



## Does Hydroxychloroquine Improve Glycemic Status and Lipid Profile in Rheumatoid Patients with Diabetes Mellitus – An Observational Study

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### ABSTRACT

Rheumatoid arthritis is an autoimmune disease, causing chronic inflammation of small joints in hands and feet. The chronic inflammation and corticosteroid use in rheumatoid patients predispose them to insulin resistance and diabetes. Hydroxychloroquine, a proven drug in rheumatoid arthritis, seems to be beneficial in diabetes and also reduces the risk of cardiovascular events. This study was done to find out the role of hydroxychloroquine on the glycemic status and lipid profile in Rheumatoid patients having treatment with Diabetes mellitus. 50 patients with both RA and DM in the middle age group were categorized into HCQ and Non-HCQ group. Both the groups were followed up for 6 months. Their glycemic status and lipid profile were compared by measuring FBS, PPBS, HbA1C, triglycerides, total cholesterol, VLDL, LDL and HDL. Statistical analysis was done by student t test. The mean FBS, PPBS, HbA1C values in HCQ Group patients decreased significantly from 155.16, 200.12 and 8.26 to 135.80, 174.60 and 7.49 respectively in the follow-up period. In the Non-HCQ group, there was no significant change in mean FBS and PPBS after 6 months. Mean HbA1C increased from 8.13 to 8.33 in Non-HCQ group. Triglycerides, total cholesterol, VLDL and LDL also were found to be reduced in patients who had taken HCQ. In Rheumatoid patients with diabetes, use of HCQ improves their glycemic status and reduces the lipid abnormalities.



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### INTRODUCTION

Rheumatoid arthritis (RA) is a chronic musculoskeletal disease with an autoimmune origin. It affects 1% of the adult population in the world (Silman and Pearson, 2002). The symmetric polyarticular synovial inflammation typically affects small joints of hands and feet. The inflammatory pannus formation leads to relentless joint damage with multiple deformities and functional loss.

These patients lead a sedentary lifestyle due to pain and disability, resulting in obesity which is a risk factor for diabetes mellitus (Mokdad et al., 2001). The chronic inflammation and corticosteroid use predispose them to insulin resistance and diabetes. Many

immunoregulatory components like IL-6 have been associated in the common pathophysiological pathways of RA and DM.

Hydroxychloroquine (HCQ) is commonly used in the management of RA. It has relatively low toxicity and is well tolerated with long term usage. Hypoglycemia is an uncommon side effect of therapy with hydroxychloroquine. The incidence of diabetes reduces by more than 75% in patients who use HCQ more than 4 years for RA.

This study was aimed at finding out the role of hydroxychloroquine in patients with rheumatoid arthritis and diabetes mellitus. The association between the laboratory indices and HCQ was studied to find out their relationship. We hypothesized that use of HCQ lowers fasting glucose, improves glycemic status and lipid profile in rheumatoid patients.

## MATERIALS AND METHODS

An Observational comparative study was done during the period March 2017-March 2020 in the Orthopaedics department. All patients registered with both rheumatoid arthritis and diabetes mellitus were included in the study. 50 patients in the age group, 30-60 years, were selected based on the exclusion and inclusion criteria.

The first group of patients had been taking 200 mg of HCQ twice daily, along with other anti-rheumatoid and oral hypoglycaemic drugs. The second group of patients were on similar anti-rheumatoid drugs and oral hypoglycemic drugs except for HCQ. Age, sex, body mass index, diabetic history and past medications, other significant co-morbid illnesses were noted. ESR, CRP, RA Factor, glycaemic indices such as FBS, PPBS and HbA1C, and lipid profile of all patients were done and recorded using a structured proforma during the initial visit. The patients were followed up for 6 months, and the studies were repeated. The treatment courses were connected to research participation.

### The inclusion criteria in this study was

1. Patients diagnosed to have both DM and RA within one year of study.
2. Age 30-60 years

### The exclusion criteria in this study was

1. Known cardiac disorders
2. History of retinopathy and those with uncorrected visual acuity

3. Those on insulin therapy
4. Steroid intake
5. Significant haematological disorder, gastrointestinal disorder, cardiovascular disorder
6. Abnormal liver functions
7. Pregnancy and lactation

Ethical committee clearance was obtained from the institution. Informed written consent was obtained from all the patients. Statistical analysis was done by student t-test using SPSS software version 21. Statistical tests were considered significant if P-value was <0.05 at a confidence interval of 95%. Descriptive statistics such as mean, the standard deviation for each continuous variable were used to summarize the demographic data.

