (dual and combination therapy) patients had greater reduction in HbA1c level when compared to Group C (dual and combination therapy*).* This fact is supported by the study conducted by **Tushar et al.**in which finally concluded that teneligliptin therapy is more effective than vildagliptin therapy.

In group A the mean FBS of dual therapy (teneligliptin with metformin) was123.62±9.31mg/d L which was significantly lower than the mean FBS in 142.89±21.10mg/d L in group C (Vildagliptin with metformin) therapy.In group A the mean FBS of combination therapy (teneligliptin with metformin plus sulfonylurea) was 121.5±22.69mg/d L, which was significantly lower than the mean FBS in 132.9±25.07mg/d L in group C (Vildagliptin with metformin plus sulfonylurea) therapy.

It is shows Group A (dual and combination therapy) patient had greater reduction of FBS than compared to Group C (dual and combination therapy). The similar result shows that the study conducted **Tushar et al.,** in which finally concluded that teneligliptin therapy is more effective than vildagliptin therapy.

In group A the mean PPBS of dual therapy (teneligliptin add on metformin) was 164.16±35.15mg/d L which was significantly lower than the mean PPBS in 190.44±29.29mg/d L mg/d L in group C (Vildagliptin add on metformin) therapy.

In group A the mean PPBS of combination therapy (teneligliptin add on metformin plus sulfonylurea) was 183.44±19.84mg/d L which was significantly lower than the mean PPBS in 199.49±21.80mg/d L in group C (Vildagliptin add on metformin plus sulfonylurea) therapy.

It is clearly evident that Group A (dual and combination therapy) patient had greater reduction of PPBS than compared to Group C (dual and combination therapy).

The similar result shows that the study conducted **Tushar et al.,** finally concluded that teneligliptin therapy is more effective than vildagliptin therapy.

A mean reduction in HbA1C of 7.1±0.5%, was seen with teneligliptin add on metformin therapy, while a same mean reduction in HbA1c of 7.1±0.5% was found with sitagliptin add on metformin therapy. Comparison both the groups demonstrated that there was no significant difference.

Mean reduction in HbA1C of 7.49±0.48% was seen with teneligliptin with metformin plus glimepiride therapy, while a slight increase of HbA1c of 7.51±0.54% was found with sitagliptin add on metformin plus glimepiride therapy. Comparison both the groups demonstrated that there was no significant difference.

Which was similar to the study conducted **Eto et al.,** Mean reduction of HbAIC in teneligliptin therapy, and was same to the mean reduction of sitagliptin therapy. **But Wakaba Tsuchimochi et al.,** study shows that teneligliptin is more effective than sitagliptin therapy because of the structural advantages of teneligliptin.

A mean reduction in FBS of 123.6±9.31mg/d L was seen with teneligliptin with metformin therapy, while a same mean reduction in FBS of 123.64±20.24mg/d L was found with sitagliptin with metformin therapy. Comparison both the groups demonstrated that there was no significant difference.

A mean reduction in FBS of 121.5±22.69mg/d L was seen with teneligliptin add on metformin plus glimepiride therapy, while a slight decrease of FBS of 121.41±19.96mg/d L was found with sitagliptin add on metformin plus glimepiride therapy.

Which was similar to the study conducted **Eto et al.,** mean reduction of FBS in teneligliptin therapy, was equaling to the mean reduction of sitagliptin therapy. **But Wakaba Tsuchimochi et al.,** study shows that teneligliptin is more effective than sitagliptin therapy because of the structural advantages of teneligliptin.

Mean reduction in PPBS of 164.1±35.15mg/d L, was seen with teneligliptin add on metformin therapy, while a same mean reduction in PPBS of 164.1±30.16mg/d L was found with sitagliptin add on metformin therapy. On the comparison both the group demonstrated no difference statistically.

A mean reduction in PPBS of 183.44±19.84mg/d L, was seen with teneligliptin add on metformin plus glimepiride therapy, while a same mean reduction in PPBS of 183.9±20.65mg/d L was found with sitagliptin add on metformin plus glimepiride therapy.

Which was similar to the study conducted **Eto et al.,** mean reduction of PPBS in teneligliptin therapy, was equality to the mean reduction of sitagliptin therapy. But **Wakaba Tsuchimochi et al** study shows that teneligliptin is more effective than sitagliptin therapy because of the structural advantages of teneligliptin.

