Research Article

Efficacy and Usefulness of DPP4 Inhibitors in NIDDM Patients on the Backdrop of Metformin and Sulfonyl Urea

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ABSTRACT

Diabetes mellitus, sometimes known as diabetes, is a collection of metabolic illnesses defined by a persistently high blood sugar level. Diabetes, if left untreated, can lead to a slew of health issues. Diabetes is caused by either a lack of insulin production by the pancreas or a lack of insulin response by the body's cells. The purpose of the study is to investigate the efficacy of dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors) in individuals with type 2 diabetes mellitus who were receiving metformin and a sulphonyl urea as a baseline medication.

Keywords: NIDDM, DPP4 inhibitors, Sulfonyl urea.

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INTRODUCTION

Diabetes is a chronic disorder caused by the body's inability to create or use insulin, and it is diagnosed by blood glucose levels that are abnormally high. Insulin is a hormone generated by the pancreas that is responsible for transporting glucose from the bloodstream to the body's cells, where it is used for energy. Insulin deficiency or ineffectiveness in a diabetic means that glucose is still circulating in the blood. The high amounts of glucose in the blood that occur (known as hyperglycemia) harm various tissues in the body over time, resulting in debilitating and life-threatening health consequences.

Genetics of Type 2 Diabetes

Although type 2 diabetes is also influenced by environmental variables, it has a greater link to family history and ancestry than type 1.Twin studies have revealed that genetics has a significant impact in the development of type 2 diabetes. Type2 diabetes is influenced by a variety of factors, including one's lifestyle. It can be difficult to determine whether your diabetes is caused by lifestyle factors or genetic predisposition if you have a family history of type 2 diabetes. It's probably a combination of the two. [1-7]

Classification of Diabetes Mellitus

- Type 1 Diabetes: is caused by the body's inability to produce insulin and necessitates the use of insulin injections.
- Type 2 Diabetes: results from Insulin resistance, a disorder in which cells fail to adequately utilise insulin and is often associated with an absolute insulin deficit, is the cause. (Formerly referred to as non-insulin-dependent diabetes mellitus, NIDDM for short, and adult-onset diabetes).
- Gestational Diabetes: when a pregnant woman who has never had diabetes has a high blood glucose level during her pregnancy. It could be a precursor to the onset of type 2 diabetes.
- Other: Congenital diabetes, which is caused by genetic anomalies in insulin production, cystic fibrosis-related diabetes, steroid diabetes caused by high doses of glucocorticoids, and numerous types of monogenic diabetes are all examples of diabetes mellitus.[8-12]

Causes

Type 1 diabetes has an etiology that is unknown. What is known is that our own immune system, which is generally responsible for fighting harmful bacteria and viruses, assaults and destroys your pancreas' insulin-producing cells. As a result, we have very little or no insulin. Sugar builds up in our bloodstream instead of being delivered to our cells.

Pre diabetes & Type 2 diabetes In Pre diabetes, which can lead to type 2 diabetes and in type 2 diabetes, Insulin resistance develops in our cells, and our pancreas is unable to produce enough insulin to overcome this resistance. Sugar accumulates up in our bloodstream instead of going into our cells, where it is needed for energy.

It's unclear why this happens, although genetic and environmental variables are thought to play a role in the development of type 2 diabetes. Although being overweight is significantly connected to the development

of type 2 diabetes, not everyone who has the disease is obese.

