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Review Article

Hydroxychloroquine pleiotropic benefits: is there any evidence beyond rheumatological diseases?

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ABSTRACT

Once used as an antimalarial medication, hydroxychloroquine (HCQ) is now widely used to treat a variety of rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). HCQ has shown benefits in rheumatic diseases because of its anti-inflammatory and immunomodulatory properties. HCQ has demonstrated cardioprotective effects in rheumatic disorders, including SLE and RA. Recently, the role of inflammatory mediators has drawn a lot of attention in the pathophysiology of prediabetes, type 2 diabetes (T2D), diabetic complications and atherosclerotic cardiovascular diseases (ASCVD). In a prospective observational study of RA patients, taking HCQ for longer than four years, the incidence of diabetes has been found to be substantially decreased. In a mechanistic human pharmacodynamic study of T2D patients, HCQ showed improvements in insulin resistance and beta-cell function. These outcomes are associated with reductions in inflammatory markers such as interleukin 6 (IL6) and high-sensitivity C-reactive protein (hs-CRP). With its anti-hyperglycemic potential, anti-inflammatory, and pleiotropic effects (lipid-lowering, antiplatelet, antithrombotic) HCQ stands out as a therapeutic option that is affordable for patients with uncontrolled T2D who are at risk for complications. The pleiotropic benefits of HCQ extend beyond rheumatic diseases with potential in prediabetes, T2D and ASCVD.

Keywords: Hydroxychloroquine, Rheumatoid arthritis, Systemic lupus erythematosus, Type 2 diabetes

INTRODUCTION

Originally developed as an antimalarial medication, hydroxychloroquine (HCQ) is now widely used to treat a variety of rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[1]

HCQ interferes with endolysosomal function, blocks Toll-like receptor activation, inhibits autophagy, T-cell multiplication, and the generation of inflammatory cytokines, including IFN-α, IFN-γ, TNF-α, IL-1, IL-6, and IL-2.[2] The beneficial therapeutic effect of HCQ in rheumatic diseases probably lies in its multifaceted properties, which also make it a promising candidate in other medical fields.[1]

In this review, we have discussed the pleiotropic role of HCQ as an anti-inflammatory, antidiabetic, lipid-lowering, anti-platelet, and anti-thrombotic agent and its use beyond rheumatic diseases, such as type 2 diabetes (T2D) with atherosclerotic cardiovascular diseases (ASCVD).

METHODS

Relevant articles were identified through various electronic databases including PubMed, Google scholar, and Scopus using MeSH terms: diabetes mellitus, type 2, diabetes mellitus, type 2/drug therapy, and humans hydroxychloroquine/therapeutic use.

Anti-inflammatory action of hydroxychloroquine in rheumatic diseases

Rheumatoid arthritis

In an observational comparative study done by Liu et al on elderly 96 RA patients, HCQ lowered inflammatory cytokines IL-6, TNF-α, and IL-1a as compared to leflunomide at the end of 3 months ($p<0.05$).[3]

Systemic lupus erythematosus

Yang et al reported that 4 weeks of therapy with HCQ plus prednisone prevented Th17 cell differentiation and IL-17 production both in vitro and in SLE patients compared with prednisone treatment alone.[4]

Role of inflammatory markers linking to diabetes development

Inflammatory markers are significantly elevated in diabetes and in patients at risk of diabetes. Interleukin (IL)-6 and C-reactive protein (CRP) are two sensitive physiological markers of subclinical inflammation, associated with hyperglycemia, IR and overt type 2 diabetes. More importantly, recent prospective trials have demonstrated an ability of inflammatory markers to independently predict diabetes.[5]

Table 1: Overview of prospective trials showing role of inflammatory markers to diabetes development.

Trials	Number of new cases of diabetes	Duration of follow up (years)	Extent of association (adjusted odds ratio for top versus bottom quartite
Pradhan et al 2001[6]	188	4	CRP 4.2 (1.5 to 12.0); IL-6 2.3 (0.9 to 5.6)
Barzilay et al 2001[7]	45	3.4	CRP 1.83 (1.24 to 2.86)
Festa et al 2002[8]	144	5	CRP 1.34 (1.11 to 1.61) (for 1 SD ↑CRP)
Lindsay et al 2002[9]	70	4.6	Adiponectin (0.59 (0.38 to 0.91) (for 1 SD ↑adiponectin)

Clinical evidence of hydroxychloroquine in prevention of diabetes in rheumatic diseases

Wasko et al carried out a prospective observational study in 4905 RA adults with 21.5 years of follow-up to demonstrate the correlation between use of HCQ and the risk of incident T2D. The authors showed that HCQ use is associated with a 77% lower risk of T2D in RA patients who had taken the drug for longer than four years as compared to patients of RA who were not prescribed HCQ.[10]

