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HYDROXYCHLOROQUINE: LOOKING INTO THE FUTURE

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Abstract

Hydroxychloroquine, an antimalarial agent has also been found to possess antidiabetic action. Onset of type-2 diabetes (T2DM) and cardiovascular disease is now considered to be the outcome of systemic inflammation. Many clinical trials are targeting systemic inflammation to reduce cardiovascular risk. Anti-inflammatory drugs with cardiovascular effects may be valuable therapeutic intervention to reduce massive cardiovascular risk in T2DM. In this review, antidiabetic action and potential cardioprotective role of hydroxychloroquine has been discussed. By virtue of its antidiabetic, lipid lowering, anti-platelet, anticoagulant and anti-inflammatory properties, hydroxychloroquine can be a key therapeutic alternative to manage patients with T2DM.

key words: *Hydroxychloroquine, type-2 diabetes mellitus, antidiabetic, anti-inflammatory, cardiovascular, cardioprotective.*

Background

Hydroxychloroquine, a hydroxylated derivative of chloroquine, is an antimalarial agent. It is widely used in the management of autoimmune inflammatory conditions such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) either alone or in combination with other agents. Many mechanisms for its immunomodulatory effect have been proposed [1]. It inhibits antigen presentation, chemotaxis, lysosomal acidification, phagocytosis and proteolysis. It decreases production of inflammatory mediators. It also inhibits matrix metalloproteinases. It has demonstrated inhibitory action on T lymphocyte, B-cell receptor and toll-like receptor signaling. [1]. Hydroxychloroquine has also been found to possess antidiabetic, lipid lowering, anti-platelet and anti-coagulant actions [2].

Antidiabetic action of hydroxychloroquine

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 [3].

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Being an acidotropic agent, hydroxychloroquine reaches high concentrations intracellularly and raises the intracellular *p*H 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. Hydroxychloroquine delays this dissociation and consecutively extend the action of insulin by increasing its half-life which may also be responsible for its antidiabetic effect [4,5].

β-cell function and insulin sensitivity play a central role in maintaining normal glucose homeostasis [6]. Hydroxychloroquine treated patients were observed to have significant improvement in insulin sensitivity and reduced insulin resistance. Wasko M et al. [6] reported enhanced insulin sensitivity and β-cell function by hydroxychloroquine. Beneficial effect of hydroxychloroquine on insulin sensitization was also reported by Mercer E et al. [7]. They found that Matsuda Insulin Sensitivity Index was increased from a median of 4.5 to 8.9 in hydroxychloroquine treated patients. The same study also reported reduction in insulin resistance assessed by HOMA-IR (Homeostasis Model Assessment-Estimated Insulin Resistance). Thus, hydroxychloroquine reduced HOMA-IR from a median of 2.1 to 1.8. Hydroxychloroquine treated patients also had a significantly increased adiponectin level as compared to placebo [6].

Antidiabetic action of hydroxychloroquine: Evidence from observational studies

Reduction in incidence of type-2 diabetes mellitus (T2DM) was observed among chronic users of hydroxychloroquine. Wasko M et al. [8], 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 hydroxychloroquine use was linked to reduced risk of incident diabetes (P<.001). Patients (n=384) treated with hydroxychloroquine for more than four years had substantial reduction in the risk of incident diabetes. In another study by Solomon D et al. [9], who analysed 13905 patients with RA or psoriasis, hydroxychloroquine led to a significant decline in the risk of diabetes in contrast to other DMARD regimens.

Bili A et al. [10] demonstrated a 71% decline in the risk of diabetes among the 1127 RA patients who were using hydroxychloroquine for more than five years. Bellomio V et al. [11] reported that use of hydroxychloroquine among the patients with SLE led to lower incidence of metabolic syndrome. Few case studies also reported hypoglycemic effect of hydroxychloroquine in individuals with or without diabetes [12-14].

Glucose-lowering efficacy of hydroxychloroquine in T2DM patients refractory to sulfonylureas

A study was conducted by Gerstein H et al. [15], where 135 obese patients with T2DM, with glycosylated hemoglobin (HbA1c) higher or equal to 11% in spite of highest dose of sulfonylureas were randomized to receive either hydroxychloroquine ≤ 300 mg, twice a day or placebo. After follow-up of 18 months, improvement in glycemic control was observed among the T2DM patients who were refractory to sulfonylurea treatment. In patients whose HbA1c was between 11% and 13.5%, hydroxychloroquine lowered HbA1c by an absolute amount of 1.02% more compared to placebo.

