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Original Research Article

A Randomized Comparative Interventional Study Assessing Improvement in Lipid Profile of the Patients with Saxagliptin as Add on Therapy in Patients of Uncontrolled Type 2 Diabetes Mellitus Who Were on Metformin Alone

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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to assess the improvement in lipid profile of the patients with saxagliptin as add on therapy in patients of uncontrolled type 2 DM who were on metformin alone.

Methods: It was a randomized, prospective, comparative, interventional study conducted in the Department of Pharmacology for 12 months. Total 50 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.

Results: Out of 50 patients, 22 were males and 28 were females. The mean age (± SD) in males and females was 60.46 yrs ± 6.94 and 56.94 yrs ± 5.75 respectively. Mean change in TC and TG from baseline at 24 weeks was 13.86% and 13.92% respectively. Mean change in LDL and HDL from baseline at 24 weeks was 14.47% and 2.05% respectively.

Conclusion: Saxagliptin has shown an improvement in lipid profile (TC, TG, LDL, HDL) during 6 months of treatment duration in patients of T2DM.

Keywords: Saxagliptin, Uncontrolled Type 2DM, Metformin, Lipid Profile.

Introduction

Patients with type 2 diabetes often require multiple antidiabetic agents to achieve and maintain glycemic control [1] because of the progressive nature of the disease. [2] Most patients receive traditional stepped-up therapy with metformin as the initial therapy, followed by the sequential addition of single oral antidiabetic drugs (OADs) as glycemic control worsens. [1] The number of antihyperglycemic agents has increased markedly, and the availability of multiple pharmacologic options is instrumental for treatment to target, which is a well-recognized strategy for the prevention of diabetes complications. Several guidelines recommend the use of dual or triple therapy based on glycated hemoglobin (HbA1c) levels, but clinical trial evidence defining the optimal use of available pharmacologic options, especially in dual or triple combinations, based on the degree of glycemic control is limited. [3-5]

Clinical inertia with substantial delay in advancing therapy despite inadequate glycemic control is a major barrier in clinical practice. [6] Adding or initiating a single therapy when HbA1c levels are substantially elevated may not achieve glycemic goals. Thus, exploring new and more proactive therapeutic approaches to get more patients to goal without the increased risk of hypoglycemia or weight gain is needed. Ectopic fat accumulation, including that of the liver, is related to increased insulin resistance.9 Weight loss results in a reduction in liver fat content. [7] Reducing liver fat content in addition to weight loss may therefore help prevent liver disease progression in patients with T2D. Saxagliptin increases the postprandial concentration of GLP-1 and potentiatesits action of

increasing glucose dependent insulin secretion and suppressing glucagon secretion. [8]

Saxagliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, also reduces HbA1c regardless of T2D stage, although with no clinically significant effects on body weight. [9] The fixed-dose combination of dapagliflozin and saxagliptin was approved by the United States Food and Drug Administration on February 28, 2017, for improving glycaemic control in adults with T2D as an adjunct to diet and exercise for those who have inadequate control with dapagliflozin or who are already being treated with dapagliflozin and saxagliptin. [10] Evidence from phase 3 studies of dapagliflozin plus saxagliptin indicates that weight loss observed with concomitant administration of dapagliflozin and saxagliptin is similar to that of dapagliflozin alone. [11,12]

DM is reaching potentially epidemic proportions in India. The morbidity and mortality associated with diabetes and its complications are enormous and pose significant healthcare burdens on both families and society. In India, the steady migration of people from rural to urban areas, the economic boom, and corresponding change in lifestyle are all affecting prevalence of diabetes. The aim of the present study was to assess the improvement in lipid profile of the patients with saxagliptin as add on therapy in patients of uncontrolled type 2 DM who were on metformin alone.

Materials and Methods

It was a randomized, prospective, comparative, interventional study conducted in the Department of Pharmacology, Netaji Subhas Medical College and Hospital,Amhara,Bihta,Patna, Bihar, India. Total 50 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 on each follow up.

