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Research Article

# Rationale for Enhancing Micro and Macrocirculation in the Lower Limbs of Patients with Arterial Insufficiency and Type 2 Diabetes Mellitus

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## Abstract

Diabetic angiopathy of the lower limbs is a serious complication of diabetes mellitus, characterized by damage to both micro- and macrovasculature, caused by prolonged hyperglycemia. This condition leads to limb amputation and significantly worsens the quality of life of patients. Optimizing therapy requires a comprehensive approach, correcting blood glucose levels, addressing vascular disorders, and improving blood rheology.

The main pathophysiological mechanism is impaired micro- and macrocirculation due to prolonged hyperglycemia, which contributes to the progression of atherosclerosis and diabetic angiopathy. Correcting blood flow and revascularization is key to reducing ischemia and improving treatment outcomes.

The primary cause of vascular damage in patients with diabetes mellitus (DM) is occlusive processes, which lead to critical ischemia and the development of necrotic complications. In this context, improving both micro- and macrocirculation in the lower limbs is a vital treatment goal to prevent amputations. Studies confirm that timely revascularization, including surgical and endovascular methods, combined with modern cellular therapy and pharmacological support, significantly reduces amputation rates and improves patient survival.

**Keywords:** Low Molecular Weight Heparins (LMWH); Diabetic Micro- and Macroangiopathy; Atomic Force Microscopy (AFM); Type 2 Diabetes Mellitus (T2DM); Blood Rheology; Sulodexide; Thermographic Examination; Erythrocyte Rigidity

## Low-molecular-weight heparins (LMWH) in the treatment of diabetic angiopathy

Low-molecular-weight heparins (LMWH) play a crucial role in the treatment of patients with diabetic angiopathy due to their ability to inhibit thrombus formation. LMWH offer advantages over unfractionated heparin, including higher bioavailability with subcutaneous administration, a longer duration of action, and a lower risk of thrombocytopenia. They are also more convenient to use, allowing therapy to be conducted with minimal laboratory monitoring.

## Mechanism of action and advantages of LMWH

LMWH inhibits factor Xa, providing a prolonged antithrombotic effect without significantly affecting standard coagulation tests, such as activated partial thromboplastin time (aPTT). This reduces the need for daily monitoring of coagulation parameters, which is convenient for patients with diabetic angiopathy. Additionally, LMWH possesses strong anti-inflammatory properties, reducing neutrophil activation and inhibiting oxidative stress, which helps protect the vascular endothelium.

It is important to note, however, that LMWH is not interchangeable. In our practice, we prefer enoxaparin (Clexane).

### Antithrombotic and lipid-lowering effects of LMWH

LMWH also improves lipid metabolism by activating lipoprotein lipase, which promotes the breakdown of triglycerides into free fatty acids and enhances the rheological properties of blood. This is especially important for patients with diabetic microangiopathy, who often experience impaired blood rheology.

### Sulodexide as a promising agent for the treatment of diabetic angiopathy

Sulodexide is a drug from the heparinoid group known for its ability to improve microcirculation and protect the vascular endothelium. The drug consists of two fractions of glycosaminoglycans: one is similar to LMWH and performs an antithrombotic function by inactivating factor Xa and thrombin, while the other is represented by dermatan, which blocks activated proteases.

### Mechanism of action and advantages of sulodexide

Sulodexide has the ability to stimulate the release of prostacyclin from the vascular endothelium, which prevents platelet adhesion and aggregation, reducing the likelihood of thrombosis. Additionally, sulodexide enhances the synthesis of cyclic adenosine monophosphate (cAMP) in platelets through the activation of nitric oxide, further reducing thrombus formation.

According to a study by Belcaro G. [1], sulodexide significantly improves microcirculation in patients with chronic vascular diseases associated with diabetes. Its ability to reduce the activity of tissue plasminogen activator inhibitor (tPA) promotes fibrinolysis activation, preventing thrombus formation in the microcirculatory system.

In the work of Viganò M. [2], sulodexide was shown to restore the endothelial barrier function, increase the negative charge of endothelial cells, and reduce their permeability to low-density lipoproteins (LDL). This helps reduce the formation of atherosclerotic plaques and the proliferation of smooth muscle cells.

### Clinical use of sulodexide

In our practice and studies involving patients with type 2 diabetes, it has been observed that the use of sulodexide leads to a significant reduction in erythrocyte rigidity, which positively affects blood rheology. This is particularly important for the prevention of thrombosis following surgical interventions in such patients, where the risk of thrombus formation is elevated.

