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A PILOT STUDY ON EFFECT OF HYDROXYCHLOROQUINE IN GLYCEMIC CONTROL OF WOMEN WITH RHEUMATOID ARTHRITIS IN A TERTIARY CARE HOSPITAL, EASTERN ZONE OF INDIA

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ABSTRACT **Objectives:** To evaluate the effect of hydroxychloroquine (HCQ) on fasting blood glucose, insulin resistance and insulin sensitivity in women with rheumatoid arthritis (RA). **Methods:** A pilot study was conducted on 48 women with RA. Women recruited for a prospective, longitudinal evaluation of glycemic control and cardiovascular risk factors were characterized by HCQ usage status. Fasting glucose, median insulin sensitivity and insulin resistance which is assessed by homeostasis model assessment (HOMA-IR) calculations methods were compared in between HCQ users and HCQ nonusers for a disease specific group. **Results:** After adjustments of age, diseases duration, prednisone dose, C-reactive proteins, menopausal status, non steroidal anti-inflammatory drugs and diseases specific indicators, serum glucose and HOMA-IR were significantly lower in HCQ-users than non-users. Insulin Sensitivity index was significantly improved analysis revealed. **Conclusions:** HCQ use was associated with lower fasting glucose in women with RA and also lower log HOMA-IR. The use of HCQ may be beneficial for reducing cardiovascular risk by improving glycemic control in these patients.

KEYWORDS :

INTRODUCTIONS:

Recent progress in the management of rheumatoid arthritis (RA) is changing attention toward co-morbidities, such as associated diabetes and cardiovascular disorders. The increased insulin resistance seen in RA is closely linked to the systemic inflammation induced by certain pro-inflammatory cytokines such as tumor necrosis factor α (TNFα) and interleukin-6.(1) TNFα decreases tyro- sine phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1) kinase and induces serine phosphorylation of IRS-1, which becomes an insulin receptor inhibitor in adipocytes and skeletal muscle cells and thereby interfering in insulin singling(2).

One possible link between the systemic inflammation of rheumatic diseases and an increased risk of CVD is worsening of insulin resistance.

Hydroxychloroquinine (HCQ), FDA approved DMRD commonly used in RA.HCQ contains a number of therapeutic properties, many of them not being fully understood at a molecular level. However, its therapeutic effect has been found to possess anti-inflammatory, immunomodulating, anti-infective, and antithrombotic actions [3].

HCQ increases insulin sensitivity and reduces insulin resistance through its indirect effect by reducing inflammation [4]. HCQ has been reported to improve insulin sensitivity through the activation of protein kinase β resulting in increased glucose uptake and glycogen synthesis [5].

According to a study done by [6], a combination of HCQ and insulin decreased the HbA1c level in patients with type II DM as compared to insulin therapy with other oral hypoglycemic agents.In two large epidemiological studies of patients with RA, an association was noted between HCQ use and a reduced risk of developing DM [7,8]

A retrospective cohort study done on patients' diagnosis with either of RA or psoriasis treated with TNFα inhibitors, methotrexate, HCQ, and other nonbiologic DMARDs reported the reduced relative risk of DM for TNFα inhibitor and HCQ compared with other nonbiologic DMARDs [9,10]. Diabetes incidence was lower for HCQ ever users than never users (HR 0.59 (95% CI 0.49 to 0.70)). HCQ seemed to decrease insulin resistance and incidence of CVD.(11)

Having a diagnosis of RA also puts one at risk, likely due, at least in part, to the adverse effects of chronic inflammation on the vasculature (12,13). HCQ use was associated with a 72% decrease in the risk of incident CVD in RA patients and can be used as primary prevention of CVD in RA or non-rheumatic high-risk patients (14).

The most possible Molecular Mechanisms of Hydroxychloroquine in glycemic control maybe it inhibits the degradation of insulin enhancing the metabolic effects of the hormone and most possible explanation for the glucose-lowering effect of HCQ may be that HCQ stabilizes intracellular lysosomes and reduces the breakdown of the internalized insulin receptor complex [15]

In light of this background, we conducted a pilot study among non-diabetic obese subjects without a known systemic inflammatory condition. We assessed HCQ's effect on insulin sensitivity and insulin resistance within a short period and hypothesized that insulin sensitivity would improve during HCQ administration in comparison of the HCQ-nonusers.

MATERIAL AND METHODS:

Study Population:

All aspects of this study were approved by the Institutional Review Board (IEC) at Burdwan Medical College and Hospital. Additionally, each patient signed an informed consent form that was obtained according to the Declaration of Helsinki and approved by the IRB at the same institution. Study was carried out over a period of 6 months. For sampling technique consecutive sampling method was used. Using G*Power 3.1.9.4, sample size calculation was done to detect medium effect size of 0.25 with 80% power for between group comparison, alpha was set at 0.05. Between groups comparison (one-way ANOVA) required 48 patients and was large in comparison to other method of analysis, 10% drop out rate included. In our study 18 did not meet the laboratory or medical tests. Women with body mass index (BMI) ≥ 30 kg/m^2 non-diabetics diagnosed case of Rheumatoid Arthritis are included. The selected patients are on treatment with either HCQ or other non-biological DMRDs minimum for 3 consecutive months (12 weeks). On the hand, patients who are diagnosed case of DM or using medications for the same ,women who were having BMI less than 30, Family history of DM, patients who were resistant to monotherapy or needed to give combination therapy, patients having any concomitant inflammatory diseases (like, history of neuromuscular disease, psoriasis, chronic inflammatory intestinal disorders or eye disease with the exception of cataracts or glaucoma) other than RA and having active severe liver or kidney diseases were excluded to reduce the biases.

