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Article

Comprehensive Assessment of Neuropathy and Metabolic Parameters in Type 1 Diabetic Patients with or Without Using Continuous Glucose Sensors

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Abstract: The present study was conducted in type 1 diabetic (T1DM) patients to evaluate the metabolic and glycemic control as well as the manifestations of neuropathy. The impact of continuous glucose monitoring (CGM) on the measured parameters was also analyzed. A total of 61 T1DM patients (age: 42.5 ± 1.8 years, DM duration: 22.8 ± 1.6 years, mean ± SE) participated in the study. In total, 24 patients had CGM sensors and 37 did not. Cardiovascular autonomic neuropathy was assessed using cardiovascular reflex tests. Peripheral sensory function was evaluated by a Neurometer and calibrated tuning fork on the upper and lower limbs. Metabolic status was characterized by the determination of triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, and glycated haemoglobin (HbA_{1c}). A positive correlation was found between HbA_{1c} and triglyceride levels ($r = 0.28$, $p < 0.05$). CGM users and non-users differed in triglyceride (0.9 ± 0.1 vs. 1.24 ± 0.12 mmol/L, $p < 0.05$), HDL cholesterol (1.7 ± 0.1 vs. 1.4 ± 0.1 $p < 0.05$ mmol/L), and HbA_{1c} (7.5 ± 0.2 vs. 8.3 ± 0.3%, $p < 0.05$) levels as well. Significant differences were found for the Valsalva ratio, Neurometer, and calibrated tuning fork results between CGM users and non-users. This study found a significant correlation between HbA_{1c} and triglyceride levels in T1DM. CGM use resulted in improved metabolic parameters and less autonomic and sensory nerve damage. As a novel finding, CGM is presumed to prevent both micro-, and macrovascular complications and, by this way, potentially reducing mortality rates.

Keywords: diabetes mellitus; continuous glucose monitoring; CGM; neuropathy; triglyceride; serum lipid; cholesterol

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1. Introduction

Diabetes mellitus is a complex metabolic disease that primarily affects carbohydrate metabolism but its impact on lipid and protein metabolic processes cannot be neglected. 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 [1]. Cardiovascular autonomic neuropathy (CAN) and distal symmetric polyneuropathy (DSPN) are frequent complications

of diabetes, mainly in individuals with prolonged periods of elevated glucose levels. In addition to hyperglycemia, several associated factors, including inflammation, oxidative stress, endothelial dysfunction, advanced glycated end products (AGEs), hypoxia, and ischemia, are implicated in their pathogenesis. Among these, the role of dyslipidemia is particularly significant (Figure 1) [2,3].

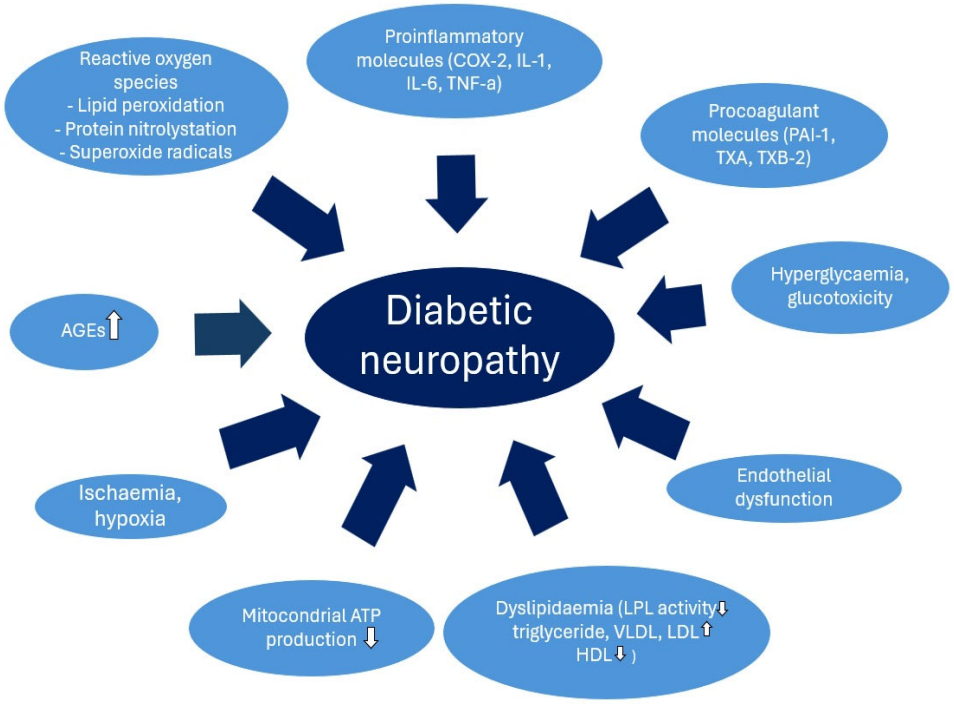

Figure 1. Pathomechanism of diabetic neuropathy.

