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To Evaluate the Effectiveness of DPP4 Inhibitors in Relation to Blood Sugar and Lipid Profile

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Abstract

The purpose of study was to compare the glycemic parameters- Fasting Blood Sugar (FBS), Postprandial blood sugar (PPBS), and HbA1C in subjects with Type 2 Diabetes Mellitus taking DPP4 Inhibitors versus other OHA either used alone or in combination with other oral hypoglycemic agents (OHA).Methods: The subjects attending outdoor and indoor clinics of the Department of Medicine suffering from type 2 diabetes mellitus and satisfying the inclusion and exclusion criteria of study were included in the study. Results: Treatment with DPP-4 Inhibitors was associated with a better gylcemic control as compared to non DPP-4 inhibitors.Conclusion: DPP-4 inhibitors also had a positive effect on beta cell function and insulin resistance as depicted by higher C-peptide levels and HOMA-IR respectively.

Keywords: diabetes mellitus, hypoglycemic agents, C-peptide levels, insulin resistance.

Introduction

Diabetes mellitus as a disease has emerged as a major epidemic all over the world over more than last two decades with increasing prevalence and additional risk factors being added. Around 425 million people have diabetes in the world where over 7.79 crore cases of diabetes in India in 2019. Prevalence of diabetes in Indian adults is 11.8%. The identification of newer risk factors helped in delineating more the underlying etiopathology of the disease process. During this period our armamentarium has been enriched by newer class of drugs[1-3].

An important and interesting addition is the incretin class of drugs, especially DPP-4 inhibitors, which lower postprandial blood sugar by releasing insulin from the pancreas in response to the food in the second part of the duodenum and by preventing the rapid degeneration of incretin in early stage of diabetic patients who have enough pancreatic reserves. Although type 2 diabetes mellitus is characterized by marked insulin resistance but there is also progressive beta cell dysfunction and insulinopenia. It is interesting to observe the insulin effect and the incretin effect in subjects with reduced pancreatic reserves : It has also been observed that

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on adding DPP-4 inhibitors to metformin therapy was efficacious independent of insulin resistance stage, body mass index (BMI), and disease duration and duration of prior metformin use [4-10].

It has been observed that the hypoglycemic response of various class of drugs in Type II Diabetes mellitus is different. Some may respond expectedly while others may not show glycemic control with higher doses and combination of drugs while the others may have hypoglycemia even with the small doses. Our recent understanding of the heterogeneity of Type II Diabetes mellitus into various subtypes- Severe Insulin Deficient Diabetes, (SIDD), Insulin Resistant Obese Diabetes, (IROD), Combined Insulin Resistant and Deficient Diabetes, (CIRDD), Mild Age-Related Diabetes, (MARD) are likely to be responsible for these differences in the treatment outcomes. Hence it is rationale to differentiate between the insulinopenic and the non-insulinopenic groups amongst Type II Diabetics. Besides, the effect of DPPIV inhibitors on lipid profile and beta cell function are the pleotropic effect which are the additional effects which needs validation. This study assumes greater significance as it attempts to evaluate these aspect of DPPIV inhibitors.

Methods

Study Design

Study was conducted as a Cross sectional observational analysis and included 2 groups.

Group A included type 2 diabetes patients on DPP 4 inhibitors either alone or in combination.

Group B included type 2 diabetes patients on OHA other than DPP 4 inhibitors either alone or in combination.

Study Area

The study was conducted in Department of Internal Medicine, Shri Mahant Indiresh Hospital, Dehradun. It is situated in foothills of Himalayas, catering the population both from the hill areas and the plains of Uttarakhand and nearby states.

Study Population

The subjects attending outdoor and indoor clinics of the Department of Medicine suffering from type 2 diabetes mellitus and satisfying the inclusion and exclusion criteria of study were included in the study. The study included two groups : group A & B.

Group A included subjects taking DPP-4 inhibitors in addition to other oral hypoglycemic agents, it included 100 patients.

Group B were taken as control and included subjects with type 2 diabetes taking oral hypoglycemic agents but not DPP-4 inhibitors. In both the groups subjects taking insulin were not be included, which included 100 patients.

Study Duration

The study was conducted from December 2018 - May 2020.

Methods

Inclusion Criteria

1. Age more than 18 years.
2. Subjects with type 2 diabetes mellitus.
3. Subjects on DPP-4 inhibitors in group A.

Exclusion Criteria

1. Age less than 18 years.
2. Type 1 diabetes.
3. Secondary diabetes.
4. Gestational diabetes mellitus.
5. Congenital forms of diabetes.
6. Subjects on insulin.
7. Chronic kidney disease.