On the comparison both the group demonstrated no difference statistically. It shows that both the regimens on comparison reveled similar efficacy there by failing to prove the superiority over each other.

In this study there was no significance difference between SrCr following 3 months of therapy with teneligliptin and its combinations when compared with sitagliptin and its combinations and vildagliptin and its combinations. SGPT level showed a slightly significant increase in three groups, but which was still in normal range. The result of this study perfectly complies with the former study conducted by, **Manish Maladkar et al.,** his study shows that gliptins do not causes any reanal and hepatic impairment.

Treatment with Teneligliptin and its combination was well tolerated over the 3 months treatment period. In monotherapy there were no ADR reported. In combination therapy 8 patients experienced ADRs. Mild hypoglycemia reported in (6%) the cases, was mostly reported ADR followed by GI irritation (8%) and less in headache (2%).

Awadhesh Kumar Singh et al., observed that in monotherapy only <1% of ADRs were occurred. In combination therapy hypoglycemia, GI irritation, head ache, peripheral edema and nasopharangytis were occurred.

There were no severe ADR was found in Sitagliptin and its combination therapy .Mild GI irritation (12%) was occurred in the group. Other ADR including nausea (2%) and headache (2%) and diarrhea (4%) were happened among the group. Supporting to this study **Jennifer Green et al.,** in her study didn't shown any hypoglycemic events in sitagliptin therapy and GI irritation, nausea and headache were found.

The frequent ADR in the vildagliptin and their combination therapy were hypoglycemia (14%) GI irritation (8%), headache (4%), dizziness (2%) and diarrhea (2%).

Which was similar to the study conducted by **Yun‐Zhao Tang et al.,** in his the ADR of vildagliptin therapy shows more in hypoglycemia (18.9%) and GI irritation (16.6%).

The cost effectiveness of teneligliptin, sitagliptin, and vildagliptin monotherapy and their combination with metformin was studied. It shows that teneligliptin and its combination with metformin was found to be more cost effective. This fact is supported by the study conducted by **Ghosh et al.,** his study shows that teneligliptin is economically effective compared with other gliptins.

8. CONCLUSION

Out of 150 patients, the prevalence of type 2 diabetes mellitus was higher in males than females in age group of 51-60 years and most of the patients were observed in the duration was 0-5 years. From this study it was observed that only female patients having the comorbid conditions were thyroid and rheumatoid arthritis.

This study provides an evidence of safety and efficacy of teneligliptin as a monotherapy or in combination therapies with a Metformin and Glimepiride in patients with type II Diabetes mellitus.

The results pointed out that all the group of patients showed an improvement in their glycemic parameters such as FBS, PPBS, and HbA1c during the study period and from the group comparison study it was observed that the patients receiving combination therapy of teneligliptin have better glycemic control than combination therapy of vildagliptin.

The study demonstrated the effectiveness of teneligliptin combination and sitagliptin combination therapy in type II diabetes mellitus patients. Both the combinations on comparison reveled similar efficacy in glycemic parameter, there by failing to prove the superiority in over each other.

There was no significance difference was found in SrCr and SGPT level for the follow-up of 3 months therapy with teneligliptin combinations, sitagliptin combinations and vildagliptin combinations.

No severe ADR were reported in the 3 groups. All the ADR reported during the study were mild. However the incidence of ADR were numerically more in vildagliptin combination therapy and the incidence of hypoglycemia is more in sitagliptin combination therapy. The teneligliptin combination shows lesser side effects than the other two combinations. Vildagliptin group shows ADR like GI irritation, Hypoglycemia, Headache and Dizziness. In that occurrence of hypoglycemia were high and other ADRs were mild. Sitagliptin groups shows ADRs like GI irritation, head ache, nausea and diarrhea, in that the major ADR was GI irritation. Compare to the

other two groups of combination drugs, teneligliptin has less ADRs like GI irritation, Hypoglycemia and Diarrhea. There was no incidence of renal and hepatic toxicity with all the three combination drugs.

The cost effective analysis of teneligliptin, sitagliptin, and vildagliptin monotherapy and their combination with metformin was done , the results shows that teneligliptin alone and its combination with metformin was found to be more cost effective than the other groups of drugs.

