Review

Discovery Medicine 2025; 37(202): 2497–2513
https://doi.org/10.24976/Discov.Med.202537202.210

Leukotrienes Implications in Diabetes and Diabetes Complications: A Narrative Review

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Submitted: 7 July 2025 Revised: 26 August 2025 Accepted: 12 September 2025 Published: 20 November 2025

Leukotrienes are a group of eicosanoids that are synthesised from arachidonic acid by 5-lipoxygenase (5-LOX) pathway and perform normal and pathological roles. Both leukotriene B4 (LTB4) and cysteinyl leukotrienes (LTC4, LTD4 and LTE4) have membrane receptors. Diabetes mellitus and its complications have complex pathogenic mechanisms, including increased leukotriene synthesis. The implications of leukotrienes and other eicosanoids in the pathogenesis of diabetes are multiple. They are only partially known and frequently completely ignored in medical practice. This review emphasizes the intricate interactions between leukotrienes and other factors in the pathogenesis of diabetes complications. In individuals with diabetes and its complications, the serum and urinary concentration of leukotrienes is significantly higher than in normal individuals. LTB4 and LTC4 inhibit insulin secretion. Leukotrienes are involved in the pathogenesis of diabetic inflammation and stimulate the synthesis of proinflammatory cytokines, in the production of atheromatosis, retinopathy, nephropathy, obesity and various other diabetes complications. Existing data strongly suggest the use of montelukast and other cys-LT1 receptor antagonists in combination with antidiabetic drugs for the treatment of diabetes and its complications. These drugs may prevent or postpone the development of complications of diabetes. This review highlights the involvement of leukotrienes in the pathogenesis of diabetes and its complications. Additionally, various viewpoints on the therapeutic application of leukotriene antagonists are discussed.

Keywords: leukotrienes; diabetes; nephropathy; lung fibrosis; dementia; atheromatosis; montelukast

Introduction

The involvement of leukotrienes in diabetes mellitus and its complications.

Diabetes mellitus is one of the most common and serious diseases in human pathology.

The total number of diabetic adults is estimated in 2021 at 536.6 million adults worldwide and there are opinions that it will increase to about 783 million in 2045 [1]. Diabetes is the cause of excess mortality. Diabetes mellitus is classified into two major groups: type I diabetes (T1DM), characterised by insufficient insulin secretion by pancreatic beta islets, and type II diabetes mellitus (T2DM) characterised by severe insulin resistance in muscle, adipose tissue, liver, and other tissues. In both types of DM, hyperglycaemia occurs, which causes numerous pathological changes. Over 90% of these cases are patients with T2DM [2]. There are several risk factors involved in the occurrence and evolution of diabetes mellitus [3]. The prevalence of T2DM is higher in people over 70 years of age than in other age groups. Diabetes and its complications significantly reduce life expectancy. Among these complications, we mention: nephropathy, retinopathy and cataract [4], depression [5], peripheral neuropathy, micro and macro-angiopathy, diabetes, cognitive decline (which evolves to dementia [6], sarcopenia [7], myocardial infarction, stroke and others. Diabetes also affects the intestines. At this level, diabetes mellitus modifies the intestinal microbiota. Microcirculation is also affected at the intestinal level. Modification of the intestinal microbiota is involved in the increase in intestinal permeability in diabetic patients.

Eicosanoids are a large group of endogenous lipid substances with 20 carbon atoms. This group includes prostaglandins, thromboxanes, prostacyclin, leukotrienes, lipoxins, resolvins and other biologically active lipids.

Arachidonic acid (AA) (C20:Δ4, n-6), an essential polyunsaturated fatty acid, is the main fatty acid from which LTs and other eicosanoids are synthesized. Arachidonic acid is present in all cell membranes in the human body. In the brain cell membrane, this acid represents 9% of the total fatty acids. However, there are also eicosanoids that are synthesized from eicosapentaenoic acid (EPA) ($C_{20:4}$, ω-6) and from linolenic acid.

There are important differences between the actions of eicosanoids derived from AA and the effects of eicosanoids that come from EPA and from linolenic acid (C18:Δ3, n-6) [8]. Phospholipase A2 (PLA2) is essential for the release of AA from phospholipids. AA is metabolised by three enzymatic pathways: the cyclooxygenase pathway (COX1

and COX2) which produces prostaglandins, prostacyclin and thromboxanes, the cytochrome 450 pathway, and the lipoxygenase pathway (5-lipoxygenase (5-LOX), 8-LOX, 12-LOX and 15-LOX). AA is also converted by reactive oxygen species (ROS) in a non-enzymatic way into isoprostanes.

Leukotrienes are eicosanoids that are derived from arachidonic acid via the 5-LOX pathway [9]. Leukotriene synthesis occurs inside the cell but outside the nucleus. 5-LOX is a cytoplasmic enzyme. AA released from cell membranes is converted by 5-LOX, an enzyme activated by 5-LOX activating protein (FLAP) to leukotriene A4 (LTA4). FLAP does not have enzymatic activity but it increases the capacity of 5-LOX to interact with its substrate. A part of LTA4 under the action of LTA4 hydrolase (LTAH) is converted to leukotriene B4 (LTB4). The remaining LTA4 molecules under the action of leukotriene C4 synthase (LTC4S) are conjugated with glutathione and transformed into cysteinyl leukotrienes (LTC4, LTD4, LTE4) (cys-LTs). Polyunsaturated fatty acids, precursors of leukotrienes and other eicosanoids, are found in variable amounts in all cell membranes in the body, but the enzymatic equipment involved in the synthesis of eicosanoids differs from tissue to tissue. In some situations, the synthesis of eicosanoids including leukotrienes requires cell-cell interactions in which intermediates in the synthesis of leukotrienes produced by a cell are taken up by other cells that do not have the ability to synthesize those intermediates but have the enzymes necessary to complete the synthesis of leukotrienes. This transcellular synthesis of eicosanoids which has proven important in various normal and pathological processes in the body [10,11].

Leukotrienes act on specific membrane receptors. There are separate receptors for LTB4 (receptors BLT1 and BLT2) and for cys-LTs (cys-LT1 and cys-LT2 receptors). Both receptors for LTB4 and those for cys-LTs are G-protein coupled membrane receptors. Their distribution in the body is different. The highest densities of cys-LT1 receptors are found in the spleen, peripheral blood leukocytes, interstitial lung macrophages and airway smooth muscle, while cys-LT2 receptors are most strongly expressed in leukocytes, heart, some smooth muscles, macrophages and the adrenal medulla [12]. The synthesis of leukotrienes and other eicosanoids from AA is shown in Fig. 1.

Leukotrienes are involved in the pathogenesis of important human diseases. Among these implications, the best known are: bronchial asthma, asthmatic bronchitis, pulmonary fibrosis, allergic rhinitis and other forms of allergy, irritable bowel syndrome. The purpose of this article is to highlight the important implications of leukotrienes in the pathogenesis of diabetes and its complications.

Diabetes Pathogeny

Several groups of eicosanoids are synthesised in the pancreas and other eicosanoids synthesized by different types of leukocytes also act on the pancreatic islets. Eicosanoids are important for insulin secretion at the pancreatic level. Here, both eicosanoids are synthesized via the cyclooxygenase pathway (COX1 and COX2) and via the lipoxygenases pathway (12-LOX and 15-LOX). Regarding 5-LOX, which is majorly involved in the synthesis of leukotrienes, there are contradictory data regarding its expression at the level of pancreatic islets. Leukotrienes that act at the pancreatic level may originate from leukocytes and blood plasma. Receptors for cys-LTs are found on the membrane of cells in pancreatic islets [13]. Prostaglandins E, in addition to their role in the pathogenesis of inflammation, are also important for the secretory activity of pancreatic beta islets. There are data that showed a regulatory role of leukotrienes and of cys-LT1 receptor regarding pancreatic insulin secretion [14].

