ORIGINAL RESEARCH PAPER

Diabetology

KEY WORDS:

NON INFERIORITY STUDY AND ANTI INFLAMMATORY EFFECT OF DPP-4 INHIBITORS IN TREATMENT NAÏVE TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRACT

CONTEXT AND OBJECTIVES: The optimal management of hyperglycemia in type 2 diabetes patients remains an elusive goal. The combination therapy with DPP-4 inhibitor plus other OAD's is an attractive combination, getting more patients to goal initially and avoiding or delaying the need for subsequent treatment regimen changes to maintain glycemic goals. The pattern of response of DPP 4 inhibitors for glycemic end points and their tolerability is variable in Indian population unlike that in other parts of world due to unique "Asian Indian Phenotype". In this study, we evaluated the efficacy and tolerability of combination DPP-4 inhibitor therapy in patients inadequately controlled with metformin monotherapy in Indian patients with type 2 diabetes mellitus. The effect of DPP4 inhibitors in amelioration of the inflammatory process was also studied by measurement of markers such as plasma C-reactive protein (CRP) and TNFα, thus reflecting the improvement in end effects of chronic inflammation.

METHODS: This is an analysis of Indian patients who participated in 24 week, open labelled, randomized controlled trial. Overall, 30 treatment naive type 2 diabetes patients were randomized to one of treatment regimens (Linagliptin 5 mg once daily [qd] + metformin 500/1000 mg [n = 15] or Other OAD + metformin 500/1000 mg [n = 15] and assessed at 12 and 24 wks.

RESULTS: As regards efficacy, DPP-4 inhibitor along with Metformin reduced fasting, postprandial plasma glucose and HbA1c as that with other oral antidiabetic drugs (Glimeperide, Gliclazide and Pioglitazone) at 12 and 24 weeks. The treatment with DPP-4 inhibitor was well tolerated without any specific adverse effects. In addition, there was reduction in systemic inflammatory markers with DPP-4 inhibitors which was not noted with other oral antidiabetic drugs.

CONCLUSIONS: The DPP-4 inhibitors along with Metformin reduced fasting, postprandial glucose, HbA1c to a similar degree without any adverse effects. Statistically significant reductions were obtained across wide range of T2DM patient subgroups irrespective of baseline characteristics or β-cell function indices such as the homoeostatic model assessment (HOMA)-β. The reduction of systemic inflammatory markers in type 2 diabetic patients' independent of glycemic control suggest potential role of DPP-4 inhibitors in cardiovascular protection.

INTRODUCTION

Impaired insulin secretion and insulin resistance are the core defects in type 2 diabetes and are present long before the onset of frank diabetes. It is known that both the level and the duration of hyperglycemia in type 2 diabetes are closely related to the risk of developing diabetic complications (1). Therefore, achieving glycemic control is a prerequisite for prevention of cardiovascular and microvascular complications in type 2 diabetes.

The optimal management of hyperglycemia in patients with type 2 diabetes remains an elusive goal. Lifestyle interventions, including dietary adjustments and increased physical activity, are cornerstones of therapy. For most patients, pharmacological intervention is required and present guidelines suggest metformin to be a first line treatment (2). Metformin reduces glycemic levels primarily by inhibiting hepatic glucose output (3, 4, 5) and improves insulin sensitivity in liver and muscle (6). Due to the progressive nature of the disease, patients may require additional agents to maintain glycemic control over time. Most often, sulphonylureas are added (2, 7). The rationale for this combination is that sulphonylureas stimulate insulin secretion. Other combinations with metformin include thiazolidinediones and insulin (8, 9, 10, 11, 12). However, the combinations with sulphonylureas and thiazolidinediones have faced problems, in that sulphonylureas increase the risk of hypoglycemia (13, 14) and thiazolidinediones result in weight gain and potential problems of cardiovascular adverse events. The GLP-1 based therapy by activating the GLP-1 receptors by exenatide or liraglutide or by preventing the inactivation of endogenous GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) has been found to be successful in combination with metformin (15, 16, 17, 18).

Furthermore, DPP-4 inhibition improves islet function by stimulating insulin secretion, by improving the glucose sensitivity of the beta cells, and by inhibiting glucagon secretion from the alpha cells (19, 20). This reduces both fasting and prandial glucose which reduces HbA1c levels.

The diabetes also causes a low-grade persistent inflammation which is mediated by cytokines like TNF-α, endoplasmic reticulum (ER) stress and is identifiable by markers such as CRP and IL-10. Activation of inflammatory pathways leads to activation of serine/threonine kinases such as JNK, which suppresses insulin signalling on one hand, and activates pro-inflammatory proteins such as activator protein-1 (AP-1) on the other. Another kinase activated is IKK, or inhibitor of NFkB kinase, that leads to activation of NFkB. Both AP-1 and NFkB induce transcription of several proinflammatory genes. SOCS3 is another signaling protein, which interferes with insulin signalling at the IRS-1 level, and the expression of which is increased by TNF-α (21). There is now a reasonable data to suggest that incretin-based therapeutic agents have an anti-inflammatory effect besides their ability to regulate blood glucose, which may provide additional benefits in the treatment of T2DM.