Ozen et al conducted an observational cohort study on 13,669 RA patients to investigate the effect of DMARDs and statin treatments on the risk of T2D for a median of 4.6 years of follow up. DMARDs were classified into four groups: methotrexate monotherapy (reference); abatacept (ABA) with or without sDMARDs; any other DMARDs with methotrexate; and all other DMARDs without methotrexate; along with separate statin, glucocorticoid and HCQ (yes/no) variables. The study found that HCQ (HR 0.67) and abatacept (in comparison with methotrexate monotherapy) (HR 0.52) were associated with decreased risk of incident T2D, whereas glucocorticoids (HR:1.31) and statins (HR:1.56) were associated with increased risk. Concomitant use of glucocorticoids with HCQ showed a significant T2D risk reduction (HR 0.69). When HCQ and statins were given at the same time, the increased risk related to statins disappeared. (HR 0.92). The study concluded that HCQ provides a sustainable and treatment duration-dependent favourable effect and eliminates the increased risk associated with GC or statins in patients with RA.[11]

Clinical evidence of hydroxychloroquine in prevention of diabetes in prediabetic patients

In a randomized, double-blinded trial, Sheikhbahaie et al recruited 39 prediabetes patients to assess the effects of HCQ on blood glucose control. The study showed that after 12 weeks, patients receiving HCQ had a significantly higher increase in insulin levels ($p=0.009$) as compared to placebo. The authors also found that the group of patients receiving HCQ experienced a reduction in glucose at 60 min of the OGTT test (from 163.0 mg/dl to 158.4 mg/dl) as compared to an increase in blood glucose in the placebo group (163.3 mg/dl to 181.7 mg/dl, $p=0.033$).[12]

Glucose lowering/insulin resistance lowering action of hydroxychloroquine in rheumatic diseases

Penn et al carried out a cross-sectional evaluation of nondiabetic women with SLE (n=149) or RA (n=177) with a mean disease duration of 16 years to determine effect of HCQ on glycemic control. The study discovered that, HCQ use was associated with lower fasting glucose in women with SLE (0.04) or RA (0.05) and also lower log HOMA-IR ($p=0.009$) in the SLE group than in HCQ nonusers.[13]

Insulin resistance lowering action of hydroxychloroquine in non-diabetics

In an open-label human pharmacodynamic study, Mercer et al found that at the end of 6 weeks of HCQ therapy, Matsuda insulin sensitivity index (ISI) increased (p=0.040) and HOMA-IR decreased (p=0.09) in 13 obese, non-diabetic subjects (BMI≥30 kg/m^2) without systemic inflammatory conditions.[14]

Anti-inflammatory and improvement of β-cell function action in insulin resistance populations

Wasko et al conducted a randomized, double-blind study on 32 non-diabetics, overweight or obese individuals, with one or more markers of insulin resistance to explore the mechanism of action of HCQ on glucose metabolism. At the end of 13 weeks, HCQ improved insulin sensitivity, beta cell function as measured by disposition index, and adiponectin levels as compared to placebo. The authors showed that HCQ has anti-inflammatory effects in adipose tissue by reporting elevated levels of adiponectin.[15]

In a randomized, double-blinded, placebo-controlled study to determine the mechanism of antidiabetic effects of HCQ, Toledo et al recruited 43 insulin-resistant people without rheumatic diseases. The study included patients with insulin resistance such as (fasting hyperinsulinaemia (>7 μU/ml); impaired fasting glucose; impaired glucose tolerance; previous gestational diabetes; polycystic ovary disease; and a waist circumference of more than 102 cm (men)or of more than 88 cm (women). The authors employed hyperinsulinaemic-euglycaemic clamp and stable-isotope tracer dilution methods to measure glucose metabolism. The study showed that HCQ 400 mg/day significantly increased systemic glucose clearance (p=0.025) and skeletal muscle insulin sensitivity by 26% (p=0.019) when compared to a placebo. The study found that circulating IL-6 was lower (p=0.01) and adiponectin was higher (p=0.045) at the end of 13 weeks, indicating that adipose tissue inflammation may have responded to HCQ treatment.[16]