In the pathogenesis of T1DM, the involvement of immunological factors and destruction of insulin-producing beta cells is very important. Hyperglycemia promotes inflammation in diabetic patients through several mechanisms such as: activation of the synthesis of proinflammatory cytokines, increased oxidative stress, increased synthesis of advanced glycation end products (AGE) and activation of their receptors (RAGE), but also by stimulating the synthesis of proinflammatory eicosanoids, especially leukotrienes and prostaglandin E. In patients with T1DM, serum LTB4 concentrations were significantly higher compared to those of the control group (7.9 $\pm$ –0.1 pg/100 microl versus non-diabetic subjects of the same age 12.1 $\pm$ –0.2 pg/100 microl). It was found that there is a positive correlation between the level of glycosylated hemoglobin and LTB4 concentrations in these patients [15]. In patients with T1DM, urinary excretion of LTE4 is significantly increased compared to normal individuals (42.1 pg/mg creatinine, compared to healthy subjects (25.5 pg/mg creatinine) [16].

The mechanisms by which LTs are involved in the pathogenesis of diabetes are multiple. Cys-LTs are involved in the aggressive action on pancreatic beta islets. Montelukast (a selective blocker of cys-LT1 receptors) administration has reduced the need for insulin in patients with latent autoimmune diabetes in adults [17]. In all pathological processes involved in the pathogenesis of diabetes and its complications, leukotrienes act together with many other factors, including other biologically active lipids from the eicosanoid group. Increased oxidative stress and chronic inflammation are two essential mechanisms involved in the pathogenesis of diabetes and its complications.

Regarding the inflammatory process, it is very important not only the existence of an increased synthesis of proinflammatory leukotrienes, but also the ratio between the

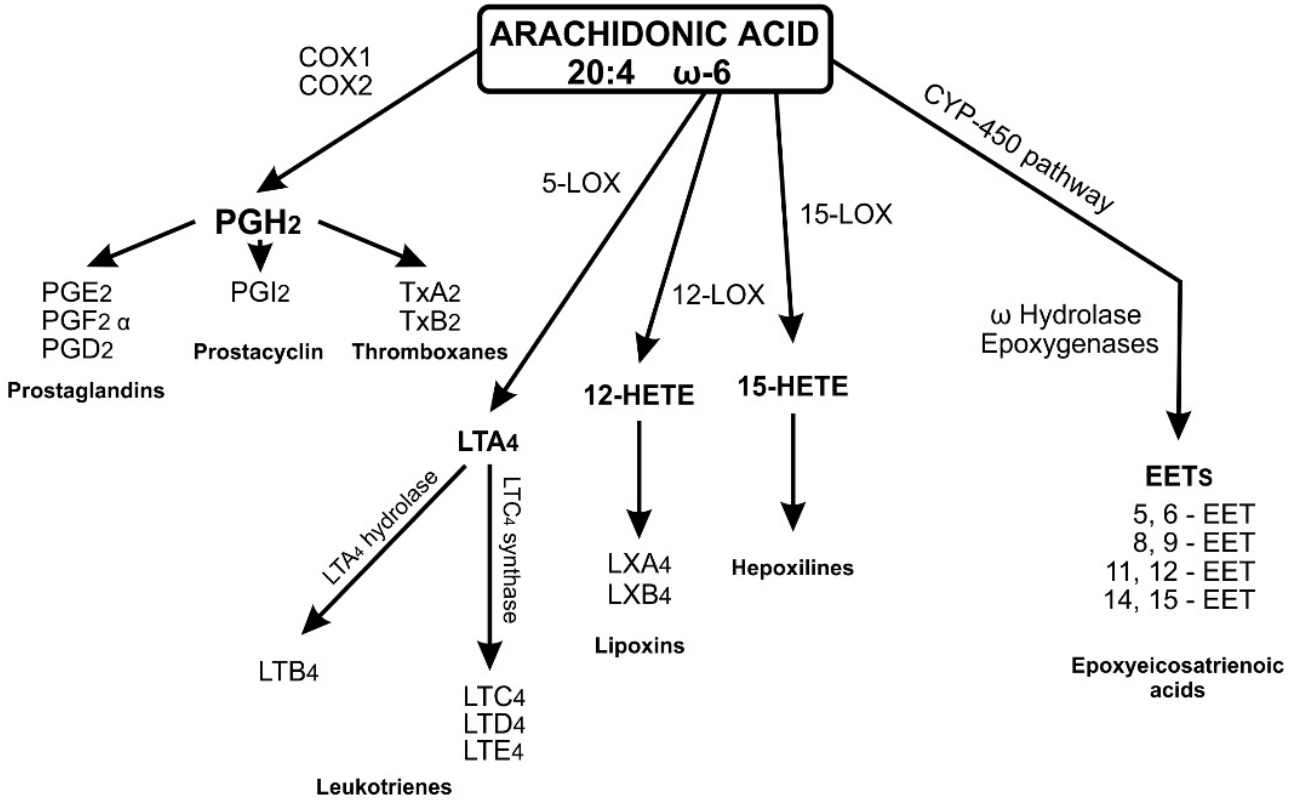

Fig. 1. The synthesis of leukotrienes and other eicosanoids from Arachidonic acid (AA). COX, cyclooxygenase; PGH_2, Prostaglandin H_2; PGE_2, Prostaglandin E_2; PGI_2, Prostacyclin I_2; T_XA_2, Thromboxane A_2; T_XB_2, Thromboxane B_2; LOX, lipoxygenase; LTA_4, leukotriene A4; LTB_4, leukotriene B4; LTC_4, leukotriene C4; LXA_4, lipoxins A4; LXB_4, lipoxins B4; EET, Epoxyeicosatrienoic acid.

quantity of leukotrienes and eicosanoids derived also from arachidonic acid, but which have an anti-inflammatory action such as lipoxins (LXA4 and LXB4). The ratio between leukotrienes and resolvins is also important [18]. LTB4 is the main factor that determines the migration of macrophages. In this case, LTB4 acts by stimulating BLT2 receptors [19]. Resolvins are eicosanoids derived from EPA and docosahexaenoic acids (DHA). Resolvins E1, E2, E3and E4 (RvE1 RvE2 RvE3 and RvE4) are synthesized from EPA and resolvins D1-6 (RvD1-RvD6) come from DHA. Oxidative stress produces an increase in the synthesis of proinflammatory cytokines, advanced glycation end-products (AGEs), increases the oxidation of low-density lipoprotein and causes mitochondrial dysfunctions [20]. Oxidative stress increases the activity of protein kinase C (PKC) and increases diacylglycerol (DAG) levels. This increase in PKC activity is involved in the production of some of the complications of diabetes, such as diabetic retinopathy, nephropathy and cardio- vascular complications [21]. An essential element in the protection of beta cells from oxidative stress is nuclear factor erythroid-2-related factor 2 (Nrf2).

LTC4 produces nuclear translocation of NADPH oxidase 4 (NOX4) and in this way causes an increase in the accumulation of ROS at the nuclear level. DNA damage and even cell death occur. The cys-LT1 antagonists pranlukast and montelukast significantly reduced the accumulation of ROS [22]. There are interactions between leukotrienes and free fatty acids in the production of cellular dysfunctions generated by oxidative stress. There are interactions between leukotrienes and free fatty acids in the production of cellular dysfunctions generated by oxidative stress.

