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The prognostic value of inflammatory and vascular endothelial dysfunction biomarkers in microvascular and macrovascular complications in type 1 diabetes

Wartość prognostyczna markerów stanu zapalnego i markerów dysfunkcji śródbłonka naczyniowego w rozwoju powikłań mikro- i makronaczyniowych cukrzycy typu 1

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Abstract

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterised by a destruction of pancreatic β cells, which leads to absolute insulin deficiency. Persistently high glycaemia causes vascular damage throughout the body. Microvascular complications comprise the following: nephropathy, retinopathy, and neuropathy. Macrovascular complications include coronary heart disease (CHD), which may result in myocardial infarction, cerebrovascular disease (leading to strokes), and peripheral vascular disease. The pathogenesis of vascular complications is multifactorial and is probably the combination of direct glucose-mediated endothelial damage, oxidative stress, production of sorbitol, and advanced glycation end-products. Precise understanding of these mechanisms could help clinicians to identify diabetic complications earlier and subsequently implement indispensable therapy on time. It is vital to determine biomarkers of microvascular and macrovascular complications in children affected with T1DM. Advanced glycation end-products and their receptors, adhesive molecules, pro- and anti-inflammatory cytokines, enzymes such as N-acetyl-β-D-glucosaminidase, and growth factors are the subject of ongoing studies. Numerous biomarkers of diabetic microangiopathy are already known and may constitute therapeutic targets in the future. Unfortunately, despite substantial progress in the understanding of the processes by which microvascular and macrovascular complications develop, much effort still needs to be devoted to the matter, and further investigations are required.

Key words:

diabetes mellitus type 1, diabetic angiopathy, cytokines, cell adhesion molecules.

Streszczenie

Cukrzyca typu 1 jest przewlekłą chorobą charakteryzującą się dysfunkcją komórek β wysp trzustki, co prowadzi do całkowitego braku wydzielania insuliny. Trwale podwyższona glikemia powoduje uszkodzenie naczyń w całym organizmie. Do powikłań mikronaczyniowych cukrzycy należą: retinopatia, nefropatia i neuropatia. Do powikłań makroangiopatycznych można zaliczyć chorobę niedokrwienną serca prowadzącą do zawału mięśnia sercowego, chorobę naczyń mózgowych mogącą skutkować udarem i chorobę naczyń obwodowych. Patogeneza powikłań naczyniowych jest wieloczynnikowa i prawdopodobnie jest wynikiem bezpośredniego działania uszkadzającego glukozy na śródbłonek naczyniowy, stresu oksydacyjnego, produkcji sorbitolu i końcowych produktów glikacji. Dokładne zrozumienie tych mechanizmów mogłoby pomóc klinicystom we wcześniejszym rozpoznawaniu powikłań cukrzycowych i następnie we wprowadzeniu wymaganej terapii w odpowiednim czasie. Określenie markerów cukrzycowych powikłań mikro- i makronaczyniowych u dzieci chorych na cukrzycę typu 1 jest niezwykle istotne. Produkty końcowej glikacji i ich receptory, cytokiny pro- i antyzapalne, enzymy, takie jak N-acetyl-β-D-glukozaminidaza oraz czynniki wzrostu, są obiektem nieustannych badań. Liczne markery mikroangiopatii cukrzycowej są już poznane i w przyszłości mogą stanowić potencjalny cel terapeutyczny. Niestety, mimo znacznego postępu w zrozumieniu procesów, które prowadzą do powstawania powikłań mikro- i makronaczyniowych cukrzycy, wciąż dalsze badania są konieczne.

Słowa kluczowe:

cukrzyca typu 1, angiopatia cukrzycowa, cytokiny, cząsteczki adhezyjne.

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Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterised by destruction of pancreatic β cells, which consequently leads to absolute insulin deficiency [1]. The etiopathology of the disease is still not fully understood. Type 1 diabetes mellitus is caused by a combination of different factors, in particular, exposure to environmental triggers, genetic susceptibility or immunological dysregulation [2]. The incidence rate of T1DM is steadily increasing. According to an International Diabetes Federation (IDF) report 1,106,200 children and adolescents under 20 years old are affected by T1DM worldwide [3]. Patients suffering from T1DM are prone to develop complications, which worsen the quality of life and may even become life-threatening. Persistently high glycaemia causes vascular damage throughout the body. Microvascular complications comprise the following: nephropathy, retinopathy, and neuropathy [3, 4]. Macrovascular complications include coronary heart disease (CHD), which may result in myocardial infarction, cerebrovascular disease, leading to strokes, and peripheral vascular disease [5-7]. The pathogenesis of vascular complications is multifactorial and is probably the combination of direct glucose-mediated endothelial damage, oxidative stress, production of sorbitol, and advanced glycation end-products (AGEs) [4].

