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

AK Das1, S Kalra2, M Tiwaskar3, S Bajaj4, K Seshadri5, S Chowdhury6, R Sahay7, S Indurkar8, AG Unnikrishnan9, U Phadke10, A Pareek11, I Purkait11

Abstract

Diabetes is a major public health emergency of the 21st century. Results of the Indian Council of Medical Research-India DIABetes (ICMR-INDIAB) study have found prevalence of diabetes and prediabetes in India to be as high as 7.3% and 10.3%, respectively with nation-wide projection of 77.2 million people with prediabetes and 69.2 million with diabetes.

It is well established that insulin resistance (IR) and islet β-cell failure are the two major features of T2D. Multiple mechanisms including glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum stress, formation of amyloid deposits in the islets, etc., have been hypothesized to participate in the pathology of the disease. In the concluding decade of the last century, numerous studies - prospective and cross-sectional, have confirmed the role of chronic low-grade inflammation as a pathogenetic factor of T2D. It has been shown that increased levels of various inflammatory markers and mediators including fundamental markers like white blood cell count, C-reactive protein (CRP) to the more specific circulating cytokines like, interleukin-6 (IL-6), IL-1β, plasminogen activator inhibitor-1 (PAI-1), etc. correlate with incident T2D.

Based on the robust evidence implying the role of inflammation in T2D pathogenesis, several studies have proven that the pro-inflammatory cytokines play a central role in the development of microvascular diabetic complications such as nephropathy, retinopathy, and neuropathy. Inflammation in T2D causes accelerated atherosclerosis which predisposes to CVD, the leading cause of mortality in these patients. Recently there is a considerable increase in the interest among the researchers about anti-inflammatory therapies in the setting of chronic disorders such as T2D and CV diseases.

In a multi-country study conducted in Asia, approximately 50% of Indian respondents had poor diabetes control. Most patients initially respond to sulfonylurea and/or metformin, and later these agents lose their effectiveness with time. Therapeutic option in patients uncontrolled on two-drug combination therapy is either to add third oral drug or insulin. However, use of insulin is limited due to its high cost and poor compliance. Majority of new treatment options like GLP1 agonists, insulin analogs and SGLT2 inhibitors are costly considering they are still under patent. The thiazolidinedione class of drugs is associated with adverse effects like fluid retention and weight gain that may result in or exacerbate edema and congestive heart failure. Thus there is a need for a safe and inexpensive treatment option for the management of uncontrolled T2D. Considering the role of inflammation in T2D pathogenesis, the drug should not only have antihyperglycemic effects but also reduce inflammatory burden thus reducing the progression and complications of T2D.

The current interest is apparently directed towards drugs targeting inflammation acting at different stages of the inflammatory cascade. In the recently published CANTOS study, canakinumab, a selective, high-affinity, fully human monoclonal antibody which inhibits IL-1β, has no consistent long-term benefits on HbA1c. Other selective inhibitors like anakinra (IL-1 receptor antagonist) and etanercept (TNF inhibitor) too have yielded modest effects on glycemic parameters and insulin sensitivity. However, hydroxychloroquine (HCQ), a broad anti-inflammatory agent has been shown to reduce HbA1c by 0.87%.

Hydroxychloroquine (HCQ) is considered as one of the safest disease modifying anti-rheumatic drug, used widely for the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The effect of HCQ in preventing development of diabetes in patients with chronic inflammatory diseases was highlighted in a prospective observational study of 4905 adults with rheumatoid arthritis and no diabetes with 21.5 years of follow-up. Patients who took HCQ for more than 4 years had a significant 77% lower risk of diabetes compared with non users of HCQ (RR, 0.23; 95% CI, 0.11-0.50). Taking cue from this study highlighting the anti-diabetic effect of HCQ, pioneering research studies evaluating these effects of HCQ were conducted in India. In 2014, hydroxychloroquine 400 mg got DCGI approval as an adjunct to diet and exercise to improve glycemic control of patients on metformin, sulfonylurea combination in Type 2 diabetes.
HCQ exerts its antidiabetic action through many mechanisms including its anti-inflammatory action, inhibition of insulin degradation and improvement in insulin sensitivity.

