Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
©Scholars Academic and Scientific Publisher
A Unit of Scholars Academic and Scientific Society, India
www.saspublisher.com

ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

Diabetology

Comparative Study to Evaluate Effect of Hydroxychloroquine Versus Sitagliptin as Add on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Combination with Metformin and Gliclazide: A Multicenter, Observational Trial

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Original Research Article

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Article History
Received: 08.05.2018
Accepted: 21.05.2018
Published: 30.05.2018

DOI:
10.21276/sjams.2018.6.5.54

Abstract: Hydroxychloroquine as an add on treatment improves glycemic profile in type 2 diabetes mellitus (T2DM) patients who were inadequately control on Metformin and Gliclazide. This 24 week multicentre observational trial compared the efficacy and safety of Hydroxychloroquine and sitagliptin in patients whose glycaemia was inadequately controlled with metformin and gliclazide. Uncontrolled adult 300 T2DM patients with glycated haemoglobin (HbA1c) 7 - 8% on fixed dose of 500 mg Metformin and 80 mg Gliclazide. This patients were randomised 1:1 to add on Hydroxychloroquine 400 mg or Sitagliptin 100 mg for 24 week. The primary efficacy analysis was a comparison of the change from baseline HbA1c, Fasting Plasma Glucose (FPG) and Post Prandial Plasma Glucose (PPG) at week 24(P = 0.001). At 24 weeks, there was a statistically significant difference in the mean HbA1c reduction in hydroxychloroquine group (0.92%) as compared to sitagliptin group (0.80%) (P = 0.001). Mean reduction in Fasting Plasma Glucose (FPG) and Post prandial Plasma Glucose (PPG) was also statistically significant in the hydroxychloroquine group as compared to the sitagliptin group (P = 0.008). There was no significant difference in terms of change in BMI (0.07 ± 0.39 kg/m2 vs. 0.08 ± 0.31 kg/m2) in hydroxychloroquine and sitagliptin groups, respectively (P = 0.644). The incidences of hypoglycemic events were also less in both the groups. In T2DM patients on hydroxychloroquine + metformin + gliclazide combination exhibited significant reduction in glycemic parameters as compared to sitagliptin + metformin + gliclazide combination. Moreover, there was no significant difference between both the groups in terms of change in BMI and incidence of hypoglycemia. Hydroxychloroquine is a potent antidiabetic and can be safely used in uncontrolled T2DM patients in place of sitagliptin.

Keywords: Hydroxychloroquine, Fasting Plasma Glucose, HbA1c, PPG, FPGsitagliptin.

INTRODUCTION

Diabetes mellitus is a prime public health problem and forthcoming epidemic all over the globe [1] and this metabolic disorder caused due to insufficient or ineffective insulin. In India, there were approximately 40 million people suffering from diabetes and this number possibly will rise up to 300 million by 2025 [2]. According to International Diabetes Federation record, worldwide the number of people with diabetes will be increase from current figure of 240 million to 380 million over the next 20 years and up to 642 million by 2040 [3].

Good glycemic control is considered to be one of the cornerstones in the management of type 2 diabetes. In addition to lifestyle modification, most patients need pharmacological treatment, and most international guidelines recommend metformin as first-line therapy. According to statements by the American Diabetes Association/European Association for the Study of Diabetes and the American Association of Clinical Endocrinologists/American College of Endocrinology, metformin is recommended (unless specifically contraindicated) as a first-line agent for monotherapy and combination therapy for patients with type 2 diabetes mellitus (T2DM) [4-6]. However, many patients, particularly those with higher baseline

glycated haemoglobin (HbA1c) values, may not achieve their glycaemic goals on metformin monotherapy and sulfonylurea (SU) was added as 2nd line treatment along with metformin in India. Gliclazide is one of the most commonly prescribed SU. Sulfonylureas like gliclazide offer effective glycemic control with good tolerability [8].

Among several new treatments introduced over the past few years, the new class of oral "incretin" drugs known as DPP-4 inhibitors is the most notable. DDP-4 inhibitors reduce the blood glucose level by inactivating DPP-4, an enzyme that metabolizes glucagon-like peptide-1 (GLP-1), which is a gastrointestinal hormone that augments insulin release in response to a rise of blood glucose [7]. Sitagliptin is an oral, highly-selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus that has been shown to provide significant improvements in key glycemic parameters relative to placebo, and to be generally well tolerated, when used as monotherapy or in combination with other OHAs [14].

