The assessment of neuropathic dysfunction in Type 1 diabetic patients: the role of metabolic and molecular/inflammatory mechanisms

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PhD Thesis

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2. List of publications linked to the thesis

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1. **Bordács B.,** Várkonyi Á., Valkusz Z., Nyiraty S., Pósa A., Menyhárt A., Lengyel C., Kempler P., Kupai K., Várkonyi T. **Comprehensive Assessment of Neuropathy and Metabolic Parameters in Type 1 Diabetic Patients with or Without Using Continuous Glucose Sensors.** Int J Mol Sci. 2025 Feb 26;26(5):2062. **IF:4,9, D/Q rank: Q1**

2. **Bordács B.,** Várkonyi Á., Valkusz Z., Nyiraty S., Pósa A., Menyhárt A., Lengyel C., Kempler P., Kupai K., Várkonyi T. **Keep the balance: the multiple effects of continuous glucose monitoring on the management of type 1 diabetes.** Diabetes, Stoffwechsel und Herz, Band 34, 3/2025, p:155. **IF:0.9, D/Q rank: Q4**

Other publications:

3. Nemes A.; **Bordács B.;** Ambrus N.; Lengyel C. **Simultaneous Assessment of Left Ventricular Volumes and Aortic Valve Annular Dimensions by Three-Dimensional Speckle-Tracking Echocardiography in Healthy Adults from the MAGYAR-Healthy Study—Is There a Relationship?** Life 2025, 15, 742. **IF: 3.2, D/Q-rank: Q1**

4. Nemes A.; **Bordács B**.; Ambrus N.; Lengyel C. **Longitudinal Systolic Excursion of the Mitral Annular Plane and Left Ventricular Rotational Mechanics Are Associated in Healthy Adults—Three-Dimensional Speckle-Tracking Echocardiography-Derived Insights from the MAGYAR-Healthy Study.** J. Clin. Med. 2025, 14, 3201. **IF: 3.0, D/Q-rank: Q1**

5. Nemes A, **Bordács B,** Ambrus N, Lengyel C. **Complex Associations Between Systolic Left Atrial and Left Ventricular Deformations in Healthy Adults-Detailed Analysis from the Three-Dimensional Speckle-Tracking Echocardiographic MAGYAR-Healthy Study.** Life (Basel). 2025 Feb 12;15(2):287. **IF: 3.2, D/Q-rank: Q1**

6. Dobra G, Gyukity-Sebestyen E, Bukva M, Boroczky T, Nyiraty S, **Bordacs B,** Varkonyi T, Kocsis A, Szabo Z, Kecskemeti G, Polgar TF, Szell M, Buzas K. P**roteomic profiling of**

serum small extracellular vesicles predicts post-COVID syndrome development. Clin Immunol. 2025 May 24;278:110532. **IF: 4.5, D/Q rank: Q2.**

3. Introduction

3.1. Diabetes mellitus

Diabetes mellitus is a chronic, non-communicable, complex metabolic disease that primarily affects carbohydrate metabolism, but its impact on protein and lipid metabolism can not be neglected. Diabetes is the most prevalent global cause of mortality and morbidity. It is estimated that around 537 million people have diabetes and the number is expected to increase constantly (Magliano et al., 2021). Diabetes is characterized by hypergylcaemia which is caused by absolute or relative insulin deficiency (Banday et al., 2020). It is generally accepted that the target for blood glucose levels should be between 4-10 mmol/L in patients with diabetes, but in case of younger individuals, the maximum glucose levels should be under 7.8 mmol/l with the minimalization of hypoglycaemia. In order to maintain glucohomeostasis, various hormones and neuropeptides interplay that are produced by the pancreas, liver, brain, intestine, adipose and muscle tissue (Röder et al., 2016). The central part is the endocrine pancreas, that secretes insuline and glucagon to sustain appropriate blood glucose levels. As the blood glucose level elevates, pancreatic **β**-cells release insulin into the blood stream. Glucose is taken up by glucose transporter type 2 (GLUT-2) and then undergoes glycolysis in the cell creating adenosine triphosphate (ATP), which leads to the closure of ATP-sensitive potassium channels. Thus the membrane potencial increases, leading to the opening of voltage-dependent calcium channels that leads to the excretion of the insulin-containing granules (Röder et al., 2016). Any harm in the system causes the inability to maintain the normal proccess.

Diabetes can be classified into 4 groups (American Diabetes Association Professional Practice Committee, 2024) (Table 1):

1.) Type 1 diabetes mellitus (T1DM),
2.) Type 2 diabetes mellitus (T2DM),
3.) Diabetes due to other causes (monogenic, neonatal, maturity-onset diabetes of the young, pancreas diseases, drug-induuced, endocrine disorders causing diabetes mellitus) and
4.) Gestational diabetes mellitus

3.2. Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease, characterized by absolute insulin deficiency due to the autoimmune destruction of pancreatic beta cells (Rodrigues Oliveira et al., 2023). It constitutes about 5-10% of all the diabetic patients (Banday et al., 2020). Human leukocyte antigen (HLA) DR and HLA DQ polymorphisms are the main risks that contribute to the development of T1DM (Xie et al., 2014). HLA DR and DQ are class II HLA molecules that present antigens to cluster of differentiation 4 positive ($CD4^+$), helper T-cells (Neefjes et al., 2011). According to previous studies, beside genetic predisposition, enviromental factors contribute to the development of T1DM by causing endoplasmatic reticule stress in beta cells (Marré & Piganelli, 2017). These include vitamin D deficiency, shortage of sunshine exposure, high maternal age (above 35 years), viral infections (retroviruses, picornaviruses, enteroviruses, herpesviruses, rotaviruses) and disorders in gut microbiome (Rodrigues Oliveira et al., 2023). For the autoreactive T-cells, the main islet B-cell autoantigens are glutamic acid decarboxylase 65 (GAD65), insulinoma antigen 2 (IA2), zinc transporter (ZnT8), non-specific islet cell autoantigens (ICA), pancreatic duodenal homeobox factor 1 (PDX1), chromogranin A (CHGA), islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), heat shock protein 60 (hsp60) and islet cell antigen 69 (ICA69) (Han et al., 2013; Rodrigues Oliveira et al., 2023). The autoantigens are the main targets for immune responses in T1DM, causing beta-cell destruction. Although, the exact steps involved in the innitiation and progress of beta-cell death are still unclear, it is known, that the autoantigens in the pancreas are processed by macrophags, dendritic cells or B-lymphocytes (funconing as antigen presenting cells) and presented to naive T-cells in pancreatic lymph nodes to create autoreactive $CD4^+$ T-cells. These autoreactive T-cells secrete cytokines, thus promoting the activation of $CD8^+$, cytotoxic T-cells and further macrophage, dendritic cell and B-lymphocyte proliferation, resulting in beta-cell destruction (Yoon & Jun, 2005). T1DM pathogenesis can be seen in Figure 1.

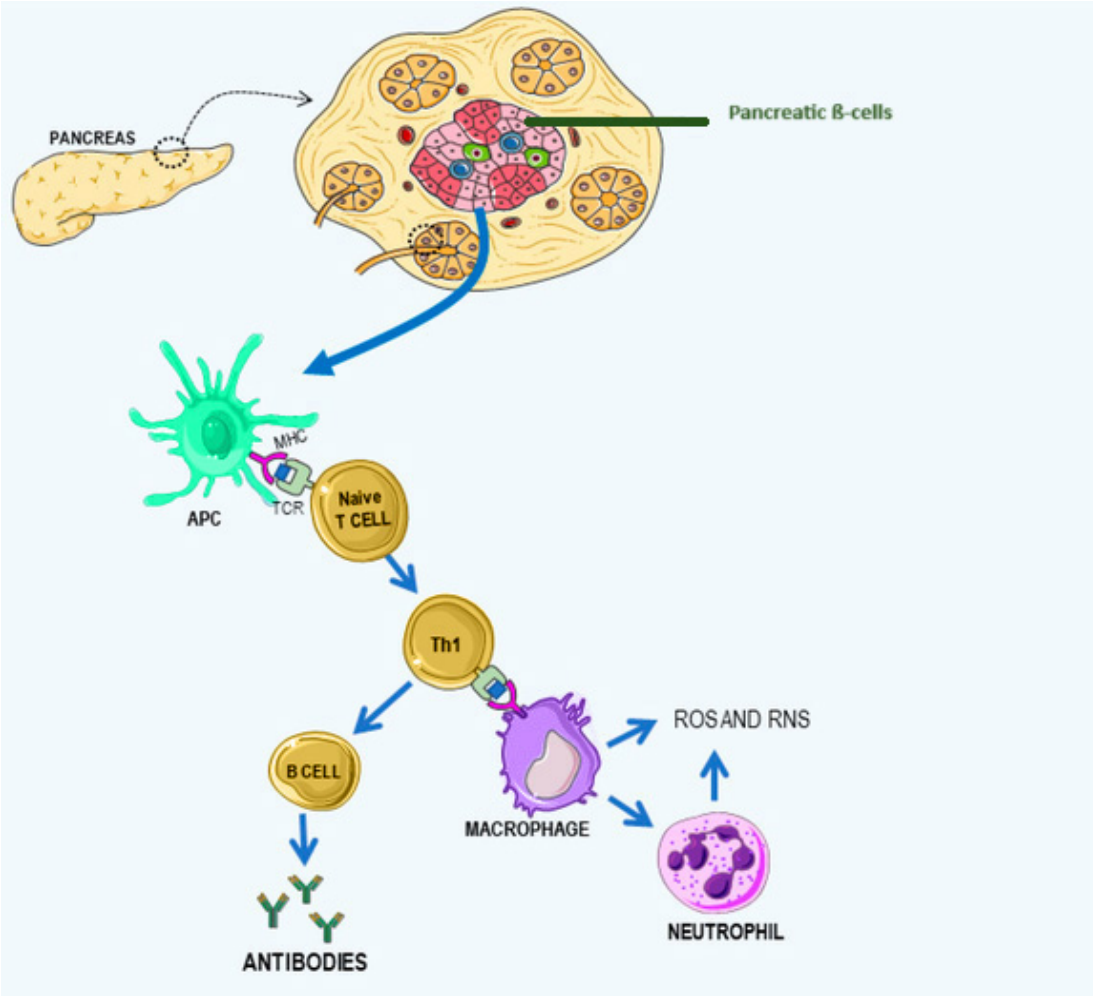

Figure 1. Pathogenesis of T1DM

APC: antigen presenting cell, MHC: major histocompatibility complex, TCR: T-cell receptor, Th: helper T-cell, ROS: reactive oxygen species, RNS: reactive nitrogen species

(Source: Oliveira et al., 2017, modified)

3.3. Complications of diabetes

There are many short-, and long-term complications attributed to diabetes mellitus. Long-term complications include micro-, and macrovascular damages. The latter includes cardiovascular diseases: coronary heart disease, atherosclerosis, peripheral arterial disease, stroke (Huang et al., 2017). The main factors that lead to these conditions are hyperglycaemia and insulin resistance. Insulin-resistance leads to high free fatty acid (FFA) levels, alters lipid metabolism, causes the overproduction of reactive oxygen species (ROS) and increases systemic inflammation. Hyperglycaemia enhances ROS production, causes endothelial dysfunction and promotes the activation of protein kinase C (PKC), that affects many other cellular proteins causing inflammation, endothelial dysfunction, vasoconstriction, prothrombotic events, all leading to accelerated atherosclerosis and the presentation of cardiovascular events (Huang et

al., 2017). Diabetes mellitus multiplies the risk of different types of tumors (gastrointestinal, pancreatic, liver, gynecological, breast and prostate cancers), liver disease, mental disorders, as well as increases the susceptibility to infections resulting in higher mortality (Tomic et al., 2022).