Inhibition of 5-LOX reduces the lipotoxic effects of palmitic acid in cells under the action of oxidative stress [23]. Substances with antioxidant action such as selenium downregulated of leukotriene pathway in diabetes [24].

Diabetic inflammation is closely associated with increased oxidative stress. The mechanisms of inflammation in diabetes are multiple and complex, and the involvement of leukotrienes is one of them. Hyperglycemia increases the formation of AGEs that induce increased release of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) [25].

Increased ROS formation increases the activity of nuclear factor kappa-B (NF-κB). This is an essential element in the development of inflammation in diabetes mellitus. NF-κB transcription factor is present in all cells of the human body and plays a key role in the pathogenesis of in-

flammation. This factor is a transcription factor with major implications in the pathogenesis of diabetes.

Following phosphorylation NF-κB dimers are translocated to the nucleus, being involved in the synthesis of cytokines, adhesion molecules and other important factors in the pathogenesis of diabetic complications. ROS, AGEs and hyperglycemia stimulate this translocation of NF-κB into the nucleus [26,27].

NF-κB stimulates the synthesis of proinflammatory cytokines, activates macrophages and increases the accumulation of leukocytes with proinflammatory action in various different organs [28]. NF-κB transcription factor is present in all cells of the human body and plays a key role in the pathogenesis of inflammation.

Free fatty acids are also important in the development of inflammation. These non-esterified acids increase the level of malondialdehyde (MDA) and reduce the concentration of reduced glutathione (GSH) [29]. Free fatty acids (FFA) increase lipid accumulation in some cells and downregulated the expression of proliferator-activated receptor alpha (PPARα) [30]. In addition to their role in increasing oxidative stress, FFA inhibit glucose-stimulated insulin secretion [31]. IL-1β-induced elevation of the level of cys-LT1 receptor in diabetic inflammation increases the expression of cys-LT1 receptor and enhances the possibilities of cys-LTs to influence cellular activity [32].

The implications of leukotrienes in diabetic inflammation are multiple. LTB4 has a strong chemoattractant effect for leukocytes and promotes the adhesion of monocytes to the vascular wall [33]. LTB4 reduces the uptake of FFA by adipocytes leaving a greater amount of these acids circulating with the possibility of being involved in the inflammatory process in diabetes in different organs [34]. Activation of the NF-κB factor significantly increases the expression of 5-LOX and with a marked increase in leukotriene levels [35]. On the other hand, montelukast blocking cys-LT1 receptors suppressed NF-κB signaling *in vitro* [36]. Another important translational factor, the nuclear factor-erythroid 2-related factor 2 (Nrf2) has anti-inflammatory action [37]. Nrf2 regulates antioxidative enzymes expression and activity [38]. Cys-LTs reduce Nrf2 activity. This is another mechanism of the pro-inflammatory action of LTs. Blocking cys-LT1 receptors with montelukast activates the Nrf2 signaling pathway and reduces the inflammatory process [39]. The action of leukotrienes at the peroxisome proliferator-activated receptors (PPARs) level is important in diabetes pathogenesis. PPARs activation increases tissue sensitivity to insulin [40] and induces the suppression of cytokine-induced insulin resistance in adipocytes and other cells [41]. PPARs alpha stimulation also decreases neutrophil infiltration in various organs, having an anti-inflammatory action through this mechanism. These receptors activation also reduces the production of LTC4 in leukocytes and implicitly reduces diabetes inflammation [42].

In addition to its direct proinflammatory action, LTB4 which is synthesized in excess, in experimentally diabetic animals, shifts macrophages towards the proinflammatory (M1) phenotype [43]. The migration of macrophages and other leukocytes is a major element in the pathogenesis of inflammation. The complications of diabetes have an important inflammatory component. In these situations, an important role is played by the ratio between the main proinflammatory eicosanoids (leukotrienes and prostaglandins) derived from AA and pro-resolving lipid mediators lipoxins and maresins (derived from DHA by the way of 12-LOX) [44]. Along with leukotrienes, these eicosanoids are involved in the regulation of pancreatic insulin secretion. LTB4, and LTC4 inhibit insulin secretion and release [45]. On the other hand, 12-HPETE and lipoxins stimulates insulin secretion [46]. Hyperglycemia increases COX-2 expression in pancreatic islets. Prostaglandin E_2 (PGE_2) reduces glucose-stimulated insulin secretion, being implicated along with leukotrienes in the pathogenesis of diabetes. Resolvins, especially RvE1, act on LTB1 receptors and decrease the effects of LTB4 [47].

The factors that determine insulin resistance in type II diabetes are multiple. One of these factors is inflammation. LTB4 is involved in both the production of diabetic inflammation and the production of insulin resistance. Experimental studies show that blocking BLT1 receptors reduces insulin resistance in animals with diabetes. Unlike leukotrienes, AA, from which these eicosanoids are synthesized, has a protective effect in experimental diabetes. Arachidonic acid stimulates insulin secretion, unlike some of its metabolites such as LTC4 and PGE2, which inhibit this secretion [48]. Inhibition of PLA2 (which releases AA from membrane phospholipids) inhibited glucose-stimulated insulin secretion, while inhibition of cyclooxygenases (COX-1 and COX-2) involved in prostaglandin synthesis or of 5-LOX which determines the synthesis of leukotrienes increases insulin secretion [49].

The protective and anti-inflammatory effect of arachidonic acid is associated with the anti-inflammatory effect of lipoxin A4 synthesized via the 12-LOX pathway from the same acid [50].

Diabetes Complications

Cardiovascular Complications

Atheromatosis

The development of atherosclerosis occurs earlier and more rapidly in diabetes. In the cardiovascular system, both cys-LT1 and cys-LT2 receptors as well as LTB4 receptors are found. However, their distribution is different. The arterial endothelium has receptors for leukotrienes but cannot synthesise these eicosanoids on its own because it does not have the enzymatic equipment necessary for the synthesis of LTA4 but possesses the enzymes necessary for the transformation of LTA4 into LTB4 and cys-LTs. At the

level of the vascular endothelium, a transcellular synthesis of leukotrienes occurs, LTA4 coming from the leukocytes that synthesize this leukotriene and that adhere to the vascular endothelium. The adhesion of polymorphonuclear cells to the vascular endothelium and the transcellular synthesis of leukotrienes were reduced after the administration of arginine, which is partially transformed into nitric oxide. Both cys-LTs and LTB4 are involved in the pathogenesis of atheromatosis. Stimulation of cys-LT1 receptors causes an increase in intracellular calcium concentration, stimulates cell proliferation and the release of proinflammatory cytokines. They are found in large numbers at the level of smooth vascular muscle [51]. At the heart level, cys-LT2 receptors are found.

Inflammation and its resolution play a major role in the occurrence and development of atherosclerosis. An important part of the leukotrienes that interact with the vascular endothelium and are involved in the development of atheromatosis come from monocytes and macrophages M1 that interact with the arterial wall through adhesion molecules. In atheromatous lesions in human carotid arteries, cys-LT1 receptor expression is three times higher than cys-LT2 expression.

One of the ways which leukotrienes are involved in the pathogenesis of atherosclerosis in diabetic patients is that macrophages of the highly pro-inflammatory M1-type (ATM1) synthesize an increased amount of inflammatory mediators such as IL-6, IL-1beta, nitric oxide and LTB4. The increased synthesis of LTB4 determines the increase in the activity of the NF-kappaB factor through the stimulation of BLT1 and BLT2 receptors. This factor has a pro-inflammatory action in the arterial wall and is involved in the pathogenesis of atheromatosis. LTB4 stimulates the adhesion of monocytes to vascular endothelium. Cys-LTs are potent inflammatory lipid mediators. They are involved in the inflammation of the vascular endothelium and promote the development of atherosclerosis. 5-LOX has been identified in atherosclerotic lesions. LTs also induce intimal hyperplasia [52]. Administration of montelukast (10 and 20 mg/kg, orally) for 8 weeks in rats with experimental diabetes caused a reduction in aortic wall thickness [53]. Of course, experimental data must be translated with caution into clinical practice, but the existing results indicate the possibility of leukotriene antagonists to reduce the development of atheromatosis in diabetic patients [54].