Intervention:

It was a prospective, longitudinal, randomized, interventional pilot form of study. After eligibility was confirmed through screening procedures, subjects who were included and signed informed consent were divided in two groups , 1)Treated with HCQ and 2) Treated with

other non-biological DMRDs. The subjects were treated for 12 weeks. Baseline investigations were done for BMI, FBS, ISI(insulin sensitivity Index) and HOMA-IR . Again, the above-mentioned parameters were recorded at 12th weeks of treatment. A record was kept of each subject's pill counts and reminder phone calls were made to keep subjects as compliant as possible. All study individuals were closely monitored and in contact throughout the twelve-week protocol.

Study Tools: The study procedure includes two methods:
1) Matsuda insulin sensitivity index
2) HOMA-IR for knowing the insulin resistance.

ISI(Matsuda) = $10000 / \sqrt{(G0 \times I0 \times Gmean \times Imean)}$
ISI, insulin sensitivity index; G_0, fasting plasma glucose (mg/dL); I_0, fasting plasma insulin (mIU/L); G_{mean}, mean plasma glucose during OGTT (mg/dL); I_{mean}, mean plasma insulin during OGTT (mIU/L)

HOMA-IR:
HOMA - IR = (Glucose X Insulin) / 405

HOMA-B:
$HOMA-\beta = \frac{360 \times Insulin}{Glucose-63}\%$

Statistical Analysis
After collection of data, frequency distribution tables were prepared. Numerical value along with percentages were described and categorical data were coded accordingly and then were analyzed using SPSS Version 17. The changes of fasting blood glucose level, ISI and HOMA-IR in comparison with the baseline values and the subsequent follow-up after 12 weeks were analyzed, between group comparison by unpaid t-test between groups and paired t- test within group followed by post hoc. Kolmogorov- Smirnov test was done for normality distributions. The demographic profile and BMI were also compared by unpaired t -test between two groups.

RESULTS:
Changes in fasting blood Sugar level was observed in the study with HCQ -user group(n=16) , where both the study groups were comparable at baseline.However, after using of HCQ for 12 weeks in patients with RA, significant reduction in fasting blood glucose occurs (p value = <0.001)

Table 1: Comparison of FBS between hydroxychloroquine receivers and non-receivers

FBS	Hydroxychloroquine group (n=16)	Non Hydroxychloroquine group (n=14)	P value (between groups)
Baseline Mean ± SD Median (IQR)	98.5±6.53 99.5 (93, 104.5)	96.29±7.70 98 (96, 100)	0.401
12 weeks Mean ± SD Median (IQR)	94.38±6.51 93 (89, 100)	114.29±4.36 114 (111, 118)	<0.001
P value (within groups)	0.105	<0.001	

*P value by unpaired T-test between groups and by paired T-test within groups (KS test for normality shows normal distribution)

The changes of Insulin sensitivity level in comparison with pre-treatment baseline values and subsequent follow up after 12 weeks showed significant improvement of insulin sensitivity index (p value = <0.001) with the HCQ user group (n=16)in comparison to the non-user(n=14).

Table 2: Comparison of insulin sensitivity between hydroxy chloroquine receivers and non-receivers

Insulin resistance	Hydroxychloroquine group (n=16)	Non- Hydroxychloroquine group (n=14)	P value
Baseline Mean ± SD Median (IQR)	5.24±0.57 5.15 (4.79, 5.75)	6.14±1.08 5.80 (4.9, 7.2)	0.007
12 weeks Mean ± SD Median (IQR)	9.71±0.73 9.65 (9, 10.5)	6.00±1.26 6.10 (4.80, 7.20)	<0.001
P value (within groups)	<0.001	0.436	

*P value by unpaired T-test between groups and by paired T-test within groups (KS test for normality shows normal distribution)

In the present study it was observed that HOMA-IR was comparable in pre-treatment phase and both group was comparable. However, after 12 weeks of treatment HCQ-user group showed significant reduction in HOMA-IR in comparison to the non-user group.

Table 3: Comparison of HOMA-IR between hydroxychloroquine receivers and non-receivers

HOMA-IR	Hydroxychloroquine group (n=16)	Non- Hydroxychloroquine group (n=14)	P value
Baseline Mean ± SD Median (IQR)	1.93±0.08 1.93 (1.89, 1.98)	1.85±0.09 1.89 (1.78, 1.90)	0.024
12 weeks Mean ± SD Median (IQR)	1.51±0.23 1.50 (1.32, 1.70)	1.88±0.11 1.89 (1.76, 1.99)	<0.001
P value (within groups)	<0.001	0.482	

*P value by unpaired T-test between groups and by paired T-test within groups (KS test for normality shows normal distribution)

Gender distribution was equal and patients were in between 44-68 years, indicating predominance of middle aged to older age groups.Study groups were comparable at baseline respect to age and sex.

