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Review Article

Is intervening inflammatory pathways a way to treat type 2-diabetes

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ABSTRACT

Over the past few decades, the prevalence of type 2 diabetes (T2D) has rapidly increased. Cardiovascular kidney-metabolic (CKM) syndrome commonly arises from excessive or defective adipose tissue or combination of both. Proinflammatory mediators secreted by dysfunctional adipose tissue, especially visceral adipose tissue damage kidney, heart and artery tissues. Excessive storage of fatty acids disrupts the endocrine functions of adipose tissue, resulting in ectopic fat accumulation that induces lipotoxicity, thereby promoting low-grade inflammation and insulin resistance (IR) in the liver. Systemic inflammation and IR are exacerbated by the onset of metabolic dysfunction-associated steatotic liver disease, formerly known as non-alcoholic fatty liver disease (NAFLD). It is well established that low grade inflammation plays an important role in T2D and its associated microvascular complications like nephropathy, neuropathy, retinopathy and macrovascular complications like atherosclerosis. Accelerated atherosclerosis predisposes to cardiovascular diseases, which is the leading cause of mortality in these patients. Till date, various anti-inflammatory drugs have been tried in the setting of chronic disorders such as T2D and CVD (cardiovascular diseases). But too selective targeting may not have produced the desired outcomes. Multiple inflammatory pathways contribute to the pathogenesis of CVD and T2D, hydroxychloroquine (HCQ), a broad anti-inflammatory agent, demonstrates beneficial effects on glucose and lipid metabolism and is the only DCGI approved anti-inflammatory drug for T2D. Due to pleotropic benefits, HCQ has the potential of reducing prediabetes for diabetics, has antidiabetic properties and also reduces complications of diabetes, most importantly, CVD associated with T2D.

Keywords: Cardiovascular disease, Hydroxychloroquine, Inflammation, Insulin resistance, Type 2 diabetes mellitus

INTRODUCTION

Over the past few decades, the prevalence of type 2 diabetes (T2D) has rapidly increased. It is concerning that the age of onset is shifting more towards younger age groups because this could have negative impact on the country's economy.[1] A cross-sectional population-based survey, the Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study evaluated representative sample of people aged 20 and over who were selected from both urban and rural regions in 31 Indian states. The survey reported 11.4% of people had diabetes, 15.3% had prediabetes, 35.5% had hypertension, 28.6% had generalized obesity, 39.5% had abdominal obesity and 81.2% had dyslipidemia.[2] T2D is associated with two-fold increased risk of vascular outcomes, including coronary artery disease, ischaemic stroke and vascular mortality, independent of other risk factors. This risk is relatively higher in women as compared to men and is exacerbated by early onset of diabetes. In India newly diagnosed T2D patients are at high ASCVD risk.[3] There is 2-4-fold increased risk of heart failure in individuals with T2D.[4] About 50% patients with T2D have CKD.[5] In this review we will discuss how inflammation plays an important role in the pathogenesis of T2D. Till date, various anti-inflammatory drugs have been tried. But Hydroxychloroquine (HCQ) is the only DCGI approved anti-inflammatory drug for T2D. Its benefits like anti-inflammatory, glucose lowering, lipid lowering, antiplatelet, anti-thrombotic, anti-atherosclerotic, reduce

not only glycemic parameters but also reduce the risk of cardiovascular diseases (CVD) associated with T2D.

REVIEW

Relevant articles were identified through various electronic databases including PubMed, Google scholar and Scopus using MeSH terms hydroxychloroquine, cardiovascular disease, inflammation, insulin resistance, type 2 diabetes mellitus

What is Low-grade chronic systemic inflammation

LGCSI is distinguished by constant, mild increase in circulating inflammatory markers, such as C-reactive protein (CRP), IL-6 and TNF-α. This type of inflammation is mainly linked with the innate arm of immune system. LGCSI develops slowly as opposed to the rapid development of acute inflammatory responses such as sepsis. It is difficult to determine its origin as compared to chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel diseases where other additional symptoms indicate the presence of deregulated localized inflammation.