In our practice, we have administered sulodexide to patients with type 2 diabetes and microangiopathy. The results showed a significant improvement in microcirculation and a reduction in erythrocyte rigidity.

In a study conducted at our clinic, it was found that sulodexide use reduced erythrocyte rigidity by 20-25%, which improved blood rheology and decreased the risk of thrombosis. This effect is especially important after surgical interventions in patients with type 2 diabetes, where the risk of thrombosis is high.

"It is worth noting that controlling glycemia levels (glycosylated hemoglobin HbA1c) at ≤7% plays a crucial role in the treatment of patients with diabetes and significantly impacts therapeutic outcomes (Smith., *et al*. 2015; American Diabetes Association, 2020). Studies have shown that maintaining HbA1c at ≤7% significantly reduces the risk of vascular complications and improves patient prognosis (Johnson., *et al*. 2018).

Below, we present the case of a patient. In this study, erythrocyte rigidity was analyzed in a patient with type 2 diabetes, who was diagnosed with diabetes 15 years ago. Additionally, thermographic examination was conducted before and after treatment using cell therapy, sulodexide, and LMWH.

### Objective of the study

The study aimed to assess changes in erythrocyte rigidity and the thermographic microcirculation profile in a patient with type 2 diabetes before and after treatment with cell therapy, sulodexide, and LMWH.

Moreover, these patients underwent various types of revascularization procedures on the arteries of the lower extremities, including bypass surgery and endovascular interventions, such as angioplasty and stenting of the lower limb arteries. The choice of surgical revascularization procedures was based on the classification referring to TASC II. According to Fontaine's classification, the severity of lower limb arterial insufficiency in these patients ranged from stage 2 to 4.

## Methods

- Erythrocyte rigidity was measured using Atomic Force Microscopy (AFM) techniques. The assessment of rigidity allowed for determining the changes in erythrocyte deformability in the context of insulin resistance, which is characteristic of type 2 diabetes.

- Thermographic examination was conducted before and after treatment to visualize changes in microcirculation and peripheral blood flow, particularly in the lower extremities. The thermal camera captured skin temperature distribution, reflecting tissue blood supply.

- **Treatment:** The patient was prescribed a course of cell therapy aimed at regenerating the vascular walls and improving endothelial function. Simultaneously, the patient received sulodexide—a drug that improves blood rheology, reduces its viscosity, and restores vascular wall function—as well as LMWH.

According to TASC II and the American Diabetes Association (ADA), restoring arterial blood flow and stimulating vascular wall regeneration are essential components of treating patients with diabetes. Cell therapy plays a particularly important role in this process, as it has the potential to stimulate angiogenesis and improve microcirculation, as evidenced by studies conducted by Ferraresi., *et al*. (2020).

## Results

- **Erythrocyte rigidity before treatment:** The patient exhibited a significant increase in erythrocyte rigidity prior to treatment, indicating a decreased ability to deform. These changes contributed to the deterioration of microcirculation, particularly in the distal regions, which is characteristic of patients with diabetes who are at high risk of developing angiopathies.

- **Erythrocyte rigidity after treatment:** Following the course of cell therapy and treatment with sulodexide and LMWH, a reduction in erythrocyte rigidity was observed, indicating a positive therapeutic effect on microcirculation.

- **Thermographic examination before treatment:** Prior to the initiation of therapy, thermographic examination revealed areas of reduced temperature, suggesting decreased blood flow and potential microcirculatory disturbances. This was particularly pronounced in the lower extremities, especially below the knee joint (Figure 1.A).

- **Thermographic examination after treatment:** After completing the treatment course, thermographic examination demonstrated improved thermography: skin temperature in the distal areas increased, indicating enhanced microcirculation and blood flow (Figure 1.B).

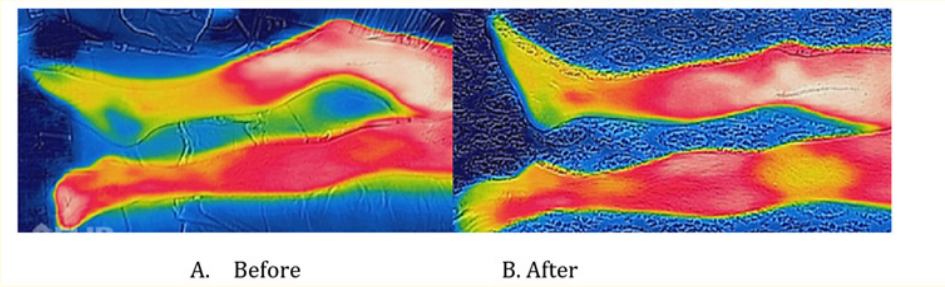


**Figure 1:** Thermographic clinical assessment of microcirculation disturbances in a patient with diabetes: photo (1.A) - before treatment, photo (1.B) - after 3 months of treatment with cell therapy, sulodexide, and LMWH.