The teneligplin has more advantages than the other two gliptins in type II diabetes mellitus patients. Teneligliptin with metformin and sulfonyl urea treatment was effective and well tolerated in patients with type II diabetes and it has long half-life of 26.9 hours with unique pharmacokinetic advantage which allows convenient once daily administration irrespective of food. It has dual mode of elimination via renal and hepatic, hence it can be administered safely in renal impairment patients. No dosage adjustment is required in mild to moderate hepatic impairment. The appropriate approach towards managing diabetes should be not only glycemic control but also preservation of islet cell function early and to delay the progression of a disease.

In conclusion teneligliptin significantly improves glycemic parameters in Indian T2DM patients with mild ADRs when prescribed as monotherapy or as add-on to Metformin and Sulfonyl ureas and it also cost effective than the other gliptins.

9. BIBLIOGRAPHY

1. Charan Kumar, Murthy, and S.D.S. A review on management of blood glucose in type 2 diabetes mellitus. Ijpajx-cas-usa 2015; 6:114-22.
2. Abdulfatai B. Olokoba, Olusegun A. Obateru, Lateefat B. Olokoba. Type 2 Diabetes Mellitus: A Review of Current Trends. Oman Medical Journal (2012) ; 27: 269-273
3. Chen, L.,Magliano, D. J., and Zimmet, P. Z. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nature Reviews Endocrinology, 2012; 8(4): 228-236.
4. Ahmed AM. History of diabetes mellitus. Saudi Med J 2002 Apr; 23(4):373-378.
5. Manish Maladkar, Srividya Sankar, Kushal Kamat. Aristo Pharmaceuticals. Teneligliptin: Heralding Change in Type 2 DiabetesJournal of Diabetes Mellitus, 2016; 6: 113-131.
6. Miyako Kishimoto. Teneligliptin: a DPP-4 inhibitor for the treatment of type 2 diabetes. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2013; 6:187–195.
7. Eiji Kutoh,Mitsuru Hirate andYu 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.
8. Seiichi Tanaka, MD, Kunihiro Suzuki, MD, PhD,and Chie Aoki, MD, PhD. Add-On Treatment with Teneligliptin AmelioratesGlucose Fluctuations and Improves Glycemic Control Index in Japanese Patients with Type 2 Diabeteson Insulin Therapy. Diabetes technology & therapeutics 2014; 6: 843-49
9. Wakaba Tsuchimoch, Halabi A, Maatouk H, Siegler KE, Faisst N, Lufft V, Klause N. Pharmacokinetics of teneligliptin in subjects with renal impairment. Clin Pharmacol Drug Dev. 2016;2(3):246–254
10. Abhijeet Jain, Singh AK. Efficacy and safety of teneligliptin. Indian Journal of Endocrinology and Metabolism.2017 Jan 1; 21(1):11.
11. Merlin C. Thomas, Deacon CF, Lebovitz HE. Comparative review of dipeptidyl peptidase-4inhibitors and sulphonylureas. Diabetes Obes Metab. 2016; 18(4):333–347.

12. Fuyuhiko Marubayashi, Kishimoto M. Teneligliptin: a DPP-4 inhibitor for the treatment of type 2 diabetes. Diabetes Metab SyndrObes. 2015; 6:187-195
13. Hamamoto.Y Aoki K, Kamiyama H, Yoshimura K, Shibuya M, Masuda K, Terauchi Y. Miglitol administered before breakfast increased plasma active glucagon-like peptide-1 (GLP-1) levels after lunch in patients with type 2 diabetes treated with sitagliptin. Acta Diabetol. 2015; 49: 225–230.
14. Takashi Kadowaki Kishimoto M, Noda M. A pilot study of the efficacy of miglitol and sitagliptin for type 2 diabetes with a continuous glucose monitoring system and incretin-related markers. Cardiovasc Diabetol. 2015; 10:115.
15. Takehiro Hashikata Eto T, Inoue S, Kadowaki T. Effects of once-daily teneligliptin on 24-h blood glucose control and safety in Japanese patients with type 2 diabetes mellitus: a 4-week, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2015;14:1040–1046
16. Rika Ito Fukuda-Tsuru S, Anabuki J, Abe Y, Yoshida K, Ishii S. A novel, potent, and long-lasting dipeptidyl peptidase-4 inhibitor, teneligliptin, improves postprandial hyperglycemia and dyslipidemia after single and repeated administrations. Eur J Pharmacol. 2015; 696 (1–3):194–202.
17. Enrique Z. Fisman Nathan DM, Buse JB, Davidson MB, Heine RJ,Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the ADA and the EAS. Diabetes Care. 2015; 29 (8):1963-72.
18. Yuya Nakamura Sone H, Tanaka S, Tanaka S, et al; Japan Diabetes Complications Study Group. Serum level of triglycerides is a potent risk factor comparable to LDL cholesterol for coronary heart disease in Japanese patients with type 2 diabetes: subanalysis of the Japan Diabetes Complications Study (JDCS). J Clin Endocrinol Metab. 2015; 96: 3448–3456.
19. Valentina Lukashevich, Mari A, Sallas WM, He YL, Watson C, Ligueros-Saylan M, Dunning BE, et al. Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed beta-cell function in patients with type 2 diabetes. J Clin Endocrinol Metab 2015; 90: 4888-94.