Data is showing that there is a leukotriene-dependent degradation of the extracellular matrix which is involved in the destabilization of atheromatous plaques and in the production of thrombotic accidents [55]. Leukotrienes stimulate vascular intimal hyperplasia and leukocyte adhesion to the endothelium, both processes being involved in the development of atheromatosis in diabetic patients.

Atheromatosis is a cause of many aortic aneurysms. A knockout study in mice has shown that in BLT1-deficient mice the formation of abdominal aortic aneurysms is significantly reduced, and those that do form are smaller in diameter. Of course, translating the results of experimental studies into human clinical practice is not easy, but there is a possibility that by selectively blocking BLT1 receptors or by inhibiting 5-LOX, the incidence of aortic aneurysms due to atheromatous causes could be reduced. Both BLT1 and BLT2 receptors are involved in the pathogenesis of atherosclerosis. Excess leukotrienes are involved in the rupture of atherosclerotic plaques. In experimental studies in mice, the administration of BIIL284 (0.3–3 mg/kg/day), a non-selective antagonist of both BLT1 and BLT2 receptors, significantly reduced atherosclerotic lesion size after 12 weeks [56]. LTB4 enhanced the synthesis and release of matrix metalloproteinases (MMPs), which are involved in the rupture of diabetic plaques. This BLT receptor antagonist reduced the extracellular matrix metalloproteinases (MMP)-2 and MMP-9 activities in stented carotid arteries in rabbits and also significantly reduced in-stent intimal hyperplasia in carotid arteries [57]. 5-LOX inhibitors reduce the development of atherosclerosis in apolipoprotein E/LDL receptor-double knockout mice. In the case of atherosclerotic lesions, macrophage infiltrates occur in the atherosclerotic intima. 5-LOX activity and leukotriene synthesis are increased in these macrophages.

Acute Coronary Syndrome

Inflammation plays a major role in the pathogenesis of acute coronary syndromes [58]. Cys-LTs are involved in the pathogenesis of this syndrome in multiple ways. In addition to their pro-inflammatory action and their promotion of the development of atheromatosis, these biologically active lipids stimulate the activity of plasma coagulation factors and activate platelets. Thrombogenesis is thus increased [59]. Montelukast (a cys-LT1 antagonist) is useful in reducing the risk of acute coronary syndrome by reducing the activation of platelets and clotting factors [60]. In macrophages of diabetic patients with acute ischemic stroke, the ratio between LTB4 and pro-resolving mediators is increased in favor of LTB4. The activity of 5-LOX (which mediates the synthesis of leukotrienes) is increased and the activity of 15-LOX (involved in the synthesis of some pro-resolving eicosanoids) is decreased [61]. In acute ischemic stroke of diabetic patients, leukotrienes stimulate ox-LDL-induced inflammation in macrophages while the resolvin RvD2 (derived from EPA) reduces the inflammatory process. A clinical study has shown that serum LTB4 concentration is significantly higher in patients with ischemic stroke than in normal subjects of the same age (70.06 ± 14.75 ng/L vs 57.34 ± 10.93 ng/L) [62].

The ratio between the concentrations of different groups of eicosanoids is important for the pathogenesis and severity of this disease. In the case of acute coronary syndrome, which is frequent in diabetic patients, it has been found that the ratio between RvD1 and LTB4 is low because the concentration of LTB4 increases and the synthesis

of RvD1 decreases compared to normal subjects [63]. Experimental data show that the coronary constrictor response to leukotriene D4 in diabetic animals is significantly greater than in the control group [64].

Cys-LTs are also involved in the production of arterial contraction by some vasopressor factors such as angiotensin II. In the case of aortic spirals from streptozotocin-induced diabetic rats, it was found that incubation in the organ bath with a 5-LOX inhibitor reduced by 37.6 ± –8.2% the contraction caused by angiotensin II. In diabetic rats, urinary excretion of LTE4 was significantly increased compared to normal animals (LTE4 13.7 ± –2.9 ng/24 h in diabetic rats versus 1.5 ± –0.5 ng/24 h in normal rats) [65]. Stimulation of cys-LT1 receptors in arterial smooth muscle causes increased arterial tone and is implicated in the frequent arterial hypertension observed in patients with T2DM [66]. Blockade of these receptors significantly reduces arterial myogenic tone. Here, too, the ratio between the different groups of eicosanoids synthesized or transported to the arterial wall by the blood (especially by leukocytes) is important.

RvD1 RvE1, prostacyclin and lipoxin A4 have actions opposite to cys-LTs and relax the arterial muscle. 12(S)-HETE is a substance that is produced from arachidonic acid by the action of 12-LOX, has a vasoconstrictor action and is also involved in the production of vasoconstriction caused by angiotensin II. This lipid is synthesized in increased quantities in macrophages and acts by stimulating BLT2 receptors [67]. Blockage of these receptors reduces the vasospastic action of angiotensin II and could be useful for reducing ischemic heart attacks in diabetic patients.

Some authors have also shown that human atherosclerotic coronary arteries are contracted by LTC4 and LTD4 [68]. In experimental myocardial infarction induced by coronary artery ligation, pretreatment with the leukotriene synthesis inhibitor BAY X1005 significantly reduced mortality and had a cardioprotective effect. A BLT1 receptor antagonist (LSN2792613) also reduced experimental myocardial ischaemia after surgical coronary artery ligation [69]. In the case of myocardial hypoxia, LTC4 synthesis and cys-LT1 receptor expression increase significantly. This increase has been observed in experimental hypoxia as well as in patients with chronic coronary artery disease [70]. Not only in acute cardiac ischemia but also in diabetic patients with chronic cardiac ischemia, LTB4 levels are significantly increased compared to controls [71].

Diabetes Ventricular Arrhythmias

Malignant ventricular arrhythmias are an important cause of sudden death in diabetic patients. The risk of sudden death from ventricular arrhythmias is about 50% higher in diabetic patients than in people without diabetes [72,73]. In DM, there is an increase in the synthesis of LTB4 but also an increase in the concentration of this leukotriene in the heart.

LTB4 synthesis inhibitors have reduced the risk of malignant cardiac arrhythmias and sudden death in diabetic patients. In knockout animals lacking LTB1 receptors, the risk of ischemia/reperfusion-induced arrhythmias was reduced when LTB4 synthesis inhibitors were administered. Zileuton (an inhibitor of 5-lipoxygenase) 3 mg/kg reduced the incidence and duration of ischemia/reperfusion-induced arrhythmias in rats [74]. Sodium glucose cotransporter 2 inhibitors (SGLT2i) have reduced not only blood glucose but also LTB4 expression. These compounds in experimental studies have also significantly decreased the incidence of malignant ventricular arrhythmias [75].

A complication of diabetes is also cardiac autonomic neuropathy. Due to this neuropathy, vagal activity at the cardiac level is reduced and the action of vagal stimulation to reduce the synthesis of pro-inflammatory mediators is inhibited [76]. Vagal dysfunctions may also be involved in the production of cardiac arrhythmias. In the case of diabetic patients with this neuropathy, the serum concentration of LTB4 is significantly increased compared to patients who do not have this complication. Cys-LTs are also implicated in other cardiac dysfunctions frequently seen in diabetes. They have a negative inotropic effect and decrease myocardial contractility.

