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Research Article

Glycemic Profile of Indian Patients Receiving Hydroxychloroquine

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Abstract

Background and Aims: Hydroxychloroquine (HCQ) is a Disease Modifying Antirheumatic Drug (DMARD) known to produce hypoglycemia, widely used in Rheumatology. The anti-diabetic and anti-atherosclerotic effects of HCQ is a novel area of interest. The aim of this study was to identify the effect of hydroxychloroquine on blood glucose levels in Indian patients with rheumatological diseases.

Material and Method: A prospective observational study was conducted in the Institute of Rheumatology, Madras Medical College. 100 successive patients newly diagnosed with a rheumatological disease were selected. Baseline Glycated hemoglobin (HbA_{1c}), fasting and postprandial blood sugar levels were measured and compared after 3 months of treatment with Hydroxychloroquine at a dose of 200 mg once daily. Efficacy was assessed by the changes in HbA_{1c}, fasting and postprandial blood glucose levels after 3 months. Based on the results they were classified as diabetes mellitus (DM), impaired glucose tolerance (IGT) and normal glucose tolerance (NGT) as recommended by American Diabetes Association [1]. The results were analyzed by paired t test.

Results: Out of 100 cases, 30 cases (30%) fell into DM group, 30 cases (30%) in IGT and 40 cases (40%) in NGT. In the DM group pre and post HCQ HbA_{1c} levels were 6.75% and 6.39%, in the IGT group it was 6.24% and 5.95% while in the NGT group it was 6.24% and 5.95% respectively.

Conclusion: Hydroxychloroquine had greater effect in decreasing blood glucose level in patients with Diabetes Mellitus compared to those with Impaired and Normal glucose tolerance.

Keywords: *Diabetes Mellitus; Glycated Hemoglobin; Hydroxychloroquine; Rheumatoid Arthritis; Systemic Lupus Erythematosus*

Background and Aims

Diabetes mellitus is the major health challenge of 21st century. Millions of dollars are spent on research in understanding the pathogenesis and the development of new drugs. In the developing countries, chronic metabolic disorders pose an increased challenge to national health than the communicable diseases [2,3]. While more researches are being carried out to find novel drugs and treatment strategies for diabetes mellitus, a retrograde analysis of existing drugs for the possible anti diabetic effects could cut down the time required to find new drugs.

Hydroxychloroquine, an age old drug is widely used in rheumatology as a disease modifying antirheumatic drug. The first drug used from this group was quinine, but due to its toxicity chloroquine and hydroxychloroquine were developed. Hydroxychloroquine differs from chloroquine by a hydroxyethyl group instead of an ethyl group on the tertiary amino nitrogen of the chloroquine sidechain. Hypoglycemia has been frequently reported in quinine and chloroquine. There are few reports of hydroxychloroquine causing hypoglycemia too. Our aim was to study whether this adverse effect of hydroxychloroquine can be used as a treatment modality in diabetes mellitus.

Materials and Methods

Ethical committee clearance

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Clearance from Institutional Ethical Committee for Human Studies was obtained. Informed consent was obtained from all individuals included in this study.

Time and place of study

This was a prospective observational study conducted at the Institute of Rheumatology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, India during the study period from May 2015 to October 2015.

Selection of patients

Patients attending rheumatology outpatient department with newly diagnosed rheumatological disease, age > 16years and prescribed hydroxychloroquine were selected. Pregnant and lactating mothers, patients with hematological disorders including anemia, critically ill patients and pediatric patients were excluded from the study. Previously diagnosed diabetic individuals were also excluded if there was a change in their diabetic medication during the course of the study. Consent for participating in the study was obtained from the patients after assuring about nondisclosure of their identity.

