

# A comparative study of effect of hydroxychloroquine (HCQ) on blood sugar levels of diabetic and non-diabetic patients at a tertiary hospital

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## Abstract

**Background:** Hydroxychloroquine is used in treatment of several inflammatory rheumatic and autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), various skin diseases and cancers. In past few years, a growing body of evidence from studies suggested that HCQ also plays a role in the regulation of glucose homeostasis in individuals with and without diabetes. In present study of we assessed effect of hydroxychloroquine (HCQ) on blood sugar levels of diabetic and non-diabetic patients, receiving HCQs at a tertiary hospital. **Material and Methods:** This was a prospective, comparative study conducted at the department of general medicine in patients attending rheumatology outpatient department with newly diagnosed rheumatological disease, age > 18years and prescribed tablet hydroxychloroquine. Based on the test results and history, 40 patients, each from diabetes mellitus and normal glucose tolerance group were selected for present study. Student's t test and Chi-Square test were used to determine statistical difference between variables. Statistical software (SPSS version 24) was used for analysis. Statistical tests were considered significant if P-value was <0.05. **Results:** Baseline data of both study group patients is shown in table 1. Mean age was comparable in both groups. Female patients were more in both groups. Other high-risk factors such as hypertension, smoking, dyslipidaemia, coronary artery disease, chronic obstructive pulmonary disease were present in both groups. In diabetes mellites group 58% patients had less than 5 years duration of diabetes. A significant difference was noted in HbA1c values in diabetes group. In normal glucose tolerance difference was not significant. In diabetes group, we noted a significant difference in fasting blood sugar values taken at 6 months follow up compared to values at start of study. A significant difference in postprandial blood sugar values noted in diabetes group, while in normal glucose tolerance difference was not significant. **Conclusion:** Hydroxychloroquine decreases HbA1c, fasting blood sugar and postprandial blood sugar values in patients with type 2 diabetes. A careful risk-benefit assessment is required for cautious use of HCQ in subjects with diabetes.

**Key Words:** Hydroxychloroquine; Type 2 Diabetes; HbA1c, blood sugar levels

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## INTRODUCTION

Hydroxychloroquine (HCQ) is hydroxyl (OH) congener of a popular antimalarial drug chloroquine. HCQ has well-known anti-inflammatory and immunomodulatory properties, to reduces production of proinflammatory cytokines.<sup>1</sup> HCQ is therefore used as a DMARD for the treatment of several inflammatory rheumatic and autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), various skin diseases

and cancers.<sup>2,3</sup> In past few years, a growing body of evidence from studies suggested that HCQ also plays a role in the regulation of glucose homeostasis in individuals with and without diabetes.<sup>4</sup> Diabetes mellitus has an inflammatory component which is counteracted by HCQ. Although the exact mechanisms of action are still not clear, research suggests that HCQ exerts multifaceted effects on glucose homeostasis, such as improved insulin sensitivity, increase in insulin secretion, reduced hepatic insulin clearance, increase in adiponectin levels, reduction of systemic inflammation, reduction of inflammation-induced insulin resistance in adipocytes and skeletal muscle cells, etc.<sup>4,5,6</sup> An increased incidence of diabetes is noted in Indian population in past 40 years. Rapid socioeconomic development, sedentary lifestyle, demographic changes increased susceptibility of Indian individuals to diabetes caused an explosive increase in diabetes mellitus.<sup>7</sup> Hydroxychloroquine, being immunomodulatory and anti-inflammatory can be used for the management of type 2 Diabetes Mellitus (T2DM) in India.<sup>8</sup> HCQ is relatively inexpensive drug with well-tolerated side effects commonly used in rheumatoid arthritis patients.<sup>8</sup> Effects of HCQ on blood sugar levels of diabetic patients are studied but few literatures available for the same in non-diabetic patients receiving HCQ. In present study of we assessed effect of hydroxychloroquine (HCQ) on blood sugar levels of diabetic and non-diabetic patients, receiving HCQs at a tertiary hospital.

## MATERIAL AND METHODS

This was a prospective, comparative study conducted at the, Department of Medicine, D. Y Patil Medical Collage, India. Study period was from May 2019 to April 2020 (1 year). Study got clearance from Institutional Ethical Committee.

### Inclusion criteria

- Patients attending rheumatology outpatient department with newly diagnosed rheumatological disease, age > 18years and prescribed tablet hydroxychloroquine.
- Willing to participate and follow up in present study

## RESULTS

Baseline data of both study group patients is shown in table 1. Mean age was comparable in both groups. Female patients were more in both groups. Other high-risk factors such as hypertension, smoking, dyslipidaemia, coronary artery disease, chronic obstructive pulmonary disease were present in both groups. In diabetes mellitus group 58% patients had less than 5 years duration of diabetes.

