Research Article

Observational Study to Compare the Efficacy of Vildagliptin – Metformin and Glimepiride – Metformin Combination in Type 2 Diabetic Patients

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ABSTRACT

Diabetes is becoming the capital of India. Treating patients with diabetes is most challenging due to its progressive nature and increasing complication with antidiabetic agents. The aim of the present study is to investigate the efficacy of vildagliptin-metformin treatment compared to those of glimepiride-metformin treatment for type 2 diabetes. The study was Single Centered prospective, randomized, comparative & observational study. The study was carried out at Ashta Criticare Hospital Ashta. The study period was six months. Totally 80 patients were enrolled in the study based on inclusion criteria. To compare the Efficacy of both the groups based on these parameters in diabetes patients, To Monitor BSL (Fasting and postprandial) every 3 Months, HbA1c after 3 Months, BMI, hypoglycemic episodes, and Renal Function Test. Maximum female patients were seen amounting (57.5%) and males (42.5%) respectively. BMI reduction is statistically significant in the vildagliptin metformin group compared to the glimepiride metformin group. FPG and PPG reduction was equal in both groups. So, in this study, we have found that vildagliptin-metformin appeared to be equally effective to that of glimepiride-metformin and it resulted in better adverse event profiles with lower risks of hypoglycemia.

Keywords: Diabetes mellitus, type 2; Glimepiride; Metformin; Vildagliptin.

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INTRODUCTION

Diabetes is a complex, chronic illness that necessitates ongoing treatment with multifactorial risk reduction methods in addition to glycemic control. Diabetes is a chronic disease that causes high blood sugar levels due to a lack of insulin secretion by the pancreas or the ineffectiveness of released insulin, which can be hereditary or acquired.

Diabetes is the most prevalent disease. Dobson was the first to demonstrate the presence of sugar in diabetic urine in 1755. Von Mering and Minkowski discovered in 1989 that pancreatectomized dogs become diabetic in addition to having digestive problems. [1] It is a type of upset marked by elevated blood glucose levels.

According to the International Diabetes Federation (IDF), there were 366 million diabetics in 2011; by 2030, this figure is expected to climb to 552 million worldwide. Diabetes has increased in prevalence from 108 million in 1980 to 422 million in 2014. Diabetes prevalence among persons over the age of 18 has risen from 4.7% in 1980 to 8.5% in 2014. India is one of the epicenters of the global diabetes epidemic, ranking second in the world in terms of diabetes prevalence with 69.2 million people in 2015, and this figure is expected to rise to 109.5 million by 2030. Diabetes was responsible for an estimated 1.6 million deaths in 2015.

Diabetes is predicted to be the seventh greatest cause of death by 2030, according to the World Health Organization (WHO). [2,3] Diabetes may have a significant role in blindness, kidney disease, heart attacks, stroke, and lower limb amputations. Diabetes can be treated and its repercussions prevented or postponed through diet, physical exercise, medication, and regular screening for complications and therapy. [3]

It is essentially defined by the degree of hyperglycemia, which increases the risk of microvascular damage (retinopathy, nephropathy, and neuropathy). It is associated with a shorter lifespan, considerable morbidity due to diabetes-related microvascular problems, an increased risk of macrovascular consequences (ischaemic cardiovascular disease, stroke, and peripheral vascular disease), and a lower quality of life. Type 2 diabetes is distinguished by insulin resistance, which may be paired with decreased insulin production. The fundamental goal of type 2 diabetes (T2DM) treatment is to achieve and maintain optimal glucose control in order to avoid long-term micro and macrovascular problems. Obesity, lack of physical activity, poor diet, stress, and other lifestyle variables are known to play a role in the development of type 2 diabetes begins with insulin resistance, a condition in which cells fail to respond appropriately to insulin. As the disease advances, an insulin deficiency may occur.

Previously, this type was known as "non-insulin-dependent diabetes mellitus" or "adult-onset diabetes."