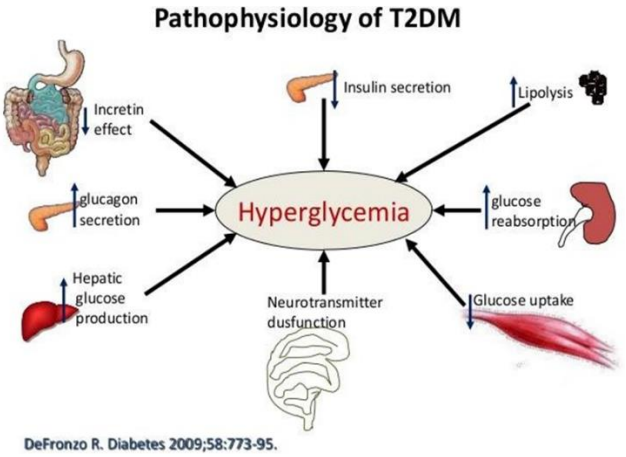

Figure 1: Pathophysiology of NIDDM

Gestational Diabetes

In many ways, gestational diabetes mellitus (GDM) is similar to type 2 diabetes, featuring a combination of relatively insufficient insulin secretion and response. It affects roughly 2% to 5% of all pregnancies, and it might improve or disappear after delivery. Gestational diabetes is completely curable, although it does necessitate close medical monitoring during the pregnancy. About 20% to 50% of women who are afflicted develop type 2 diabetes later in life. Untreated gestational diabetes can harm the foetus or the mother's health, even if it is only temporary. Macrosomia (excessive birth weight), congenital heart and central nervous system defects, and skeletal muscle deformities are all potential risks for the newborn. Increased prenatal insulin can cause respiratory distress syndrome by inhibiting foetal surfactant synthesis. Destruction of red blood cells can cause hyperbilirubinemia.

Perinatal death can occur in severe situations, most typically as a result of insufficient placental perfusion caused by vascular dysfunction. Reduced placental function may need labour induction. If there is significant foetal discomfort or an increased risk of harm associated with macrosomia, such as shoulder dystocia, a caesarean section may be performed.[13]

Dipeptidyl Peptidaseiv (DPP4) Inhibitors

Sitagliptin, saxagliptin, linagliptin, alogliptin and vildagliptin are the five DPP-4 inhibitors currently on the market. Teneligliptin, anagliptin, omarigliptin, and trelagliptin are four other gliptins that are only licensed in Japan and Korea. Despite having the similar mode of action, the pharmacologic and pharmacokinetic features of the various gliptins varied, which may be clinically significant for some individuals. However, their efficacy in reducing plasma DPP-4 activity and as antidiabetic drugs appears to be comparable.[14-19]

Despite having the identical mode of action, gliptins have pharmacologic and pharmacokinetic features that may be therapeutically relevant for some patients However, their efficacy appears to be comparable, both in terms of decreasing plasma DPP-4 activity and as antidiabetic drugs. Potency, target selectivity, oral bioavailability, elimination half-life, binding to plasma proteins, metabolic pathways, formation of active metabolite(s), main excretion routes, dosage adjustment for renal and liver insufficiency, and potential drug-drug interactions are the most significant differences between them.[20-23]

On October 17, 2006, the FDA authorized sitagliptin as the first medication for the treatment of type 2 diabetes (for use as monotherapy, or combination therapy, with either metformin or a thiazolidinedione). The second, saxagliptin, was approved in 2009, and the others followed suit. With the exception of vildagliptin, which is dosed twice a day, DPP-4 inhibitors are taken once a day. Within 5 minutes of treatment, they show a substantial reduction in plasma DPP-4 activity. They can be given regardless of meals because there is no clinically significant increase with a high fat meal. In humans, oral bioavailability is generally high (87 percent for sitagliptin, 85 percent for vildagliptin, and 67 percent for saxagliptin), though slightly lower (30 percent) for linagliptin. In terms of pharmacokinetic, pharmacodynamic, and excretion features, most inhibitors have modest, reversible protein binding in the plasma (38 percent for sitagliptin, 10% for vildagliptin, and insignificant for saxagliptin).[24]

Linagliptin, on the other hand, binds significantly to plasma proteins in a concentration- dependent manner, and it has been estimated that at the therapeutic dose (5 mg), the majority of the medication will be bound to plasma proteins (primarily to DPP-4). The DPP-4 inhibitors are largely removed by the kidney, with renal clearance exceeding glomerular filtration, implying active transport. The exception is linagliptin, which has a 6% urine excretion rate. This could be due, at least in part, to the high degree of protein binding, which allows the medication to bypass glomerular filtration. Instead, linagliptin is eliminated by the liver, with 78 percent of its remaining unchanged in the stool. The major metabolite of linagliptin (CD1790), which undergoes further metabolic actions and is similarly removed in the faeces, has a minor renal excretion.[25-30]

MATERIALS AND METHODS

Three community pharmacies participated in this investigation. Out-patients were the only ones chosen for the study. A distinct data entry format (Proforma) was created for including patient information. Patient information such as name, ID number, age, and gender are included in proforma-I, as well as general information such as height, weight, and BMI, general examination details, provisional diagnosis, diabetic and hypertensive history, social history, and diabetes family history. The values of the diabetic profile study, lipid profile study, and biochemistry are included in the Proforma-II research chart. Medication chart in Proforma-III.