20. Jun-ichiro Mera Kutoha E, Hiratea M, Ikenoa Y. Teneligliptin as an Initial Therapy for Newly Diagnosed, Drug Naïve Subjects With Type 2 Diabetes. J Clin Med Res. 2015; 6(4):287-94.
21. Hirotoshi Ohmura Tsuchimochi W, Ueno H, Yamashita E, Tsubouchi C, Sakoda H, Nakamura S, et al. Teneligliptin improves glycemic control with the reduction of postprandial insulin requirement in Japanese diabetic patients". Endocr J. 2015; 62(1):13-20.
22. Yun‐Zhao Tang Kutoha E, Hiratea M, Ikenoa Y. Teneligliptin as an Initial Therapy for Newly Diagnosed, Drug Naïve Subjects With Type 2 Diabetes. J Clin Med Res. 2015; 6(4):287-94.
23. Atef Halabi, Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2016 executive summary. Endocr Pract. 2014; 22(1):84–113.
24. Seiichi Tanaka, Kutoh E, Hirate M, Ikeno Y. Teneligliptin as an initial therapy for newly diagnosed, drug naive subjects with type 2 diabetes. J Clin Med Res.2014; 6(4):287–294.
25. Wakaba Tsuchimochi, Ueno H, Yamashita E, Tsubouchi C, Sakoda H, Nakamura S, et al. Teneligliptin improves glycemic control with the reduction of postprandial insulin requirement in Japanese diabetic patients". Endocr J. 2015; 62(1):13-20.
26. Brian Green, Scott LJ. Teneligliptin: a review in type 2 diabetes. Clin Drug Investig. 2015; 35(11):765–772
27. Line P. Malha, Deacon CF, Lebovitz HE. Comparative review of dipeptidyl peptidase-4 inhibitors and sulphonylureas. Diabetes Obes Metab. 2016; 18(4): 333–347
28. Fatemeh Hayati, Halabi A, Maatouk H, Siegler KE, Faisst N, Lufft V, Klause N. Pharmacokinetics of teneligliptin in subjects with renal impairment. Clin Pharmacol Drug Dev. 2014; 2(3):246–254
29. Chun-Jun Li, Otsuki H, Kosaka T, Nakamura K, Shimomura F, Kuwahara Y, Tsukamoto T. Safety and efficacy of teneligliptin: a novel DPP-4 inhibitor for hemodialysis patients with type 2 diabetes. Int Urol Nephrol. 2014; 46(2):427–432.