Antidiabetic medications are chosen based on efficacy as well as drug safety. Metformin is the most commonly prescribed monotherapy for the initial treatment of T2DM.[4-6] However, in the long run, the majority of patients have urged ombination therapy to preserve glycemic control. The combination regimens are helpful in reducing the dosage of antihyperglycemic drugs and, as a result, their side effects. Because of its cost-effectiveness and efficacy in improving glycemic control, the combination of glimepiride and metformin is frequently utilized in Indian clinical settings. [7,8]

A combination of glimepiride with metformin, on the other hand, is usually associated with side effects like as weight gain and hypoglycemia.[9,10] As a result, clinicians and researchers are looking for a combination with more efficacy and fewer adverse effects than the current antidiabetic agents. The combination treatments are efficient in reducing the dosage of antihyperglycemic medications and, as a result, their side effects. Because of its cost-effectiveness and efficacy in improving glycemic control, the combination of glimepiride and metformin is frequently used in Indian clinical settings. However, glimepiride with metformin side effects includes weight gain and hypoglycemia episodes. Because of their comparable mechanisms of action, whether vildagliptin was taken as an add-on medication or as an initial combination therapy with metformin, satisfactory glycemic control was established. Many randomized clinical trials have demonstrated the comparative efficacy of glimepiride and vildagliptin as metformin add-on treatments. However, their findings do not necessarily correspond to what might be expected in practical practice. As a result, the current study is to assess the efficacy of glimepiride-metformin and vildagliptin-metformin in T2DM patients.

In non-obese diabetics, glimepiride is usually the first-line treatment option, while metformin is used in obese diabetics. Because of its inexpensive cost, the combination of metformin and sulfonylureas is most often used in India and can achieve a higher reduction in haemoglobin A1c (HbA1c) than either medicine alone.[11] This combo therapy, however, is associated with weight gain and severe hypoglycemia. Despite well-planned dose regimens using oral hypoglycemic agents (OHAs), some Type 2 diabetic patients have poor glycemic control, and many OHAs cause adverse drug reactions (ADRs) such as weight gain and hypoglycemia. In this context, the search for better OHAs is ongoing.

The importance of "incretins," notably glucagon-like peptide (GLP-I), has been well recognised. In response to an increase in plasma glucose, the peptide GLP-I enhances insulin secretion while decreasing glucagon levels. However, due to its very short plasma t1/2 (2 minutes) and chemical composition, this peptide hormone cannot be taken orally. As a result, drugs that block dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for GLP-1 metabolic breakdown, have been developed to extend the duration of the action of endogenous GLP-I.

Vildagliptin is a strong, specific, and reversible DPP-4 inhibitor that improves glycemic control in Type 2 diabetes patients (T2DM).[12,13] In this context, the current study was designed to assess and compare the efficacy and safety of metformin-vildagliptin and metformin-glimepiride combinations in T2DM patients.

Vildagliptin is an oral antidiabetic drug with moderate efficacy and a favorable overall safety profile, including a low risk of hypoglycemia, a low risk of edema, a lipid-neutral impact, and weight neutrality.[14] Because of their complementary mechanisms of action, whether vildagliptin was taken as an add-on treatment or as the first combination therapy with metformin, satisfactory glycemic control was established.[15] Many randomized clinical trials have established the comparative efficacy of glimepiride and vildagliptin as metformin add-on treatments.[16-18] However, their findings may not necessarily reflect what might be expected in practical practice.

MATERIALS AND METHODS

The present Study Site was carried out at Ashta Criticare Hospital Ashta. It was Single Centered prospective, randomized, comparative & observational study. The study period was six months. Totally 80 patients were enrolled in the study based on inclusion criteria. Patients were selected as per inclusion criteria and exclusion criteria as per study protocol. Medical examination of patients will be performed at the beginning and end of the study for each patient. The entire subjects will be screened for 6 months and results will be segregated.