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 type 1 (T1DM) and type 2 diabetic (T2DM) patients. 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 hyperlipidemia as well, especially in patients with T2DM. A significant correlation was established between CAN and age, diabetes duration, higher glycated hemoglobin (HbA_{1c}), fasting triglyceride (TG), and lower high-density lipoprotein (HDL) levels in T1DM patients [4]. HbA_{1c} is associated with dyslipidemia, including elevated low-density lipoprotein (LDL) and TG [5], and is also an important parameter in predicting coronary artery disease in T2DM subjects [6]. Patients with T1DM are also at higher risk of developing any diabetes-related complications and all-cause mortality. Inadequate glycaemic control and glucose variability are associated with higher cholesterol, LDL, and TG levels and lower HDL levels [7].

A recent meta-analysis found that continuous glucose monitoring (CGM) metrics might determine not only the microvascular but also the macrovascular complications in T1DM [8]. The use of HbA_{1c} 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 hyperglycemia or hypoglycemia. 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 [9,10]. It is widely accepted, that CGM plays a key role in improving carbohydrate metabolism and achieving

optimal HbA_{1c}. However, its impact on micro- and macrovascular complications of diabetes and lipid metabolism is still poorly understood. To explore the details of the relationship between the components of the complex metabolic control and diabetic neuropathy in T1DM, we organized a trial in which we evaluated the diabetic autonomic and peripheral sensory functions as well as the glycemic and lipid parameters. We focused on the role of the application of CGM as a new potential tool in the improvement of metabolic control and preservation of neuronal function.

2. Results

Synthesis of Results

A total of 61 patients (age: 42.5 ± 1.8 years, DM duration: 22.8 ± 1.6 years, BMI: 25.3 ± 0.9, HbA_{1c}: 8.1 ± 0.2%; mean ± SE) were studied (Table 1). In total, 24 patients used CGM sensors (age: 35.7 ± 2.5, DM duration: 20.0 ± 1.8, BMI: 24.5 ± 0.8, HbA_{1c}: 7.5 ± 0.8%) and 37 did not (age: 45.9 ± 1.8, DM duration: 25.0 ± 1.9, BMI: 26.5 ± 0.8, HbA_{1c}: 8.3 ± 0.3%, Table 2). 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 1. Patients's data.

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 2. Data on CGM users and non-users.

Patients	CGM Users	CGM Non-Users	*p*-Value
Number of patients	24	37	/
Age (years)	35.7 ± 2.5	45.9 ± 1.8 *	0.01
Duration of diabetes	20.0 ± 1.8	25.0 ± 1.9	0.1
BMI (kg/m^2)	24.5 ± 0.8	26.5 ± 0.8	0.1
HbA_{1c} (%)	7.5 ± 0.8	8.3 ± 0.3 *	0.04

*: $p < 0.05$.

A significant positive correlation was found between HbA_{1c} and TG levels in the overall group of T1DM patients (r = 0.28, $p = 0.045$) (Figure 2). The mean lipid parameters were within the normal range. However, neither the HbA_{1c} nor the lipid parameters showed a significant correlation with the cardiovascular autonomic or peripheral sensory function ($p > 0.05$ in all cases).

For further analysis, the diabetic group was divided into two subgroups based on CGM usage. 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 3). No significant differences were observed in the results of the remaining three tests (Table 3) although results were more physiological in the CGM group.

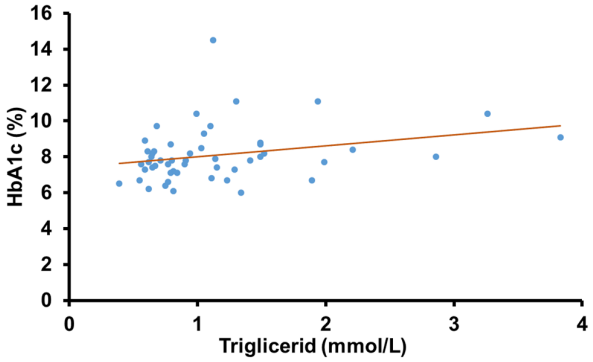

Figure 2. Correlation between HbA_{1c} and triglyceride levels in T1DM patients.

