Journal of Gastroenterology Research and Practice

www.jjgastro.com

Review Article

Open Access, Volume 4

Inflammation and the emerging role of colchicine and Il-1 inhibitors in type 2 diabetes: A comprehensive review

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Received: Jun 26, 2024

Accepted: Jul 22, 2024

Published: Jul 29, 2024

Archived: www.jjgastro.com

Keywords: Colchicine; IL-1 inhibitors; Chronic inflammation; NLRP3 inflammasome; Type 2 Diabetes (T2DM).

Abstract

Type 2 Diabetes Mellitus (T2DM) stands as one of the most prevalent chronic metabolic disorders globally, presenting an ongoing challenge in terms of prevention and management. Inflammatory reactions are essential to the development and course of type 2 diabetes. NLRP3 inflammasome, along with its downstream inflammatory factors, is a key mediator of these responses. Recent data underscore the significance of Interleukin-1β (IL-1β) in instigating and sustaining inflammation-related organ dysfunction in T2DM. Consequently, factors governing NLRP3 activation and IL-1β expression emerge as potential therapeutic targets.

Colchicine, as an anti-inflammatory medicine, has the ability to inhibit the assembly and activation of the NLRP3 inflammasome via a variety of mechanisms, thereby mitigating inflammation. In this context, we will discuss the mechanisms that link metabolic disorders with the onset of chronic inflammation. Moreover, we delve into the therapeutic implications of IL-1 inhibitors and colchicine for the prevention and management of T2DM.

Introduction

Diabetes is a widespread and serious health problem around the world. In 2021, it was estimated that 485 million adults between the ages of 20 and 79 worldwide were affected by diabetes, with a standardized global prevalence of 6.1%. Projections indicate a troubling increase to 9.8% between 2021 and 2050, resulting in a staggering 1.31 billion people living with diabetes by 2050 [1]. Furthermore, reports indicate that up to 10% of pre-diabetics progress to diabetes each year, with an estimated 70% developing diabetes during their lifetimes [2].

Despite the development of numerous treatment options, proven medical therapies for diabetes prevention remain limited [3]. The ongoing challenge of preventing and controlling Type 2 Diabetes (T2DM) underscores the critical need for effective novel therapeutic approaches to address diabetes and its complications.

Type 2 diabetes accounts for 90-95% of all diabetes cases, resulting from a gradual loss of β-cell insulin secretion capacity due to peripheral Insulin Resistance (IR) [4]. IR is the primary driver in the progression from prediabetes to overt T2DM which is defined by impaired insulin-mediated glucose uptake in target cells. Substantial research indicates that persistent low-grade systemic inflammation plays a critical role in the pathogenesis of both Type 1 (T1DM) and T2DM and its complications [5-10]. However, we will focus here only on the inflammation that is involved in T2DM. This inflammation is characterized by elevated levels of acute phase proteins, pro-inflammatory cytokines, chemokines, and adipokines, as well as a decrease in anti-inflammatory and insulin-sensitizing adipokines. Noteworthy contributors to T2DM risk include C - Reactive Protein (CRP), IL-1β, TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1). Among these, IL-1β is a key cytokine that regulates chemokines and cytokines in patients with T2DM [11,12]. This pro-inflammatory state occurs even before the onset of overt

diabetes during the prediabetes period and is implicated in the subsequent development of T2DM. To release IL-1β, the NLRP3 inflammasome must be activated [13,14], and research on IL-1β inhibition supports its role in the disease's pathophysiology [15]. Given the persistent low-grade inflammation in the prediabetes period, addressing inflammatory pathways could be an important component of diabetes prevention and management efforts.

Studies targeting this inflammation especially in suppressing the IL-1β and Nod-Like Receptor Protein 3 (NLRP3) inflammasome pathways, show promising results [16-18]. Colchicine, an ancient anti-inflammatory medicine, exhibits a broad spectrum of anti-inflammatory activities, including the inhibition of macrophages and the NLRP3 inflammasome [19-22]. This review aims to highlight the expanding importance of inflammation in diabetes pathogenesis and provide insight on the efficacy of colchicine and IL-1 inhibitor therapy for T2DM prevention and management.

The role of inflammation in T2DM

Individuals at risk for type 2 diabetes exhibit hypersecretion of insulin in their β-cells, compensating for their initial state of insulin resistance. As the disease progresses, this functional reserve of the pancreas eventually depletes, paving the path for the onset of overt diabetes. While the relative contributions of β-cell malfunction and insulin resistance can differ among people with T2DM, poor insulin sensitivity is generally accepted to predate the clinical diagnosis of diabetes by up to five years [23]. Notably, steatosis, the accumulation of fat in the liver, occurs earlier to overt T2DM and is regarded a primary predictor of impaired hepatic insulin sensitivity [24,25].

It is now widely accepted that a high-calorie diet and lack of physical activity lead to fat buildup in subcutaneous tissue and later in the liver, pancreas, muscles, and endothelium [25]. Pancreatic fat buildup not only contributes to β-cell failure but also enhances insulin resistance in the tissues [26].