This complexity makes it difficult to develop therapeutic approaches that simultaneously address both the underlying cause and the inflammatory symptoms of LGCSI in coordinated manner. LGCSI produces elevated levels of inflammatory markers and immune cell infiltration while showing no structural changes or loss of primary functions of major organ systems (Table 1).[6-8] LGCSI plays crucial role in the development of metabolic diseases, such as dyslipidaemia, atherosclerosis, T2D and systemic arterial hypertension. Because of its close link with the onset of cardio-metabolic diseases in obese patients, LGCSI has recently been termed as "meta-inflammation or metabolic inflammation".[9]

Metabolic syndrome

Metabolic syndrome comprises five important conditions that can cause heart disease, diabetes, stroke and other diseases. Metabolic syndrome is identified when an individual has three or more of the following risk factors: Elevated blood glucose levels, reduced HDL, elevated triglyceride levels in the blood, elevated waist circumference or "apple-shaped" body and hypertension.[10]

Emergence of cardio diabetology

T2D further leads to manifestation like atherosclerosis, endothelial dysfunction, arterial stiffness, vascular inflammation and oxidative stress.[11]

Cardiorenal syndrome

T2D can cause both CKD and/or CVD and CVD can cause renal disease. CVD and T2D are closely related risk factors for CKD.[12]

Cardiovascular kidney-metabolic syndrome and metabolic dysfunction-associated fatty liver disease

CKM syndrome is a systemic disorder characterized by pathophysiological interactions between metabolic risk factors, CKD and the cardiovascular system resulting multiorgan dysfunction and increased adverse cardiovascular outcomes. CKM syndrome comprises individuals at risk for CVD due to metabolic risk factors, CKD or combination of both, as well as those with existing CVD that may be associated with or exacerbated by metabolic risk factors or CKD. CKM syndrome commonly arises from excessive or defective adipose tissue, or combination of both.

Proinflammatory mediators secreted by dysfunctional adipose tissue, especially visceral adipose tissue damage kidney, heart and artery tissues. Insulin sensitivity is decreased by inflammatory mediators, which impairs glucose tolerance. Systemic inflammation and IR are exacerbated by the onset of MAFLD, formerly known as non-alcoholic fatty liver disease (NAFLD). In addition to these systemic effects, steatotic liver disease linked to metabolic dysfunction has emerged as the primary cause of liver failure and the requirement for liver transplantation (Table 2). The pathophysiological effects of CKM syndrome are a reflection of the complex interactions between the cardiovascular system, CKD and metabolic risk factors.[13]

MAFLD appears to be tightly linked to incident CKD. Multiple shared risk factors including T2D, arterial hypertension, obesity, dyslipidaemia and IR. Inflammation, oxidative stress, fibrosis and gut dysbiosis are all very common in these disease states, so it is possible to find similarities in how they affect the body at the molecular level. Genetic predisposition to MAFLD due to gene polymorphisms which may also propagate renal dysfunction.[14]

Visceral adiposity and IR

An increased amount of visceral adipose tissue, which is now thought to be the most significant predictor of cardiometabolic diseases. Visceral adipocytes release adipose-specific cytokines, including leptin and adiponectin, as well as inflammatory cytokines like TNF-α and IL-6. The recruitment of macrophages in adipose tissue induces lipolysis and the release of inflammatory cytokines. The propensity of visceral adipose tissue to increase inflammation and subsequently secrete cytokines impairs insulin signalling, contributing to systemic IR in central obesity. The migration of excess ectopic fat to the liver and muscles also results in IR.[15]

Impaired glucose tolerance triggers

Factors such as genetic predisposition, age, pregnancy and IR associated with obesity contribute to elevated blood glucose levels. Genetic alterations disrupt β-cell

metabolism and ATP synthesis, inhibiting K-ATP channel closure and consequently diminishing insulin secretion, worsens hyperglycemia, resulting in overt diabetes.[16]

Hypertriglyceridemia in MetS and T2D

IR can modify systemic lipid metabolism, resulting in dyslipidemia characterized by the triad: (1) Elevated plasma triglycerides (2) Reduced HDL-C (3) Presence of LDL-C.[17]

Hypertriglyceridemia and CV risk

Excess visceral adipose tissue is often associated with elevated triglyceride levels and low HDL-C levels. The metabolic triad, which includes hyperinsulinemia, elevated apo B levels and an increase in small, dense LDL-C particles, significantly elevates cardiovascular risk.[18]