Table 3. Results of the cardiovascular autonomic function tests in CGM users and non-users.

Patients	CGM Users	CGM Non-Users	*p*-Value
Heart rate response to deep breathing (beats/min)	24.7 ± 2.9	18.9 ± 1.9	0.22
Valsalva ratio	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

*: $p < 0.05$.

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, $p = 0.01$). 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 4).

Table 4. Peripheral sensory function in CGM users and non-users by the 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).

Neurometer	CGM Users	CGM Non-Users	*p*-Value
n.medianus 2000 Hz	224 ± 21.2	290 ± 17.7 *	0.01
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

*: $p < 0.05$.

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, $p = 0.01$) and the right hallux (7.2 ± 0.2 vs. 6.1 ± 0.3, $p = 0.005$, Table 5). However, five out of six CPT values were higher, indicating some degree of hypesthesia among non-CGM users.

Table 5. Vibratory perception threshold evaluated by calibrated tuning fork in CGM users and non-users.

Calibrated Tuning Fork	CGM Users	CGM Non-Users	*p*-Value
right radius	7.4 ± 0.1	7.1 ± 0.1 *	0.01
left radius	7.0 ± 0.4	6.9 ± 0.2	0.35
right hallux	7.2 ± 0.2	6.1 ± 0.3 *	0.005
left hallux	6.7 ± 0.4	6.1 ± 0.3	0.32

*: $p < 0.05$.

Additionally, 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 HbA_{1c} (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).

Table 6. Metabolic parameters in CGM users and non-users.

Metabolic Parameters	CGM Users	CGM Non-Users	*p*-Value
HbA_{1c} (%)	7.5 ± 0.8	8.3 ± 0.3 *	0.04
Trigliceride (mmol/L)	0.9 ± 0.1	1.2 ± 0.1 *	0.034
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 *	0.02

*: $p < 0.05$.

3. 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 on T1DM [11]. Unlike previous research, our study aimed to investigate the potential relationships among the glycemic and lipid 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 HbA_{1c} and fasting TG levels among our participants. Previous research demonstrated that TG does not impair, in a clinically significant manner, the performance of HbA_{1c} measurement so the correlation is not due to a methodological problem [12]. 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 insulin resistance in these patients [13]. Hypertriglyceridemia observed in T1DM patients may be attributed to increased VLDL production secondary to relative insulin deficiency [14] and decreased lipoprotein lipase activity in patients inadequately treated with insulin [7]. Both hyperglycemia and hyperlipidemia can exacerbate oxidative stress, endothelial dysfunction, and inflammation, leading to a multiplicity of cardiovascular risks in T1DM patients. Given the significant correlation between HbA_{1c} 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 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 HbA_{1c} 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 profiles, possibly through preventing the extreme fluctuations of glucose, promoting 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 [15].

The detrimental effects of hypoglycemia manifest in decreased nitric oxide (NO) levels, increased oxidative stress, the production of free oxygen radicals, endothelial dysfunction, the activation of the sympathoadrenal system, and the stimulation of proinflammatory and procoagulant pathways, all of which enhance the susceptibility to thrombosis, atherosclerosis, and cardiovascular events [16]. 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 (Figure 1). Several studies showed that in case of higher glycemic variability, the harmful effects of hypo- and hyperglycemia add up, exacerbating vascular damage (Figure 3) [17]. Although patients with T1DM are less frequently affected by obesity, dyslipidemia, or any of the further components of the metabolic syndrome in T2DM, they are also at higher cardiovascular risk compared to the healthy population [7]. 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.

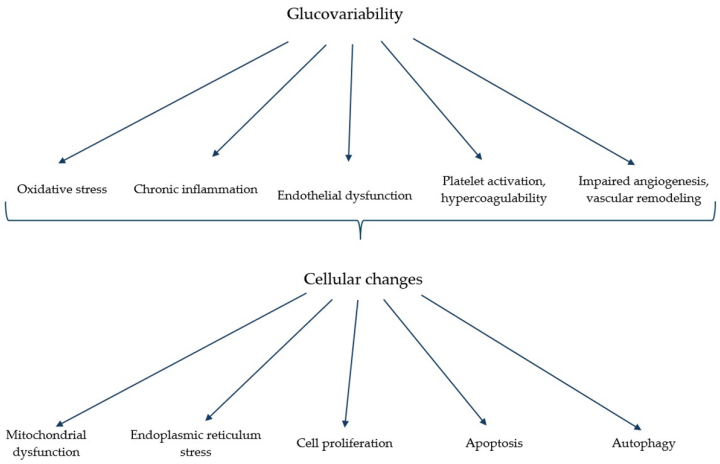

Figure 3. Glucovariability biochemical, pathophysiological, and cellular changes.

