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PRACA POGLĄDOWA
REVIEW

Blood rheology in type 2 diabetes: The impact of metabolic disorders on microcirculation and the risk of vascular complications

Reologia krwi w cukrzycy typu 2 – wpływ zaburzeń metabolicznych na mikrokrążenie i ryzyko powikłań naczyniowych

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ABSTRACT

INTRODUCTION: Type 2 diabetes mellitus (T2DM) is a prevalent and progressive metabolic disorder marked by chronic hyperglycemia and associated with significant vascular complications. While insulin resistance and β cell dysfunction remain central to its pathogenesis, recent attention has turned to the role of blood rheology in the disease. Abnormalities in hemorheological parameters are increasingly recognized as contributors to microvascular dysfunction in diabetes, exacerbating tissue hypoxia and potentially accelerating the progression of diabetic complications. The purpose of this review is to summarize the current knowledge on the rheological disturbances observed in T2DM, with a focus on their pathophysiological basis, clinical relevance, and potential as therapeutic targets.

STATE OF KNOWLEDGE: Hemorheological disturbances play a crucial role in the vascular pathology of T2DM. These changes impair microcirculation, promote tissue hypoxia, and increase vascular resistance, contributing to vascular complications such as retinopathy, nephropathy, stroke, and ischemic heart disease. Growing evidence also highlights the role of plasma proteins (e.g., AGER or HSP) and oxidative stress in modulating blood rheology. Hemorheological parameters are thus gaining importance not only as diagnostic indicators, but also as therapeutic targets. In addition to glycemic control, increasing emphasis is placed on interventions that improve blood rheology, including statins to reduce fibrinogen levels and pentoxifylline to enhance erythrocyte deformability and reduce viscosity.

CONCLUSIONS: Increased plasma viscosity, increased fibrinogen levels, red blood cell aggregation, and decreased erythrocyte deformability are the most important rheological parameters that are worth monitoring. Maintaining optimal levels of glycemia and lipids, as well as drugs such as statins and pentoxifylline, improve blood rheology, reducing the risk of vascular complications.

KEYWORDS

blood rheology, blood viscosity, aggregability of erythrocytes, deformability of erythrocytes, type 2 diabetes mellitus, microcirculation

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STRESZCZENIE

WPROWADZENIE: Cukrzyca typu 2 (*type 2 diabetes mellitus* – T2DM) to powszechne i postępujące zaburzenie metaboliczne, charakteryzujące się przewlekłą hiperglikemią i związane z istotnymi powikłaniami naczyniowymi. Chociaż insulinooporność i dysfunkcja komórek β pozostają kluczowe w jej patogenezie, uwaga skupia się ostatnio na roli reologii krwi w procesie chorobowym. Zmiany parametrów hemoreologicznych są coraz częściej uznawane za czynniki przyczyniające się do dysfunkcji mikrokrążenia w cukrzycy, nasilające niedotlenienie tkanek i mogące przyspieszać postęp powikłań cukrzycowych. Celem niniejszego przeglądu jest podsumowanie aktualnej wiedzy na temat zaburzeń reologicznych obserwowanych w T2DM, ze szczególnym uwzględnieniem ich podłoża patofizjologicznego, znaczenia klinicznego i potencjału jako celów terapeutycznych.

STAN WIEDZY: Zaburzenia hemoreologiczne odgrywają kluczową rolę w patologii naczyniowej T2DM. Zmiany te upośledzają mikrokrążenie, wpływają na niedotlenienie tkanek i zwiększają opór naczyniowy, przyczyniając się do powikłań naczyniowych, takich jak retinopatia, nefropatia, udar mózgu i choroba niedokrwienna serca. Coraz więcej dowodów wskazuje również na rolę białek osocza (np. AGER, HSP) i stresu oksydacyjnego w modulacji reologii krwi. Parametry hemoreologiczne zyskują zatem na znaczeniu nie tylko jako wskaźniki diagnostyczne, ale także jako cele terapeutyczne. Oprócz kontroli glikemii coraz większy nacisk kładzie się na interwencje poprawiające reologię krwi, w tym statyny w celu obniżenia poziomu fibrynogenu oraz pentoksyfilinę w celu zwiększenia odkształcalności erytrocytów i zmniejszenia lepkości.