Increased thrombotic risk and link with PAI

Hyperinsulinemia, hypertriglyceridemia, activation of the renin-angiotensin-aldosterone system (RAAS) and oxidative stress contribute to increased synthesis of plasminogen activator inhibitor-1 (PAI-1). Increased PAI levels are associated with an elevated thrombotic risk.[19]

Lipotoxicity to NAFLD

LGCSI occurs in various metabolic tissues, including adipose tissue, liver, muscle, brain and gut. Adipose tissue serves as a physiological reservoir for fatty acids. Excessive storage of fatty acids disrupts the endocrine functions of adipose tissues, resulting in ectopic fat accumulation that induces lipotoxicity, thereby promoting low-grade inflammation and IR in the liver. Lipotoxicity is currently considered the primary mechanism driving the progression of disease from simple steatosis to non-alcoholic steatohepatitis (NASH).

Fatty liver can arise from mechanisms such as increased free fatty acids (FFAs), heightened dietary fat intake, elevated de novo lipogenesis (DNL), reduced free fatty oxidation and diminished hepatic triglyceride secretion. Lipotoxicity induces inflammation and IR, which subsequently enhance adipocyte lipolysis and worsen lipotoxicity. Moreover, IR and inflammation form vicious circle where each condition exacerbates the other, thereby accelerating the progression of NAFLD.[20]

CENTRAL OBESITY AND CONSEQUENT INFLAMMATION DRIVES IR IN INDIANS

Visceral adipose tissue (VAT) serves as a site of chronic low-grade inflammation in obesity. Chemerin derived from VAT recruits circulating plasmacytoid dendritic cells (pDCs). Once activated, pDCs produce type I IFNs, which subsequently drive the polarization of M2 macrophages into proinflammatory M1 macrophages. M1 macrophages play a significant role in the prolongation of chronic inflammation in VAT and contribute to systemic IR.

Adipose tissue (AT) stores about 90% of the free fatty acids after feeding. Significant adipocyte remodelling primarily by hypertrophy and to lesser extent by hyperplasia, occurs to meet the increasing demand to store more triglycerides. Increased gene expression of inflammatory proteins and peptides leads to increased production of cytokines, chemokines and other inflammatory mediators, including 12LO.

This process facilitates the recruitment and activation of immune cells within adipose tissue, encompassing T cells (CD4+ and CD8+), macrophages (MΦ), natural killer cells (NK) and dendritic cells (DC). Upon arrival in the adipose tissue, immune cells contribute to the production of pro-inflammatory mediators. The formation and release of adipokines released by adipocytes is altered with elevated leptin production and decreased adiponectin levels.[21]

All circulating factors function in an endocrine manner and contribute to dysfunction of pancreatic β cells. Increased levels of free fatty acids (FFAs) result in lipotoxicity, oxidative stress, mitochondrial dysfunction and endoplasmic reticulum (ER) stress in β cells. Moreover, elevated leptin levels, coupled with leptin resistance in β cells, may lead to reduced insulin secretion. Inflammatory mediators originating from adipose tissue and produced locally by the islets, along with infiltrating immune cells further contribute to reduction in insulin secretion.

Adiponectin reduces oxidative stress and endoplasmic reticulum stress in β cells. Decreased adiponectin levels in obesity diminishes its beneficial effects. Increased insulin demand resulting from IR adversely affects β cells via endoplasmic reticulum stress and islet expansion. Inflammatory responses in β cells associated with obesity lead to decrease in functional β cell mass, which in conjunction with systemic IR, contributes to the development of T2D (Figure 1).[22]

Diabetes and vascular diseases

Diabetic pan vascular disease (DPD) is clinical syndrome in which atherosclerosis is common link between macro vessels and micro vessels in the cardiac, cerebral, renal, ophthalmic and peripheral vessels in patients with diabetes. The main consequences would be cardiovascular and cerebrovascular events and the prognosis could be improved through aggressive treatment of metabolic abnormalities. Diabetes risk is equivalent to those in one-fifth of CVD free adults living with diabetes. High HbA1c, long diabetes duration and diabetes medication use were predictors of CVD risk equivalence.[23]