Metabolic Complications

Obesity

Obesity and hepatic steatosis are frequently found in patients with type II diabetes. This disease is a factor that contributes to insulin resistance in patients with type II diabetes [58]. Hepatic infiltration with macrophages that produce these pro-inflammatory factors also plays a role in increasing the hepatocyte resistance to insulin. Human adipocytes, as well as those from other mammalian species, produce significant amounts of leukotrienes. An experimental study is showing that they are involved in insulin resistance in obese mice [59]. LTB4 concentration is increased in obese subjects and in type II diabetes compared to normal individuals. An experimental study has shown that LTB4 and the BLT1 and BLT2 receptors are essential for the development of insulin resistance in hepatocytes of obese mice [77]. Inhibition of LTB4 synthesis reduced insulin resistance in obese mice. LTB4 also stimulates the synthesis of proinflammatory cytokines. LTs are also implicated in both the insulin resistance of these cells and the inflammation associated with obesity and diabetes in human clinics [78]. A double-blind, randomized, placebo-controlled trial showed that blocking LT1 receptors with montelukast 10 mg/day for 12 weeks in obese patients with type II diabetes significantly reduced HbA1c levels, proinflammatory cytokine concentrations, adiponectin, body weight, body mass index and also caused a decrease in LTB4 concentrations compared to the placebo group [79]. In the lipid depots of obese patients, 5-LOX is overexpressed. The increased quantity of leukotrienes

stimulates not only the synthesis of proinflammatory cytokines but also of TNF-α, monocyte chemotactic protein-1 and nuclear factor-κB. Abdominal obesity is particularly associated with an increase in the synthesis of leukotrienes and a significantly higher urinary elimination of LTE4. In obese women with T2DM, the synthesis of leukotrienes in subcutaneous adipose tissue is significantly increased compared to normal people. In these women, both the amount of AA and the activity of 5-LOX in the adipose tissue are increased. Experimental data have shown that in obese high-fat diet (HFD)-fed mice, the synthesis and concentration of LTB4 is much higher than in non-obese animals. This is a mechanism by which obesity contributes to the production of inflammation and insulin resistance in diabetes [80]. 5-LOX inhibition with zileuton in mice that received a high-fat diet-fed, decreased insulin resistance, decreased infiltration of proinflammatory M1 macrophages, and reduced adipose tissue inflammation [81].

Liver Metabolism

The liver has complex implications in metabolism and suffers from several pathological changes in diabetic patients. At least three complications of diabetes at the hepatic level are known: steatohepatitis, sinusoidal fibrosis, and glycogenic hepatopathy. Diabetic microangiopathy has also been observed in the diabetic liver. Diabetic hyperglycemia increases oxidative stress and the synthesis of proinflammatory cytokines in the liver and produces mitochondrial dysfunction.

At the hepatic level, there is a transcellular biosynthesis of cys-LTs. Kupfer cells have 5-LOX and synthesize LTA4 but cannot convert this leukotriene into cys-LTs. Hepatocytes do not have 5-LOX and cannot synthesize LTA4 but can convert this leukotriene synthesized by Kupffer cells into cys-LTs. Leukotrienes synthesized in neutrophils and in other leukocytes also act at the hepatic level [82]. In addition to leukotrienes, prostaglandins, lipoxins and resolvins [83] are also synthesized in the liver and prostacyclin is produced in the vascular endothelium. An important fact is the relationship between splenic macrophages and Kupffer cells. Proinflammatory factors stimulate the synthesis of LTB4 in macrophages, and this leukotriene increases the synthesis of TNF-α, in Kupffer cells in the liver [84]. In the liver, there is also a capture of leukotrienes from the blood.

In streptozotocin diabetes rats, a significant increase in the concentration of LTB4, thromboxane B2 and 15-HETE in the liver was observed, as well as an increase in hepatic 5-LOX and 15-LOX activity [85]. Activation of lipoxygenases occurs rapidly, only three days after the induction of experimental diabetes. At the level of hepatocytes there are receptors for LTB4 and cys-LT1 receptors. LTB1 receptor antagonists increased insulin sensitivity in the liver and reduced proinflammatory immune cell infiltration.

An experimental study has shown LTB4 stimulates lipogenesis in hepatocytes [86]. The mechanism of this activation of lipogenesis involves the stimulation of the cAMP-protein kinase A (PKA). In experimental studies, genetic deletion of the LTB4 receptor BLT1 and also BLT1 receptor antagonists reduced insulin resistance in mice [87]. The implications of leukotrienes in the pathogenesis of diabetes complications are presented in Fig. 2.

Neurological and Psychiatric Complications

Diabetic Neuropathy

Diabetic neuropathy is common and occurs in approximately half of diabetic patients. In this neuropathy, both the sensorimotor nerves and the peripheral autonomic nervous system are affected. Hyperglycemia, oxidative stress, bioenergetic failure in the peripheral nerves, inflammation and other factors are involved in the pathogenesis of this important and frequent complication of diabetes.

The eicosanoid levels are involved in the occurrence and worsening of diabetic neuropathy [88]. The most important is the imbalance between vasodilating prostaglandins (PGE1, PEG2) and vasoconstrictor eicosanoids cys-LTs, TXB2 and others.

Montelukast reduced docetaxel-induced peripheral neuropathy in rats. This indicates the involvement of cys-LTs and cys-LT1 receptors in the pathogenesis of neuropathy. The mechanism of this neuropathy has many common elements with the pathogenesis of diabetic peripheral neuropathy. Increased oxidative stress, excessive synthesis of TNF-α and proinflammatory interleukins are elements of the pathogenesis of peripheral neuropathy. This drug reduced the synthesis of these factors involved in the production of neuropathy and limited histopathological lesions The concentration of MDA was decreased and SOD activity increased after administration of this leukotriene antagonist [89]. Leukotrienes, dysfunction of the endogenous opioid system and other factors are involved in the pathogenesis of neuropathic pain. In an experimental study in rats, montelukast reduced this pain and potentiated the analgesic effect of morphine [90].

Dementia and Cognitive Decline

Diabetic hyperglycemia is implicated in the occurrence of dementia and other neurodegenerative disorders through several mechanisms: increased synthesis of proinflammatory cytokines, increased oxidative stress, increased synthesis of amyloid-β peptide (Aβ), reduced response of central insulin receptors to their natural agonists, but also through changes in cerebral vessels. The risk of Alzheimer's disease is significantly increased in patients with diabetes [91]. In addition to the increased risk of developing dementia, diabetic patients frequently experience moderate cognitive dysfunctions but with a tendency to worsen, such as poorer performance on tasks requiring attention, psychomotor speed, executive functions, learning and memory.

In Alzheimer's disease, which is considered a complication of diabetes (and by some authors also due to insufficient insulin action in the brain), 5-LOX expression is also upregulated [92]. 5-LOX and leukotrienes also have a modulatory role in the formation of amyloid in the brains of these patients [93]. Blocking cys-LT1 receptors reduced the permeability of the blood-brain barrier in cases of brain injuries [94]. We believe that a hypothesis only, that montelukast may also reduce the passage of beta amyloid from the blood into the brain and thus could be useful in the therapy of Alzheimer's disease.

In addition to Alzheimer's disease, diabetes is relatively frequently associated with other dementias, Parkinson's disease and other neurodegenerative diseases. Some authors believe that selective 5-LOX inhibitors could be a useful medication in these complications of diabetes [95].