Informed Consent forms were developed in two different regional languages (English & Marathi) & were administered to the subject or their legally acceptable representatives in the language well understood. Subjects were explained about the study and asked for their willingness in being a part of the study. On obtaining verbal approval, ICF was provided to the subject; as per the language feasibility. After obtaining the sign informed consent form from the subjects they were enrolled for the present study according to inclusion criteria.

Inclusion Criteria:

a) Type 2 Diabetes Mellitus Patients. b) Patients age group above 18 years.

Exclusion Criteria:

a) Patients age group less than 18 years. b) Type 1 Diabetes Mellitus Patients. c) Pregnant and lactating women. d) Renal & Liver Failure. e) Unwilling or unable to give informed consent.

Method of study:

1) Patient Data collection proforma: All necessary and relevant baseline information will be collected on a patient data collection Proforma. 2) Follow up: - Patients will be re-evaluated for 3 months at the interval of one month.

A total 80 patients were enrolled & the patients were divided in 2 groups based on treatments viz. A and B to evaluate the comparative efficacy of diabetic drugs. **In combination therapy**: Group A (40 patients) Vildagliptin & Metformin. Group B (40 patients) Glimepiride & Metformin.

Data analysis

All the data observed were analysed as per GraphPad software. The percentage, proportions were calculated and p-value (<0.05) was considered statistically significant.

RESULTS

Table 1: Demographic data

Sr. No	Variable	Number of Patients	Percentage of Patients
1.	**Gender**		
	Male	34	42.5%
`	Female	46	57.5%
	Total	80	100%
2.	**Education Status**		
	Illiterate	24	30%
	Literate	56	70%
	Total	80	100%
3.	**Marital status**		
	Married	79	98.75%
	Unmarried	01	1.25%
	Total	80	100%
4.	**Age**		
	25-35	04	5%
	36-45	08	10%
	46-55	18	22.5%
	56-65	32	40%
	66-75	12	15%
	76-85	06	7.5
	Total	80	100%
5.	**Occupation**		
	Housewife	33	41.25%
	No work	31	38.75%
	Service	13	16.25%
	Retired	03	3.75%
	Total	80	100%
6.	**Family History**		
	Yes	10	12.5%
	No	70	87.5%
	Total	80	100%
7.	**Body Mass Index**		
	Normal	32	40%
	Underweight	00	00
	Overweight	16	20%
	Obese	15	18.75%
	Total	80	100%

Demographic details of the patients involved in our study included Gender, Educational status, Marital status, Age, Occupation, Family history and BMI etc.

Table 2: Prevalence of diabetes patients among different age groups A & B.

Age	Male	Female	Total
20-35	1	3	4
36-45	6	2	8
46-55	4	14	18
56-65	13	19	32
66-75	7	5	12
76-85	3	3	6
Total	**34**	**46**	**80**

The age range was from 20 to 85 years. The maximum number of female patients were 46 and male patients were 34 only.

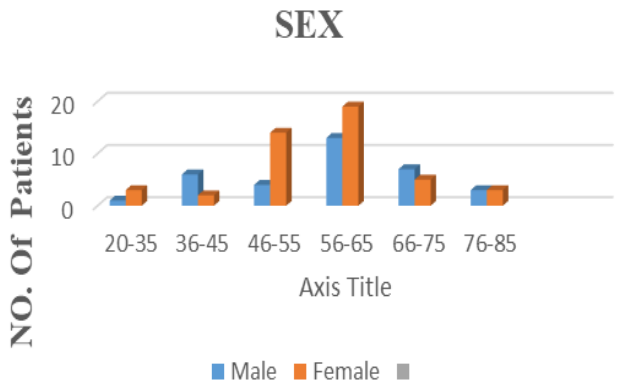

Figure 2: Graphical presentation of the prevalence of patients based on age group.