30. Dongsheng Cheng, Ou SM, Shih CJ, Chao PW, et al. Effects on clinical outcomes of adding dipeptidyl peptidase-4 inhibitors versus sulfonylureas to metformin therapy in patients with type 2 diabetes mellitus. Ann Intern Med.2013; 163(9):663–672.
31. Paul Craddy, Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies. Prospective Diabetes Study Group. J2013 281(21):2005–2012.
32. Yoshinobu nabikaru, Halabi A, Maatouk H, Siegler KE, Faisst N, Hinrichsen H. Pharmacokinetics and safety of teneligliptin in subjects with hepatic impairment. Clin Pharmacol Drug Dev. 2013; 3 (4):290–296.
33. Kazuoki Kondo, Inoue S, Kadowaki T. Effects of once-daily teneligliptin on 24-h blood glucose control and safety in Japanese patients with type 2 diabetes mellitus: a 4-week, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2013; 14(11):1040–1046.
34. Miyako KishimotoK Sandhu-Minhas, Kosaka T, Nakamura K, Shimomura F, Kuwahara Y, Tsukamoto T. Safety and efficacy of teneligliptin: a novel DPP-4 inhibitor for hemodialysis patients with type 2 diabetes. Int Urol Nephrol. 2013; 46(2):427–432
35. Sandhu-Minhas, Kulasa KM, Henry RR. Pharmacotherapy of hyperglycemia. Expert Opin Pharmacother 2009;10:2415-32
36. Masaya Sakamoto, Kadowaki T, Kondo K. Efficacy, safety and dose–response relationship of teneligliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients withtype 2 diabetes mellitus. Diabetes Obes Metab. 2013; 15(9):810–818.
37. Hyun Jeong Jeon, Tae Keun Oh Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone.Diabetes care. 2011 Dec 1; 29(12):2638-43.
38. Chahal. H, Trivedi S, Sanyal D, Modi KD, Kharb S. Teneligliptin real-world efficacy assessment of type 2 diabetes mellitus patients in India. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2007; 9: 347.

39. Matthews DR, Dejager S, Ahren B, Fonseca V, Ferrannini E, Couturier A, *et al*. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. Diabetes Obes Metab. 2010; 12(9):780-9.
40. Filozof C, Gautier JF. A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with Type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study. Diabet Med. 2010; 27(3):318-26.
41. Pan C, Xing X, Han P, *et al*. Efficacy and tolerability of vildagliptin as add-on therapy to metformin in Chinese patients with type 2diabetes mellitus. Diabetes Obes Metab. 2012; 14: 737 744.
42. Bosi E, Dolta F, Jia Y, *et al*. Vildagliptin plus metformin combination therapy provides superior glycemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2009; 11: 506–515.
43. Ahren B, Gomis R, Standl E, *et al*. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. Diabetes Care. 2004; 27: 2874–2880.
44. Chatterjee S, Chatterjee S. Glycemic effects of vildagliptin and metformin combination therapy in Indian patients with T2 diabetes: an observational study. J Diabetes. August 27, 2013; 6:237–242.
45. Cail L, Cai Y, Lu Y, et al. The efficacy and safety of vildagliptin in patients with type 2 diabetes: a meta-analysis of randomized clinical trials. J Clin Pharm Ther. 2012; 37: 386–398
46. Aaboe K, Knop FK, Vilsboll T, Deacon CF, Holst JJ, *et al.* Twelve weeks treatment with the DPP-4inhibitor, sitagliptin, prevents degradation of peptide and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2010; 12: 323–333.
47. He YL, Foteinos G, Neelakantham S, Mattapalli D, Kulmatycki K, *et al.* Differential effects of vildagliptin and glimepiride on glucose fluctuations in patients with type 2 diabetes mellitus assessed using continuous glucose monitoring. Diabetes Obes Metab 2013; 15: 1111–1119.

48. Vella A, Bock G, Giesler PD, Burton DB, Serra DB, *et al.* Effects of dipeptidyl peptidase-4 inhibition on gastrointestinal function, meal appearance, and glucose metabolism in type 2 diabetes. Diabetes 2007; 56: 1475–1480.

49. Eto T, Inoue S, Kadowaki T Effects of once daily teneligliptin on 24-h blood glucose control and safety in Japanese patients with type 2 diabetes mellitus: a 4-week, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab 2012; 14: 1040–1046.

50. DeFronzo RA. Current issues in the treatment of type 2 diabetes. Overview of newer agents: where treatment is going. Am J Med. 2010; 123:S38-48.

51. Ahren B. Use of DPP-4 inhibitors in type 2 diabetes: focus on sitagliptin. Diabetes Metab Syndr Obes. 2010; 3: 31-41.

52. Bicsak TA, Taylor K, et al. Synthetic exendin-4 significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. J Clin Endocrinol Metab. 2003; 88(7):3082-3089

53. Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, Ito C, *et al.* Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig. 2010;1(5):212-228.

