Curcumin – a polyphenol with molecular targets for diabetes control?

Kristina Blaslov

Department of Diabetology, Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, University of Zagreb, Zagreb, Croatia

Abstract

The aim of this narrative review is to analyze the potential role of curcumin in treatment of prediabetes, Types 1 and 2 diabetes and their complications. This literature provides evidence for the beneficial effect of curcumin in glucoregulation and diabetic microvascular complications. Although the mechanism of action remains unclear, the yellow flavonoid’s therapeutic efficacy may stem from the regulation of antioxidant defenses and inflammatory mediators with subsequent genetic regulation through modulation of various transcription factors. However, further studies are needed to confirm the potential of curcumin in diabetes management.

Key words: Complications; curcuma; curcumin; diabetes mellitus; insulin; prediabetes

Corresponding author:
Kristina Blaslov, Department of Diabetology, Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, University of Zagreb, Dug dol 4a, HR-10000 Zagreb, Croatia, Telephone: +385 1 23 53 923, Fax: +385 1 23 31 515, e-mail: kblaslov@gmail.com

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1. Introduction

Diabetes mellitus (DM) reflects a group of carbohydrate, protein, and fat metabolism disorders, characterized by hyperglycemia, which leads to long-term micro- and macrovascular complications. According to the International Diabetes Federation, it affects ∼415 million people worldwide [1]. Because of the increasing prevalence, and the incurable nature of the disease, a common treatment approach is disease control with lifelong use of anti-diabetic drugs. However, these regimens are not economically accessible and are often not well tolerated because of treatment-related toxicities. Therefore, the focus nowadays is to identify new effective therapeutic agents, with relatively low cost and toxicity, which can be used to control the progression of DM as well as its complications.

Curcumin is the principal curcuminoid found in turmeric (Curcuma longa Linn.), a popular spice in Asian cuisine whose beneficial effects on glycemic control have been used in ayurvedic [2] and traditional Chinese medicine for thousands of years. However, it only recently received scientific attention as a potential therapeutic agent for the treatment of DM and its complications [3]. Curcumin effectively reduces glycemia and hyperlipidemia but also has beneficial effects on diabetic complications due to its anti-inflammatory and antioxidant properties, in a relatively inexpensive and safe manner [4,5]. Accordingly, in the past two decades, numerous studies have examined the biological and pharmacological properties of curcumin and its interaction with multiple molecular targets that are involved in the pathogenesis of Types 1 and 2 DM.

2. The Effect of Curcumin on Glycemia in Types 1 and 2 Diabetes Models

Various experimental models of diabetes have been used to explore the effect of curcumin on glycemia. In alloxan-induced diabetic rats, streptozotocin- (STZ-) induced rats, and STZ-nicotinamide-induced rat models, all of which resemble Type 1 DM, oral administration of curcumin in various dosages [6-9] prevented weight loss, reduced glucose and glycated hemoglobin A1c (HbA1c) levels [5], and improved insulin sensitivity, and hypoinsulinemia [10]. Similarly, oral administration of curcumin improved glucose homeostasis and insulin resistance in rats with high-fat diet-induced Type 2 DM [11].

These findings are not surprising considering the effect of curcumin on pancreatic cells and insulin sensitivity, which have been extensively studied [12-19].

Curcumin might increase islet viability by inhibiting the production of reactive oxygen species (ROS). This may be mediated by the inhibition of poly ADP-ribose polymerase-1 activation and the normalization of proinflammatory cytokines ([tumor necrosis factor α (TNFα), interleukin 1β (IL-1β), and interferon-γ]) and their inducement of nuclear factor kappa B translocation by the prevention of inhibitor kappa B α phosphorylation, without affecting normal islet function, which results in increased pancreatic glucose transporter-4 (GLUT 2) levels and glucose clearance [12]. As a consequence of these two effects, pancreatic islet cell lymphocyte infiltration and destruction are decreased [13]. Finally, curcumin increases the opening and activation of anion channels and depolarizes the pancreatic β-cell membrane potential, which results in electronic activity and insulin release [14]. In addition, curcumin is involved in the aberrant misfolding of human islet amyloid polypeptide and formation of pancreatic amyloid deposits [15]. These stimulatory actions of curcumin on pancreatic β-cells could contribute to hypoglycemia in diabetes.