In a retrospective cohort study done in RA patients, Sharma et al. showed that the treatment with HCQ was independently associated with a 72% reduction in all incident CVD events and a 70% reduction in the risk of incident composite CAD, stroke, and TIA. The biological explanation of this protective action is supported by its favorable associations with beneficial alterations in lipid profiles, reductions in risk of thrombotic events and inhibitory effect on platelet aggregation.

Several clinical studies are being conducted globally to demonstrate the effect of HCQ on glucose metabolism including the OXI trial which is evaluating its effect in preventing recurrent cardiovascular events among myocardial infarction patients. In the future HCQ can emerge as a valuable therapeutic option in the management of T2D patients uncontrolled on conventional oral therapies.

### Epidemiology of Type 2 Diabetes Mellitus

Diabetes is a major public health emergency of the 21st century. Globally, 415 million people were affected by diabetes in 2015; and this prevalence is projected to rise to 642 million by the year 2040.1 Type 2 diabetes mellitus (T2D) is the most prevalent form of diabetes with 87% to 91% of adults with diabetes having T2D. India is reported to have the second highest number of diabetic individuals in the world.2 Results of the Indian Council of Medical Research-INdia Diabetes (ICMR-INDIAB) study have found prevalence of diabetes and prediabetes to be as high as 7.3% and 10.3%, respectively with nation-wide projection of 77.2 million people with prediabetes and 69.2 million with diabetes.3

**Diabetes and Inflammation: The link**

**Historical Aspects**

The concept of chronic low-grade inflammation as a pathogenetic factor of T2D is not recent. More than a century ago, sodium salicylate in high doses of 5.0–7.5 g/d were demonstrated to reduce glycosuria in patients presumably having T2D.4 In 1957, Reid and colleagues rediscovered this effect in insulin-treated diabetic patients, given high-dose aspirin to treat the arthritis associated with rheumatic fever, and found that they no longer required daily insulin injections.5 In the concluding decade of the last century, numerous studies—prospective and cross-sectional, confirmed and extended these early findings. It has been shown that increased levels of various inflammatory markers and mediators including fundamental markers like white blood cell count, C-reactive protein (CRP) to the more specific circulating cytokines like, interleukin-6 (IL-6), IL-1β, plasminogen activator inhibitor-1 (PAI-1), etc. correlate with incident T2D.6,9

**Pathogenesis of Type 2 Diabetes – an auto-inflammatory disease**

It is well established that insulin resistance (IR) and islet β-cell failure are the two major features of T2D. Multiple mechanisms including glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum stress, formation of amyloid deposits in the islets, etc. have been hypothesized to participate in the pathology of the disease, with inter-individual differences depending on genetic background, nutrition, physical activity and other environmental factors.10

Inflammation in the peripheral tissues leads to insulin resistance

Adipocytes are the pathogenic site of insulin resistance in T2D.3 In obese individuals, excess calorific intake is stored in the form of triglycerides within the adipocytes of white adipose tissue. If there is insufficient capacity in mature adipocytes, new adipocytes are formed from pre-adipocytes in order to increase storage capacity. There may be a limited ability to produce mature adipocytes from pre-adipocytes (hyperplasic adipocyte expansion) in some individuals and excess fatty acids are stored in existing mature adipocytes leading to an increase in their size i.e hypertrophic expansion. Larger adipocytes tend to be more dysfunctional, and subsequently they become insulin resistant.11

Subsequent failure of angiogenesis and inadequate blood supply to hypertrophic adipocytes leads to necrosis, macrophage infiltration into adipose tissue and inflammation and adipokine release. “Spillover” of fatty acids unable to be retained in subcutaneous adipocytes leads to an increase in the visceral fat and eventually flux of fatty acids into ectopic sites, stored as intracellular lipid droplets in tissues, such as liver and the pancreas. The formation of ectopic fat is closely linked to the development of IR and T2D.11

Inflammation in the islets leads to β-cell dysfunction

Glucotoxicity and especially lipotoxicity increase the local level of free fatty acids (FFA) and long chain fatty acids in the islets.12 Prolonged exposure to elevated glucose concentrations and FFA leads to increased formation of reactive oxygen species (ROS) causing oxidative stress.13 Since pancreatic islets have low antioxidant defence, hence are vulnerable to oxidative stress.

