Review Article

Effect of Hydroxychloroquine in Diabetes Mellitus: A Review on Preclinical and Clinical Trial Studies

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ABSTRACT

Hydroxy chloroquine is a commonly used drug for its anti-malarial and anti-rheumatic effects. It is shown to have hypoglycemic effects and is proven to reduce the risk of Diabetes mellitus. Diabetes is seen in majority of population all over the world. Often efforts for diabetes prevention are limited by long term use of costly medicines and their potential side effects and poor adherence to lifestyle modifications. Hydroxy chloroquine is a generic and low cost medicine which can help treat diabetes patients effectively and also prevent progression in risk patients from pre diabetes to diabetes. Here our objective is to provide the information from clinical and preclinical studies and case reports on this topic and discuss them under a single review article.

Keywords: Hydroxy chloroquine, Diabetes mellitus treatment, Anti-diabetic, Hypoglycemic.

INTRODUCTION

Diabetic patients treated with HCQ showed improvement in their glycemic levels. This could be an effective and a cost friendly approach for treating DM. As per various number of studies done including preclinical and clinical trials, a combination therapy of HCQ and insulin for Type 2 DM patients, decreased HbA1c levels were seen which is better relatively than treatment with insulin and other hypoglycaemic agents.

Also, HCQ to insulin therapy is proven to show reduced hypoglycaemia incidence.

Hydroxy chloroquine

Hydroxy chloroquine (HCQ), is an anti-malarial drug which is used to treat and prevent malaria. It is also used in the treatment of SLE, rheumatoid arthritis and porphyria cutanea tarda. It is orally taken.

It is also widely used to treat primary Sjögren syndrome, but still not been proven to be effective. Hydroxy chloroquines have both an anti-spirochaete activity and an anti-inflammatory activity. Fig. 1 shows us the molecule structure of HCQ.

It is also presently being studied as an potential treatment for COVID-19 (Corona virus disease).[1, 2, 3]

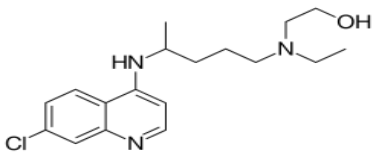


Figure 1: *Hydroxy chloroquine free base molecule*

Trade Names: Plaquenil, Others

Other Names: Hydroxychloroquine Sulphate

Elimination Half-Life:32-50 DAYS

Excretion: Kidney (23-25% as Unchanged Drug); Biliary (<10%)

Class: Anti-malarial

Common Side Effects

Most commonly seen side effects of hydroxyl chloroquine are headache, muscle weakness and vision problems. Some of the more severe side effects that are very rare may be cardiac problems or allergic reactions.

Treatment with HCQ should be done with caution in children as they are more vulnerable to developing adverse effects.[2, 3]

Diabetes mellitus

Diabetes mellitus (DM), more commonly known as diabetes, is a cluster of various metabolic disorders marked by high blood sugar level over a long period of time. Symptoms of DM are increase in thirst, frequent urination ad also increase in hunger. Diabetes may cause many complications if it is untreated for a long time.

Main causes of diabetes is either because the cells of the body not responding effectively to the insulin produced in the body or when pancreas are not able to produce enough insulin. [4, 5]

Mainly there are three types of diabetes mellitus:

- Type 1 diabetes usually occurs when the pancreas are unable to produce enough insulin because of loss of beta cells. It used to be referred as 'insulin independent diabetes mellitus' (IDDM) or also as 'juvenile diabetes'. It occurs due to an auto immune response.

- Type 2 diabetes is when the cells in the body are unable to respond to insulin in the body accurately. With the further progression of the disease the patient also suffers insulin deficiency. It used to be referred to as 'non insulin-dependent diabetes mellitus' (NIDDM) or also as 'adult onset diabetes'. This kind of diabetes usually seen in patients with excessive body weight and lack of exercise.
- Gestational diabetes is a condition where a pregnant women without any kind of past history of diabetes, develops a high blood sugar level.[4-7]

Effects of Hydroxy chloroquine on patients with Diabetes mellitus

Many clinical studies and trials were done to demonstrate the safety and efficacy of HCQ, some of them are mentioned in the following pages.