Hydroxychloroquine (HCQ) improve glucose tolerance and insulin sensitivity by inhibition of insulin degradation. It slows breakdown of the internalized insulin-receptor complex and a study in obese, non-diabetic individuals reported a significant increase in insulin sensitivity index and trends toward reduced insulin resistance and insulin secretion [10]. An Indian randomized controlled trials showed that HCQ lowers HbA1c and LDL cholesterol levels in patients with type 2 diabetes [11].

In a recent Indian clinical trial [12], HCQ was evaluated against one of the DPP4i teneligliptin and it has observed that HCQ significantly reduced HbA1c, FPG and PPG as compare to teneligliptin based treatment. Moreover 61% patients has achieve HbA1c >7%. In an another Indian trial [13], it has seen that that hydroxychloroquine 400 mg can be an effective alternative to DPP-4 inhibitor like vildagliptin for add on therapy to the patients who are inadequately controlled with metformin and glimepiride combination therapy.

In this trial we try to evaluate efficacy and safety of Hydroxychloroquine in combination with metformin and Gliclazide compared with sitagliptin in combination with metformin and Gliclazide among adult patients with type 2 diabetes mellitus.

METHODS

Uncontrolled adult 384 T2DM patients with glycated haemoglobin (HbA1c) 7 - 8% on fixed dose of 500 mg Metformin and 80 mg Gliclazide were initially selected for this observational clinical trial. Among them 310 uncontrolled T2DM patients were included who are on fixed dose combination of Metformin and Gliclazide for at least 12 weeks. This patients were randomised 1:1 to add on Hydroxychloroquine 400 mg or Sitagliptin 100 mg for 24 week. The primary efficacy analysis was a comparison of the change from baseline HbA1c, Fasting Plasma Glucose (FPG) and Post Prandial Plasma Glucose (PPG) at week 24.

Inclusion criteria

- Uncontrolled adult T2DM patients with glycated haemoglobin (HbA1c) 7 - 8% on fixed dose of 500 mg Metformin and 80 mg Gliclazide.
- Body weight: ≥ 60 kg
- Willing to give informed consent for the study.

Exclusion criteria

- Subjects with a history of retinopathy. Subjects with uncorrected visual acuity <20/100, abnormal visual fields, difficulty examining the optic disc, or evidence of retinal pigment, epithelial abnormalities and history or risk of macular edema.
- History or risk of psoriasis, rash, scaling or scaling eczema, porphyria, recent cardiovascular events, active gastrointestinal or haematological disorders, diabetic ketoacidosis & Subjects with G6PD deficiency
- Pregnant or lactating women

Monitoring for adverse experiences, physical examinations, vital signs, body weight, ECG, laboratory measurements comprising routine hematology, serum chemistry and urinalysis were performed. Adverse experiences of special interest included hypoglycemia.

This study was conducted in accordance with the good clinical practice guidelines and with the Helsinki Declaration principles. Individual ethical committee approval was obtain prior to the trial. Also prior to conduct of study related procedure/investigation, a voluntary written informed consent was taken from the patient /legally acceptable representative.

The qualitative data were expressed in percentages and quantitative data were expressed as mean ± standard deviation. Student's t test and Chi-Square test were used to determine statistical difference between variables. Statistical software (Graph Pad Prism5; version 5.01) was used for analysis. Statistical tests were considered significant if P-value was <0.05 at confidence interval of 95%.

RESULTS

Baseline of the 384 T2DM participants screened, 74 were excluded from the study. Of the 310 randomized participants, 300 completed the 24 week study (150 in hydroxychloroquine group and 150 in sitagliptin group) and 10 participants were either dropouts or lost to follow up. Complete disposition of study participants is given in Figure-1.