ROS plays a key role in activation of several transcription factors including NF-kB, leading to production of IL-1β. This islet-derived IL-1β further induces various cytokines and chemokines including IL-6, IL-8, TNF and chemokine-attactant proteins that lead to the attraction of macrophages and other immune cells. Immune cells recruitment is further enhanced by the vicious cycle of IL-1β ‘autostimulation’ ultimately leading to β-cell dysfunction (Figure 1).

In diabetic patients, NADPH oxidase (NOX), the major source of ROS in the cardiovascular system is increased.14,15 NOX is an enzyme complex involved in numerous proinflammatory signalling cascades including signaling of TNFα via TNF-receptor 1 (TNFRI) and IL-1β via IL-1R. Thus, inhibition of the endosomal NOX can massively reduce the downstream activation of nuclear factor-xB (NF-xB) via these pathways.16

In addition to adipose tissue, the liver is affected by obesity and may lead to non-alcoholic fatty liver disease (NAFLD) which often accompanies T2D.3 Different mechanisms have been suggested to explain initiation of inflammation in the liver. It has been suggested that similar to the adipose tissue inflammation that follows adipocyte lipid accumulation, hepatocyte lipid accumulation...
(steatosis) induces a subacute inflammatory response in liver. Inflammation has also been noted in the skeletal muscles, another important site of insulin resistance. This trigger is thought to be due to intracellular lipid infusion and not the increased adiposity as in the adipose tissues or liver. Thus, just like the portal delivery of abdominal fat–derived cytokines and lipids contribute to hepatic inflammation and insulin resistance, the proinflammatory and proatherogenic mediators produced in the adipose tissue and liver create a systemic inflammatory diathesis that promotes insulin resistance in skeletal muscle and other tissues and atherogenesis in the vasculature (Figure 2).

In summary, multiple mechanisms contribute to inflammation in T2D, some of which are general and others are tissue specific.

Progressive decline in β cell mass in patients with Type 2 Diabetes

T2D is a progressive disease characterized by continuing loss of β cell function. Insulin secretion is usually increased two- to three-fold to compensate insulin resistance in obese non-diabetic individuals. On the other hand, only a 0% to 50% increase in β cell mass in obese non-diabetic individuals has been observed by histological analyses, implying that insulin secretion per β cell, i.e., β cell workload, increases in the face of obesity.

Increase in β cell workload makes them dysfunctional which causes residual β cells to work harder to maintain normoglycemia. Eventually, when the reduction in functional β cell mass crosses the threshold, hyperglycemia develops. Hyperglycemia itself causes a further increase in β cell workload and a further reduction in functional β cell mass. This vicious cycle explains the progressive nature of T2D (Figure 3) and highlights the importance of early intervention and treatment of T2D to preserve and restore functional β cell mass in T2D patients.

Complications of T2D

Macrovascular complications; Role of inflammation in Diabetic Cardiovascular Disease

One of the most important medical concerns today is not only the rapidly increasing rate of T2D but also the target organ complications secondary to diabetes. Diabetes predisposes to CVD which is the leading cause of mortality in these patients.

Atherosclerosis is a multifactorial disease that is considered as a chronic inflammatory response of intima to tissue damage. There is strong evidence that chronic hyperglycemia is associated with a low-grade activation
Fig. 4: Over-nutrition, metabolic syndrome and/or genetic predisposition may contribute to obesity development and modulate adipokines profile resulting in a low-grade inflammatory state which is associated with increased risk of insulin resistance and atherosclerosis.

Microvascular complications: Role of inflammation in Diabetic nephropathy, Diabetic retinopathy, Diabetic neuropathy

Based on the robust evidence implying role of inflammation in T2D pathogenesis, the obvious question that arises is: is inflammation related to the development of diabetic complications? Several studies show that pro-inflammatory cytokines play a central role in the development of microvascular diabetic complications such as nephropathy, retinopathy, and neuropathy. General pathway in the progression of diabetic microvascular complications is given in Figure 5.

Inflammation in Diabetic Nephropathy

Diabetic nephropathy (DN) is a common complication affecting approximately 40% of persons with diabetes and is the leading cause of chronic kidney disease. The intricate mechanisms leading from chronic hyperglycaemia to the development of renal injury are complex and are still being elucidated. A number of experimental and clinical studies have demonstrated that DN exhibits signs of inflammation.