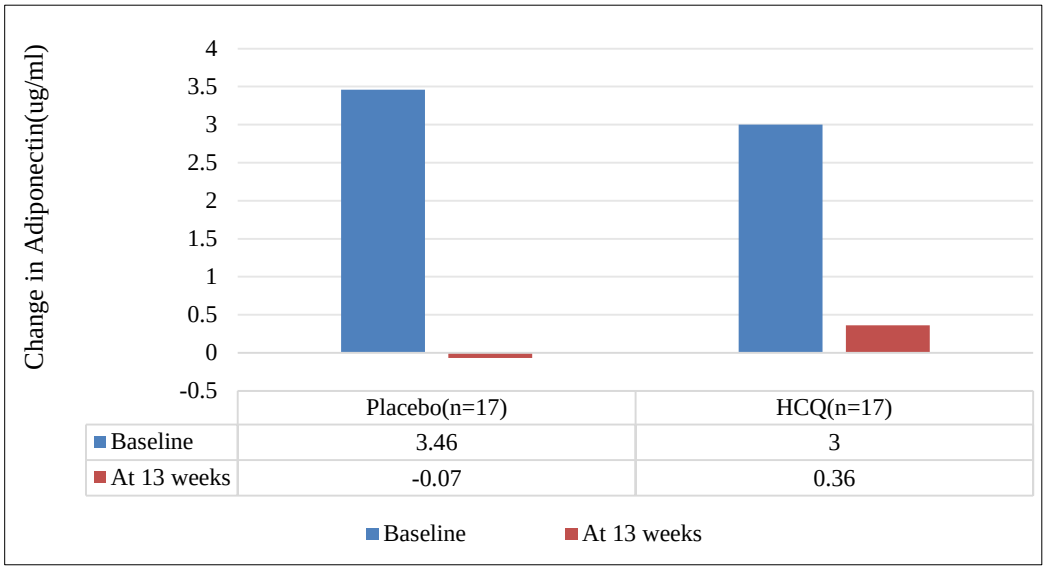

Figure 1: Effect of HCQ on adiponectin levels (p=0.045).

Anti-inflammatory action and β-cell preservation action of hydroxychloroquine in diabetes

In another experimental study, Abdel-Hamid et al demonstrated that after 4 weeks, HCQ in the T2D group showed preservation of islets of Langerhans (IOL), structure, a significant increase in the β-cell area ($p<0.05$), % mass, IOL proliferation, and neogenesis, as well as correction of the significantly increased α-cell area ($p<0.05$), %, disturbed glucose homeostasis, and lipid profile as compared with the T2D group without HCQ. HCQ also decreased serum levels of MCP-1 as well as pancreatic levels of IL-1b, IL-6, TNF-a, and TGF-B1, which were markedly elevated in T2D.[17]

Glucose lowering action of hydroxychloroquine in diabetes

International studies in treatment of type 2 diabetes

In a prospective, randomized placebo double-blind trial, Quatraro et al evaluated the effectiveness and safety of HCQ in 38 patients with noninsulin-dependent diabetes (NIDDM) resistant to commonly used therapies (oral drugs, insulin, combination of insulin and oral drugs). The patients had HbA1c values between 12.1% and 12.5%. The study involved two study groups: one received insulin (n=22) and the other, glibenclamide (n=16). The 22 insulin-treated diabetic patients were divided into two groups, each consisting of 11 patients: one group (insulin and placebo) continued insulin treatment whereas other

received insulin and HCQ. The 16 patients treated with glibenclamide were also divided into two groups, each consisting of 8 patients: one group received glibenclamide and placebo whereas the other received the glibenclamide and HCQ. The study showed that addition of HCQ to insulin caused a statistically significant decrease in glucose profile (glucose profile decrease, -11.7 mmol/l; p=0.001; HbA1c decrease, -3.3%; p=0.001) as compared to insulin treated placebo at the end of 6 months. The patients receiving combined insulin and HCQ therapy required a 30% average reduction in their daily insulin dose. Patients treated with a combination of glibenclamide and HCQ also showed a significant reduction of both the glucose profile and HbA1c levels (glucose profile decrease, -10.8 mmol/l; p=0.001; HbA1c decrease, -3.3%; p=0.001) as compared to the glibenclamide-treated placebo at the end of 6 months.[18]

In a randomized double-blind placebo controlled trial Gerstein et al recruited 135 obese T2D patients with poor glycemic control on maximal doses of sulfonylurea to the addition of HCQ or placebo. The authors reported that during the first 6 months, HCQ decreased HbA1c by an absolute amount of 1.02% more than placebo. The study demonstrated that in patients whose HbA1c was between 11 and 13.5%, HCQ was effective for a mean period of 1 year and lowered the HbA1c by an absolute amount of 1% more than placebo.[19]

In one open-label, comparative proof-of-concept study done by Hsia et al, on 32 T2D patients taking maximally-tolerated doses of metformin plus sulfonylurea with HbA1c levels of ≥7.5% to <11.0% were randomized to add-on treatment with HCQ 400 mg or pioglitazone 45 mg, respectively. The study reported at the end of 4 months that HCQ significantly reduced HbA1c levels by 1.2%. The authors concluded that decreased hsCRP levels in both groups support the paradigm that anti-inflammation may be a useful therapeutic strategy for treating T2D.[20]