Microvascular and macrovascular complications in type 1 diabetes mellitus

Diabetic nephropathy is defined as a constant proteinuria above 500 mg/24 h or albuminuria greater than 300 mg/24 h. Microalbuminuria is confirmed by finding two or three samples abnormal during 3-6 months [8]. It is a very important marker of glomerular alteration. Microalbuminuria provides the first clinical evidence for diabetic nephropathy and is a predictor of its progression [9, 10]. However, researchers emphasise the fact that, despite the improvement of glycaemic control, in a certain percentage of patients, microalbuminuria constitutes an advanced, practically irreversible stage of microangiopathy [11]. Furthermore, the relatively frequent failure of angiotensin-converting-enzyme inhibitor (ACEI) treatment has been revealed [11, 12]. In a study conducted on the paediatric population, microalbuminuria was diagnosed in 25.7% of patients after 10 years of the disease and in as many as 50.7% after 19 years [13]. Nephropathy is the major culprit responsible for morbidity and mortality in young adolescents with T1DM. Thus, early recognition of nephropathy and implementation of treatment is crucial in the prevention of end-stage renal failure. Moreover, regular follow-up is essential to capture the progression to albuminuria or regression to normoalbuminuria [8].

According to literature data, microalbuminuria indicates not only the existence of nephropathy, but also is a manifestation of general capillary blood vessel damage in other organs of the body, including the eyes [14].

Diabetic retinopathy is the most frequent cause of blindness in diabetic patients [4]. The prevalence of retinopathy varies from 50% to 90% after 10 and 20-30 years of the disease, respectively. Adolescents are more vulnerable to develop vision-threatening stages of retinopathy than adults. Therefore, it is vital to perform an ophthalmological examination regularly. It is recommended to begin screening for diabetic retinopathy from age 11 years, with two to five years diabetes duration [8]. Treatment may be implemented only in advanced phases of the disease. In its early stages patients are encouraged to pay greater attention to the control of risk factors such as hyperglycaemia and hypertension [15].

Researchers underline the fact that subclinical changes of retinal vessels, such as disrupted blood-retina barrier and increased retinal blood flow, may precede the first clinical signs [12]. New circulating biomarkers could enable the detection of subclinical disease and may be helpful in monitoring the progression of retinopathy [15].

Furthermore, diabetes may affect the somatic and autonomic nervous system. Diabetic neuropathy is recognised in < 10% to 27% of cases in the paediatric population [8]. Researchers have demonstrated an increased prevalence of peripheral nerve abnormalities during the years 1990-2002, whereas the rate of retinopathy and microalbuminuria declined [16]. Interestingly, according to other studies, proper control of type 1 diabetes leads to decreased retinopathy and nephropathy, but also to a lower rate of neuropathy [17, 18]. According to ISPAD guidelines, screening for neuropathy should start from age 11 years, with two to five years diabetes duration [8]. It is diagnosed on the basis of presented symptoms and physical examination [4]. Physicians diagnose neuropathy by exclusion, and even if the symptoms are present, less than one third of doctors recognise diabetic neuropathy or even discuss the matter with patients [12]. It is worth mentioning that the most frequent form of neuropathy, distal symmetrical sensorimotor neuropathy, is asymptomatic in almost 50% of cases [4]. The mortality and morbidity of cardiovascular disease (CVD) are significantly higher in diabetic patients than in the general population. Diabetic patients are 2-4 times more predisposed to developing coronary disease [6, 8]. Atherosclerosis, ensuing in narrowing of arterial walls throughout the body, constitutes the central pathological mechanism in macrovascular disease. It is caused by chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system [5, 19]. Atherosclerotic changes are reported in childhood and adolescence by measuring intima-media thickness in intravascular ultrasound in T1DM patients [8]. Hypertension and dyslipidaemia frequently coexist in individuals affected with diabetes [6]. Hypertension plays a more important role in coronary vascular disease development in diabetic patients than in healthy individuals. Cholesterol is a major culprit in the initiation and progression of atherosclerosis. Hence, screening of blood pressure and lipids is essential. According to ISPAD guidelines, blood pressure measurement should be carried out annually and lipid profile assessment is obligatory every two years [8]. The ADA recommends the evaluation of all the cardiovascular risk factors regularly, at least annually [7].