Table 3: Comparison of both the groups A & B based on BMI of Diabetic patients.

	BMI	
Drugs	**1ST Month**	**2nd Month**
Group A	26.63%	27.34%
Group B	25.24%	24.52%

Data based on factors related to patients' BMI in Group A patients 1st month was 26.63% & 2nd month BMI was 27.34% & Group B 1ST month BMI was 25.24% & in 2nd month BMI was 24.52%. Therefore, in group B there was a reduction in BMI, and it is significant to the p-value (>0.05).

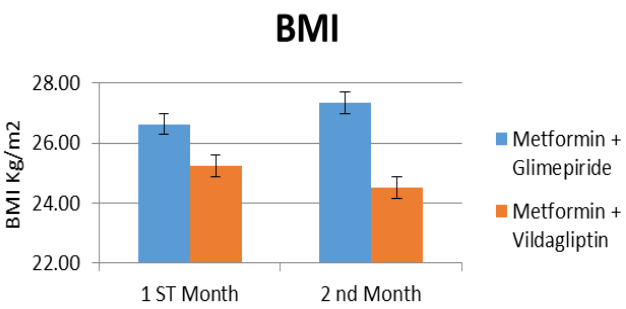

Figure 3: Graphical presentation based on the BMI of diabetic patients

Table 4: Comparison of both the group's A & B BSL of Diabetic patients.

		BSL					
		Initial visit		1st Month		2nd Month	
		Fasting	Post-Prandia	Fasting	Post Prandial	Fasting	Post Prandial
Group A		193.40 mg/dl	288.70 mg/dl	153.80 mg/dl	223.80 mg/dl	132.98 mg/dl	188.78 mg/dl
Group B		206.00 mg/dl	310.40 mg/dl	148.03 mg/dl	213.65 mg/dl	137.15 mg/dl	199.33 mg/dl

Data based on BSL Fasting & Post Prandial of Groups A & B, therefore both the groups are compared. Therefore both the group p-value is greater than <0.05, hence it is not significant.

