The Effect of Hydroxychloroquine Treatment on Blood Sugar Level, Serum Lipid Profile and the Retina in Systemic Lupus Erythematosus Patients

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Abstract

The aim of this study was to evaluate the effect of hydroxychloroquine (HCQ) on blood sugar level, lipid profile and retina in newly diagnosed systemic lupus erythromatosus (SLE) patients. Fifty newly diagnosed SLE patients were collected from Immunology and Rheumatology outpatient clinics in Beni Suef University hospital. All patient's questionnaire included name, age, sex, smoking status, the date of the diagnosis, drugs taken during the follow up period and present history of other diseases. Only HCQ was prescribed to the patients within one year follow-up. They were with a mean (SD, range) age 30 (7.07, 25, 35) years old. Their total lipid profile which included total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) and fasting blood sugar (FBG) and postprandial blood glucose levels (PPBG) were analyzed in MASTER LAB in Beni suef before and after 6 months from the using of HCQ as well as our patients were converted to Ophthalmology Department in Beni Suef University hospital before and at the end of six months of HCQ therapy to undergo to complete eye examinations. The mean (SD) of TC, TG, LDL, FBG and PPBG were significantly decreased after HCQ than before using it while HDL was increased at $p<0.05$. There was no observed effect on retina. HCQ has beneficial effects in protection against thrombosis, hyperglycemia and the absence of retina toxicity in the short term of the use.

Keywords: Systemic lupus erythematosus, hydroxychloroquine, blood sugar, lipid profile, retina

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease of unknown etiology. It can affect any organ system, especially the skin, joints and kidneys system [1]. Antimalaria agents (AM) and corticosteroids drugs are included in the management, although the improvements in patient survival, these drugs are complicated by adverse effects [2]. HCQ is indicated as in our study for the treatment of SLE and have been shown to reduce the risk of complications [3].

Therefore, the goal of the treatment by HCQ in our study was to approve its effect in decreasing total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL),fasting blood glucose (FBG) and postprandial blood glucose (PPBG) levels and increasing in high density lipoprotein (HDL) levels [4]. In addition, it's safely use without any eye problems after the short term of the use [5].

It was previously documented that there were significant decreases in fasting total lipid profile TC, TG, LDL and HDL plasma levels after three months of HCQ treatment with a significant increase in HDL. At 12 months after treatment, the levels of two lipid TC and HDL parameters had fully recovered to the normal limits [6-8].

HCQ had a hypoglycaemic effect in patient with SLE due to different reasons as the inhibition of intracellular degradation of insulin [9,10]. The risk of incident diabetes was found to be reduced with increased duration of therapy [11-13]. Visual impairment may occur in those patients and require urgent assessment by the ophthalmologist [14].

So, our study was undertaken to examine the ocular structure in SLE patients to determine the role of HCQ on it. As in our research and others had been indicated that HCQ rarely causes ocular toxicity in a short term of the use [15-17].

Materials and Methods

Study site

The Immunology and Rheumatology department at University Hospital and a private clinic concerned with immunity in Beni Suef.

Sample

A well-controlled blinded study was carried out on fifty patients who had a clinical evidence of Systemic lupus erythematosus (SLE) disease, we chose the patients who were newly diagnosed, the mean (SD, range) age 30 (7.07, 25, 35) years old and they started taking hydroxychloroquine (HCQ) therapy only and follow up for 6 months. A local hospital research ethics committee approval was obtained for the SLE patients study and written informed consent was obtained from them. Participation was voluntary.

Subject

Systemic lupus erythematosus patients were excluded if they were reported to have taken any other drugs except HCQ during the 6 months of follow up before screening or if they had a history of diabetes mellitus (DM), cardio vascular diseases (CVD) or retinal diseases or evidence of any other disorders on physical examination or laboratory testing.