The microvascular conditions include the classic triad: retinopathy, nephropathy and neuropathy (Vithian & Hurel, 2010). The main cause of the process is hyperglycaemia (Vithian & Hurel, 2010). The damage arises mainly in tissues, where the glucose uptake from the blood is independent from the activity of the insulin (retina, endothelium in the vessels and glomeruli in the kidney) as it tightly correlates with the level of blood glucose (Vithian & Hurel, 2010).

Diabetic retinopathy occurs in 17-97.5% of diabetic patients, depending on the duration of diabetes (Klein, 1984). The constant hyperglycaemia causes the thickening of basement membrane, increases the capillary permeability and leads to the formation of microaneurysms, intravascular coagulation and ischaemia, resulting in the first stage of diabetic retinopathy: background retinopathy (Vithian & Hurel, 2010). As the disease proceeds, new vessels start to grow in the damaged part of the retina, leading to the worsening of the symptoms and the formation of proliferative retinopathy with many complications (Vithian & Hurel, 2010).

Diabetic nephropathy is the combination of the thickening of basal membrane of the glomeruli due to hyperglycaemia, atrophy, interstitial fibrosis and arteriosclerosis. Beside the abnormalites in carbohydrate metabolism, hypertension as a cause of diabetes also contributes and worsens the condition (Holt & Flyvbjerg, 2024). At the beginning, the glomelural filtration increases, resulting in albuminuria and later with the progressive destruction of glomeruli, chronic kidney disease develops (Vithian & Hurel, 2010).

3.4. Diabetic neuropathy and cardiovascular risks

Polyneropathies are the degenerations of peripheral and autonomic nerves due to different etiologies that are causing are causing different clinical symptoms (Sommer et al., 2018, Kempler and Várkonyi, 2025). Diabetic neuropathy severely impacts the quality of life of patients by causing lower extremity pain, leg ulceration, an increased need for amputations, and higher mortality rates in both T1DM and T2DM patients. Around 50% of diabetic patients are affected by different forms of neuropathy (Pop-Busui et al., 2022).

There are many factors that contribute to neuronal damage by causing demyelination and axonal degeneration mainly in Schwann cells and myelin sheath (Garcia-Perez et al., 2018; Malik et

al., 2005). Hyperglycaemia causes direct harm to the neurons by damaging the basement membrane of the endothelial cells participating in blood-nerve barrier resulting in the influx of glucose and other molecules toxic to the neurons (Galiero et al., 2023). With the increase of the blood glucose levels, alternative metabolic pathways are becoming activated, advanced glycation end products (AGEs) accumulate, cytokines, proinflammatory molecules are appearing (Galiero et al., 2023). Oxidative stress is also a main contributor to the progression of the neuronal damage caused by the ROS production. The stimulation of cyclooxygenase-2 (COX-2) leads to oxidative stress by increasing superoxide production, lipid peroxidation and protein nitrolysation and also inflammation, increases the activity of prothrombotic thromboxanes and prostaglandins, promotes autophagia and cellular death (Galiero et al., 2023).

Recent studies have found correlation between the development of peripheral neuropathy and metabolic syndrome as well as with lipid abnormalities in Type 2 diabetes mellitus (T2DM). The exact mechanism is still unknown, but it is supposed that lipid peroxidation and dyslipidaemia play the crucial roles (Kazamel et al., 2021; Rumora et al., 2021). Among these, role of dyslipidaemia is particularly significant (Pang et al., 2020; J. Zhu et al., 2024). Figure 2 illustrates the complex pathomechanism of diabetic neuropathy.

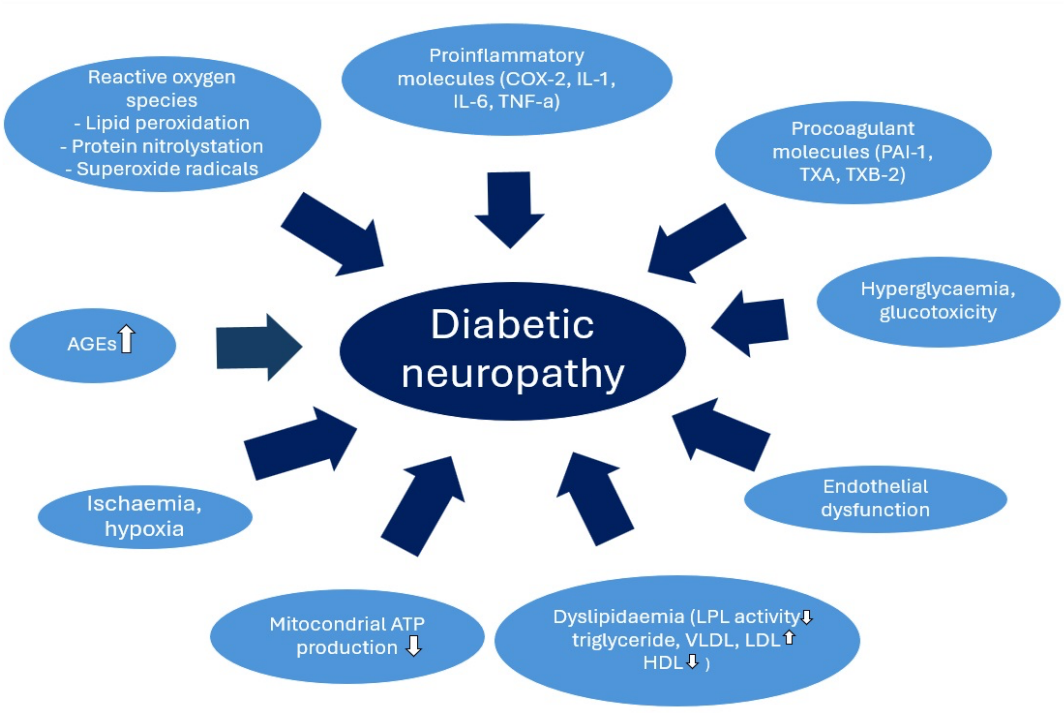

Figure 2. Diabetic neuropathy pathogenesis

AGE: advanced glycated end-product, ATP: adenosine triphosphate, LPL: liporpotein lipase, VLDL: very low density lipoprotein, LDL: low density lipoprotein, HDL: high density

lipoprotein, PAI-1: plasminogen activator inhibitor-1, TXA, B: thromboxane A and B, COX-2: cyclooxigenase-2, IL-1,6: interleukin-1,6, TNF-a: tumour necrosis factor alpha

Classification of diabetic neuropathy (Pop-Busui et al., 2017) (Table 2):

1.) Distal Symmetrical Peripheral Neuopathy (DSPN): primarily small-, and large-fiber neuropathy, mixed small- and large-fiber neuropathy.
2.) Autonomic neuropathy: cardiovascular, gastrointestinal, urogenital and sudomotor dysfunction.
3.) Mononeuropathy (mononeuritis multiplex).
4.) Radiculopathy or polyradiculopathy.

All forms of diabetic neuropathy worsen the quality of life of the patients and also cause higher risk of morbidity. In case of distal symmetric polyneuropathy (DSPN), first the large fibres are injured, resulting in the loss of protective sensation and the formation of leg ulcers. With the progression of the neuronal damage, small fibers also become involved, leading to pain, increasing the risk of amputation and autonomic nervous system impairment. Compared to the healthy population, patients with diabetes have a higher risk of cardiovascular complications and mortality, particularly due to the elevated levels of detrimental metabolic parameters that contribute to atherosclerosis (Dal Canto et al., 2019). Cardiovascular autonomic neuropathy (CAN) is the main reason for the high mortality. First the parasympathetic nervous system is concerned with silent ischaemia, tachycardia while resting, increased sympathetic tone, arrhythmias, abnormal adaptation, higher risk for cardiovascular events, while later the sympathetic nerves injure, manifesting in orthostatic blood pressure drop on standing up causing dizziness, frailty, syncope (Ziegler et al., 2021).

3.5. Lipid abnormalities in diabetes mellitus

Impaired sympathetic and parasympathetic autonomic function due to neuropathy contributes significantly to the elevated incidence of cardiovascular events and increased mortality in diabetic individuals. The risk of death is much higher in cases of dyslipidaemia as well, especially in patients with T2DM. Dyslipidaemia includes elevated fasting triglicerides (TGs), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) cholesterol, total cholesterol levels and decreased high density-lipoprotein (HDL) cholesterol. It is known that HbA1c is associated with dyslipidaemia including elevated LDL and TG (Buková et al., 2020), and also an important parameter in predicting coronary artery disease in T2DM subjects (Artha

et al., 2019). Patients with T1DM are also at higher risk of developing any diabetes related complications and all cause mortality. Inadequate glycaemic control and glucose variability is associated with higher cholesterol, LDL and TG levels and lower HDL levels (Salsa-Castelo et al., 2023). In T2DM, dyslipidaemia is mainly explained by the pathological role of the insulin resistance in the patients (Zheng et al., 2019), while in T1DM it may be attributed to incresed VLDL production, secondary to insulin deficiency (Vergès, 2009) and reduced lipoprotein lipase activity in individuals inadequetly treated with insulin (Salsa-Castelo et al., 2023). The presence of dyslipidaemia worsens the prognosis of neuropathy as in a comprehensive study a significant correlation was established between CAN and age, diabetes duration, higher glycated haemoglobin (HbA1C), fasting TG and lower HDL levels in T1DM patients (Kempler et al., 2002).