WNIOSKI: Zwiększona lepkość osocza, podwyższone stężenie fibrynogenu, agregacja erytrocytów i zmniejszona odkształcalność erytrocytów to najważniejsze parametry reologiczne, które warto monitorować. Utrzymanie optymalnego poziomu glikemii i lipidów, a także przyjmowanie leków takich jak statyny i pentoksyfilina poprawiają reologię krwi, zmniejszając ryzyko powikłań naczyniowych.

SŁOWA KLUCZOWE

reologia krwi, lepkość krwi, agregacja erytrocytów, odkształcalność erytrocytów, cukrzyca typu 2, mikrokrążenie

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a heterogeneous and chronic metabolic disorder characterized by persistent hyperglycemia, which contributes to the development of both microvascular and macrovascular complications [1]. Currently, the global prevalence of diabetes among adults is estimated at 10.5% (536.6 million adults), with substantial regional and national variability. This figure is projected to rise to 12.2% (783.2 million adults) by the year 2045 [2]. T2DM represents the most prevalent form of diabetes, accounting for approximately 90% of all diabetes cases globally. Although it traditionally affects individuals over the age of 45, its incidence among children, adolescents, and young adults is steadily increasing. This trend is primarily driven by the global rise in obesity, physical inactivity, and poor dietary habits [3]. The pathogenesis of T2DM involves a complex interplay of genetic, environmental, and metabolic factors. A central feature is insulin resistance (IR), which often precedes a progressive decline in insulin secretion by pancreatic β cells. Although the precise mechanisms remain incompletely understood, both IR and β cell dysfunction are recognized as key contributors to the development and progression of the disease [4].

Although the effects of diabetes on blood flow have been studied for years [5,6], in recent years, increasing attention has been paid to disturbances in blood rheology parameters as an important, although often underestimated, component of the pathophysiology of T2DM. Rheology is the scientific study of the flow and deformation of matter – particularly fluids and plastic materials – focusing on their mechanical properties such as viscosity and elasticity [7].

Hemorheology is concerned specifically with the physical properties of blood and phenomena accompanying this flow. Blood flow disturbances, especially microcirculation dysfunction caused by increased whole blood viscosity or endothelial damage, for example, are a significant problem underlying many chronic diseases, including T2DM [8,9]. The rheological determinants of blood flow include hematocrit (Hct), whole blood and plasma viscosity (Pv), and erythrocyte deformability and tendency to aggregate. Blood viscosity reflects the internal resistance between the layers of flowing fluid. Hemorheological studies examine how these parameters change in relation to vessel diameter and geometry, flow velocity, and shear rate [10]. Understanding these factors is particularly important in pathological states such as diabetes mellitus, where altered hemorheological properties contribute to disease progression. Circulatory disorders in diabetes are also observed in thermographic imaging and correlate with a tendency toward higher Pv and disorders of erythrocyte deformability and aggregation [11].

Under hyperglycemic conditions, Pv increases due to non-enzymatic glycation of proteins, along with enhanced erythrocyte aggregation and reduced red cell deformability. These alterations impair tissue perfusion and contribute to hypoxia. Hemorheological abnormalities, when combined with vascular endothelial dysfunction, play a crucial role in the pathogenesis of diabetic microangiopathy, ultimately contributing to the progression of retinopathy, nephropathy, and neuropathy [7,12].

The aim of this review is to provide an up-to-date overview of the current knowledge of blood rheology in the context of T2DM. This article discusses the physiological and pathophysiological foundations of the rheological properties of blood, their alterations in diabetes, and the clinical relevance of these disturbances. Particular emphasis is placed on the molecular and cellular mechanisms affecting blood viscosity, microcirculation, and vascular complications, as well as on therapeutic and preventive strategies aimed at improving blood rheology in patients with T2DM.

STATE OF KNOWLEDGE

Basics of blood rheology

It has been demonstrated that blood exhibits several rheological characteristics typical of non-Newtonian fluids, including shear-thinning behavior (pseudoplasticity), viscoelasticity (the ability to behave both as a fluid and a solid), and thixotropy, where viscosity depends on the flow history [13]. Understanding these properties is crucial for assessing tissue perfusion, particularly in the microcirculation, where rheological parameters significantly influence vascular resistance and oxygen delivery. The rheological properties of blood are primarily determined by its cellular components and plasma characteristics. Key factors affecting whole blood viscosity – an important rheology factor – include Pv, Hct, red blood cell aggregation (RBCa), and the ability of erythrocytes to deform and orient when flowing [14,15].