RESULTS AND DISCUSSION

Categorization of Patients According to Gender, Age, Associated Disease

Figure 2 depicts the categorization of patients in group A (Met+su) based on gender, age, and associated disease, Social habits, Familial history. There were 15 male patients (60%) and 10 female patients (40%) among the 25 patients chosen. Patients aged 30-39 and 40-49 made up 32% of the total.4 patients (16%) were in the age group of 50-59 years, 2 patients (8 %) were in the age group of 60-69 years, 2 patients (8%) were in the age group of 70-79 years, 1 patient (4%) were in the age group of above 80 years.40% of individuals had hypertension and 16% of individuals had cardiovascular disease as a co-morbid condition.13 patients (52%) had none of the following habits, 7 patients (28%) were Alcoholics, 5 patients (20%) were Alcoholic and smokers. The fathers of 4 patients (16%) were diabetes, mother of 6 patients (24%) were diabetes, sibling of 1 patient (4%) were diabetes, others of 3 patients (12%) were diabetes, 11 patients (44%) none of any familial diabetes history.

Categorization of Patients According to Gender, Age, Associated Disease

In group B (Met+DPP4), Figure 3 depicts the categorization of patients based on Gender, Age, and Associated Disease, Social habits, Familial history. 14 patients (56%) and 11 patients (44%) were males and females, respectively, of the 25 patients chosen. Patients aged 30-39 and 40-49 made up 32% of the total, 3 patients (12%) were in the age group of 50-59 years, 2 patients (8 %) were in the age group of 60-69 years, 3 patients (12%) were in the age group of 70-79 years, 1 patient (4%) were in the age group of above 80 years. Hypertension and cardiovascular disease were shown to be related in 40% and 20% of patients, respectively, 4 patients (16%) had dyslipidemia,4 patients (16%) had none of the following disease.11 patients (44%) had none of the following habits, 9 patients (36%) were Alcoholics, 3 patients (12%) were Alcoholic and smokers, 2 patients (8%) were tobacco smokers. the fathers of 10 patients (40%) were diabetes, mother of 5 patients (20%) were diabetes, sibling of 3 patient (12%) were diabetes, others of 3 patients (12%) were diabetes, 4 patients (16%) none of any familial diabetes history.