Biomarkers of micro- and macrovascular complications in type 1 diabetes mellitus

For nearly two decades researchers have been endeavouring to determine biomarkers of microvascular and macrovascular complications in children with type 1 diabetes. Advanced glycation end-products (AGEs) and their receptors, adhesive molecules, pro- and anti-inflammatory cytokines, growth factors, or enzymes, such as N-acetyl-β-D-glucosaminidase (NAG), are the subject of ongoing studies. The correlation of inflammation, endothelial dysfunction, and hypercoagulability plays an important role in the development of vascular complications [20]. A new diagnostic tool could be useful in early detection of microangiopathy, and thereby it could allow implementation of treatment on time. It has been stated that retinal and renal alterations in children with T1DM may take place in the first years of the disease, and at that time the changes are probably reversible. Thus, during the first years of the disease is the most convenient time to take appropriate measures and avoid the development of irreversible complications [11].

Advanced glycation end products and their receptors

Advanced glycation end products play a vital role in the pathogenesis of diabetic retinopathy, nephropathy, neuropathy, and cardiomyopathy. They also constitute an important risk factor for other disorders, such as rheumatoid arthritis, osteoporosis, and aging. They are formed by glycation of proteins, which takes place during a long-standing hyperglycaemic state. Advanced glycation end products bind to the plasma membrane receptor for AGEs (RAGE) and entail an alteration of gene expression and intracellular signalling. Due to this interaction, pro-inflammatory cytokines, like interleukin 1α (IL-1α), IL-6, or tumour necrosis factor α (TNF-α), adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), and free radicals are released. This process enhances, in turn, inflammation and oxidative stress [21]. Researchers have demonstrated the prognostic value of AGEs in predicting the prevalence of diabetic microangiopathy, unlike RAGE levels [14]. Wada *et al.* found elevated AGE serum levels in peripheral nerves obtained from diabetic patients [22]. According to literature data, several AGEs are good biochemical markers for the early detection of diabetic retinopathy and may be used as a warning factor in the pre-proliferative stage of this complication [15]. In addition, AGE-RAGE interaction has been proven to be one of the mechanisms responsible for diabetic neuropathy development [23]. Experimental studies point to the fact that AGEs, acting directly as well as via receptor-mediated mechanisms, enhance the development of macrovascular diseases [6]. Moreover, it has been assumed that soluble forms of RAGE, acting as decoys for RAGE, may have a protective role in inflammation in atherosclerosis in T1DM patients [24]. Inhibition of AGE formation and the blocking of RAGEs may contribute to the prevention of diabetic complications [21]. It has been shown that linagliptin, an inhibitor of dipeptidyl peptidase-4 (DPP-4), blocks renal damage in type 1 diabetic rats by suppressing the AGE-RAGE axis [25].

Pro- and anti-inflammatory cytokines

Inflammatory cytokines, especially TNF-α, are also involved in development of diabetic complications. Tumour necrosis factor α interacts with immune system cells and leads to the secretion of other cytokines. Numerous studies have shown that serum rates of TNF-α are elevated in diabetic patients affected with microangiopathy [14, 20, 23, 26-30]. A group of researchers reported the highest prognostic value of TNF-α in predicting the occurrence of microvascular complications in comparison to 12 other studied parameters, such as AGEs or VEGF [14]. In another study, a correlation between TNF-α activity and the degree of renal damage was suggested [26].

In addition, TNF-α plays an important role in the process of atherosclerosis and seems to be involved in CHD by affecting lipid metabolism, insulin resistance, and endothelial function. Vendrell *et al.* reached the conclusion that −308 TNF-α gene polymorphism predisposes to CHD development and may become an useful predictive marker for CHD in type 2 (T2DM) diabetic women [31].