Methodology

Fifty newly diagnosed SLE patients were collected from Immunology and Rheumatology outpatient clinics at the University hospital and a private clinic concerned with immunity in Beni Suef. All patient's questionnaire included name, age, sex, smoking status, education, family history, the date of the diagnosis, drugs taken during the follow up period and present history of other diseases. Only HCQ was prescribed to the patients within 1 year follow-up. They were with a mean (SD, range) age 30 (7.07, 25, 35) years old. Their total lipid profile which included total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) and fasting blood sugar (FBG) and postprandial blood glucose levels (PPBG) were analyzed in MASTER LAB in Beni Suef before and after 6 months from the using of HCQ treatment, in addition, our patients were converted to Ophthalmology Department in Beni Suef University hospital before and at the end of six months of HCQ therapy to undergo to complete eye examinations using the slit lamp and indirect ophthalmoscope apparatuses. With the help of physicians in The Immunology and Rheumatology department at University Hospital, SLE Disease Activity Index (SLEDAI) was measured to all our cases of lupus patients, and most of them (45 patients) were in mild flares and only 5 were in moderate flares.

Data and sample collection techniques

At the Immunology and Rheumatology outpatient clinics at Beni suef University hospital and a private clinic concerned with immunity in Beni Suef, we found about 260 cases of Systemic lupus erythematosus patients files, some (n=125) were not newly diagnosed lupus as they suffered from it from many years, ranged from 2 to 6 years ago, others (n=63) had different diseases as hypertension (HT), diabetes mellitus (DM), cardiovascular diseases (CVD), liver diseases and retinopathy associated with lupus and we also found some patients (n=17) were taken various drugs like corticosteroids, cyclophosphamide, azathioprine, mofetil drugs and vitamin D beside to HCQ therapy due to different reasons as most of these patients were severe cases and required a combination of drugs or others had certain diseases beside lupus. Therefore, we excluded all of these cases (n= 205) as they not concern us in this study. Finally only 55 lupus patients, (50 females and 5 males) were chosen to complete our study as they were newly diagnosed lupus patients without any concurrent diseases and depended on HCQ therapy only but during the work 50 patients of them, only 45 females and 5 males completed to the end of the study, 5 females didn't complete the study because 2 females from those patients become pregnant women during the study and this required special care with different strategy of therapy and 3 patients not responded to HCQ drug and needed other additives as corticosteroids.

Dosing

For most indications of HCQ, the normal maintenance dose is 200 mg/d, and it is doubled in the first 15 days of the drug use and in the incidence of lesion flare ups.

This dose is calculated according to the ideal weight of the patient. Examples of these formulas for calculating the ideal weight are as follows; for women (height in cm - 100) - 15% and for men (height in cm - 100) - 10%. If the patient weighs less than the ideal weight, the doses are adjusted according to the real weight. The dose to be administered is calculated as follows; 6-6.5 mg × ideal body weight in kg [18].

Inclusion criteria

Patients who were newly diagnosed SLE, with a mean (SD, range) age 30 (7.07, 25, 35) years old and they start taking HCQ drug only in a dose 400 mg daily without any other concurrent diseases.

Exclusion criteria

Patients were excluded if they were reported to have taken any other drug except HCQ during the 6 months before screening or if they had any other diseases as D.M, CVD, liver diseases or retinal disease or they were not newly diagnosed systemic lupus.

All patients were evaluated by well –designed structural questionnaire which filled by the investigator himself:

1- Detailed history thorough the clinical examination

Name, age, sex, smoking status, education, present history of other diseases, drugs taken and family history of similar condition among persons with SLE disease.

2- Laboratory investigations included:

Measurement of total lipid profile including total cholesterol (TC), Tri glyceride (TG), Low density lipoprotein (LDL), high density lipoprotein (HDL) and measurement of serum fasting blood glucose level (FBG) and post prandial blood glucose levels (PPBG). 3- Complete eye examination included: using the slit lamp and indirect ophthalmoscope apparatus.

All laboratory tests were carried out in MASTER LAB in Beni suef and the eye examination was done at ophthalmogy department in Beni suef university hospital.