The fluctuation in glucose levels and their associated harmful outcomes contribute to neuronal injury. In our study, all cardiovascular autonomic reflex tests showed better values while there was a significant difference between CGM users and non-users regarding heart rate responses to the Valsalva maneuver, with non-CGM users exhibiting fewer physiological parameters. Supporting this, Jun J.E. et al. reported that in T1DM patients using CGM, glucose variability was strongly associated with CAN, independent of mean glucose levels [18]. Nyiraty Sz et al. have also proven that several parameters of glucose variability are abnormal in the presence of CAN [19]. Cardiac autonomic dysfunction is known to increase mortality [20] primarily through impaired cardiac adaptation and the relatively augmented sympathetic tone, resulting in sudden arrhythmia, silent cardiac ischemia, and orthostatic hypotension. Our findings suggest that effective therapy for preventing CAN should not only target average glucose levels but also prioritize glucose stability. 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 by the Valsalva maneuver 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 with 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 fibers, which were found to be in a more physiologic state in CGM users. 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 [21]. 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. The presence of cardiovascular disease further doubled the risk of large-fiber damage [22]. Our findings highlight the pathophysiological significance of improved glycemic and lipid control facilitated by CGM. 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 and more frequently recommended [23], its beneficial effect on the outcomes of the whole T1DM population is estimated.

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 demonstrating 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. Also, all our patients were adherent and followed the carbohydrate restriction in their diet, as calculated individually. Another limitation is the cross-sectional design of our study. In addition, this study is based on laboratory parameters, CGM data, and functional neuronal tests, without taking into account participants' detailed lifestyle characteristics or medications for diabetes or other comorbid conditions. While the beneficial effect of CGM on glycemic control was evident in improved HbA_{1c} levels, other potential outcomes or confounding variables were not assessed, limiting the scope of our findings.

4. Materials and Methods

4.1. Patients

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 (age: 42.5 ± 1.8 years, DM duration: 22.8 ± 1.6 years, BMI: 25.3 ± 0.9, HbA_{1c}: 8.1 ± 0.2%; mean ± SE) were studied (Table 1). In total, 24 patients used CGM sensors regularly (age: 35.7 ± 2.5, DM duration: 20.0 ± 1.8,

BMI: 24.5 ± 0.8, HbA_{1c}: 7.5 ± 0.8%) and 37 did not (age: 45.9 ± 1.8, DM duration: 25.0 ± 1.9, BMI: 26.5 ± 0.8, HbA_{1c}: 8.3 ± 0.3%, Table 2).

4.2. Evaluating Sensory Dysfunction

Peripheral sensory nerve function was assessed by a Neurometer (MSB Ltd., Balatonfüred, Hungary) and a calibrated tuning fork was applied to the upper and lower extremities. The Neurometer device was designed to quantify the sensory function of different types of nerve fibers and provides a simple, non-invasive measurement of peripheral sensory function [24]. 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 to 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 consistently 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 fibers.

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 the right and left legs [25]. The normal range was declared as 7 to 8, 6 was classified as borderline, and scores between 1 and 5 indicated an impaired sense of vibration.

4.3. Assessment of Autonomic Neuropathy

Autonomic function was characterized by Ewing's standard cardiovascular reflex tests in this study [26]. The Ewing tests are the gold standards for diagnosing autonomic dysfunction; they provide non-invasive, clinically relevant, standardized, and reproducible data on autonomic functions. Reflex tests were performed by measuring the blood pressure and obtaining continuous six-lead ECG signals. The signals were digitized with a multichannel data acquisition system (CA-12 v.2.85 software, 2021, MSB Ltd., Balatonfüred, Hungary). Parasympathetic dysfunction was examined by measuring deep breathing tests, the Valsalva ratio (VR), and the 30:15 ratio while sympathetic nervous system impairment was tested by assessing orthostatic blood pressure drop on standing up. As the handgrip test is becoming a marker of hypertension and its complications more and more, we did not use it in our evaluation [27].

4.4. Laboratory Measurements

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, LDL <3.0, and total cholesterol: <5.20.

4.5. 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.