Data collection and methods

Patients satisfying the inclusion and exclusion criteria were included in the study. Blood samples were taken from the patient as soon as a diagnosis of rheumatological illness is made. Complete blood count, renal function and liver function tests were done. Before initiating Tablet Hydroxychloroquine at a dose of 200 mg once daily, for the treatment of their rheumatological illness, baseline HbA_{1c} and Fasting Blood Sugar (FBS) 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. Serum glycated hemoglobin was determined using high performance liquid chromatography. Based on the results, patients were grouped into one of the three groups namely, Diabetes Mellitus, Impaired Glucose Tolerance and Normal Glucose Tolerance as defined by American Diabetes Association.

Patients were periodically followed up for 3 months while they came to refill their medications. Efforts were taken to prevent attrition from the study via telephone communication. At the end of 3 months while receiving hydroxychloroquine for their rheumatological illness, blood samples were collected and HbA_{1c}, fasting and postprandial blood sugar levels were measured. The results were then subjected to statistical analysis.

Statistical analysis

The results were analyzed using SPSS software version 21. Association between the two variables was analyzed using paired-sample t test. The primary efficacy measures were the mean change in HbA_{1c}, FBS and PPBS from the baseline to 3 months. Statistical significance was assumed with a p value of 0.05.

Results

Out of 100 patients who participated in the study 70% (70 cases) were diagnosed with rheumatoid arthritis and 30% (30 cases) with systemic lupus erythematosus. Patients with other connective tissue disorders had either anemia or features listed in the exclusion criteria and were not included in the study. In our study group females were 72% (72 cases) and males were 28% (28 cases) with a Female to Male sex ratio of 2.57:1. There was a female preponderance in our study which can be explained by the increased incidence of connective tissue disorders among females. The group comprising 20 - 30 years of age had 17%, 30 - 40 years of age had 45%, 40 - 50 years of age had 26% and 50 - 60 years of age had 12% of cases. Clustering of cases were seen in the 30 - 50 years age group (71%). Patients in 30 - 40 years age group constituted maximum percentage (45%) in the study population. The oldest patient was 59 years old and the youngest was 26 years old.

On the 1st visit 27.78% (n = 20) of females had diabetes mellitus, 29.17% (n = 21) had impaired glucose tolerance and 43.05% (n = 31) had normal glucose tolerance. In males 35.72% (n = 10) had diabetes mellitus, 32.14% (n = 9) had impaired glucose tolerance and 32.14% (n = 9) had normal glucose tolerance. In our study majority of females had Normal Glucose Tolerance (43.05%). Males were almost equally distributed in all the three groups. Out of 30 SLE cases, 23.33% (n = 7) had diabetes mellitus, 20% (n = 6) had impaired glucose tolerance and 85% (n = 17) had normal glucose tolerance. Out of 70 RA cases 32.89% (n = 23) had diabetes mellitus, 34.29% (n = 24) had impaired glucose tolerance and 32.86% (n = 23) had normal glucose tolerance (Figure 1). In our study, majority of patients with Systemic Lupus Erythematosus had Normal Glucose Tolerance (56.66%), while Rheumatoid Arthritis patients were equally distributed in all the three group.