Inflammation in macrovascular complications of T2D

Proinflammatory cytokines, interleukins and cellular components of the inflammatory response facilitate each

stage of atherogenesis, beginning with endothelial cell dysfunction and progressing to foam cell formation, plaque development and finally plaque rupture due to architectural instability. Inflammation plays important role in all phases of atherothrombosis.[24]

Inflammation in microvascular complications of T2D

Diabetes and hyperglycaemia create proinflammatory microenvironment that contributes to microvascular complications, including nephropathy, retinopathy and neuropathy. Diet-induced IR leads to increased inflammatory cytokines and the development of a chronic low-grade inflammatory state. Advanced glycation end-products (AGEs) and their receptor, the AGE receptor, along with reactive oxygen species and hypoxia, collectively contribute to the exacerbation of microvascular complications associated with diabetes.[25]

Role of inflammatory markers in the pathogenesis of T2D

In the WOSCOPS study, Dilys J. Freeman et al, recruited 5,974 middle-aged men to evaluate the role of CRP in the development of diabetes. During follow-up period of five years, 127 out of 5,245 subjects developed diabetes. In a multivariate analysis, the authors found that men in the highest quintile of CRP (>4.18 mg/l) exhibited more than 3-fold increased risk of developing diabetes as compared to those in the lowest quintile (<0.66 mg/l). The authors concluded that CRP independently predicted the development of T2D, regardless of baseline BMI, fasting triglycerides and glucose concentration.[26]

In a prospective study, Twig et al, assessed WBC count in 24,897 young, normoglycemic men over mean follow-up period of 7.5 years. The study reported that, over 185,354 person-years of follow-up, 447 subjects were diagnosed with diabetes. The study reported 7.6% increase in incident diabetes for every increase of 1,000 cells/mm of WBC (p= 0.046). A baseline WBC count exceeding 6,900 cells/mm (3) had an independent 52% increase in diabetes risk when compared to the lowest quintile (WBC<5,400 cells/mm). The authors concluded that white blood cell count is an independent risk factor for the development of diabetes in young men.[27]

In the diabetes prevention program (DPP), Mather et al, randomly assigned 2,842 subjects with elevated fasting glucose, impaired glucose tolerance and overweight or obesity to one of three interventions intensive lifestyle intervention, metformin treatment or placebo treatment. The study demonstrated significant increases in adiponectin from baseline in all three treatment groups after one year. The mean increases were 0.83±0.05 g/ml for the lifestyle group, 0.23±0.05 g/ml for the metformin group and 0.10±0.05 g/ml for the placebo group, with a statistically significant difference (p<0.001 for increases versus baseline, p<0.01 comparing among groups). The authors concluded that if baseline adiponectin level is higher, progression to T2D is slower.[28]

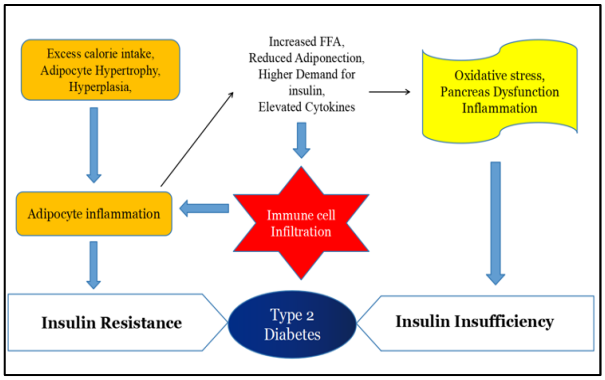

Figure 1: Central obesity and consequent inflammation link to type 2 diabetes.

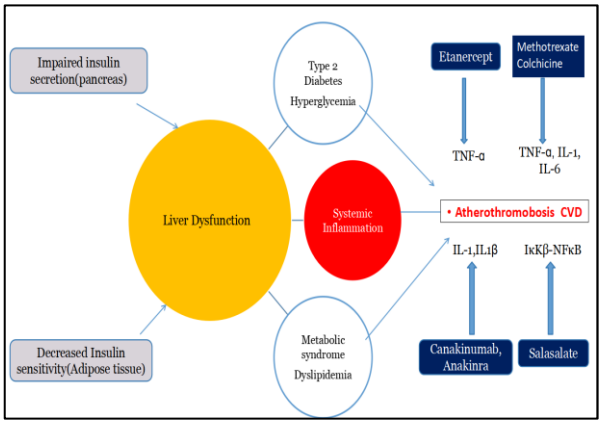

Figure 2: Anti-inflammatory drugs used in T2D and associated CVD.