A study involving patients with T2DM measured whole blood viscosity at various shear rates and analyzed correlations with glycated hemoglobin (HbA1c) levels and plasma fibrinogen concentrations. The results showed that blood viscosity was elevated in patients with higher HbA1c levels, although this correlation was not statistically significant. In contrast, plasma fibrinogen levels exhibited a strong positive correlation with blood viscosity in T2DM patients, suggesting that fibrinogen plays a crucial role in increasing blood viscosity in this population [14].

Another study, involving 410 individuals, showed that Pv was higher in those with hypercholesterolemia. Pv appears to be influenced by both low-density lipoproteins (LDL) and high-density lipoproteins (HDL), whereas blood viscosity remains unaffected. Triglyceride levels below 400 mg/dl do not demonstrate a significant impact, at least in healthy individuals and under the shear conditions assessed in this study. Overall, the effect of LDL- and HDL--cholesterol on Pv seems to be relatively minor [16].

Microscopic investigations using atomic force microscopy have also revealed significant alterations in the morphology and mechanical properties of erythrocytes in individuals with T2DM. These erythrocytes demonstrate reduced deformability, increased membrane stiffness and cellular aggregation, and higher stiffness index. Morphological changes such as cellular flattening, reduced biconcavity, and structural membrane abnormalities have been observed – likely the consequences of chronic hyperglycemia and glycation of membrane proteins. These alterations adversely affect blood rheology and may impair microvascular flow, contributing to the development of vascular complications typical of T2DM. These findings highlight the importance of both glycemic control and cellular blood properties in assessing the risk of complications in diabetic patients [17]. Reduced erythrocyte deformability in patients with T2DM may contribute to reduced perfusion and tissue hypoxia [18]. This may be related to the accumulation of advanced glycation end-products (AGEs) of erythrocyte membrane proteins and hemoglobulin [19] and to the reduction of cholesterol, sphingomyelin, and phosphatidylcholine content in the outer layer of the plasmalemmal of red blood cells (RBCs) [20].

In recent years, increasing attention has been directed toward the role of plasma proteins in the pathophysiology of T2DM and its vascular complications. A study published in 2023 demonstrated that certain proteins, such as the AGE receptor and heat shock proteins HSPA1A and HSPA1B, may be genetically linked to the development of diabetes and vascular injury [21]. These findings suggest that specific plasma proteins may not only contribute to inflammation and oxidative stress, but also influence blood rheology properties, thereby increasing the risk of microangiopathy.

Monitoring and managing plasma fibrinogen levels and improving blood rheological properties may represent important strategies for preventing vascular complications in patients with T2DM [14].

Metabolic disorders in type 2 diabetes

Several environmental and genetic factors contribute to impaired insulin production by pancreatic β cells and impaired tissue sensitivity to insulin, resulting in hyperglycemia, a typical symptom of T2DM [22]. Of all of these factors, obesity (body mass index ≥ 30 kg/m^2) is the strongest risk factor for T2DM [23]. The disease is characterized by a progressive deterioration of glucose homeostasis, primarily due to a combination of IR and β cell dysfunction. In the early stages of the disease, IR develops in key metabolic tissues such as skeletal muscle, adipose tissue, and the liver. This resistance impairs peripheral glucose uptake and enhances hepatic glucose production. Initially, pancreatic β cells attempt to compensate by increasing insulin secretion. However, over time, the persistent metabolic stress (particularly glucotoxicity and lipotoxicity) leads to β cell dysfunction and a decline in insulin production. The resulting chronic hyperglycemia further exacerbates IR, creating a vicious cycle that accelerates the progression of the disease. This complex interplay between defective insulin action and secretion underscores the multifactorial nature of glucose dysregulation in T2DM [22].

However, T2DM is accompanied by other disorders such as dyslipidemia, anemia, oxidative stress, and inflammation [24,25,26,27].

