

Comparison between the Clinical Efficacy and Safety of Hydroxychloroquine and Sitagliptin Added to Inadequately Controlled with Glimepiride and Metformin in Indian Patients with Type 2 Diabetes Mellitus: A Real World Observational Study

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Abstract

Aim: The present study was aimed to compare the clinical efficacy and safety of Hydroxychloroquine and sitagliptin added to inadequately control with Glimepiride and Metformin in Indian type 2 diabetes mellitus (T2DM) patients.

Methods: This is an observational trial done at various diabetic care units of India in 600 inadequately controlled T2DM patients with Glimepiride and Metformin. All patients were randomly allotted into two groups, in one group 320 patients were started with Hydroxychloroquine 400 mg/day along with metformin 1000 mg/day and Glimepiride 2 mg/day. In other group 320 patients were started with Sitagliptin 100 mg/day while continuing with metformin 1000 mg/day and Glimepiride 2 mg/day. After 24 week 300 patient's data in each group were available for analysis. Changes from baseline in HbA1c, 2-hour PPG and FPG levels, serum creatinine, lipid profile (triglyceride, total cholesterol, LDL-cholesterol and HDL-cholesterol), inflammatory markers (hs-CRP) and fasting insulin level after 24 weeks of treatment were calculated.

Result: There was almost 1.4% reduction in HbA1c in hydroxychloroquine group after 24 week from baseline which was 1.2% with sitagliptin group ($p < 0.01$). Fasting Blood Glucose (FBG) was significantly reduced in Hydroxychloroquine group than sitagliptin group (-29.5 ± 10.2 vs -26.7 ± 10.8 , $p < 0.01$) and the same effect was also shown in Post Prandial Blood Glucose (PPBG) reduction in both the groups (-92.6 ± 21.2 vs -78.7 ± 23.1 , $p < 0.01$). Both QUICKI and HOMA-IR were significantly changed in both Hydroxychloroquine and sitagliptin group after 24 weeks. No marked changes in renal function for eGFR and creatinine levels were found in patients in the two groups. Plasma hs-CRP at week 24 declined more in the Hydroxychloroquine group than the Sitagliptin group ($P < 0.001$) from baseline. There was more favourable reduction in triglyceride, total cholesterol, LDL-cholesterol and significant increase in HDL-C with hydroxychloroquine group than sitagliptin group.

Conclusion: Hydroxychloroquine decreased the levels of insulin, TG and LDL-C in subjects with type 2 diabetes mellitus with a significant effect on FPG, PPG and HbA1c. Moreover, insulin sensitivity, as a major factor of chronic complications of type 2 diabetes, significantly improved with Hydroxychloroquine in the present study as compare to patients receiving Sitagliptin. This observational trial had proved that Hydroxychloroquine can be a therapeutic alternative of highly priced Sitagliptin in Indian type 2 diabetes patients.

Keywords: Blood Glucose; Diabetes; Hydroxychloroquine; Sitagliptin; Insulin Sensitivity; hs-CRP

Introduction

Type 2 diabetes mellitus (T2DM), a growing public health concern, is mostly associated with remarkably increased morbidity and mortality rates [1]. Some secondary complications of DM2 including kidney, nervous system, infectious and microvascular disorders are believed to be limited by tight glycemic control [2]. Moreover, some studies have shown that insulin sensitization can improve both glycemic control and endothelial function, resulting in less incidence of atherosclerosis [3]. In spite of the availability of the conventional pharmaceutical treatments, it is often difficult to achieve and maintain proper glycemic control.