Phase-3, phase-4 studies in India

In a double-blind comparative study, Pareek et al randomized 267 uncontrolled T2D patients after-treatment with glimepiride/gliclazide and metformin with HbA1c ≥7.5% and ≤11.5% to receive HCQ 400 mg/day or pioglitazone 15 mg/day. The study found that at week 12 and week 24, HbA1c, FBG, and PPG significantly reduced from baseline in both groups. At week 12 (HbA1c: -0.56% versus -0.72%; FBG: -0.99 mmol/l versus -1.05 mmol/l; PPG: -1.93 mmol/l versus -1.52 mmol/l) and at week 24 (HbA1c: -0.87% versus -0.90%; FBG: -0.79 mmol/l versus -1.02 mmol/l; PPG: -1.77 mmol/l versus -1.36 mmol/l). There was no significant difference in the mean decrease in glycemic parameters at week 12 and at week 24 between the HCQ and pioglitazone groups.[21]

In a prospective, multicentric, phase 4 study conducted by Pareek et al, 747 uncontrolled T2D patients on sulfonylureas+metformin combination received HCQ 400 mg/day for 52 weeks. The study reported that there was 1.18%, 1.17% and 0.8% reduction in HbA1c at week 12, week 24, and week 52 respectively from baseline (p<0.0001). The authors found that that fall in HbA1C was significantly higher at weeks 12 and 24 in patients with high inflammatory load (hsCRP>3) (p<0.0001) as compared to patients with hsCRP<3. There was a significant reduction in mean FBG and PPG from baseline at all visits throughout the study (p<0.05).[22]

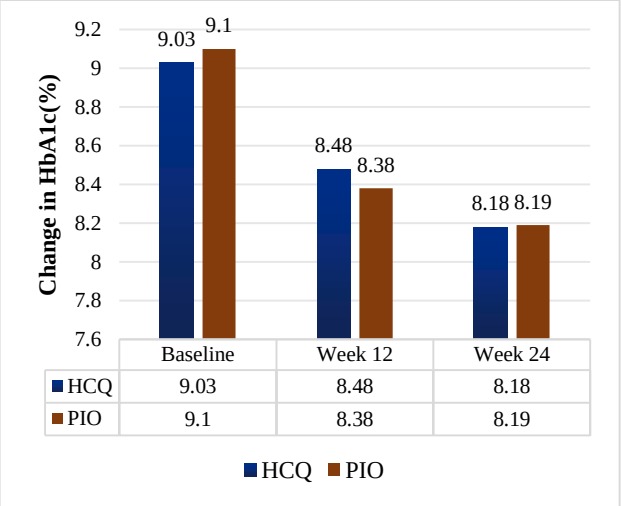

Figure 2: Change in HbA1c from baseline at week 12 and week 24 (p<0.0001).

Indian observational studies in type 2 diabetes

Type 2 diabetes

In one multicenter, open-label comparative observational study, Baidya et al evaluated the relationship between hs-CRP and HbA1c. The study randomized 240 patients with T2D who were poorly controlled with a high, stable insulin dose, glimepiride, and metformin to either HCQ 200 or 400 mg once daily for 6 months. The authors reported that at the completion of 6 months, statistically significant dose-dependent mean decreases in HbA1C from baseline were seen in both the HCQ 200 and 400 mg groups (-0.8% and -1.3%, respectively) (p<0.0001). The study showed a significant decrease in total daily insulin dose of -3.6 IU/day with HCQ 200 mg and -9.8 IU/day with HCQ 400 mg at the end of the study. The authors found that reducing Hs-CRP by ≥1 is associated with a reduction of HbA1c in a range of 0.8-1.3%.[23]

In one multicenter observational trial, Baidya et al evaluated the long-term efficacy and safety of 400 mg of HCQ on 498 T2DM patients with inadequate glycemic control on diet and exercise in combination with metformin, sulfonylurea and basal insulin. The study demonstrated that apart from a significant reduction in glycemic parameters (HbA1c, FPG and PPG (p>0.001 for all), HCQ reduced inflammatory load and hs-CRP at the end of 72 weeks. It has also been found that there was a

26% reduction in the daily insulin dose at the end of 72 weeks.[24]

In a 12-week study, Rajput et al evaluated the effect of HCQ in 30 uncontrolled T2D patients on a glimepiride and metformin combination with an HbA1c between 7.5 and 10%. The study showed significant improvement in FPG, PPG, and HbA1c along with significant improvement in IL6, hsCRP, and adiponectin levels after 12 weeks of adjunctive treatment with HCQ. The authors reported that the mean beta cell function of patients increased significantly as measured by the HOMA-B formula and insulin resistance (IR) decreased significantly as measured by the HOMA-IR formula ($p<0.0001$ for both). The authors concluded that the changes in beta cell function and IR correlated significantly with the changes in IL6, hsCRP, and adiponectin levels.[25]