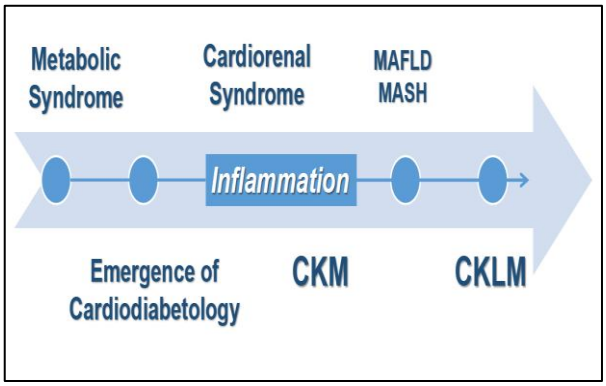

Figure 3: CKM to CKLM: A Continuum.

In a prospective cohort study known as the Second Manifestations of arterial disease (SMART), Sharif S et al. assessed 1679 high-risk patients with T2D to investigate the association between hs-CRP and cardiovascular events as well as all-cause mortality. At the end of 15.9 years, the study reported 307 new cardiovascular events. The authors noted that each 1 mg/l increase in hs-CRP correlates with 21% increased risk of vascular events and 26% elevated risk of all-cause mortality. The authors concluded that low-grade inflammation, as measured by hs-CRP, is an independent risk factor for vascular and all-cause

mortality, but not for cardiovascular events in high-risk patients with T2D.[29]

NON-PHARMACOLOGICAL MANAGEMENT

Nutritional interventions for remission of diabetes

Lean et al, in (DiRECT) trial recruited people between the ages of 20 and 65 who were not on insulin, had BMI of 27 to 45 kg/m2 and was diagnosed with T2D during the previous six years. The intervention included the stoppage of antidiabetic and antihypertensive medications, comprehensive diet replacement (825–853 kcal/day formula diet for 3–5 months), gradual food reintroduction (2–8 weeks) and organized assistance for sustained weight loss maintenance. The study reported that diabetes remission occurred in 68 (46%) participants from the intervention group as compared to six (4%) participants in the control group. The authors showed nearly 50% of participants attained remission to non-diabetic state without the use of antidiabetic medications at the end of 12 months.[30]

According to Taylor et al and his associates, losing weight and preventing weight gain can reverse T2D.The hallmark of T2D is the build-up of excess fat in the pancreas and liver. Because everyone has distinct threshold for fat, only around half of those with T2D are obese and some have healthy BMI. If liver fat drops to low-normal levels, IR which is caused by excess fat in the liver cells will completely disappear. Insulin can then function normally once more, fasting blood glucose levels quickly return to normal and prevent the liver from releasing glucose into the blood. The liver provides the rest of the body with triglycerides, thus when liver fat suddenly decreases, the high rate of triglyceride supply returns to normal. All ectopic fat stores and pancreatic fat levels consequently steadily decline. The insulin response to food returns to normal over time.[31]

ANTI-INFLAMMATORY AGENTS USED IN T2D

Salasalate

In a placebo-controlled trial known as TINSAL-T2D (Targeting inflammation using salsalate in T2D), Goldfine et al, evaluated the 1-year efficacy and safety of salsalate in patients with T2D. The study randomized 286 participants to 48 weeks of treatment with placebo (n=140) and salsalate at a dosage of 3.5 g/d (n=146), in addition to current treatment. The authors observed modest reduction of -0.37% in mean HbA1c levels over 48 weeks in the salsalate group as compared to the placebo group ($p<0.001$). Salsalate also reduced inflammatory mediators, including circulating leukocyte, neutrophil and lymphocyte counts. Salsalate did not demonstrate significant impact on hsCRP levels. Salasalate increased LDL cholesterol ($p<0.001$) and urine albumin levels as compared to placebo. According to the authors, more research is required to demonstrate the cardiovascular and renal safety of salasalate in patients with T2D and ongoing assessment of mixed cardiorenal signals is warranted.[32]