Statistical analysis

The result of power analysis of the study showed that sample size of 45 patients are sufficient to get power of >90% and $\alpha = 0.05$. The analysis was made by student paired t test at $p < 0.05$ by showing the descriptive statistics of maximum, minimum, mean, standard deviation of all resulted data of total fasting lipid profile, fasting blood sugar and postprandial blood sugar before and 6 months after HCQ use.

Results

A number of 50 newly diagnosed non diabetic patients with the lupus, a mean (SD, range) age 30 (7.07, 25, 35) years old completed the study. Table 1 shows the general characters of all lupus patients. Their results were studied as one whole group of patients and the all analysis of FBG, PPBG, TC, TG, LDL, HDL and complete retina examination were done before and after taking HCQ for 6 months. There was a statistical significant difference in all the tested parameters of fasting lipid profile, total FBG and PPBG at $p< 0.05$ between before and after HCQ use as shown in Table 2 and Figure 1, 2. By indication the data, TC, TG and LDL levels were lower compared to using HCQ while HDL level was increased. Also, FBG and PPBG levels were reduced. While by the complete eye examination including the fundus in all lupus patients, there wasn't any effect on retina after 6 months from HCQ use.

Table 1. General characters of all lupus patients

Parameter	**Total No. (%)**
Gender: Female	45(90.0)
Male	5(10.0)
Smoking Status	2(4.0)
Family history	6(12.0)
Education	3(6.0)
Other concurrent diseases	Zero (0. 0)
Drugs taken (except HCQ)	Zero (0. 0)

Table 2. The mean (SD) of fasting blood sugar and total lipid profile

Parameter	Before Mean (SD)	After Mean (SD)	P value
FBG	89.74 (30.6)	82.56 (25.3)	<0.001
PP	106.12 (34.7)	99.2 (26.7)	<0.001
CH	151.33 (22.72)	139.98 (25.8)	<0.001
TG	145.84 (16.31)	133.53 (21.01)	<0.001
LDL	72.62 (22.08)	61.30 (24.79)	<0.001
HDL	50.20 (14.24)	51.96 (13.33)	0.041