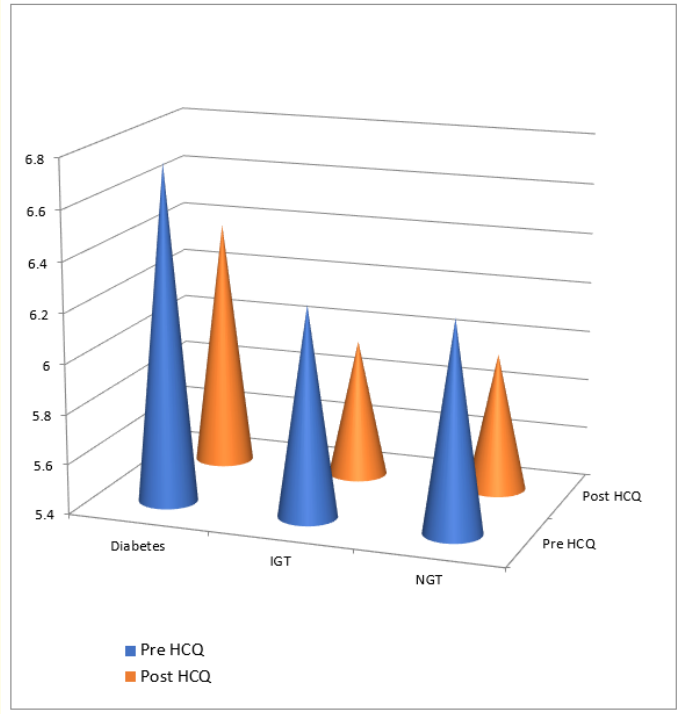

Figure 1: *Comparison of HbA1c levels in the three groups before and after treatment with hydroxychloroquine.*

From table 1, it is evident that all the values were statistically significant (p value < 0.05) and the correlation of HbA_{1c} levels were highest for diabetic group followed by NGT group and the least correlation was observed in IGT group.

Glycemic status	Investigation	Number of cases	Mean	Standard deviation	Standard error (Mean)	Correlation	Significance (p value)
Diabetes	PreHCQHbA_{1c}	30	7.636	0.621	0.113	0.993	0.001
	Post$HCQHbA_1$	30	7.153	0.486	0.088		
Impaired glucose tolerance	PreHCQHbA_{1c}	30	6.140	0.183	0.033	0.646	0.001
	PostHCQHbA_{1c}	30	5.816	0.087	0.015		
Normal glucose tolerance	PreHCQHbA_{1c}	40	5.272	0.182	0.028	0.773	0.001
	PostHCQHbA_{1c}	40	5.125	0.146	0.023		

Table 1: *Analysis of HbA1c in all 3 groups. Paired sample statistics and correlations.*

From table 2, it is evident that mean decrease in HbA_{1c} levels were highest in diabetic group followed by IGT group and the least in IGT group. From table 3, it is evident that the fasting blood sugar levels had a greater mean decrease with HCQ therapy than the postprandial glucose levels in the total population included in the study.

Glycemic status	Investigation	Paired Differences					T	df	Significance (p value)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Diabetes mellitus	PreHCQHbA1c - PostHCQHbA1c	0.48333	0.14875	0.02716	0.42779	0.53888	17.797	29	0.001
Impaired glucose tolerance	PreHCQHbA1c - PostHCQHbA1c	0.32333	0.14308	0.02612	0.26991	0.37676	12.378	29	0.001
Normal glucose tolerance	PreHCQHbA1c - PostHCQHbA1c	0.12000	0.11591	0.01833	0.08293	0.15707	6.548	39	0.001
Diabetes mellitus	PreHCQFBS – PostHCQFBS	13.7000	0.61743	0.84302	11.97582	15.42418	16.251	29	0.001
Impaired glucose tolerance	PreHCQFBS - PostHCQFBS	9.63333	4.16457	0.76034	8.07826	11.18841	12.670	29	0.001
Normal glucose tolerance	PreHCQFBS – PostHCQFBS	3.60000	3.47740	0.54983	2.48787	4.71213	6.548	39	0.001
Diabetes mellitus	PreHCQPPBS – PostHCQPPBS	20.7667	22.03083	4.02226	12.54022	28.9931	5.163	29	0.001
Impaired glucose tolerance	PreHCQPPBS - PostHCQPPBS	9.63333	6.39225	1.16706	7.24643	12.02024	8.254	29	0.001
Normal glucose tolerance	PreHCQPPBS - PostHCQPPBS	3.75000	3.76727	0.59566	2.54517	4.95483	6.296	39	0.001

Table 2: *Paired sample t test.*

Investigation	Number	Minimum	Maximum	Mean	Std. Deviation
HbA1c - Before Therapy	100	5.0	8.8	6.242	1.0529
HbA1c - After Therapy	100	5.0	8.1	5.952	0.8839
FBS - Before Therapy	100	97	206	132.810	29.8527
FBS - After Therapy	100	97	186	124.370	25.1523
PPBS - Before Therapy	100	120	280	200.120	37.5847
PPBS - After Therapy	100	141	260	196.150	25.9943