## RESULTS

The age for both groups had a mean of 55 years, and female patients outnumbered males in both groups. Mean height, weight and BMI of the groups were comparable to each other. The duration of disease and treatment was 5.6 years in the HCQ group and 6.08 years in Non-HCQ group. These parameters were not statistically significant between the groups. All patients selected were RA factor positive and Anti-CCP positive.

During the follow up at 6 months, ESR and CRP in HCQ group were lesser, showing the anti-inflammatory properties of HCQ. There was no significant change in BMI in both groups after the study period. The mean FBS, PPBS and HbA1C in HCQ group improved from 155.16mg/dl, 200.12mg/dl and 8.26 in the initial visit to 135.8mg/dl, 174.60mg/dl and 7.49 at final follow-up. This showed a statistically significant change in glycemic status in HCQ group, as shown in Table 1.

On the other hand, in the Non-HCQ group, the mean FBS, PPBS and HbA1C were 156.96mg/dl, 198.76mg/dl and 8.13 during the initial visit. During the follow-up, the mean FBS, PPBS and HbA1C were 152.16mg/dl, 198.88mg/dl and 8.33. Increase in HbA1C was significant in Non-HCQ group, as shown in Table 2. On comparing the groups, the glycemic status shows better improvement in HCQ group.

In HCQ group, mean total cholesterol, triglycerides and LDL showed statistically significant decrease from 223.32mg/dl, 201.88mg/dl and 96.28mg/dl to 215.92mg/dl, 188.16mg/dl and 90.64mg/dl.

**Table 1: Comparison of Parameters in the HCQ group**

HCQ		Mean	N	Std. Deviation	t - Value	P-Value
BMI	Pre	28.4516	25	3.91125	1.584	0.126
	Post	28.02	25	3.009		
FBS	Pre	155.16	25	15.897	6.728	0.000*
	Post	135.80	25	8.893		
PPBS	Pre	200.12	25	21.881	8.519	0.000*
	Post	174.60	25	12.363		
HbA1c	Pre	8.268	25	.5893	8.445	0.000*
	Post	7.49	25	.343		
Total cholesterol	Pre	223.32	25	27.029	2.413	0.024*
	Post	215.92	25	19.229		
LDL	Pre	96.28	25	24.220	3.633	0.001*
	Post	90.64	25	18.828		
HDL	Pre	44.32	25	7.004	-5.381	0.000*
	Post	48.28	25	6.282		
Triglycerides	Pre	201.88	25	45.120	4.820	0.000*
	Post	188.16	25	37.744		
VLDL	Pre	58.36	25	12.470	0.782	0.442
	Post	57.64	25	9.995		

Mean HDL increased from 44.32mg/dl to 48.28mg/dl, as seen in Table 1.

In Non-HCQ group, mean triglycerides, LDL and VLDL showed statistically significant increase from 200.84mg/dl, 95.64mg/dl and 59.28mg/dl to 206.20mg/dl, 97.52mg/dl and 60.64mg/dl as seen in Table 2. However, there was no significant change in total cholesterol and HDL in this group.

Comparing both the groups, as shown in Table 3 LDL, VLDL and triglycerides did not show significant change. But, changes in mean total cholesterol and HDL were significant. The reduction in these lipid values in the HCQ group, even though statistically significant from the values of that of the non-HCQ group, were lesser compared to the glycemic status improvement in the same group.

## DISCUSSION

Rheumatoid patients are at increased risk of impaired glucose tolerance due to increased pro-inflammatory cytokines. They may eventually develop type 2 DM. The link between insulin resistance and rheumatoid arthritis shows clearly that chronic inflammation plays a role in the development of these conditions. Their insulin sensitivity improves when their disease process is adequately controlled. The severity and duration of RA is an important factor which influences the risk of developing type 2 DM.

Antimalarials have been commonly used in rheumatoid arthritis for a long time now. They have a superior safety profile than the other conventional drugs, even though their disease-modifying ability is not so dramatic as the other treatment options. This has led to its use in mild to moderate disease and in combination therapy for rheumatoid arthritis. They do not have any increased risk of malignancy or infection. They are well-tolerated, and no routine laboratory monitoring is needed. Their toxicity is rare, and yearly ophthalmologic examinations are recommended.