Clinical and experimental research have identified adipose tissue as a source of inflammation. In animal studies, Brown Adipose Tissue (BAT) has been demonstrated to play a critical role in controlling energy and glucose homeostasis, which is associated with peripheral insulin resistance [27,28]. However, White Adipose Tissue (WAT), particularly visceral WAT in the trunk, upper body, and abdomen, appears to be the primary source of inflammatory markers in T2DM. It generates a variety of bioactive substances, including resist in, chemokines, serum amyloid protein, leptin, adiponectin, IL-1, IL-6, IL-10, angiotensinogen, and many more substances collectively known as adipokines [29-32]. Adipocytes gradually become hypertrophic due to an excessive high-calorie diet and lack of exercise, resulting in increased adiposity. This increase in adiposity leads to the accumulation of immune cells (B cells and T cells) and the activation of genes that encode pro-inflammatory molecules [33-35].

Proinflammatory responses are triggered by the synergistic contributions of multiple mechanisms. These are summarized as increased nuclear factor κB (NF-κB) and c-Jun NH2-Terminal Kinase (JNK) activity by hypertrophied adipocytes, altered Unfolded Protein Response (UPR) due to Endoplasmic Reticulum (ER) stress, hypoxic stress from hypertrophied adipocytes' vasculature insufficiency, activation of Toll-Like Receptors (TLR) by excess Free Fatty Acids (FFAs), or increased chylomicron-mediated transit from the intestinal lumen into the circulation in a high-fat diet [11,36-38]. Through these mechanisms stressed adipocytes produce a variety of cytokines and chemokines that promote immune cell activation and accumulation within adipose tissue. Additionally, persistent lipid buildup in adipose tissues causes macrophages to transition from an alternatively activated, anti-inflammatory M2 phenotype to a classically activated, pro-inflammatory M1 phenotype [33,35,39]. The stimulation of hypertrophied adipocytes by the imbalance caused by increased M1 (pro-inflammatory) macrophages triggers a pro-inflammatory response, leading to an increase in the secretion of inflammatory molecules. Tissue-resident macrophages, largely activated by adipocyte-derived FFAs via TLR or NOD-Like Receptor family, Pyrin domain-containing 3 (NLRP3) pathways, release cytokines that inhibit insulin action in metabolic organs [40].

Nutrient overload increases macrophages in metabolic tissues, leading to an inflammatory milieu with high levels of TNF-α, IL-1, and inducible Nitric Oxide Synthase (iNOS). In metabolic organs such as the liver, adipose tissue, and muscle, the buildup of these pro-inflammatory macrophages directly suppresses insulin action, resulting in insulin resistance and hyperglycemia [41-43].

The role of inflammation in insulin resistance

Insulin resistance is a result of increased visceral adiposity and nutrient overload, with inflammation emerging as a major etiological factor in this complex process. Insulin's signaling cascade begins when it binds to its receptor, resulting in the phosphorylation of tyrosine residues in Insulin Receptor Substrate 1 (IRS-1). This phosphorylation then triggers subsequent insulin signaling events. However, in insulin resistance, pro-inflammatory molecules activate serine kinases such as JNK, inhibitor of NFκB Kinase subunit β(IKK-β), Extracellular-signal-Regulated Kinase (ERK), ribosomal protein S6 Kinase (S6K), mammalian Target Of Rapamycin (mTOR), Protein Kinase C (PKC), and glycogen synthase kinase 3β. These kinases inhibit insulin action by phosphorylating serine residues in the insulin signaling pathway rather than tyrosine residues [44,45].

Insulin resistance is linked to two important transcription factor signaling pathways: JNK and IKKβ/NF-κB. Activating these pathways requires a variety of proinflammatory stimuli, including those that both activate and upregulate NF-κB. Receptors for Advanced Glycation End products (RAGE) and other pattern recognition receptors, like TLRs, also contribute to the activation of these pathways. Elevated levels of FFAs lead to an increase in Diacylglycerol (DAG), activating PKC isoforms, which, in turn, activate the JNK and NFκB pathways [46,30]. Additional stimuli include the rise in Reactive Oxygen Species (ROS) production, Endoplasmic Reticulum (ER) stress, and alterations in adiposity [47,48].

Phosphorylation of IKK-β leads to proteasomal degradation of IκBα, allowing NF-κB to translocate to the nucleus and increase the expression of target genes [8]. Insulin resistance is induced by the byproducts of these NFκB target genes. A detrimental cycle of insulin resistance is sustained by the generation

of inflammatory molecules, which then activate the JNK and NF-κB pathways via a feed-forward mechanism [11].

Pancreatic islet inflammation in T2DM

The reduction of β-cell mass and function appears to stem from inflammation within pancreatic β-cell islets, irrespective of the etiopathogenetic mechanism underlying various forms of diabetes - a condition termed insulitis. Some theories posit that stressed β-cells may incite local inflammation in individuals with a genetic predisposition [49,50]. Recent research on human islets and monocytes shows that the principal stresses, both hyperglycemia and increased FFAs, cause a more potent pro-inflammatory phenotype. Substantial evidence suggests that islet inflammation related to hyperglycemia leads to β-cell apoptosis [51-53,12]. Hyperglycemia-induced β-cell apoptosis is thought to be caused by β-cells producing IL-1β in reaction to glucose. However, this inflammatory process likely results from the combined effects of dyslipidemia, hyperglycemia, and increased circulating adipokines [53,54].