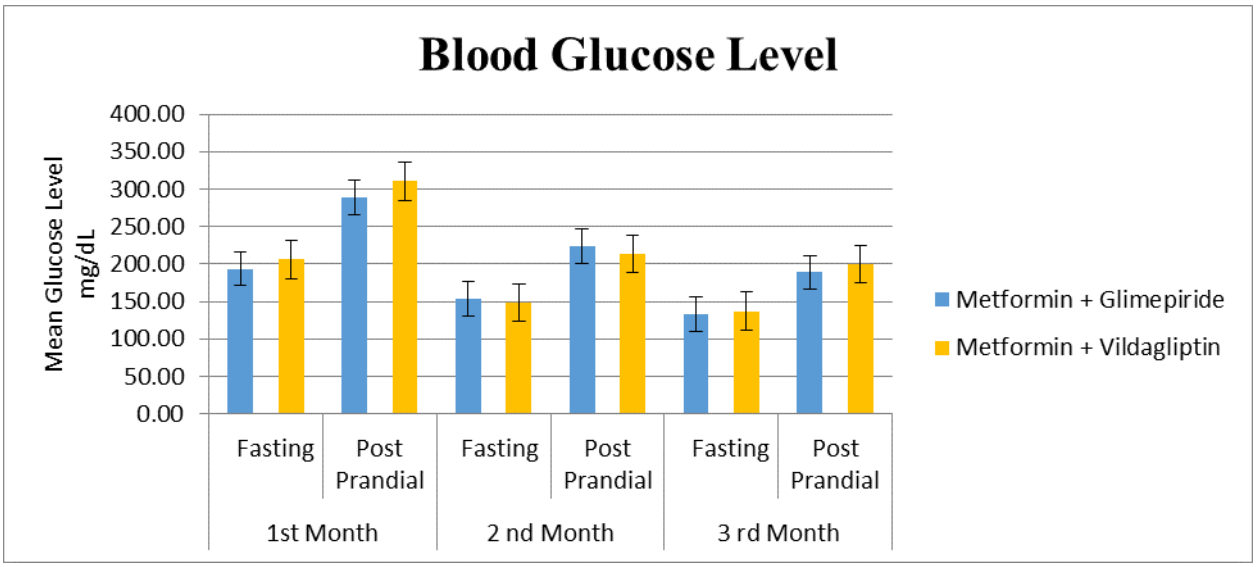

Figure 4: Graphical presentation based on BSL Fasting and Post Prandial of Diabetic patients.

Table 5: Comparison of both groups A & B based on HbA1c of Diabetic patients.

Drugs	HbA1c	
	1st Month	2nd Month
Group A (n=40)	7.68	6.24
Group B (n=40)	8.19	6.99

Based on data the HbA1c of Groups A & B, therefore Group A 2nd month shows reduction 6.24% and also Group B 2nd month shows reduction 6.99%.

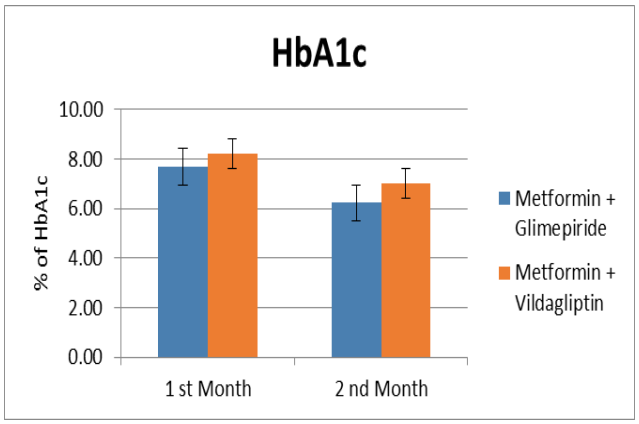

Figure 5: Graphical presentation based on HbA1c of diabetic patients.

Table 6: Comparison of both the groups A & B based on Episodes of Hypoglycemia of Diabetic patients.

Episodes of hypoglycemia	Group A (n=40)	Group B (n=40)
NO	34	40
YES	6	0

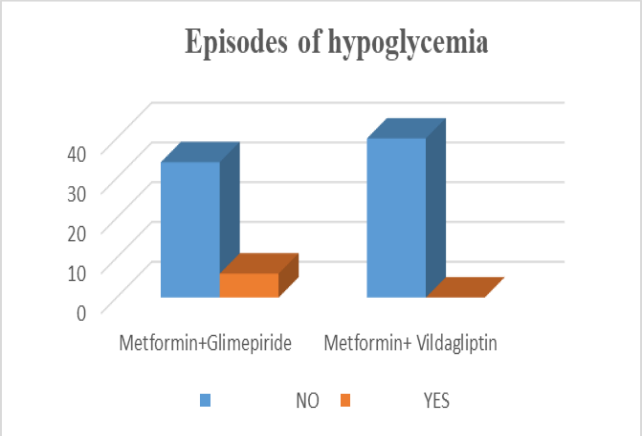

Figure 6: Graphical presentation-based Episodes of Hypoglycemia of diabetic patients

DISCUSSION

Diabetes is a complex, chronic illness, it is a major health problem in India and throughout the worldwide. Treating patients with diabetes is most challenging due to its progressive nature and increasing complication with antidiabetic agents. Many type 2 diabetic patients require more than two oral hypoglycemic agents since treatment with a single agent often results in sub-optimal outcomes. Combination therapy early in diabetes management would be an appropriate approach. The combined treatments are effective to minimize the dosage of antihyperglycemic agents and thereby unwanted effects. Hence the aim of the present study was comparing the efficacy of vildaglptin with metformin and glimepiride.