RECENT PUBLISHED ARTICLES

Effect of Hydroxy chloroquine on Type 2 Diabetes Mellitus Unresponsive to More Than Two Oral Antidiabetic Agents[8]

Methods: In this open-labelled comparative observational study, two groups of 100 uncontrolled Type 2 Diabetes Mellitus (T2DM) patients in each were studied for 24 Weeks (6 months). Both the groups were divided into patients who were on triple drug combinations. One group receiving Metformin, Glimepiride and Teneleglipti and the other group received Metformin, Glimepiride and Hydroxy chloroquine. In each group fasting blood sugar and as postprandial blood sugar were tested at the start of the study and at 4 weeks intervals. HbA1c was tested at the beginning of study, at 12 Weeks (3 months) and at the end of 24 weeks (6 months).

Results: After 24 weeks of treatment, there was significant fall in fasting, as well as postprandial blood sugar and HbA1c levels in patients containing hydroxy chloroquinine in comparison to Teneleglipti.

Conclusions: Hydroxy chloroquine significantly improves glycaemic control in patients with T2DM when prescribed as an add-on therapy in addition to two other commonly prescribed antidiabetic drugs such as Glimipirde and metformin combination, and even its efficacy to reduce blood sugar is comparable to newer generation drugs like Teneligliptin. Hydroxy chloroquine may be considering as an ideal add-on third drug therapy in the treatment of uncontrolled T2 DM patients.

Efficacy of hydroxychloroquine as a potential antidiabetic drug[9]

Methods: A systematic search was done in MEDLINE database with key words 'Type 2 Diabetes Mellitus', 'Hydroxy chloroquine'. Articles assessing the antidiabetic efficacy of hydroxyl chloroquine were reviewed and their results summarized.

Results: With extensive literature search, we found out three RCTs and four Cohort studies assessing the efficacy of HCQ on glycaemic markers in patients with type 2 diabetes mellitus. Two randomized controlled trials done by Gerstein H C et al, Pareek A et al, comparing hydroxyl chloroquine with established antidiabetic drugs showed that there is significant reduction in glycaemic parameters with comparable similarity in both the groups (HbA1c: -0.91%±0.4%). Solomon et al in their study on patients with RA concluded that HCQ improved insulin sensitivity. Two cohort studies by Chen Y M et al and Wasko MCM et al respectively showed reduced incidence of diabetes mellitus in Systemic lupus erythematosus (Hazard ratio=0.26) and rheumatologic disease (relative risk=0.23) patients who received hydroxyl chloroquine. In a cohort study by Rekedal LR et al, HCQ reduced HbA1c by 0.66% compared to baseline in patients with RA. These studies also showed that hydroxyl chloroquine has favourable effect on lipid profile and good tolerability

Conclusions: Hydroxy chloroquine has a potential to enter antidiabetic armamentarium due to its efficacy and low toxicity profile. More studies are required to confirm this.

The effect of hydroxychloroquine on glucose control and insulin resistance in the prediabetes condition[10]

Methods: In a randomized, double-blinded, controlled trial, 39 consecutive patients who were suffering from prediabetes and were referred to the Isfahan Endocrinology Center in January 2013 were randomly assigned to receive hydroxyl chloroquine (6.5 mg/kg/day) (n = 20) or placebo (n = 19) for 12 weeks. The biomarker indices and anthropometric parameters were tested before and after completion of treatment.

Results: In both groups of patients receiving hydroxyl chloroquine and placebo, except for serum level of insulin that was significantly elevated after treatment by hydroxyl chloroquine, the changes in other parameters remained insignificant. Both groups experienced increase of insulin level, but this change was considerably higher in those groups receiving hydroxyl chloroquine. The group receiving hydroxyl chloroquine experienced reduction of glucose at 60 min of Oral Glucose Tolerance Test (OGTT) test after intervention, while the placebo group experienced increase of blood glucose at the same time.

Conclusion: The use of hydroxyl chloroquine may increase the serum insulin level in patients with prediabetic states who are at risk of developing diabetes mellitus.