During this inflammatory process, the number of intra-islet macrophages increases, making them the predominant source of proinflammatory cytokines within the islets. Communication between islet macrophages and β-cells, facilitated by hIAPP, chemokines (e.g., CCL2 and CXCL1), and proinflammatory cytokines (e.g., IL-1β), initiates and amplifies the M1 (pro-inflammatory) polarity shift of islet macrophages and islet inflammation. Among these cytokines, IL-1β, secreted by M1 macrophages, plays a crucial role in initiating and exacerbating islet inflammation [55]. In the islets of T2DM patients, upregulation of IL-1β serves as a major cytokine that regulates other cytokines and chemokines. This master cytokine recruits immune cells and induces IL-1β in β-cells, leading to a vicious inflammatory cycle [12].

Human islet cultures treated with IL-1Ra almost completely inhibited the induction of proinflammatory factors, such as IL-6, IL-8, IL-1β, CXCL1, CCL2, and TNF-α, caused by a diabetic milieu (fatty acid and/or glucose) or by activating Toll-Like Receptors (TLR) 2 and 4. This implies that cytokine and chemokine expression in human islets is regulated by IL-1β, with cytokines being produced subsequent to IL-1 receptor activation [52]. Furthermore, the inhibition of IL-1β by IL-1Ra has been linked to decreased expression of inflammatory markers, enhanced β-cell function, and decreased hyperglycemia [56]. Thus, inhibiting IL-1 as a target for islet inflammation holds the potential to be a successful therapeutic approach.

Activation of inflammasome in T2DM

IL-1β, which is produced predominantly by macrophages and β-cells is transformed to bioactive form by the multi-protein complexes within the cytosol upon activation, called inflammasomes. Inflammasomes are cytosolic platforms found in myeloid cells that detect damage associated molecular patterns (DAMPs) and regulate the release of IL-1β and IL-18 during metabolic stress [57]. Inflammasomes are made up of three components: A Nod-Like Receptor (NLR), an apoptosis-Associated Speck-like protein with a CARD (ASC) adaptor protein, and caspase-1. Several NLR molecules, such as NLRP1, NLRP3, and NLRC4 regulate caspase-1 activation and production of pro-IL-1β and pro-IL-18 into bioactive forms. However, NLRP3 activation is a major mechanism producing metabolic inflammation and insulin resistance, according to experimental and clinical research [58].

The NLRP3 inflammasome, also known as NALP3 or cryopyrin, is typically activated by PAMPs (pathogen-associated molecular patterns), which are evolutionary conserved structures on pathogens such as bacteria, viruses, and fungi that result in the production of IL-1β and IL-18 and plays a vital role in host defense as part of innate immunity. The NLRP3 inflammasome, also known as NALP3 or cryopyrin, is typically activated by PAMPs, which are evolutionary conserved structures on pathogens such as bacteria, viruses, and fungi that result in the production of IL-1β and IL-18 and plays a vital role in host defense as part of innate immunity. Interestingly, it can also be activated by endogenous DAMPS, resulting in "sterile inflammation." These metabolic "danger signals" (DAMPs) mostly include islet amyloid peptides, cholesterol crystals, urate, extracellular ATP, and saturated fatty acids [59].

The NLRP3 inflammasome is assembled and activated under the control of several mechanisms. These include oxidative stress, malfunctioning autophagy, and unfolded protein response. Increased oxidative stress from mitochondria, as well as an unfolded protein response caused by ER malfunction, have been associated to metabolic distress, inflammation, and insulin resistance development [60]. It is also demonstrated that hyperglycemia in T2DM patients induces an increase in Reactive Oxygen Species (ROS) in myeloid cells, leading to increased production of IL-1β and IL-18, which are inflammasome-dependent. Another study demonstrated that inhibiting AMP-activated protein kinase causes reactive oxygen species-dependent activation of the NLRP3 inflammasome. Furthermore, metformin treatment for two months reversed the increase in caspase-1 activation and myeloid cell production of IL-1β and IL-18 in drug-naïve T2DM patients by activating AMP-activated protein kinase [61]. Additionally, ablation of NLRP3 and ASC in chronically obese mice boosted islet growth and protected pancreatic β-cells from inflammation-induced death. This study offers direct in vivo evidence that the diet-induced obesity-related activation of the NLRP3 inflammasome is a major initiator of pancreatic damage and a key mechanism of progression to overt T2DM [62]. Thus, inhibiting NLRP3 inflammasome activation may prevent the progression from insulin resistance state to an overt type 2 diabetes by preventing β-cells from apoptosis.

IL-1 inhibitors and T2DM

It has been proposed that targeting cytokine production and secretion could halt the onset and progression of type 2 diabetes by preventing additional activation. Initially considered a potential therapeutic target, TNF-α has, however, shown unsatisfactory outcomes for both acute and long-term care in humans [63,64]. To assess the clinical advantages of TNF-α antagonist treatment in patients with T2DM, particularly regarding insulin sensitivity, long-term prospective studies are crucial.

IL-1 family members can be either pro-inflammatory or anti-inflammatory, and their balance affects the inflammation level and severity of many chronic inflammatory rheumatic diseases. IL-1α is mainly associated with skin conditions among pro-inflammatory members, while IL-1β plays a crucial role in inflammation in auto inflammatory diseases and is increased in the joints during arthritis [65]. Several animal studies of T2DM have shown that IL-1β's mechanism and action are consistent with the development and progression of T2DM. For example, IL-1 receptor antagonist (IL-1Ra) treatment decreased immune cell invasion into the pancreatic islets and improved glycemic control and insulin secretion in GK rats, a spontaneous, non-obese type 2 diabetes model [66]. IL-1Ra therapy also decreased in-

flammation and enhanced β-cell function in a rat model of islet amyloidosis [67]. Moreover, recombinant IL-1Ra anakinra can partially restore β-cell dysfunction in human islet cells damaged by lipotoxicity and glucotoxicity [68,69]. The antihyperglycemic effects of IL-1 inhibitors are summarized in Table 1.