3.6. Role of NETosis markers in diabetes (PAD4, Citrullinated Histone H3, Neutrophil Elastase)

Recent studies show that the process of NETosis plays an important role both in the pathogenesis and the complications of T1DM and T2DM (Njeim et al., 2020). Neutrophil granulocytes are crucial parts of the innate immune system by phagocytosing and degrading pathogens (mainly bacteria and fungi) with their cytotoxic enzymes. During the process, they create neutrophl extracellular traps (NETs), that are weblike dexocyribonucleotid acids (DNAs) containing substances released by neutrophils. These include histones, granule proteins (neutrophil elastase [NE], proteinase 3 [PR3], myeloperoxidase [MPO]) and cytosolic proteins (actin, alpha-actinin, S100 calcium-binding proteins) (Thiam et al., 2020). However NETosis also occurs in sterile inflammation (Sorvillo et al., 2019) and in autoimmune diseases and cancer (Jorch & Kubes, 2017). As the first step os NETosis, neutrophils are activated by different stimuli via their surface receptors, which increases intracellular calcium concentration resulting in the production of ROS and kinase signaling cascades and actin filaments disassembly. Next, microtubules (MT) disassembly, microvesicle shedding in the plasma membrane and in the ER (Thiam et al., 2020). Calcium is also needed for the activation of peptidyl-arginine-deiminase 4 (PAD4) enzyme (Wong & Wagner, 2018). The next step is chromatin decondensation, which is mediated by histone posttranslational modifications, including acetylation, citrullination and cleavage (Hamam et al., 2019; Wang et al., 2009). Proteases, like elastase and PR3 take part in the process via histon cleavage, thus releasing DNA from histons (Papayannopoulos et al., 2010). Histone citrullination–which is a posttranslational modification- is mediated by PAD4 (Wang et al., 2009). During the process, arginine is

converted to citrulline, leading to total mass reduction, the loss of positive charge, while releasing ammonia (Smith & Denu, 2009). PAD4 is known to locate near the nucleus of the neutrophil granulocyte an mediates. the citrullination of nucleosome histones H1, H2A, H4 and mainly H3 at 4 different arginine locations resulting in chromatin decondensation. The nuclear envelope and plasma membrane become permeable and first the chromatin gets into the cytoplasm and next plasma membrane ruptures and NET is released (Thiam et al., 2020). In T1DM as the autoimmune destruction of beta-cells starts, the neutrophiles taking part in the process are stimulated to release DNA-binding cathelicidin-related antimicrobal peptide (CRAMP), inducing the production of interferon-alpha, resulting in the release of NETs (Diana et al., 2013). Previous studies revealed, that in case of T1DM, the absolute number of neutrophils in the peripheral blood is decreased, while the NE, PR3 and PAD4 was significantly higher in neutrophils from T1DM patients, than in the control groups and correlated positively with autoantibodies against beta-cells (Harsunen et al., 2013; Wang et al., 2014; Wong et al., 2015).

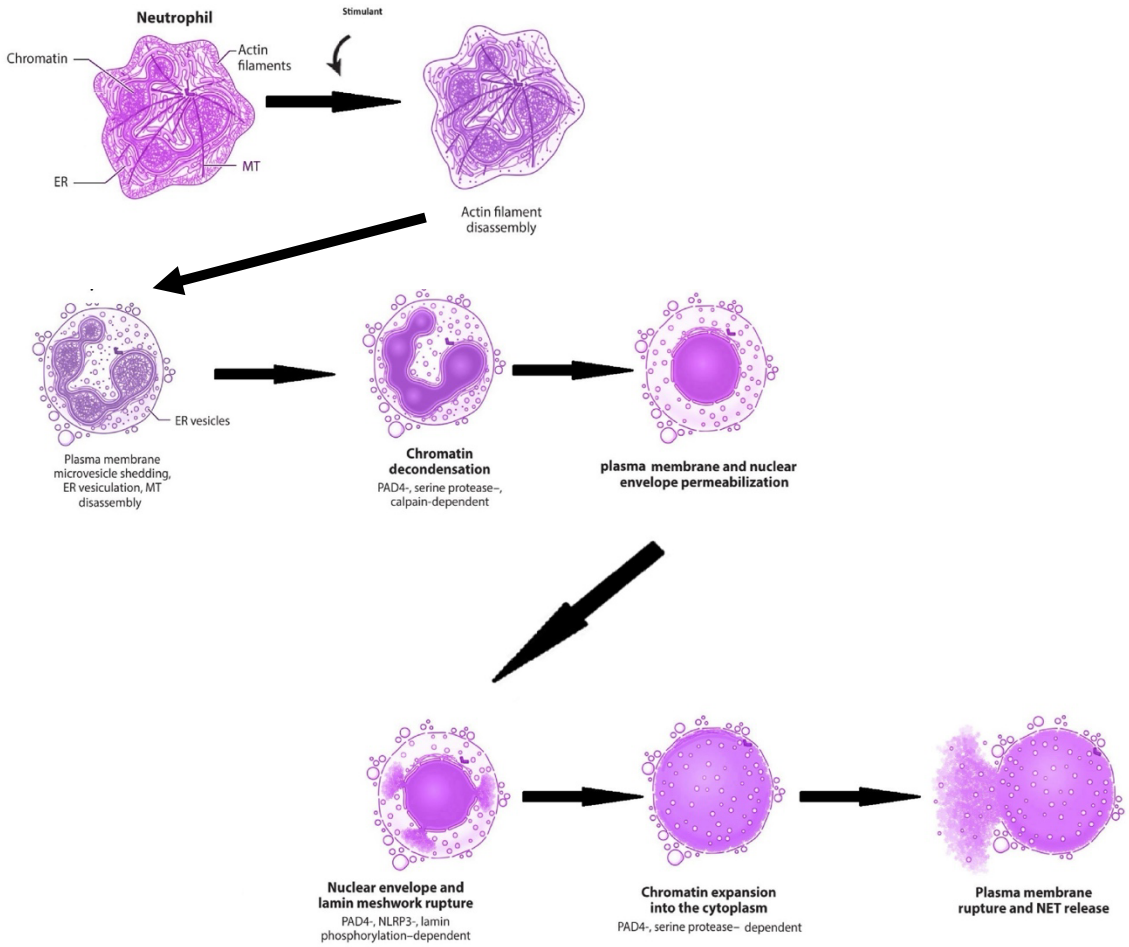

Figure 3. NETosis cellular mechanism

ER: endoplasmatic reticule, MT: microtubule, PAD4: peptidyl-arginine-deiminase 4

(Source: Thiam et al., 2020, modified)

3.7. Continuous Glucose Monitoring (CGM) Technology

Intensive blood glucose monitoring includes capillary glucose monitoring at least four times a day and regular haemoglobin HbA1C monitoring in every three months. In the 2010s, a new technique was developed in which glucose levels in the interstitial space in the subcutis are detected by an electrode placed under the skin. The method is based on the electric potential generated by the chemical reaction of the enzyme glucose oxidase, which allows the glucose level in the interstitial fluid to be detected, after a delay of 5-15 minutes (Lee et al., 2021). These devices supply real-time glucose readings, trend arrows indicating the direction and rate of glucose change, and customizable alerts for impending hypoglycemia or hyperglycemia (Raubertas et al., 2019; Vashist et al., 2013).

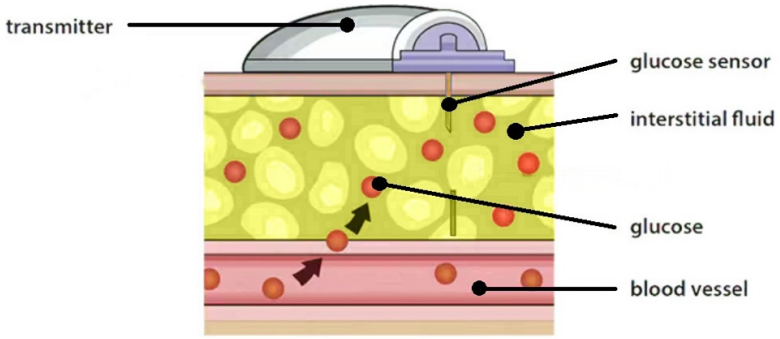

Figure 4. Glucose sensor mechanism

(Source: Medtronic webpage, modified)

3.8. Advantages of the use of glucose sensors

CGM has significantly transformed the management of T1DM by providing a dynamic and comprehensive assessment of glucose levels, surpassing the limitations of traditional fingerstick measurements. The use of HbA1C alone is not sufficient to determine the effectiveness of therapy, as it is a measure of average blood glucose levels and does not provide information on

episodes of hyperglycaemia or hypoglycaemia. Unlike traditional HbA1c measurements that reflect average glucose levels over several months, CGM captures the daily fluctuations of glycemic excursions, elucidating patterns of variability and clinically significant episodes of hypo- and hyperglycemia (Bergenstal et al., 2018). Capillary blood glucose measurements are usually taken at different random time points, and thus cannot be relied upon for accurate data. The use of CGM has significantly increased in recent years and decades. Several studies have shown the benefits of CGM in diabetic patients by providing real-time blood glucose values, thus enhancing the management of glycaemic therapy (Fleischer et al., 2017; Friedman et al., 2023). The detailed data supplied by CGM facilitates personalized therapeutic adjustments, particularly for individuals utilizing insulin, thereby addressing the limitations of HbA1c in fully representing the spectrum of glycemic control (Bergenstal et al., 2018).

It is widely accepted, that CGM plays a key role in improving carbohydrate metabolism and achieving optimal HbA1C. Systematic review indicated that CGM can reduce HbA1c levels by 0.17% to 0.70% in type 1 diabetes patients (Bertini et al., 2022). It was shown that HbA1c and TIR are closely related, predicting the risk of diabetic complications (Vigersky & McMahon, 2019) and measuring outcome in diabetes-related clinical trials (Beck et al., 2019). In a metaanalysis including both T1DM and T2DM patients, strong correlation was found between diabetic complications and CGM metrics: lower time in range (TIR) and higher glucovariability associated with different complications due to diabetes (Yapanis et al., 2022). The quartile decrease of TIR and increase of glucovariability augmented the prevalence of diabetic retinopathy (both non-proliferative and proliferative retinopathy) in patients with T2DM (Lu et al., 2018). In an other study, diabetic neprhopathy and albuminuria was more severe in patients with less TIR and more time above range (TAR). In parallel, with target TIR and TAR the prevalence of renal impairment was significantly lower (Yoo et al., 2020). CGM metrics determine the severity and progression of neuropathy. Any decrease in TIR quartiles caused the increase of extent and intensity of painful diabetic neuropathy (Yang et al., 2021). In addition, independently from HbA1c, TIR is strongly associated with the presence of CAN (Guo et al., 2020).

This improvement in glycemic control is crucial, as hyperglycemia is known to adversely affect lipid metabolism, leading to dyslipidemia, which is a risk factor for cardiovascular disease (Salsa-Castelo et al., 2023). Moreover, the GOLD trial demonstrated that patients using CGM exhibited not only better glycemic control but also improved physical activity levels, which are positively correlated with better lipid profiles (Nyström et al., 2024). This continuous feedback

mechanism is particularly beneficial as it helps in maintaining glucose levels within a target range, which has been associated with favorable lipid profiles (Jamiołkowska et al., 2016; Salsa-Castelo et al., 2023). A recent metaanalysis found that continuous glucose monitoring (CGM) metrics might determine not only the microvascular, but the macrovascular complications also in T1DM (Bezerra et al., 2023).

Regarding complications of diabetes, the incorporation of CGM systems presents opportunities for personalized interventions and targeted therapies to address specific autonomic nerve dysfunctions. By reducing the frequency and severity of the extreme glucose excursions, CGM use may help to mitigate the metabolic stress on autonomic nerves, potentially slowing the progression of neuropathy (Bergenstal et al., 2018). Important findings in the literature have shown that reducing glucose variability not only decreases the direct effects of glucose but also leads to a reduction in oxidative stress (Klimontov et al., 2021). This phenomenon also explains the beneficial effects on complications.