In the brain, there are both cys-LT1 receptors and cys-LT2 receptors. Cerebral cys-LT2 receptors located in most of the cortex and in astrocytes. In focal cerebral ischemia induced by middle cerebral artery occlusion in mice, it was found that both cys-LT1 and cys-LT2 receptors were upregulated in neurons in the ischemic cerebral region. In the case of cerebral ischemia that develops more slowly due to atherosclerotic processes, the same thing probably occurs. It is possible that the administration of cys-LT1 receptor antagonists can reduce the neurodegenerative processes that occur as consequence of cerebral ischemia. In an experimental study in mature male rats with renovascular hypertension, montelukast at doses of 5.0 and 10.0 mg/kg/day improved cognitive deficit, endothelial dysfunction, and oxidative stress [96]. These data show that this cys-LT1 receptor antagonist could also improve vascular dementia, which is also more common in diabetic patients than in people of the same age without diabetes. Rosiglitazone, an oral antidiabetic agent, increased cerebral lipoxin A4 synthesis, changed the ratio between LX4 and LTB4 and reduced middle cerebral artery occlusion-induced LTB4 synthesis [97].

Diabetic Complications in Various Other Organs

Retinopathy

In various ocular tissues in mice and other animals, both 5-LOX and FLAP are found, as well as cys-LT1 and cys-LT2 receptors as receptors for LTB4. The affinity of BLT1 for LTB4 is much higher than the affinity of BLT2 receptors. However, their distribution is uneven. 5-LOX and FLAP are expressed in all ocular structures. This fact is well-known in humans as well as in mammals and probably in other mammals. Leukotriene receptors are, however, differently distributed between different tissues. Cys-LT1 receptors are predominantly found in ocular epithelial cells, while cys-LT2 receptors are mainly located at the neuronal level [98]. At the retinal level, there are both cys-LT1 receptors and cys-LT2 receptors. There are no differences between sexes. In the case of diabetic retinopathy, degeneration of retinal capillaries occurs, retinal neovascularization, and an increase in the apoptotic death of retinal neurons. In diabetics, retinal leukocyte stasis occurs, and numerous vascular endothelial lesions appear [99]. As in the case of other complications of diabetes, inflammation plays an important role in retinopathy. The retinal pigment epithelium contains significant amounts of AA and DHA. Therefore, the synthesis of different types of eicosanoids (including leukotrienes) is possible.

LTs are implicated in diabetic retinopathy. These eicosanoids stimulate retinal angiogenesis, increase oxidative stress, and are implicated in retinal inflammation and macular edema. Increased retinal angiogenesis leads to retinal neovascularization, retinal hemorrhages, and vitreous hemorrhage [100]. In diabetes, the number of pericytes, cells that are in contact with endothelial cells and are important for the functioning of the blood–retinal barrier. Hyperglycemia and excess leukotrienes cause dysfunction of these cells and their accelerated death. Pericytes play an important role in vascular permeability at the retinal level, and not only. These cells do not express 5-LOX and cannot transform AA into LTA4, but they have the enzymatic equipment that makes it possible the synthesis of cys-LTs from LTA4. Polymorphonuclear cells that can synthesize LTA4 are the ones that supply this leukotriene to pericytes from which they synthesize LTC4, LTD4 and LTE4 (transcellular synthesis). Cys-LTs cause capillary pericytes contraction. Thus, increasing the pore size of endothelial intercellular junctions. By this mechanism, cys-LTs are involved in the production of retinal edema [101].

In the vitreous of diabetics, the concentration of 5-HPETE (the intermediate compound that results from the action of 5-LOX on arachidonic acid and which is then transformed into LTA4) but also of 5-HETE is significantly increased compared to normal individuals [102].

An important process that occurs at the retinal level in diabetes is the transcellular synthesis of leukotrienes. The retina of non-diabetic mammals does not produce leukotrienes due to the lack of 5-LOX. Under conditions of hyperglycemia, LTA4 is released from blood leukocytes at the retinal level, which allows the synthesis of cys-LTs. Cultured retinal glial cells also synthesize significantly increased amounts of LTB4 in diabetic patients. This is an argument for the major role played by transcellular synthesis of cys-LTs in the pathogenesis of this complication of diabetes [103]. Administration of montelukast to rats with streptozotocin diabetes prevented the appearance of diabetic retinopathy. This substance administration reduced diabetic macular edema, decreased retinal microvascular permeability and decreased leukocyte transmigration at the microvascular level. It is noteworthy that PGE2 derived from arachidonic acid but under the action of COX 1 and COX2 is in increased concentration in diabetic eyes and is involved in the pathogenesis of proliferative diabetic retinopathy. Not only retinopathy but also keratitis occur in diabetic patients (sometimes associated with retinopathy).

In experimental keratitis in rabbits, an increase in the concentration of LTD4 in the aqueous humor was found. In the production of diabetic retinopathy, the most important role is played by cys-LT1 receptors because their blockade with montelukast in experimental diabetes prevented the appearance of retinopathy. The ratio of different eicosanoids synthesized from arachidonic acid is crucial for the involvement of these biologically active lipids in the pathogenesis of retinopathy. LTX4 has an action opposite to that of LTB4 and some authors recommend the use of LTX4 as a drug in the treatment of retinopathy [104].

Nephropathy

Like retinopathy, diabetic nephropathy is a common and serious complication of diabetes. The most important changes that occur at the renal level in diabetes are: glomerular hypertrophy, matrix accumulation, renal hemodynamic disorders and mesangial cell proliferation. In the diabetic kidney, there is an increased migration of macrophages and T cells and an increased release of proinflammatory factors [105]. In rats with experimental diabetes and renal lesions, it was found that 5-LOX activity in leukocytes and LTB4 synthesis are increased by 54% compared to normal animals. LTs are involved in the pathogenesis of this nephropathy through several mechanisms. One of these mechanisms is the stimulation of fibrosis by LTs [106]. Inhibition of leukotrienes synthesis by blocking 5-LOX reduced proteinuria in diabetic animals [107] and cys-LT1 receptor antagonists reduced the nephrotoxicity of substances such as cyclosporine and gentamycin. LTB4 by stimulating BLT1 receptors increases apoptosis of renal tubular epithelial cells and stimulates recruitment of neutrophils to the kidney. BLT1 receptors are strongly expressed at the level of leukocytes while BLT2 receptors are present on the membrane of several types of cells in the kidneys. The concentration of the FLAP is significantly increased in glomeruli from diabetic compared to normal animals. Experimental studies have shown that LTC4 produces at the renal level an increase in oxidative DNA damage lesions to proximal tubular cells and cell death. Inhibition of 5-LOX diminished these effects [108]. In rats with streptozotocin-induced diabetes, administration of montelukast 10 mg/kg/day daily for 8 weeks significantly reduced the intensity of glomerular lesions, renal interstitial leukocyte infiltration and tubular damage [109].

In mesangial cell cultures, AGEs increase oxidative stress, apoptosis and the levels of TNF-α. Blocking cys-LTs receptors with zafirlukast reduced these effects of AGEs.

Lung Fibrosis

Diabetic pulmonary fibrosis is involved in the respiratory dysfunctions encountered in these patients. The receptors for cys-LTs are found in the lung on the membrane of fibroblasts, macrophages, pneumomonocytes and other cells [12].

In experimental diabetes [110] but also in human clinical practice, pulmonary inflammation is increased. Cys-LTs increase the synthesis of proinflammatory cytokines (Il-6, TNF-α) in the lung [111], stimulate the activity of fibroblasts and increase pulmonary vascular permeability. Fibroblasts in diabetic lungs, but also senescent lung fibroblasts synthesize an increased amount of leukotrienes which promote lung fibrogenesis [112]. In experimental diabetes induced with streptozotocin in rats, the administration of montelukast (cys-LT1 antagonist) significantly reduced the development of pulmonary fibrosis, pulmonary edema and decreased the pulmonary lesion score of diabetic animals [113]. LTB4 increases leukocyte migration into the diabetic lung.