After the introduction of Hydroxychloroquine into the treatment for diabetes, it has been widely used because of its capability and safety. Hydroxychloroquine (HCQ) improves glucose tolerance and insulin sensitivity by inhibition of insulin degradation. Treatment with Hydroxychloroquine 400 mg leads to improvements in glycemic control, with a low risk of hypoglycemia, if used in combination with agents like pioglitazone 15 mg which are not associated with an increased risk of hypoglycemia during monotherapy [4]. Even in a recent observational trial [5], it has been observed that hydroxychloroquine based therapy exhibits significant reduction in glycemic parameters as compared to sitagliptin based therapy without altering BMI and incidence of hypoglycemia was almost similar in two comparing groups. In a recent Indian clinical trial [6], HCQ was evaluated against one of the DPP4i, teneligliptin, and it has been observed that HCQ significantly reduced HbA1c, FPG and PPG as compared to teneligliptin based treatment. Moreover, 61% of patients have achieved HbA1c < 7%. In another Indian trial [7], it has been seen 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.

Even Di Peptidyl Peptidase - 4 (DPP-4) inhibitors like Sitagliptin have been widely used for their safety and efficacy to reduce glycemic parameters in uncontrolled type 2 diabetes patients. DPP-4 inhibitors are a class of oral anti-diabetic agents that increase circulating concentrations of the incretin gastrointestinal hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide [8]. Sitagliptin, the first of the DPP-4 inhibitors approved in the United States, has been used as an adjunct to diet and exercise in monotherapy and in combination regimens with other oral anti-diabetic drugs [9-11].

Homeostasis model assessment (HOMA IR) and quantitative insulin sensitivity check index (QUICKI) are widely used in the assessment of insulin resistance [12]. They are calculated with insulin and fasting blood glucose (FBG) levels. However, the usage of these indexes might not be accurate in patients with a low body mass index (BMI), decreased beta-cell function and high FBG levels [12,13]. As a matter of fact, Asian populations including Indians often represent such features. Furthermore, in patients with impaired hepatic and/or renal functions where insulin metabolism may be distorted, HOMA indexes might not be accurate.

Hs-CRP is a biomarker for inflammation and a recent RCT trial [14] with Hydroxychloroquine in T2DM patients treated with insulin along with other oral therapy shows that a significant reduction in hs-CRP influences the magnitude of reduction in other glycemic parameters.

Therefore, the present study was aimed to investigate the effects of hydroxychloroquine on the levels of fasting plasma glucose, glycosylated haemoglobin (HbA1c), serum creatinine, lipid profile, inflammatory markers and insulin sensitivity in Indian T2DM patients over a 6-month period as compared to sitagliptin based therapy.

Materials and Methods

Study design

This study was a real world observational trial performed on patients with T2DM aged between 38 and 65 years of both sex and an average body mass index (BMI) of 29.5 kg/m². The subjects with type 2 diabetes for at least 2 years and without blood pressure abnormality were recruited for this study. The study included 600 adults with sub-optimal glycemic control and elevated hs-CRP levels.

Patients received counselling on exercise and a weight-maintenance diet consistent with American Diabetes Association recommendations throughout the study. Initially 760 patients were assessed for eligibility, among which 640 patients were randomised. All patients were randomly allotted into two groups, in one group 320 patients were started with Hydroxychloroquine 400 mg/day along with metformin 1000 mg/day and Glimepiride 2 mg/day. In other group 320 patients were started with Sitagliptin 100 mg/day while continuing with metformin 1000 mg/day and Glimepiride 2 mg/day. Dose adjustment of Hydroxychloroquine or Sitagliptin or Metformin and Glimepiride was not done at any time after randomization. No additional oral antidiabetic drug was added during study period. After 24 week 300 patient’s data in each group were available for analysis (Figure 1).

