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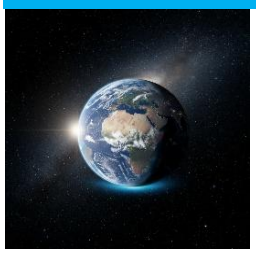

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Type 2 Diabetes — A Disease of Small Vessels: Clinical Perspectives on Microangiopathy

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Abstract

Introduction and purpose:

Type 2 diabetes mellitus (T2DM) is a major cause of microangiopathy, leading to structural and functional impairment of microcirculation. Diabetic microvascular dysfunction underlies key chronic complications, including retinopathy, nephropathy, neuropathy, and cardiomyopathy. The aim of this study was to summarize the pathophysiological mechanisms of diabetic microangiopathy and review current diagnostic methods for microcirculation assessment in T2DM.

Review methods:

A narrative review of the literature was conducted using PubMed and Google Scholar. Peer-reviewed studies published between 2000 and 2025 addressing microvascular complications of T2DM and diagnostic techniques for evaluating microcirculation were analyzed.

State of knowledge:

Chronic hyperglycemia induces endothelial dysfunction, basement membrane thickening, increased vascular permeability, and impaired tissue perfusion. These alterations contribute to progressive organ damage, often asymptomatic in early stages. Diagnostic tools range from classical methods such as fundus examination and fluorescein angiography to advanced non-invasive techniques including optical coherence tomography angiography (OCT-A), laser Doppler flowmetry (LDF), capillaroscopy, near-infrared spectroscopy (NIRS), and perfusion MRI.

Summary:

Early identification of microcirculatory disorders in T2DM is essential to prevent irreversible complications. The development of modern, predominantly non-invasive diagnostic methods increases the potential for earlier detection and improved clinical management.

Key words:

type 2 diabetes mellitus; microangiopathy; microcirculation; diabetic complications; diagnostic methods

Importance of microcirculation in human physiology

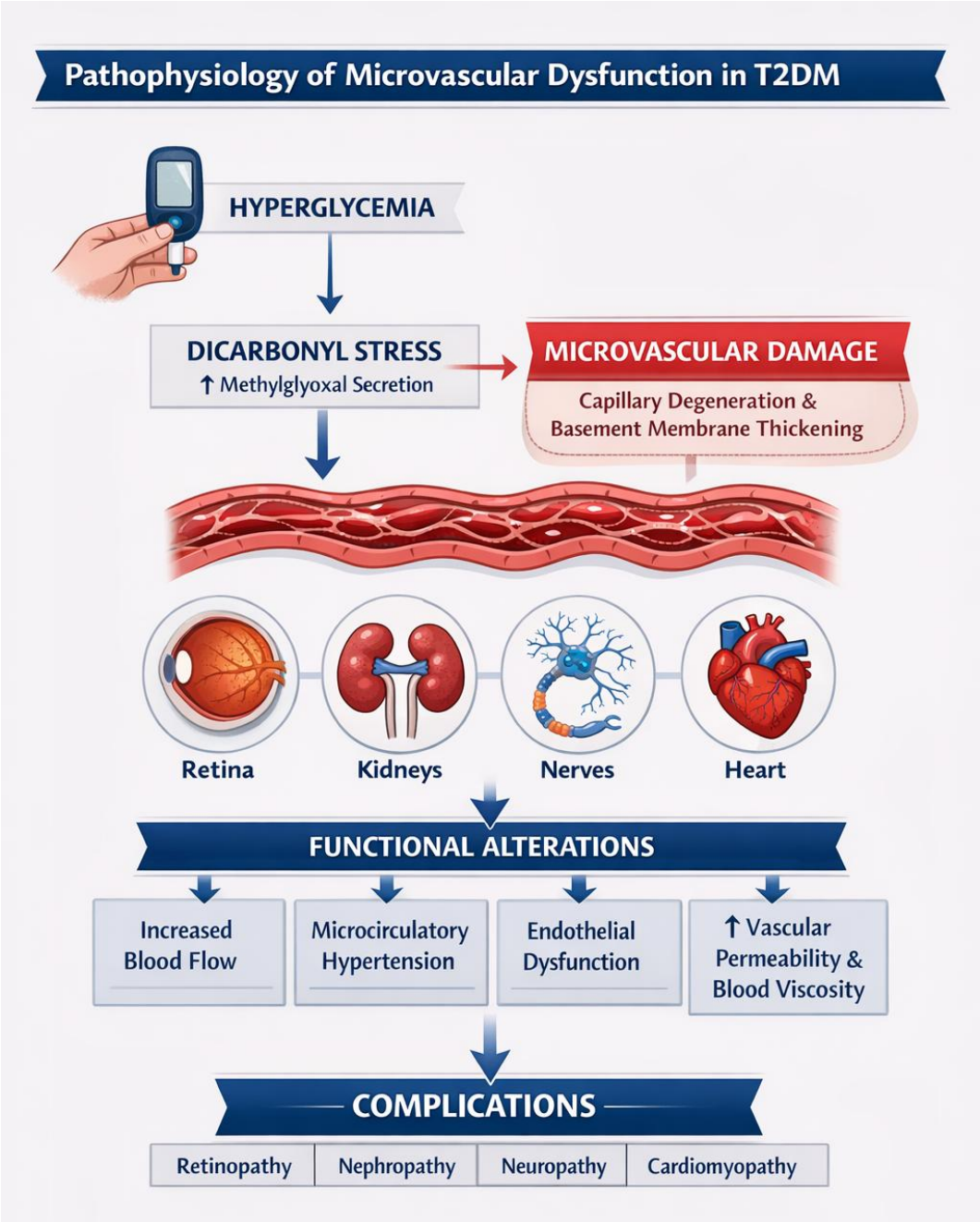
Microcirculation disorders, described as microangiopathies, caused by pathological changes are complications of numerous disease entities such as type 2 diabetes (T2D). Due to the prevalence of T2D it is a leading cause of above-mentioned microangiopathies. As a result, World Health Organisation assumpted T2D the first non-infectious epidemy. [1]