Table 1: Antihyperglycemic effects of IL-1 blocking treatment. (e.g., anakinra, canakinumab, gevokizumab)*

Inflammatory marker and cellular functions related with glucose metabolism	IL-1 blocker effect
CRP	↓
IL-1	↓
IL-6	↓
Insulin resistance	↓
β-cell dysfunction	↓
Apoptosis	↓
Pancreatic islet amyloid deposits	↓
Excessive glucagon secretion from pancreatic α-cells	↓
β-cell function	↑
Insulin secretion	↑

*Rilonacept is not included since there is insufficient data demonstrating these effects.

Several IL-1 blocking drugs are already available. These include IL-1 Receptor antagonist (IL-1Ra) anakinra, human monoclonal antibody against IL-1β canakinumab and gevokizumab, and a soluble IL-1 receptor chimeric fusion protein that neutralizes both IL-1α and IL-1β rilonacept [70]. IL-1 blocking agents are used to treat various rheumatic diseases such as Rheumatoid Arthritis (RA) and autoinflammatory disorders such as Familial Mediterranean Fever (FMF), gout, adult-onset Still's disease, and systemic-onset juvenile idiopathic arthritis [71-73]. Metabolic diseases such as T2DM and atherosclerosis are also potential targets [15,56].

IL-1 blocking agents have also been tested in patients with T2DM. A randomized clinical trial showed that anakinra treatment significantly lowered glycemia, HbA1c, and beta-cell dysfunction in T2DM patients. Anakinra treatment also increased circulating IL-1Ra and insulin secretion capacity of the pancreas but did not affect insulin sensitivity [56]. Smaller studies also reported improvements in HbA1c levels after treatment with monoclonal antibodies against IL-1β [74,75]. A meta-analysis of 2921 participants investigating eight studies composed of phases I to IV discovered that IL-1 antagonism had a substantial lowering effect on HbA1c. Furthermore, a meta-regression analysis revealed a strong relationship between baseline CRP and C-peptide levels, and HbA1c outcomes [76]. However, a large randomized clinical trial involving more than 4000 participants who had previous myocardial infarction found that canakinumab treatment for 3.7 years did not decrease the risk of developing diabetes [77].

Some studies also suggest that IL-1 inhibitor treatment may reduce the risk of macrovascular and microvascular complications of diabetes [78,79]. IL-1 receptor antagonist Anakinra and monoclonal antibody-mediated suppression of IL-1β with canakinumab had similar effects in other trials [16,80,81]. They both increased insulin secretion and lowered HbA1c levels, but anakinra did not show significant improvement in insulin sensitivity in nondiabetic patients with metabolic syndrome. Larsen et al. performed a follow-up study after the initial 13-week of anakinra treatment. The patient group demonstrated a better blood proinsulin/insulin ratio, lower CRP and IL-6 levels even thirty-nine weeks after stopping anakinra treatment, however there was no difference in HbA1c levels [16]. Moreover, Cavelti-Weder et al. studied the safety and efficacy of gevokizumab, a human monoclonal anti-IL1β antibody, on T2DM patients in a placebo-controlled setting [75]. After 3 months, gevokizumab significantly reduced HbA1c levels, which was also linked to an increase in C-peptide secretion, improved insulin sensitivity, and a decrease in CRP levels. However, Ridker et al. did not find any improvement in HbA1c, glucose, and insulin levels after canakinumab treatment in well-controlled T2DM patients with high cardiovascular risk [82].

Anakinra may have stronger effects because it blocks both IL-1α and IL-1β signaling. Inflammation is a continuous process. IL-1 inhibitors can reduce inflammation when they are given, but they may not be able to reverse it if there has been previous damage from inflammation. Therefore, starting treatment earlier would be more helpful to prevent pancreatic damage. Also, studies with RA patients who do not have diabetes could show whether IL-1 inhibitor therapy can prevent prediabetes and T2DM in specific patient risk groups, such as those who have RA and obesity or metabolic syndrome [83].

Anti-cytokine treatments may have some side effects. Therefore, the benefits and potential risks should be carefully balanced. Some of the most serious side effects are infections including the reactivation of latent hepatitis B and tuberculosis, rare demyelinating disorders of the central nervous system, and other severe adverse events related to their use [84]. These aspects need more research in future studies.

Colchicine: Its mechanisms of action and therapeutic uses

Colchicine, an alkaloid derived and purified from the ancient medicinal plant colchicum autumnale, has been employed for millennia to alleviate pain and mitigate tissue swelling. Historical references, such as the Ebers Papyrus from before 1550 BC, attest to its early usage [85]. The year 1820 marked its first purification by French chemists Jean Bienaime and Pierre Joseph Pelletier. Simultaneously, pathologist Biaggio Pernice unearthed its anti-mitotic properties. The formal naming and purification of colchicine occurred in 1833 under Geiger et al. Colchicine's structural classification as a bioactive component within the tricyclic alkaloid category was established in 2005. Subsequently, the US FDA granted approval in 2009 for its use in FMF and for the prevention and treatment of gout attacks [86].

