# The Emerging Role of Continuous Glucose Monitoring in the Management of Diabetic Peripheral Neuropathy: A Narrative Review

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## ABSTRACT

The aim of this narrative review is to present data on the role of continuous glucose monitoring (CGM) in the management of peripheral diabetic neuropathy (DPN) among individuals with type 1 and type 2 diabetes mellitus. Adequate glycaemic control is crucial to prevent the development or progression of DPN. CGM systems are valuable tools for improving glycaemic control and reducing glycaemic variability (GV). Chronic hyperglycaemia is known to be a risk factor for the development of diabetic microvascular complications, including DPN. In addition, there is now evidence that GV, evaluated by mean amplitude of glycaemic excursions, may be a novel factor in the pathogenesis of diabetic complications. Increased GV appears to be an independent risk factor for DPN and correlates with painful neuropathy. Similarly, time-in-range correlates positively with peripheral nerve function and negatively with sudomotor dysfunction. However, relevant studies are rather limited in scope, and the vast majority are cross-sectional and use different methodologies for the assessment of DPN. Therefore, the causal relationship between CGM-derived data and the development of DPN cannot be firmly established at the present time. It also remains to be elucidated whether CGM measures can be considered the new therapeutic targets for DPN management.

**Keywords:** Diabetic peripheral neuropathy; Continuous glucose monitoring; Glycaemic variability; Time-in-range

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| Key Summary Points |
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| Continuous glucose monitoring systems (CGM) provide valuable information on the levels of and variations in glucose, enabling a more personalised approach to diabetes management. |
| Glycaemic variability (GV) may be a novel factor in the pathogenesis of diabetic complications. |
| GV appears to be an independent risk factor for diabetic peripheral neuropathy (DPN) and correlates with painful neuropathy. |
| Conversely, time-in-range correlates positively with peripheral nerve function and negatively with sudomotor dysfunction. |
| It remains to be confirmed whether data from CGM may help define new therapeutic targets for DPN. |

## INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common microvascular complication of diabetes mellitus (DM). Importantly, DPN is also the major risk factor for the development of diabetic foot ulcers, possibly leading to lower-extremity amputations [1]. Stringent glycaemic control remains the most important aspect of diabetic neuropathy management [2, 3].

The use of continuous glucose monitoring (CGM) devices has been associated with an improvement of glycaemic control. CGM is increasingly used due to its many advantages, namely accuracy and easiness of use, as well as the ability to assess daily variations in glucose [4]. Thus, the use of CGM devices may improve therapeutic decisions in comparison with conventional self-monitoring blood glucose (SMBG) systems [4].

Glycated haemoglobin A1c ($HbA_{1c}$) remains the reference marker for assessing glycaemic control and predicting the risk of future diabetes complications. Nonetheless, $HbA_{1c}$ has several limitations in this context. First, it provides the average glucose level over the previous 2–3 months but offers no information on glycaemic variability (GV) or hypoglycaemic events on a daily basis. Second, $HbA_{1c}$ can be affected by multiple factors, as age, race, anaemia, haemoglobinopathies, iron deficiency, chronic kidney disease and pregnancy, resulting in discrepancies between the measured $HbA_{1c}$ and true glycaemic control. For these reasons, $HbA_{1c}$ is not a valuable tool for a personalised diabetes management [5, 6].

On the contrary, CGM systems with CGM metrics provide more information on daily glycaemic status and glucose variations [7]. GV describes the intra-day glycaemic excursions, including episodes of hyperglycaemia and hypoglycaemia. CGM systems can more accurately detect GV than SMBG systems, and GV can be evaluated from CGM data using complex formulas [7]. Although chronic hyperglycaemia is known to enhance the risk for diabetes complications, both postprandial spikes of glucose and hypoglycaemias have also been reported to be associated with cardiovascular events in diabetes [7, 8]. A potential association between GV and autonomic neuropathy has also been reported [8]. More importantly, there is increasing evidence for a role of GV in the development of diabetic microvascular complications [9]. Also, GV has been proposed to be a predictor of diabetic complications independently of $HbA_{1c}$ in persons with type 2 DM (T2DM) [10].

Time-in-range (TIR) is defined as the percentage of time at glucose levels ranging from 70 to 180 mg/dL (3.9–10.0 mmol/L). This metric is considered to be an emerging surrogate marker of glycaemic control and to correlate with $HbA_{1c}$ [11]. Although $HbA_{1c}$ remains the key surrogate marker for the development of long-term diabetes complications, TIR has been also associated with microvascular complications (diabetic retinopathy and microalbuminuria) [11].

The role of CGM systems on preventing or improving DPN has not been extensively investigated. In the present narrative review, we summarise emerging data on the relationship of TIR and GV (evaluated by CGM systems) with DPN.