Microcirculation vessels for an adult make up to 99% of all the blood vessels, which is the quantity of around 10^11 in numbers. The units of microcirculation consist of arterioles, metarterioles, capillaries, veinlets, arteriovenous anastomoses, lymph vessels and precapillary sphincters. Classification depends either on the size or the physiological role. According to the first criteria, vessels of up to 150pm diameter are classified as microcirculation vessels. According to the second criteria we can classify vessels to the microcirculation if an increase of the blood pressure causes their constriction. [2]

Pathophysiology of Microvascular Dysfunction in T2DM

Microangiopathies were categorised as diabetic complications in the literature long ago with the negative consequences for cellular function, blood flow or intracellular homeostasis. Diversity and intensity of those pathologies is related to the stage of T2D, precisely to the ratio of variable progression pace and different adaptation of tissues and organs to progressive changes. Diabetic changes per se are an effect of individual factors causing a microangiopathy. [3] Slow progression of those changes results in asymptomatic complications, hence early prevention and diagnosis play a key role.

Hyperglycemia damages intraepithelial cells by dicarbonyl stress, which leads to increased methylglyoxal secretion, which might be a major pathway that harms the microcirculation vessels [4]. The diabetic microangiopathy results in capillary degeneration, especially in retina, kidneys, neurons and heart leading to serious malfunctions based on basement membrane thickening. Consequently, functional alterations occur such as increase of local blood flow, hypertension of the microcirculation, endothelium impairment, increase of vascular permeability and increase of blood viscosity [5].



Microcirculation and Diabetic Complications

To microvascular dysfunction (MVD) emerging in T2D we classify diabetic retinopathy (DRP), diabetic nephropathy (DNP), diabetic neuropathy (DNR) and cardiomyopathy (CMP). Common complications are diabetic foot syndrome (DFS) and erectile dysfunction (ED).

Diabetic retinopathy is considered the most common diabetic microangiopathy. It is divided into two stages: 1) non-proliferative diabetic retinopathy (NPDR), that is an early stage , during which we observe increase of vascular permeability and capillaries occlusion; 2) proliferative diabetic retinopathy (PDR), the most advanced stage, characterised by neovascularisation, microaneurysms and haemorrhages, causing vitreous haemorrhages and retinal detachment, and eventually serious visual disturbances [6].