Colchicine's application extends beyond these conditions to include Behcet's Disease (BD), Calcium Pyrophosphate Deposition Disease (CPPD), and pericarditis. Its broad anti-inflammatory effect suggests potential applications in diverse conditions. Emerging data, particularly in cardiovascular patients with atherosclerosis, indicate promising outcomes. There is also evidence that it improves glucose metabolism and lowers the risk of developing T2DM [19-22,87].

The mechanisms of colchicine's action can be categorized in two parts. At the cellular level, it mitigates inflammation by impeding smooth muscle cell proliferation, platelet activation, macrophage adhesion, and endothelial cell expression of E-selectin. On a molecular level, colchicine binds to tubulin, hindering the assembly and activation of the NLRP3 inflammasome, along with the release of cytokines [88,86] (Table 2).

Table 2: Anti-inflammatory effects of colchicine.

At the cellular level	At the molecular level
E-selectin expression from endothelial cells ↓	By binding to tubulin;
Smooth muscle cell proliferation ↓	- Microtubule growth ↓ (at low concentration)
Macrophage adhesion ↓	- Microtubule depolymerization ↓ (at high concentration)
Platelet activation ↓	Cytokine release ↓
Cancer cell migration ↓	(IL-1β. IL-18, TNF-α, IL-6, NF-κB, TGF- β)
Angiogenesis ↓	ROS ↓
ATP influx into mitochondria ↓	iNOs ↓
Caspases and cytochrome-c release ↓	β-TG ↓
Apoptotic cell death ↓	VEGF ↓
Ca^{++} influx into neutrophils ↓	NLRP3 inflammasome assembly ↓ and
	NLRP3 inflammasome activation ↓ → IL-1β, IL-18 ↓

Tubulin disruption and anti-mitotic effect of colchicine

Colchicine's most extensively studied therapeutic mechanism lies in its capacity to bind to tubulins, preventing the assembly and polymerization of microtubules. Microtubules, comprising α-tubulin and β-tubulin heterodimers, constitute vital components of the cytoskeleton. They play diverse roles, including maintaining cell shape, facilitating intracellular transport, regulating cytokine and chemokine secretion, modulating ion channels, supporting cell migration, and orchestrating cell division. By binding to tubulins, colchicine disrupts these microtubule functions, hindering leukocyte recruitment, impairing their functions, and inhibiting phagocytosis [89,90].

Simultaneously, colchicine functions as a classical anti-mitotic drug, specifically blocking mitotic cells in metaphase. It exerts its effects by arresting microtubule growth at low concentrations and promoting the depolymerization of microtubules at higher concentrations. Notably, higher concentrations of colchicine pose toxicity risks to normal tissues, restricting its utility as an anti-cancer treatment [89]. Beyond its impact on microtubules, colchicine exhibits inhibitory effects on cancer cell migration and metastatic potential. It interferes with cellular processes such as cell blebbing through the Rho/Rho-associated coiled-coil protein kinase/myosin light chain kinase pathway (Rho/ROCK/MLCK pathway). Additionally, colchicine hampers angiogenesis, limits Adenosine Triphosphate (ATP) influx into mitochondria, and curtails the release of caspases and cytochrome-c, showcasing its multifaceted influence on cancer cell behavior [90].

Inhibition of neutrophil mobilization, recruitment, and superoxide production

Colchicine exerts a comprehensive inhibitory effect on the immune response, targeting key processes involved in leukocyte function. It inhibits leucocyte chemotaxis, adhesion, and recruitment by disrupting the production of IL-18 and Myeloid Inhibitory C-type Lectin-like receptor (MICL). This disruption, in turn, impedes the chemotaxis of neutrophils and macrophages. Colchicine further inhibits neutrophil adhesion and recruitment via modifying microtubule dynamics and reducing the expression of L-selectin on neutrophils and E-selectin on endothelial cells [91-93].

Moreover, colchicine regulates immune response by blocking TNF receptors on macrophages and endothelial cells, reducing TNF-α production from monocytes and macrophages [94]. Notably, in vitro studies demonstrate that colchicine selectively suppresses Monosodium Urate (MSU)-induced superoxide production by neutrophils through the inhibition of microtubules [95]. Chia et al. discovered that colchicine, even at doses 100 times lower than generally required, efficiently prevents MSU-induced superoxide generation by murine peritoneal macrophages in vivo, supporting the possible use of non-toxic, low-dose colchicine therapy [96].

Furthermore, colchicine exhibits antioxidant properties by reducing oxidative stress. It achieves this by limiting the influx of Calcium (Ca^{2+}) into neutrophils, contributing to a broader suppression of inflammatory responses [97]. Colchicine has been found in animal studies to inhibit the release of tumor necrosis factor α (TNF-α) by liver macrophages, indicating its anti-inflammatory properties at the cellular level [94]. Additionally, experimental studies reveal that colchicine treatment significantly attenuates NF-κB and IL-1β expression, along with a decrease in the production of Reactive Oxygen Species (ROS) and inducible Nitric Oxide Synthase (iNOs) [98].

Effects of colchicine on platelet activation

Platelet activation is intricately regulated by dynamic depolymerization and repolymerization of microtubules. Colchicine slows down the course of platelet activation by affecting microtubular dynamics. Cimmino et al. found that colchicine reduces platelet aggregation by altering cytoskeleton rearrangement, which is performed by inhibiting cofilin and LIM domain kinase 1, two phosphorylated forms of myosin [99].