Inflammation in Diabetic Retinopathy

Diabetic Retinopathy (DR) is the leading cause of vision loss in adults globally and is ranked as the fifth most common cause of preventable blindness. Both experimental and clinical data from the past two decades have highlighted the central and causal role of chronic subclinical inflammation in the pathogenesis of DR.

Inflammation in Diabetic Neuropathy (DNO)

More than 50% of the patients with T2D develop DNO. Multiple pre-clinical and clinical studies demonstrate a pathogenic role for inflammation, especially cytokine and chemokine production, in the disease course of DNO. The central role of inflammatory stress, in presence of the metabolic dysfunction, leading to nerve damage in diabetes has been discussed in the Position Statement on Diabetic Neuropathy by the American Diabetes Association – 2017.

Other complications of T2D: NAFLD & NASH, Adhesive capsulitis

NAFLD, T2D and metabolic syndrome (MetS) are the conditions that commonly co-exist and can act synergistically to drive adverse

Fig. 5: General pathway in the progression of diabetic microvascular complications

of the innate immune system, which in turn, is associated with accelerated atherosclerosis. Numerous adipokines have been implicated in maintaining the inflammatory environment leading to atherosclerosis.

Adiponectin, which is reduced in obesity and diabetes, has been shown to play a protective role in atherosclerosis. On the other hand, adipokines such as leptin, IL-6, MCP-1 and TNF-α increase the atherogenic process and favor plaque rupture and thrombus formation (Figure 4).

The role of inflammation in the pathogenesis of atherosclerosis and consequently, atherosclerotic cardiovascular disease (ASCVD) has been discussed in statements and recommendations by the American College of Cardiology and the American Association of Clinical Endocrinologists and American College of Endocrinology.

Normal Adipocytes

Over Nutrition
Metabolic Syndrome
Genetics

\[ \downarrow \text{Adiponectin} \]

\[ \uparrow \text{MCP-1} \]

\[ \uparrow \text{IL-6} \]

\[ \uparrow \text{TNF-\(\alpha\)} \]

\[ \uparrow \text{Leptin} \]

\[ \downarrow \text{Inflammation} \]

Atherosclerosis
Insulin Resistance

Hyperglycemia and Hyperlipidemia

Age - RAGE

Oxidative Stress

Hypoxia

Inflammatory Signaling Cascades

Local Activation of Pro-inflammatory cytokines

Inflammation

Nephropathy
Retinopathy
Neuropathy

Fig. 4: Over-nutrition, metabolic syndrome and/or genetic predisposition may contribute to obesity development and modulate adipokines profile resulting in a low-grade inflammatory state which is associated with increased risk of insulin resistance and atherosclerosis.

Fig. 5: General pathway in the progression of diabetic microvascular complications
Adhesive capsulitis (AC), or frozen shoulder, with an estimated prevalence of 10% to 29%, is five-fold higher in the diabetic population than in the general population. AC is considered severe and resistant to treatment in diabetic population. The underlying reason may be due to chronic inflammatory state in T2D, which can lead to excessive accumulation of collagen and other extracellular matrix components, resulting in destruction of normal tissue architecture. The accumulation of advanced glycation end products (AGEs) due to non-enzymatic oxidative reactions between glucose and collagen results in formation of adducts and cross-linking between neighbouring collagen fibrils, thereby increasing the stiffness. Thus, chronic inflammatory reactions are at the focal point of both DM and AC.

Need gap in T2D therapy

In a multi-country study conducted in Asia, approximately 50% of Indian respondents had poor diabetes control. Uncontrolled hyperglycemia has deleterious effects on the human vascular tree and are the major source of morbidity and mortality in T2D. Anti-inflammatory drugs via different modes of action are used alone or in combination to improve glucose homeostasis. Most patients initially respond to sulfonylurea and/or metformin, and later these agents lose their effectiveness with time. Therapeutic option in patients uncontrolled on two-drug combination therapy is to add third oral drug or insulin. However, use of insulin is limited due to its high cost and poor compliance. Majority of new treatment options like gliptins and SGLT2 inhibitors are costly considering they are still under patent. Many diabetic patients may not be able to afford such costly medicines considering the chronic treatment required in T2D. The thiazolidinedione class of drugs is associated with adverse effects like fluid retention and weight gain that may result in or exacerbate edema and congestive heart failure. Thus there is a need for a safe and inexpensive treatment option for the management of T2D.