Methodology

The subjects so included were subjected to a detailed clinical history with special emphasis on duration of illness and treatment history and a thorough clinical examination was done in each case. The diagnosis of Diabetes was based on ADA guidelines (2019). A informed consent was taken in all cases included in the study. The subjects on DPP-4 inhibitors for atleast 3 months(180 days) prior to the study were included. The subjects included in the study continued to be treated by the respected medical consultants and were investigated as per the protocol, however

FBPS, PPBS, HbA1c, F.Insulin, C-peptide levels & lipid profile done in each case. C-peptide levels and insulin resistance were correlated with FBS, PPBS, HbA1c and lipid profile. The results so obtained were analyzed using suitable statistical methods.

These subjects were categorized in 2 groups:

Group A included subjects taking DPP-4 inhibitors in addition to other oral hypoglycemic agents, it included 100 patients.

Group B were taken as control and included subjects with type 2 diabetes taking oral hypoglycemic agents but not DPP-4 inhibitors. In both the groups subjects taking insulin were not be included.

Results

Baseline characteristics of group A (DPP-4 Inhibitor)

Variable	mean±sd
Age	59.47±12.02
Duration of diabetes	9.06±4.74
T.Cholesterol	211.61±66.69
BMI(kg/m2)	23.97±1.59
WHR	0.86±0.04
FBS (mg/dl)	146.53±31.74
PPBS (mg/dl)	193.08±45.87
HbA1C	8.43±1.05
Fasting Insulin (uU/L)	6.11±3.15
HOMA-IR	2.20±1.30
Fasting C-Peptide (mg/dl)	4.79±1.65

Baseline characteristics of group B (non DPP-4 Inhibitor)

Variable	mean±sd
Age	61.44±10.39
Duration of diabetes	8.82±4.56
T.Cholesterol	278.60±59.58
BMI(kg/m2)	24.66±1.49
WHR	0.86±0.02
FBS (mg/dl)	120.61±25.65
PPBS (mg/dl)	220.32±49.44
HbA1C	8.16±1.20
Fasting Insulin (uU/L)	5.85±2.69
HOMA-IR	1.74±1.41
Fasting C-Peptide (mg/dl)	3.56±1.94

Number of study participant in age group 35-45 are 15% in group A and 5% in group B, in 46-55yr 24% in group A and 30% in group B, In 56-65yr 26% in group A and 32% in group B, in 66-75yr 27% in group A and 22% in group B, In >75yr 8% in group A and 11% in group B.

Males in study participants in 44% in group A & 52% in group B & Female 56% in group A and 48% in group B.

Mean c-peptide levels for group A is 7.05 and 6.28 in group B in first 4 years

Mean c-peptide levels during 4-8 years of DM were 4.82 & 3.53 in group A&B respectively

Mean c-peptide levels during 8-12 years of DM were 3.74 & 2.84 in group A&B respectively

Mean c-peptide levels during 12-16 years of DM were 3.59 & 2.64 in group A&B respectively

Mean c-peptide levels during 16-20 years of DM were 2.92&1.91 in group A and B

Mean c-peptide levels >20years duration were 1.89&0.94 in group A and B.

The results were found to be significant in patients with diabetes duration of more than 4 years.

FBS was found to be higher in Group A as compared to group B,

PPBS was found to be higher in group B as compared to group A

HbA1C was found to be higher in group A as compared to group B.

All 3 findings were found to be statistically significant.

Fasting insulin and HOMA-IR were found to be higher in group A as compared to group B and the difference was found to be statistically significant.

Fasting C-peptide levels are higher in group A as compared to group B and this difference was found to be statistically significant.

BMI was found to be significantly lower in group A as compared to group B and this difference was found to be statistically significant. For WHR no significant difference was found in neither of the two groups.

Total cholesterol was found to be lower in group A

as compared to group B and the result was found to be statistically significant

No significant difference in glycemic and non glycemic parameters were seen in all 3 members of DPP-4 inhibitors

Discussion

The study was conducted in the Department of Medicine at Shri Gruru Ram Rai Institute Of Medical And Health Sciences, Dehradun and was planned as a cross sectional observational study with the aim to evaluate the effectiveness of DPP-4 Inhibitors with relation to C-peptide and Insulin resistance.