People with diabetes are at a higher risk of developing dyslipidemia. In patients with T2DM, there is increased hepatic production of very-low-density lipoprotein (VLDL) and impaired clearance of VLDL and intestinally absorbed chylomicrons. Thus, remnants are retained in the plasma, including cholesterol--enriched intermediate-density lipoproteins, which are highly atherogenic [24,25].

In T2DM there is increased production of reactive oxygen species (ROS). Under hyperglycemia, mitochondria increase ROS production and cause oxidative stress and tissue damage [26], which leads to microvascular (nephropathy, retinopathy, or neuropathy) and macrovascular complications (stroke or myocardial ischemia) [27].

Rheological changes in blood in type 2 diabetes

High blood glucose levels affect metabolic processes in erythrocytes by altering enzyme activity and protein structure, which in turn leads to modifications of cytoskeletal proteins, the cell membrane, and hemoglobin, ultimately resulting in impaired function, altered morphology, and reduced lifespan of RBCs [28,29,30]. In patients with diabetes, chronic hyperglycemia affects the mechanical properties of erythrocytes, leading to reduced deformability and altered cell shape compared to those of healthy individuals [31].

Reduced deformability of erythrocytes is associated with a stiffening of the cell membrane, induced by high glucose concentrations due to non-enzymatic glycation of membrane proteins [32,33]. In diabetic conditions, the fluidity of the erythrocyte membrane is also altered due to changes in its lipid composition, particularly in cholesterol and phospholipid content. These changes affect various membrane functions, including ion transport, hormonal receptor activity, and enzymatic activity [34,35]. The hyperglycemia-induced change in membrane fluidity further contributes to reduced erythrocyte deformability and increased aggregation [30].

Increased fibrinogen levels can cause endothelial damage and impaired blood flow and platelet function, leading to hyperviscosity [36,37]. Fibrinogen is an acute phase protein that increases in inflammatory conditions; some researchers suggest that fibrinogen levels may be an indicator for treatment in diabetic foot, among other conditions [37,38].

In diabetes, the tendency of erythrocytes to aggregate is altered, increasing with elevated glucose concentration. The aggregation process is promoted by elevated fibrinogen levels, which are higher in diabetic patients compared to healthy individuals [30,31,39,40]. Some studies suggest that the higher aggregation may also be associated with a reduction in the erythrocyte surface electric charge, resulting from decreased sialic acid content in the cell membrane [30,41].

In patients with T2DM, the described cellular and biochemical alterations lead to significant changes in blood rheology, which contributes to impaired microcirculation and a higher risk of vascular complications. Blood viscosity, particularly under low shear rates, is strongly influenced by Hct, RBC count, and mean corpuscular volume. Elevated Hct increases flow resistance, often accompanied by a higher RBC count and smaller cell volume. Additionally, increased RBC aggregation promotes the formation of rouleaux, further raising blood viscosity under low shear rate and impairing the transport of oxygen, glucose, and insulin. At high shear rates, aggregation plays a minimal role, as rouleaux structures are mechanically disrupted. Instead, blood viscosity is mainly determined by elevated Hct and reduced RBC deformability. As a result, both increased aggregation and decreased deformability contribute to abnormal flow dynamics and vascular complications in T2DM [14].

The reduced erythrocyte deformability and increased aggregation observed in diabetes may lead to changes in erythrocyte cytology – such as poikilocytosis, hypochromia, and anisocytosis – and in combination with changes in whole blood count may be part of the complicated etiology of the disease [42]. Affected erythrocytes are more susceptible to destruction in the circulation, which leads to a higher proportion of younger cells. This may be related to impaired Na^+/K^+-ATPase function in the cell membrane, which causes an ionic imbalance and accelerates cell aging [5]. It is also worth noting the influence of oxidative stress on lipid peroxidation. Some studies suggest a correlation between the number of altered lipids in the cell membrane and the rate at which microangiopathy develops. Treatment options leading to lower malondialdehyde levels increase erythrocyte deformability and reduce the effect of free radicals on RBCs. It also has a positive effect on whole blood viscosity, which returns to normal once the proper membrane properties of erythrocytes are restored [5,43].