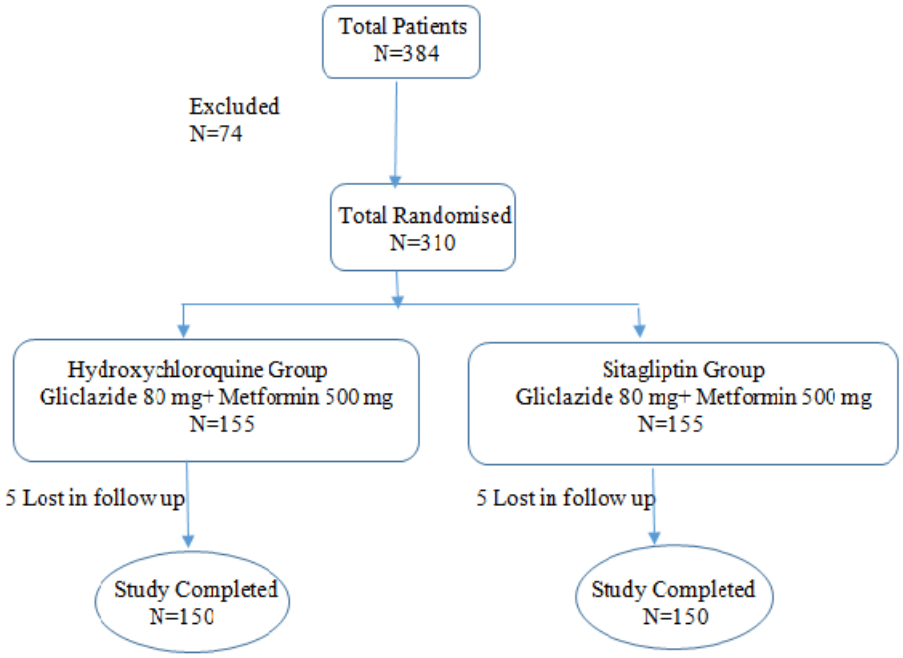

Fig-1: Disposition of study participants

The baseline blood glucose parameters including HbA1c, FPG, and PPG were similar in both the groups. Other baseline parameters such as body weight, BMI, duration of T2DM were comparable in both groups. The demographic and baseline characteristics are summarized in Table 1. Out of the total evaluable study population, 69% patients are male in HCQ group and 76% patients are male in sitagliptin group.

The addition of hydroxychloroquine or sitagliptin, to metformin and gliclazide did not cause the occurrence of AEs. The occurrence of hypoglycemic events was shown to be comparable among the groups.

Table-1: Baseline demographic and anthropometric characteristics of patients

Characteristics	HCQ + Metformin+SU N = 150	Sitagliptin + Metformin+SU N=150
Age, years	60±11	60±9
Male, n (%)	104 (69.3%)	115 (76.6%)
Body Weight, kg	64.05±9.68	64.72±9.65
BMI, kg/m2	24.64±2.99	24.34±2.64
Duration of T2DM, years	7.4±5.5	7.4±5.3
HbA1c, %	7.76±0.4	7.77±0.4
FPG	142.01±19.27	142.55±20.88
2-hour PPG	261.21±29.82	262.38±31.26

Abbreviation: BMI, body mass index. Values are mean ± standard deviation.

At 24 weeks, both treatment groups exhibited an improvement in HbA1c from baseline, which was statistically significant (Student's t test, P = 0.001). However, the mean reduction in HbA1c from baseline in the hydroxychloroquine group was significantly more as compared to the sitagliptin group (0.92±0.33% vs. 0.80± 0.36% respectively, Student's t test P = 0.001). The mean reduction in FPG (−24.41±13.21 mg/dl) and PPG (−51.01±21.88 mg/dl) from baseline up to 24 weeks was statistically significant in the hydroxychloroquine group, P = 0.001. The sitagliptin group also resulted in a statistically significant reduction in FPG (−17.01±21.88 mg/dl) and PPG (−46.09±28.22 mg/dl) from baseline up to 24 weeks, P = 0.001. However, the mean reduction in FPG (24.41 vs. 17.01 mg/dl) and PPG (51.01 vs. 46.09 mg/dl) was significantly more in the HCQ group as compared to sitagliptin group, respectively, P = 0.008. The efficacy parameters from baseline to end of study are depicted in Table 2.