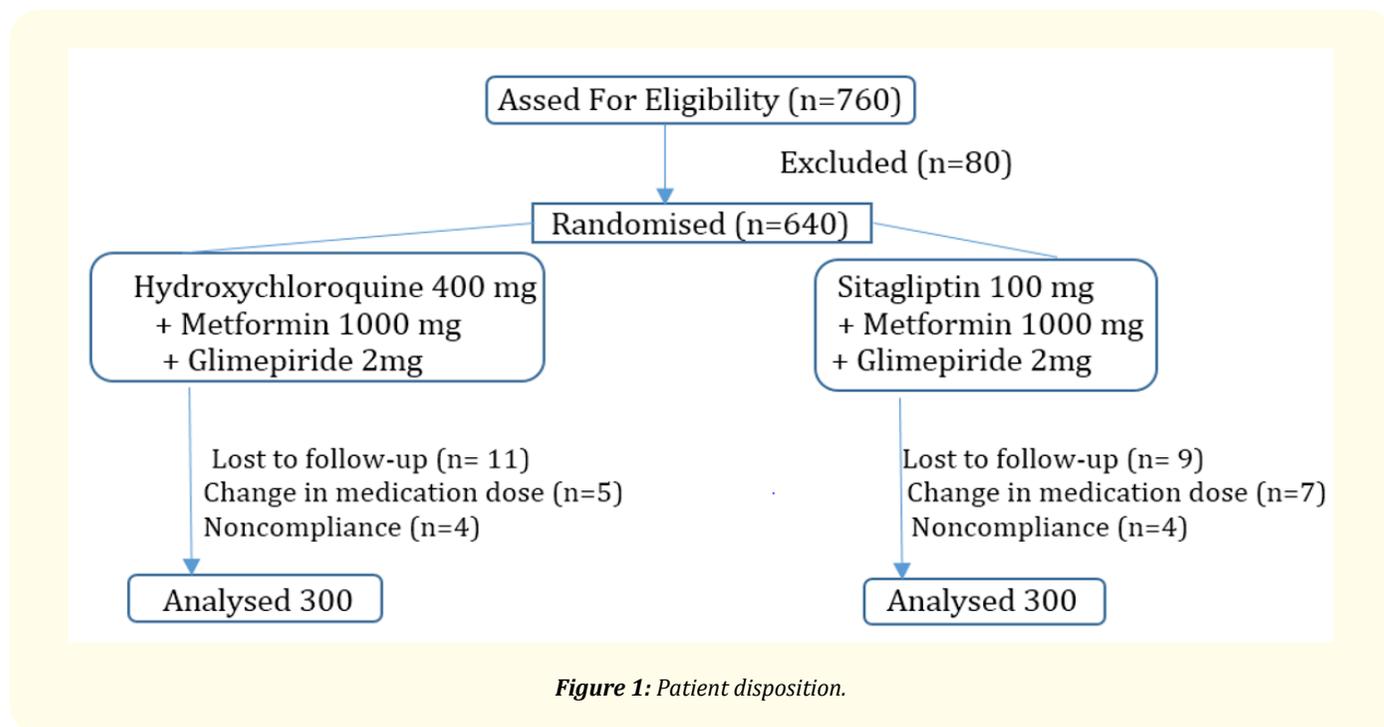


Figure 1: Patient disposition.

The primary objectives of the present study were to assess the safety and efficacy of Hydroxychloroquine for a period of 24 weeks compared with sitagliptin. Changes from baseline in HbA1c, 2-hour PPG and FPG levels, serum creatinine, lipid profile (triglyceride, total cholesterol, LDL- cholesterol and HDL-cholesterol), inflammatory markers (hs-CRP) and fasting insulin level after 24 weeks of treatment were calculated.

Inclusion Criteria

- Patients receiving stable doses of sulfonylurea and at least 1000 mg metformin for at least 3 months with HbA1c ≥ 7%.
- Patients with ideal body weight > 60 kg Compliance.
- Patient able to understand and willing to fully comply with study procedures and restrictions.
- Patients ready to undergo a follow-up period of 24 weeks.