Etanercept

Stanley et al, conducted one randomized trial involving 40 obese subjects showing symptoms of metabolic syndrome. Participants received etanercept at dosage of 50 mg twice weekly for three months, followed by 50 mg once weekly for an additional three months or placebo. The authors observed that etanercept led to significant reduction in fasting glucose (-10.8±4.4%, p=0.02) and an increase in the ratio of high molecular weight adiponectin to total adiponectin when compared to placebo after 6 months. (+22.1±9.2% vs placebo, p=0.02).[33] Bernstein et al, conducted one randomized trial involving 56 subjects with metabolic syndrome to receive either etanercept 50 mg subcutaneously once weekly or an identical placebo for duration of 4 weeks. The authors reported decrease in CRP levels (−2.4±0.4 vs 0.5±0.7 mg/l, $p<0.001$) and an increase in adiponectin levels (0.8±0.4 vs −0.3±0.3 µg/ml, p=0.03) in the etanercept group as compared to the placebo group. The study showed that TNF-a blockade using etanercept did not demonstrate beneficial effects on insulin sensitivity or glucose metabolism in patients with IR, despite reduction in CRP levels.[34]

Anakinra

In a double-blind, parallel-group trial, Larsen et al, randomly assigned 70 patients with T2D to receive 100 mg of anakinra subcutaneously once daily or a placebo for duration of 13 weeks. The authors observed that at 13 weeks, the HbA1c in the anakinra group was 0.46 percentage points lower than that in the placebo group (p=0.03). Modest reductions in HbA1c, the necessity for daily injections, the magnitude of effects and associated costs are subjects of debate regarding the use of anakinra in T2D.[35]

Table 1: Differentiating features between classical and low-grade inflammation.[9]

	Classical inflammation	Low grade systemic inflammation
Duration	Acute (rapid)	Chronic (slow)
Site of origin	Local tissue	Systemic, liver, skeletal muscle
Types of cells	Neutrophils, Eosinophils, NKcells, Macrophages, T-lymphocytes	Macrophages, T-lymphocytes
Inflammatory mediators	TNF-α, IL-1β, IL-6, ROS	TNF-α, IL-6, CRP, ROS
Organ damage	Present	Absent

Methotrexate

In a randomized, double-blind trial, Ridkar et al, recruited 4,786 patients with history of myocardial infarction or multi-vessel coronary disease, along with T2D or metabolic syndrome, to receive low-dose methotrexate (15-20 mg weekly) or a placebo, in conjunction with standard care. The trial was halted by the data and safety monitoring board due to futility after median duration of 2.3 years. The authors observed that Methotrexate did not lead to reductions in IL-1β, IL-6 or CRP as compared to placebo. The final primary endpoint was observed in 201 patients in the methotrexate group as compared to 207 patients in the placebo group. The authors found that in patients with stable atherosclerosis, methotrexate did not lead to reduction in cardiovascular events as compared to placebo.[36]

Canakinumab

Ridker et al, conducted the CANTOS trial, which randomized 10,061 patients with history of myocardial infarction and hsCRP levels of≥2 mg/l to receive either placebo or canakinumab at doses of 50 mg, 150 mg or 300 mg administered subcutaneously once every three months. The authors observed that patients receiving 150 mg of canakinumab showed 15% reduction in the risk of major adverse cardiovascular events (MACE), defined as composite of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death as compared to the placebo group (3.86 vs. 4.50 events per 100 person-years).[37]

The reduction in HbA1c was only -0.1% at the highest dosage among patients with diabetes. At 48 months, the median reduction in hsCRP levels was significantly lower from baseline in the canakinumab group as compared to the placebo group. Despite reductions in hsCRP and IL-6, canakinumab did not decrease the incidence of new-onset diabetes and only reduced haemoglobin A1c during the initial 6 to 9 months of treatment, with no sustained long-term benefits observed. The loss of efficacy may result from the production of antibodies against the biological agent. Further, the modest effects of canakinumab on cardiovascular events and minimal effects on glycaemic parameters could be due to targeting selective inflammatory pathway (i.e., IL-1b only).[38]