3.9. Glycemic Metrics: TIR, TAR, TBR and Their Clinical Significance

The most important dynamic metrics in CGMs are TIR, TAR and time below range (TBR) (Bergenstal et al., 2018). TIR, defined as the percentage of time a person's glucose levels remain within a target range, offers a more comprehensive and clinically relevant assessment of glycemic control by quantifying the amount of time spent within the desired therapeutic window (Bergenstal et al., 2018). The target range is most commonly between 3.9-10 mmol/L. The recommended percent of time spent in target ranges are 70% for TIR, below 25% for TAR and below 5% for TBR (American Diabetes Association Professional Practice Committee, 2025) (Figure 5.). For older patients with T2DM and comorbidities, the aim is to achieve a TIR of at least 50%. The importance of this is underlined by the fact that every 5% increase in TIR is associated with clinically significant benefits in terms of complications in both T1DM and T2DM patients (American Diabetes Association Professional Practice Committee, 2024). In addition to improving glycaemic control in pregnant women, the use of CGM reduces maternal complications, fetal and neonatal morbidity and mortality.(American Diabetes Association Professional Practice Committee, 2024). In a retrospective cohort study, involving both T1DM and T2DM pregnant patients, it was found that for every 5% reduction in TIR, a 28% reduction in risk was observed, including increased birth weight, intensive care unit admission, hypoglycaemia, need for caesarean section. A 5% increase in TAR increased morbidity and mortality by more than 40%, while a 5% increase in glucovariability increased risk by 35% of

several complications, including preterm delivery, lower birth weight, increased the risk of preeclampsia and preterm birth. Uniquely, an increase in TBR did not worsen outcome. For the data, there was no difference between types of diabetes. This study highlighted the significance of appropriate glucose management in pregnant diabetic patients, in particular the importance of lower blood glucose levels (Sanusi et al., 2024). According to the recent ADA recommendations, the target ranges are different with less TAR and higher TIR (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Hilliard, et al., 2024). Deviations from this target range, both above and below, carry distinct risks, and the extent of these deviations is directly correlated with the severity of potential complications (Danne et al., 2017). In recent studies, a more strict classification determined time in tight range (TITR) and TIR to be the most important measures in glycaemic management (De Meulemeester et al., 2024). TAR and TBR provide additional insights into the nature of glycemic excursions and their potential impact on health outcomes (Bergenstal et al., 2018).

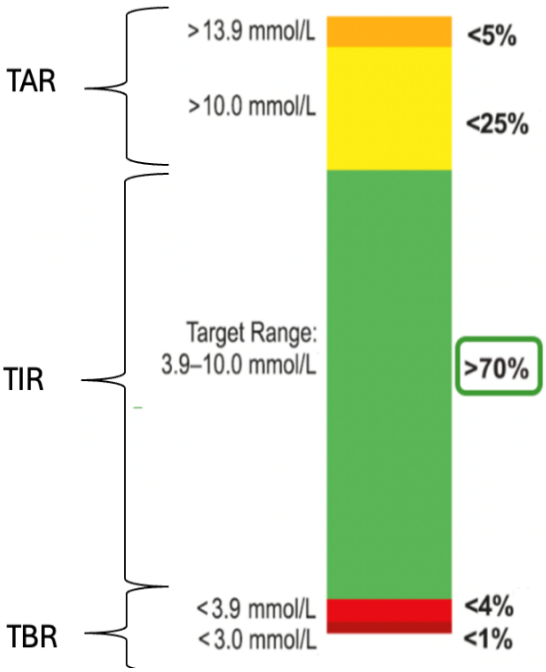

Figure 5. CGM target ranges in T1DM

TAR: time above range, ,TBR: time below range, TIR: time in range

(Source: American Diabetes Association Professional Practice Committee et al., 2025, modified)

4. Objectives and Hypotheses

The aim of the thesis was to evaluate the effects of CGM on both microvascular and macrovascular complications of diabetes, as well as on lipid metabolism, that remained insufficiently characterized until now in T1DM. We aimed to investigate the potential associations between various components of complex metabolic control and diabetic neuropathy in individuals with T1DM in a comprehensive clinical study. This trial assessed autonomic and peripheral sensory nerve functions, inflammatory/NETosis biomarkers, as well as metabolic parameters including glycemic and lipid profiles. Particular emphasis was placed on the potential of CGM to enhance metabolic and inflammatory regulation and to preserve neuronal function. Furthermore, we systematically analyzed key CGM-derived metrics in our T1DM cohort to explore their correlations with cardiovascular risk factors.

5. Materials and Methods

5.1. Patient Selection and Grouping

Patients were recruited in a diabetology outpatient clinic (Department of Medicine, Albert Szent-Györgyi Medical School, University of Szeged, Szeged, Hungary). The inclusion criteria were a diagnosis of T1DM and an age between 18–65 years. During the visits, blood sampling, neuropathy tests, and the collection of CGM data were performed. Patients were divided into two groups based on whether they used CGM or not. A total of 61 patients were studied (Table 3). In total, 24 patients used CGM sensors and 37 did not (Table 4). A total of 19 of the CGM user patients had been wearing sensors for more than 4 years while 5 of them used sensors for between 6 months and 4 years. All measurements involved in the thesis were conducted with prior approval from the relevant ethics committee (67/2022-SZTE, approval date: 7 JUNE 2023).

5.2. Laboratory Analysis of Metabolic and Inflammatory Markers

The metabolic state was evaluated by measuring TG, HDL, LDL and total cholesterol, HBA_{1c} levels. The reference ranges for these parameters in our laboratory are: TG: <1.70 mmol/L, HDL: >1.40 mmol/L, LDL <3.0 mmol/L, and total cholesterol: <5.20 mmol/L.

Citrullinated histone H3, PAD4 and NE levels of 29 T1DM and 9 healthy individuals from human serum regarding NETosis markers were measured with enzyme-linked immunosorbent assay (ELISA). It is based on antigen-antibody reactions. After centrifuging the blood samples,

we used the serum and added to the ELISA plate. The target antigen (citrullinated histone H3 and PAD4) binded to the previously added capture antibody. As a next step, enzyme-linked detection antibodies and a chromogenic substrate were added and measured the converted product using a plate reader with the help of a standard curve, calculated the concentration of antigen using optical density. The unit of measurement is pg/mg for citrullinated histone H3, ng/mg for PAD4 and pg/mg for NE.

5.3. Assessment of CGM Metrics

Among the T1DM patients, 24 individuals wore CGM. 19 of them had been wearing the glucose sensor for more than 4 years, while 5 of them used sensors between 6 months and 4 years. We collected electronical reports from the patients at the same time with the laboratory testing of the blood samples. Examinating all the values, we used TIR, TAR and TBR data for finding correlations.

5.4. Neuropathy and Autonomic Function Testing

Peripheral sensory nerve function was assessed by a Neurometer (MSB Ltd, Balatonfüred, Hungary) and a calibrated tuning fork applied to the upper and lower extremities. The Neurometer device was designed to quantify the sensory function of different types of nerve fibres and provides a simple, non-invasive measurement of peripheral sensory function (Lv et al., 2015). A transcutaneous low voltage electric sine wave stimulation was delivered on the upper and lower limbs, and the current perception threshold (CPT) values were determined. In this study, the sensory functions of the median and peroneal nerves on the left side were tested. The surface electrodes were fixed on the terminal phalanx of the index and the great toes. The electrodes were positioned only on intact skin. The amplitude of the delivered stimuli ranged from 0.01 and 9.99 mA. The stimulus was gradually increased until a sensation was reported by the patient, then short stimuli (2 to 5 s) were applied at progressively lower amplitudes until a consistantly minimal threshold for detection was found. The CPT values of the upper and lower limbs were detected at three different stimulating frequencies (2 kHz, 250 Hz, and 5 Hz) to ensure the separate testing of the large and small sensory fibres.

The 128-Hz Rydel-Seiffer graduated tuning fork was used to evaluate the vibration sense at the ulnar styloid process and at the interphalangeal joint of the hallux of right and left legs (Martina et al., 1998). The normal range was declared as 7-8, 6 was classified as borderline and scores between1-5 indicated an impaired sense of vibration.

Autonomic function was characterized with Ewing's standard cardiovascular reflex tests in the study (Spallone et al., 2011). The Ewing tests are the gold standards for diagnosing autonomic dysfunction; they provide non-invasive, clinically relevant, standardized and reproducible data of autonomic functions. Reflex tests were performed by measuring the blood pressure and obtaining continuous 6-lead ECG signals. The signals were digitized with a multichannel data acquisition system (CA-12v2.85 software, 2021, MSB Ltd., Balatonfüred, Hungary), the sampling rate was 2 kHz and the data were stored for later analysis. Parasympathetic dysfunction was examined by measuring deep breathing test, Valsalva ratio (VR), and 30:15 ratio, while sympathetic nervous system impairment was tested by orthostatic blood pressure drop on standing up. As handgrip test is becoming a marker of hypertension and its complications more and more, we did not use in our evaluation (Körei et al., 2024).

5.5. Statistical Analysis

During data analysis, continuous variables were expressed as means and standard error (mean ± SE) while categorical variables were expressed as frequencies and percentages (n, %). Univariate analyses were performed using independent sample t-tests and Pearson correlation coefficients (r). Statistical analyses were performed using PAST 4.09 (University of Oslo, Oslo, Norway). During the analyses, p values <0.05 were considered statistically significant.

5.6. Ethics

This study was performed in line with the Good Clinical Practice guidelines and the Declaration of Helsinki in its latest form. The study protocol was approved by the Regional and Institutional Review Board of Human Investigations at the University of Szeged (67/2022-SZTE, approval date: 7 JUNE 2023). All subjects signed an informed consent form for this study.

6. Results

6.1. Patients' characteristics

A total of 61 patients (age: 42.5 ± 1.8 years, DM duration: 22.8 ± 1.6 years, BMI: 25.3 ± 0.9, HbA1c: 8.1 ± 0.2%; mean ± SE) were studied (Table 3). In total, 24 patients used CGM sensors (age: 35.7 ± 2.5, DM duration: 20.0 ± 1.8, BMI: 24.5 ± 0.8, HbA1C: 7.5 ± 0.8%) and 37 did not (age: 45.9 ± 1.8, DM duration: 25.0 ± 1.9, BMI: 26.5 ± 0.8, HbA1C: 8.3 ± 0.3%, Table 4). A total of 19 of the CGM user patients had been wearing sensors for more than 4 years while 5 of them used sensors for between 6 months and 4 years.

Table 3. Patients' data (mean±SE)

T1DM patients	
Number of patients	61
Age (years)	42.5±1.8
Duration of diabetes (years)	22.8±1.6
BMI (kg/m^2)	25.2±0.9
HbA$_{1C}$ (%)	8.1±0.2

Table 4. Data of CGM users and non-users (mean±SE)

Patients	**CGM users**	**CGM non-users**	**p value**
Number	24	37	x
Age (years)	35.7±2.5	45.9±1.8 *	0.01
Duration of diabetes (years)	20.0±1.8	25.0±1.9	0.1
BMI (kg/m^2)	24.5±0.83	26.5±0.82	0.1
HbA$_{1C}$ (%)	7.5±0.8	8.5±0.3*	<0.05

6.2. CGM metrics, glycemic control and neuropathy

The mean sensor parameter values of the patients were close to the target range (TIR: 70.4±2.5%, TAR: 24.6±2.3%, TBR: 4.6±1.2%, mean±SE [Table 5]).