The present study is a single-centered, prospective, randomized, interventional, comparative clinical study, conducted at ASHTA CRITICARE HOSPITAL ASHTA. For prospective analysis, a total of 80 patients were enrolled and they were divided into TWO groups based on treatment viz. A and B to evaluate the comparative efficacy of diabetic agents in the study (Group A, n=40) Glimepiride-Metformin Versus (Group B, n=40) Vildagliptin-Metformin.

Demographics Data: The prevalence of diabetes in India has increased in both urban and rural subjects. In the present study, the prevalence of diabetes has been found to be higher in rural areas 73 (91.25%) as compared to urban areas 7 (8.75%). The demographic result of the present study indicated that the incidence of DM in females was 57.5% and in males 42.5%. And the greatest number of patients in the age group of 56-65 (40%). Family history was found in 12.5% of patients and normal BMI was (40%) overweight (20%), and obese was (18.75%). Literate patients were 56 (70%).

In the present study, the vildagliptin with metformin treatment showed a more reduction in blood glucose parameters viz. HbA1c, fasting, and postprandial then glimepiride with metformin treatment over a 3-month period. Furthermore, vildagliptin-metformin and glimepiride-metformin treatments did not induce weight gain, whereas vildagliptin-metformin provided definite advantages in terms of reduction in the incidence of hypoglycemia.

In the present study, measurement of HbA1c was done at 1 st follow-up and 3rd follow-up as it provides an estimate of plasma glucose level over a period of 3 months. The glycemic control not only facilitates clinical trials but also assists routine management. When treatment is recognized and glycemic control appears stable, testing one or two times a year is usually adequate. In our study, at the end of the study period (3 months), satisfactory results were obtained in the glucose level. All three parameters (HbA1c, FPG, and PPG) remained significantly lower compared to the baseline in both groups. Combination therapy can be good approach to managing T2DM.

The mean HbA1c level was 8.19% and 7.68% in the vildagliptin- metformin and glimepiride-metformin group at the baseline which was reduced to 6.99% and 6.24% at 12 weeks follow-up, respectively. No significant difference in HbA1c reduction between treatment groups. This is in accordance with the earlier studies where both treatment groups showed similar efficacy in reducing HbA1c.[19,21] However, in contrast to Sarkar BS et al.,[22] in a prospective observational comparative study in West Bengal, India, where it was found that significantly more reduction in HbA1c when glimepiride and metformin were added than vildagliptin and metformin at 3 months follow-up. A significant decrease in FPG and PPG levels was observed within a vildagliptin-metformin group glimepiride-metformin group. In Vildagliptin- metformin group baseline FPG significantly decrease from 206mg/dl to 148mg/dl in the second month and 137mg/dl in the third month whereas FPG in the glimepiride- metformin group decreased from baseline value of 193mg/dl to 153mg/dl in the second month and 132mg/dl in the third month. However, by applying t-test for equality of means and considering 95% confidence interval of the difference reduction of FPG is statistically not significant in the second month (p-value 0.621) and third month (p-value 0.676). PPG in the vildagliptin-metformin group significantly decreases from a baseline value of 310mg/dl to 213mg/dl in the second month and 199mg/dl in the third month. Whereas PPG decreased from a baseline value of 288mg/dl to 223mg/dl in the second month and 188mg/dl in the third month. By applying the t-test for equality of means and considering the 95% confidence interval of the difference the reduction in PPG is statistically not significant in the second month (p-value 0.535) and third month (p-value 0.392). Sarkar et al. and Jeon HJ et al.in contrast with the results of the present study showed that vildagliptin added to metformin is inferior to glimepiride plus metformin in reducing blood glucose parameters. Conversely, a longitudinal interventional study by Gullapalli H. and Desai S. compared vildagliptin-metformin and glimepiride-metformin in patients who were already on metformin with poor glycemic control.