4.6. 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.

5. Conclusions

In summary, our findings suggest that better glycaemic control, as reflected by HbA_{1c} levels, is associated with lower TG levels in T1DM patients. Those using CGM experienced further benefits, including more favorable TG and HDL levels. In addition, these patients had significantly better cardiovascular autonomic and peripheral sensory function. The advantage of CGM use might be realized through the better glycemic control and the lower lipid levels as well. The combined metabolic effects underline the potential of CGM as a valuable tool not only for managing diabetes but also, as a novel finding, for preventing or postponing the development of neural dysfunction as well. This highlights the promise of CGM technology to contribute to long-term cardiovascular and neurological health in T1DM patients.

Author Contributions: Conceptualization, T.V. and K.K.; methodology, T.V.; software, S.N.; validation, Z.V., C.L. and P.K.; formal analysis, A.M.; investigation, B.B.; resources, A.P. and K.K.; data curation, Á.V.; writing—original draft preparation, B.B.; writing—review and editing, K.K., T.V., C.L. and P.K.; visualization, S.N.; supervision, P.K.; project administration, Á.V.; funding acquisition, K.K. and A.P. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Szeged (67/2022-SZTE).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: Our figures contain mean ± SE data of our T1DM patients.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AGE	Advanced glycated end products
BMI	Body mass index
CAN	Cardiovascular autonomic neuropathy
CGM	Continuous glucose monitoring
COX-2	Cyclooxygenase-2
CPT	Current perception threshold
DSPN	Distal symmetric polyneuropathy
HbA_{1c}	Glycated hemoglobin
HDL	High-density lipoprotein
IL-1	Interleukin-1
IL-6	Interleukin-6

LDL	Low-density lipoprotein
LPL	Lipoprotein lipase
PAI-1	Plasminogen activator inhibitor-1
TAR	Time above range
TBR	Time below range
TIR	Time in range
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TG	Triglyceride
TNF-a	Tumor necrosis factor-alpha
TXA	Thromboxan A
TXAB-2	Thromboxan B-2
VLDL	Very low-density lipoprotein
VR	Valsalva ratio

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CEDA diabetes

Zentraleuropäische Diabetesgesellschaft
Central European Diabetes Association

Föderation der Internationalen Donau-Symposia über Diabetes mellitus
Federation of International Danube-Symposia on Diabetes mellitus

Keep the balance: the multiple effects of continuous glucose monitoring on the management of type 1 diabetes

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Summary

Continuous glucose monitoring (CGM) has emerged as a crucial tool in managing type 1 diabetes (T1DM), offering real-time insights into glucose fluctuations. By providing continuous data on blood glucose levels, CGM systems enable patients to make informed decisions regarding insulin dosing and dietary choices. Recent studies have demonstrated that CGM significantly improves glycemic control, reduces the incidence of hypoglycemic episodes, and improves lipid profile parameters and autonomic neuronal functions.
Patients and methods: 24 T1DM patients were included in the study (age: 35.7 ± 2.5 years, diabetes duration: 20.0 ± 1.8 years, BMI: 24.5 ± 0.8 kg/m^2, HbA_{1c}: 7.5 ± 0.8 %, mean ± SE). 19 of the patients wore the glucose sensor for more than four years, while five of them wore them between six months and four years. Regarding the CGM parameters, time in range (TIR), time above range (TAR) and time below range (TBR) were assessed. Cardiovascular autonomic neuropathy was measured by 4 cardiovascular reflex tests. The metabolic state was characterized by the determination of triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, and glycated hemoglobin (HbA_{1c}).
Results: The mean sensor parameter values of the patients were close to the target range (TIR: 70.4 ± 10.1 %, TAR: 24.6 ± 9.2 %, TBR: 4.6 ± 4.5 %, mean ± standard deviation). Among the metabolic values, positive correlations were found for HbA_{1c} and TAR ($r = 0.56$, $p < 0.05$) and TG and TAR ($r = 0.53$, $p < 0.05$). The autonomic tests revealed correlations between TAR and orthostatic blood pressure drop on standing up ($r = 0.57$, $p < 0.05$) and between TBR and 30:15 ratio ($r = 0.53$, $p < 0.05$,).
Conclusion Overall, CGM represents a transformative advancement in type 1 diabetes care, promoting better health outcomes through providing solution for the achievement of stable glycemic control of the patients.