Table-2: Change from baseline to end of study

Parameters	HCQ Group			Sitagliptin Group			P (between group difference)
	Baseline	End of study	Mean difference	Baseline	End of study	Mean difference	
Body weight (kg)	64.05±9.68	64.20±9.58	-0.15±0.97	64.72±9.65	64.94±9.57	-0.22±0.82	0.53
BMI (kg/m2)	24.64±2.99	24.71±3.03	-0.07±0.39	24.34±2.64	24.42±2.61	-0.08±0.31	0.644
HbA1c (%)	7.76±0.4	6.84±0.38	-0.92±0.33	7.77±0.4	6.97±0.39	-0.80± 0.36	0.001
FPG (mg/dl)	142.01±19.27	117.6± 11.23	−24.41±13.21	142.55±20.88	125.54±12.85	−17.01±21.88	0.008
PPG (mg/dl)	261.21±29.82	210.2±16.79	−51.01±21.88	262.38±31.26	216.29±19.94	−46.09±28.22	0.008

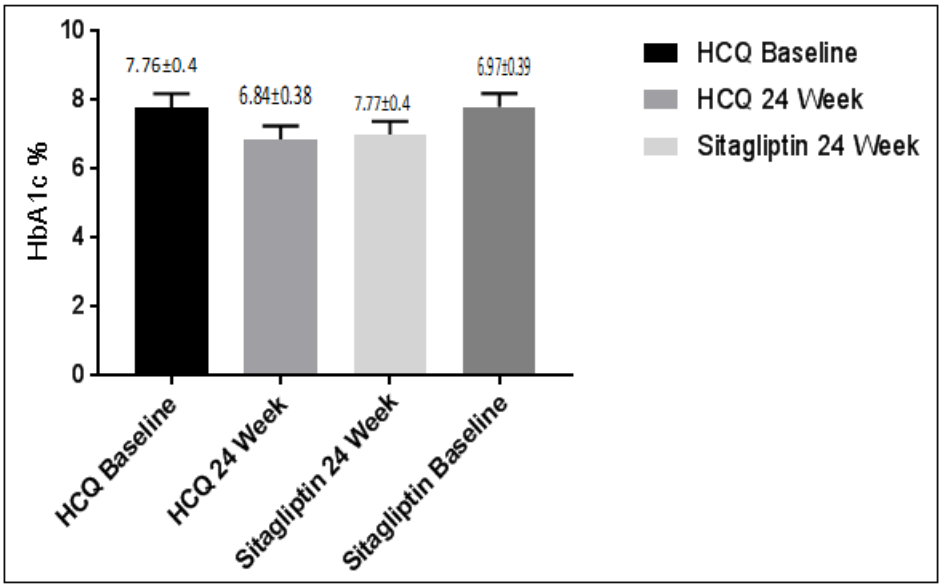

Fig-1: Comparison of Glycated Haemoglobin (HbA1c) from baseline to 6th month of the treatment (Mean±SD)

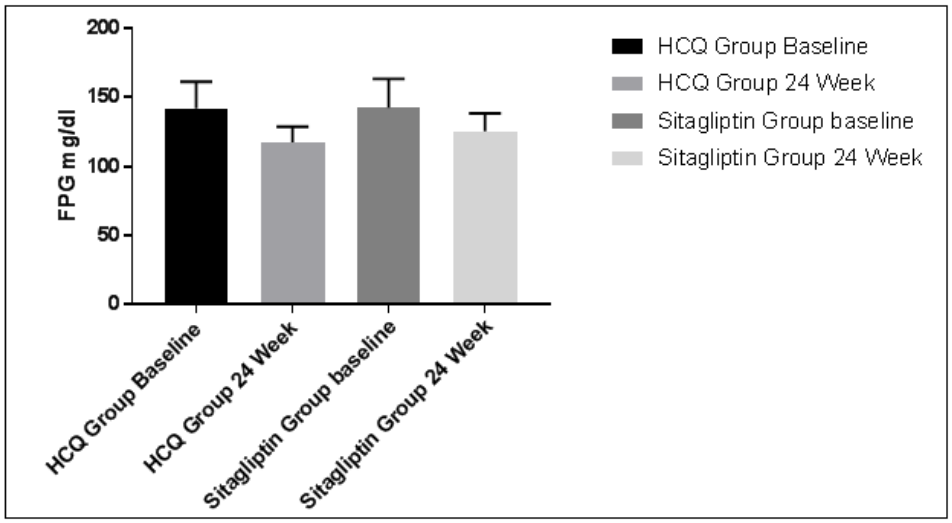

Fig-2: Comparison of Fasting Plasma Glucose (FPG) from baseline to 6th month of the treatment (Mean±SD)