Table 5. CGM metrics (mean±SE)

Patients	**CGM-user T1DM**
TAR (%)	24.6±2.3
TIR (%)	70.4±2.5
TBR (%)	4.6±1.2

Metabolic parameters were 7.5±0.8 % for HbA1c, 0.9 ± 0.1 mmol/L for TG, 4.7 ± 0.2 mmol/L for cholesterol, 2.6 ± 0.1 mmol/L for LDL, 1.7 ± 0.1 mmol/L for HDL (mean±SE, [Table 1]). Among the metabolic values, positive correlations were found between HbA1c and TAR ($r=0.56$, $p<0.05$) [Figure 6]) and between TG and TAR ($r=0.53$, $p<0.05$ [Figure 7]). The autonomic tests revealed correlations between TAR and othostatic blood pressure drop on standing up ($r=0.57$, $p<0.05$) and between TBR and 30:15 ratio ($r=0.53$, $p<0.05$).

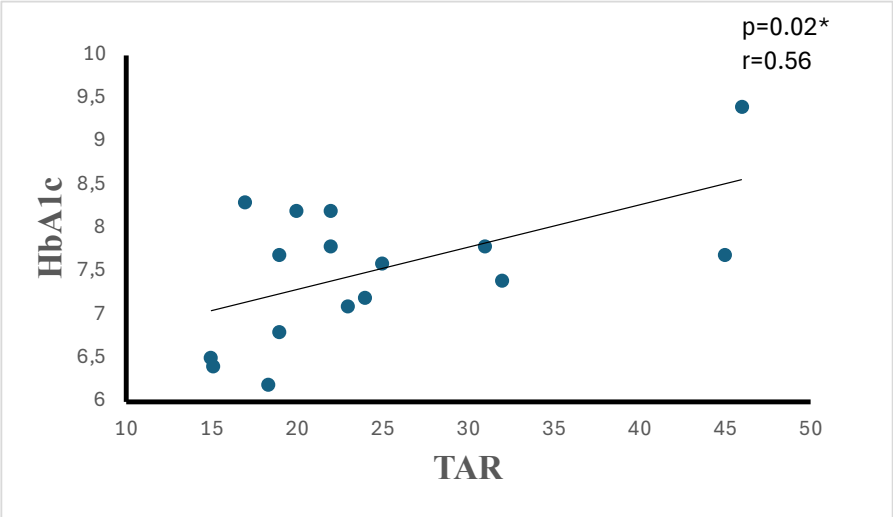

Figure 6. Correlation between HbA1c and TAR

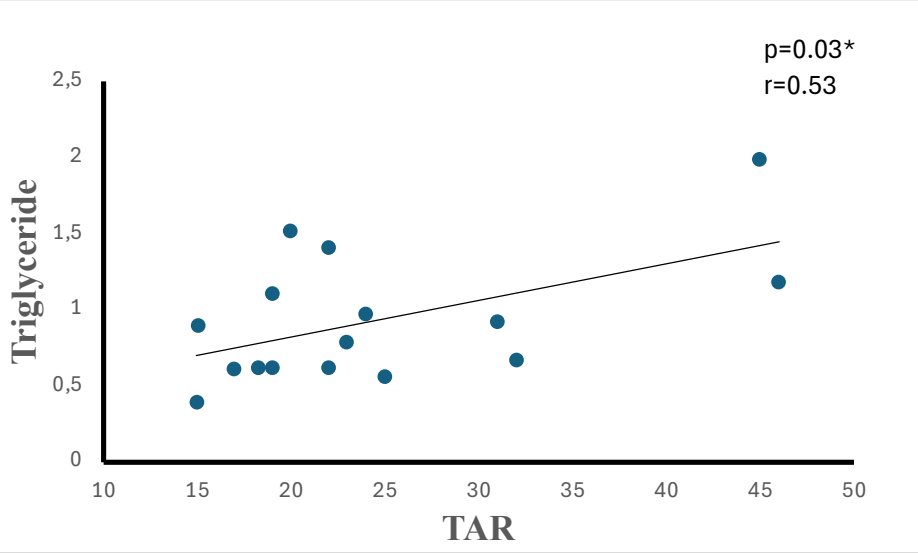

Figure 7. Correlation between TG and TAR

6.3. Metabolic and Lipid Profile

A significant positive correlation was found between HbA1c and TG levels in the overall group of T1DM patients ($r = 0.28$, $p = 0.045$) (Figure 8). The mean lipid parameters were within the normal range. However, neither the HbA1c nor the lipid parameters showed a significant correlation with the cardiovascular autonomic or peripheral sensory function ($p > 0.05$ in all cases).

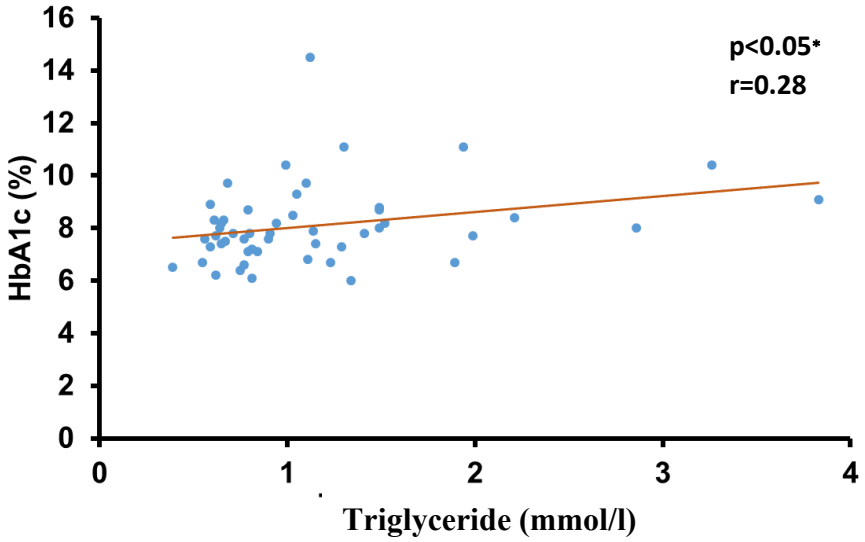

Figure 8. Correlation between HbA_{1C} and triglyceride levels in T1DM patients

For further analysis of the metabolic differences, the diabetic group was divided into two subgroups based on CGM usage.

24 patients wore CGM, their parameters were: HbA1c: 7.5 ± 0.8 %, TG: 0.9±0.1 mmol/L, cholesterol: 4.7 ± 0.2, LDL: 2.6 ± 0.1 mmol/L, HDL: 1.7 ± 0.07 mmol/L (Table 6).

Among the 37 CGM non-users: HbA1c: 8.3 ± 0.3 %, TG: 1.2±0.1 mmol/L, cholesterol: 4.9 ± 0.1, LDL: 2.9 ± 0.1 mmol/L, HDL: 1.4 ± 0.076 mmol/L (Table 6).

CGM users exhibited significantly different metabolic parameters, including lower TG (0.9 ± 0.1 vs. 1.2 ± 0.1 mmol/L, p = 0.034) and HbA1C (7.5 ± 0.2% vs. 8.3 ± 0.3%, p = 0.04) levels, as well as higher HDL cholesterol levels (1.7 ± 0.1 vs. 1.5 ± 0.1 mmol/L, p = 0.02), compared to non-users (Table 6, Figure 9).

Table 6. Metabolic parameters in CGM users and non-users (mean±SE)

Patients	**CGM users**	**CGM non-users**	**p-value**
Number	24	37	x
HbA_{1C} (%)	7.5±0.8	8.5±0.3*	<0.05
Trigliceride (mmol/l)	0.9±0.1	1.2±0.1*	<0.05
Cholesterol (mmol/l)	4.7±0.2	4.9±0.1	0.13
LDL (mmol/l)	2.6±0.1	2.9±0.1	0.07
HDL (mmol/l)	1.7±0.07	1.4±0.06*	<0.05

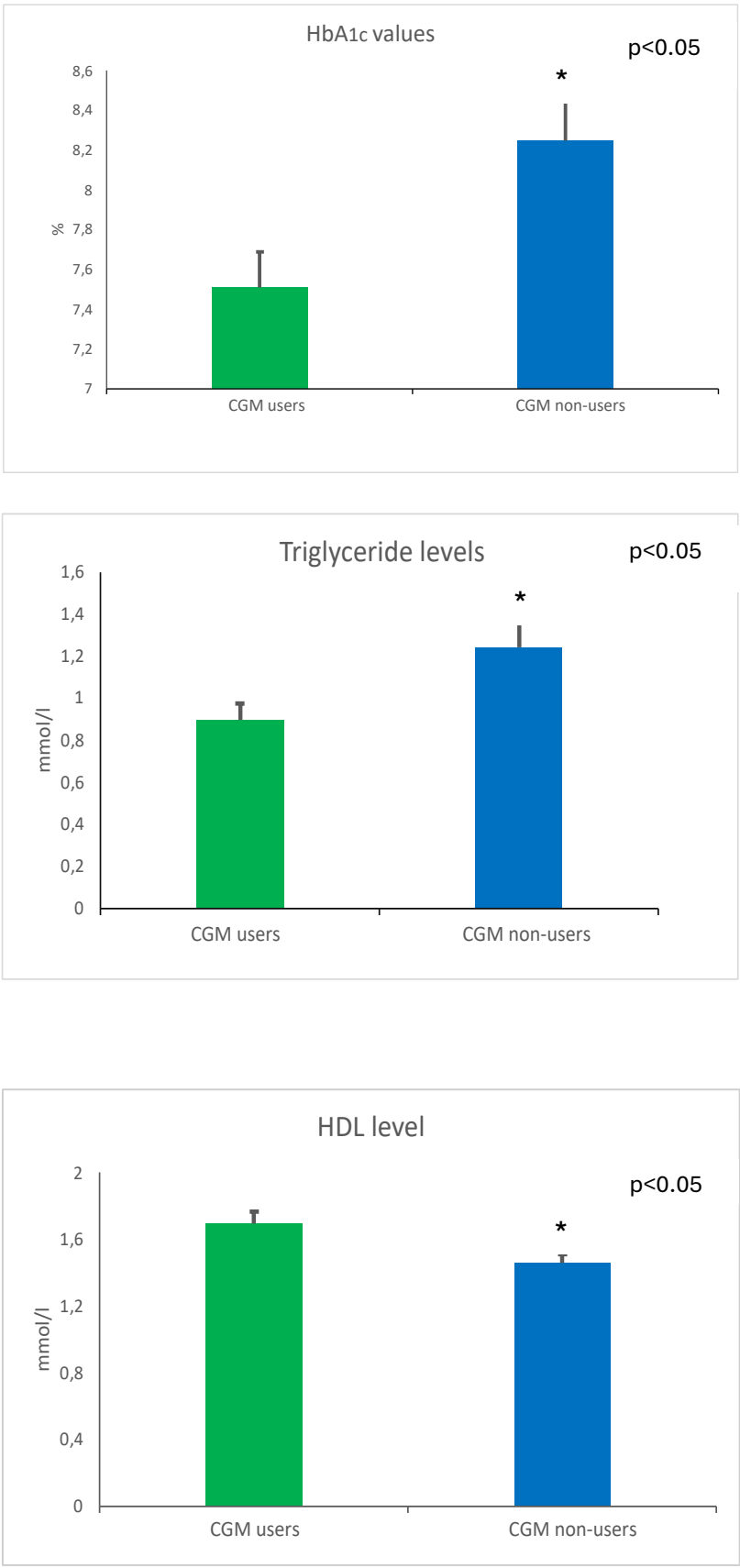

Figure 9. Metabolic parameters in CGM-user and non-user T1DM patients

6.4. Neurological Findings and Autonomic Tests

The evaluation of the cardiovascular autonomic reflex tests revealed a significant difference in VR values between CGM users and non-users (1.38 ± 0.06 vs. 1.27 ± 0.04, p = 0.045, Table 7, Figure 10). No significant differences were observed in the results of the remaining three tests (Table 8) although results were more physiological in the CGM group.

