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Hydroxychloroquine: A Therapeutic Choice in Diabetes Mellitus

Narayan Deogaonkar

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a heterogeneous disease with diverse pathophysiological processes. Association between hyperglycemia, chronic inflammation and vascular complications in diabetes is now well established. Chronic inflammation plays an important role in the development and progression of diabetes and its complications. Better understanding of the inflammatory basis for diabetes may provide improved modalities for diabetes prevention and treatment. HCQ was first approved in 1955 as an antimalarial agent. Large scale prospective as well as retrospective studies have shown that the use of HCQ was associated with a reduced incidence of T2DM. Use of HCQ for >4 years reduced the risk of diabetes by 77% in a prospective observational study conducted in 4905 RA patients. A renewed interest has been generated in the last decade due to research focused on T2DM, lipid lowering action, antiplatelet action, antithrombotic action and CV protective effects.

HCQ: NOVEL ANTIDIABETIC ACTION

Inhibition of Insulin Degradation

Insulin has a short plasma half-life of 4–6 minutes due to its rapid uptake and degradation in the cells by insulin-degrading enzymes (IDE). Chloroquine, akin to HCQ, is an acidotrophic drug. At a pH of ≤6, IDE has little proteolytic activity which may result in inhibition of endosomal degradation of insulin and intracellular insulin accumulation. HCQ significantly elevated blood insulin concentration and reduced glucose levels in an experimental study.

Reduction in Inflammation

Inflammation plays a crucial intermediary role in the mediating the progression from obesity to T2DM. It also influence all processes of atherogenesis. Insulin resistance is attributed to activation and release of various inflammatory markers such as IL-6, C-reactive protein (CRP), TNF-α etc.

HCQ was shown to inhibit production of TNF-α, IL-1, IL-6 and interferon-γ (IFN-γ) and other inflammatory markers in chronic inflammatory states. An improvement in CRP levels was also seen in RA patients. It also inhibits prostaglandin synthesis and leukocyte activation and migration.

Preservation of β-Cells

Prediabetes reflects failing beta-cell compensation for an underlying state of insulin resistance. Progressive pancreatic beta-cell defect that drives the deterioration of metabolic control over time begins early and may be present before the diagnosis of diabetes.

Administration of HCQ in diabetic animals preserved islets of langerhans structure. Lowering of pancreatic levels of inflammatory mediators such as IL-1β, IL-6, TNF-α and Transforming growth factor-β1 also occurred. There was a significant increase in the β-cell area with a corresponding decrease in α-cell area along with suppression of β-cell apoptosis with HCQ.

Improvement in Insulin Sensitivity

A 6 weeks course with HCQ 6.5 mg/kg was demonstrated to improve insulin sensitivity in 13 obese non-diabetic individuals. HCQ significantly improved insulin sensitivity index from 4.5 to 8.9 and decreased HOMA-IR from 2.1 to 1.8.

An improvement in insulin sensitivity and β-cell function was induced by treatment with HCQ 400 mg daily for 13 weeks in 17 obese individuals who had risk factors for insulin resistance. Significant increase in insulin sensitivity (20.0%), β-cell function (45.4%) and plasma adiponectin level (18.7%) occurred with treatment with HCQ. Actions of adiponectin include improvement in insulin sensitivity, protection from β-cell dysfunction and additional antiinflammatory and antiatherogenic properties.

TREATMENT OF T2DM

Add on to Sulfonylureas: Comparison to Placebo

Addition of HCQ improved the glycemic control in sulfonylurea-refractory T2DM patients. Sixty nine patients received HCQ 300-600 mg daily while 65 patients received placebo in addition to glyburide 10 mg twice daily. Addition of HCQ decreased HbA1c by an absolute amount of 1.02% more than placebo at 6 months.[41]

HCQ was shown to exert a positive glycemic effect in decompensated, sulfonylurea refractory diabetics. Sixteen patients on glibenclamide therapy (15 mg/day) were randomized to receive either HCQ (600 mg/day) or placebo for six months. A reduction in glucose profile was evident within 10-14 days after initiation of HCQ therapy. There was a significant reduction in glucose profile (-10.8 mmol/L) and HbA1c level (-3.3%) in patients who received glibenclamide and HCQ.

Add on to Insulin: Comparison to Placebo

HCQ was shown to decrease the daily insulin requirements

Table 1: Mean decrease in HbA1c, FBG and PPG in HCQ and pioglitazone groups at week 24 compared to baseline. P value: Intergroup comparison between HCQ and pioglitazone groups

Glycemic parameters	Mean decrease at week 24		
	HCQ	Pioglitazone	P value
HbA1c (%)	0.87	0.90	0.909
FBG (mmol/L)	0.79	1.02	0.648
PPG (mmol/L)	1.77	1.36	0.415

by 30% in T2DM patients. 22 insulin-treated (70-110 units/day) diabetic patients were allocated randomly to receive either insulin along with placebo (n=11) or insulin and HCQ (600 mg/day; n=11) for six months. There was a significant reduction in glucose profile (-11.7 mmol/L) and HbA1c level (-3.3%) in patients who received insulin and HCQ along with a significant reduction in daily insulin dose by 24 units.