Approximately one fourth patients with T2D suffers from retinopathy [7]. United Kingdom Prospective Study (UKPDS) estimated 40% of patients with newly diagnosed T2D have retinopathy, which may indicate that the onset of this complication starts relatively late [8].

Vision loss is the most severe repercussion of retinopathy, usually caused by diabetic macular edema (DME). Macula is the central part of the retina, with the highest receptor density, thus its defects result in vision impairment. Blood retinal barrier (BRB) damage occurring in the retinopathy leads to oedema and thickening of macula, with excessive fluid accumulation, described as the mechanism of DME. DME may start in any stadium of DR, causing image distortion and decreased visual acuity [9]. Diabetic complications related to eyes can as well lead to cataract and glaucoma, which may also contribute to vision loss [10].

The most important risk factors of DR include persistence of T2D, poor glycemic control (high HbA1c level) and comorbid hypertension. Among other retinopathy risk factors are nephropathy, dyslipidemy, tobacco smoking and high body mass index. DR onset is also more likely during gestation and lack of physical activity [11]. Retinopathy diagnosis is based on clinical outcomes of microangiopathy of retinal vessels [9].

We distinguish diabetic nephropathy as another form of diabetic microangiopathy. It develops in the process of hyperglycemia and concomitant arterial hypertension, which lead to glomerular hyperfiltration and secondary cardiac hyperfiltration. It is a result of pathophysiological changes in the microvessels, such as basement membrane thickening, atrophic changes, interstitial fibrosis, and atherosclerotic lesions [9]. It manifests clinically by the presence of >500 mg proteinuria in 24-hour urine collection, preceded by microalbuminuria in the early stages . Microalbuminuria itself presents in the excretion of 30-300 mg of albumin in 24-hour urine collection with typical values of 2.5-30 mg/mmol in men and 3.5-30 mg/mmol in women. Values below the detection threshold indicate early onset of diabetic nephropathy [13]. There is no known protective mechanism that prevents patients with poor glycemic control who do not suffer from kidney disease, including nephropathy [8]. This does not change the

fact that nephropathy belongs to the main characteristic circle of type 2, leading to end-stage disease, a major cause of death worldwide [9].

Epidemiological studies indicate that diabetic nephropathy occurs in 30% of patients in Europe and 50% in the USA receiving renal replacement therapy. The percentage of diabetic patients who develop microalbuminuria after 20 years of diabetes is 10–30%. In patients with type 2 diabetes, the rate of diabetic nephropathy is 15–20%. The risk of developing renal failure is significantly higher than in people with other conditions [13].

Serious health consequences are also associated with diabetic neuropathy. In general, it is characterized by the presence of nerve dysfunction in patients with diabetes after excluding other causes [14]. It is the most common and incurable microvascular complication of diabetes [15]. The risk of neuropathy increases along with the duration of diabetes. It causes insufficient blood flow in microvessels due to microcirculation disorders, with peripheral nerves being particularly sensitive to ischemia. Phenomena such as abnormal phosphorylation lead to pathologies in nociceptive nerve fibers, leading to pain in the areas where these abnormalities occur [16]. The most common symptoms of diabetic neuropathy experienced by patients include: numbness, tingling, pain, and/or weakness beginning in the distal parts of the lower limbs, intermittent or continuous paresthesia described by patients as a sudden and transient burning sensation, a ‘’feeling of pins and needles”, a sensation of electric shock and pain in response to cold [9].

It should be noted that diabetic neuropathy is detected relatively rarely, as approximately 50% of cases are asymptomatic or present nonspecific symptoms. Therefore, progressive diagnostic activity is essential to detect it as early as possible, initiate treatment, and avoid its most serious health consequences [17]. Diabetic foot is a particular example. It is defined as infection, ulceration, or destruction of foot tissue in a person diagnosed with diabetes, associated with neuropathy developing in the lower limb [18]. The most important risk factors for diabetic foot include: patient age, previous ulcers, and diabetic sensorimotor polyneuropathy [18].