Hydroxychloroquine in decompensated, treatment refractory T2DM

Quatraro A et al. [16] demonstrated favorable effect of hydroxychloroquine in patients with T2DM resistant to oral hypoglycemic agents, insulin and antidiabetic drugs combined with insulin. After six months of treatment, addition of hydroxychloroquine to insulin resulted in the reduction of diurnal plasma glucose by 11.7 mmol/L and addition of hydroxychloroquine to glibenclamide reduced diurnal plasma glucose level by 10.08 mmol/L. After addition of hydroxychloroquine to insulin or glibenclamide, significant reduction in HbA1c was obtained in comparison to placebo. In the patients receiving insulin, add-on therapy with hydroxychloroquine resulted in decreased requirement of insulin by 30%.

Hydroxychloroquine versus pioglitazone in T2DM

Pareek A et al. [17] clinically explored antidiabetic activity of hydroxychloroquine versus pioglitazone. T2DM patients with uncontrolled glycemic parameters in spite of treatment with sulfonylureas (glimepiride/gliclazide) in combination with metformin ≥1000 mg per day were selected. As an add-on therapy they received either 400 mg per day of hydroxychloroquine (n=115) or 15 mg per day of pioglitazone (n=117) for six months.

Both therapies resulted in significant decline of fasting blood glucose (FBG), post-prandial blood glucose (PPG), as well as HbA1c. At the end of three months and six months, hydroxychloroquine was as effective as 15 mg of pioglitazone in controlling glycemic parameters from the baseline. Also, percentage of patients who achieved improvement in their target glycemic parameters was similar for both therapeutic regimens.

Significant improvement in total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) was observed among patients using hydroxychloroquine as compared to pioglitazone. There was significant reduction in triglycerides in both groups at six months. Both therapies were well tolerated. Hydroxychloroquine users had marginal weight reduction. No patient among the hydroxychloroquine treated group experienced hypoglycemia. Thus Pareek A et al. had conclusively shown that hydroxychloroquine has similar hypoglycemic effect as compared to the third line antidiabetic agents like pioglitazone in Indian diabetic patients.

T2DM, cardiovascular risk and inflammation

The inflammation-diabetes paradigm is now gaining a momentum. Inflammatory mediators have been critically implicated in the pathogenesis of diabetes mellitus. Thus, cytokines, including interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α) have significant contribution in the pathogenesis of T2DM [18]. β-cell function can be affected by these circulating cytokines as they increase the adipocyte inflammation [18]. Cytokines like TNF-α, IL-1β, and Interferon-γ (IFN-γ) can impair release of insulin by altering calcium level in β-cells. TNF-α leads to accelerated apoptosis of β-cells by increasing expression of islet amyloid polypeptide [18]. Glucotoxicity and lipotoxicity increase free fatty acid levels in the islets, which causes activation of oxidative stress and jun N-terminal kinase (JNK), which ultimately results in increased cytokine and chemokine levels in the islets leading to β-cell dysfunction [18]. Levels of inflammatory mediators have been found to be correlated with insulin resistance and were significantly increased in the patients at risk of T2DM [19].

Elevated cardiovascular risk is a serious issue in people with T2DM and it is often linked to increased morbidity and mortality [20]. A 50-year-old diabetic person with no previous macrovascular ailment will die almost six year earlier than a person without diabetes [21]. In the diabetic patients, atherosclerosis was responsible for ~80% of deaths [22]. In an 18-year follow-up study of Finnish subjects, Juutilainen A et al. [23] demonstrated that T2DM and prior episode of myocardial infarction (MI) has equivalent risk of death due to coronary heart disease.

T2DM and cardiovascular disease (CVD) are now considered to be outcome of systemic inflammation with many common inflammatory features. Studies have mentioned that, atherosclerosis, metabolic disorder as well as obesity were strongly correlated with the markers of inflammation. Underlying inflammatory process is thought to be like 'common soil' for these pathologies and T2DM [24].

Pedicino D et al. [25] commented that, early onset of macrovascular complications in T2DM patients is caused by multiple factors. Advanced glycation end-products in plasma and vascular wall along with insulin resistance, hyperinsulinemia and hyperglycemia initiates a pro-inflammatory state which leads to dysregulation of immune system and prothrombotic state. From the formation till the onset of its complications, inflammation has been implicated in every step of atherosclerosis. It is also involved in the typical metabolic dysregulation observed in T2DM [25].

The anti-inflammatory drugs can be important in the prevention of major cardiovascular event like MI, stroke, and cardiovascular death. Some evidence is available for the beneficial impact of hydroxychloroquine on cardiovascular risk, particularly in diabetes and dyslipidemia. The anti-inflammatory agents frequently prescribed in RA or psoriatic arthritis are being evaluated in the management of CVD. Similarly, the role of hydroxychloroquine has been already established to control CVD like MI in high risk individuals such as RA patients. Hydroxychloroquine reduces inflammatory markers like TNF alpha, IL-6 and IFN-γ [26,27]. Sharma T et al. [28] observed 72% decreased risk of CVD among the 1266 RA patients using hydroxychloroquine.