Glimepiride is known for weight gain hence we compare glimepiride with vildagliptin in terms of BMI at the end of the third month. Baseline BMI is 26.62kg/m2 and 25.23kg/m the for glimepiride metformin group and vildagliptin metformin group respectively. BMI increase to 27.33kg/m2 in the glimepiride- metformin group at the end of three month and BMI reduced to 24.52kg/m2 in the vildagliptin metformin group at the end of three months. By applying the t- test for equality of means and considering a 95% confidence interval of difference BMI reduction is statistically significant in the vildagliptin metformin group (p value -0.003) compared to the glimepiride metformin group.[20]

When safety results were considered, there were no hypoglycemia events observed with vildagliptin metformin, while mild hypoglycemia was reported with glimepiride added to metformin. Similarly, a previous randomized comparative study of vildagliptin and glimepiride add on to metformin showed better adverse events profile with a

10fold lower incidence of hypoglycemia in the vildagliptin group. A real-life study from Asia reported 9% adverse events including one hypoglycemic event in drug naïve patients with T2DM. The initial combination therapy with vildagliptin and metformin was well tolerated in these patients related with high HbA1c and cardiovascular risk factors.[23] This is attributed to the glucose-dependent nature of vildagliptin with insulinotropic polypeptide mediated effect that helps to lower the incidence of hypoglycemia.[24] Moreover, vildagliptin has weight-neutral activity. As the risk of hypoglycemia is more often associated with weight gain, previous studies by (Sarkar et al. and Jeon HJ et al.) reported no weight gain with vildagliptin metformin therapy.[25,26] This is confirmed by the present study findings.

CONCLUSION

Diabetes is increasing in India newer modalities of treatments are coming up. In this study, we have compared the efficacy between vildagliptin-metformin and glimepiride-metformin groups. In our study female patients are more than males and most of the patients are literate and fall between the age of group 56-65. And also we found HbA1c reduction in both groups. But both groups were not superior to each other. FPG and PPG reduction was equal in both groups.

With regards to efficacy, we found that there is a significant weight reduction in the vildagliptin-metformin group compared to the glimepiride-metformin group. The incidence of hypoglycemia is lower in the vildagliptin-metformin group.

So, in this study, we have found that vildagliptin-metformin appeared to be equally effective to that as glimepiride-metformin and it resulted in better adverse event profiles with lower risks of hypoglycemia.

REFERENCES

1. Santoskar,R S, Bhandarkar, S D, Rege N Nirmala, Revised 12th edition, pharmacology and pharmcotheraputics 2007.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS medicine. 2006 Nov 28;3(11):e442.
3. World Health Organization. World Health Organization Diabetes Fact Sheet. WHO: Geneva, Switzerland. 2011.
4. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment. *Diabetes Care.* 2017;40(Suppl 1):S64–74. [PubMed] [Google Scholar]
5. International Diabetes Federation Guideline Development Group. Global guideline for type 2 diabetes. *Diabetes Res Clin Pract.* 2014;104:1–52. [PubMed] [Google Scholar]
6. McGuire H, Longson D, Adler A, Farmer A, Lewin I. Guideline Development Group. Management of type 2 diabetes in adults: Summary of updated NICE guidance? *BMJ.* 2016;353:i1575. doi: 10.1136/bmj. [PubMed] [Google Scholar.
7. Singh SK. Commentary on "Consensus recommendations on sulfonylurea and sulfonylurea combinations in the management of type 2 diabetes mellitus: International task force" *Indian J Endocr Metab.* 2018;22:158–9. [PMC free article]

   [PubMed] [Google Scholar]
8. Unnikrishnan AG, Pandit K, George J, Venkataraman S, Abhyankar MV. Clinical utilization pattern of multiple strengths of glimepiride and metformin fixed dose combinations in Indian type 2 diabetes patients. *J Assoc Physicians India.* 2020;68:57–61. [PubMed] [Google Scholar]
9. Prasanna Kumar KM, Seshadri K, Aravind SR, Deb P, Modi KD, Gopal RA, et al. Real-world observational study of glimepiride and metformin fixed-dose combination along with insulin in the management of type 2 diabetes mellitus: Indian experience? *Cureus.* 2021;13:e13020. doi: 10.7759/cureus.13020. [PMC free article]