Hydroxychloroquine is safely used in many autoimmune disorders, most commonly rheumatoid arthritis. Antimalarials are noted to produce hypoglycaemia as a serious but relatively uncommon side effect in diabetic as well as nondiabetic individuals. The exact mechanism by which hydroxychloroquine exerts its hypoglycaemic action is not clear, and it's a known fact that the inflammatory cytokines alter the sugar levels. The hypoglycaemic action of chloroquine is attributed by its effect on slowing down the insulin clearance by stabilising the lysosomes and slowing down the lysosome-receptor complex breakdown in the cytoplasm (Emami *et al.*, 1998). Weber and Levitz demonstrated that Chloroquine regulates TNF production by inhibiting its transcription through mitogen-activated protein kinase pathways. HCQ modulates immune response by these effects on TNF production (Weber and Levitz, 2000).

**Table 2: Comparison of parameters in Non-HCQ group**

Non-HCQ		Mean	N	Std. Deviation	t - Value	P-Value
BMI	Pre	28.0012	25	3.51109	1.120	0.274
	Post	27.99	25	3.525		
FBS	Pre	156.96	25	17.252	1.211	0.238
	Post	152.16	25	24.465		
PPBS	Pre	198.76	25	21.206	-0.029	0.977
	Post	198.88	25	32.137		
HbA1c	Pre	8.128	25	.6275	-2.348	0.027*
	Post	8.33	25	.660		
Total cholesterol	Pre	225.88	25	25.807	0.264	0.794
	Post	224.80	25	31.365		
LDL	Pre	95.64	25	22.732	-3.911	0.001*
	Post	97.52	25	23.017		
HDL	Pre	45.76	25	7.790	-1.816	0.082
	Post	46.76	25	7.838		
Triglycerides	Pre	200.84	25	45.573	-2.599	0.016*
	Post	206.20	25	43.758		
VLDL	Pre	59.28	25	12.435	-3.827	0.001*
	Post	60.64	25	12.540		

Hydroxychloroquine also reduces the action of insulin metabolising enzyme, hence increasing insulin levels in blood (Emami *et al.*, 1999). Chloroquine increases C-peptide response, thereby improving beta cell functioning leading to hypoglycaemia (Powrie, 1991; Gerstein *et al.*, 2006). In obese non-diabetic patients, 6 weeks of HCQ use was associated with significantly increased insulin sensitivity and reduction in insulin resistance in the study by Mercer (Mercer *et al.*, 2012).

Ramser indicated that HCQ has an antiproliferative effect in tissues by induces autophagy of fibroblasts (Ramser *et al.*, 2009). Their observations suggest HCQ has a regulatory effect on homeostasis of cellular energy. Jin and White stressed that cellular autophagy under stress plays an important role in malignancies (Jin *et al.*, 2017). So, the role of HCQ as an adjunct to conventional therapies for solid tumours is being studied.

#### Effects of Usage

Petri *et al.* concluded HCQ was found to be associated with a reduction in blood glucose levels in SLE patients (Petri and Yoo, 1994). Shojania, in their case report in 1999, found the insulin requirements were lesser in a patient with RA and Diabetes by the use of HCQ (Shojania *et al.*, 1999). In 2007, Wasko in their large multicentre study in 4905 patients with 21.5 years followed up found that the development of diabetes was reduced by 77% in rheumatoid patients on HCQ therapy for more than

4 years (Wasko *et al.*, 2007). Compared to those not on HCQ, the adjusted relative risk of developing diabetes was 0.23.

In a retrospective study done on 1127 patients over 5 years, Bili found a favourable outcome with regards to the incidence of diabetes among those on HCQ compared with nonusers (Bili *et al.*, 2011). Their findings support the fact that HCQ attenuates the risk of diabetes in rheumatoid patients.

In their study on the safety and efficacy comparing hydroxychloroquine and pioglitazone in uncontrolled diabetic patients, Pareek reported a significant reduction in glycaemic parameters from baseline in both groups at 12 and 24 weeks (Pareek *et al.*, 2014). Total cholesterol and LDL-C reduction was significant in the HCQ group. At week 24, both groups showed a significant reduction in triglycerides level. There was no change in Mean HDL-C. So, they concluded that HCQ could be a safe treatment option for T2DM. In our study, mean total cholesterol, triglycerides, and LDL showed a reduction with the use of HCQ. In contrast to the above study, mean HDL also increased in 6 months follow-up in the HCQ group (Table 1).