Table 7. Results of the cardiovascular autonomic function tests in CGM users and non-users (mean±SE)

Patients	CGM users	CGM non-users	p-value
Number	24	37	x
Heart rate response to deep breathing (beats/min)	24.7±2.9	18.9±1.9	0.22
Valsalva ratio (VR)	1.4±0.06	1.2±0.04*	0.045
30:15 ratio	1.1±0.03	1.1±0.01	0.32
Orthostasis (mmHg)	4.7±1.35	7.7±1.9	0.26

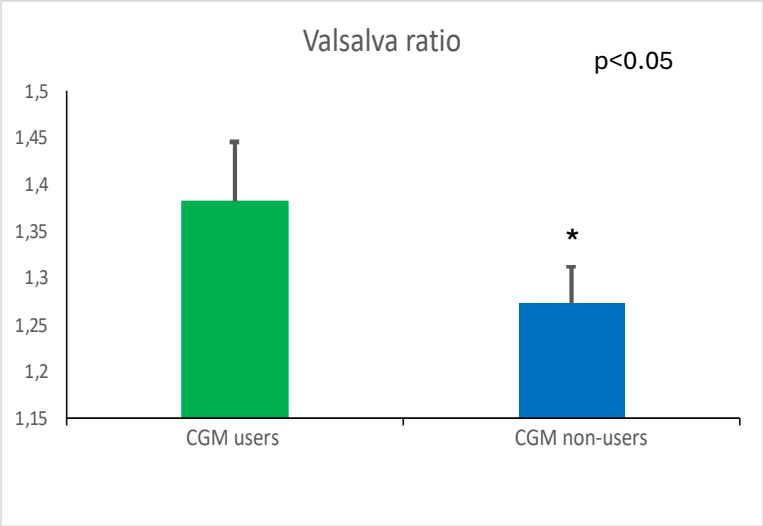

Figure 10. Valsalva ratio in CGM user and non-user T1DM patients

Using the Neurometer, we found a significant difference in large sensory nerve fiber function between CGM users and non-users, specifically in the perception thresholds at the median nerve during 2000 Hz stimulation (224.4 ± 21.2 vs. 290.6 ± 17.7, p = 0.01, Figure 11). No significant

differences were observed in the results of further tests on the median and peroneal nerves between the CGM users and non-users (Table 8).

Table 8. Peripheral sensory function in CGM users and non-users by Neurometer assessing the threshold of the current sensations at the median and peroneal nerves at three different stimulating frequencies (2 kHz, 250 Hz, 5 Hz) (mean±SE).

Patients	CGM users	CGM non-users	p-value
Number	24	37	x
n.medianus 2000 Hz	224±21.2	290±17.7*	<0.05
n.medianus 250 Hz	87.2±11.8	116±11.4	0.08
n.medianus 5 Hz	59.1±7.8	63.6±7.5	0.38
n.peroneus 2000 Hz	399.1±33.8	407.3±20.1	0.34
n.peroneus 250 Hz	189.2±21.7	200.7±12.6	0.42
n.peroneus 5 Hz	127.8±17.4	123.2±9.3	0.46

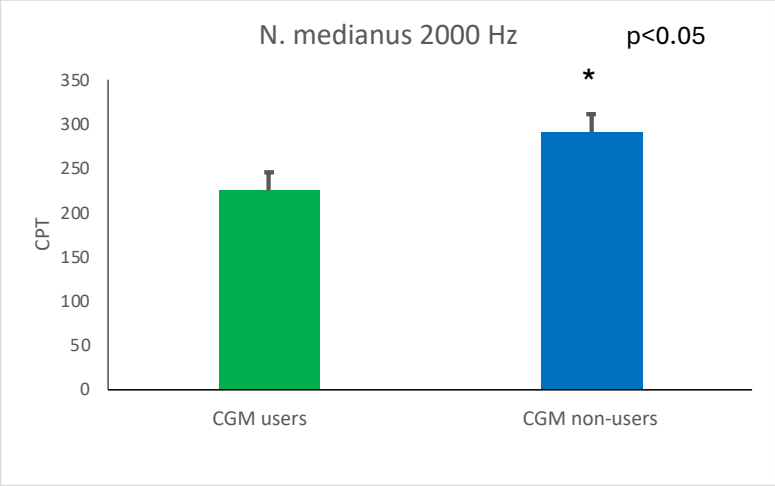

Figure 11. Peripheral sensory function in CGM user and non-user T1DM patients,

Calibrated tuning fork tests revealed significant differences in the vibration sense between CGM users and non-users at the right radius (7.4 ± 0.1 vs. 7.1 ± 0.1, p = 0.01, Table 10, Figure 12) and the right hallux (7.2 ± 0.2 vs. 6.1 ± 0.3, p = 0.005, Table 9, Figure 12). However, five out of six CPT values were higher, indicating some degree of hypesthesia among non-CGM users.

Table 9. Vibratory perception threshold evaluted by calibrated tuning fork in CGM users and non-users (mean±SE)

Patients	CGM users	CGM non-users	p-value
right radius	**7.4±0.1**	**7.1±0.1***	**<0.05**
left radius	7.0±0.4	6.9±0.2	0.35
right hallux	**7.2±0.2**	**6.1±0.3***	**<0.05**
left hallux	6.7±0.4	6.1±0.3	0.32

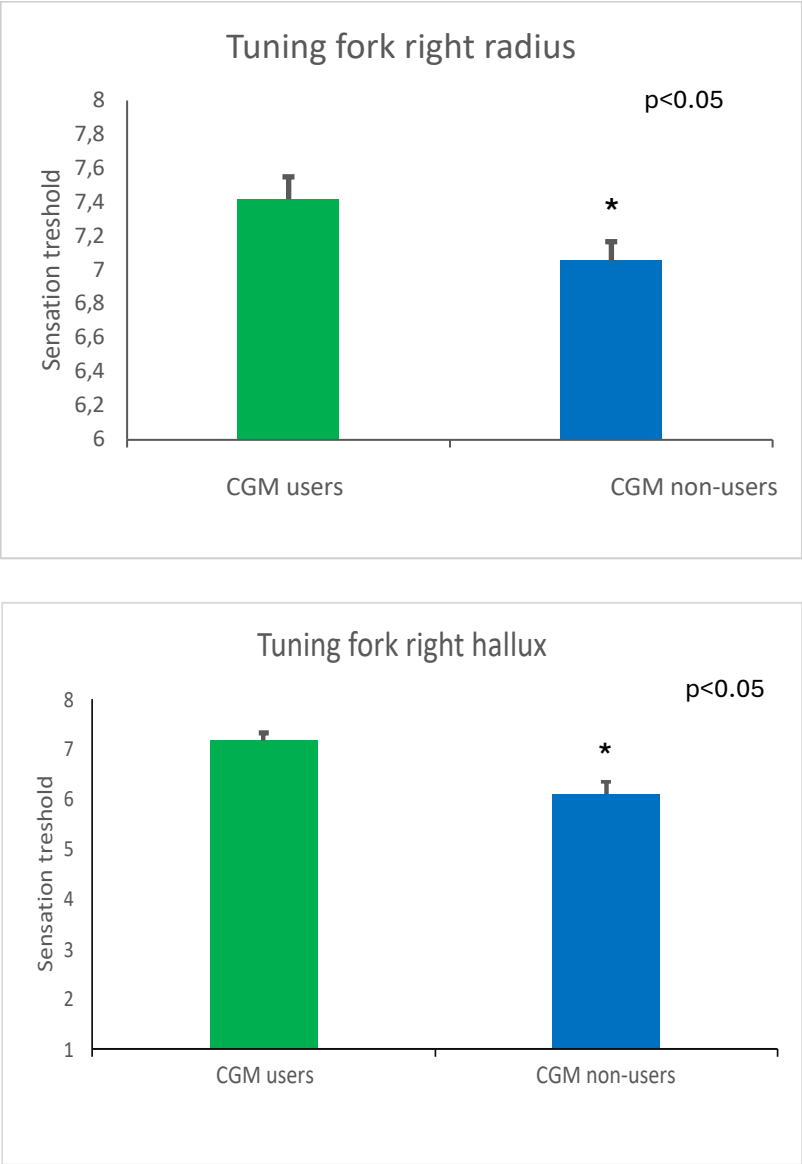

Figure 12. Vibratory perception in CGM user and non-user T1DM patients

6.5. Levels of Citrullinated Histone H3, PAD4 and NE

We evaluated plasma citrullinated histone H3 (cit-H3), PAD4 and NEbregarding NETosis markers in 29 T1DM (age: 40.9±1,7, HbA1c: 7.6± 0.18 [means±SE]) patients and 9 healthy individuals with normal HbA1c and lipid parameteres (age: 32.3±2.6 [mean±SE]).

The values for cit-H3 showed a significant difference between T1DM and healthy individuals: 0.21±0.03 vs. 0.27±0.01 (mean±SE), p=0.003 (Figure 13), while there was no significant difference between CGM-user and non-user group (0.21±0.01 vs. 0.20±0.01 (mean±SE), p=0.47).

The level of cit- H3 showed no significant correlations with any of the metabolic parameters, including cit-H3 and HbA1c (r=-0.13- p=0.49), cit-H3 and TG (r=0.17, p=0.35), cit-H3 and total cholesterine (r=-0.08, p=0.57), cit-H3 and LDL (r=-0.07, p=0.67), cit-H3 and HDL (r=-0.29, p=0.12).