In a double-blind, placebo-controlled study done by Chakravarti et al, 304 uncontrolled T2D subjects on glimepiride 4 mg and metformin 500 mg) were randomized to HCQ 200 mg, 300 mg, 400 mg once daily, or placebo. The study showed that HCQ was associated with a significant reduction in HbA1c from baseline (7–8.5%) at the end of 12 weeks −0.78%, −0.91%, and 1.2% for HCQ 200 mg, 300 mg, and 400 mg OD, respectively, versus 0.13% with placebo ($p<0.005$).[26]

Action of hydroxychloroquine on glycemic variability

Rajput et al conducted an open label, single centre study to assess the effect of HCQ on glycemic variability in 30 uncontrolled T2D patients taking glimepiride and metformin. The glycaemic variability parameters such as standard deviation of 24 hours of blood glucose, mean of daily differences (MODD) and mean amplitude of glycaemic excursion (MAGE) were assessed by continuous glucose monitoring system (CGMS) data at baseline and at 12 weeks after the addition of HCQ 400 mg. The study reported that at the end of 12 weeks, there was a significant reduction in MAGE, MODD, average blood glucose, and the standard deviation of 24-hour blood glucose with a significant p value <0.0001.[27]

Lipid lowering action of HCQ in rheumatic diseases

Rheumatoid arthritis

In a prospective longitudinal study by Kerr et al, 1,011 patients were enrolled to assess the relationship between lipid profiles and HCQ use in a veterans affairs cohort. The study found that, with the exception of HDL ($p=0.165$), mean levels of TC: -13.5 mg/dl, LDL-C: -11.7 mg/dl, and triglycerides (TG): -21.8 mg/dl were significantly lower for HCQ users as compared with HCQ nonusers. In addition, NCEP-ATP III target (TC<200 mg/dl, LDL-C<100 mg/dl, HDL>40 mg/dl) levels were met in a higher number of patients in HCQ users as compared to HCQ nonusers, regardless of statin use or disease activity. The authors concluded that HCQ use for at least 3 months was associated with better lipid control irrespective of statin use or disease activity.[28]

Systemic lupus erythematosus

Of the 384 SLE patients included in the Baltimore Lupus cohort, 35% used HCQ. Using the Baltimore lupus cohort, in 71 lupus patients, serum cholesterol was found to be lower in those who used HCQ (8.9±3.4%mg). Mean glucose level was also found to be significantly lower in the HCQ group (84.9±15.2 mg/dl) than those who were not taking HCQ (89.0±21.5 mg/dl).[29]

Lipid lowering action of HCQ in non-rheumatology settings

In patients with primary dyslipidaemia

A double-blind, randomized, comparative, outpatient, phase III study was conducted by Pareek et al to evaluate the efficacy and safety of atorvastatin 10 mg + HCQ 200 mg FDC tablets in comparison with atorvastatin 10 mg alone in 328 patients with primary dyslipidemia having LDL-C ≥130 mg/dl to ≤250 mg/dl and TG ≤400 mg/dl. Patients receiving atorvastatin plus HCQ combination treatment showed significantly greater reductions in LDL-C (-32.52 versus -39.54; $p=0.008$), TC (-24.41 versus -29.30; $p=0.013$), and non-HDL-C (-30.37 versus -36.76; $p=0.009$) at week 24 as compared to atorvastatin alone. In an exploratory analysis of patients with pre-diabetes, the authors found that diabetes developed in 8 patients (15.09%) in the atorvastatin group as compared to 1 patient (1.96%) in the atorvastatin plus HCQ combination group ($p<0.034$).[30]

In type 2 diabetes

In one multicentre observational, retrospective study, Singh et al substituted teneligliptin with HCQ in uncontrolled T2D patients. The study demonstrated that at the end of 24 weeks, after switching from teneligliptin to HCQ, there was a significant decrease in HbA1c (-1.1±0.17%), FBG (-29.87±8.9 mg/dl), and PPBG (-56.89±9.2 mg/dl), with 52% of patients attaining HbA1c less than 7%. The authors reported that there was also a significant decrease in lipid parameters (TC reduced from 181.28±5.60 mg/dl to 161.68±4.44 g/dl, TG reduced from 152.64±18.15 mg/dl to 113.34±12.71 mg/dl and LDL-C reduced from 132.84±9.35 mg/dl to 120.14±5.89 mg/dl) after the switch from teneligliptin to HCQ.[31]

In a phase-3 double-blind comparative trial Pareek et al showed that the HCQ group experienced a significant decrease in TC (-0.37 mmol/l versus - 0.03 mmol/l, $p<0.002$) and LDL-C (-0.23 mmol/l versus -0.09 mmol/l, $p<0.003$) levels from baseline at weeks 12 and week 24 in comparison to the rise in these parameters in patients treated with pioglitazone. TG levels in the pioglitazone group were only significantly reduced at week 24 ($p<0.008$), while in the HCQ group they also significantly

decreased at weeks 12 (p<0.006) and week 24 (p<0.011) relative to baseline.[21]