Table 3: *Descriptive statistics of all 100 cases.*

Discussion

Hydroxychloroquine is a weak base and hence can pass through cytoplasmic membrane inside the cytoplasmic vesicles and accumulate there. It increases the intravesicular pH to 6.0 from 4.0 thus interfering with the acid dependent subcellular functions. This increased pH is noted to have many postulated immunoregulatory effects including attenuation of antigen processing and its presentation; stabilization of lysosomal membranes; inhibition of cell-mediated cytotoxicity [4]. It has an overall inhibitory effect on proinflammatory cytokines. Hydroxychloroquine has been observed to block Interleukin - 1, Interleukin - 6, Interferon gamma production by monocytes [5,6]. Most of the drug is excreted unchanged in urine. A part of the drug is metabolized to a des-ethyl derivative and the rest excreted in the faeces [7].

Hydroxychloroquine has been shown to improve peripheral insulin sensitivity and insulin secretion in animal and *invitro* studies. There is a potential ability for Hydroxychloroquine to decrease HbA_{1c} in diabetic patients and coexisting systemic inflammatory disease [8]. Hydroxychloroquine decreases the plasma glucose levels by the inhibition of insulin degradation inside the Golgi apparatus and prolonging its half-life [5,9]. There is reduced risk in incidence of diabetes in Rheumatoid Arthritis patients even after glucocorticoid use and control of disease activity [10].

Inflammation has been considered to play a very important intermediary role in the pathogenesis of a number of co-existing diseases including diabetes. Elevated Interleukin-6 and C-reactive protein are the two sensitive physiological markers associated with insulin resistance, hyperglycemia, overt diabetes mellitus and sub-clinical inflammation. Hydroxychloroquine is thought to exert anti-diabetic effect by anti-inflammatory potential and by inhibiting interleukin - 6 and C - reactive protein production [11].

In our study comprising 100 patients at the end of 3 months the mean decrease in HbA_{1c} was 0.48, 0.32 and 0.12% in Diabetes, Impaired glucose tolerance and Normal glucose tolerance patients respectively. At the end of 3 months mean decrease in Fasting blood sugar was 13.70, 9.63 and 3.60 mg/dl in Diabetes, Impaired glucose tolerance and Normal glucose tolerance patients respectively. At the end of 3 months mean decrease in postprandial blood sugar was 20.77, 9.63 and 3.75 mg/dl in Diabetes, Impaired glucose tolerance and Normal glucose tolerance patients respectively. All of them had a p value of less than 0.05 and were of high statistical significance.

Laura R Rekedal, Elena Massarotti, Rajesh Garg., *et al.* conducted a study in which 45 patients taking Hydroxychloroquine and 37 patients taking Methotrexate for Rheumatoid arthritis were chosen. HbA_{1c} was measured at baseline and after 12 months after starting the treatment. The mean reduction in HbA_{1c} from the pretreatment values were 0.66% in the Hydroxychloroquine and 0.11% in Methotrexate receiving patients. In our study we included patients once the diagnosis was made and hence we didn't compare it with methotrexate group. The mean HbA_{1c} reduction in our study was 0.48% in the diabetic group and 0.12% in the normal glucose tolerance group compared to 0.66% reduction in their study.

Pareek A, Chandurkar N, Thomas N., *et al.* conducted a double - blind, double - dummy, randomized, comparative, multicenter study in 15 centers across India between December 2009 and July 2013 on 267 uncontrolled type 2 diabetes patients, post 3 months treatment

with glimepiride/gliclazide and metformin. Hydroxychloroquine was started on 400 mg daily for 6 months. The efficacy was assessed at 12 weeks and 24 weeks by measuring HbA_{1c}, fasting blood sugar and postprandial blood sugar. At the end of 12 weeks and 24 weeks all the three parameters reduced significantly from the baseline values. At the end of 12 weeks and 24 weeks the reduced values were HbA_{1c} - 0.56% and 0.87%, FBS - 17 mg/dl and 14.22 mg/dl, PPBS - 34.74 mg/dl and 31.86 mg/dl respectively. The result was compared with another set of patients started on pioglitazone. The results were compared and was found to be nonsignificant. In our study the HbA_{1c} was almost identical (0.58%) even with a dose of 200 mg per day. In our study we had compared non-diabetic patients who were not included in their study.

