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Improvement in lipid profile of the patients with saxagliptin as add-on therapy to metformin in patients of type 2 DM

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Abstract
Aim: To assess the improvement in lipid profile (TC, TG, LDL and HDL) in patients of type 2 diabetes mellitus who were previously on metformin monotherapy with uncontrolled diabetes.
Material and Method: This prospective analytical study was carried out in the Department of Pharmacology at Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar from October 2019 to March 2020. A total of 100 patients were enrolled who were on metformin monotherapy and with uncontrolled diabetes. Patients were given metformin 500 mg twice a day and saxagliptin 2.5 mg once a day. Patients were followed up at First, Third and Sixth month and lipid profile (TC, TG, LDL and HDL) estimation was done during the follow up period.
Results: Amongst the 100 patients' studies for diabetes 65 of the patients were male and 35 were female. Most commonly affected age group was 50 to 60 years of age followed by 40-50 years of age. The mean change in value from baseline at 24 weeks was TC=13.60± 17.71, TG = 10.63± 19.79, LDL = 11.59± 17.29, HDL = 2.24± 5.77. A highly significant difference has been seen at 0 v/s 1, 0 v/s 3 and 0 v/s 6 months in TC, TG, LDL and HDL values.
Conclusion: Saxagliptin has shown an improvement in lipid profile (TC, TG, LDL, HDL) during 6 months of treatment in patients of type 2 DM.

Keywords: saxagliptin, uncontrolled type 2dm, metformin, lipid profile

Introduction

Diabetes is a chronic degenerative disease that can result in long-term complications affecting the heart and blood vessels, eyes, kidneys, and peripheral and autonomic nervous systems [1]. Diabetes is associated with an increased risk of heart disease and stroke, and cardiovascular disease is the major cause of death in people with type 2 diabetes [2]. Neuropathy and reduced blood flow in the feet increase the chance of ulcers and infection, and, in developed countries, lower-limb amputations are ≥10-times more common in people with diabetes than those without the disease [3]. Diabetic retinopathy is responsible for 1% of all-cause blindness worldwide [4], and diabetes is among the leading causes of kidney failure in both developed and developing countries [3]. Diabetes is also associated with an increased risk of overall and site-specific cancers, including pancreatic, liver, colorectal, endometrial, and breast [5]. Over 380 million people are estimated to have diabetes mellitus, with type 2 diabetes, characterised by insulin resistance and/or relative insulin deficiency, accounting for at least 85–95% of cases [6]. In recent estimates, 6–16% of all-cause deaths worldwide are due to diabetes [6, 7]. In addition, diabetes care and management is associated with significant costs, and accounted for an estimated 12% of global healthcare expenditure in 2010 [8].

India had 69.2 million people living with diabetes (8.7%) as per the 2015 data. Of these, it remained undiagnosed in more than 36 million people [9]. The pathogenic processes involved in the development of diabetes range from autoimmune destruction of the β- cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. Long-term complications of diabetes include hypertension and abnormalities of lipoprotein metabolism - which causes increased incidence of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease [10]. Elevated cholesterol levels, are believed to be a major factor in promoting atherosclerosis, it is now recognized that triglycerides are an independent risk factor. Atherosclerosis is characterized by the deposition of cholesterol from the plasma lipoproteins into the artery wall. In DM, prolonged elevated levels of VLDL, IDL, chylomicron remnants and LDL occur in the blood [11]. DM is reaching potentially epidemic proportions in India. The level of morbidity and mortality due to diabetes and its potential complications are enormous, and pose significant healthcare burdens on both families and society. Worryingly, diabetes is now being shown to be associated with a spectrum of complications and to be occurring at a relatively younger age. In India, the steady migration of people from rural to urban areas, the economic boom, and corresponding changes in lifestyle are all affecting the incident of diabetes. Yet despite the increase in diabetes there remains a paucity of studies investigating the precise status of the disease because of the geographical, socioeconomic, and ethnic nature of such a large and diverse country. Given the disease is now highly visible across all sections of society within India, there is now the demand for urgent research and intervention at regional and national levels to try to mitigate the potentially catastrophic increase in diabetes that is predicted for the upcoming years.

Materials and Methods

This prospective analytical study was carried out in the Department of Pharmacology at Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar from October 2019 to March 2020.

Inclusion criteria

Patients taking metformin in the doses of 1500 mg
Patients having HbA1c level between 7% to 10% along with FPG levels 126 mg/dl and / or 2hPG 200 mg/dl
Patients who has given the informed consent

Exclusion criteria: Patients with

- Acute complications of diabetes
- Hyperglycemic hyperosmolar state
- Diabetic ketoacidosis
- Renal or liver disease
- Congestive heart failure
- Acute coronary syndrome
- Pregnancy

Methodology

Total 100 patients were enrolled after screening for diabetes status with the help of HbA1C, FPG, PPPG. Detailed history taking, clinical examination and lab investigation including lipid profile (TC, TG, LDL, HDL) were done. Patients were given 500 mg metformin twice a day and 2.5 mg saxagliptin once a day. The patients were followed up at 1st, 3rd and 6th month. Lipid profile was repeated during each follow up.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages and means. Test applied for the analysis was paired t-test. The level confidence interval and p-value were set at 95% and 5%.