A favorable effect of hydroxyl chloroquine on glucose and lipid metabolism beyond its anti-inflammatory role[11]

Case presentation: A 24-year-old woman diagnosed at the age of 11 years with type 1 diabetes mellitus presented at the age of 15 years in 2003 to our institution for continuity of her diabetes care. Her glycemic control was suboptimal despite an adjustment of her insulin

doses. In September 2011, she was diagnosed with Sjogren syndrome and was started on HCQ 200 mg once daily. An improvement in her glycemic control as evidenced by self glucose monitoring was noted within 1 month of HCQ therapy, with no remarkable hypoglycemic episodes. Her glycated hemoglobin A1C (HbA1C) was successfully reduced to target in January 2011. No C-peptide levels were obtained before and after HCQ treatment since the patient has longstanding type 1 diabetes and has no insulin reserve left. Interestingly, a slight improvement in her low-density lipoprotein cholesterol (LDL-C) was also seen a few months after HCQ initiation. After reviewing the literature, our case seems to be the first case report of a patient with type 1 diabetes who had improvement in her glycemic control while on HCQ therapy.

Conclusion: This case and review highlight the need to re-examine HCQ as a potential therapy for T2DM and consider its use especially in patients with rheumatism and diabetes. Furthermore, endocrinologists and rheumatologists should be aware of the potential hypoglycemic effect of antimalarials and the need for close monitoring. The favorable lipid-lowering and antidiabetic properties of HCQ render this drug an attractive medical option. Given the elevated cardiovascular risk associated with RA and SLE, the addition of HCQ to patients' usual treatment could counteract the dyslipidemic effect of glucocorticoids, resulting in a potential minimization of atheroma progression and thus possibly lowering mortality due to cardiovascular diseases. In conclusion, HCQ is a relatively safe and inexpensive medication and has a favorable glucose and lipid lowering effect that provides a rationale for its use in addition to its known benefits in rheumatic diseases. Further studies are needed in patients with type 1 diabetes who receive HCQ treatment for other rheumatologic conditions to clarify the mechanism by which HCQ affects their glycemic control.

Hydroxy chloroquine: Looking into the Future[12]

Antidiabetic action of hydroxyl chloroquine

After binding with insulin receptor, insulin and insulin receptor (IR) complex undergoes internalization in the endocytic vesicles. Later, acidification of these vesicles causes dissociation of insulin from IR. Subsequently IR is returned to plasma membrane which can be readily available to bind new insulin. Insulin is either degraded in the endosomes or transported out of the vesicle by a membrane protein transporter.

Being acidotropic agent, hydroxyl chloroquine reaches high concentrations intra cellularly and raises the intracellular pH which causes inactivation of various proteolytic enzymes responsible for degradation of insulin. This results in recirculation of substantial proportion of insulin in the active form. In the process of degradation of insulin, the rate- limiting step is the dissociation of insulin from IR. Hydroxy chloroquine delays this dissociation and consecutively extends the action of insulin by increasing its half-life which may also be responsible for its antidiabetic effect. lb-cell function and insulin sensitivity play a central role in maintaining normal glucose homeostasis. Hydroxy chloroquine treated patients were observed to have significant improvement in insulin sensitivity and reduced insulin resistance. Wasko M et al. [él reported enhanced insulin sensitivity and ß-cell function by hydroxyl chloroquine. Beneficial effect of hydroxyl chloroquine on insulin sensitization was also reported by Mercer E et al. [Z]. They found that Matsuda Insulin Sensitivity Index was increased from a median of 4.5 to 8.9 in hydroxyl chloroquine treated patients. The same study also reported reduction in insulin resistance assessed by HOMA-IR (Homeostasis Model Assessment-Estimated Insulin Resistance). Thus, hydroxyl chloroquine reduced HOMA-IR from a median of 2.1 to 1.8. Hydroxy chloroquine treated patients also had a significantly increased adiponectin level as compared to placebo

Evidence from observational studies

Reduction in incidence of type-2 diabetes mellitus (T2DM) was observed among chronic users of hydroxyl chloroquine.