Testicular Complications

Diabetes has a complex negative influence on male sexual function and also on sexual organs, sperm production and sexual behaviour. Various pathological changes occur at the testicular level. Some of these changes occur directly through the action of hyperglycemia (and the absence of insulin action) at the testicular level, and others indirectly through the reduction of the secretion of gonadotropin-releasing hormone), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. There is an increase in oxidative stress, a decrease in the number of Leydig and Sertoli cells, and a reduction in sperm motility and density. Leukotrienes are involved in the production of these pathological changes. Sometimes there is retrograde ejaculation, testicular atrophy and a reduction in sexual potency. In addition, approximately 59% of diabetic men have erectile dysfunction [114]. Leukotrienes are synthesized at the testicular level. Here, LTA4 and LTA4 hydrolase have been identified. 5-LOX is also present at the testicular level. Inhibition of this enzyme reduces both testicular synthesis of LTB4 and cys-LTs. Leydig cells secrete LTB4. In experimental studies, this secretion of LTB4 was not influenced by LH. LTC4 and LTD4 inhibited basal testosterone secretion in Leydig cells while LTA4 and LTB4 did not alter it. Gonadotropin-releasing hormone increases testosterone secretion in Leydig cells, but neither leukotrienes nor other eicosanoids such as prostaglandins appear to be involved in this process. In cell cultures, cys-LTs inhibited B-1 F cell growth in a dose-dependent manner. This effect is mediated by cys-LT1 receptors [115].

Montelukast improved testicular lesions in experimental streptozotocin-induced diabetes in rats, increased the size of seminiferous tubules, and increased spermatogenesis [53]. This substance reduces oxidative stress, testicular lipid peroxidation, synthesis of TNF-α, and pro-apoptotic caspase 3 [116]. Montelukast also has protective action against other toxic effects at the testicular level, such as those of doxorubicin.

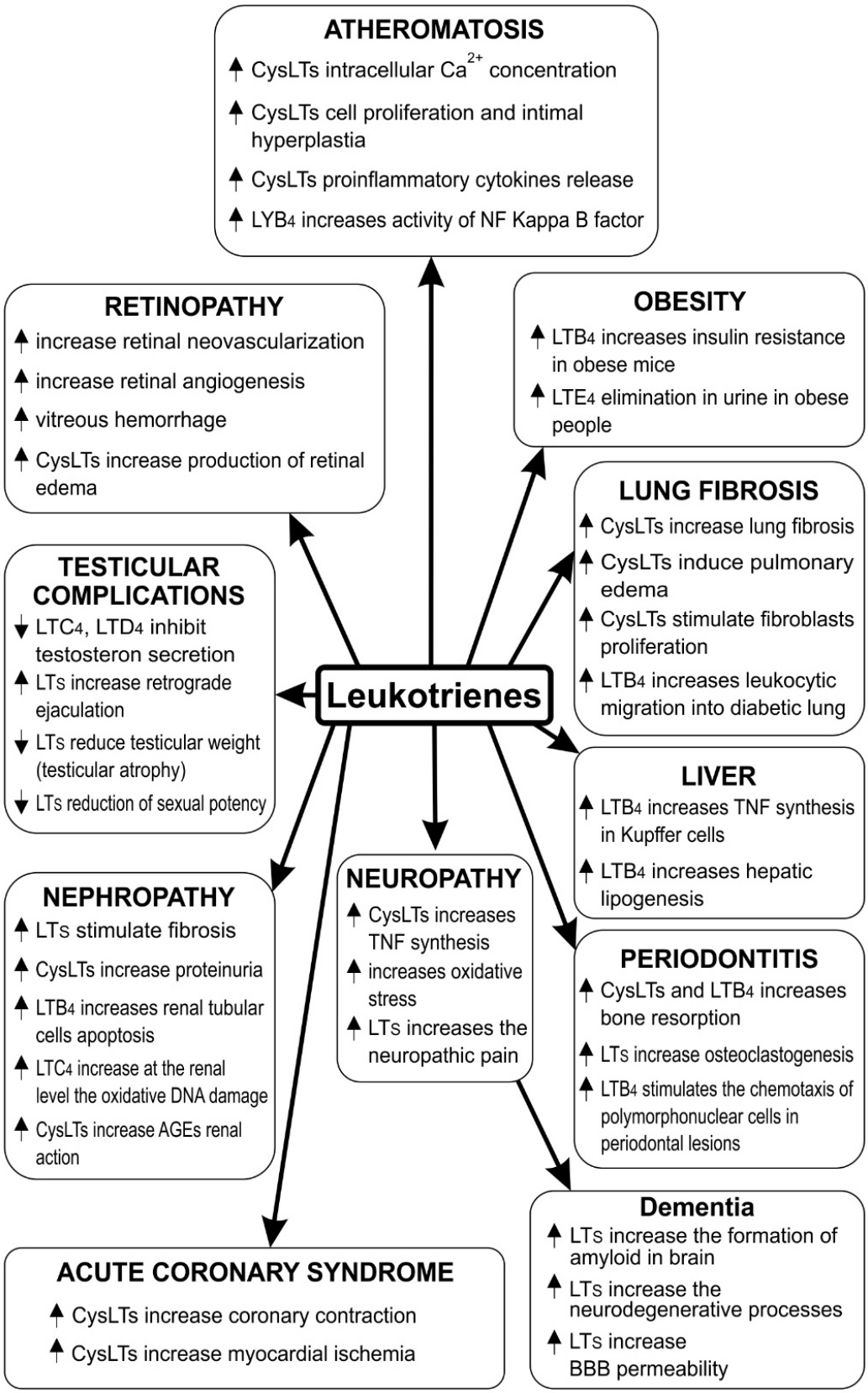

Fig. 2. The implications of leukotrienes in the pathogenesis of diabetes complications. Up arrow, increasing activity or quantity; down arrow, decreasing activity or quantity.

Periodontitis

Periodontal diseases are chronic inflammatory diseases that affect 10–15% of adults. Diabetes increases the susceptibility and risk of developing periodontitis by about three times and aggravates pre-existing periodontitis.

This disease is a frequent complication of diabetes mellitus. Essentially, they are inflammatory diseases characterized by loss of alveolar bone, destruction of connective tissue and finally the loss of teeth Chronic inflammation causes local periodontal tissue destruction, and the increased synthesis of proinflammatory cytokines causes increased insulin resistance In the case of human diabetes but also in an experimental study, the gingival concentration of IL-6, TNF-α, IL1-β is significantly higher than in normal individuals. These cytokines are involved in the bone resorption. Cys-LTs and LTB4 are also involved in bone resorption and remodeling. In crevicular fluid samples in patients with periodontitis, LTB4, LXA4 and PGE2 have been identified [117]. Neutrophils, which are important factors in injury in periodontal disease pathogenesis, synthesize all these eicosanoids. In experimental periodontitis in rats, the concentration of cys-LTs in the submandibular salivary gland increases significantly. Osteoclastogenesis is down-regulated by the inhibition of 5-LOX, which means that leukotrienes produced by the action of this enzyme increase the formation of osteoclasts, which play a role in bone destruction in periodontitis. In experimental periodontitis in rats, administration of montelukast 10 or 30 mg/kg/day for 3 weeks significantly reduced alveolar bone loss, myeloperoxidase activity of gingival tissues and periodontal inflammation [118]. Experimental administration of lipopolysaccharide (LPS) intragingivally produces gingival disease. The synthesis of TNF-α, IL-12, IL-10 and other interleukins is increased. Administration of a 5-LOX inhibitor significantly reduced the synthesis of LTB4, but also of interleukins. This proves that LTB4 stimulates the synthesis of proinflammatory cytokines at the gingival level. There is a positive correlation between the concentration of LTB4 in the crevicular fluid and the severity of periodontal lesions. This leukotriene stimulates the chemotaxis of polymorphonuclear cells in the area of periodontal lesions. In severe human periodontitis there is a significant increase in the concentration of LTB4 in saliva. There is a positive correlation between the salivary concentration of this leukotriene and bone resorption. Inhibition of 5-LOX also produced a reduction in the number of osteoclasts and bone resorption at the gingival level [119]. In other studies, montelukast inhibited osteoclast formation and reduced bone loss. Porphyromonas gingivalis is one of the most important bacteria involved in the pathogenesis of periodontitis. The lipopolysaccharide released by this bacterium strongly stimulates the synthesis of cys-LTs in mast cells. There are also studies which show, on the contrary, that the activity of osteoclasts decreased in the presence of BLT1 antagonist, but was not influenced by blocking cys-LT1 receptors. There is a possibility of different actions of cys-LTs and LTB4 at the periodontal level regarding bone resorption.