A crucial biomarker of platelet activation, β-Thromboglobulin (β-TG), is produced by platelets during their activation. In a study involving patients with FMF, it was found that colchicine effectively lowers the levels of β-TG, underscoring its impact on sensitive indicators of platelet activation [100]. Previous studies

have also demonstrated colchicine's ability to reduce platelet aggregation by modulating the production of collagen, epinephrine, and ADP in vitro, highlighting its multifaceted influence on platelet function [101,102].

Pennings et al. made noteworthy contributions by revealing that colchicine significantly inhibits platelet aggregation in vivo at pharmacologically relevant concentrations (20 nmol/L). This inhibition is achieved through its interaction with P2Y12 and collagen glycoprotein receptors. Notably, at higher concentrations (2 mmol/L), colchicine also impedes an additional platelet activation pathway involving GPII/IIa and P-selectin [103]. These findings provide valuable insights into the nuanced and concentration-dependent effects of colchicine on platelet activation pathways.

Inhibition of NF-κB

The classical NF-κB signaling pathway serves as a promoter of coagulation and inflammation. NF-κB activation is triggered by different insults such as pathogenic autoantibodies, infectious agents, genetic mutations, and pro-inflammatory cytokines. Upon activation, NF-κB stimulates the production of IL-6, IL-8, and TNF-α, which activate endothelial cells, neutrophils, and monocytes, causing endothelial cell damage [104]. TNF-α and IL-1β can impact plasminogen activators and inhibitors, contributing to microvascular thrombosis [105]. Additionally, NF-κB is implicated in various inflammatory diseases in humans, including rheumatoid arthritis, atherosclerosis, sepsis, and plays a pivotal role in the pathogenesis of diabetes-related vascular complications [106].

Colchicine's main mode of action is NF-κB inhibition. Mackenzie et al. found that colchicine had reduced nuclear NF-κB binding activity [107]. Jackman et al. reported that colchicine suppressed NF-κB activation in HeLa cells, which is consistent with observations in colchicine-treated Familial Mediterranean Fever (FMF) patients [108,109]. Cimmino et al. also discovered that colchicine therapy decreased the nuclear levels of NF-κB and Tissue Factor (TF) induced by oxLDL [110]. Through the regulation of various upstream factors, including ROS, colchicine not only inhibits NF-κB expression but also, consequently, controls the expression of inflammatory cytokines [86].

Inhibition of NLRP3 inflammasome activation and IL-1β release

The abnormal chronic activation of the NLRP3 inflammasome is implicated in the onset of various diseases, including the metabolic syndrome, T1DM, T2DM, gout, Alzheimer's disease, and atherosclerosis [111,112]. Martinon et al. initially demonstrated that colchicine could inhibit the activation of the NLRP3 inflammasome in cultured monocytes [113]. Subsequent investigations have consistently validated colchicine's efficacy in preventing NLRP3 inflammasome activation. Current studies elucidate three primary mechanisms underlying the inhibition of the NLRP3 inflammasome by colchicine. Firstly, colchicine effectively inhibits pore formation induced by P2X7 receptors [114,115]. The NLRP3 inflammasome is activated by ATP-activated P2X7 receptors, opening K+ channels and reducing intracellular K+ concentration. Inhibition of P2X7 receptors prevents K+ outflow, blocking the NLRP3 inflammasome from assembling and activating. Secondly, colchicine hinders microtubule synthesis and promotes microtubule degradation, effectively impeding the assembly of NLRP3 inflammasome complexes [116]. This, in turn, inhibits the cleavage process of pro-IL-1β and pro-IL-18 into IL-1β and IL-18, respectively. The final mechanism involves the inhibition of caspase-1. Studies using NLRP3-/- transgenic mice demonstrated that colchicine reduces inflammation by repressing caspase-1 expression [117]. Additionally, colchicine has been shown by Robertson et al. to reduce monocyte IL-1β levels in individuals with acute coronary syndrome by reducing pro-caspase-1 and caspase-1 proteins [118].

In vitro research indicates that colchicine must be administered at supratherapeutic doses clinically to suppress inflammasomes effectively. However, therapeutically used doses may still be adequate for inflammasome suppression due to the accumulation of colchicine in leukocytes, with intracellular neutrophil colchicine concentrations demonstrated to be much higher (up to 16 times) than peak plasma concentrations [22,90].

Anti-fibrotic effects

Chronic inflammatory reactions, stemming from recurrent infections, autoimmune responses, allergic reactions, chemical insults, radiation, and tissue damage, ultimately culminate in fibrosis. This condition is frequently observed in patients with advanced type 1 and type 2 diabetes, leading to organ dysfunction. Hyperglycemia and lipotoxic injury induce fibrosis by activating inflammatory pathways, neurohumoral processes, oxidative stress, Transforming Growth Factor-Beta (TGF-β) activation, and producing Advanced Glycation End products (AGE). Certain organs, such as the kidney, liver, and heart, are particularly susceptible to fibrotic remodeling during the course of diabetes [119].