Exclusion criteria:

- Patients with a history of any retinopathy of any grade including diabetic retinopathy, evidence of an imminent need for retinal laser therapy, uncorrected visual acuity < 20/100, abnormal visual fields, difficulty to examine optic disc, or evidence of retinal pigment epithelial abnormalities and patients with history or risk of macular edema.
- Patients with history of myalgia, aplastic anemia or agranulocytosis, granulocytopenia, psoriasis, porphyria, rash, scaling, scaling eczema, and G6PD deficiency.
- Patients with significant cardiovascular illness limiting participation of patient in a clinical trial.
- Patients with dementia or other cognitive impairment prohibiting informed consent.
- Pregnant or lactating women.
- Women of childbearing potential not practicing contraception.

Statistical analysis

The data were analysed by Statistical software (Graph Pad Prism5; version 5.01) and the results were expressed as mean ± standard deviation (SD). The normality of the distribution of variables was determined by the Kolmogorov–Smirnov test. The background characteristics and baseline experimental data in the two groups were compared using independent chi-square and sample t-tests. Analysis of covariance (ANCOVA) was used to identify any differences in anthropometric parameters, levels of FBG, PPBG, hs-CRP, Serum creatinine, eGFR, TC, TG, LDL-C, HDL-C, HbA1c, insulin, QUICKI and HOMA indexes between the two groups after intervention. Changes in anthropometric measurements, blood glucose, lipid profile, HbA1c, insulin, QUICKI and HOMA for all participants between the beginning and end of the trial were compared by paired sample t-tests. Differences with p < 0.05 were considered to be statistically significant.

Ethics approval and consent to participate

All studies included in this analysis were conducted in accordance with the ethical principles that comply with the Declaration of Helsinki and are consistent with good clinical practices and applicable regulatory requirements. Study protocols and amendments were approved by independent ethics committees. All patients provided written informed consent prior to participation.

Results

Table 1 presents baseline characteristics of the participants in two groups. No statistically significant differences regarding the body Weight, BMI, age, blood glucose, insulin and HbA1c existed between the Hydroxychloroquine and Sitagliptin groups at the baseline.

Variables	Hydroxychloroquine Group N = 300	Sitagliptin Group N = 300	p Value in between Groups
Age (years)	49.2 ± 5.1	53.1 ± 7.9	0.953
Gender (male/female)	169/131	172/128	
Weight (kg)	76.3 ± 9.6	72.8 ± 8.5	0.191
BMI (kg/m ²)	29.2 ± 4.0	29.8 ± 5.0	0.446
SBP (mmHg)	124 ± 13	123 ± 13	0.329
DBP (mmHg)	79.9 ± 8	79.1 ± 8.5	0.261
FBG (mg/dl)	147.7 ± 24	149.8 ± 26.3	0.347
PPBG (mg/dl)	278.3 ± 36	278.6 ± 36	0.112
HbA1c (%)	8.3 ± 1	8.3 ± 1	0.017
Creatinine (mg/dl)	0.65 ± 0.2	0.58 ± 0.1	0.312
eGFR	101.7 ± 47.1	102.6 ± 26.6	0.915
hs-CRP (mg/dl)	3.2 ± 1.3	3.1 ± 1.2	0.047
Insulin (mU/ml)	14.5 ± 2.9	14.8 ± 2.6	0.915
HOMA IR	5.09 ± 1.1	5.14 ± 1.35	0.439
QUICKI	0.358 ± 0.011	0.358 ± 0.011	0.347
Triglyceride	162.3 ± 58.4	159.3 ± 58.4	0.616
Total cholesterol	176.9 ± 25.2	172.9 ± 25.4	0.217
LDL-C	109.6 ± 20.2	107.4 ± 20.2	0.315
HDL-C	44.5 ± 8.5	44.5 ± 8.5	0.101

Table 1: Baseline characteristics of study participants.

Changes in HbA1c, PPBG and FBG levels

Significant improvement in HbA1c levels was found in both Hydroxychloroquine and sitagliptin groups (Figure 1), namely in patients in the sitagliptin group, in whom HbA1c levels changed from 8.3 ± 1% to 7.1 ± 0.5 (%) and in patients in the Hydroxychloroquine group, in whom levels changed from 8.3 ± 1% to 6.9 ± 0.5%. There was almost 1.4% reduction in HbA1c in hydroxychloroquine group after 24 week from baseline which was 1.2% with sitagliptin group (p < 0.01).