54. Nomiyama T, Akehi Y, Takenoshita H, Nagaishi R, Terawaki Y, Nagasako H, Kudo T, *et al.* Contributing factors related to efficacy of the dipeptidyl peptidase-4 inhibitor sitagliptin in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract. 2012;95 (2):e27-28.

55. Tajima N, Kadowaki T, Okamoto T, Sato A, Okuyama K, Minamide T, Arjona Ferreira JC. Sitagliptin added to voglibose monotherapy improves glycemic control in patients with type 2 diabetes. J Diabetes Investig. 2013; 4 (6):595-604.

56. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. DiabetesCare. 2010; 33 (8):1859-1864.

57. Kim SA, Shim WH, Lee EH, Lee YM, Beom SH, Kim ES, Yoo JS, et al. Predictive clinical parameters for the therapeutic efficacy of sitagliptin in korean type 2 diabetes mellitus. Diabetes Metab J. 2011; 35 (2):159-165.

58. Hare KJ. Role of GLP-1 induced glucagon suppression in type 2 diabetes mellitus. Dan Med Bull. 2010; 57(9):4181.
59. Bando Y, Kanehara H, Aoki K, Hisada A, Toya D, Tanaka N. Obesity may attenuate the HbA1c-lowering effect of sitagliptin in Japanese type 2 diabetic patients. J Diabetes Investig. 2012; 3(2):170-174.
60. Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. Diabetologia. 2013; 56 (4):696-708.
61. Lamers D, Famulla S, Wronkowitz N, Hartwig S, Lehr S, Ouwens DM, Eckardt K, *et al*. Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome. Diabetes. 2011; 60 (7):1917-1925.
62. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo- Jack S, Fish L, Heller SR, *et al*. Hypoglycemia and diabetes: a report of a workgroup of the American DiabetesAssociation and the Endocrine Society. Diabetes Care.2013; 36(5):1384-1395.
63. Engel SS, Round E, Golm GT, Kaufman KD, Goldstein BJ. Safety and tolerability of sitagliptin in type 2 diabetes: pooled analysis of 25 clinical studies. Diabetes Ther. 2013;4(1):119-145
64. Vilsboll T, Rosenstock J, Yki-Jarvinen H, Cefalu WT, Chen Y, Luo E, Musser B, *et al*. Efficacy and safety of sitagliptin when added to insulin therapy in patients withtype 2 diabetes. Diabetes Obes Metab. 2010; 12(2):167- 177.
65. Samann A, Lehmann T, Heller T, Muller N, Hartmann P,Wolf GB, Muller UA. A retrospective study on the incidence and risk factors of severe hypoglycemia in primarycare. Fam Pract. 2013; 30(3):290-293.
66. Perez-Monteverde A, Seck T, Xu L *et al.* Efficacy and safety of sitagliptin and the fixed- dose combination of sitagliptin and metformin vs. pioglitazone in drugnaive patients with type 2 diabetes. Int J Clin Pract. 2011; 65: 930–8.
67. Reasner C, Olansky L, Seck TL *et al*. The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2011; 13: 644–52.

68. Wainstein J, Katz L, Engel SS et al. Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with pioglitazone monotherapy in patients with type 2 diabetes. Diabetes Obes Metab. 2012; 14: 409–18.
69. Kennedy M, Roberts A. Complex type 2 diabetes mellitus–management challenges and pitfalls. Aust Fam Physician. 2013; 42(4):207–10.
70. Davidson JA. The placement of DPP-4 inhibitors in clinical practice recommendations for the treatment of type 2 diabetes. Endocr Pract. 2013; 19(6):1050–61.
71. Lukashevich V, Schweizer A, Shao Q, et al. Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial. Diabetes Obes Metab. 2011; 13(10):947–54.
72. Kothny W, Shao Q, Groop PH, Lukashevich V. One-year safety, tolerability and efficacy of vildagliptin in patients with type 2 diabetes and moderate or severe renal impairment. Diabetes Obes Metab. 2012; 14(11):1032–9.
73. Chan JC, Scott R, Arjona Ferreira JC, et al. Safety and efficacy of sitagliptin in patients with type 2diabetes and chronic renal insufficiency. Diabetes Obes Metab. 2008; 10(7):545–55.
74. Monami M, Iacomelli I, Marchionni N, Mannucci E. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes:a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis. 2010; 20(4):224–35.
75. Neumiller JJ, Wood L, Campbell RK. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus. Pharmacotherapy.2010; 30(5):463–84.
76. Scheen AJ, Charpentier G, Ostgren CJ, Hellqvist A, Gause-Nilsson I. Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. Diabetes Metab Res Rev. 2010; 26 (7):540.