The onset process and location of the nerves affected by diabetic changes determine different types of neuropathy and contribute to its development. The pathological basis underlying this condition is essential to understanding the clinical management of this complex disorder [19]. However, it is important to note that the pathogenetic mechanism underlying diabetic neuropathy is still not fully described. Nevertheless, early diagnosis and appropriate treatment of diabetic neuropathy can significantly alleviate its consequences and improve patients' life

quality [20]. It is worth noting that early detection may reverse the toxic effects of hyperglycemia on nerve fibers. This is a significant argument in favor of diagnostic activity aimed at early detection of neuropathy, particularly for sensorimotor disorders and symptoms of autonomic dysfunction [18].

In the discussed issue, it is also necessary to address diabetic cardiopathy. Until recently, its inclusion in the group of diabetic microangiopathy was controversial. Recent studies provide increasing evidence that microcirculation disorders in the myocardium and coronary system are a consequence of developing diabetes, provided there are no other factors of these disorders. The American College of Cardiology Foundation, the American Heart Association (ACC/AHA), and the European Society of Cardiology (ESC), in collaboration with the European Association for Cardiology (EASD), have defined diabetic cardiomyopathy as a clinical condition of ventricular dysfunction that occurs in the absence of coronary atherosclerosis and hypertension in patients with diabetes [21]. The premise supporting the statement of diabetic cardiopathy is that its incidence is correlated with the increase in the incidence of diabetes [22]. It is confirmed by the results of epidemiological studies [23].

Cardiopathy initially can be asymptomatic, which, similarly to neuropathy, is an indication for proactive diagnostic intervention. In its early stages, cardiopathy leads to subjectively imperceptible structural and functional changes in the myocardium, including left ventricular hypertrophy, fibrosis, and impaired cell signaling. As diabetes progresses, these changes evolve toward clinically symptomatic diastolic dysfunction, then systolic dysfunction, and ultimately heart failure [23].

Diabetic cardiopathy causes diagnostic challenges not only because of its asymptomatic nature in the initial stages, but also because its pathogenetic mechanism is still not fully understood. This results in the imperfection of diagnostic tools. Furthermore, there are no clinical studies that unequivocally confirm that hyperglycemia or hyperinsulinemia independently increase the risk of developing diabetic cardiomyopathy [23]. This does not change the fact that there is growing evidence supporting this assumption, especially in cases of cardiopathy that occur despite the absence of other causes.

	Type of Microangiopathy	Localization	Clinical Symptoms	Complications	Prevalence	Pathogenesis Mechanism	Diagnostic Methods
1	Retinopathy (DRP)	Retina	Visual disturbances, DME	Blindness, cataract, glaucoma	25-40% of patients with T2DM	Blood-retina barrier damage, neovascularization	OCT-A, FA, eye fundus examination
2	Nephropathy (DNP)	Renal glomeruli	Proteinuria, hypertension	End-stage renal disease	15-20% of patients with T2DM	Glomerular basement membrane thickening, microalbuminuria	Albuminuria, eGFR, biopsy (rarely)
3	Neuropathy (DNR)	Peripheral nerves	Numbness, paresthesia, neuropathic pain	Diabetic foot, amputations	>50%, often asymptomatic	Nerve ischemia, oxidative stress, conduction disturbances	Nerve conduction studies, symptom assessment, neuropathy scales
4	Cardiomyopathy (CMP)	Myocardium	Dyspnea, fatigue, edema (late symptoms)	Heart failure, cardiac deaths	Hard to estimate, increasing data	Myocardial fibrosis, impaired signaling	Echocardiography, cardiac MRI, cardiac biomarkers
5	Muscle Infarction (DMI)	Skeletal muscles	Muscle pain, swelling, restricted movement	Muscle necrosis, diagnostic difficulties	Very rare	Local necrosis due to microvascular ischemia	MRI, muscle ultrasound, perfusion studies