Based on the robust evidence implying the role of inflammation in T2D pathogenesis, several studies have proven that inflammation plays a central role in the development of microvascular diabetic complications such as nephropathy, retinopathy, and neuropathy. Inflammation in T2D causes accelerated atherosclerosis which predisposes to CVD, the leading cause of mortality in these patients.

Hence we need to look for a drug which not only has antihyperglycemic effects but also reduces inflammatory burden thus reducing the progression and complications of T2D.

Anti Inflammatory drugs in T2D

High doses of salicylates such as aspirin are known to lower glycosuria in diabetic patients since the 19th century. There is a considerable increase in the interest among the researchers about anti-inflammatory therapies in the setting of chronic disorders such as type 2 diabetes and CV diseases. However, because inflammation acts along multiple pathways, the identification of an appropriate target may be difficult (Figure 6).

The current interest is apparently directed toward new drugs targeting inflammation which are innovative molecules acting at different stages of the inflammatory cascade.

**NF-κB inhibitors: Salsalate**

Salsalate, a prodrug of salicylate, has demonstrated beneficial effects on glycaemia and insulin sensitivity, probably through inhibition of the NF-κB pathway. To date, there are seven independent clinical trials that demonstrate improvement in glycaemia with salsalate. In the TINSAL study, improvement in glycaemic control and decreased inflammatory mediators was observed among the T2D patients treated with Salsalate. However, its long-term cardiovascular and renal safety is questionable as increase in LDL cholesterol and urinary albumin levels have been observed in patients taking salsalate.

**TNF-α inhibitor: Etanercept**

Looking into the inflammatory pathways responsible for T2D, patients may benefit from TNF blockade. TNF inhibition has shown significant risk reduction of developing T2D in rheumatoid arthritis or psoriasis patients but, various studies performed until now with the aim to obtain amelioration of insulin resistance and hence hyperglycemia by blocking the TNF system yielded negative results not only in people with T2D, but also in non-diabetic, insulin resistant subjects. Also, clinical trial of etanercept failed to demonstrate improvement insulin sensitivity in subjects metabolic syndrome despite lowering CRP. The absence of any consistent effect on insulin sensitivity by anti-TNF therapies has been disappointing.

**IL-1 antagonism: Anakinra and canakinumab**

Clinical studies have demonstrated that antagonism of IL-1 pathway has the potential to improve glycaemia in patients with type 2 diabetes.
Could be due to targeting a selective minimal effects on glycemic parameters of canakinumab on CV events and inflammatory Thrombosis Outcomes atherosclerosis. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), 45 drives the progression of inflammatory in the inflammatory pathway which inhibits IL-1ß, a key cytokine affinity, fully human monoclonal daily injection.

Moreover, the patient compliance remains a concern for modest (0.4%).10 Moreover, the patient levels. But reduction in HbA1c was reduced C-reactive protein (CRP) function of insulin associated with both hyperglycemia and secretory levels. However, the magnitude of the effects is often a matter of debate. Anakinra, a recombinant human interleukin-1 receptor antagonist, first to be used in clinical practice in type 2 diabetes reported benefits on both hyperglycemia and secretory function of insulin associated with reduced C-reactive protein (CRP) levels. But reduction in HbA1c was modest (0.4%).10 Moreover, the patient compliance remains a concern for anakinra due to its administration as daily injection.

Canakinumab, a selective, high-affinity, fully human monoclonal antibody inhibits IL-16, a key cytokine in the inflammatory pathway which drives the progression of inflammatory atherosclerosis. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS),45 with an aim to prove the inflammatory hypothesis of atherothrombosis is considered as one of the landmarks and long duration study conducted by Novartis. Canakinumab showed improvement in glycosylated in diabetic patients but at a median follow-up of 3.7 years, it showed a modest (15%) reduction in risk of primary cardiovascular end points (composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) as compared to placebo (3.86 vs. 4.50 events per 100 person years). In addition, despite reductions in hsCRP and interleukin-6, there was no reduction in the incidence of new onset diabetes. The reduction in Hba1c was only 0.3% for the dose of 300 mg during the first 6 months of treatment, with no consistent long-term benefits.46 The modest effects of canakinumab on CV events and minimal effects on glycemic parameters could be due to targeting a selective inflammatory pathway i.e. IL-1β.