### Exclusion criteria

- Pregnant and lactating mothers,
- Patients with hematological disorders for e.g. anemia (hemoglobin less than 9 gm/dl), Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Uncontrolled diabetes mellitus, Type 1 DM
- Patients with cardiomyopathy or heart failure, retinopathy/maculopathy, chronic kidney disease,
- Patients lost to follow up

Patients with rheumatological illness are treated at rheumatology OPD. After clinical examination and necessary investigations, patients with rheumatoid arthritis were started with tablet hydroxychloroquine 200-400 mg once daily dose. Such patients were considered for study after applying inclusion and exclusion criteria. Study was explained to patients in native language and a informed written consent was taken. Demographic details, clinical history was noted and detailed physical examination was done. Before initiating tablet hydroxychloroquine CBC, LFT, KFT were done. Baseline HbA1c and Fasting Blood Sugar values were measured after an overnight fasting of 8 hours. 2 hours after 75-gram oral glucose challenge, Postprandial Blood Sugar (PPBS) levels were measured. Based on the test results and history, patients were divided into three groups as diabetes mellitus, impaired glucose tolerance and normal glucose tolerance as per criteria given by American Diabetes Association. 40 patients, each from diabetes mellitus and normal glucose tolerance group were selected for present study. Patients were periodically followed up till 6 months while they were coming for follow up in rheumatology OPD. At the end of 6 months, blood samples were collected for HbA1c, fasting and postprandial blood sugar level estimation. All details were recorded in case proforma and entered in Microsoft excel for analysis. The qualitative data were expressed in percentages and quantitative data were expressed as mean  $\pm$  standard deviation. Student's t test and Chi-Square test were used to determine statistical difference between variables. Statistical software (SPSS version 24) was used for analysis. Statistical tests were considered significant if P-value was <0.05.

**Table 1:** Baseline data of patients

| Patient parameters   |                                       | Normal Glucose Tolerance group (%) | Diabetes Mellitus group (%) |
|----------------------|---------------------------------------|------------------------------------|-----------------------------|
|                      | Age (in years)                        | 48.6 ± 11.2                        | 49.2 ± 8.5                  |
| Gender               | Male                                  | 18                                 | 16                          |
|                      | Female                                | 22                                 | 24                          |
|                      | Male : Female                         | 0.8:1                              | 0.7:1                       |
| High risk factors    | Hypertension                          | 7 (18%)                            | 10 (25%)                    |
|                      | Smoking                               | 7 (18%)                            | 5 (13%)                     |
|                      | Dyslipidaemia                         | 6 (15%)                            | 11 (28%)                    |
|                      | Coronary artery disease               | 4 (10%)                            | 7 (18%)                     |
|                      | Chronic obstructive pulmonary disease | 3 (8%)                             | 4 (10%)                     |
| Duration of diabetes | 0-5 years                             | 0                                  | 23 (58%)                    |
|                      | 5-10 years                            | 0                                  | 14 (35%)                    |
|                      | >10 years                             | 0                                  | 3 (8%)                      |

We analysed HbA1c, fasting blood sugar and postprandial blood sugar values from both groups. A significant difference was noted in HbA1c values in diabetes group. In normal glucose tolerance difference was not significant.

**Table 2:** Analysis of HbA1c

| Glycemic status          | Mean ± Standard deviation |                | Significance (p value) * |
|--------------------------|---------------------------|----------------|--------------------------|
|                          | At start                  | After 6 months |                          |
| Normal glucose tolerance | 5.272 ± 0.182             | 5.125 ± 0.146  | 0.53                     |
| Diabetes                 | 7.636 ± 0.621             | 7.153 ± 0.486  | 0.001                    |

\*(Statistical tests considered significant if P-value is <0.05)

In diabetes group, we noted a significant difference in fasting blood sugar values taken at 6 months follow up compared to values at start of study. Small reduction in fasting blood sugar values noted at 6 months follow up in normal glucose tolerance as compared to values at start of study, difference was not significant.

**Table 3:** Analysis of fasting blood sugar (FBS)

| Glycemic status          | Mean ± Standard deviation |                | Significance (p value) * |
|--------------------------|---------------------------|----------------|--------------------------|
|                          | At start                  | After 6 months |                          |
| Normal glucose tolerance | 89.8 ± 19.5               | 86.5 ± 16.1    | 0.091                    |
| Diabetes                 | 116.4 ± 26.2              | 99.3 ± 25.3    | 0.001                    |

\*(Statistical tests considered significant if P-value is <0.05)

A significant difference in postprandial blood sugar values noted in diabetes group, while in normal glucose tolerance difference was not significant.