Table 1: Forms of Diabetic Microangiopathy

Diagnostic Methods for Assessing Microcirculation

It is crucial to use and develop methods that detect pathological diabetic changes before the patient begins to experience them, but more importantly, when the detection of these changes still allows to treat these complications effectively with appropriate management. The key is

to use these methods to gain critical insight into the early stages of microcirculation disorders in T2DM [24]. Methods and techniques for early detection of microcirculation disorders allow for the identification of early microcirculation disorders in patients with T2DM, even at the stage of possible reversibility of the resulting changes [25]. This paper discusses both older methods of microcirculation assessment, still used in clinical practice, and newer methods based on advanced diagnostic technologies. These methods are based on various physical phenomena, such as optical phenomena, ultrasound, and the Doppler effect.

Non-invasiveness is a significant advantage of currently used microcirculation assessment methods for diagnosing diabetic pathological changes in T2DM, despite these methods' drawbacks and limitations. They are used to assess microcirculation in terms of the risk of specific diabetic complications in T2DM, such as retinopathy, neuropathy, nephropathy, cardiomyopathy, and diabetic muscle infarction (DMI).

One of the most common complications of T2DM is diabetic retinopathy, which is indicated by impaired retinal microcirculation. A number of methods are used to assess retinal microcirculation, both older and newer, based on the capabilities of modern technologies. Fundus examination using an ophthalmoscope (slit lamp) is one of the most common methods. It allows for the detection of varying degrees of arteriolar narrowing and changes in arteriolar reflexes. Glaucoma is a contraindication for slit lamp use, which should be noted, as it is one of the complications occurring in the diabetic retinopathy [26].

A more advanced method for assessing retinal microvessels is fluorescein retinal angiography (FA). This involves intravenous administration of a dye followed by a series of photographs of the anterior or posterior segment of the eye. However, its invasiveness remains a significant limitation. This means that its use requires the patient's written consent. Despite this, this method was considered a breakthrough in retinal examination. Since the 1970s, a variant of FA, known as indocyanine green angiography (ICGA), has been introduced into ophthalmological practice, due to the use of indocyanine green as a dye [27]. A significant limitation of FA use, in addition to its invasiveness, is its contraindication for patients with a documented allergic reaction to fluorescein, patients with a multifactorial allergic history, and gestation [28].

Microvessel assessment in the diagnosis of diabetic changes related to T2DM is also performed for the skin. This allows to determine the pathogenesis of the relatively rare, however increasingly common diabetic myocardial infarction (DMI). It is assumed that it occurs due to impaired local muscle perfusion [29] . Available classic, yet non-invasive, methods for

assessing microcirculation in skin tissues include: 1) capillaroscopy – a method of analyzing capillary morphology and microcirculation in real time in a microscopic image, performed within the nail folds of the fingers and toes. It is sensitive and repeatable, but has the disadvantage of insufficient penetration depth; 2) videocapillaroscopy – a type of capillaroscopy in which the assessment of microcirculation is performed using a moving head equipped with a light source and a camera, allowing the visualization of microcirculation, mainly of the nail fold (although it can be used in any area of the body, also for mucous membranes) in real time [30].

Optical coherence tomography angiography (OCT-A) is the most common method for assessing retinal microvessels, which enables non-invasive examination in the macular area. The decline in the use of FA is partly due to the wrong assumption that OCT-A can replace this invasive procedure [29]. In the examination of retinal microvessels diagnosing retinopathy, FA has the advantage of being reusable, unlike OCT-A, which is currently the "gold standard" for patients with T2DM. The main advantages of OCT-A include its non-invasive nature and high resolution, which translates into accuracy in imaging the microvessels and microvascular network. This allows it to detect even minor abnormalities and irregularities within them, something that FA cannot provide [30]. OCT-A is considered a very useful method in assessing the microvasculature of patients with T2DM, mainly because of the overall image of the retinal microvascular network can be used to "numerically describe the severity of vascular abnormalities," which allows for the conclusion that "they are significantly smaller in patients with diabetes, both in the superficial and deep layers of the retina" [31]. In this way we can assess whether the obtained abnormalities are an effect of diabetic changes or other causes.