**Hydroxychloroquine**

Hydroxychloroquine (HCQ) is considered as one of the safest disease modifying anti-rheumatic drug, used widely for the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The effect of HCQ in preventing development of diabetes in patients with chronic inflammatory diseases was highlighted in a prospective observational study46 of 4905 adults with rheumatoid arthritis and no diabetes with 21.5 years of follow-up. The relative risk of developing diabetes gradually declined. Patients who took HCQ for more than 4 years had a significant 77% lower risk of diabetes compared with non users of HCQ (RR, 0.23; 95% CI, 0.11-0.50). This finding supported a biological action of this drug on glucose metabolism. Taking cue from these studies highlighting the anti-diabetic effect of HCQ and considering the pleiotropic benefits of HCQ (lipid lowering and anti-platelet) in rheumatologic patients, pioneering research studies evaluating these effects of HCQ were conducted in India. In 2014, hydroxychloroquine 400 mg got DCGI approval as an adjunct to diet and exercise to improve glycemic control. In another experimental study, demonstrated preservation of IOL structure in diabetic rats treated with hydroxychloroquine. 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 hydroxychloroquine 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: Preclinical studies**

Pre-clinical studies determined the mechanisms of HCQ in diabetes.

Abdel-Hamid AA et al.56 in an experimental study, demonstrated preservation of IOL structure in diabetic rats treated with hydroxychloroquine. 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 hydroxychloroquine 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 (Table 1).

**Guideline recommendations in T2DM**

R S S D I c l i n i c a l p r a c t i c e recommendations for the management
metabolism may contribute to lower the risk of developing diabetes compared with HCQ non-users. (RR, 0.23; 95% CI, 0.11-0.50) (Figure 11). This finding substantiated the action of this drug on glucose metabolism pathway.

Clinical evidence from these studies substantiates the fact that, HCQ has a potential to enter antidiabetic armamentarium due to its efficacy and low toxicity profile.

Pleotropic benefits of HCQ

HCQ through its beneficial effects on lipids, coagulation, and glucose metabolism may contribute to lower the high CV risk in the patients treated for inflammatory conditions like RA and SLE. In a retrospective cohort study done in RA patients, Sharma et al. showed that the treatment with HCQ was independently associated with a 72% reduction in all incident CVD events and a 70% reduction in the risk of incident composite CAD, stroke, and TIA (Figure 12).

The biological explanation of this protective action is supported by its favorable associations with beneficial alterations in lipid profiles, reductions in risk of thrombotic events and inhibitory effect on platelet aggregation. L

Anti platelet and anti-thrombotic effect of HCQ: HCQ prevents platelet activation and the mechanisms proposed range from membrane stabilization, prevention of platelet granular release, inactivation of phospholipase A2 and inhibition of membrane bound calcium. Achuthan S et al. showed 11% reduction in platelet aggregation with HCQ and 31.2% reduction when combined with aspirin. In SLE, several studies—both prospective and retrospective—have found reduction in thrombosis risk with HCQ.

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.

HCQ: Safety, precautions and contraindications

HCQ and Retinopathy

Presence of a hydroxyl group in HCQ makes it less toxic, more effective and it also restricts its ability to traverse the blood-retinal barrier, thus, it has less ocular toxicity as compared to chloroquine.

In a study of 2361 patients using HCQ continuously for at least five years, the prevalence of retinal toxicity remained less than 2% within the first 10 years of use. Yam JC et al. through meta-analysis and extensive literature search showed very low clinically significant retinopathy due to HCQ (Table 2).

Though studies in the past showed evident bull’s eye changes on fundus examination in a small number of patients on chronic therapy examination but recent studies have utilized spectral-domain optical coherence tomography (SD OCT) and other techniques to detect early toxicity.

Guidelines/Recommendations on screening for HCQ retinopathy

Looking into the extensive use of HCQ in clinical practice, American Academy of Ophthalmology (AAO) in 2016 has recommended and provided guidelines on the screening frequency to deem a fair balance of risk. The cumulative risk of toxicity is dependent on daily dose and duration of use. At
HCQ-related hyperpigmentation is the scientific literature. The incident hyperpigmentation are published in majority of reported cases were effect of antimalarial agent but the one of the most reported skin adverse

75 association with cumulative dose or HCQ and hyperpigmentation within the reversible stage. 73 maculopathy is rare and no reliable therapy, as clinically significant required until after 5 years of cumulative state that annual screening is not recommended doses, the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2% (Table 3).