   [PubMed] [Google Scholar]
10. Jeon HJ, Oh TK. Comparison of vildagliptin-metformin and glimepiride-metformin treatments in type 2 diabetic patients. *Diabetes Metab J.* 2011;35:529–35. [PMC free article] [PubMed] [Google Scholar]
11. Charbonnel B, Schernthaner G, Brunetti P, Matthews DR, Urquhart R, Tan MH, Hanefeld M. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. Diabetologia. 2005 Jun;48(6):1093-104.
12. Winkler G. Incretin enhancers, incretin mimetics–from therapeutic concept to clinical application. Orvosi hetilap. 2007 Apr 1;148(13):579-87
13. Holst JJ. Treatment of type 2 diabetes mellitus with agonists of the GLP-1 receptor or DPP-IV inhibitors. Expert opinion on emerging drugs. 2004 May 1;9(1):155-66.
14. Mathieu C, Degrande E. A new oral treatment for type 2 diabetes mellitus. *Vasc Health Risk Manag.* 2008;4:1349–60. [PMC free article]

   [PubMed] [Google Scholar]
15. Viollet B, Foretz M. Revisiting the mechanisms of metformin action in the liver. *Ann Endocrinol (Paris)* 2013;74:123–9. [PubMed] [Google Scholar]
16. Gullapalli H, Desai S. Comparison of efficacy and safety of metformin and vildagliptin versus metformin and glimepiride in patients of Type 2 diabetes mellitus. *Natl J Physiol Pharm Pharmacol.* 2018;8:521–5. [Google Scholar]

17. Mokta JK, Ramesh, Sahai AK, Kaundal PK, Mokta K. Comparison of safety and efficacy of glimepiride-metformin and vildagliptin- metformin treatment in newly diagnosed type 2 diabetic patients. *J Assoc Physicians India.* 2018;66:30–5. [PubMed] [Google Scholar]

18. Sarkar BS, Mukherjee S, Maji M, Biswas S. A prospective observational study to compare the efficacy and adverse effects of glimepiride and vildagliptin added to metformin in type 2 diabetes mellitus. *J Clin Diagn Res.* 2019;13:9–11. [Google Scholar]

19. Misra A, Khurana L. Obesity-related non-communicable diseases: South Asians vs White Caucasians. Int J Obes (Lond). 2011;35(2):167-87

20. Mohan V, Shah S, Saboo B. Current glycemic status and diabetes related complications among type 2 diabetes patients in India: data from the A1chieve study. JAPI (Suppl). 2013; 61:12-15.

21. Rastogi A, Bhadada SK, Saikia UN, Bhansali A. Recurrent diabetic myonecrosis: a rare complication of a common disease. Indian J Med Sci. 2011;65(7):311-5.

22. Iyer SN, Drake AJ 3rd, West RL, Tanenberg RJ. Diabetic muscle infarction: a rare complication of long-standing and poorly controlled diabetes mellitus. Case Rep Med. 2011;11:407921.

23. Robertso,RP,Antagonist diabetes and insulin resistance –philosophy, science ,and the multiplier hypothesis. J Lab clin Med 1995;125(5):560-564.

24. Harris MI, Klein R, Welborn TA, Kneuman MW. ON SET OF NIDDM occurs at least 4-7 year before clinical diagnosis. Diabetes car 1992;15:815-819 14.

25. Gillett MJ. International expect committee report on the role of the assay in the diagnosis care 2009; 32(7):1327-1334.

26. Diabetes Care "January 2010" Diabetes care. 33 S3. 2009. From the original on 13 January 2010. Retrieved 29 January 2010.

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