Result

Table 1: based on demographic parameter

Gender	N=100	%
Male	65	65
Female	35	35
Age		
Below 30	7	7
30-40	10	10
40-50	33	33
50-60	42	42
Above 60	8	8
Family History of diabetes		
Yes	72	72
No	28	8

Table 2: Changes in TC levels over a period of 6 months

Investigation	Duration (Month)	Saxagliptin (Mean ± SD)	Mean change
TC	0	199.10 ± 18.69	13.60± 17.71
	1	196.40 ± 22.20*	
	3	192.61 ± 19.56**	
	6	185.48 ± 16.79**	

Normal value: < 200mg/dl. * indicates p≤0.05

Table 3: Changes in TG levels over a period of 6 months

Investigation	Duration (Month)	Saxagliptin (Mean ± SD)	Mean change
TG	0	150.53 ± 12.66	10.63± 19.79
	1	147.26 ± 12.12**	
	3	140.40 ± 12.10**	
	6	139.90 ± 13.21**	

Normal value: <150 mg/dl. * indicates p≤0.05

Table 4: Changes in LDL levels over a period of 6 months

Investigation	Duration (Month)	Saxagliptin (Mean ± SD)	Mean change
LDL	0	103.69 ± 15.49	11.59± 17.29
	1	100.25± 15.31**	
	3	96.36 ± 13.65**	
	6	92.10 ± 13.32**	

Normal value: 60-130 mg/dl. * indicates p≤0.05

Table 5: Changes in HDL levels over a period of 6 months

Investigation	Duration (Month)	Saxagliptin (Mean ± SD)	Mean change
HDL	0	52.64 ± 5.31	2.24± 5.77
	1	52.89 ± 4.31	
	3	53.11 ± 4.21	
	6	54.88 ± 4.12*	

Normal value: 30-65 mg/dl. * indicates p≤0.05

Discussion

American Diabetic Association guidelines have recommended Metformin as first line drug to be used in type II Diabetes mellitus patients. If there is glycemic variability with Metformin, add-on drugs like Sulphonylureas, DPP-4 Inhibitors or other OHA's or insulin to be considered depending on the clinical scenario. It is well established that patients with type 2 diabetes mellitus (T2DM) are at increased risk of cardiovascular (CV) disease [12, 13]. Therefore, it is important to consider the effects of glucose-lowering medications not only on glycemic control, but also on cardiovascular risk [14, 15]. Saxagliptin belongs to dipeptidyl peptidase inhibitors which prevent deactivation of glucagon like peptide (GLP-1) and glucose dependent insulinotrpic polypeptide. Both GLP-1 and glucose dependent insulinotropic polypeptide are secreted from gut, they decrease glucose level by secreting insulin [16].

Lipid profile is a strong determinant of cardiovascular risk in T2DM. Current guidelines recommend an accurate control of hypercholesterolemia in order to reduce macrovascular complications. The fact that type 2 diabetic patients are more likely to be dyslipidemic than the general population is well known for decades. Lipid abnormalities associated with T2DM refer to high serum triglyceride levels, a high proportion of small dense low-density lipoprotein (LDL) particles, higher triglyceride-enriched, verylow-density lipoprotein (VLDL) particles, and lower protective high-density lipoprotein cholesterol (HDL) levels, together with glycation of apolipoproteins and increased LDL oxidation, all of which contribute to genesis of foam cell in atherosclerosis [17, 18]. According to Derosa *et al*, the addition of sitagliptin to existing hypoglycemic therapy might lead to a better and durable (over 7 years of therapy) improvement of lipid profile. This beneficial effect is supposed to be due to delayed gastric emptying [19].

Our study results elucidated that saxagliptin improve lipid status in T2DM patients, The mean TC levels before and

after treatment were found to be 199 .10 ± 18.69and 185.48 ± 16.79 respectively. There was a significant reduction was found from baseline to end of the treatment after 24 weeks the P value 0.05 at 0 vs 1, and ** p < 0.001 at 0 vs 3 and 0 vs 6 months on intra group comparison and mean change in TC from baseline at 24 weeks was 13.60± 17.71. The mean LDL levels before and after treatment was found to be 103.69 ± 15.49 and 92.10 ± 13.32 respectively. There was a significant reduction was found from baseline to end of the treatment after 24 weeks the p value P value< 0.001 at 0 vs 1, 0 vs 3 and 0 vs 6 months on intra group comparison and the mean change in LDL from baseline at 24 weeks was 11.59± 17.29. The mean triglycerides levels before and after treatment were found to be 150.53 ± 12.66and 139.90 ± 13.21 respectively. There was a significant reduction was found from baseline to end of the treatment after 24 weeks the p value P value 0.001 at 0 vs 1, 0 vs 3 and 0 vs 6 months on intra group comparison. Mean change in TG from baseline at 24 weeks was 10.63± 19.79.The result were correlated with other studied [20, 21]. Possible explanation for beneficial lipid effects of DPP4 inhibitors may be connected to its stimulating effect on the activated proteine-kinase pathway, which leads to increase in glucose and lipid catabolism [22]. On the other hand, HDL parameters were increased in our study, which is in correlation with the findings of Saad *et al*. [21]

Conclusion

The present analytical investigation concluded that Saxagliptin has shown an improvement in lipid profile (TC, TG, LDL, HDL) during 6 months of treatment in patients of type 2 DM. This study opens new vistas for future research.

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