The amelioration in the inflammatory processes can be judged by improvement in levels of markers such as plasma C-reactive protein (CRP), TNF-α and IL-10 or changes in generation of ROS and in tissue expressions of proinflammatory factors such as NFkB, JNK, and SOCS-3. The clinical benefits likely to be obtained from these changes should reflect in improvement in end effects of chronic inflammation.

MATERIALS AND METHODS

Study design and patient selection

This is an analysis of Indian patients who participated in 24-week, open labelled, randomized controlled trial. The study protocol was approved by the local institutional ethics committee. Overall, 30 treatment naive type 2 diabetes

patients were enrolled after a 4-week run-in period wherein all patients received Metformin and were later randomized to one of treatment regimens (Linagliptin 5 mg once daily [qd] + metformin 500/1000 mg [*n* = 15] or other OAD + metformin 500/1000 mg [*n* = 15] and assessed at 12 and 24 wks. The inclusion criteria of study participants were treatment naïve type 2 diabetes patients aged 30–60 years with HbA1C of 7–9% and free of serious concurrent medical conditions and exclusion criteria included type 1 diabetes patients or diabetic gastroparesis or significant renal impairment (estimated creatinine clearance 60 ml/min).

Study endpoints and safety measurements

Primary efficacy endpoint

The efficacy and tolerability of combination DPP-4 inhibitor therapy in patients inadequately controlled with metformin monotherapy.

Secondary endpoints

To assess the combined estimation of insulin secretion and insulin sensitivity and assessment of change in inflammatory markers with treatment.

Statistical analysis

Insulin sensitivity and β-cell function was assessed using a mathematical model for Homeostasis Assessment Model (HOMA β) using unpaired t test and statistical analysis was done using statistical software SPSS (Version 16).

RESULTS

Patient disposition, demographics and clinical characteristics

The mean age of cases group was 49.93 yrs while it was 53.47 yrs for controls. Both the cases and controls included in the study were either normal in weight or were mild to moderately obese and had comparable waist to hip ratios. The mean fasting plasma glucose in cases and controls at baseline was 193 and 175 mg/dl and mean post prandial glucose values were 323 and 293 mg/dl which were comparable between both the groups (p value 0.373 for fasting and 0.288 for postprandial glucose values). The baseline demographics and clinical characteristics of the study population are presented in Table 1.

Table 1.

Characteristics	Cases	Controls	p-value
Age	49.93±6.99	53.47±6.33	0.158
WHR	0.99±0.07	0.98±0.04	0.555
S Creatinine	1.0407±0.34	1.1567±0.20	0.273
HDL Cholesterol	37.00±6.57	34.93±7.06	0.414
Triglycerides	191.53±56.98	169.60±45.67	0.255
Fasting Glucose (mg/dl)	193.60±59.13	175.80±47.91	0.373
PP Glucose	323.93±72.87	293.93±78.58	0.288
HbA1C	8.72±1.10	8.14±0.82	0.114
Insulin	2.19±1.50	2.04±0.66	0.111
C Peptide	0.45±0.12	0.45±0.09	0.985
hs CRP	4878.1±2810.59	6186.2±1387.62	0.117

Efficacy and tolerability parameters:

Both groups achieved a similar degree of glycemic control at 12 weeks and 24 weeks, and there was no statistical significant difference between both groups (p value of 0.834 at 12 weeks and 0.710 at 24 weeks for fasting glucose and 0.959 at 12 weeks and 0.943 at 24 weeks for postprandial glucose). All active treatments in both groups produced statistically significant ($P < 0.001$) changes in fasting and postprandial glucose levels from baseline at week 12 and 24 and a similar effect was seen in HbA1c in both groups. Our study showed that DPP-4 inhibitors along with Metformin reduced fasting plasma glucose and postprandial glucose levels, HbA1c to a similar degree and a tolerability profile that did not differ from that of placebo/other oral antidiabetic drugs. These clinically relevant reductions in fasting plasma and postprandial glucose, HbA1c were obtained with DPP-4 inhibitors across a wide range of T2DM patient subgroups irrespective of baseline characteristics or β-cell function indices such as the homoeostatic model assessment (HOMA)-β. In general, the treatment with DPP-4 inhibitors was well tolerated and incidence of any specific AE was low (most common being urinary tract infections, arthralgia and nasopharyngitis) and no increased incidence of hypoglycemic events. The use of DPP-4 inhibitors compared to sulfonylureas as second line therapy added onto patients inadequately controlled on metformin therapy, provided non-inferiority data for use of DPP-4 inhibitors as regards glycemic control.