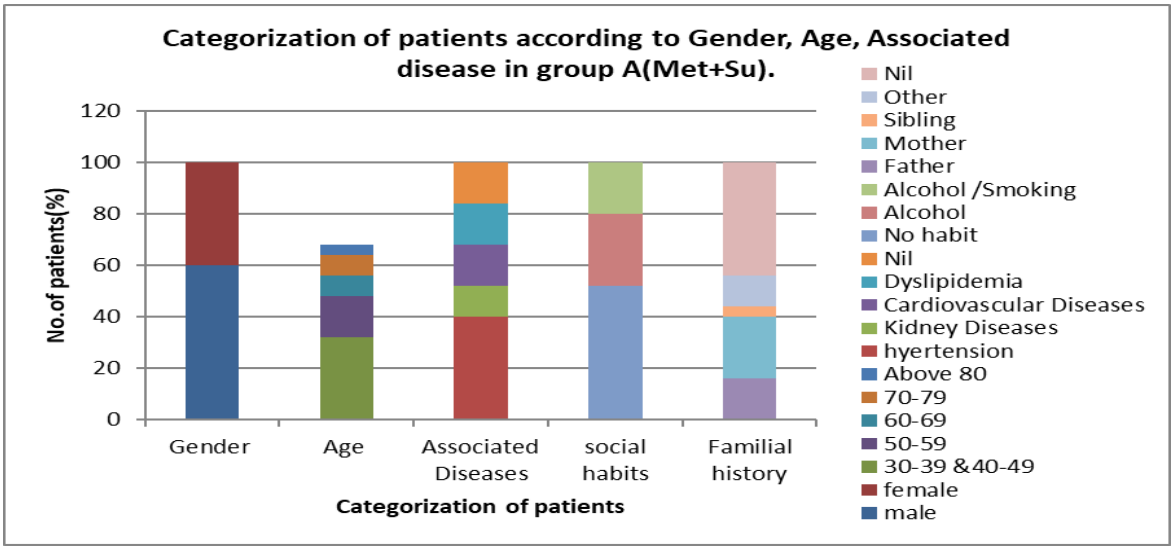

Figure 2: Group A (Met+Su)

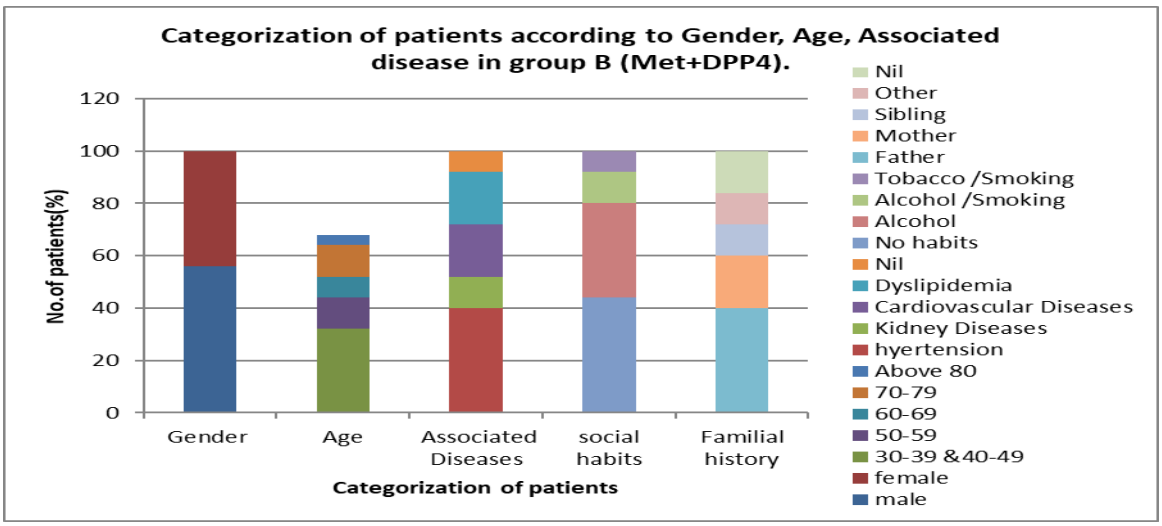

Figure 3: Group B (Met+DPP4)

Table 1: Mean ± SE Reduction in Fasting Blood sugar of Group A and Group B

Groups	No. of patients	Mean ± SE change of Group A & Group B in Fasting Blood sugar - Mg/dL			% mean Reduction
		Base	Rev I	Rev II	
Group A Metformin + Sulfonyl urea	25	145 ± 3.847	125 ± 3.744	103 ± 3.155	28.96%
Group B Metformin + Sulphonyl urea + DPP4-Inhibitor	25	153 ± 3.511	122 ± 3.511	104 ± 2.524	32.02%

Table 2: Mean ± SE Reduction in Post Prandial Plasma glucose of Group A and Group B

Groups	No. of patients	Mean ± SE change of Group A & Group B in Post Prandial Plasma glucose - Mg/dL			% mean Reduction
		Base	Rev I	Rev II	
Group A Metformin + Sulfonyl urea	25	182 ± 6.827	157 ± 6.515	132 ± 6.429	27.47%
Group B Metformin + Sulphonyl urea + DPP4-Inhibitor	25	190 ± 5.416	150 ± 5.901	124 ± 5.196	34.73%