Wasko M et al. conducted a multicenter observational study involving 4905 patients with RA but without diabetes or not on the treatment of diabetes. Patients were observed for an average period of 21.5 years. Increased duration of hydroxyl chloroquine use was linked to reduced risk of incident diabetes (P<.OOI). Patients (11—384) treated with hydroxyl chloroquine for more than four years had substantial reduction in the risk of incident diabetes.

In another study by Solomon D et al., who analysed 13905 patients with RA or psoriasis, hydroxyl chloroquine led to a significant decline in the risk of diabetes in contrast to other DM.ARD regimens.

Bili A et al. demonstrated a 71% decline in the risk of diabetes among the 1127 RA patients who were using hydroxyl chloroquine for more than five years.

Bellomio V et al. reported that use of hydroxyl chloroquine among the patients with SLE led to lower incidence of metabolic syndrome. Few case studies also reported hypoglycemic effect of hydroxyl chloroquine in individuals with or without diabetes.

Expert Group Consensus Opinion: Role of Anti-inflammatory Agents in the Management of Type-2 Diabetes (T2D)[13]

Role and relevance of HCQ in T2D

Mechanism of action

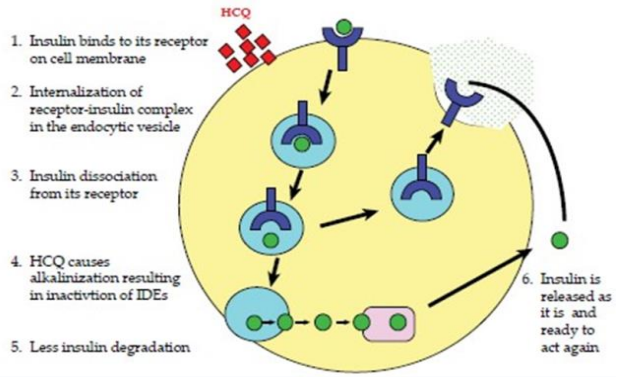
HCQ exerts its antidiabetic action through many mechanisms; including its anti-inflammatory action,

inhibition of insulin degradation and improvement in insulin sensitivity.

Anti-inflammatory properties of HCQ are attributed through the inhibition of TNF-α and other cytokines and inhibition of leukocyte activation. Long term use of HCQ has shown favourable effects in reduction of CRP and other inflammatory markers in SLE and RA patients. Various novel mechanism of action of how HCQ exerts its therapeutically relevant anti-inflammatory effects are: inhibition of endosomal NADPH oxidase (NOX), selective inhibition of extracellular oxidants released from human neutrophils, inhibition of inducible NO synthase (iNOS). Inhibition of insulin degradation: Insulin is known to have a short plasma half-life of 4–6 minutes due to its rapid uptake and degradation in the cells. HCQ, an acidotrophic drug, selectively concentrates in endosomes causing an increase in pH which in turn inhibits the action of insulin degrading enzymes, and thus there is less insulin degradation. Insulin is released as it is thereby increasing its level and it is ready to act again.

Improvement in insulin sensitivity: Wasko M et al. in a 13 weeks study in non-diabetic adults at the University of Pittsburgh demonstrated that HCQ improves both insulin sensitivity and β cell function.

Another novel observation in this study was significant (18.7%) increase in plasma adiponectin level after 400 mg/day of HCQ treatment but not after placebo treatment (0.7%) suggesting the possibility of its anti-inflammatory effects in adipose tissue.



HCQ in T2D: Preclinical studies

Pre-clinical studies determined the mechanisms of HCQ in diabetes. Abdel-Hamid AA in an experimental study, demonstrated preservation of IOL structure in diabetic rats treated with hydroxyl chloroquine. HCQ was responsible for keeping almost all the cellular component of the IOL intact, the matrix of IOL had a minimal hyaline deposition and nearly absent inflammatory cells as compared with un-treated diabetic group. The IOL of un-treated diabetic subjects had cellular as well as nuclear degeneration as well as it exhibited fewer insulin expressing cells as compared to control and hydroxyl chloroquine treated group. HCQ also lowered the pancreatic levels of IL-1β, IL-6, TNF-α and TGF-β1 which were significantly elevated in un-treated diabetic subjects.