It included consecutive type 2 diabetic subjects attending the inpatient and outpatient department of the institute and were included only if they satisfied the inclusion and exclusion criteria of study. These subjects were categorized into 2 groups- Group A & Group B. Group A included subjects who were on either DPP-4 inhibitor alone or in a combination whereas group B included the subjects not on DPP-4 inhibitor. Both groups were carefully matched for age, sex and duration of illness (table 1-4).

The effectiveness of DPP4 inhibitors was evaluated in terms of various glycemic and non-glycemic parameters. The glycemic parameters in the study included FBS, PPBS and HbA1c whereas the non glycemic parameters included lipid profile and anthropometry. For this study the patients were stabilized with the drugs for a minimum period of 3 months.

Type 2 diabetes mellitus is a heterogeneous group comprising of predominantly insulinopenia, predominant insulin resistance, combination of both or age related deterioration of beta cell function (4,5,6). It is further observed that at the time of diagnosis of Type 2 Diabetes Mellitus as a heterogeneous group majority of beta cell mass (and functions) are already lost (118), however the preservation of the function and mass is significant in a sub group with insulin resistance, or a combination of insulinopenia or insulin resistance, hence this would have a significant bearing on the management of the disease.

The glycemic parameters were compared in the two groups and there was significant difference observed in FBS, PPBS and HbA1c in these groups where DPP-4 inhibitors were found to be more potent in reducing PPBS as compared to non-DPP-4 group. As far as the glycemic control is concerned, the other contemporary group of drugs have a similar glucose lowering effect. Rather the non-sulfur containing sulphonylureas are more potent in terms of reducing glycemic status. However in the present study the number of drugs in either group is not compared. It has been observed that DPP4 inhibitors reduce HbA1C by 0.8- 1.4% (depend on type of DPP 4 inhibitor used). A study by Dror Dicker *et al* observed that the treatment with saxagliptin showed an average decrease in HbA1C levels of 0.43-1.17% whereas treatment with vildagliptin showed an average decrease in HbA1C levels of 1.4% after 24 weeks as monotherapy in a subgroup of patients with no prior oral treatment and after a short period of time from the diagnosis of diabetes. But secretagogues are more potent glucose lowering agents whereas SGLT- 2 inhibitors have also almost similar HbA1C lowering effect. In a meta-analysis that included information regarding treatment of type 2 diabetes with sitagliptin and vildagliptin for ≥12 weeks compared with placebo and other oral antidiabetic drugs, Amori et al. showed a reduction of 0.74% in HbA_{1c} levels. The result proved DPP-4 inhibitors were only slightly less effective than sulfonylureas and as effective as metformin and thiazolidinediones in regard to reducing blood glucose. In studies with combination therapy of DPP-4 inhibitors and metformin in one pill, the results were even better because of two possible causes. First, metformin has an upregulating effect on the level of glucagon like peptide 1 (GLP-1), and therefore it enhances the incretin effect of the DPP-4 inhibitors. A second possible explanation for the improved results in the combined drug is the improved compliance of patients when taking one oral drug instead of two[136].

These observations also implies that DPP-4 inhibitors are non inferior to other classes with regards to lowering blood sugar levels (glycemic parameters). Further the degree of glucose lowering by these agents also depends upon the nature of type 2 diabetes mellitus - insulinopenic predominant, insulin resistance predominant, combination of both or mild adult onset type. Our recent understanding of the heterogeneity of Type II Diabetes mellitus into various subtypes- Severe Insulin Deficient Diabetes, SIDD, Insulin Resistant Obese Diabetes, IROD, Combined Insulin Resistant and Deficient Diabetes, CIRDD, Mild Age-Related Diabetes, MARD are likely to be responsible for these differences in the treatment outcomes. Hence it is rationale to

differentiate between the insulinopenic and the non-insulinopenic groups amongst Type II Diabetics. It would also depend upon the mean duration of illness. Despite these intra-group variations, the adjustment of various OHAs have been made in both the groups to maintain HbA1c in a reasonably achievable range.

Conclusion

In conclusion, the results of this study suggest

1. Treatment with DPP-4 Inhibitors was associated with a better gylcemic control as compared to non DPP-4 inhibitors.
2. DPP-4 inhibitors also had a positive effect on beta cell function and insulin resistance as depicted by higher C-peptide levels and HOMA-IR respectively.
3. DPP-4 inhibitors are also associated with a significant reduction in Total Cholesterol levels but were found to be weight neutral.

Ethical clearance- Taken from ethical committee of institution

Source of funding - Self

Conflict of Interest – Nil

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