Microcirculation in type 2 diabetes

The circulatory system allows for long-distance transport of substances throughout the body. Microcirculation, which occurs in vessels from a few micrometers to hundreds of micrometers in diameter, serves as a bridge between large vessels and individual cells. While different types of microcirculation exist at the tissue level, the basic structure can be described as arterioles that branch out into capillaries, which then drain into venules. The main function of this network is to distribute substances – most importantly, oxygen – to the cells' immediate vicinity. This allows for an exchange of substances between blood in the capillary and the cells via diffusion. Microvasculature also participates in regulating blood flow to the respective tissues [44].

Dysfunctional microcirculation plays a crucial role in the development of microvascular complications of T2DM: nephropathy, retinopathy, and neuropathy. Hyperglycemia is the primary factor contributing to the microvascular pathology, but many additional risk factors have been identified. Even though numerous studies have addressed the molecular mechanisms leading to the changes in microcirculation observed in T2DM patients, these mechanisms are still not completely understood and require further research. Evidence indicates several pathways contributing to the microvascular disease: activation of the polyol pathway, generation of ROS and oxidative stress, production of AGEs, the hexosamine pathway, altered expression and action of growth factors, activation of the diacylglycerol/protein kinase C pathway, the microbiota-gut-retina axis, endothelial dysfunction, and IR [45]. On the other hand, there are protective mechanisms which can potentially be enhanced to reduce the risk of complications: increased glycolytic flux and mitochondrial function and the production of antioxidant enzymes, anti-inflammatory cytokines and factors, growth factors, and cytoprotective factors [46]. The relationship between macrovascular disease (such as coronary artery disease, stroke, and peripheral artery disease) and changes at the microvascular level is not well established, but there is evidence suggesting that microcirculation plays a significant role in the development of macroangiopathy in T2DM patients [47]. A recent study showed that T2DM patients with macrovascular complications have a higher risk of developing microvascular complications [48].

However, recent studies also suggest that microangiopathy affects less obvious organs, such as the brain (increasing the risk of stroke) and lungs (impairing respiratory function) [49]. In T2DM, mic-rovascular damage affects various organs, leading to significant pathological changes and clinical complications. In the brain, high blood sugar causes oxidative stress, inflammation, and endothelial dysfunction, reducing nitric oxide production. This results in a leaky blood–brain barrier, impaired astrocyte communication, pericyte loss, and increased vascular permeability. Clinically, T2DM increases the risk of lacunar strokes by 65%, cognitive decline by 25%, mild cognitive impairment by 34%, Alzheimer's disease by 43%, and vascular dementia by nearly 100%. Even prediabetes raises the risk of dementia and Alzheimer's disease by 18% and 36%, respectively. In the lungs, hyperglycemia induces microangiopathy and non-enzymatic glycosylation of connective tissues, leading to thickened alveolar epithelium, reduced pulmonary capillary blood volume, impaired vascular diffusion, and decreased lung elasticity. These changes contribute to lower forced vital capacity, forced expiratory volume in one second, and diffusing capacity for carbon monoxide and to higher risks of asthma, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary hypertension, pneumonia, tuberculosis, and respiratory complications from COVID-19 compared to non-diabetics [50].

Vascular complications associated with rheological disorders

Diabetic retinopathy (DR) is one of the most common microvascular complications of T2DM. It is considered to be a leading cause of blindness among individuals ranging from 20 to 74 years of age [51]. DR is classified into three main phases: diabetic macular edema, non--proliferative DR, and proliferative DR. While these are different stages, the underlying mechanism remains the same. It is considered to be a response of retinal blood vessels and erythrocytes to hyperglycemia [52]. Multiple metabolic pathways have been implicated in hyperglycemia-induced vascular damage, including the polyol pathway, AGE accumulation, the protein kinase C pathway, and the hexosamine pathway [53,54]. Moreover, there is a cell loss of pericytes and endothelial dysfunction. It is crucial to include the hemorheological changes that occur in T2DM. Diabetes often leads to increased blood viscosity, primarily due to higher levels of plasma proteins, such as fibrinogen and alpha-2-macroglobulin, as well as elevated levels of immunoglobulin M. Changes in the structure and function of erythrocytes resulting from alterations in membrane composition, oxidative stress, and glycation cause impaired deformability. Moreover, they are more susceptible to aggregation and the formation of clusters [45]. Bertram et al. [55] performed a study that included blood rheology parameters such as Hct, Pv, RBCa and RBC count in T2DM patients. They found that the values of Hct and red blood cell rigidity (RBCr) were similar to those in healthy subjects; however, Pv and RBCa were significantly higher, mainly due to fibrinogen and alpha-2-macroglobulin levels. Thus, they hypothesized that this may be one of the reasons for disrupted circulation. All the above-mentioned pathologies result in fragile capillaries, microaneurysms, small hemorrhages, cotton-wool spots, and capillary non-perfusion, ultimately leading to tissue ischemia and blindness.