Jagnani, in their study on HCQ on refractory diabetic patients, found significant improvement in glycaemic control when it is prescribed as an add-on therapy. Its efficacy in controlling blood sugar was comparable to agents like Teneligliptin. So, they suggested HCQ may be used in uncontrolled T2 DM

**Table 3: Comparison of parameters between HCQ and Non-HCQ group**

Post Test	Group	N	Mean	Std. Deviation	t - Value	P-Value
BMI	HCQ	25	28.0172	3.00854	.032	.974
	NON HCQ	25	27.9872	3.52524		
FBS	HCQ	25	135.80	8.893	-3.142	.003*
	NON HCQ	25	152.16	24.465		
PPBS	HCQ	25	174.60	12.363	-3.526	.001*
	NON HCQ	25	198.88	32.137		
HbA1c	HCQ	25	7.4920	.34269	-5.648	.000*
	NON HCQ	25	8.3320	.66000		
Total cholesterol	HCQ	25	215.92	19.229	-2.207	.032*
	NON HCQ	25	224.80	31.365		
LDL	HCQ	25	90.64	18.828	-1.157	.253
	NON HCQ	25	97.52	23.017		
HDL	HCQ	25	48.28	6.282	.757	.453
	NON HCQ	25	46.76	7.838		
Triglycerides	HCQ	25	188.16	37.744	-1.561	.125
	NON HCQ	25	206.20	43.758		
VLDL	HCQ	25	57.64	9.995	-.935	.354
	NON HCQ	25	60.64	12.540		

patients as an add-on drug (Jagnani *et al.*, 2017; Quatraro, 1990; O'Dell *et al.*, 1996). In our study too, HCQ group had better glycaemic control than the Non-HCQ group as evidenced by the decrease in FBS, PPBS and HbA1C.

#### Effects in Rheumatoid Arthritis and Diabetes Mellitus

In their study on 135 obese patients, Gerstein demonstrated the impact of HCQ on quality of life and its glucose-lowering efficacy when used as an add on an agent in sulfonylurea refractory type 2 diabetes (Gerstein *et al.*, 2006). Rekedal found that the baseline HbA1c reduced by 0.66% in patients with both diabetes and RA on HCQ (Rekedal *et al.*, 2010). They compared the effects of HCQ and MTX on this factor and concluded that HCQ significantly lowered glycated haemoglobin in comparison to MTX. Our results also showed a significant decrease in HbA1C in 6 months. On prolonged usage of HCQ, the glycaemic status will have a better beneficial effect.

Quatraro, from their study among patients with refractory diabetes, concluded that glycaemic control was better in those who took HCQ (Quatraro, 1990). Serum C-peptide levels were not changed, indicating that the insulin secretion was not increased. In another study by Powrie done in 20 diabetic patients, they found that the chloroquine reduces insulin clearance as well as increases its secretion in the circulation (Powrie, 1991).

#### Effect on Lipid Profile and Cardiovascular Diseases

Rheumatoid arthritis imparts higher mortality and morbidity due to cardiovascular disorders. The beneficial effect on the reduction of cardiovascular risk factors by antimalarials have been shown (Tam *et al.*, 2000; Petri, 1996; Booth *et al.*, 2006). Tam found favourable lipid profile in patients who take antimalarials and prednisone concomitantly in 123 patients with Lupus (Tam *et al.*, 2000). Usage of HCQs was associated with lesser damage in SLE patients (Akhavan *et al.*, 2013). Wasko noted that HCQ showed lower LDL and total cholesterol values than nonusers in SLE women (Wasko *et al.*, 2007).

Significant reduction in LDL, total cholesterol and triglycerides was noted in the HCQ group in our study. Morris concluded from their results that HCQ is an important adjunct therapy in Rheumatoid patients who are at high risk for CVD (Morris *et al.*, 2011). Restrepo, in their prospective cohort study over a period of 14 years in RA patients, found a significant reduction in TC, TG and LDL and an increase in HDL (Restrepo *et al.*, 2017). HDL increase has been shown to play a significant role in reducing the cardiovascular events, especially in postmenopausal women. We also found an increase in HDL in HCQ group, which will benefit rheumatoid patients prone for cardiovascular morbidity and mortality. Considering their beneficial effects on the reduction of risk factors for Coro-

nary vascular diseases like diabetes and hyperlipidaemias, antimalarials can reduce the risk of cardiovascular events. Further work is needed to find out patients' subsets who will be particularly beneficial from HCQ.

## CONCLUSIONS

HCQ is a relatively safe, a cheaper drug used commonly in treatment autoimmune diseases like RA and SLE. HCQ improves glycaemic status and lipid profile in diabetic patients with RA. These findings clearly show a protective role for them in the prevention of cardiovascular diseases in them.

## Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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