Table 3: Mean ± SE Reduction in GRBS of Group A and Group B

Groups	No. of patients	Mean ± SE change of Group A & Group B in GRBS - Mg/dL			% mean Reduction
		Base	Rev I	Rev II	
Group A Metformin + Sulfonyl urea	25	286 ± 7.102	249 ± 7.721	221 ± 6.633	22.72%
Group B Metformin + Sulphonyl urea + DPP4-Inhibitor	25	277 ± 7.588	241 ± 7.679	201 ± 7.116	27.43%

Table 4: Mean ± SE Reduction in HbA1c of Group A and Group B

Groups	No. of patients	Mean ± SE change of Group A & Group B in HbA1c - Mg/dL			% mean Reduction
		Base	Rev I	Rev II	
Group A Metformin + Sulfonyl urea	25	10 ± 0.150	9 ± 0.156	8 ± 0.198	20%
Group B Metformin + Sulphonyl urea + DPP4-Inhibitor	25	8 ± 0.123	8 ± 0.119	6 ± 0.124	25%

Comparative Mean Reduction in Fasting blood sugar of Group A& B

Table 01 shows in Group A (Metformin + a Sulfonyl urea) patients (n = 25), the mean value change of Fasting blood sugar at the base line was 103±3.155 and after treatment for a mean period of 6 months, it was observed 145±3.847.

In Group B (Metformin + Sulphonyl urea + DPP4 inhibitor) patients (n = 25) the mean value change of Fasting blood sugar at the base line was104±2.524 and after treatment for a mean period of 6 months, it was observed 153.2±3.511.

In Group A (Metformin + Sulfonyl urea) patients (n = 25), the percentage mean change value is 28.96%.

In Group B (Metformin + Sulphonyl urea + DPP4-Inhibitor) patients (n = 25) the percentage mean change value is 32.02%.

Comparative Mean Reduction in Post Prandial Plasma glucose of Group A& B

Table 02 shows in Group A (Metformin + a Sulfonyl urea) patients (n = 25), the mean value change of Post Prandial Plasma glucose at the base line was132 ± 6.429 and after treatment for a mean period of 6 months, it was observed 182 ±6.827

In Group B (Metformin + Sulphonyl urea + DPP4 inhibitor) patients (n = 25) the mean value change of Post Prandial Plasma glucose at the base line was124 ± 5.196 and after treatment for a mean period of 6 months, it was observed190 ± 5.416.

In Group A (Metformin + Sulfonyl urea) patients (n = 25), the percentage mean change value is 27.47%.

In Group B (Metformin + Sulphonyl urea + DPP4-Inhibitor) patients (n = 25) the percentage mean change value is 34.73%.

Comparative Mean Reduction in GRBS of Group A & B

Table 03 shows in Group A (Metformin + Sulfonyl urea) patients (n = 25), the mean value change of GRBS at the base line was 221 ± 6.633 and after treatment for a mean period of 6 months, it was observed 286 ± 7.102.

In Group B (Metformin + Sulphonyl urea + DPP4 inhibitor) patients (n = 25) the mean value change of GRBS at the base line was 201 ± 7.116 and after treatment for a mean period of 6 months, it was observed 277 ± 7.588.

In Group A (Metformin + Sulfonyl urea) patients (n = 25), the percentage mean change value is 22.72%

In Group B (Metformin + Sulphonyl urea + DPP4-Inhibitor) patients (n = 25) the percentage mean change value is 27.43%.

Comparative Mean Reduction in HbA1c of Group A & B

Table 04 shows in Group A (Metformin + Sulfonyl urea) patients (n = 25), the mean value change of HbA1c at the base line was8 ± 0.198 and after treatment for a mean period of 6 months, it was observed 10 ± 0.150

In Group B (Metformin + Sulphonyl urea + DPP4 inhibitor) patients (n = 25) the mean value change of HbA1c at the base line was 6 ± 0.124 and after treatment for a mean period of 6 months, it was observed 8 ± 0.123

In Group A (Metformin + Sulfonyl urea) patients (n = 25), the percentage mean change value is 20%

In Group B (Metformin + Sulphonyl urea + DPP4-Inhibitor) patients (n = 25) the percentage mean change value is 25%.

CONCLUSION

In this study, T2DM was successfully treated with metformin and a sulfonylurea, as well as DPP4 inhibitors, to dramatically lower blood glucose levels and enhance patient quality of life.

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