Add on to Metformin And Sulfonylurea: Comparison to Pioglitazone

The favorable glycemic effects of HCQ in Indian T2DM patients was established by Pareek A et al. T2DM patients uncontrolled (HbA1c: 7.5-11.5%) on a combination of metformin 1000 mg/day and glimepiride 4 mg/day or gliclazide 160 mg/day were randomized to receive either HCQ 400 mg/day (n=135) or pioglitazone 15 mg/day (n=132) for 24 weeks. There was a significant reduction in the mean HbA1c, FBG and PPG from baseline at week 24 in both the groups (Table 1). A marginal weight reduction of 1.08 kg was also reported with HCQ.[6]

PLEIOTROPIC EFFECTS

Lipid Lowering Effects

Studies spanning over the last three decades by various researchers have reported beneficial lipid lowering effects (TC, LDL-C, TC/HDL-C, LDL-C/HDL-C, VLDL-C and TG) with HCQ. The latest in this series of studies was a study conducted by Pareek A et al who showed the beneficial effects of fixed dose combination of hydroxychloroquine with atorvastatin in the treatment of dyslipidemia. There was a significantly greater percentage reduction in LDL-C, non-HDL-C and TC in patients treated with combination therapy than atorvastatin alone at 24 weeks. Atorvastatin increased the HbA1c level by 0.24% while the combination decreased HbA1c level by 0.18% with an intergroup difference of 0.42% (p=0.002). Fewer patients with prediabetes developed diabetes in combination group.

Antiplatelet Effects

Achuthan S et al (2014) showed that the reduction in platelet aggregation was by 11% with HCQ and 31.2% on combining it with aspirin. There was also a significant decrease in fibrinogen and erythrocyte sedimentation rate values.

Antithrombotic Effects

A study conducted in 2144 patients receiving HCQ before total hip arthroplasty reported a significant reduction in fatal and non-fatal emboli. In the multiethnic LUMINA study use of HCQ was associated with a significant decrease in the risk of thrombotic events (hazard ratio: 0.54). These effects may be due to the inhibition of platelet aggregation and adhesion, decrease in lipid levels and inhibition of antiphospholipid antibody production.[64]

Nephroprotection

Use of HCQ protects from renal damage in patients with lupus nephritis. HCQ takers exhibited a lower frequency of WHO Class IV glomerulonephritis, lower disease activity and received lower glucocorticoid doses than non-takers in a study.

REDUCTION IN CV DISEASE RISK AND EVENTS

The proven lipid lowering, antiplatelet, antithrombotic and nephroprotective effects offer an edge over other oral hypoglycemic agents and maybe beneficial in improving survival in diabetic patients. A retrospective cohort study among RA patients showed that HCQ treatment (400 mg/day) had a significant protective effect against CV events such as MI, stroke, TIA and venous events. The dose of 200 mg/day demonstrated a significant protective effect against MI.

A retrospective cohort study showed that use of HCQ was associated with a 72% CV disease risk reduction in RA patients. During the observation period 3 CV disease events occurred among 547 HCQ users and 99 occurred among 719 nonusers. The hazard ratio was 0.28 (p=0.002) for CV disease events and 0.30 (p=0.004) for composite CAD, stroke, and transient ischemic attack for hydroxychloroquine users versus nonusers respectively.

SAFETY AND TOLERABILITY

The lower toxicity of HCQ makes it more popular for use in conditions where relatively high drug dosages are required over long periods. It has been prescribed since 60 years in RA and >20 year long term studies are available in RA and >8 years long term studies are available in Lupus patients.

Anorexia, abdominal pain, nausea, diarrhea and vomiting are the common adverse effects. Uncommon and reversible effects are pigmentary changes in skin and mucous membranes, bleaching of hair and alopecia. The frequency of hypoglycemia with HCQ is not known. The incidence of hypoglycemia was 0% in the HCQ group while it was 1.5% in the pioglitazone group in the RCT conducted in Indian diabetic patients.

HCQ differs from chloroquine by the presence of a hydroxyl group which decreases the crossing through the blood retinal barrier. A large series of rheumatology patients showed only 1 case of clear toxicity among 1207 HCQ users. A cohort of 526 patients showed 0% incidence of retinopathy in first 6 years and 0.5% incidence after 8.7 years. Retinopathy is very uncommon if the recommended daily dose is not exceeded. American Academy of Ophthalmology in 2011 recommended a baseline retinal examination for patients starting HCQ

to serve as a reference point and annual screening after 5 years of use. It is contraindicated in patients with pre-existing retinopathy.

CONCLUSION

HCQ has a novel mechanism of action i.e. post receptor inhibition of insulin degradation for reducing blood glucose levels. Reduction in FBG, PPG and HbA1C (0.87-3.3%) is established in various settings. Considering the anti-hyperglycemic potential, anti-inflammatory activity and pleiotropic effects such as lipid lowering action, antiplatelet action, antithrombotic action and nephroprotective action, HCQ may emerge as a cost-effective therapeutic option for uncontrolled diabetes patients. None of the newer drugs act on the core pathophysiologic process of beta cell dysfunction in diabetes. HCQ has shown promising results in improving beta cell function and has shown CV risk reduction in the settings of RA & lupus. The relevance of inflammatory mediators in pathogenesis of prediabetes, T2DM and diabetic complications has recently attracted considerable interest. Antidiabetic, anti-inflammatory and CV friendly benefits of HCQ makes it a therapeutic choice in various diabetic subgroups as an add on drug to OHAs as well as insulin.