β cell effects with a combination of DPP4 inhibitors and Metformin

Our study showed that along with the reduction in fasting, prandial glycemia and HbA1C values, the mean fasting plasma insulin levels which were comparable in both cases and controls at baseline (p value 0.111) increased significantly in cases in comparison to controls (p value <0.001). Similar effect was seen in mean fasting plasma C-peptide, being comparable at baseline increased to significant higher values at 24 weeks in cases in comparison to controls (p value 0.007). This shows that the combination of DPP-4 inhibitors with metformin improves beta cell function. HOMA-β for assessment of β cell function also increased significantly in cases in comparison to controls (p value 0.004).

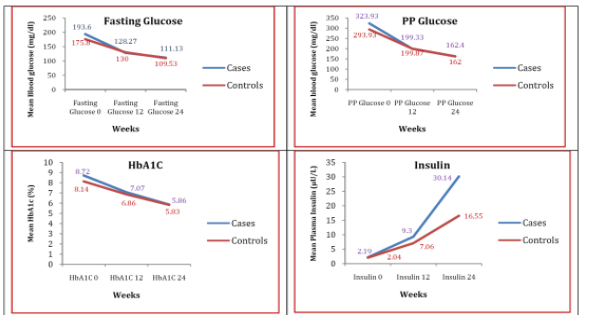
Effect of DPP4 inhibitors and Metformin on inflammatory markers

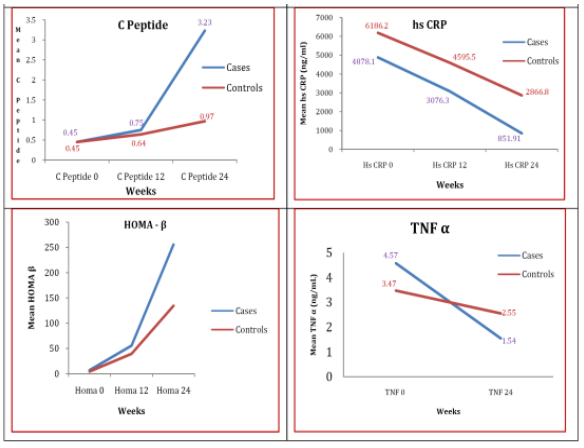
The effect of DPP4 inhibitors in amelioration of the inflammatory process was also studied by measurement of markers such as plasma C-reactive protein (CRP) and TNFα, thus reflecting the improvement in end effects of chronic inflammation.

hs CRP decreased significantly in cases as compared to controls, at 12 weeks (p value 0.052) and 24 weeks (p value 0.001). hs CRP was not found to correlate with fasting or postprandial plasma glucose, fasting insulin or C-peptide levels or HOMA which showed that this decrease in inflammatory markers was independent of glycemic control, an effect likely caused per se by DPP4 inhibitors.

TNF-α also decreased significantly in cases as compared to controls, at 24 weeks (p value 0.038). TNF-α was also not found to correlate with fasting or postprandial plasma glucose, fasting insulin or C-peptide levels or HOMA but correlated with hs CRP, showing that both inflammatory markers decreased significantly with DPP 4 inhibitors independent of the glycemic control. The decrease in the inflammatory markers may have long term implications in form of improvement in end effects of chronic inflammation and hence decreasing the chronic complications of diabetes.

Comparison of Glycemic Control, β cell function and Inflammatory Markers during the Study





DISCUSSION

The current diabetes management guidelines recommend using combination therapy with metformin in patients who present with an HbA1c >7.5% or who do not reach their target HbA1c with metformin monotherapy. Initial combination with metformin plus a sulfonylurea is a common therapy in Indian patients. However, this combination suffers from certain drawbacks such as an increased risk of hypoglycemia, weight gain, and potential cardiovascular disease.

The use of DPP-4 inhibitors compared to sulfonylureas as second line therapy added onto patients inadequately controlled on metformin therapy, provided non-inferiority data for use of DPP-4 inhibitors as regards glycemic control. DPP-4 inhibitors along with Metformin reduced fasting plasma glucose and postprandial glucose levels, HbA1c to a similar degree and a tolerability profile that did not differ from that of placebo / other oral antidiabetic drugs. These findings are compatible with the known clinical effect of DPP-4 inhibitors to reduce fasting as well as postprandial glucose (22, 23, 24, 25) and improvement in islet function. The clinically relevant reductions in fasting plasma and postprandial glucose, HbA1c were obtained with DPP-4 inhibitors across a wide range of T2DM patient subgroups irrespective of baseline characteristics or β-cell function indices such as the homoeostatic model assessment (HOMA)-β.

The DPP-4 inhibitors (Linagliptin) treatment is associated with reduction of systemic inflammatory markers in type 2 diabetic patients' independent of glycemic control which may later reflect improvement in end effects of chronic inflammation and a potential for cardiovascular protection and anti-atherosclerotic action. Our study is in confirmation with other previous studies which showed that that incretin-based therapeutic agent have an anti-inflammatory effect besides their ability to regulate blood glucose. (21).

The main limitation of this analysis is that the number of patients per arm is not sufficient to test for a statistical comparison with the overall population.

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