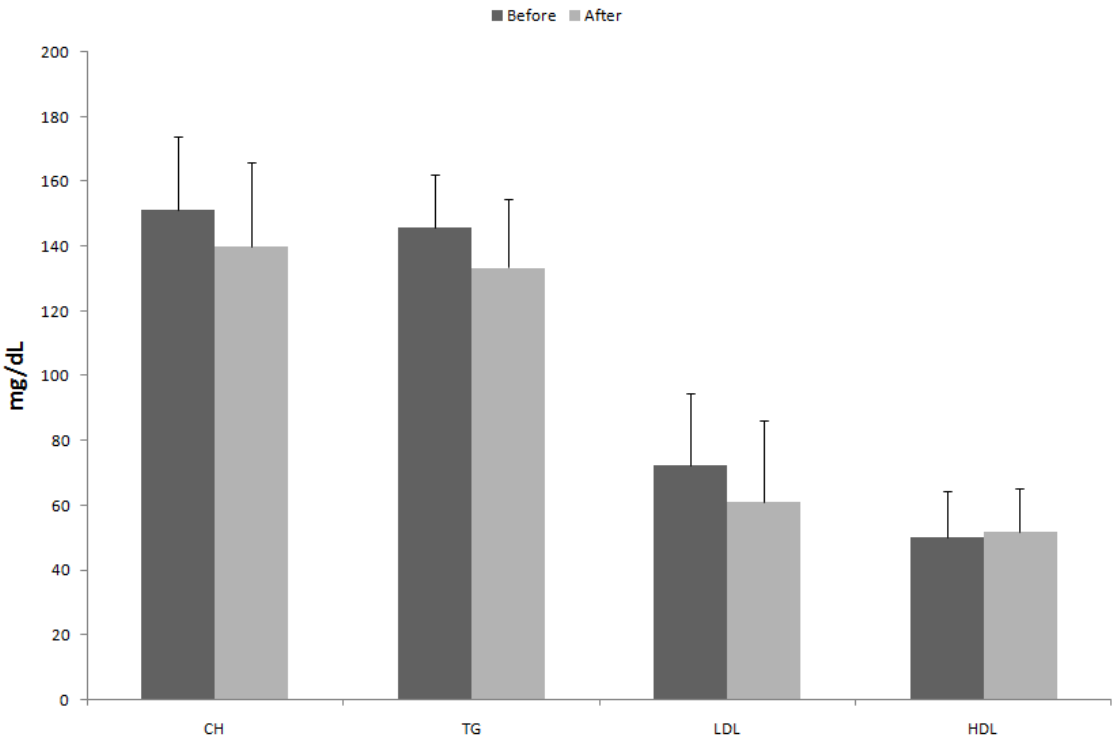

Figure 1. The difference between total lipid profile before and after HCQ

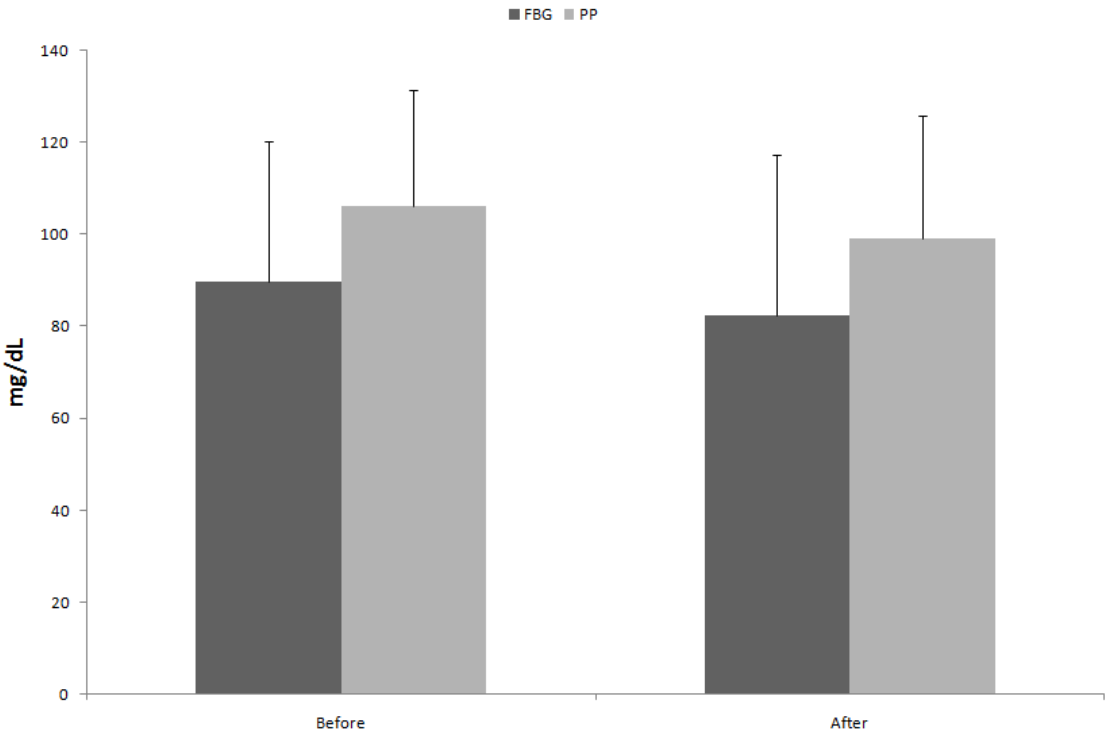

Figure 2. The difference between FBG and PPBG before and after HCQ

Discussion

The present study aimed to explore the effect of HCQ on total lipid profile, serum fasting and postprandial blood sugar levels and on retina in 55 SLE patients after using it for 6 months at constant variables which were newly diagnosed SLE patients, the same range of age 30 (7.07, 25, 35), they didn't have any other concurrent diseases with lupus and used HCQ therapy only. 50 SLE patients (45 females) completed the study. As 5 patients were excluded because 2 females from those patients become pregnant women and this required special care with different strategy of therapy and 3 patients not responded to HCQ drug and needed other additives as corticosteroids.