Post prandial Blood Glucose (PPBG) and Fasting Blood Glucose (FBG) was reduced significantly in both Hydroxychloroquine and Sitagliptin group. In hydroxychloroquine group PPBG was reduced from 278.3 ± 36 mg/dl to 185.7 ± 26.8 mg/dl with a difference of -92.6 ± 21.2 mg/dl whereas FBG was reduced from 147.7 ± 24 mg/dl to 118.2 ± 16.3 mg/dl with a difference of -29.5 ± 10.2 mg/dl. In sitagliptin group PPBG was reduced from 277.6 ± 32 mg/dl to 198.9 ± 24.4 mg/dl with a difference of -78.7 ± 23.1 mg/dl whereas FBG was reduced from 149.8 ± 26.3 mg/dl to 123.1 ± 18.3 mg/dl with a difference of -26.7 ± 10.8 mg/dl.

Changer in HOMA IR and QUICKI

Both QUICKI and HOMA-IR were significantly changed in both Hydroxychloroquine and sitagliptin group after 24 weeks (Table 2). The results of analysis revealed significant differences between two groups in insulin (p < 0.001), HOMA (p < 0.01) and QUICKI (p < 0.02) which is more favourable with hydroxychloroquine group than sitagliptin group.

Circulating inflammatory markers

Plasma hs-CRP at week 24 declined more in the Hydroxychloroquine group than the Sitagliptin group (P > 0.001; Table 2). Correlation analyses indicated that reductions in plasma hs-CRP were related to improvements in insulin sensitivity or glucose tolerance. This suggests that the anti-inflammatory effects of Hydroxychloroquine were related to its beneficial actions on glucose homeostasis.

Variables	Hydroxychloroquine Group N = 300			Sitagliptin Group N = 300			p Value in between Groups
	Baseline	24 Week	Changes	Baseline	24 Week	Changes	
Weight (kg)	79.3 ± 11.8	78.4 ± 11.4	-0.9 ± 0.19	76.8 ± 14.5	76.9 ± 14.1	-0.21 ± 0.10	< 0.039
FBG (mg/dl)	147.7 ± 24	118.2 ± 16.3	-29.5 ± 10.2	149.8 ± 26.3	123.1 ± 18.3	-26.7 ± 10.8	< 0.01
PPBG (mg/dl)	278.3 ± 36	185.7 ± 26.8	-92.6 ± 21.2	277.6 ± 32	198.9 ± 24.4	-78.7 ± 23.1	< 0.01
HbA1c (%)	8.3 ± 1	6.9 ± 0.5	1.4 ± 0.8	8.3 ± 1	7.1 ± 0.5	1.2 ± 0.2	< 0.01
Creatinine (mg/dl)	0.65 ± 0.2	0.64 ± 0.2	-0.01 ± 0.01	0.58 ± 0.1	0.60 ± 0.2	0.02 ± 0.01	0.079
eGFR	101.7 ± 47.1	102.0 ± 43.8	0.3 ± 0.01	102.6 ± 26.6	99.0 ± 28.9	-3.6 ± 0.2	0.87
hs-CRP (mg/dl)	3.2 ± 1.3	2 ± 1.1	-1.2 ± 0.8	3.1 ± 1.2	2.8 ± 1.2	- 0.5 ± 0.4	< 0.001
Insulin (mU/ml)	14.5 ± 2.9	12.5 ± 2.4	-2 ± 1.1	14.8 ± 2.6	13.1 ± 2.4	-1.7 ± 1.1	< 0.001
HOMA IR	5.09 ± 1.1	3.23 ± 1.1	-1.86 ± 0.5	5.14 ± 1.35	3.31 ± 1.1	-1.83 ± 0.5	< 0.01
QUICKI	0.358 ± 0.011	0.367 ± 0.012	0.009 ± 0.01	0.358 ± 0.011	0.364 ± 0.012	0.006 ± 0.01	< 0.02
Triglyceride (mg/dl)	162.3 ± 58.4	139.5 ± 22.7	-22.8 ± 4.7	159.3 ± 58.4	142.5 ± 24.9	-16.8 ± 6.7	0.045
Total cholesterol (mg/dl)	176.9 ± 25.2	165.8 ± 29.8	-11.1 ± 7.3	172.9 ± 25.4	166.2 ± 29.8	-6.7 ± 7.3	0.039
LDL-C (mg/dl)	109.6 ± 20.2	99.5 ± 14.8	-10.1 ± 4.6	107.4 ± 20.2	101.2 ± 13.6	-6.2 ± 4.6	0.761
HDL-C (mg/dl)	44.5 ± 8.5	45.8 ± 5.4	1.3 ± 0.8	44.3 ± 8.5	44.8 ± 4.1	0.3 ± 0.8	< 0.01