What is more, it has been stated that TNF-α and IL-12 equilibrium is a prerequisite for diabetes type 1 free from late complications in the paediatric population [32]. Another study revealed that IL-12 predominance might prevent or postpone nephropathy development; however, it does not protect from retinopathy [33].

Diabetic patients suffering from vascular complications also present an elevated rate of serum IL-6 [20, 30]. Interleukin 6 plays a key role in CVD pathogenesis; thus, reduction of its concentration may have a cardioprotective effect [34]. It is worth noting that IL-6 – 174 GG genotype may have beneficial potential in decreasing the risk of diabetic retinopathy and nephropathy, whereas 174 – CC genotype indicates the higher susceptibility to T1DM [35].

In addition, raised levels of inflammatory cytokines IL-1β, IL-6, IL-8, IL-17A, and TNF-α were reported in aqueous humour of patients with diabetic retinopathy. Researchers concluded that the higher levels of these cytokines might be associated with the earlier appearance of retinal complications [36].

Furthermore, increased IL-1, IL-6, TNF-α, and transforming growth factor β (TGF-β) concentrations are associated with the progression of nerve degeneration in diabetic neuropathy. It has been demonstrated that these cytokines affect glial cells and neurons. Although IL-6 or TNF-α seem to be involved in the pathogenesis of diabetic neuropathy, they are probably not responsible for the development of peripheral neuropathic pain [37].

The mechanisms by which pro-inflammatory cytokines cause β-cell demise are roughly elucidated. Therefore, attention is paid to the cytoprotective role of anti-inflammatory molecules

such as IL-4, IL-10, IL-13, and especially to the recently discovered IL-35 [38-40]. A large body of evidence indicates that functional polarisation of T-helper lymphocytes towards Th1 cells is involved in T1DM development. Peripheral blood mononuclear cells obtained from T1DM patients and their first-degree relatives establish a decreased anti-inflammatory cytokine secretion. Furthermore, it has been proven that administration of cytokines secreted from Th2 lymphocytes, such as IL-4, IL-10, and IL-13, has a protective potential against diabetes progression in rodents. This novel immunotherapeutic strategy allows the onset of spontaneous diabetes to be delayed and reduces its prevalence in non-obese diabetic (NOD) mice [38]. Another group of researchers reported a decrease of IL-10 levels in T1DM patients and came to the conclusion that there was a correlation of higher secreting activity of IL-10 and protection against late diabetic complications [26]. Moustafa *et al.* showed the decrease in IL-10 contents along with increased IL-6 levels in streptozotocin-induced diabetic rats [41].

Recently, considerable efforts have been invested to investigate the therapeutic potential of IL-35, a newly discovered inhibitory cytokine. It has been demonstrated that IL-35 expression in β-cells protects NOD mice against autoimmune diabetes. It highlights the possibility of IL-35 use to treat T1DM [39, 40].

It has been revealed that IL-37, a newly discovered anti-inflammatory cytokine, belonging to the IL-1 family, may have a protective effect in the process of the vascular calcification and atherosclerosis in diabetic patients [42]. Moreover, it has been proven that individuals with CHD present decreased levels of cytokines IL-35, IL-10, and TGF-1 [43].

Growth factors

Vascular endothelial growth factor (VEGF), involved in vasculo- and angiogenesis, seems to be another promising biomarker of diabetic microangiopathy. VEGF serum levels are increased in T1DM patients, and they are additionally elevated along with the longer duration of the disease and in children with microvascular complications like retinopathy and nephropathy [14, 44-48]. Moreover, Myśliwiec *et al.* underlined the fact that VEGF concentrations correlate with the stage of retinopathy; therefore, it may serve as a prognostic marker of diabetic retinopathy development. In addition, intravitreal injections of anti-VEGF agents are currently used in the treatment of vision-threatening stages of retinopathy, enabling the reduction of the rate of visual loss. On the other hand, the reduction of VEGF epidermal expression has been observed in T1DM patients with neuropathy [49]. Current studies indicate the protective role of VEGF-induced angiogenesis of vasa nervorum in diabetic neuropathy [50].

Sasso *et al.* showed increased myocardial mRNA and protein expression of VEGF along with decreased mRNA and protein expression of VEGF receptors in diabetic patients with chronic CHD in comparison with non-diabetic ischaemic patients [51].