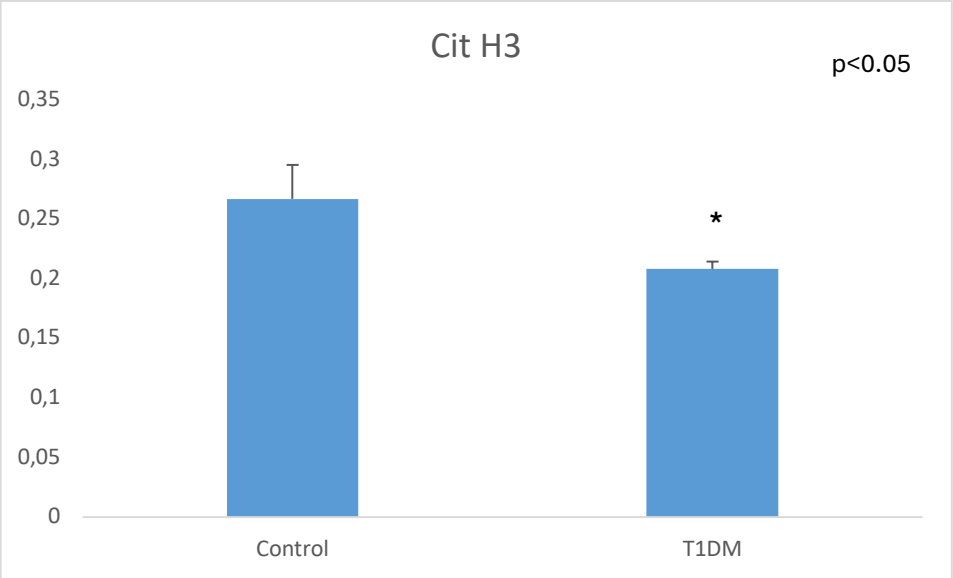

Figure 13. Citrullinated histone H3 levels in healthy individuals and T1DM patients

Regarding PAD4, there was no significant differences neither between the T1DM and control (0.005±0.0002 vs. 0.007±0.002, mean±SE, p=0.13), nor the CGM-user and non-user groups (0.005 ±0.0003 vs. 0.0052±0.0004, mean±SE, p=0.21).

After further analysation, PAD4 and TG levels showed a strong positive correlation (r=0.49, p=0.006, [Figure 14]), while HbA1c and PAD4 (r=0.33, p=0.07), PAD4 and total cholesterol (r=-0.29, p=0.12), PAD4 and LDL (r=0.26, p=0.17), PAD4 and HDL (r=-0.33, p=0.07) showed no significant correlations.

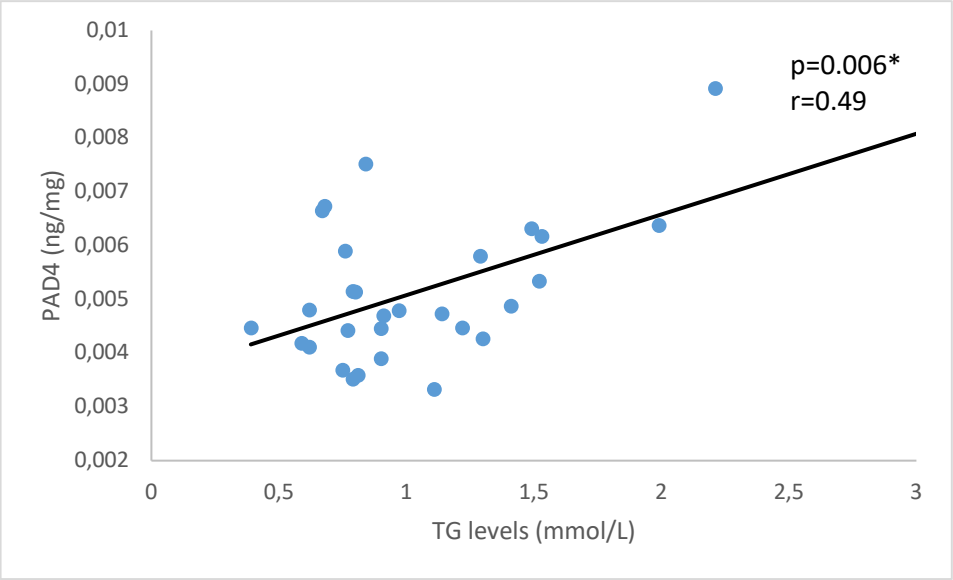

Figure 14. Correlation between PAD4 and trigliceride in T1DM patients

Serum NE levels were higher in the control group, but the difference was not significant (p=0.39). The CGM and non- CGM groups did not differ statistically significantly. The NE of our T1DM patients showed no relevant correlations with HbA1C (r=-0.06, p=0.77), TG (r=-0.1, p=0.67), LDL (r=-0.18, p=0.36), HDL (r=-0.11, p=0.53), total cholesterol (r=-0.17, p=0.37).

7. Discussion

Several studies have explored the relationship between glycemic control, diabetic complications and lipid metabolism in patients with T2DM, but much less evidence is available in T1DM (Weir, 2024). Unlike previous research, our study aimed to investigate the potential relationships among the glycemic and lipid and NETosis parameters as well as the autonomic and peripheral neuronal dysfunctions in T1DM patients. Recognizing that CGM offers an opportunity for improved glycemic control, we also focused on comparing these parameters between CGM users and non-users.

A clear positive correlation was found between HbA1C and fasting TG levels among our participants. This relationship suggests that poor glycemic control is associated with elevated TG levels in T1DM patients as well. Alternatively, the presence of hypertriglyceridaemia may coinside with higher HbA1c levels. Previous research demonstrated that TG doesn't impair, in a clinically significant manner, the performance of HbA1c measurement, so the correlation is not due to a methodological problem (Rodriguez-Gutierrez et al., 2019). It is published in the literature, that elevated TG levels are associated with inadequate glycemic control in T2DM,

and it is explained mainly by the pathogenetic role of the insulin resistance in these patients (Zheng et al., 2019). Hypertriglyceridemia observed in T1DM patients with poor or suboptimal glycemic control may be attributed to increased VLDL production secondary to relative insulin deficiency (Vergès, 2009). Moreover, hyperglycaemia contributes to hypertriglyceridaemia by reducing lipoprotein lipase activity in patients inadequately treated with insulin (Salsa-Castelo et al., 2023). In line with the observed correlation, our adequately treated individuals had more optimal TG levels due to the efficient insulin treatment. Both hyperglycemia and hyperlipidaemia can exacerbate oxidative stress, endothelial dysfunction and inflammation leading to multiplicity of cardiovascular risk in T1DM patients. Given the significant correlation between HbA1c and TG levels, either parameter may serve as a predictor of metabolic control in T1DM. Moreover, our findings highlight that elevated TG levels are not exclusively a sign of insulin resistance but are also associated with the worse glycemic control in insulin-dependent patients.

As CGM usage means a promise of better glycemic control in both types of diabetes, we divided our T1DM patients into two groups based on CGM use. Our findings revealed that patients not using CGM exhibited significantly higher HbA1c and fasting TG levels, whereas CGM users demonstrated higher HDL levels. The more optimal glycaemic control as a result of utilizing CGM seems to positively influence lipid profils, possibly through preventing the extreme fluctuations of glucose. The application of CGM promotes a more stable glycemic condition by reducing hypoglycemic episodes and enabling timely management of hyperglycemia with additional insulin boluses. The reduced glucovariability, potentially lowers the risk of vascular complications primarily through the reduction of oxidative stress (Vergès, 2024).

The detrimental effects of hypoglycaemia manifests in decreased nitric oxide (NO) levels, increased oxidative stress, production of free oxygen radicals, endothelial dysfunction, activation of the sympatoadrenal system and stimulation of proinflammatory and procoagulant pathways, all of which enhance the susceptibility to thrombosis, atherosclerosis and cardiovascular events (Amiel, 2021). A recent comparative retrospective cohort study established that in individuals with T1DM, severe hypoglycaemic events increase the risk for hospitalization and cardiovascular complications (Eeg-Olofsson et al., 2025). Moreover, the risk for CGM users from the same database was significantly lower both for hospitalization and cardiovascular events, than in the CGM non-user group (Eeg-Olofsson et al., 2025).

Conversely, hyperglycemia leads to glucotoxicity, characterized by oxidative stress, AGE production, activation of alternative metabolic pathways, inflammation, endothelial dysfunction, and ischaemia, resulting in both micro-, and macrovascular complications. Several studies showed that in case of higher glycemic variability, the harmful effects of hypo-, and hyperglycaemia add up exacerbating vascular damage (Ajjan, 2024). Although patients with T1DM are less frequently affected by obesity, dyslipidaemia or any of the further components of the metabolic syndrome than in T2DM, they are also at higher cardiovascular risk compared to the healthy population (Salsa-Castelo et al., 2023). CGM is not only an important tool for achieving optimal glycaemic control, but also for fostering favourable changes in lipid profiles. In our study CGM users exhibited significantly lower fasting TG and higher HDL levels, correlating with a reduced cardiovascular risk profile. Our findings suggest that CGM usage in T1DM patients may contribute to a decreased risk of cardiovascular events by improving both glycemic stability and lipid parameters.

The fluctuation in glucose levels and their associated harmful outcomes contribute to neuronal injury. In our study there was a significant difference between CGM users and non-users regarding heart rate reponses to the Valsalva manouevre, with non-CGM users exhibiting less physiological parameters. The evaluation of cardiovascular autonomic reflex tests revealed better performance for all tests in the CGM user group, with a significant difference noted in VR values. Supporting this, Jun JE et al. reported that in T1DM patients using CGM, glucose variability was strongly associated with CAN, independent of mean glucose levels (Jun et al., 2019). Nyiraty et al have also proven that several parameters of glucose variability are abnormal in the presence of CAN in T1DM (Nyiraty et al., 2018). Cardiac autonomic dysfunction is known to increase mortality primarily through impaired cardiac adaptation and the relatively augmented sympathetic tone (Vági et al., 2021). Sudden arrythmias, silent cardiac ischaemia, orthostatic hypotension are characteristic manifestations leading to lower quality of life and shorter life expactancy. Our findings suggest that effective therapy for preventing CAN should not only target average glucose levels, but also prioritize glucose stability. It should be noted that glucose instability may itself result from manifestations of autonomic neuropathy, due to impaired gastric emptying or a reduced ability to counteract hypoglycemia (Kempler et al., 2016). Our study design does not allow for detailed differentiation of the underlying pathogenic mechanisms linking improved cardiovascular function to CGM use. Regardless of that, the fact that the more physiologic response is proven to Valsalva manouvre in patients with CGM

highlights the importance of the glucose measuring method in the prevention of the undesirable consequences of cardiovascular dysfunctions.