Table 2: Change from baseline to 24 week study end point with Hydroxychloroquine or Sitagliptin treatment.

Renal function

Renal function was evaluated on the basis of the eGFR (ml/min/1.73 m²) and blood creatinine levels (mg/dl). The eGFR (ml/min/1.73 m²) changed from 102.6 ± 26.6 to 99.0 ± 28.9 in patients in the sitagliptin group and from 101.7 ± 47.0 to 102.0 ± 43.8 in patients in the hydroxychloroquine group. Blood creatinine levels (mg/dl) changed from 0.58 ± 0.1 to 0.60 ± 0.2 in patients in the sitagliptin group and from 0.65 ± 0.2 to 0.64 ± 0.2 in patients in the Hydroxychloroquine group. No marked changes in renal function for eGFR and creatinine levels were found in patients in the two groups.

Change in Lipid profile

No statistically significant differences existed in blood lipid parameters between the ginger and control groups at baseline. There was significant reduction in Triglyceride in both the groups -22.8 ± 4.7 mg/dl vs -16.8 ± 6.7 mg/dl, p=0.045). Reduction in total cholesterol (TC) and LDL-C is more favourable with hydroxychloroquine group than to sitagliptin group (TC: -11.1 ± 7.3 mg/dl vs -6.7 ± 7.3 mg/dl, p=0.039; LDL-C: -10.1 ± 4.6 mg/dl vs -6.2 ± 4.6, p =0.761). HDL-C was markedly improved in hydroxychloroquine group (1.3 ± 0.8 mg/dl) as compared to Sitagliptin group (p > 0.01).

Safety and tolerability

There were no meaningful differences between groups in incidences of overall clinical adverse experiences or of those assessed as serious, drug-related, or leading to discontinuation. Three patients had a serious drug-related adverse experience (one on Hydroxychloroquine group) discontinued for cholecystitis and two on sitagliptin 100 mg, including one with mild non-alcoholic steatohepatitis with increased hepatic enzymes noted at discontinuation and one with mild diarrhea. Two other patients were discontinued for drug-related adverse experiences (one on Hydroxychloroquine [tachycardia] and one on sitagliptin 100 mg [depression]).

The incidence of hypoglycemia was similar among groups. No episode of hypoglycemia exhibited marked severity (i.e., loss of consciousness or requirement for medical assistance). The proportion of patients reporting gastrointestinal adverse experiences was slightly higher with Hydroxychloroquine group versus sitagliptin group, but for the pre specified specific gastrointestinal adverse experiences, the incidences were not statistically significant between groups.