Inclusion criteria: Patients aged between 18 to 80 years with T2DM, taking metformin in the dose of 1500 mg having HbA1c levels 7% to 10% along with FPG levels ≥ 126 mg/dl and / or 2hPG ≥ 200 mg/dl were included in the study.

Exclusion criteria: Patients with

1. Acute complications of diabetes.
a) Hyperglycemic hyperosmolar state.
b) Diabetic ketoacidosis.
2. Renal or liver disease.
3. Congestive heart failure.
4. Acute coronary syndrome.
5. Pregnancy

Statistical analysis: At the end of 6th month analysis was done using Microsoft excel version 2013.

Results

Table 1: Gender distribution

Gender	N (%)	Mean±SD
Male	22 (44)	60.46 yrs ± 6.94
Female	28 (56)	56.94 yrs ± 5.75
Total	50 (100)	

Out of 50 patients, 22 were males and 28 were females. The mean age (± SD) in males and females was 60.46 yrs ± 6.94 and 56.94 yrs ± 5.75 respectively.

Table 2: TC levels and TG levels over a period of 6 months

Investigation	Duration(Month)	(Mean± SD)
TC	0	198.72 ±19.88
	1	196.34 ±24.12
	3	192.88±22.58
	6	184.86±16.84
TG	0	152.74 ± 12.92
	1	147.43 ± 12.38
	3	142.28 ± 12.28
	6	138.82 ± 13.27

Mean change in TC and TG from baseline at 24 weeks was 13.86% and 13.92% respectively.

Table 3: LDL and HDL levels over a period of 6 months

Investigation	Duration(Month)	Saxagliptin(Mean±SD)
LDL	0	104.76 ±15.35
	1	98.12±15.40
	3	95.50±14.90
	6	91.29±13.6
HDL	0	53.37 ± 5.40
	1	52.28 ± 4.36
	3	52.86 ± 4.26
	6	55.42 ± 4.03

Mean change in LDL and HDL from baseline at 24 weeks was 14.47% and 2.05% respectively.

Discussion

In India 69.2 million people were living with diabetes (8.7%) as per the 2015 data. Of these, it remained undiagnosed in more than 36 million people. [13] 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 insulin resistance. Long-term complications of diabetes include hypertension and abnormalities of lipoprotein metabolism, which causes increased incidence of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease. [14] 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 arterial wall. In DM, prolonged elevated levels of VLDL, IDL, chylomicron remnants and LDL occur in the blood. [15]

Out of 50 patients, 22 were males and 28 were females. The mean age (± SD) in males and females was 60.46 yrs ± 6.94 and 56.94 yrs ± 5.75 respectively. Mean change in TC and TG from baseline at 24 weeks was 13.86% and 13.92% respectively. Mean change in LDL and HDL from baseline at 24 weeks was 14.47% and 2.05% respectively. It is well established that patients with type 2 diabetes mellitus (T2DM) are at increased risk of cardiovascular (CV) disease. [16] Therefore, it is important to consider the effects of glucose-lowering medications not only on glycemic control, but also on cardiovascular risk. [17,18] 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.

Elevated ectopic fat is a significant contributor to the pathogenesis of T2D. [19] Because liver fat correlates with increased mortality from liver disease, [20] the significant reduction in liver fat content observed in this sub study indicates that the combination of dapagliflozin plus saxagliptin added to metformin could help prevent the progression of liver disease in patients with T2D. Although the mechanisms by which liver fat reduction occurs with SGLT2 inhibition are not fully established, there are several possibilities. These include reduced hepatic lipogenesis, increased hepatic insulin extraction as seen with dapagliflozin, [21] improvements in insulin concentrations and/or resistance, and/or, as seen in some animal models, suppression of inflammatory cytokines and/or mitigation of oxidative stress. [22-24] Additionally, dapagliflozin's possible role as an alpha cell secretagogue that has been shown to promote glucagon secretion [25] is consistent with its ability to reduce intrahepatic lipid content.

Conclusion

Saxagliptin has shown an improvement in lipid profile (TC, TG, LDL, HDL) during 6 months of treatment duration in patients of T2DM.

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