Key words
continuous glucose monitoring, CGM, lipid, cardiovascular autonomic neuropathy, cardiovascular disease

Introduction

CGM and diabetes mellitus

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. These devices, which involve the insertion of a small sensor under the skin to continuously measure glucose levels in interstitial fluid, supply real-time glucose readings, trend arrows indicating the direction and rate of glucose change, and customizable alerts for impending hypoglycemia or hyperglycemia [Raubertas 2019, Vashist 2013]. As the patient receives continuous reports about glucose, individuals with diabetes and their healthcare providers are supplied with information for decisions regarding insulin dosing, dietary choices, and physical activity [Raubertas 2019]. This technological advancement offers a substantial advantage over self-testing glucose strips, which necessitate frequent and often inconvenient blood sampling, thus impeding patient adherence and offering only intermittent glimpses of glucose levels [Kim 2018]. Unlike traditional HbA_{1c} 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 2018]. CGM shifts the focus from traditional measures of HbA_{1c} to more dynamic metrics such as time in range (TIR), time above range (TAR), and time below range (TBR) [Bergenstal 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 2018]. The target range is most commonly between 3.9 – 10 mmol/L. The recommended percent of time spent in target ranges are above 70 %, below 25 % for TAR and below 5 % for TBR [American Diabetes Association 2025]. Deviations from this target range, both above and below, carry distinct risks, and the extent of these

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deviations is directly correlated with the severity of potential complications [Danne 2017]. TAR and TBR provide additional insights into the nature of glycemic excursions and their potential impact on health outcomes [Bergenstal 2018]. The detailed data supplied by CGM facilitates personalized therapeutic adjustments, particularly for individuals utilizing insulin, thereby addressing the limitations of HbA_{1c} in fully representing the spectrum of glycemic control [Bergenstal 2018].

Hypoglycemic episodes lead to oxidative stress, endothelial dysfunction, the stimulation of proinflammatory and procoagulant molecules, and also the activation of sympatoadrenal system, thus resulting in atherosclerosis, thrombosis and cardiovascular events [Amiel 2021]. Hyperglycemia causes oxidative stress, activation of alternative metabolic pathways, endothelial dysfunction, ischemia, inflammation, thus precipitating micro-, and macrovascular complications [Ajjan 2024]. The frequent alterations of blood glucose levels including hypo- and hyperglycemia add up and accelerate vascular damage [Ajjan 2024]. There is an inversive relationship between TIR and time in tight range in patients with T1DM and microvascular complications, including neuropathy [De Meulemeester 2024], which means that better glycemic control is important in reducing the risk of chronic complications of diabetes.

Lipid metabolism in T1DM

The interplay between T1DM, CGM and plasma TG levels represents a critical area of investigation in metabolic health [Bergenstal 2018]. Elevated plasma TG levels, a common lipid abnormality in individuals with T1DM, are closely intertwined with glycemic control and insulin sensitivity. Poor glycemic control, characterized by persistent hyperglycemia, fuels the overproduction of very-low-density lipoproteins (VLDL) in the liver, the primary carriers of triglycerides in the bloodstream. The relationship between CGM and plasma TGs lies in the ability of CGM to facilitate improved glycemic control, which in turn can positively impact TG levels. By providing real-time glucose data and enabling more precise insulin adjustments, CGM helps to minimize hyperglycemic excursions and reduce overall glucose variability. This improved glycemic stability can reduce hepatic VLDL production and enhance triglyceride clearance from the circulation, leading to lower serum triglyceride concentrations.

Cardiovascular autonomic dysfunction in T1DM

Autonomic neuropathy represents a significant and often debilitating complication of T1DM, affecting various organ systems and contributing to increased morbidity and mortality [Aleppo 2017]. This condition arises from the damaging effects of chronic hyperglycemia on the autonomic nerves, which regulate essential bodily functions such as heart rate, blood pressure, digestion, and bladder control [Galiero 2023]. 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 2018]. The effectiveness of CGM in improving glycemic control has been demonstrated in several randomized controlled trials [Aleppo 2017]. Moreover, the incorporation of CGM systems presents opportunities for personalized interventions and targeted therapies to address specific autonomic nerve dysfunctions. 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 2021]. This phenomenon also explains the beneficial effects on complications.

Our aim was to assess cardiovascular autonomic neuropathy and complex metabolic status as well as to analyze the most important CGM metrics in our T1DM patients in order to find correlations between CGM parameters and cardiovascular risk factors.