The guidelines issued by the British Royal College of Ophthalmologists and the British Society for Rheumatology state that annual screening is not required until after 5 years of cumulative therapy, as clinically significant maculopathy is rare and no reliable test exists for detecting this retinopathy within the reversible stage. 73

**HCQ and hyperpigmentation**

Cutaneous hyperpigmentation is one of the most reported skin adverse effect of antimalarial agent but the majority of reported cases were attributed to chloroquine treatment. Very few cases of HCQ induced hyperpigmentation are published in the scientific literature. The incident HCQ-related hyperpigmentation is estimated at 7-13%. 74 Unlike HCQ-related retinopathy, there is no clear association with cumulative dose or duration of use. 75

According to a study conducted by Jallouli M et al., only 13 cases (7.3%) of pigmentation were attributable to a median cumulative dose of 720 g of HCQ. Involvement of common sites and its link with the factors predisposing to bruising, patient interviews and the skin histology substantiates the fact that HCQ-related pigmentation occurs secondary to ecchymosis or bruising. The hyperpigmentation generally begins after a few months or years of treatment. In this study, skin pigmentation appeared after median treatment duration of 6.1 years (range, 3 months–22 years). 76

Clinically, patients on these medications present with yellow-brown to slate-gray patches. The biochemical mechanism casing this remains unknown. HCQ-induced hyperpigmentation can arise within 1 year after initiation of therapy. Systemic adverse sequelae are not generally observed with HCQ-induced hyperpigmentation. After discontinuation of the drug, the drug-associated pigmentation slowly fades. Spontaneous clinical remission of the HCQ-induced skin discoloration is reported to be observed within 2 to 6 months. 77 Persistent cutaneous hyperpigmentation with minimal resolution one year after treatment discontinuation has also been reported. 78

**Precautions**

Because HCQ may concentrate in liver, the drug should be used with caution in patients with hepatic disease or alcoholism and in conjunction with known hepatotoxic drugs.

Hydroxychloroquine should be discontinued if there is evidence of adverse hematologic effects that are severe and not attributable to the disease being treated. Caution has to be exercised while administrating HCQ to the patients with G-6-PD (glucose-6-phosphate dehydrogenase) deficiency.

HCQ may induce skin reactions thus; care should be taken when it is administered to the patient receiving an agent with propensity to cause dermatitis.

If serious toxic symptoms occur, administer ammonium chloride (8 g daily in divided doses for adults) 3 or 4 days a week for several months after therapy has been stopped; acidification of the urine increases renal excretion by 20% to 90%. Exercise caution in patients with impaired renal function and/or metabolic acidosis.

**HCQ in ESRD**

The optimal dose of HCQ in ESRD cannot be determined from the clinical studies. In a retrospective cohort study involving 10,276 ESRD patients with SLE, there was often no dose