**Table 4:** Analysis of postprandial blood sugar (PBS)

| Glycemic status          | Mean ± Standard deviation |                | Significance (p value) * |
|--------------------------|---------------------------|----------------|--------------------------|
|                          | At start                  | After 6 months |                          |
| Normal glucose tolerance | 114.1 ± 31.2              | 109.5 ± 21.4   | 0.061                    |
| Diabetes                 | 152.2 ± 27.4              | 132.1 ± 25.3   | 0.001                    |

\*(Statistical tests considered significant if P-value is <0.05)

## DISCUSSION

Basic management of type 2 diabetes mellitus (T2DM) consists of lifestyle measures (diet and exercise), oral antidiabetic drugs, and if required then insulin. Drug Controller General of India (DCGI) approved Hydroxychloroquine (HCQ) as add-on therapy in Type 2 Diabetes (T2DM) patients inadequately controlled despite lifestyle management along with sulfonylurea and metformin combination therapy.<sup>9</sup> Research Society for the Study of Diabetes in India (RSSDI) in clinical practice

recommendations 2017, recommended hydroxychloroquine (HCQ) as add-on therapy in Type 2 Diabetes patients.<sup>9</sup> In a randomized, placebo-controlled trial in nondiabetic patients with stable RA, Solomon *et al.* noted that treatment with HCQ had no significant change in insulin sensitivity index and insulin resistance compared to placebo, but a significant reduction in total cholesterol and LDL-cholesterol was noted.<sup>10</sup> In present study we noticed insignificant difference in HbA1c, fasting blood sugar and postprandial blood sugar values of non-diabetic

patients. Other studies demonstrated that HCQ use is associated with a significantly reduced risk of developing diabetes in nondiabetic subjects with inflammatory rheumatic diseases, such as rheumatoid arthritis, SLE, Sjogren syndrome and psoriasis.<sup>11-13</sup> Gupta A. noted in study with poorly controlled type 2 diabetes patients not willing to start insulin, noted that hydroxychloroquine (400 mg/d) is associated with marked reductions in fasting plasma glucose, hemoglobin A1c and body weight.<sup>6</sup> Similar findings were noted in Indian randomized controlled trial.<sup>14</sup> In present study we noted significant reduction in HbA1c, fasting blood sugar and postprandial blood sugar values in diabetic patients at end of 6 month HCQ treatment. In a review evaluating the effect of hydroxychloroquine on indices of glycemic control and/or cardiovascular events in people with Type 2 Diabetes, they noted abundant evidence for metabolic benefit of HCQ.<sup>15</sup> In a clinical study in nondiabetic, obese individuals, it was noted that HCQ improved b-cell function, insulin sensitivity and adiponectin levels significantly as compared to placebo.<sup>5</sup> Though in present study hypoglycemia was not reported by any patient during study period, but case reports are present for hypoglycemia due to hydroxychloroquine in diabetic and non-diabetic patients.<sup>16-18</sup> For patients receiving chloroquine or hydroxychloroquine, physicians should warn patients about the possibility of hypoglycemia and describe its manifestations.<sup>19</sup> Management of hypoglycemia involves cessation of the drug and administration of supplemental glucose or parenteral dextrose if needed. Clinical data on long-term safety and efficacy of HCQ in diabetes are still lacking. HCQ use in patients with diabetes should be carefully evaluated. Common complications due to long term HCQ use are retinal toxicity. HCQ-mediated cardiotoxic effects (heart rhythm disorders, such as prolonged QT interval, ventricular arrhythmia, and Torsade's de Pointes), particularly in high-risk subjects.<sup>20</sup> In chronic kidney diseases, HCQ clearance can be reduced, causing increased drug bioavailability and subsequent augmented risk of HCQ related side effects.<sup>20</sup> Whole world is facing coronavirus disease-2019 (COVID-19) pandemic, which is one of the important event in the recent history of mankind, declared a global pandemic by the World Health Organization on 11 March 2020. A Chinese study, showed that chloroquine and HCQ inhibit SARS-CoV-2 in vitro with HCQ and found it to be more potent than chloroquine. So, HCQ was recommended for treatment of COVID 19 patients. A proper risk-benefit assessment of HCQ use in diabetic patients should also be considered in relation to the current coronavirus disease 2019 (COVID-19) pandemic.<sup>22</sup> In diabetic patients who are already on HCQ for treatment of diabetes, the effect of HCQ on glycemia, cardiovascular function and viral load

needs to be researched. Limitations of present study were short duration of treatment and small sample size. Prospective multicentric clinical trials with longer follow-up of subjects are required to confirm the results of the present study.

## CONCLUSION

Hydroxychloroquine decreases HbA1c, fasting blood sugar and postprandial blood sugar values in patients with type 2 diabetes. Considering the anti-hyperglycemic potential, anti-inflammatory activity HCQ can considered as a therapeutic option for uncontrolled diabetes patients. A careful risk-benefit assessment is required for cautious use of HCQ in subjects with diabetes.

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