## METHODS

### Search Strategy

For this narrative review, we searched relevant published articles in PubMed up to January 2022 using combinations of the key words "continuous glucose monitoring" and "diabetic peripheral neuropathy". The electronic search yielded 68 articles (including 12 reviews). Those articles addressing an association or lack of association of CGM with DPN were included in this review, and ten articles were excluded. Searches were not restricted by study design, but only articles published in the English language were included.

### Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## CATEGORIES OF CGM SYSTEMS

CGM systems can be divided in real-time CGM (rtCGM) and intermittently scanned CGM (isCGM) systems (also called "flash" CGM). CGMs use a sensor to measure interstitial fluid glucose and, therefore, finger-sticks are not needed, thus allowing the individual to avoid pain derived from blood glucose measurements [7, 12].

An important difference between the two CGM systems is the way data are transmitted to the user. RtCGM systems can automatically transmit data to the user's receiver and/or smartphone [12], while isCGM systems require the patient to "swipe" the receiver close to the sensor to obtain glucose data. Most importantly, users of isCGM systems must scan at least every 8 h with the device, as only the most recent data of the last 8 h will be retained and available for evaluation.

Both CGM systems provide information on glucose levels during sleep. Similarly, both rtCGM and isCGM devices are able to provide a "high" or "low" alarm when glucose levels are above or below the target range, respectively, thus protecting patients from dangerous episodes of hyper- or hypoglycaemia. Some systems can also share data with clinicians or family/caregivers [12] and thus enable improved glycaemic control among children or people who need help in the adjustment of insulin dose. Moreover, certain CGMs can also be combined with an insulin pump, allowing automatic adjustment or interruption of insulin delivery should significant changes in glucose occur [13].

## COMMONLY USED CGM METRICS

Among all standardised CGM metrics [4], the most commonly used are:

- Average glucose: average glucose level is highly correlated with $HbA_{1c}$ and measures of hyperglycaemia, but this metric provides no information on GV.
- GV: GV describes the intra-day glycaemic excursions, including episodes of hyperglycaemia and hypoglycaemia. It is an index that can be affected by diet, lifestyle, comorbidities, as well as by diabetes treatment and insulin injection technique [14].
- Mean amplitude of glycaemic excursion (MAGE): MAGE is a simple index of GV. It is the mean of blood glucose values exceeding one standard deviation (SD) from the 24-h mean blood glucose and has been proposed as the "gold standard" for assessing the short-term within-day GV [15].
- Glucose management indicator (GMI): This index calculates an approximate $HbA_{1c}$ based on the average glucose level measured by CGM and enables glucose management and individual goals when the laboratory $HbA_{1c}$ and the estimated $HbA_{1c}$ do not

closely match. GMI provides the current state of a person's glucose management [16].

- TIR: TIR is the most commonly used CGM metric. It is the duration of time that a patient's glucose level is in the target range, usually between 70 and 180 mg/dL (3.9–10.0 mmol/L). The use of CGM systems has been associated with increased TIR and reduced incidence of severe episodes of hypoglycaemia [16].
- Time-below-range (TBR): This metric is the duration of time that a patient's glucose level is $< 70$ mg/dL (3.9 mmol/L) or $< 54$ mg/dL ($< 3$ mmol/L). It is a valuable parameter for optimising glucose management [12]. An ideal CGM target is a high TIR with a minimal TBR.
- Time-above-Range (TAR): This metric is the duration of time that a patient's glucose level is $> 180$ mg/dL ($> 10$ mmol/L) or $> 250$ mg/dL ($> 13.9$ mmol/L). It is also an important parameter for optimising glucose management [12].

## CGM AND DPN

### CGM and DPN in T2DM

The relationship between GV and DPN was evaluated in a study conducted among 90 well-controlled subjects with T2DM (HbA$_{1c}$ < 7.0%). Of these subjects, 45 had DPN and were recruited from an inpatient department of the Second Affiliated Hospital of Nantong University (China) and 45 had no DPN and were recruited from outpatient as controls [7]. The two groups were matched for age and T2DM duration. The diagnosis of DPN was based on the criteria recommended by The Toronto Diabetic Neuropathy Expert Group, including the presence of a symptom/symptoms (decreased sensation, positive neuropathic sensory symptoms predominantly in the toes, feet or legs) or a sign/signs of neuropathy (symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes) and presence of abnormality of nerve conduction (NC) test results [7]. Glucose was monitored with a CGM system (MiniMed

system; Medtronic, Northridge, CA, USA) for 72 h [7]. GV was estimated with multiple parameters, such as glucose SD (SDgluc), mean of daily differences (MODD) and MAGE. Blood pressure, body mass index (BMI) and laboratory parameters were measured, included insulin sensitivity index (ISI; Matsuda index), total cholesterol, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol [7]. Subjects with DPN had higher SDgluc, MODD and MAGE ($p < 0.05$). Multivariate logistic regression analysis revealed a significant correlation of DPN with MAGE (odds ratio [OR] 2.05, 95% confidence interval [CI] 1.36–3.09, $p = 0.001$) and BMI (OR 0.85, CI 0.73–0.99, $p = 0.033$) [7].