Consistent findings were observed during the assessment of the peripheral sensory function of our patients. The calibrated tuning fork test indicated a better vibratory sensory function on the upper and lower extremities in patients wearing CGM. Similarly, Neurometer measurements revealed lower perception thresholds within the normal range at 2000 Hz stimulating frequency on the median nerve in CGM users suggesting a better sensory condition in these subjects. Both methods assess the functionality of the large sensory nerve fibres which were found to be in a more physiologic state in CGM users. This indicates that hypaesthesia of the large fibres is less common in T1DM patients utilizing CGM. Preserving intact vibratory function is critical in preventing vascular complications as impaired vibration sensation, identified at the start of the EURODIAB IDDM Prospective Trial, was shown to be a significant predictor of severe lower extremity complications and mortality (Tesfaye et al., 2005). Patients with abnormal vibration thresholds were more likely to develop lower extremity complications, such as ulcers and gangrene, and more frequently required lower extremity bypass surgery or angioplasty. Additionally, these patients faced a six times higher risk of amputation compared to those with normal vibration sensation. Multivariate regression analysis identified that HbA1C, triglyceride levels, hypertension, smoking, BMI were independent risk factors for impaired vibration sensation. The presence of cardiovascular disease further doubled the risk of large-fiber damage (Elliott et al., 2009). In a pilot study, it was found that patients with painful neuropathy have much higher glucose levels and gycemic excursions compared to individuals with better glycaemic control, who had less damage in the nerves (Oyibo et al., 2002). In a systematic review of 110 records, a significant association was found between TIR and microvascular complications including diabetic neuropathy, retinopathy and nephropathy in T2DM patients, also suggesting that more optimal glycaemic control and less excurcions in blood glucose levels are associated with less complications and better quality of life (Raj et al., 2022). Our findings highlight the pathophysiological significance of improved glycemic and lipid control facilitated by CGM. Regarding the peripheral sensory neuropathy it is unlikely that this condition contributes to unstable glucose levels. Instead, the use of CGM appears to play a crucial role in supporting better peripheral sensory function, emphasizing its importance in the comprehensive management of T1DM. As the broader application of digital health technology is currently more an more frequently recommended (American Diabetes Association Professional Practice

Committee et al., 2025) its beneficial effect on the outcomes of the whole T1DM population is estimated.

Upon analyzing CGM parameters, a significant positive correlation was identified between TAR and TG levels, as well as between TAR and HbA1c. This indicates a close association between poor metabolic control and elevated TG levels, which are frequently observed in individuals with diabetes mellitus (Smellie, 2006). Dyslipidemia is recognized as a major risk factor for cardiovascular disease; while elevated LDL cholesterol has traditionally received considerable attention, the role of hypertriglyceridemia is also increasingly emphasized (Chehade et al., 2013; Sone et al., 2011). Although hypertriglyceridemia has become a significant concern in the context of diabetes mellitus (Hirano, 2018), its implications in T1DM remain less understood (Vergès, 2024). The persistent state of relative insulin deficiency, even in the presence of exogenous insulin therapy, fosters increased lipolysis in adipose tissue, resulting in an overproduction of free fatty acids that subsequently accumulate in the liver. This hepatic overload of fatty acids stimulates the synthesis and secretion of VLDL, which serve as the primary carriers of triglycerides in circulation (Adiels et al., 2006). Furthermore, insulin deficiency hampers the activity of lipoprotein lipase, the enzyme responsible for hydrolyzing TGs in VLDL and chylomicrons, thereby exacerbating hypertriglyceridemia. CGM technology can be utilized to identify specific patterns of hyperglycemia that may contribute to hypertriglyceridemia, such as postprandial glucose spikes or nocturnal hyperglycemia. These insights can facilitate targeted interventions, including adjustments to insulin regimens, modifications to dietary carbohydrate intake, or lifestyle changes aimed at mitigating these hyperglycemic patterns and improving TG levels. In this context, continuous glucose monitoring emerges as a vital tool for optimizing glycemic control in individuals with T1DM, which can positively influence serum TG levels and overall cardiometabolic health (Bergenstal et al., 2018).

The impairment of parasympathetic functions typically precedes sympathetic dysfunction, resulting a relative dominance of the sympathetic tone recognized as a serious late-stage complication of diabetes (Bokhari et al., 2018). Disruption in cardiac autonomic control can lead to a myriad of cardiovascular dysfunctions, including resting tachycardia, exercise intolerance, orthostatic hypotension, and an increased risk of sudden cardiac death (Galiero et al., 2023). The type of arrhythmia that is caused by hypoglycaemia has a diurnal pattern (Novodvorsky et al., 2017). Hypoglycaemia causes the activation of sympathoadrenal system leading to premature ventricular contractions, tachycardia, non-sustained ventricular

tachycardia, QTc prolongation resulting in ventricular tachycardia and high-degree AV block (Reno et al., 2013). During the night, the sympatoadrenal response and QTc prolongations are less pronounced, while vagal tone is increased, leading to bradycardia, AV-block and cardiac arrest (Andersen et al., 2020). Moreover, a recent study showed that the role of parasympathetic nervous system in cardiac arrhythmias are a major concern. According to their animal model, under hypoglycaemic episodes, acetilcholin acts as a proarrhythmogenic agent and the pharmacological blockade of parasympathetic nervous system protects againt arrhythmias, while sympathectomy did not alter cardiac arrhythmias and mortality (Reno et al., 2019). Hpoglycaemia, mainly nocturnal hypoglycaemia is also strongly associated with DSPN, which is worsened by glycaemic excursions, greater glucovariability (Shen et al., 2021). By using CGM, hypoglycaemic episodes can be minimised and avoided, thus reducing the risk of sympathetic and parasympathetic nervous system impairment (Marigliano et al., 2024).It was shown that worse glycaemic control leading to lower TIR is in connection with the decrease of microvascular complications, hospitalization and acute conditions, like diabetic ketoacidosis (El Malahi et al., 2022).

Our findings demonstrate significant positive correlations between TAR and orthostatic blood pressure changes upon standing, as well as between TBR and the 30:15 ratio, indicating that hyperglycemia adversely affects the sympathetic function, while hypoglycemia impacts the parasympathetic regulation. Together, these factors contribute to a markedly increased cardiovascular risk. Moreover, the presence of cardiac autonomic neuropathy can exacerbate other diabetes-related complications, such as diabetic cardiomyopathy including diastolic dysfunction, further increasing the risk of heart failure and mortality (Jia et al., 2018, Zhou et al., 2014).

The application of CGM in individuals with T1DM has shown promise in mitigating the progression and severity of autonomic neuropathy through enhanced glycemic management. CGM provides a continuous stream of glucose data, enabling the identification of glycemic excursions and patterns that may be overlooked through traditional self-monitoring of blood glucose (Bergenstal et al., 2018). By decreasing the frequency and severity of such glucose extremes, the use of CGM may alleviate metabolic stress on autonomic nerves, potentially slowing the progression of neuropathy (Bergenstal et al., 2018). The clinical implications of employing CGM in T1DM extend to improved management of autonomic neuropathy by optimizing glucose control and minimizing glucose excursions as well as hypoglycemic events,

thereby reducing the risk of both acute and chronic complications associated with diabetes(Toschi & Wolpert, 2016).

The importance of the role of NETosis in diabetes and its complications is constantly growing. NETosis is an abnormal response in diabetes mellitus and can contribute to many unfavourable outcomes. Exaggerated reactions lead to tissue damage by endothelial damage, thrombosis and ischaemic injury. Diabetes is known to upset the equilibrium between defence of the body and self-damage (Fadini et al., 2016). It also plays a major role in the pathogenesis of cardiovascular disease (Fadini et al., 2016). In individuals diagnosed with diabetes, there is a notable elevation of products associated with the release of NETs in the bloodstream. These observations lend robust support to the established correlation between NETosis and various complications arising from diabetes. Such complications include impaired wound healing, diabetic retinopathy, and the development of atherosclerosis (Y. Zhu et al., 2023). A study revealed that the circulating levels of PR3 and NE exhibit heightened activity in patients with T1DM when juxtaposed with control subjects, with particularly notable increases occurring in individuals whose disease duration is less than one year (Wang et al., 2014). The pronounced elevation in NE and PR3 levels has been strongly associated with a rise in both the quantity and titer of positive β-cell autoantibodies, thereby suggesting an augmentation of NETosis as a contributing factor in the pathogenesis of pancreatic β-cell autoimmunity. These observations underscore a positive correlation between elevated circulating levels of NE and PR3 and the presence of T1DM (Wang et al., 2014). Moreover, another investigation has identified that elevated circulating levels of NE and PR3 are also present in T1D patients who are negative for autoantibodies. However, a paradox emerges, as other studies have documented significantly lower levels of NE and PR3 in patients who have been diagnosed with T1D for up to three years (Y. Zhu et al., 2023). The previous studies focused on PR3 and NE, but differently, we investigated cit-H3 and PAD4 markers. Several studies showed the significance of NETosis markers in diabetic retinopathy, mainly cit-H3 and MPO (Y. Zhu et al., 2023). NE and PR3 also promote atherogenesis (Y. Zhu et al., 2023). Among metabolic parameteres, the role of cholesterol crystals is emphasized (Adamidis et al., 2024). The mean duration of diabetes among our patients was more than 20 years, which means a long-term duration, that is different from previous studies. The level of both cit-H3 and PAD4 of our T1DM patients was significantly lower than the control group, suggesting that with the advance of diabetes, NETosis markers are lower in the periphery, which coincides with a cross-sectional study (Aukrust et al., 2022). While previous studies suggest that the extent of NETosis is associated

with inadequate glycaemic values and total cholesterine crystals, as a novum finding we identified a strong positive correlation between serum trigliceride and PAD4 levels and an inverse relationship between HDL and PAD4. The pathogenetic role of PAD4 is known in many autoimmune diseases, tumor formation, vasculitis, thrombosis and sepsis (Lewis et al., 2015). PAD4 participates in acute thrombotic complications (Franck et al., 2018), activates coagulation cascade and platelet aggregation (Li et al., 2020), causes atherosclerosis via chronic inflammatory process (Li et al., 2020). Cholesterol crystals are known to trigger NETosis (Warnatsch et al., 2015) as NETs are present in eroded plaques (Warnatsch et al., 2015) and severe coronary atherosclerosis (Borissoff et al., 2013), but its role in cardiovascular diseases and lipid metabolism is still unknown. With our finding it arises that PAD4 is a possible macrovascular risk factor in T1DM by having an influence on lipid metabolism, especially TG levels.

Our study had some limitations. One notable limitation was the significant age difference between the two groups. This disparity might be attributed to younger patients being more adept at using smart devices and demonstrated more openness to apply advanced diagnostic and therapeutic technologies. It should be noted, however, that there was no significant difference in the duration of diabetes, which is one of the most important risk factors for the development of neuropathy in T1DM. Another limitation is the cross-sectional design of our study. In addition, the study is based on laboratory parameters, CGM data and functional neuronal tests, without taking into account participants' lifestyle characteristics or medications for diabetes or other comorbid conditions. While the beneficial effect of CGM on glycemic control was evident in improved HbA1c levels, other potential outcomes or confounding variables were not assessed, limiting the scope of our findings.

8. Conclusions and Future Directions

In conclusion, our research indicates that enhanced glycaemic control, proven by HbA1C levels, correlates with reduced TG levels in patients with T1DM. Those utilizing CGM systems experienced additional advantages, including improved TG and HDL levels. Furthermore, these individuals exhibited markedly better cardiovascular autonomic and peripheral sensory functions. The benefits of using CGM may be derived from improved glycaemic management and lower lipid levels. These combined metabolic effects emphasize the potential of CGM as a crucial tool not only for the effective management of diabetes but also as a novel finding in the prevention or postponing of neural dysfunction and reducing cardiovascular risk. It is assumed

that CGM is not only beneficial for avoiding micro-, but also for macrovascular complications. This highlights the promise of CGM technology in contributing to long-term cardiovascular and neurological health for patients with T1DM. Moreover, the finding that serum PAD4 levels have a strong positive correlation with TG levels and how it impacts cardiovascular diseases can form the basis for further detailed, molecular researches

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