The measurement of erythrocyte rigidity was performed using Atomic Force Microscopy (AFM) techniques. The assessment of rigidity allowed for determining how erythrocyte deformability changes in the context of insulin resistance, which is characteristic of type 2 diabetes (Figures 2, 3, 4).

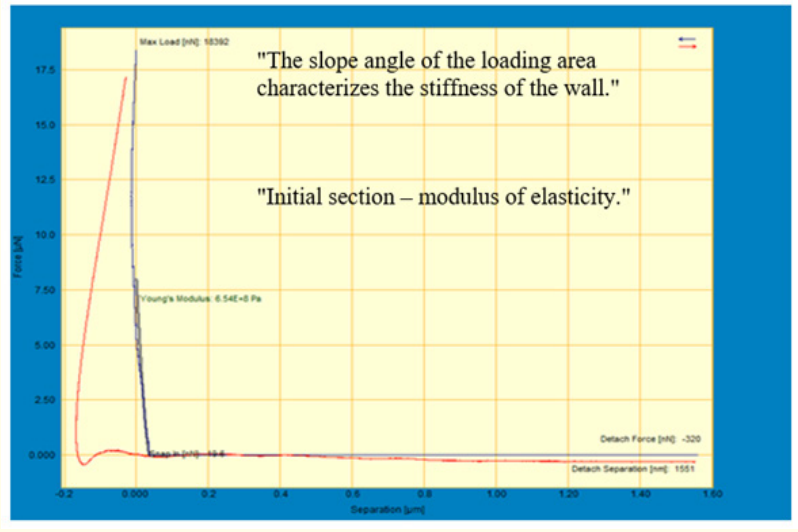


**Figure 2:** Example of force curve analysis.

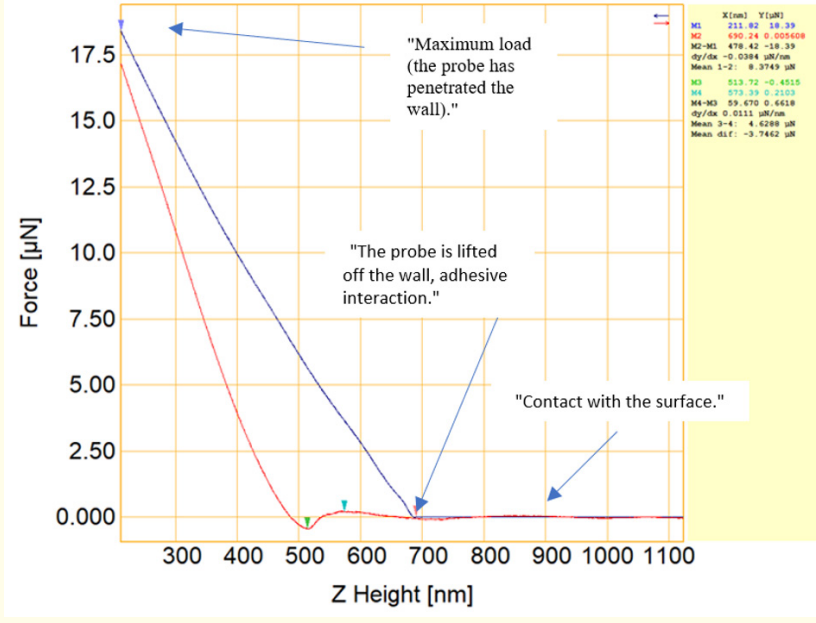


**Figure 3:** Example of a force curve (loading/unloading curves).

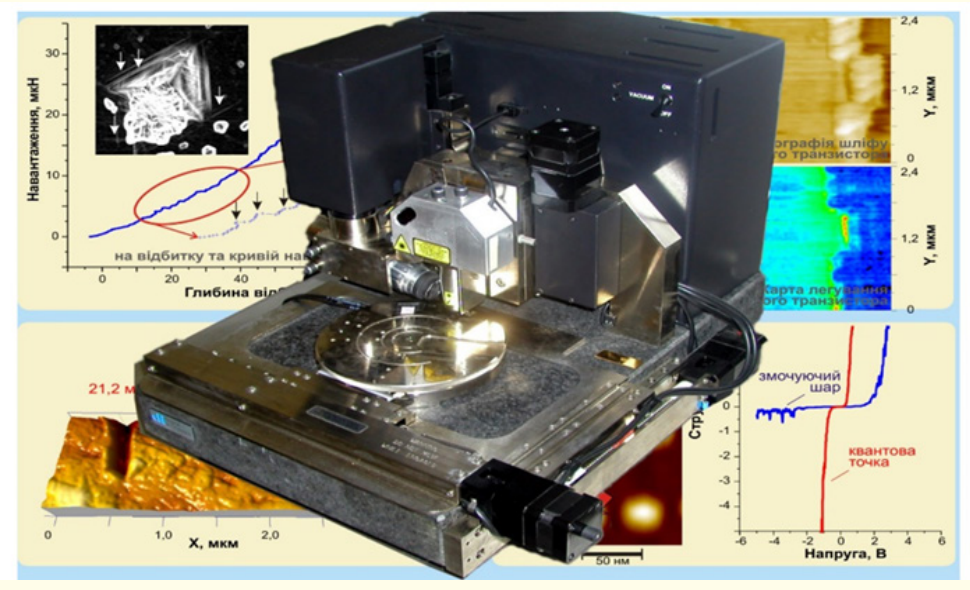


**Figure 4**

Measurements were conducted using a NanoScope IIIa Dimension 3000 scanning probe microscope (Bruker Inc., formerly Digital Instruments, USA) in intermittent contact mode with a silicon probe featuring a nominal tip radius of 10 nm [3-10].

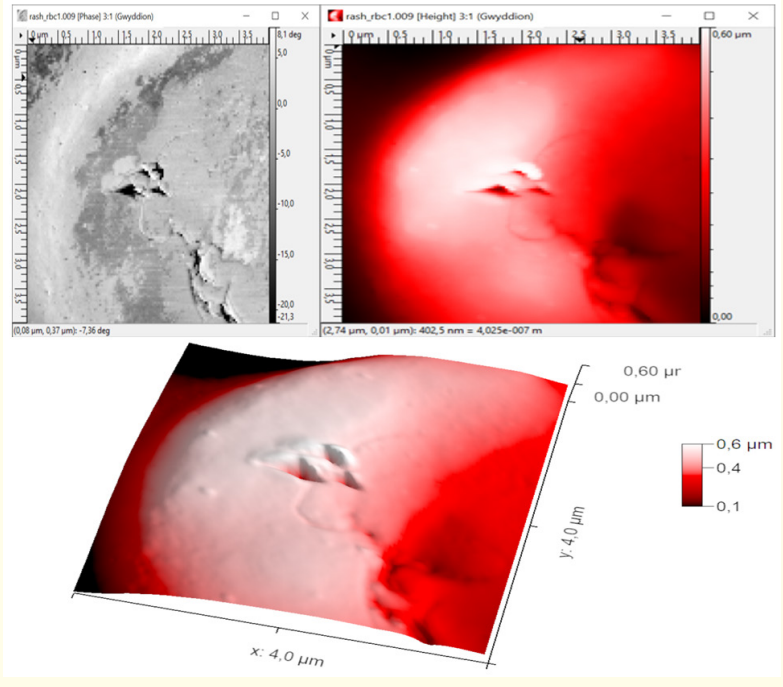


**Figure 5:** Series of indenter punctures on the erythrocyte membrane to determine the degree of rigidity.

## Conclusion

- The treatment of diabetic micro- and macroangiopathy in the lower extremities should be based on the use of low-molecular-weight heparins and sulodexide. LMWH provides reliable control of thrombosis, while sulodexide demonstrates high efficacy in restoring microcirculation and protecting the vascular endothelium. A comprehensive therapeutic approach reduces the risk of complications and improves the quality of life for patients with diabetes.

- The application of cell therapy in combination with sulodexide and LMWH positively affected the condition of erythrocytes and microcirculation in a patient with type 2 diabetes. The reduction in erythrocyte rigidity and improvement in thermographic examination results indicate enhanced blood flow, which may aid in the prevention and treatment of vascular complications associated with diabetes.

- Thus, a comprehensive approach to improving micro- and macrocirculation includes modern surgical interventions, endovascular methods, and the use of innovative technologies, allowing for a reduction in ischemic complications and an improved overall prognosis for patients with type 2 diabetes.

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