Another biomarker of microangiopathy taken into account is transforming growth factor β1 (TGF-β1). It is responsible for cellular processes such as proliferation, differentiation, migration, and survival. In addition, it plays an essential role in physiological processes, including embryonic development, angiogenesis, and wound healing. This TGF-β1 isoform establishes the strongest relationship with tissue fibrosis [52, 53]. Studies point to the fact that TGF-β1 serum concentrations are elevated in patients with T1DM; moreover, patients affected by microvascular complications present higher TGF-β1 levels than patients without microangiopathy. It has been demonstrated that TGF-β1 concentrations correlate with the severity of microvascular complications and the duration of diabetes. Increased TGF-β1 activity has been revealed also in urine of diabetic patients and in vitreous humour of T1DM adults [53, 54]. Zyiadeh *et al.* demonstrated the prevention of glomerulosclerosis and renal insufficiency, resulting from T2DM, by using an anti-TGF β antibody in diabetic mice, whereas Voelker *et al.* did not prove the efficacy of TGF-β1 monoclonal antibody therapy in patients affected by T1DM and T2DM [55, 56].

Although TGF-β1 was thought to be a pro-atherogenic factor for many years, recent studies have shown that, in reality, it seems to limit the atherosclerosis by modulating a number of processes such as inflammatory response or the accumulation of lipids in the vessel wall [57, 58]. The effect of increased TGFβ1 levels in diabetics on atherogenesis is not fully elucidated, and further investigations are necessary. A group of researchers has proven that simvastatin may have a therapeutic role in atherosclerosis in patients affected by T2DM diabetes. Simvastatin therapy results in increased expression of TGF-β1 and decreased expression of VEGF [59]. Yang *et al.*, on the other hand, have highlighted the fact that TGF-β1 is a potent activator of proteoglycan synthesis, which entails increased binding to LDL. Blocking growth factor actions on proteoglycan synthesis may constitute a potential therapeutic target [60].

N-acetyl-β-D-glucosaminidase

Furthermore, evidence is mounting that disorders of glycoprotein and glycosaminoglycan metabolism, including NAG enzyme, are involved in the development of diabetic retinopathy and nephropathy. It has been shown that T1DM patients present higher concentrations of NAG and its A and B isoforms in serum and urine than healthy individuals. Mysliwiec *et al.* proved that children affected with retinopathy displayed higher levels of NAG and its isoforms in urine in comparison to juvenile patients without retinopathy. NAG, isoform A and B levels in serum were elevated as well; however, the difference was not statistically significant [26]. Furthermore, Vaidya *et al.* demonstrated that low NAG concentrations were associated with the regression of microalbuminuria in T1DM patients. Moreover, it has been stated that the appearance of the detectable serum TNF-α activity in T1DM children, presenting no sign of diabetic retinopathy, nephropathy, and no microalbuminuria, with the concomitant increase of NAG and its isoforms levels in serum

and urine, might predict prompt occurrence of these complications [29]. Vaidya *et al.* found that low NAG concentrations were associated with the regression of microalbuminuria in T1DM patients [61]. In addition, it was revealed that increased urinary NAG levels are associated with the prevalence of cardiovascular autonomic neuropathy in patients with T1DM, and NAG activity correlates positively with its severity [62]. A relationship between elevated urinary NAG levels and carotid artery atherosclerosis in T1DM and T2DM patients has been observed as well [63, 64].

Cell adhesion molecules

In view of currently available studies, cell adhesion molecules (CAMs) seem to play an important role in the pathogenesis of vascular complications. Cell adhesion molecules take part in cell growth, differentiation, cell junction formation, or cell polarity as well as in leukocyte activation, circulation, or accumulation in inflammatory locations. They initiate the process of atherosclerosis by triggering the attachment of monocytes and lymphocytes to endothelial cells [65]. The majority of CAMs belong to one of the following families: integrins, selectins, cadherins, and immunoglobin superfamily (IgSF) molecules. The activity of intercellular adhesion molecule 1 (ICAM-1), present on leukocytes and endothelial cells, may be increased by a number of cytokines [66]. Soluble forms of ICAM-1 (sICAM-1) constitute a biomarker of endothelial damage and inflammation [67]. Elevated levels of sICAM-1 are found in autoimmune conditions, including T1DM [65, 66]. Increased ICAM-1 concentrations in retinal tissue have been shown in patients with diabetic retinopathy [68]. A study conducted on a group of African Americans with T1DM revealed that sICAM-1 levels were associated with the elevated risk of progression of normoalbuminuria or microalbuminuria to overt albuminuria [69]. Zhou *et al.* proved that ICAM-1 levels were higher in patients with neuropathy in comparison to non-neuropathic individuals [37]. In addition, ICAM-1 may constitute a strong CVD predictor in diabetes [70].