Hypoglycemia, retinopathy, peripheral neuropathy, myopathy, alopecia, elevated liver and renal parameters were not reported during the study period at this dose of hydroxychloroquine. However, 9 patients reported nausea, 3 had diarrhea and one patient had giddiness following intake of hydroxychloroquine. These symptoms were present after the first dose of hydroxychloroquine but disappeared after 2 days.

Limitations of the Study

All the patients were receiving Tablet prednisolone 10 mg once daily. The impact of steroid on the glycemic levels could not be ruled out in our study. However, all the patients received the same dose of prednisolone. The amount of physical activity done by individual patients was another factor that could not be standardized. The study was done in a single center and in a smaller sample size, but the observations suggested that hydroxychloroquine could be used as an antidiabetic drug.

Conclusion

There was a statistically significant decrease in the HbA_{1c}, fasting and postprandial blood sugar level in patients with rheumatological diseases treated with hydroxychloroquine. The mean decrease in blood sugar level was more in diabetic patients compared to normal and impaired glucose tolerant patients. Though the reported incidence of hypoglycemia is less with this drug, it probably counteracts the hyperglycemic effects of corticosteroids concomitantly taken by these patients. The decreased incidence of diabetes mellitus among patients suffering from rheumatological diseases in spite of glucocorticoid treatment for years together may be due the counter effect on blood glucose level provided by hydroxychloroquine. Studies done on diabetic patients and individuals without corticosteroid intake in a multicenter level may provide better understanding about this existing drug and its possibility to be used in the management of diabetes mellitus.

Conflicts of Interest

None.

Funding Received

None.

Bibliography

1. "Diagnosis and classification of diabetes mellitus. American Diabetes Association". *Diabetes Care* 35.1 (2012): S64-S71.
2. Ramachandran A., *et al*. "Diabetes in Asia". *Lancet* 375.9712 (2010): 408-418.
3. Ramachandran A and Snehalatha C. "Current scenario of diabetes in India". *Journal of Diabetes* 1.1 (2009): 18-28.
4. Wozniacka A., *et al*. "Antimalarials in cutaneous lupus erythematosus: mechanisms of therapeutic benefit". *Lupus* 11.2 (2002): 71-81.

5. Sperber K., *et al*. "Selective regulation of cytokine secretion by hydroxychloroquine: inhibition of interleukin 1 alpha (IL-1) and IL-6 in human monocytes and T cells". *Journal of Rheumatology* 20.5 (1993): 803-808.

6. Van den Borne B., *et al*. "Chloroquine and hydroxychloroquine equally affect tumor necrosis factor interleukin 6 and interferon production by peripheral blood mononuclear cells". *Journal of Rheumatology* 24.1 (1997): 55-60.

7. McChesney E., *et al*. "Studies on the metabolism of some compounds of the 1-amino-7-chloroquinoline series". *Journal of Pharmacology and Experimental Therapeutics* 151.3 (1966): 482.

8. Quatraro A., *et al*. "Hydroxychloroquine in decompensated, treatment-refractory noninsulin -dependent diabetes mellitus: a new job for an old drug?" *Annals of Internal Medicine* 112.9 (1990): 678-681.

9. Blazar B., *et al*. "*In vivo* chloroquine-induced inhibition of insulin degradation in a diabetic patient with severe insulin resistance". *Diabetes* 33.12 (1984): 1133-1136.

10. Wasko MC., *et al*. "Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis". *Journal of the American Medical Association* 298.2 (2007): 187-193.

11. Ben-Zvi I., *et al*. "Hydroxy Chloroquine: from malaria to autoimmunity". *Clinical Reviews in Allergy and Immunology* 42.2 (2012): 145-153.

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