Colchicine exhibits anti-fibrotic effects, as demonstrated in animal studies. In mouse macrophages, colchicine has been shown to reduce the formation of Reactive Oxygen Species (ROS) and the release of Nitric Oxide (NO) and IL-1β [98,90]. In an in vitro study, colchicine diminishes oxidative stress. Moreover, it inhibits TGF-β activation and Vascular Endothelial Growth Factor expression (VEGF) [120-122]. Colchicine is also observed to inhibit caspase-3 and promote B-cell lymphoma-2 (Bcl-2), preventing tubulointerstitial fibrosis [123]. Studies in rats with liver fibrosis indicate that colchicine has beneficial effects through the inactivation of hepatic stellate cells [124]. Entzian et al. reported that colchicine is a potent in vitro inhibitor of fibroblast functions, including collagen synthesis and fibroblast proliferation [125]. In a study using a sterile pericarditis model in rats, Wu et al. discovered that colchicine prevents the promotion of atrial fibrillation by reducing IL-1β-induced IL-6 release and atrial fibrosis [126].

Efficacy of colchicine in atherosclerosis

Atherosclerosis is believed to originate from endothelial damage and is closely associated with aseptic inflammation. According to the theory of endothelial injury, disturbances in hemodynamics or local vasculature affected by hypoxia can cause endothelial damage. Additionally, apolipoproteins carrying cholesterol may continuously accumulate beneath the endothelium [127]. These lipoproteins are primarily composed of oxidized Low-Density Lipoproteins (oxLDL) and Cholesterol Crystals (CCs) [128]. Through the pattern recognition receptor (PRR), oxLDL activates the NF-κB signaling pathway, leading to increased production of NLRP3, pro-caspase, and ASC, as well as pro-IL-1β and pro-IL-18. Additionally, through membrane receptors, oxLDL can be ingested by macrophages and transformed into CCs in the lysosome, triggering the inflammasome [129,130].

As an anti-inflammatory medicine, colchicine may be effective in Cardiovascular Disease (CVD) in several ways. Primarily, it inhibits NF-κB signaling and activation of NLRP3, thereby reducing proinflammatory cytokines. Additionally, it inhibits inflammation and endothelial cell dysfunction, as well as platelet activation, smooth muscle cell proliferation, and migration, adhesion, and chemotaxis of macrophages [86].

Large-scale trials involving colchicine for CVD began in 2013. Nidorf et al. conducted the low-dose colchicine trial (LoDoCo trial), revealing that low-dose colchicine (0.5 mg/day) effectively reduces the occurrence of cardiovascular events in patients with stable coronary disease [131]. In 2017, the CANTOS trial, using the IL-1β monoclonal antibody canakinumab, also demonstrated the efficacy of IL-1β inhibitor treatment in decreasing the risk of Myocardial Infarction (MI), indicating that anti-inflammatory therapy is an effective strategy in CVD. However, it did not reduce blood lipid levels [132]. Additionally, The COLCOT trial at the end of 2019 revealed that the use of low-dose colchicine (0.5 mg/day) for just 30 days initiated after Acute Myocardial Infarction (AMI) can reduce the risk of ischemic cardiovascular events [133]. The subsequent LoDoCo2 trial in 2020, involving 5522 patients with chronic coronary artery disease, demonstrated a significant reduction in spontaneous myocardial infarction, ischemia-driven coronary revascularization, and cardiovascular deaths in the colchicine group after a 2.4-year follow-up. Colchicine is found safe, with no statistically significant differences in serious adverse events compared to the placebo. However, non-cardiovascular deaths were more common in the colchicine group [134]. The COPS trial (the Australian COPS randomized clinical trial) did not show significant differences in the primary outcomes but was associated with higher mortality. Despite unsatisfactory results for the one-year primary endpoint, a 24-month follow-up of patients who were only on standard medical therapy after discontinuing colchicine at the end of 12 months, revealed a significant decrease in the all-cause mortality, Acute Coronary Syndrome (ACS), ischemia-related unplanned urgent revascularization, and non-cardioembolic ischemic stroke [135,136].

A meta-analysis by Samuel et al. of randomized controlled trials demonstrated that adding low-dose colchicine to standard medical therapy can lower the incidence of major cardiovascular events, with the exception of cardiovascular mortality [137]. Regarding mortality, Opstal et al. conducted a detailed analysis and concluded that colchicine usage in the LoDoCo2 trial had no negative impact on the total number of fatalities or specific causes of death. Cancer and infection related deaths were found to be equivalent for colchicine and placebo, emphasizing the role of comorbidities as a driver of all-cause mortality in patients included in $LoDoCo_2$ trial [138].

Finally, the most recent American Heart Association (AHA) guidelines on chronic coronary disease recommend low-dose (0.6 mg/day) colchicine as a secondary preventive agent to reduce Atherosclerotic Cardiovascular Disease (ASCVD) [139]. Colchicine, along with anti-platelet and statin therapy, may be the third pillar of secondary prevention in patients with chronic coronary disease. Colchicine appears to have even greater benefits when initiated within the first three days following myocardial infarction, indicating a realistic therapy strategy [140].

Colchicine: Dosing, safety and tolerability

Colchicine exhibits a dose-dependent response with a narrow therapeutic index. Most side effects tend to resolve upon dose reduction or discontinuation. When divided into two daily doses and gradually increased, it is well-tolerated. For acute gout attacks, the recommended initial dose is 1.0 mg or 1.2 mg, followed by a 0.5 mg or 0.6 mg dose after 1 hour. The maintenance dose is 0.5-0.6 mg, once or twice daily after the attack subsides. In Familial Mediterranean Fever (FMF) patients, it is well-tolerated up to 0.5 mg three times daily for the prevention of attacks and amyloidosis, in the absence of renal impairment [22,72,141].