HCQ in T2D: Clinical studies

HCQ has been explored and found effective as an adjunct to insulin and oral hypoglycaemic agents for poorly controlled T2D

HCQ in T2D: Dosage and indications

400 mg once in a day. HCQ is indicated as an adjunct to diet and exercise to improve glycemic control of patients on metformin, sulfonylurea combination in Type 2 diabetes.

Inflammation plays an important role in the pathogenesis, progression and complications of T2D. Various clinical studies have been done to explore the role of anti-inflammatory drugs in the management of T2D but they have been found to either have poor glycemic control or different adverse effects. A broad anti-inflammatory agent, hydroxyl chloroquine used over decades in the management of RA and SLE has been found to have profound effects on glycemic parameters through its novel mechanism of action. It has shown to decrease incident T2D, lipid levels and CV events in various prospective and retrospective studies. In India, Hydroxy chloroquine 400 mg has been approved as adjunct to diet and exercise to improve glycemic parameters in T2DM patients using metformin and sulfonylurea. It can emerge as a valuable therapeutic option in the management of T2D patients uncontrolled on conventional oral therapies.

DISCUSSION

As per reference to all the above mentioned clinical studies and preclinical studies based upon the trials and case reports it can be seen that treatment which included Hydroxy chloroquine showed better results in patients with diabetes. As inflammation plays a major role in the pathogenesis and progression of complications of Type 2 diabetic condition, many anti-inflammatory drugs were explored for desired therapeutic effects on the patients. But all of those drugs were ruled out due to their poor glucose control in the body and also to prevent other adverse effects. But Hydroxy chloroquine being an multifaceted drug with broad spectrum anti-inflammatory action and also anti-coagulant, lipid lowering properties it has shown profound effects of glycemic parameter control and has the potential to become an best alternative to reduce patients risk of progression from prediabetes to diabetic condition and also to treat the patients with existing diabetic condition by maintaining the glucose levels.

As per some studies we can see that hydroxyl chloroquine has beneficial effects on glucose control in subjects with prediabetic condition which maybe beneficiary in controlling the condition in progression from prediabetes to diabetes state. It is seen that treatment with hydroxyl chloroquine reduced the

serum glucose levels in the patients. Hydroxy chloroquine is shown positively effecting the insulin and glucose metabolism.

According to some studies use of Hydroxy chloroquine along with insulin, significantly reduced the insulin dose required by patients. In most of the under developing and developing countries the cost of new anti-diabetic drugs to majority of the people is pretty much costly comparatively. In such conditions hydroxy chloroquine is a cost friendly, generic alternative to various conditions of DM.

Despite the desirable effects of hydroxyl chloroquine on glucose control and diabetes control it is important to monitor and control its dosage. Certain studies show that long term and high dose intake of hydroxyl chloroquine can result in congestive heart failure or certain rhythmic disturbances. In patients with pre-existing conditions such as renal failure or cardiac disease act as risk factors, thus caution should be maintained as long term administration of HCQ may result in non desirable problems. In patients with pre-existing hepatic diseases this drug should be used with caution as HCQ may concentrate up in the liver and may interact with hepatotoxicity drugs. One of the other major side effect of long term use of hydroxyl chloroquine is Retinopathy which is seen in very less percentage of patients and can be prevented by monitoring the dosage of the daily administration of drug as per the guidelines. According to some major studies and trials the need of screening for retinopathy is necessary only after 5 years of Hydroxy chloroquine use.

In India Hydroxy chloroquine 400mg is approved as an adjuvant to diet and exercise in diabetic patients who are using Metformin and Sulfonylurea to ensure better glucose control in the body.

CONCLUSION

In conclusion Hydroxy chloroquine has the potential to be included as an anti-diabetic due to its effective therapy in maintaining the glucose levels and helping increase insulin levels and is also relatively safe and inexpensive medication. In patients with prediabetic states hydroxyl chloroquine can be used to prevent the risk of developing diabetes mellitus.

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