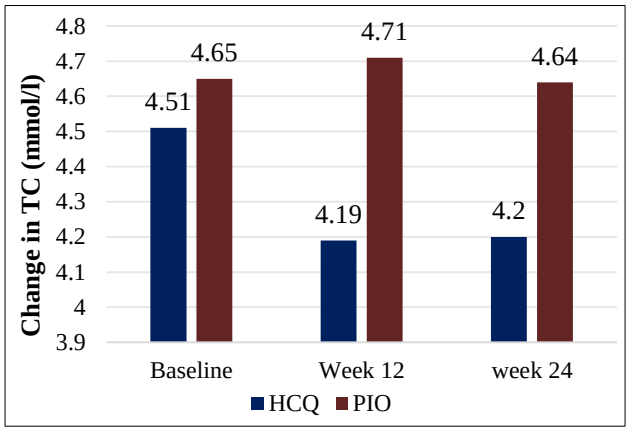

Figure 3: Change in TC at 12 weeks and 24 weeks.

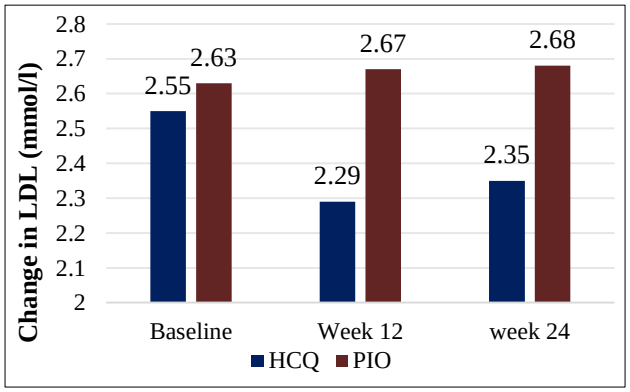

Figure 4: Change in LDL at 12 weeks and 24 weeks.

In a prospective, multicentric, phase 4 study, Pareek et al, reported an absolute reduction of 5.92%, 9.19%, and 8.06% at Week 52 in TC, LDL-C, and non-HDL-C, respectively (p<0.05) with the use of HCQ. Although not significant, there was a fall in TG levels at week 52 from baseline and an increase in HDL at week 52 from baseline with HCQ.[22]

Antiplatelet action of hydroxychloroquine in healthy human volunteers

Achuthan et al assessed the antiplatelet activity of HCQ alone, in combination with aspirin (ASA), and compared it to ASA alone and ASA plus clopidogrel in healthy human volunteers. In part 1 of the study, 8 volunteers were given HCQ for 7 days and in part 2 of the study, 12 volunteers were randomly divided in a 1:1:1 ratio to the 3 groups: ASA, ASA plus HCQ and ASA plus clopidogrel. Treatment periods lasted 7 days and were separated by a 14-day washout period. HCQ administered alone significantly reduced platelet aggregation when arachidonic acid (AA) was used as an agonist (p=0.03) as compared to when ADP, collagen was used as an agonist. Inhibition of platelet aggregation (IPA) was significantly increased when ASA plus HCQ was compared with ASA alone. When HCQ was used alone or in conjunction with ASA, there was a significant decrease in the values of fibrinogen and ESR. The results of the present study demonstrated that HCQ has antiplatelet properties, possibly through the AA pathway (downstream to thromboxane A2 production), which potentiates the antiplatelet effect of ASA and reduces fibrinogen levels.[32]

Antithrombotic action of hydroxychloroquine in rheumatic diseases

Benefit in primary antiphospholipid syndrome (PAPS)

Nuri et al in a retrospective cohort study, evaluated the effect of HCQ on aPL titers and the incidence of thrombotic events in 57 HCQ-exposed patients compared to 57 HCQ-unexposed patients. The study found that both the levels of IgG anti-cardiolipin and IgG/IgM anti-β2-glycoprotein I were significantly reduced at the end of 72 months compared to the baseline in HCQ-exposed patients, while there was no significant change in the HCQ-not-exposed group. The study showed a decrease in the incidence of arterial thrombosis recurrence in patients treated with HCQ as compared to the 1.14% incidence in the HCQ-non-exposed group.[33]

Antithrombotic action of hydroxychloroquine in non-rheumatic diseases

Prevention of deep venous thrombosis (DVT)

In a double-blind placebo-controlled trial, Hansen et al recruited 153 patients with fractures of the hip, pelvis, or thoracolumbar spine to assess the efficacy of HCQ in preventing DVT. The study demonstrated that HCQ significantly reduced the number of thromboembolic complications (p<0.005) as compared to placebo.[34]