The results showed by the end of the 6 months, there are reduction in total lipid profile except HDL which was increased, reduction in fasting and postprandial sugar levels and no effect either positive or negative on retina. The mechanism of action of HCQ in the management of lupus patients is not well known but it acts through a different pathways and has immunomodulatory and anti-inflammatory actions [19].

For example, HCQ is a weak base which can cross cell membranes and accumulates in acidic cytoplasmic vesicles as lysosomes or endosomes where it remains trapped in a protonated state.The pH in lysosomes increases as HCQ accumulates there, so, interfering in binding of antigenic peptides with class II molecules of the major histocompatibility complex, leading to inhibition of the production of cytokines which are responsible to the induction of inflammatory response [20,21].

Lipid abnormalities in patients with SLE are common and are likely to be one of the causes of atherosclerosis which a cause of mortality in SLE by increasing the risk of coronary heart disease (CHD) in those patients [22,23]. It was characterized by elevated levels of TC, TG, LDL and decrease in HDL levels. Unfortunately, an increase in TG levels determined low HDL, these data suggest that SLE itself promotes a proatherogenic lipid profile [24]. Therefore, it was necessary to study the effect of our drug HCQ on lipids to indicate its role on lupus patients.

Although the mechanism of cholesterol lowering effect of HCQ is not well indicated, it has beneficial properties as hypolipidemic drug in lupus patients [21]. It has been approved that

HCQ acts as an inhibitor of cholesterol biosynthesis in the hepatocytes of the rats while in human fibroblasts, it has multiple effects on cholesterol metabolism by inhibition lysosomal hydrolysis of cholesterylesters through the increase in the pH within lysosomes and inactivates acid proteases. As well as, it stimulates the activity of hydroxymethylglutaryl CoA (HMG-CoA) and retards the degradation of it [25].

Another Toll like receptors (TLR)- independent mechanism by HCQ may indicate its cholesterol lowering effect through upregulation of the LDL receptor gene transcription, LDL receptors capacity stimulation and enhancement of LDL removal from plasma by LDL receptors [26]. Several authors have also approved that the hypolipidemic effect of HCQ is due to its systemic inflammation control [27].

It was found that the mean of the lipids parameters TC, TG, LDL before treatment with HCQ were significantly higher than after the treatment while HDL mean was lower at $p < 0.05$.

Like most previous studies, the reduction in total lipid profile including TC, TG and LDL were 7.50 %, 8.43 %, 15.5 % respectively while the increase in HDL was 3.38 % in percentage values. So, there was a significant difference between the patients before and after taking HCQ treatment [6-8,28].

It is known that patients with rheumatic diseases as SLE have an elevated risk of insulin resistance which refers to a state of impaired insulin sensitivity and glucose metabolism, which lead to the development of Diabetes mellitus (DM) [29-31]. So, our study aimed to investigate the association between HCQ treatment use and diabetes mellitus risk in SLE patients. The mechanism of action of HCQ as a hypoglycemic drug appears in those patients through the better control of glucose levels , improve insulin secretion, decreased insulin resistance, and lower levels of hemoglobin A1c [10,32].

By the analysis of fasting blood glucose (FBG) and postprandial blood glucose (PPBG) levels, it was observed that the mean of FBG and PPBG were significantly higher than after the treatment with HCQ for 6 months in lupus patients at $p < 0.05$. As the reduction in FBG, PPBG were 8%, 6.5 % respectively therefore, this meant a significant difference between the patients before and after using HCQ therapy [29,33]. Plasma levels of fasting insulin, glucose and lipids were measured in a certain number of Finally, like many studies, SLE patients and

a healthy, age-matched control subjects and by Comparing between them, SLE patients showed higher plasma levels in insulin, TC, LDL, TG, and lower levels in HDL than control subjects. These abnormalities contribute to the incidence of diabetes and atherosclerosis in patients with SLE [34-36].