Colchicine

Nidorf et al, conducted one double-blind trial (LoDoCo2) that randomized 5522 patients with chronic coronary disease to receive either low-dose colchicine (0.5 mg once daily) or placebo for median duration of 28.6 months. The study showed in patients with clinically stable ASCVD who were administered colchicine 0.5 mg daily reduced risk of recurrent cardiovascular events as compared with placebo. The primary endpoint of composite of cardiovascular death, spontaneous myocardial infarction, ischemic stroke or ischemic-driven revascularization, was reported in 6.8% of patients in the colchicine group as compared to 9.6% in the placebo group.[39] Tardif et al, conducted Colcot trial involving 4,745 patients within 30 days post-myocardial infarction, administering either low-dose colchicine (0.5 mg once daily) or placebo for median duration of 22.6 months. The study showed that among patients with acute coronary syndrome (ACS) the primary endpoint (comprising death from cardiovascular causes, myocardial infarction (MI), resuscitated cardiac arrest, stroke or urgent hospitalization for angina necessitating coronary revascularization) was observed in 5.5% of patients receiving colchicine at dosage of 0.5 mg daily as compared to 7.1% in the placebo group (p=0.02). The authors concluded that in patients with recent myocardial infarction, a daily dose of 0.5 mg colchicine resulted in significantly reduced risk of ischemic cardiovascular events as compared to placebo40

In this multicentre trial, Jolly et al, randomly assigned 7,062 patients with myocardial infarction to receive either colchicine or placebo, as well as spironolactone or placebo.

The research showed that primary-outcome event consists of composite of death from cardiovascular causes, recurrent myocardial infarction, stroke or unplanned ischemia-driven coronary revascularization was observed in 322 of 3528 patients (9.1%) within the colchicine group as compared to 327 of 3534 patients (9.3%) in the placebo group, over median follow-up duration of 3 years. The study concluded that in patients with myocardial infarction, early treatment with colchicine did not decrease the incidence of MACE.[41]

Broad spectrum vs selective targeting in CVD and diabetes

Multiple inflammatory pathways contribute to the pathogenesis of CVD and T2D, therefore too selective targeting may not produce the desired outcomes. HCQ, a broad anti-inflammatory agent, demonstrates beneficial effects on glucose and lipid metabolism.[38]

PLEOTROPIC BENEFITS OF HCQ

Prevention of diabetes: reduction in incident diabetes in rheumatology settings:

Wasko et al, conducted one prospective, multi-center observational study involving 4905 adults with rheumatoid arthritis to evaluate the association between HCQ use and the incidence of new-onset diabetes. A total of 1808 participants had taken HCQ, while 3097 had not. The research showed that the use of HCQ for more than four years was linked to 77% reduction in the risk of developing diabetes.[42]

Anti-inflammatory and antidiabetic effect of HCQ in insulin resistant populations: clinical studies

Toledo et al, conducted one double-blind, placebo-controlled trial involving 34 insulin-resistant adults

without rheumatic disease, randomized to receive 13 weeks of HCQ (400 mg/day). The study demonstrated that HCQ resulted in significant improvement in skeletal muscle insulin sensitivity by 26% (p=0.019) and enhanced systemic glucose clearance (p=0.025) relative to placebo. HCQ reduced circulating interleukin-6 (IL-6) levels (p=0.01) and elevated adiponectin levels (p=0.045). The insulin-sensitizing properties offer mechanistic basis for the antidiabetic effects observed in patients receiving HCQ treatment.[43]

Wasko et al, conducted one randomized, double-blind, parallel-arm trial involving 32 non-diabetic volunteers with one or more markers of IR to HCQ. The study demonstrated improvement in insulin sensitivity (mean±SEM: +20.0%±7.1% vs −18.4%±7.9%, respectively; p<0.01) and significant improvement in beta cell function (+45.4%±12.3% vs −19.7%±13.6%; p<0.01) with HCQ as compared to placebo. Adiponectin levels showed significant improvement after HCQ treatment as compared to placebo, with changes of +18.7% and +0.7%, respectively (p<0.001). The study postulated that HCQ significantly elevated levels of both HMW and LMW adiponectin, suggesting potential anti-inflammatory effects in adipose tissue.[44]