KOVAI MEDICAL CENTER AND HOSPITAL - COIMBATORE

DATA COLLECTION FORM

Date: **IP No:**

Name: **Age:** **Sex: M/F**

Height: **Weight:** **BMI:**

Marital status: Married ☐ **Single** ☐

Social habits: Smoker ☐ **Alcoholic** ☐

Past history: Jaundice ☐ **Pancreatitis** ☐ **Rhinitis** ☐ **Others** ☐

Family history: Diabetes Mellitus: Yes ☐ **No** ☐

Co-exiting illness: Thyroid ☐ **Rheumatoid Arthritis** ☐ **Others** ☐

Duration of type II Diabetes Mellitus: 0-5 years ☐ **6-10 years** ☐ **>10 years** ☐

LAB INVESTIGATIONS

Parameter	Teneligliptin		Sitagliptin		Vildagliptin	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
FBS(mg/dl)						
PPBS (mg/dl)						
HbA1C (gm %)						
SrCr (mg/dl)						
SGPT(IU/L)						

TREATMENT CHART:

Sl.no	Drug name	Price/tablet	Dose	Freequency
1.	Teneligliptin	Rs. 7	20 mg	Once a day
2.	Sitagliptin	Rs. 42	25mg/ 50mg/ 100mg	Twice a day
3.	Vildagliptin	Rs.19.28	50mg/ 100mg	Twice a day

TENELIGLPITIN USED AS		
First line:	Yes ☐	No ☐
Second line:	Yes ☐	No ☐
Third line:	Yes ☐	No ☐

ADVERSE DRUG REACTIONS OF TENELIGLIPTIN

Hypoglycemia	Yes ☐	No ☐
Constipation	Yes ☐	No ☐
Nasopharyngitis	Yes ☐	No ☐
Proteinuria	Yes ☐	No ☐
Ketonuria	Yes ☐	No ☐
Glucosouria	Yes ☐	No ☐
ECG abnormality (QT prolongation)	Yes ☐	No ☐
Others	Yes ☐	No ☐

ADVERSE DRUG REACTIONS OF SITAGLIPIN

Nasopharyngitis	**Yes** ☐	**No** ☐
Hypoglycemia	**Yes** ☐	**No** ☐
Constipation	**Yes** ☐	**No** ☐
Diarrhea	**Yes** ☐	**No** ☐
UTI	**Yes** ☐	**No** ☐
Upper respiratory tract infection	**Yes** ☐	**No** ☐
Peripheral edema	**Yes** ☐	**No** ☐
Others	**Yes** ☐	**No** ☐

ADVERSE DRUG REACTIONS OF VILDAGLIPIN

Dizziness	**Yes** ☐	**No** ☐
Pancreatitis	**Yes** ☐	**No** ☐
Constipation	**Yes** ☐	**No** ☐
Head ache	**Yes** ☐	**No** ☐
UTI	**Yes** ☐	**No** ☐
Hypoglycaemia	**Yes** ☐	**No** ☐
Osthers	**Yes** ☐	**No** ☐

OTHER ANTIDIABETIC DRUGS:

Category	Name of drug	Price	Dose	Freequency
Oral anti diabetic drugs				
Sulfonylurea				
Glitazones				
Biguanide				
∝-glucosidase inhibitor				

ADVERSE DRUG REACTIONS OF OTHER ANTIDIABETIC DRUGS:

Hypoglycaemia	**Yes** ☐	**No** ☐
Nausea	**Yes** ☐	**No** ☐
Hyponatremia	**Yes** ☐	**No** ☐
Lactic acidosis	**Yes** ☐	**No** ☐
Renal insufficiency	**Yes** ☐	**No** ☐
Liver disease	**Yes** ☐	**No** ☐
Metallic taste	**Yes** ☐	**No** ☐
Diarrhea	**Yes** ☐	**No** ☐
Weight gain	**Yes** ☐	**No** ☐
Fluid retention	**Yes** ☐	**No** ☐
Heart failure	**Yes** ☐	**No** ☐