Diabetic nephropathy (DN) is one of the most predominant consequences of uncompensated T2DM. It is known to occur in almost one third of diabetic patients and is closely related to diabetes morbidity, mainly due to its cardiovascular complications. In developed countries, DN accounts for approximately one third of new cases of dialysis-dependent kidney failure [56]. The main factors that account for DN progression are related to complications of long-term hyperglycemia, such as chronic inflammatory process, oxidative stress, and hemorheological alterations. These processes trigger glomerular hyperfiltration, hypertrophy, and – eventually – fibrosis and scarring of the renal parenchyma, subsequently leading to end--stage renal failure. The principal mechanisms are the generation of AGEs, the activation of protein kinase C, and the overexpression of the renin-angiotensin-aldo-

sterone system. Inflammatory cascades play a pivotal role, notably those involving cytokines such as transforming growth factor β and nuclear factor kappa B [57], leading to changes in blood rheology expressed by such parameters as Hct, Pv, RBCa, and RBCr. Zimmermann et al. [58] conducted a study that involved, among other factors, blood rheology parameters in assessing the risk of cardiovascular mortality in patients suffering from DN. They concluded that patients with a greater risk of cardiovascular incidents had significantly higher Pv, RBCa, and RBCr. Furthermore, in diabetic patients, the rate of progression of renal failure showed weak – but statistically significant – correlations with Pv, plasma fibrinogen, C-reactive protein, and proteinuria. Both Pv and plasma fibrinogen have been shown to correlate significantly with proteinuria. However, authors point out that these changes may reflect the higher level of acute phase proteins and it is yet to be determined whether it is the cause or the effect of renal failure [59]. On the other hand, some hemorheological parameters have been shown to play a potential role in the progression of DN. For instance, in multiple regression analysis, the ratio of fibrinogen×erythrocyte sedimentation rate to elongation index was identified as an independent predictor of the urinary albumin to creatinine ratio and progression of microalbuminuria [60]. Another potential clinical tool seems to be erythrocyte deformability, measured with a microfluidic ektacytometer and expressed as elongation index (EI). EI has been shown to correlate well with the levels of glycated hemoglobin and creatinine and the progression of renal failure. Additionally, EI corresponds to the changes induced by microangiopathy despite blood glucose and glycated hemoglobin being maintained by drug therapy [61]. More research is needed; exploring hemorheological changes may bring further diagnostics and curative opportunities [62].

Another complication of T2DM is peripheral neuropathy, which results from the progressive destruction of vessels that supply the peripheral nerves. Common symptoms include paresthesia in the hands and feet, painful muscle contractions, sensory deficits, and autonomic nervous system impairments such as tachycardia, orthostatic hypotension, and gastrointestinal motility disorders. Although it has been considered a more advanced stage of T2DM, in one study, no specific blood rheological variables were confirmed in patients with DN compared to T2DM patients with no peripheral neurologic disorders [63]. Patients with T2DM demonstrated a loss of the vasoconstriction reflex (studied indirectly by measuring transcutaneous oxygen tension on the foot in different body positions at 44 °C), probably as a result of sympathetic neuron damage [64]. For this reason, it is believed that increased hydrostatic pressure, especially in combination with other adverse blood rheological changes in the course of DM2, poses a serious risk of developing limb ischemia and foot ulceration [64].