In clinical practice, the most widespread and highly regarded diagnostic methods are those based on the Doppler effect. One of the first non-invasive methods for assessing microcirculation was laser Doppler flowmetry (LDF). It "assesses erythrocyte flow by assessing the reflection of red blood cells flowing in a vessel relative to a stationary surface" [27]. As the light wave penetrates the examined tissue, it interacts with statistical elements and moving blood cells, resulting in an image of the microcirculation [26]. Technically, LDF helps evaluate blood flow in the microcirculation in real time using a laser beam emitted by a Doppler probe applied to the skin surface [31].

LDF is used in the skin and oral cavity [26]. It also examines the blood supply to damaged organs, providing data that allows us to determine a coefficient expressing the ratio of vessel

wall thickness to the diameter of its lumen. In more advanced cases, LDF is combined with OCT, using a non-contact device. This primarily aims to assess the total velocity of blood cells flowing through the microcirculation [27]. The main advantages of LFD include its ease of use, the ability to be performed by a person without advanced training and the short measurement time. A disadvantage is that pigmentation can alter the penetration depth of the light beam and alter the analysis of the penetration. Furthermore, the measurement is limited only to a small area [26].

Other modern, non-invasive techniques include magnetic resonance imaging (MRI) – a method based on the phenomenon of nuclear magnetic resonance (NMR), which can be supported by the administration of a contrast agent, allowing a more accurate image of the microcirculation in the examined skin tissues. Another method is near infrared spectroscopy (NIS), which uses infrared light that is partially absorbed and partially scattered during the examination, e.g., hemoglobin, myoglobin. NIS is distinguished into non-absorptive (monitoring the velocity of blood flow in the microcirculation) and non-absorptive (determining the degree of oxygenation and nourishment of tissues in the examined area of microcirculation). In addition to the methods described above, many other methods deserve consideration, such as tissue reflectance spectrophotometry (TRS), photoplethysmography, venous occlusion plethysmography (VOP), and orthogonal spectral polarization (OSP) [30].

Diagnostic method	Area of application	Principle of operation	Clinical use	Disadvantages/limitations
OCT-A (optical coherence tomography angiography)	Retina	Non-contrast vessel imaging	Diagnosis of diabetic retinopathy	Does not show leakage, limited imaging depth
FA (fluorescein angiography)	Retina	Fluorescein injection, flow imaging	Gold standard for DRP	Invasive, risk of allergic reaction

Capillaroscopy	Nail dermis, mucosa	Visual assessment of capillaries	Evaluation of microcirculation morphology	Superficial, difficult to standardize
LDF (laser Doppler flowmetry)	Skin, oral cavity	Flow registration based on light reflection	Assessment of perfusion disorders, diabetic foot	Limited range, variability
NIRS	Muscles, skin	Tissue oxygenation measurement	Perfusion assessment (e.g., muscles in DMI)	Sensitive to external interference
Perfusion MRI	Heart, kidneys, brain, muscles	Imaging of contrast distribution over time	Cardiomyopathy, nephropathy, DMI	High cost, limited availability
Doppler ultrasonography of microcirculation	Skin, extremities	Flow in small-caliber vessels	Diagnosis of skin disorders, DMI	Low sensitivity in deep tissue layers

Table 2: Microcirculation Diagnostic Methods

Conclusions

To summarize the above, it can be concluded that diabetic changes in microcirculation take the form of microangiopathy, which means they can potentially affect 99% of all blood vessels in an adult. It is a complication of type 2 diabetes, leading to changes in microvessels that are often asymptomatic, making early detection difficult, and therefore restricting the implementation of timely and effective treatment.

From the clinical point of view, but also from the point of view of the patient's well-being, two factors are important in the use of microcirculation assessment methods: non-invasiveness and the possibility of early detection of pathological changes in the microcirculation, preferably in the phase when they are still reversible.
Methods for assessing microcirculation for patients with T2DM are becoming more and more technologically advanced, which primarily allows to increase the possibility of early diagnosis of complications.

Disclosure

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Not applicable

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Declaration of the Use of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the author(s) used ChatGPT 5.2 for the purpose of stylistic review. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the substantive content of the publication.

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