Methods

Patients and methods: 24 T1DM patients were included in the study (age: 35.7 ± 2.5 years, diabetes duration: 20.0 ± 1.8 years, BMI: 24.5 ± 0.8 kg/m^2, HbA_{1c}: 7.5 ± 0.8 %, mean ± SE [Table 1]). 19 of the patients wore the glucose sensor for more than four years, and five of them between six months and four years. Regarding the CGM parameters, TIR, TAR, and TBR were assessed (Table 2). The metabolic state was characterized by the determination of TG, HDL, LDL, total cholesterol, and HbA_{1c} (Table 1).

Neuropathy test: Cardiovascular autonomic neuropathy (CAN) was measured by four of Ewing's standard cardiovascular reflex tests. The tests were performed by measuring the blood pressure and obtaining continuous six-lead electrocardiogram (ECG) signals. The signals were digitized with a multichannel data acquisition system (CA-12 v.2.85 software, 2021, MSB Ltd., Balatonfüred, Hungary). Parasympathetic dysfunction was examined by measuring deep breathing tests, the Valsalva ratio (VR), and the 30:15 ratio while sympathetic nervous system impairment was tested by assessing orthostatic blood pressure drop on standing up. Then, we evaluated the results on autonomic score.

Statistical analysis: During data analysis, continuous variables were expressed

Abbreviations

BMI	Body mass index
CAN	Cardiovascular autonomic neuropathy
CGM	Continuous glucose monitoring
CVD	Cardiovascular disease
HbA_{1c}	glycated haemoglobin
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
SE	Standard error
TAR	Time above range
TBR	Time below range
TG	Triglyceride
TIR	Time in range
T1DM	Type 1 diabetes mellitus
VLDL	Very low-density lipoprotein
VR	Valsalva ratio

as means and standard error (mean ± SE) while categorical variables were expressed as frequencies and per-centages (n, %). Univariate analyses were performed using 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.

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: June 7 2023). All patients signed an informed consent form for this study.

Results

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 2]). Metabolic parameters were 7.5 ± 0.8 % for HbA_{1c}, 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 for HbA_{1c} and TAR (r = 0.56, p < 0.05) [Figure 1]) and TG and TAR (r = 0.53, p < 0.05 [Figure 2]). 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) (Table 3).

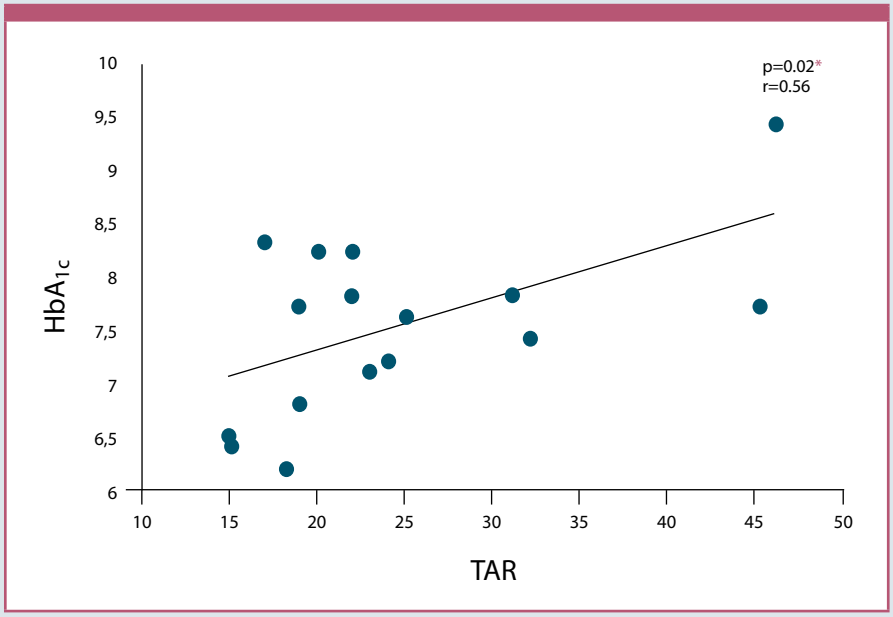

Fig. 1: Correlation between HbA_{1c} and time above range (TAR).