However, the insulin-sensitizing activity of curcumin has been its most established effect. Curcumin favorably affects hepatic glucose regulating enzymes by increasing glucokinase activity and inhibiting hepatic gluconeogenesis through suppression of glucose 6-phosphatase and phosphoenolpyruvate carboxykinase [16]. Another positive effect of curcumin in diabetes is the reduction of circulating free fatty acids (FFAs). FFA-induced lipotoxicity is an important contributor of insulin resistance. This mechanism has been suggested to deteriorate pancreatic β-cell function [17] and impair the insulin signaling pathway through activation of NF-kb. Downstream products of the NF-kb pathway, such IL-6, interfere with the transcription of insulin receptors (such as insulin receptor substrate-1) and transporters (such as GLUT-4),...
thus impairing insulin sensitivity [18]. Finally, curcumin can induce peroxisome proliferator-activated receptor-gamma activation [19]. The findings of these studies are presented in Figure 1.

3. The Role of Curcumin in Diabetic Complications: Neuropathy, Nephropathy, and Retinopathy

The hyperglycemia of diabetes results in various vascular complications such as neuropathy, nephropathy, and retinopathy, which represent major causes of diabetes-related morbidity and mortality. Oxidative stress, inflammation, and the associated pathophysiological pathways represent the key pathogenic events underlying the hyperglycemia-associated vascular complications [20]. These events activate various cellular pathways and result in inflammatory episodes that contribute to endothelial damage in the retina, peripheral neurons, and kidneys, leading to retinopathy, neuropathy, and nephropathy, respectively. Other proposed pathways involved in the pathogenesis of diabetic complications include activation of protein kinase c, formation of intracellular sorbitol and advanced glycation end products, and mitochondrial superoxide generation [21]. All of these pathways can contribute to the generation of nitrosative/oxidative stress, which can be negated using various natural antioxidants that have proved to be beneficial in experimental models of diabetic complications. Curcumin is a natural polyphenolic compound with potent antioxidant and anti-inflammatory activity and has been found to be useful in various diseases associated with oxidative stress and inflammation, including diabetic complications [22].

Diabetic neuropathy is the most common complication of DM, which develops as a consequence of hyperglycemia-induced peripheral nerve damage [23]. Hyperglycemia induces oxidative/nitrosative stress that leads to the activation of NF-kB transcription factor in peripheral neurons. The NF-kB-mediated proinflammatory cytokines such as IL-6, TNF-α, cyclooxygenase-2, and inducible nitric oxide synthase (iNOS) generation drives the neuroinflammatory-mediated nerve damage in peripheral neuropathy [24]. High reactive nitrogen species/ROS generation leads to the depletion of endogenous antioxidants. It has been observed that tetrahydrocurcumin, a major metabolite of curcumin, is able to inhibit the development of STZ-induced diabetic nephropathy and neuropathy by induction of antioxidant defenses [25]. Few experimental studies in rats using a combination of insulin and curcumin, and gliclazide plus curcumin have demonstrated the high efficacy of combination regimens in preventing the STZ-induced alterations in sensory and motor functions compared with insulin or gliclazide monotherapy [26]. Curcumin is also reported to exhibit an anti-TNF-α activity and nicotinamide adenine dinucleotide phosphate oxidase inhibitory effect through which it ameliorates the sensorimotor disturbances associated with diabetic neuropathy [27]. Since poor oral bioavailability represents a major rate-limiting factor in allowing curcumin to exert its therapeutic effect, various formulation strategies such as micronization, nanonization, amorphous solid dispersion, combination with piperine, complexation with hydroxypropyl-b cyclodextrin complex, and spray-dried curcumin-milk composite have been tried to improve the oral bioavailability of curcumin [28]. The self-nanoemulsifying drug delivery system formulation of curcumin had higher physiological concentrations of curcumin and more improvement in sensorimotor nerve disturbances associated with diabetic neuropathy than naïve curcumin. It also reduced neuroinflammation associated with neuropathy by reducing the expression of proinflammatory mediators such as IL-6, TNF-α, and iNOS through inhibition of NF-kB [29].