In a prospective, randomized study, Pareek A et al. [29] evaluated atorvastatin along with hydroxychloroquine versus atorvastatin monotherapy in the management of dyslipidemia. Combination therapy led to a significant decrease in LDL-C, TC and non-high-density lipoprotein cholesterol (non-HDL-C) at the end of six months compared to monotherapy of atorvastatin. In the combination therapy group, a higher number of patients achieved their lipid goals as compared to the monotherapy group. Addition of hydroxychloroquine to atorvastatin resulted in incremental fall in LDL-C by 5.16% and 7.02% at end of three and six months respectively. Pre-diabetic and patients with T2DM had better improvement in their lipid levels due to combination therapy. In six months, atorvastatin monotherapy group had 15.09% incidence of statin-induced diabetes compared to only 1.96% in the combination group.

The focus of therapies aimed to reduce cardiovascular risk in vulnerable patients is shifting towards anti-inflammatory agents. There are many ongoing clinical trials which are targeting specific inflammatory markers to reduce burden of CVD.

Assessment of efficacy of anti-inflammatory drugs to reduce enhanced cardiovascular risk

OXI trial: Managing recurrence of cardiovascular events in MI by hydroxychloroquine

OXI trial [30] has randomized 2500 patients with MI to receive either active hydroxychloroquine or placebo for at least one year. In this event-driven clinical trial, potential benefits of hydroxychloroquine on mortality, cardiovascular events and coronary interventions among the patients hospitalized for MI are being evaluated. Trial will also evaluate whether hydroxychloroquine has any benefits on incidence of T2DM, HbA1c as well as lipid levels and inflammatory parameters.

The results of the OXI trial are being eagerly awaited. Outcome of the trial will determine the role of hydroxychloroquine in reducing recurrence of cardiovascular events in MI. If positive, then this trial will justify the use of anti-inflammatory drugs for secondary prevention of CVD and according to the investigators, it will represent a multi-target approach for the prevention of atherosclerotic CVDs.

Ocular safety of hydroxychloroquine

Ocular toxicity is the most important concern linked with chronic use of hydroxychloroquine. To manage ocular risk, use of minimum effective dose of hydroxychloroquine and periodic ophthalmological screening is recommended. Mavrikakis I et al. [31] followed up 526 patients with RA and SLE to assess retinopathy associated with chronic use of hydroxychloroquine. Ophthalmological screening was done for every 6 months from 1985 to 1995 and yearly thereafter.

Among all patients, throughout the treatment of six years, no evidence of retinopathy was observed. Incidence of retinopathy was only 0.5% when used for 8.7 years. Mavrikakis I et al. concluded that hydroxychloroquine at a maximum dose of 6.5 mg per kg can be given in patient without kidney disease, and may continue safely for six years.

To monitor retinopathy due to chronic use of hydroxychloroquine, the American Academy of Ophthalmology (AAO) revised its recommendations in 2016 [32]. AAO also enumerated risk factors for the development of retinopathy, which comprises; use of hydroxychloroquine at a dose of >5.0 mg/kg, use for more than five years, pre-existing kidney disease, maculopathy and simultaneous tamoxifen therapy. It recommended that, the baseline ophthalmological screening should be done before initiation of hydroxychloroquine therapy and yearly screening should be performed after five years of use when risk factors are absent. Regular yearly ophthalmological screening is recommended for the patients with risk factors.

Conclusion

A plethora of clinical evidence is available regarding the role of systemic inflammation in the pathogenesis of diabetes and CVDs. The focus of cardiovascular risk management therapies is shifting towards reducing the systemic inflammation. The cardiovascular safety of many antidiabetic drugs is a concern; prompting the US FDA to require cardiovascular safety trials as part of the approval process for new antidiabetic drugs. New antidiabetic drugs are comparatively costly to the vast majority of people residing in developing and underdeveloped countries. Anti-inflammatory drugs with cardiovascular effects may be valuable therapeutic intervention to reduce

massive cardiovascular risk in T2DM. Hydroxychloroquine is a generic, relatively well tolerated and cost-effective alternative to manage various inflammatory conditions. Hydroxychloroquine 400 mg has been approved in India in T2DM as an add-on therapy to diet and exercise to improve glycemic parameters in patients using metformin and sulfonylurea. By virtue of its antidiabetic, lipid lowering, anti-platelet, anticoagulant and anti-inflammatory properties, hydroxychloroquine has a potential to become a therapeutic alternative to reduce cardiovascular risk among the patients with T2DM.

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