Gastrointestinal intolerance, including diarrhea, nausea, vomiting, and abdominal pain or discomfort, is the most common adverse reaction, occurring in up to 20% of patients. Treatment dosages may lead to mild leukopenia. Depending on the administered dosages and the presence of renal dysfunction, aplastic anemia, granulocytopenia, pancytopenia, and thrombocytopenia may also occur. Myopathy and rhabdomyolysis are additional but rare side effects [22,142].

The hepatic P450 cytochrome CYP3A4 enzyme metabolizes colchicine, and the P-glycoprotein (P-gp; also known as multidrug resistance protein-1; MDR1) efflux pump in the liver and kidneys removes it. The MDR1 gene, encoding P-gp, and specific MDR1 polymorphisms have been associated with elevated P-gp expression and decreased serum colchicine concentrations [143,144]. Consequently, drugs strongly inhibiting CYP3A4 and the P-glycoprotein efflux pump, such as clarithromycin, fenofibrate, cyclosporine, and antifungals like itraconazole and ketoconazole, should be avoided, as they increase colchicine concentrations. Amiodarone, carvedilol, verapamil, and diltiazem may impede clearance, necessitating lower doses [145,142]. While statins are generally well-tolerated, combining colchicine with atorvastatin has been linked to rare cases of rhabdomyolysis [146]. Dose adjustments are recommended for patients with chronic kidney disease, liver disease, and in the elderly. Hemodialysis patients require dose reduction. Toxicity symptoms of colchicine typically resolve within a week to several months after discontinuation [142].

Data from patient studies indicate the safety of colchicine use during the peripartum period and breastfeeding [147,148]. However, there is controversy regarding its effects on sperm production and function despite the belief that paternal exposure is consistent [149,150].

Conclusion and prospects

Chronic, low-grade systemic inflammation plays a pivotal role in the pathophysiology of insulin resistance and diabetes progression. In this inflammatory milieu, the activation of NLRP3 inflammasomes and heightened synthesis, secretion, and signaling of IL-1β take precedence. The inhibition of these signaling pathways emerges as a promising treatment option. Positive outcomes have been observed in atherosclerosis, another chronic, low-grade inflammatory disease, where colchicine is now recommended alongside lipid-lowering and antiplatelet medications for preventing atherosclerotic cardiovascular diseases [139].

Studies targeting IL-1β and NLRP3 inflammasome signaling pathways in type 2 diabetics offer promising results in experimental settings. However, clinical studies of IL-1 inhibition have presented conflicting outcomes. For instance, anakinra, a recombinant human IL-1 receptor antagonist, demonstrated improvements in β-cell function and reduced HbA1c in type 2 diabetic adults but not in individuals with impaired glucose

tolerance [15,151]. Canakinumab, an IL-1β antibody, effectively suppressed hsCRP and IL-6 but did not significantly affect fasting plasma glucose levels, insulin resistance, or the risk of diabetes development in the CANTOS trial.

Conversely, studies involving colchicine in prediabetics and type 2 diabetics, though smaller in scale, provide promising results. Notably, a veteran study by Wang et al. documented a decreasing trend in diabetes development associated with increased duration of colchicine exposure [19]. Chu et al.'s nationwide cohort study recently indicated that colchicine treatment in gout patients is linked to a reduced risk of T2DM [20].

Colchicine demonstrated a significant reduction in inflammatory markers (CRP, ESR, and WBC) in Metabolic Syndrome (MetS) patients, with improvements in HOMA-IR, fasting insulin, and glucose effectiveness, suggesting enhanced metabolic function [21].

While targeting a single cytokine like IL-1 might fall short of achieving clinically significant improvements due to the involvement of multiple inflammatory pathways in the prediabetic state, colchicine's impact on various pro-inflammatory cell types, cytokines, and pathways active in obesity and diabetes positions it as a comprehensive intervention [152,142]. Colchicine's mechanisms, including preventing neutrophil diapedesis, inhibiting M1 macrophage differentiation, decreasing chemotactic and adhesion molecules, reducing NLRP3 inflammasome activation, and suppressing superoxide production, contribute to its metabolic benefits [153,154].

Colchicine could be employed preventively for prediabetics, complementing dietary and lifestyle changes at prophylactic doses used in chronic atherosclerosis patients over an extended period. A preventive strategy targeting the NLRP3 inflammasome at an early stage holds potential benefits, necessitating future large-scale prospective studies to validate colchicine's effect on diabetes risk reduction by monitoring inflammatory parameters and insulin sensitivity.

While treatment with IL-1 inhibitors alone appears less effective, studies of longer duration starting at an early stage might yield better results before significant β-cell loss occurs. Colchicine, a cost-effective and well-tolerated drug validated in large-scale studies for atherosclerotic cardiovascular diseases, requires further investigation to determine optimal doses and assess effectiveness in diverse patient groups for preventing diabetic complications.

In conclusion, the emerging role of colchicine as an anti-inflammatory agent in diabetes management is promising. If proven effective and safe in larger clinical trials, colchicine could serve as an innovative adjunct therapy to conventional approaches. Its ability to address underlying inflammation associated with diabetes may present a novel strategy for prevention, improving glycemic control, and reducing the risk of complications.

Declarations

Conflicts of interest: All authors declare no conflict of interest.

Funding statement: Not applicable.

Acknowledgments: Not applicable.

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