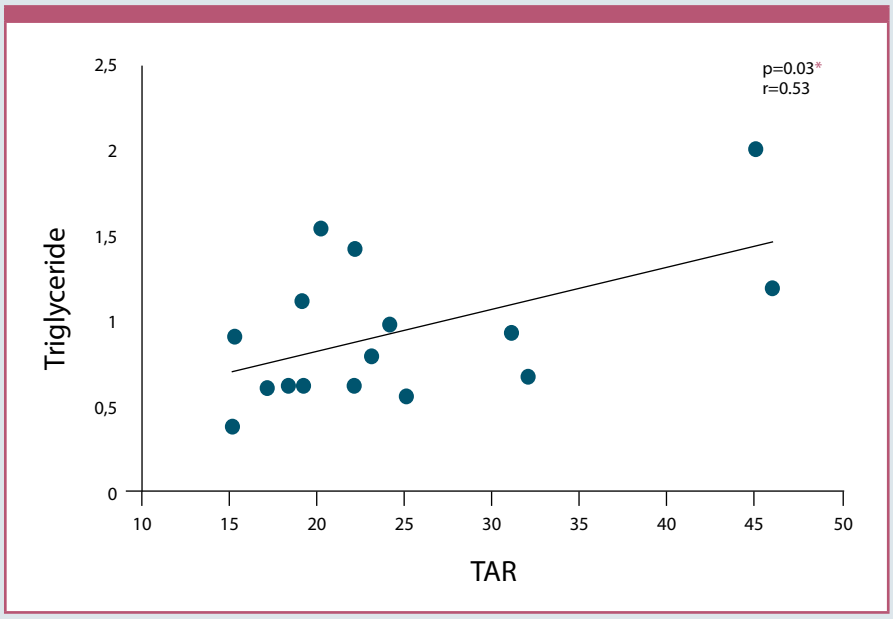

Fig. 2: Correlation between triglycerides and TAR.

Discussion

The objective of our study was to investigate the relationship between various glucose sensor parameters and cardiovascular risk factors. Upon analyzing CGM parameters, a significant positive correlation was identified between TAR and TG levels, as well as between TAR and HbA_{1c}. 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 2013, Sone 2011]. Although hypertriglyceridemia has become a significant concern in the context of diabetes mellitus [Hirano 2018], its implications in T1DM remain less understood [Vergés 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 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

Patients	CGM-user T1DM
Age (years)	35.7 ± 2.5
Duration of diabetes (years)	20.0 ± 1.8
BMI (kg/m²)	24.5 ± 0.8
HbA_{1c} (%)	7.5 ± 0.8
Total cholesterol (mmol/L)	4.7 ± 0.2
LDL cholesterol (mmol/L)	2.6 ± 0.1
HDL cholesterol (mmol/L)	1.7 ± 0.07
TG (mmol/L)	0.9 ± 0.1

Tab. 1: T1DM CGM user patients and their metabolic parameters (mean ± SE).

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

Table 2. CGM metrics (mean ± SE).

Patients	CGM-user T1DM
Heart rate response to deep breathing (beats/min)	24.7 ± 2.9
Valsalva ratio	1.4 ± 0.06
30:15 ratio	1.1 ± 0.03
Orthostasis (mmHg)	4.7 ± 1.35

Tab. 3: Cardiovascular reflex tests (mean ± SE).

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 2018]. Dyslipidemia, commonly observed in individuals with T1DM, significantly contributes to the heightened risk of cardiovascular disease in this population. It has also been implicated in neuronal damage, leading to impairment of both sympathetic and parasympathetic functions, and resulting in silent arrhythmias, tachycardia, myocardial ischemia, and infarction [Filipovic 2023]. The EURODIAB IDDM Complications Study identified hypertriglyceridemia as a novel risk factor for autonomic neuropathy [Kempler 2002]. 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 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 2023].

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. The pathogenesis of cardiac autonomic neuropathy is multifactorial, involving chronic hyperglycemia, oxidative stress, inflammation, and the accumulation of advanced glycation end products, all of which contribute to neuronal damage and dysfunction [Mooradian 1988]. The resulting dysregulation of cardiac autonomic control can have profound implications for cardiovascular health, affecting not only heart rate and rhythm but also blood pressure regulation and overall cardiac function [Hammes 2003]. 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 2018, Zhou 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 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 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 2016].

Conclusions

CAN is frequently undiagnosed in individuals with diabetes mellitus. Implementing intensive, multifactorial interventions that focus on lifestyle changes, glycemic management, and cardiovascular disease (CVD) risk factors can help prevent the onset and slow the progression of CAN. It is crucial to identify patients with CAN, as the condition is linked to increased mortality rates, cardiovascular and lower-limb issues. By taking into account the parameters displayed by the CGM, we can predict and influence metabolic and neurological abnormalities, thereby reducing cardiovascular risk.

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Conf icts of interest:
The authors declare no conflicts of interest.