Carter et al recruited 565 patients undergoing major surgery (upper and lower abdominal, mastectomy, laparotomy) to assess the effect of HCQ on the incidence of lower-limb venous thrombosis and consequent pulmonary embolism (PE) in the postoperative period. The incidence of clinically apparent DVT was none in the HCQ group and 25 in the controls (p<0.001). The incidence of PE was 6% in the controls and 1% in the HCQ group (p<0.001).[35]

Reno protective action of hydroxychloroquine in rheumatic diseases

Rheumatoid arthritis

In an observational cohort study, Wu et al followed up 2619 newly diagnosed RA patients up to 13 years to evaluate the association of HCQ use with the risk of developing CKD. This study demonstrated that HCQ use was associated with a 36% lower risk of incident CKD in HCQ users than in HCQ nonusers.[36]

Systemic lupus erythematosus

Pons-Estel et al in a longitudinal observational cohort study on 203 lupus nephritis patients from LUMINA trial evaluated the protective effect of HCQ on renal damage. Sixty-three (31.0%) of 203 patients developed renal damage over a mean disease duration of 5.2 years. The authors reported that the cumulative probabilities of developing renal damage at five and 10 years for those patients who were on HCQ were 20% and 38% compared to 47% and 70% for those who were HCQ non-users ($p \leq 0.0001$). The study found that 79.3% of HCQ users showed a lower occurrence of class IV glomerulonephritis and had received lower glucocorticoid doses ($p=0.0247$) than HCQ non-users.[37]

Reno protective action of hydroxychloroquine in preclinical study

In a preclinical study conducted by Pareek et al evaluated the role of HCQ in diabetic nephropathy. The study showed for the first time that biochemical and renal oxidative stress parameters such as serum creatinine and glutathione (GSH) improve when HCQ and its combinations with losartan, azilsartan, and telmisartan (ARBs) and ramipril (ACEI) are used. The study suggested that marked improvement in these parameters indicates recovery from renal damage.[38]

Reno protective action of hydroxychloroquine in clinical study

Baidya et al conducted a real-world study in 67 T2D patients with evidence of diabetic kidney disease (DKD) to explore the effects of HCQ in combination with rosuvastatin on the lipid profile and HbA1c. All patients were taking DPP4i and metformin along with short acting insulin. The study found that at the end of 3 months, serum creatinine decreased in the HCQ group (from 2.01±0.81 mg/dl to 1.61±0.70 mg/dl), while it increased in the non-HCQ group (from 1.56±0.788 mg/dl to 1.99±0.866 mg/dl). Additionally, eGFR increased in the HCQ group (from 39.95±19.9 ml/min to 51.10±23.2 ml/min) and decreased in the non-HCQ group (from 55.99±21.241 ml/min to 41.93±19.112 ml/min). Also, urinary ACR decreased in the HCQ group and increased in the non-HCQ group. The authors concluded that HCQ can be an option for patients in the early stages of DKD, and it may be combined with rosuvastatin for better lipid levels and better control of HbA1c.[39]

Antiatherosclerosis effect/cardiovascular protective effect of hydroxychloroquine in rheumatic diseases

Rheumatoid arthritis

Sharma et al examined the association of HCQ use with incident CVD in a retrospective cohort of RA patients excluding patients with CVD prior to RA diagnosis from 2001 to 2013. The study included 1266 RA patients, 547 HCQ users, and 719 nonusers. Median observation time was 6.0 years. The study observed that treatment with HCQ was independently associated with a 72% reduction in all incident CVD events and 70% reduction in the risk of incident composite CAD, stroke, and TIA as compared with HCQ non-users.[40]

Shapiro et al in a retrospective cohort study between 2003-2013 investigated the effect of HCQ treatment on CV morbidity in 514 RA patients. HCQ treated patients had Disease duration of 11.3 years. The authors found that of HCQ-treated patients 32 (13.3%) experienced cardiovascular events as compared to 104 (38.1%) in the non-treated group. In addition, HCQ showed a protective effect on all CV events that were studied (HR=0.456) as well as arterial events alone (HR=0.461). The study concluded that higher dose (400 mg/day) of HCQ showed more protection from CV events as compared to lower dose (200 mg/day) (HR=0.432).[41]

Rheumatic diseases

Chen et al conducted a retrospective cohort study on 1007585 patients from a hospital-based population from year 2010 to 2022. In this cohort, 146862 patients had newly diagnosed HTN or DM. Among these patients, 1903 patients had HCQ exposure and 136396 patients had no HCQ exposure after exclusion of previous CVD events or invasive cardiovascular procedures. The included patients in HTN or DM group had rheumatic diseases, such as RA, SLE, pSS, vasculitis, systemic sclerosis, inflammatory myositis, palindromic rheumatism and APS, while most of the patients without exposure to HCQ did not have rheumatic diseases. Patients were followed-up until the earliest of the occurrence of CVD events, the date 30 September 2022 was reached, or the withdrawal from the patient database. The study found that in HTN/DM patients, HCQ was linked to a 33% lower risk of experiencing composite CVD events, such as ischemic stroke and acute myocardial infarction (AMI) when compared with non-HCQ group.[2]