Vascular cell adhesion molecule 1 (VCAM-1) is a member of the sIgF family and displays a potent role in angiogenesis; hence, it seems to be a major culprit in the development of retinopathy [66]. Blum *et al.* reported increased concentrations of soluble forms of VCAM-1 (sVCAM-1) concurrently with elevated severity of retinopathy [71]. Soedamah-Muthu *et al.* demonstrated a positive correlation between the activity of sVCAM-1 and diabetic complications like retinopathy, micro- and macroalbuminuria, and CVD [72]. The role of sVCAM-1 in predicting CVD is contradictory. A number of studies failed to reveal a strong positive relationship between sVCAM-1 levels and CVD [72]. Moreover, Jude *et al.* did not find a correlation between sVCAM-1 and macrovascular disease; however, the study group in this research was small [70]. Conversely, in the Hoorn Study a strong independent relation of sVCAM-1 level and seven-year CVD mortality in type 2 diabetic patients was demonstrated [72]. There is scarce evidence confirming the relationship between VCAM-1 concentrations and diabetic neuropathy [73].

The family of selectins consists of E-selectin, P-selectin, and L-selectin. E-selectin, expressed on endothelial cells, is up-regulated by cytokines like TNF or IL-1β. Its soluble forms (sE-selectin) have been proven to be increased in some disorders, for example atherosclerosis, T1DM, and T2DM diabetes [66]. Glowinska *et al.* showed the relationship between increased sE-selectin concentrations and T1DM, whereas no correlation with T1DM was found for sP-selectin and sL-selectin levels [65]. Other research points towards the positive correlation between sE-selectin levels and retinopathy, nephropathy, and CVD [54, 71, 74, 75]. However, the role of sE-selectin in prediction of cardiovascular complications in diabetes is not fully elucidated. According to two prospective studies, its increased levels were not associated with CHD [72]. On the other hand, in the study carried out on a group of children and adolescents with T1DM, a positive correlation between sE-selectin levels and intima-media thickness (IMT) of carotid arteries, and significant negative correlation between sE-selectin and flow mediated dilation (FMD) of the brachial artery was found. Impaired brachial artery dilation and elevated IMT are biophysical proof of structural changes in the vessels [76]. What is more, T2DM patients with peripheral arterial disease present increased sE-selectin levels [77]. Moreover, Lopes-Virella *et al.* stated that sE-selectin seems to be a good predictor of macroalbuminuria [78]. Research indicates that levels of adhesion molecules like ICAM-1, P-selectin, and E-selectin are associated with neuropathy [37, 79]. In addition, patients presenting painful neuropathy have higher sE-selectin concentrations [37]. Conversely, Fatthollahi *et al.* reported lower levels of sE-selectin in T1DM patients than in a control group. Sasongko *et al.* have not revealed any significant association between T1DM and adhesion molecules such as sVCAM-1, sICAM-1, and sE-selectin.

Conclusions

In conclusion, a wide range of studies are conducted all over the world to broaden the knowledge of diabetic microangiopathy and macroangiopathy pathogenesis. The precise comprehension of these mechanisms could help clinicians to identify diabetic complications earlier and subsequently implement indispensable therapy on time. Numerous biomarkers of diabetic microangiopathy are already known, and they may constitute therapeutic targets in the future. Unfortunately, despite substantial progress in the understanding of the processes by which microvascular and macrovascular complications develop, still a great deal of effort is needed. It should be noted that there are very few studies considering the pathogenesis of macrovascular complications in diabetic patients, and the vast majority of these focused on the group of adults affected with T2DM. It is crucial to carry out further investigations. Currently the intensive treatment of hyperglycaemia and improvement of glycometabolic control are still the most effective strategies to stem the development of complications [81].

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