**Figure 1.** The effect of curcumin in pathophysiology of diabetes mellitus free fatty acids, nuclear factor kappa-light-chain-enhancer of activated B cells, nuclear transcription factor α, monocyte chemoattractant protein-1, interleukin 6, interleukin 1β
Diabetic nephropathy is a serious complication of diabetes and the most common cause of end-stage renal disease worldwide [30]. Pathophysiological changes such as mesangial cell expansion, the accumulation of extracellular collagen, fibronectin, and laminin, glomerular and tubular membrane thickening, tubulointerstitial fibrosis, glomerulosclerosis, and finally renal endothelial dysfunction occur in diabetic kidney disease [31]. Multiple mechanisms such as oxidative stress, lipid disorders, renal hemodynamic changes, increased non-enzymatic glycosylation of proteins, and the activation of the polyol and mitogen-activated protein kinase signaling pathways contribute to the development and outcome of diabetic nephropathy [31].

Curcumin was found to mitigate nephropathy through the induction of antioxidant defenses and reduction of ROS-mediated oxidative stress and the inflammatory cascade in kidneys regardless of the signaling pathway through which it acts. It was also found to increase kidney function and integrity by reducing proteinuria and inhibiting leaching of renal enzymes and acid phosphatases [32]. Moreover, a clinical study was also performed on patients with overt Type 2 DM associated nephropathy, in which oral turmeric supplementation was found to be beneficial through its effects on glomerular function and inflammation [33-35]. However, further large-scale studies are needed to confirm the clinical utility of curcumin in diabetic nephropathy treatment.

More than 150 million people worldwide are affected by diabetic retinopathy (DR), and according to the World Health Organization, the number of people suffering from DR will double by the year 2025 [36]. DR is characterized by retinal damage, and diabetes-induced hyperglycemia ultimately leads to DR through activation and amplification of various pathophysiological mechanisms. Mainly, oxidative stress and inflammation are implicated in the pathogenesis of DR [36]. This management includes laser photocoagulation, intravitreal steroids, and anti-vascular endothelial growth factor (anti-VEGF) treatment along with systemic blood sugar control [36]. Curcumin attenuates the condition by reducing oxidative stress-mediated damage to proteins, nucleic acids, and NF-kB-mediated inflammation [37]. An in vitro study conducted in human retinal endothelial cells showed that curcumin inhibits the high glucose-induced cell proliferation by reducing VEGF expression [38]. In addition, curcumin was also found to inhibit retinal endothelial cell migration by inhibiting stromal-derived factor (SDF)-1a activation and SDF-1a - mediated PI3K/AKT activation [37].

4. The “Curcumin Issue” in Clinical Trials

As stated previously, the main obstacle toward large-scale clinical trials is the low bioavailability of curcumin. Phase 0 studies reported extremely low concentrations of curcumin in the blood [39]. However, a few phase 3 clinical trials have demonstrated high efficacy of pure curcumin [40]. There are several potential explanations for this phenomenon. First of all, curcumin cannot be absorbed when taken orally in the fasting state, but when taken with a meal, it binds to dietary glucuronides, amino acids and phospholipids, which increases its water solubility, making it more easily absorbed. Indeed, studies have shown that despite low levels of curcumin in the blood, a substantial amount of curcumin glucuronide and curcumin sulfate compounds was found [5]. Moreover, studies in animal models showed that only 30% of ingested curcumin was found in feces, while the rest was absorbed into the bloodstream [41-44]. According to these findings, it is obvious that the bioavailability of curcumin depends on how it is being ingested. In addition to this, several patent-protected curcumin formulations have been developed to increase its bioavailability [45,46]. The majority of them consist of fatty acids, amino acids, and phospholipids because the combination of these dietary compounds with curcumin increases its absorption when taken in the fasting state. Although the theory of curcumin’s low bioavailability is unlikely, the fact that the absorption of curcumin depends on its relation to meals raises a lot of issues when it comes to large clinical trials. This is probably the main reason why such trials are currently missing.

5. Conclusions

Many studies provide evidence for the beneficial effect of curcumin in glucoregulation and diabetic microvascular complications. Although the mechanism of action remains unclear, the yellow flavonoid’s therapeutic efficacy
may stem from the regulation of antioxidant defenses and inflammatory mediators with subsequent genetic regulation through modulation of various transcription factors. However, further studies are needed to confirm the potential of curcumin in diabetes management.

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