In developed countries, coronary artery disease (CAD) and stroke are predominant causes of death. Both of these conditions are macroangiopathies associated with chronic processes that damage vessel walls: hyperglycemia, hyperlipidemia, or oxidative stress, for instance. These risk factors promote the development of atherosclerosis in crucial organ-perfusing arteries. Thrombosis on exposed collagen fibers from ruptured atherosclerotic plaque is the most common cause of fatal cardiovascular events. Myocardial infarction in most cases is a life-threatening manifestation of CAD, in the course of which cardiomyocyte necrosis progresses rapidly. Importantly, myocardial cell necrosis can not only occur during critical occlusion of one of the major coronary arteries, but can also be associated with serious dysfunction at the microvascular level. These phenomena are caused by increased blood viscosity and aggregation combined with RBC deformability [65]. Recent studies revealed a significant correlation between rheological disorders and CAD progression while indicating the substantial role of lower RBC deformability [66,67]. The increased morbidity of diabetic patients with CAD may be correlated with erythrocyte membrane impairment in the course of T2DM [66]. Blood rheological factors are also essential in microvascular blood flow and oxygen delivery to tissues in ischemic stroke [68]. Increased Pv, higher erythrocyte aggregation, and reduced erythrocyte deformability have been noted and laser doppler flowmetry has confirmed tissue hypoxia in stroke patients [68]. Moreover, the prognostic utility of blood rheological properties in stroke patients has been demonstrated in prospective studies [69]. Laboratory tests in patients who suffered a second stroke within 2 years revealed elevated blood viscosity, RBCa, plasma and serum viscosity, cholesterol, and fibrinogen levels [69].

Another significant complication in diabetics may be diabetic foot syndrome, which is due to impaired microcirculation. Impaired blood flow in the capillaries may lead to the development of ulcers, wounds that are difficult to heal, and limb amputation [70,71]. The passage of time, influencing the progression of the disease, increases the risk of developing skin and subcutaneous lesions, which can lead to infection and even gangrene [72].

Therapeutic and preventive options associated with blood rheology

Therapeutic and preventive strategies targeting blood rheology are crucial in managing cardiovascular and metabolic disorders. Elevated blood viscosity and impaired erythrocyte deformability can hinder microcirculation and oxygen delivery, contributing to disease progression. Effective glycemic control is paramount, as hyperglycemia increases Pv and promotes erythrocyte aggregation, exacerbating vascular complications. Conversely, hypoglycemia can induce

a prothrombotic state, enhancing platelet aggregation and fibrin formation and thereby adversely affecting blood flow properties [73,74,75].

Lipid-lowering therapies, particularly statins, have demonstrated benefits beyond reducing cholesterol. Pravastatin and simvastatin have been demonstrated to reduce plasma fibrinogen levels and improve blood rheology in patients with type II hyperlipoproteinemia. Similarly, lovastatin therapy in hypercholesterolemic patients resulted in improved RBC morphology and reduced whole blood filtration time, indicating enhanced hemorheologic properties [74,76,77,78,79,80].

Pentoxifylline, a hemorheologic agent, has been effective in diabetic patients with angiopathic complications. Long-term administration led to significant reductions in blood and Pv, fibrinogen levels, and erythrocyte aggregation, while increasing erythrocyte filterability – independent of glycemic control [81,82,83].

Additionally, extracorporeal therapies such as LDL apheresis have shown immediate improvements in blood rheology by reducing plasma fibrinogen concentrations, Pv, and whole blood viscosity in patients with familial hypercholesterolemia [73,77]. The HELP method (heparin-induced extracorporeal LDL precipitation) improves the endothelial response to vasodilators and inhibits coagulation due to the removal of cholesterol [71,84,85].

CONCLUSIONS

Key hemorheological parameters significantly affected in diabetes include increased Pv, elevated fibrinogen levels, RBCa, and reduced erythrocyte deformability. These changes impair microcirculation, contributing to tissue hypoxia and the development of diabetic complications such as retinopathy, nephropathy, and stroke. Pv and RBCa in particular show strong potential as diagnostic indicators of circulatory dysfunction in diabetic patients. Monitoring these parameters may help assess the risk and progression of vascular complications, supporting the role of hemorheology in clinical practice. Maintaining optimal glycemic and lipid levels, along with pharmacological interventions such as statins and pentoxifylline and extracorporeal therapies, are significant elements of improving blood rheology, thereby potentially reducing the risk of vascular complications.

Authors' contribution

Study design – M. Radke, A. Marcinkowska-Gapińska, A. Kutaj, K. Brzezińska, M. Kmiecik, M. Nowak, W. Firlej, K. Sobczyk, M. Fiutak, M. Mińkowski

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