Anti-inflammatory and antidiabetic effect of HCQ in T2D: clinical studies

In a prospective, multicentric, phase 4 study, Pareek et al, recruited 747 patients with uncontrolled T2D (HbA1c≥7%) who were on sulfonylureas and metformin combination to receive HCQ at a dosage of 400 mg per day for 52 weeks. The authors observed decrease in HbA1c of 1.18%, 1.17% and 0.8% at weeks 12, 24 and 52, respectively as compared to baseline. A significant reduction was observed in FBG, PPG, LDL-C, TG, TC, HDL and non-HDL-C at weeks 24 and 52, regardless of baseline hsCRP (p<0.0001 for all). At weeks 12 and 24, the reduction in A1C was significantly greater in patients with high inflammatory load (hsCRP>3). Additionally, there was significant decrease in hsCRP at weeks 24 and 52 as compared to baseline (p<0.0001).[45]

Lipid lowering effect of HCQ

In a prospective longitudinal study on RA cohort, Kerr et al, found that HCQ users had significantly lower mean levels of TC: -13.5 mg/dl, LDL-C: -11.7 mg/dl and triglycerides (TG): -21.8 mg/dl than HCQ nonusers, with the exception of HDL (p=0.165).[46]

In a double-blind phase III study done by Pareek et al,, in patients with primary dyslipidemia demonstrated that those receiving combination treatment of atorvastatin and HCQ showed significantly greater reductions in LDL-C, TC and non-HDL-C as compared to those receiving atorvastatin alone at the end of 24 weeks.[47] In another phase-3 double-blind trial, Pareek et al, found that the HCQ group significantly reduced their baseline TC and LDL-C levels at weeks 12 and 24 as compared to the rise in these parameters in patients receiving pioglitazone treatment for T2D.[48]

Antiplatelet and antithrombotic effect

In healthy human volunteers, Achuthan et al, demonstrated that when arachidonic acid (AA) was used as an agonist, HCQ given alone significantly decreased platelet aggregation (p=0.03) in comparison to when ADP or collagen was used as an agonist. The study also found that the inhibition of platelet aggregation (IPA) was considerably higher when ASA with HCQ was compared to ASA alone.[49]

In a retrospective cohort study of PAPS (primary antiphospholipid syndrome) patients, Nuri et al, found that patients treated with HCQ had lower incidence of arterial thrombosis recurrence than the group that was not exposed to HCQ, which had 1.14% incidence.[50]

Reno protective effect

In a longitudinal observational cohort study involving 203 patients with lupus nephritis from the LUMINA trial, Pons-Estel et al, found that patients who were taking HCQ had cumulative probabilities of developing renal damage at five and ten years of 20% and 38%, respectively, whereas those who were not using HCQ had cumulative probabilities of 47% and 70%. (p≤0.0001).[51]

CV protective effect

In one retrospective study of RA patients, Sharma et al, found that HCQ therapy was independently linked to 70% decrease in the risk of incident composite CAD, stroke and TIA and 72% decrease in total incident CVD events when compared to HCQ non-users.[52] Ulander et al, conducted one randomized study involving 125 myocardial infarction patients, with a median of 43 hours post-hospitalization. At the end of 6-months, HCQ (HCQ) significantly reduced IL-6 levels as compared to placebo (p=0.042, between groups). The authors concluded that HCQ showed beneficial effect in reducing cardiovascular inflammation.[53]

CONCLUSION

HCQ, a widely used anti-inflammatory agent for the management of rheumatoid arthritis and systemic lupus erythematosus, has demonstrated significant effects on glycaemic parameters via its unique mechanism of action. It has been demonstrated to reduce the incidence of T2D, lipid levels and cardiovascular events in multiple prospective and retrospective studies. It is the sole DCGI - approved anti-inflammatory drug for the management of diabetes. Due to its pleotropic benefits, HCQ has the potential of reducing prediabetes to diabetics, has antidiabetic properties and also has the potential to reduce CVDs associated with T2D.

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