Table 4: Demographic profile of patients of rheumatoid arthritis

Category	Hydroxychloroquine group (n=16)	Non Hydroxychloroquine group (n=14)	P value
Age Range Mean ± SD Median (IQR)	44, 59 52.00±5.68 52.50 (47, 57)	44, 68 53.14±7.69 51 (48, 57)	0.644
Sex Male Female	 0 16	 0 14	NA
BMI Mean ± SD Median (IQR)	 31.5±3.54 31.25 (29, 34.35)	 29.55±1.79 29.75 (27.9, 30.8)	0.093

*P value by unpaired T-test (KS test for normality shows normal distribution)

DISCUSSION:
The present study was carried out as a hospital-based study in a tertiary care hospital. The initial study population was 48, among them 18 did not met the subsequent follow up and medical tests. It was observed that there is an increasing tendency of prescribing of DMRDs, has substantially improved the ease of treating Rheumatoid Arthritis. In the present study it was observed that HOMA-IR was comparable in pre-treatment phase and both group was comparable. However, after 12 weeks of treatment HCQ-user group showed significant reduction (p value =<0.001) in HOMA-IR in comparison to the non-user group.Moreover, the changes of Insulin sensitivity level in comparison with pre-treatment baseline values and subsequent follow up after 12 weeks showed significant improvement of insulin sensitivity index (p value = <0.001) with the HCQ user group (n=16)in comparison to the non-user(n=14).

Choice of drug was made jointly between the patient and health professionals. Probably the prescribing pattern was more influenced by the socio-economic status of the patients and availability of drugs in the hospital pharmacy.

A similar study was done to know the association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. The primary objective of the study was to compare the risk of newly recorded DM among participants diagnosed with RA or psoriasis based on use of a variety of disease-modifying antirheumatic drugs (DMARDs) and the study concluded

that among patients with RA or psoriasis, the adjusted risk of DM was lower for individuals starting a TNF inhibitor or hydroxychloroquine compared with initiation of other non-biologic DMARDs.(16) Another systemic review was done on potential effect of hydroxychloroquine in diabetes mellitus of different preclinical and clinical trials (17). In alloxan-induced diabetic rats, an experimental study was done to investigate the antihyperglycemic effect of HCQ and atorvastatin. The study reported that a high dose combination of HCQ (10mg/kg) and atorvastatin (200mg/kg) exhibited the highest reduction (21%) in blood glucose levels than low dose combinations and individual treatments [18]. Another study was done on hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients and its findings supported the potential benefit of hydroxychloroquine in attenuating the risk of diabetes in rheumatoid arthritis patients (19). Another valuable study conducted regarding effect of hydroxychloroquine on obesity-associated insulin resistance and hepatic steatosis by regulating lipid metabolism and it revealed the evidences that hydroxychloroquine plays a role in improving obesity-induced lipo-toxicity and insulin resistance though the peroxisome proliferator-activated receptor gamma pathway (20). Probably it attenuates the insulin signaling pathway in liver tissues and suggested that HCQ improved hepatic lipo-toxicity and insulin resistance.(21)

The metabolic effect of HCQ is reducing dissociation of insulin from its receptor (tyrosine kinase) and increase the biologic half-life of insulin receptor complex which prolongs the action of insulin [22]. HCQ is basically acidotrophic agent, so when intracellular concentration of HCQ reaches high, intracellular pH is raised causing inactivation of proteolytic enzyme (insulinase) that is responsible for degradation of insulin-resulting recirculation of substantial proportion of insulin in the active form [23].These findings offer a mechanistic explanation for the antidiabetic properties of HCQ and suggest that this medication might be useful in conditions linked to insulin resistance such as type 2 diabetes.(24)

The present pilot study demonstrate that HCQ treatment improves, insulin sensitivity in obese non diabetic women. We also found that statistically significant increased in ISI and reduction in HOMA-IR with use of HCQ in compare with other HCQ - non user.

However, the limitation of the study is its small sample size, short duration and use of Matsuda ISI as surrogate for clinical outcome, such as DM. Although different mechanisms for HCQ in type II DM have been proposed, available shreds of evidence are preliminary; further mechanistic, efficacy, and safety-related preclinical and clinical studies are still necessary to verify the usefulness of this agent in treating DM.

CONCLUSION:

Cheap and old medications could be a cost-efficient and useful choice in the treatment of individuals with metabolic disorders in RA.HCQ is a potential drug that can improve insulin sensitivity and can help in glycemic control in the rheumatic populations. An important next step in this line of investigation would be a larger and longer study examining the effect of HCQ on insulin sensitivity , focusing on subjects with systemic inflammatory conditions, a population at an increased risk of insulin resistance and Diabetes Mellitus and cardiovascular diseases.

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