Lupus

Haugaard et al conducted an observational cohort study in 4587 patients with cutaneous lupus erythematosus (CLE) or SLE to investigate whether HCQ treatment is associated with the risk of major adverse cardiovascular outcomes (MACE) (between 1997 and 2017). Furthermore, the number of events and incidence rates (IRs) of MACE per 1000 person-years were calculated for HCQ users and nonusers, respectively. The authors found that there is a negative correlation between the use of HCQ and the risk of MACE in patients with CLE (adjusted HR: 0.71) and SLE (adjusted HR: 0.65) as compared with HCQ nonusers. Among the HCQ users 59 patients experienced MACE compared with 396 among the nonusers. When stratifying according to SLE and CLE, the number of MACE was higher for patients with SLE than CLE. The IRs (per 1000 person-years) were 7.33 (95% confidence interval [CI],

5.68-9.46) and 12.70 (95% CI, 11.52-14.03) for HCQ users and nonusers, respectively.[42]

HCQ in acute coronary syndrome (ACS) patients

Lotta Ulander et al randomly assigned 125 myocardial infarction (MI) patients, at a median of 43 hours post-hospitalization, to receive HCQ 300 mg (n=64) once daily or placebo (n=61) as part of a multicenter, double-blind, placebo-controlled OXI study. Laboratory parameters were measured at baseline, 1, 6, and 12 months. At 6 months, HCQ lowered IL-6 levels more than placebo (p=0.042, between groups) while at the end of 1 year there were no differences between groups (p=0.907).

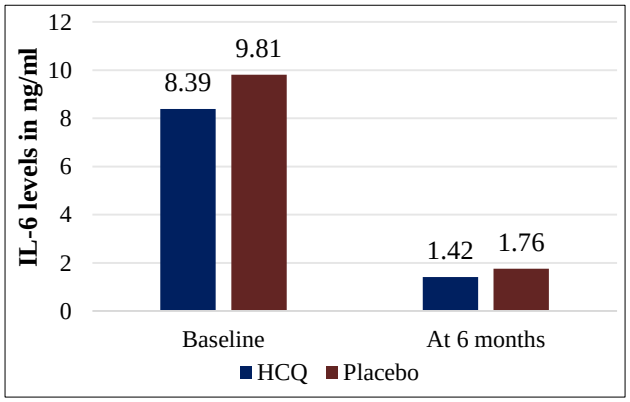

Figure 5: IL-6 level at 6 months between two groups (p<0.0019).

At the start of the study (p=0.127) and at 1 month (p=0.087) QTc intervals were comparable in the HCQ and placebo groups. In two cases (one in each group), QTc was prolonged during the medication period to >500 ms, leading to the withdrawal of the study medication. At the end of 1 year, the QTc intervals were again similar in the two groups (p=0.632) but lower than at study onset (p<0.0001 for all patients at study onset versus at 1 year). All patients, particularly those in the HCQ group, had QTc intervals that were lower at one month (427 ms), six months (424 ms), and one year (411 ms) than the baseline value (436 ms), resulting in a descending graph. The authors reported that there were no differences in the rates of arrhythmia, heart failure, cardiac damage measured by troponin release, or death between groups during the study. The study suggested a beneficial effect of HCQ in reducing cardiovascular inflammation.[43]

Role of HCQ in non-alcoholic fatty liver disease (NAFLD)

In a preclinical study, conducted at the Institute of Pharmaceutical Education and Research (IPER) Wardha evaluated the role of HCQ in NAFLD. The study showed that combination of HCQ + an insulin sensitizing agent (metformin) + a lipid-lowering agent (atorvastatin) found positive effects in treating NAFLD.[44]

CONCLUSION

HCQ, used as an immunomodulatory and anti-inflammatory drug since decades for the management of autoimmune diseases, has the most abundant evidence for metabolic benefits. It has shown cardiovascular disease risk reduction in the cohort of rheumatoid arthritis, SLE patients. By virtue of its antidiabetic, lipid lowering, antiplatelet, and anti-inflammatory properties, HCQ may develop into a therapeutic alternative to lower cardiovascular risk not only in rheumatic diseases but also in non-rheumatic diseases like type 2 diabetes. Pioneering research studies from India highlight the potential of HCQ in prediabetes, diabetes complications, steroid induced dysglycemia and dyslipidaemia and comorbidities of diabetes including metabolic syndrome, NAFLD and nephropathy which must be further explored.

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