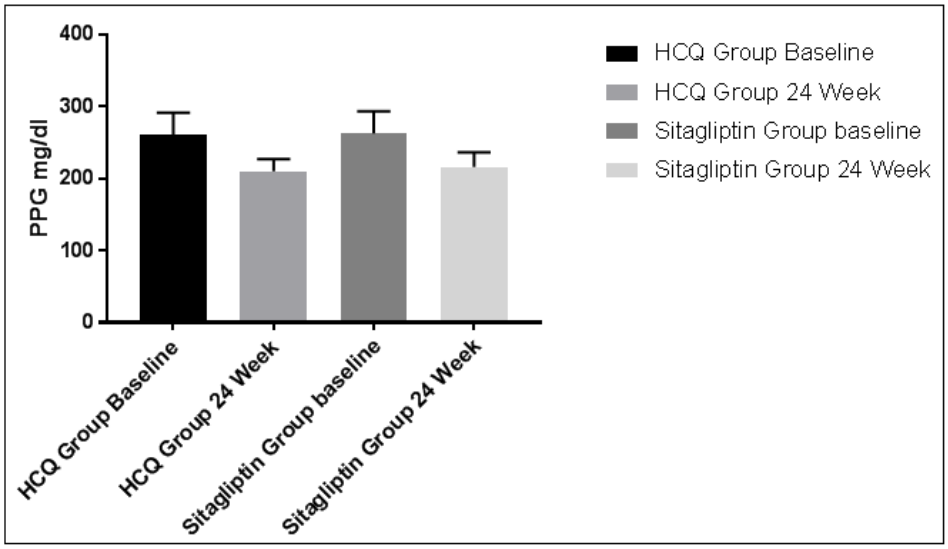

Fig-3: Comparison of Post Prandial Plasma Glucose (PPG) from baseline to 6th month of the treatment (Mean±SD)

During the study period we observed 9 episodes of hypoglycemia, 3 in hydroxychloroquine group and 6 in sitagliptin group. The incidence of severe events of hypoglycemia was not noted in any group, and there was no hypoglycemic events requiring medical assistance.

Eye scanning was done at 24th week. Eye check-up done to evaluate corrective lenses, it has been found that in all patients (n=300) pupils are equal and reactive to light and accommodation, normal fundus oculi, no arteriovenous nicking, no retinopathy.

DISCUSSION

T2DM is a disorder characterized by insulin resistance and a progressive decline in pancreatic β-cell function associated with increasing hyperglycemia. Defective β-cell function occurs early and can be detected in individuals with impaired fasting and post-prandial glucose levels.

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 [4]. In addition to the improvements in glycemic control, combination therapy may help reduce pill burden and improve treatment adherence. Initial combination with metformin plus a sulfonylurea is a common therapy in Indian patients. Data from the United Kingdom Prospective Diabetes Study have indicated that intensive treatment of newly diagnosed T2DM patients can lead to long-term benefits including decreased micro vascular complications and cardiovascular events [9].