---

**Table 1: Clinical studies of HCQ in T2DM**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quatraro A et al. 1990</td>
<td>Prospective, randomized, double-blind. 38 patients with T2D resistant to oral hypoglycemic agents, insulin and antidiabetic drugs combined with insulin.</td>
<td>After six months of treatment, addition of HCQ (200 mg three times a day) to insulin or glibenclamide resulted in significant reduction of diurnal plasma glucose compared to placebo. Addition of HCQ to insulin or glibenclamide resulted in significant reduction in HbA1c in comparison to placebo (HbA1c reduced by -3.3% for both groups)</td>
</tr>
<tr>
<td>Gerstein HC et al. 2004</td>
<td>Double-blind placebo controlled trial 135 obese patients with T2D despite maximum sulfonylureas</td>
<td>Add-on therapy with HCQ resulted in decreased requirement of insulin by 30%. In 6 months, addition of HCQ (up to 300 mg bid) decreased Hb1c by an absolute amount of 1.02% more than placebo (95% CI 0.24, 1.81).</td>
</tr>
<tr>
<td>Pareek A et al. 2014</td>
<td>Double-blind, double-dummy, randomized, multicenter phase III trial 267 T2D patients uncontrolled (HbA1c ≥7.5% and ≤ 11.5%) on metformin + sulfonylurea, after 3 months’ treatment with glimepride/gliclazide and metformin, additionally received HCQ 400 mg/day (or pioglitazone 15 mg/day for 24 weeks.</td>
<td>Glucose tolerance and LDL-C improved during the first 3 months of therapy. HCQ was found to be non-inferior to pioglitazone wrt to fall in HbA1c, PPG and FBG after 12 and 24 weeks of therapy (HbA1c: -0.87% with HCQ vs. -0.90% with Pioglitazone. p = 0.909) Importantly, total cholesterol and LDL-C decreased in HCQ group vis-à-vis comparator group. (TC: -0.37 mmol/L vs. 0.03 mmol/L, p = 0.002; LDL-C: -0.23 mmol/L vs. 0.09 mmol/L, p = 0.003)</td>
</tr>
<tr>
<td>Jagannani VK et al. 2017</td>
<td>Open-labeled comparative observational study 200 uncontrolled T2D patients</td>
<td>After 6 months of therapy, the reduction from baseline in HbA1c (-1.8% vs -1.6 %), FPG (-46 mg/dl vs -40 mg/dl) and PPG (-78 mg/dl vs -72 mg/dl) in HCQ treated patients was significantly greater compared to the patients treated with Tenereliglitin.</td>
</tr>
<tr>
<td>Baidya A et al. 2018</td>
<td>Multicentre, open-labelled comparative observational study, randomised 240 patients with T2D poorly controlled with a high stable insulin dose, glimepiride and metformin allocated to either HCQ 200 or 400 mg once daily</td>
<td>Significant reduction in the HbA1C (-1.3%), FPG (-33.2 mg/dl) and PPG (-49.8 mg/dl) after 6 months with HCQ.</td>
</tr>
<tr>
<td>Pareek A et al. (AACE 2018)</td>
<td>Open-labeled multicentric study of 208 uncontrolled (A1c ≥7%) T2DM patients receiving stable doses of metformin and sulfonylurea for at least 3 months prior enrolment. Eligible patients received HCQ 400 mg/day in addition to existing therapy for 52 weeks. Patients were divided into 2 groups based on baseline hsCRP (≥3 and &gt;3 mg/l). Both groups were comparable at baseline with respect to mean A1C, FBG, PPG and lipids.</td>
<td>HCQ led to significant fall in glycemic parameters in both groups with numerically higher fall in hsCRP ≥3 arm: A1c (-1.42 vs -1.19%), FBG (-22 vs -15 mg/dl) and PPG (-43 vs -33 mg/dl). Total, LDL-, non-HDL-cholesterol and triglycerides were reduced significantly in both groups.</td>
</tr>
</tbody>
</table>
adjustment made for HCQ dosage. The mean daily dose of HCQ prescribed was 321 mg with a median of 400 mg and a range of 58–2000 mg.79

Anti-inflammatory drugs: Future horizons

There is a vast scope and a research gap at present in evaluating the role of anti-inflammatory agents including HCQ in these areas. The inflammatory hypotysis of atherothrombosis is being explored in the ongoing prospective OXI trial76 involving 2500 patients with MI. In this event-driven clinical trial, conducted at Helsinki University, potential benefits of HCQ on mortality, cardiovascular events and coronary interventions among the patients hospitalized for MI are being evaluated. Trial will also evaluate whether HCQ has any benefits on incidence of T2D, HbA1c as well as lipid levels and inflammatory parameters. Estimated completion date of pilot study is last quarter of 2018.

Summary and conclusion

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, hydroxychloroquine 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, Hydroxychloroquine 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.

Table 2: Summary of important case series for the incidence of hydroxychloroquine retinopathy

Table 3: Screening recommendation for HCQ

References

2. https://www.google.co.in/search?num=100&ei=yzzLWpjf
3. https://www.google.co.in/search?num=100&ei=yzzLWpjf
9. Levy et al, 1997 Retrospective 12 years 0 in 758 (0) 400 mg/day >1 years
10. Wang et al, 1999 Prospective 15 years 0 in 94 (0) 200-400 mg/day >1 year
11. Levy et al, 1997 Retrospective 8 years 0 in 403 (0) 200-400 mg/day >1 years
19. h t t p : / / w w w . a c c . o r g / l a s t e s t - i n - c a r d i o l o g y / a r t i c l e s / 2016/10/27/14/27/atherosclerosis-in-patients-with-systemic-inflammatory-disease/latest accessed on 20th April 2017.