Thereafter, the study of effect of HCQ therapy on total lipid profile and blood sugar levels in lupus patients was required. It was found that HCQ has attraction to the melanin in the pigmentary epithelium of the retina, however, the mechanism by which retinopathy can occur is not well known. If exposure to the drug continues, the retinopathy gives rise to an image with a bull's eye appearance with macular paleness which surrounded by several rings , the damage is irreversible in this case [37].

The incidence of retinopathy caused by HCQ is low, especially in the first five years of using it, but with the longer treatment duration, it can rise to 1%. Of ocular toxicity especially in patients with cumulative doses more than 1000 g of HCQ [38]. The results as we indicated above, illustrates the importance of HCQ drug on SLE patients when taken regularly to get the optimum benefit in lipids and sugar levels during the treatment period, especially, that our patients were pure adverse effect samples without any diseases or drugs taken as we required, and this made the effect of HCQ was more related on SLE patients unlike the previous researches.

In other hand, our study included the effect of HCQ on retina in lupus patients, Since ocular inflammation in SLE can affect every ocular Structure, if not treated, leading to a significant visual loss or blindness [39]. Therefore, all patients with SLE should be screened for ophthalmologic involvement to institute early treatment in order to prevent complications and also to screen for systemic involvement.

At Ophthalmology Department in Beni Suef University Hospital, the lupus patients undergone to eye examination by using two mainly instruments, the slit lamp and indirect ophthalmoscope. The slit lamp is an apparatus which is used in examination of the anterior and posterior segments of the eye and this examination provides a magnified view of the eye structures enabling us to make a diagnosis to a variety of eye conditions [40]. As our patients were undergone to the slit lamp examination for detection the conjunctivitis, cataract, corneal injury such as corneal ulcer or corneal swelling, diabetic retinopathy retinal detachment,

retinal vessel occlusion and retinitis pigmentosa [41]. Also, in our study, the lupus patients underwent to examination through a laser indirect ophthalmoscope (LIO). Fundus examination and eye lesions of our patients were investigated as a marker for progression to SLE through the LIO apparatus by determination contact allergic dermatitis, tinea faciei, rosacea, polymorphous light eruption, and cutaneous lymphocytic infiltrates [42]. There were no any changes on our SLE patient's eye at the end of the 6 months of HCQ treatment. And it was indicated that results have not been reflected any problems in eye through the 6 months duration of treatment by HCQ. Finally, we didn't observe any positive or negative results on our SLE patient's eye during the duration of the treatment by HCQ. This may be considered a limitation in our study, may be due to the short term of the therapy, low number of the sample size of the patients and the power calculations were not present because the Beni Suef university hospital have different disciplines not only ophthalmology department in addition the high cost of the use of those apparatuses.

Therefore, this may be considered an important point for the study in the future researches.

There some issues in the study which need to be addressed. The patients did not overload by any financial matter, as we gave them HCQ for free and we assured the patients were taken the drug regularly; then focusing on the role of HCQ on lipid profile, serum blood sugar and retina.

Conclusion

Through our study, it was approved that HCQ can be used to a large extent safely in lupus patients with many beneficial properties as it protects against thrombotic events through the relation between HCQ use and lipid parameters by improving lipid levels in those patients by the decrease in TC, TG and LDL levels and the increase in HDL levels. In addition, it can act as a hypoglycemic drug, appears in the relation between it and FBG and PPBG by reducing their levels. It has no toxicity on retina with the doses used the short duration of the treatment.

Author Disclosure Statement

No Conflict of Interest and no competing financial interests exist.

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