The latest position statement from the ADA recommends initiating a combination of two non-insulin agents when the patients have a high baseline A1c (≥9.0%) because these patients are unlikely to achieve target A1c with metformin monotherapy [16]. It has been hypothesized that combining metformin and an agent from another class with a different mechanism of action may help to preserve β-cell function and thereby maintain a long-term glycaemic efficacy or 'durability' [17]. The major classes of oral antidiabetic medications include biguanides, sulfonylureas, meglitinide, thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter (SGLT2) inhibitors, and α-glucosidase inhibitors. If the HbA1C level rises to 7.5% while on medication or if the initial HbA1C is ≥9%, combination therapy with two oral agents, or with insulin, may be considered [18]. However, most patients initially respond to sulfonylureas and/or metformin at the starting stage, later on these agents lose their effectiveness with time; comparable long-term data is not yet available for the alpha glucosidase inhibitors, the meglitinides and the thiazolidinediones [19]. Insulin therapy is not only costly but is not preferred due to poor patients' compliance in parenteral application [20]. New generation thiazolidinediones class of antidiabetic drugs, though useful in glycemic control, is associated with several adverse effects such as excessive risk of congestive heart failure, acute myocardial infarction, increased rate of bone loss and liver toxicity [21]. In the light of failure of mono-therapy of anti-diabetic drugs in glycemic control and increased adverse effects when administered at high doses of anti-diabetic drugs for getting better glycemic control, newer medications for diabetes are needed, which will have good anti-hyperglycemic effect, as well as good tolerability profile [22]. Therefore the need of adding second oral antihyperglycaemic agent is required when metformin or sulfonylureas do not achieved a HbA1C target or metformin monotherapy at maximal tolerated dose over 3 to 6 months.

There are several study which confirms the powerful glycemic effect of sitagliptin. Management of T2DM has changed dramatically with the introduction of newer antidiabetic agents including dipeptidyl peptidase‑4 inhibitors (DPP4i), sodium glucose co-transporter 2 inhibitors, glucagon‑like peptide‑1 (GLP‑1) analogs, and insulin analogs. DPP4i are a well‑established class of oral agents having moderate efficacy with a good overall safety profile including low risk of hypoglycemia and weight neutrality [15].

The study presented here is the first to directly compare efficacy and safety/tolerability of hydroxychloroquine and sitagliptin, in patients with type 2 diabetes who are uncontrolled with metformin and gliclazide therapy. Both drugs in this study were used at their expected maximal effective and recommended doses. In this trial we had seen that Hydroxychloroquine can be a therapeutic option for those uncontrolled T2DM patients who are not able to continue high priced gliptins like sitagliptin. At 24 weeks, both treatment groups exhibited an improvement in HbA1c from baseline, which was statistically significant (Student's t‑test, P = 0.001). However, the mean reduction in HbA1c from baseline in the hydroxychloroquine group was significantly more as compared to the sitagliptin group (0.92±0.33% vs. 0.80± 0.36% respectively, Student's t‑test P = 0.001). Pareek *et al*., [11] reported 0.87% HbA1c changes from baseline in T2DM patients uncontrolled on maximum dose of metformin and sulfonylurea. Jagnani VK *et al*., [12] examined the efficacy of hydroxychloroquine against teneligliptin and found that there was 1.8% HbA1c reduction in HCQ group as compare to teneligliptin arm where there was 1.3% reduction in HbA1c among patient who unresponsive to more than two oral antidiabetic agents.

Postprandial hyperglycemia has been reported to trigger vascular disorders and cause cardiovascular events, and is more common in patients with high HbA1c levels [23]. In this trial both hydroxychloroquine and Sitagliptin effectively suppresses postprandial hyperglycemia contributes to the maintenance of ideal HbA1c levels.

Evaluating the effect of hydroxychloroquine on bodyweight, mean body weight decreased by 0.15±0.97 kg in the HCQ group. This once again confirm the weight neutrality effect of hydroxychloroquine in accordance with all previous trial don on T2DM patients.

Both drugs were well tolerated. Hypoglycemia is a matter of great concern with anti hyperglycemic agents. The incidence of hypoglycaemia was almost negligible between the two treatment groups. HCQ added to metformin and gliclazide showed a 1% hypoglycemia whereas sitagliptin and metformin plus gliclazide group had 2% incidence of hypoglycemia. This finding was in accordance with the previous study conducted by Baidya *et al*., [13].

CONCLUSION

In T2DM patients on hydroxychloroquine + metformin + gliclazide combination exhibited significant reduction in glycemic parameters as compared to sitagliptin + metformin + gliclazide combination. Moreover, there was no significant difference between both the groups in terms of change in BMI and incidence of hypoglycemia. Hydroxychloroquine can be a therapeutic option for those uncontrolled T2DM patients who are not able to continue high priced gliptins like sitagliptin in India.

Limitations

The sample size for this study was small. However, based on the encouraging results of this study, longer duration studies in larger population can be conducted to further confirm these findings.

Disclosure

The authors report no conflicts of interest in this work. No funding sources.

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