Discussion

The incidence of coronary heart disease in diabetic patients is associated with many known classic risk factors such as hypertension, smoking, increased total serum cholesterol, and decreased HDL cholesterol. In addition to a marked improvement in the lipid profile (triglyceride, total cholesterol, LDL-cholesterol and HDL-cholesterol) our study demonstrated that Hydroxychloroquine significantly decreased non-traditional cardiovascular risk markers such as hs-CRP in patients with type 2 diabetes mellitus and hyperlipidemia. Inflammation is a major risk factor of cardiovascular disease [15,16]. Diabetes is associated with inflammation that promotes the development of cardiovascular disease [17]. Effects of intensive glucose control on hs-CRP vary according to the strategy and agent(s) used for glucose control. Glucose lowering for CVD prevention may yet be beneficial in a subset of diabetic patients, they also invite consideration of alternate therapeutic targets. Subclinical inflammation is one such modifiable risk factor [18]. Pro inflammatory mechanisms have been linked to the core metabolic defects of beta-cell insufficiency and insulin resistance [19-21] and elevations in levels of inflammatory biomarkers [22], including high-sensitivity C-reactive protein (hs-CRP), IL-6, and soluble tumor necrosis factor receptor 2 (sTNFr2), predict incident type 2 diabetes among apparently healthy individuals. These markers [23] also predict incident myocardial infarction and stroke and more recent clinical trial [24] data have demonstrated hs-CRP reduction is associated with marked improvement in vascular outcomes. According to a study of patients with advanced atherosclerosis, hs-CRP, and HbA1c jointly predict future cardiovascular risk [25]. In our study, there was significant reduction in hs-CRP with Hydroxychloroquine as compared to sitagliptin arm. This had demonstrated pleotropic benefits of Hydroxychloroquine beyond glycemic control.

Insulin resistance exists when a normal concentration of insulin produces a less than normal biological response. As our understanding of the mechanisms underlying the genesis of glucose intolerance has grown, the role of insulin resistance (IR) has emerged as a critical one. Insulin resistance, as a common metabolic abnormality in type 2 diabetes, is an underlying trait for many cardiovascular and metabolic disorders such as hypertension and dyslipidemia provoking a widespread interest in developing new insulin sensitization agents. In the present study, HOMA and QUICKI indexes were determined as the predictors of insulin resistance and insulin sensitivity, respectively. According to our results, fasting plasma insulin levels ($p > 0.001$) and HOMA ($p > 0.01$) significantly decreased and QUICKI ($p > 0.02$) significantly increased after 6 months of intervention in the Hydroxychloroquine group.

Subclinical inflammation and insulin resistance, forerunners to CHD and T2DM, may be patho-physiologically interlinked. In a trial, it had established that, hs-CRP concentrations significantly correlate with insulin resistance and the metabolic syndrome in adults. In another study, significant increase in hs-CRP was seen with increasing BMI and waist circumference which are clinical markers of insulin resistance and it was also observed that even in normoglycemic healthy subjects, as insulin resistance increases, hs-CRP also increases. In our study, statistically significant reduction in hs-CRP is associated with improvement in insulin resistance.

Impaired renal function is common in patients with T2D, especially in those ≥ 65 years [4] and is independently associated with increased mortality, cardiovascular events, and hospitalization [18,19]. Pharmacotherapy in patients with T2D can be challenging and therapeutic options may be limited because a reduced GFR results in the accumulation of certain drugs and/or their metabolites that may increase the risk of side effects or hypoglycemia. In our trial, no marked changes in renal function for eGFR and creatinine levels were found in patients in the two groups [26-31].

Conclusion

In conclusion, in this study Hydroxychloroquine decreased the levels of insulin, TG and LDL-C in subjects with type 2 diabetes mellitus with a significant effect on FPG, PPG and HbA1c. Moreover, insulin sensitivity, as a major factor of chronic complications of type 2 diabetes, significantly improved with Hydroxychloroquine in the present study as compare to patients receiving Sitagliptin. This observational trial had proved that Hydroxychloroquine can be a therapeutic alternative of highly priced Sitagliptin in Indian type 2 diabetes patients.

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Disclosure

The authors declare they have no conflicts of interest.

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