The proinflammatory action of leukotrienes at the gingival level is partially counterbalanced by the anti-inflammatory action of other eicosanoids, such as LTA4 and also by resolvins. There are no data on the concentration of resolvins in the crevicular fluid of patients with periodontitis, but there are studies that show that the administration of Resolvin E1 (RvE1) to rabbits with experimental periodontitis reduced the severity of the disease, diminished local lesions and decreased the concentration of some proinflammatory interleukins [120]. The ratio between leukotrienes and resolvins is important in the pathogenesis of periodontitis as well as in other complications of diabetes.

Diabetic Foot

Foot ulcers represent the most prevalent diabetic wounds and a major cause of diabetic foot amputation. One of the major causes of difficult wound healing in diabetic patients is the dysfunction of macrophages in these wounds.

The number and phagocytic activity of macrophages in the wounds of diabetics is reduced compared to those of macrophages in the wounds of normal people. The same thing is found in the wounds of animals with experimental diabetes. In wounds, macrophages phagocytize cellular debris, stimulate the synthesis of factors involved in tissue repair such as vascular endothelial growth factor (VEGF)-A and -C and stimulate the formation of new blood and lymphatic vessels. In the case of diabetes, all these activities are reduced and wound healing occurs much more slowly. In the evolution of inflammation in diabetic wounds and the production of their healing, the ratio between leukotrienes (strongly pro-inflammatory) and resolvins which have an anti-inflammatory action is important. Among these anti-inflammatory factors and that favor wound healing, the important ones are also the protectins and maresins. Resolvins (RvE1, RvD1 and RvD2), enhance macrophage phagocytosis. Some authors claim that the healing of various lesions in patients with T1DM depends on the synthesis and concentration of eicosanoids synthesized via the 5-LOX pathway [121]. The excess synthesis of LTB4 and cys-LTs is a cause of difficult wound healing in diabetic patients. In an experimental study in diabetic animals with skin lesions, the administration of selective antagonists of cys-LT1 receptors and LTB1 receptors resulted in faster skin healing [122].

Infectious Diseases

Diabetes produces an increased susceptibility to infections and a reduced capacity of the body to fight them. Hyperglycemia acts through several mechanisms resulting in a decrease in anti-infective defense: reducing polymorphonuclear leukocyte transmigration through the endothelium, decreasing the phagocytic capacity of polymorphonuclear leukocytes. Glucose-6-phosphate dehydrogenase (G6PD) activity is also reduced. In T1DM, low insulin

secretion and hyperglycemia contribute to chronic inflammation and to the reduction of antimicrobial defense and to the increase in the incidence of infections. LTB4 plays a trigger role in these pathological processes [123].

Hyperglycemia induces immune system dysfunctions in which leukotrienes are also involved. The systemic concentration of LTB4 and the activity of phagocytes (in which leukotrienes are also involved) are increased. A consequence of these immune dysfunctions is the increase in the frequency of infections with *Leishmania braziliensis* and skin infections. Diabetes is an additional risk factor for diseases such as COVID-19 and tuberculosis.

The association of tuberculosis with diabetes raises numerous therapeutic problems. In the case of patients who associate these two diseases, it was found that the ratio of serum concentrations of LXA4 to LTB4 is increased compared to patients who have only tuberculosis [124]. An explanation for this observation does not yet exist.

Fournier Gangrene

Fournier's gangrene is a necrotizing fasciitis of the external genitalia and the perineal region. This condition is mild but severe and diabetic patients have a significantly increased risk of developing this dangerous gangrene [125]. Hyperglycemia, peripheral ischemia, increased free radical formation, inflammation, increased phospholipase A2 activity and excess formation of leukotrienes and other eicosanoids are involved in the pathogenesis of gangrene.

Conclusions

Leukotrienes are involved in the pathogenesis of diabetes mellitus and its complications. Future research will need to provide more data on how different groups of eicosanoids are involved in the onset and progression of diabetes complications. The translation of experimental data into clinical practice must always be done with caution, but they indicate that cys-LT1 receptor antagonists such as montelukast, pranlukast, zafirlukast should be introduced into antidiabetic therapy and in the treatment of diabetes complications. Montelukast is a selective and orally active antagonist of cys-LT1 receptors. Montelukast is a drug introduced into therapeutic practice after the major role of peptidoleukotrienes in the pathogenesis of bronchial asthma was demonstrated. This drug is generally well tolerated in long-term administration. The oral bioavailability of montelukast is 60–70%. This drug is largely metabolized in the liver. Montelukast is an effective drug in the treatment of both bronchial asthma and asthmatic bronchitis in both adults and children. In its use in the therapy of diabetes mellitus and its complications, the adverse effects of this drug must also be taken into account. The most important are neuropsychiatric adverse effects. These effects are more common in children and young adults [126,127]. Among these adverse effects, the most common are attention disorders, anxiety disorders, sleep-related disorders, agitation and behaviour disorders. Nausea and vomiting symptoms, paresthesias, drowsiness and headache have also been observed occasionally [128]. Recent clinical studies have not confirmed the assumption that montelukast would be associated with suicide- and depression-related events [129].

The development of clinically useful selective competitive antagonists of LTB4 receptors should be done as soon as possible. 5-LOX inhibitors such as zileuton, which is used clinically in antiasthmatic therapy, could also be useful in the therapy of diabetes complications. Clinical trials are needed to evaluate the efficacy of combining cys-LTs receptor antagonists (such as montelukast) with oral antidiabetic drugs with different mechanisms of action. Data are needed on the effect of leukotriene receptor antagonists in juvenile diabetes as well as results on the efficacy of these drugs in the early stages of the disease, before complications development. We consider, as a hypothesis only, that the administration of leukotriene antagonists (montelukast 10mg/day) could prevent or slow down the onset of diabetes complications.

Another important future direction of research is that of the relationships between leukotrienes, eicosanoids with proinflammatory action involved in the pathogenesis of diabetes and its complications, and resolvins. We believe that understanding the implications of the relationships between different groups of biologically active lipids in the pathogenesis of diabetes and its complications represents a future path of progress in the therapy of this disease and its complications.

Availability of Data and Materials

Not applicable.

Author Contributions

MN made contributions to the design of the paper, analysis and interpretation of data, and drafting of the manuscript. CG made contributions to data acquisition and interpretation. Both authors have been involved in critically revising the manuscript for important intellectual content and gave final approval of the version to be published. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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