Similarly, another study of 982 subjects with T2DM (197 with DPN) from the inpatient department of the Affiliated Hospital of Nantong University and Second Affiliated Hospital of Nantong University (China) examined the association of GV and other conventional risk factors with DPN [17]. DPN was diagnosed based on both neuropathic symptoms/signs and abnormal NC test results. Using a CGM system (Gold system; Medtronic), multiple GV parameters were calculated, including MACE, MODD, SD and 24-h mean glucose (24-h MG). Those T2DM subjects with DPN exhibited higher MAGE, MODD, SD, and 24-h MG ($p < 0.001$) [10]. Regression analysis showed that MAGE, T2DM duration, Homeostasis model assessment for insulin resistance (HOMA-IR) and HbA$_{1c}$ were independent risk factors for DPN (OR 4.57, 95% CI 3.48–6.01; OR 1.10, 95% CI 1.03–1.17; OR 1.24, 95% CI 1.09–1.41; OR 1.33, 95% CI 1.15–1.53, respectively). Moreover, 4.60 mmol/L was the optimal MAGE cutoff for DPN identification (sensitivity 64.47%, specificity 75.54%) [17].

The Continuous Glucose Monitoring to Assess Glycemia in Chronic Kidney Disease (CANDY) study enrolled 105 subjects with T2DM who were treated with insulin or sulfonylurea (81 with moderate-to-severe chronic kidney disease [CKD] and estimated glomerular filtration rate [eGFR] $< 60$ mL/min/1.73 m$^2$) and 24 controls from the same centre (eGFR $\geq 60$ mL/min/1.73 m$^2$). Glucose was monitored using a CGM system for two 6-days

periods [18]. Participants were enrolled from nephrology clinics, the Diabetes Care Centre and referring clinics associated with the University of Washington, Seattle (USA). TIR (glucose 70–180 mg/dL) and GMI were assessed. DPN was diagnosed by the Michigan Neuropathy Screening Instrument (MNSI) questionnaire. DPN was seen in 63% of participants with CKD and in 46% of controls. Lower TIR and higher GMI were associated with a higher risk of DPN symptoms (OR 1.25, 95% CI 1.02–1.52) per 10% lower TIR; OR 1.79, 95% CI 1.05–3.04 per 1% higher GMI). Interestingly, no significant association between laboratory $HbA_{1c}$ values and DPN symptoms was observed [18]. The majority of participants in this study had CKD. As one explanation of these results, the authors commented that as CKD is a factor affecting $HbA_{1c}$ ($HbA_{1c}$ tends to be lower in individuals with end-stage-kidney disease), $HbA_{1c}$ in the enrolled patients with CKD was a less precise parameter for estimating glucose management compared with CGM metrics (TIR and GMI). Other potential explanations for their findings could include the limitations acknowledged by the authors: the cross-sectional observational design of the study, the relatively small sample size, the diagnosis of DPN by subjective symptoms (MNSI questionnaire), as well as the CGM-data being obtained from two 6-day-periods [18]. In view of the association between lower TIR and DPN symptoms, the need for adequate glycaemic control to prevent DPN was implied [18].

In agreement with these findings, the authors of another study reported for the first time a link between TIR and peripheral nerve function among 740 patients with T2DM patients [19]. TIR was assessed by CGM (Medtronic). Participants were divided into tertiles according to TIR values (low TIR: ≤ 53%; medium TIR: 54–76%; high TIR: ≥ 77%), and composite Z-scores of nerve conduction velocity (NCV), latency and amplitude were calculated [12]. Higher TIR values were associated with elevated composite Z-scores of NCV and amplitude and lower composite Z-scores of latency (all $p < 0.05$) [19]. In addition, the risk of TIR tertiles and worsening NCV was independent of $HbA_{1c}$ (medium TIR: OR 0.48,

$p = 0.001$; high TIR: OR 0.41, $p < 0.001$) [19]. Specifically, the authors used linear regression analysis to explore whether $HbA_{1c}$ or TIR was more strongly associated with peripheral nerve function. $HbA_{1c}$ was more closely related to the composite Z-score of the nerve function parameters, but TIR had an additional role [19]. Moreover, the risk of reduced NCV decreased with higher TIR after controlling for $HbA_{1c}$ and other parameters. Finally, according to ROC analysis, adding TIR to the models increased the predictive performance of the logistic models to decreased NCV and to amplitude, suggesting that TIR might assess peripheral nerve function independent of $HbA_{1c}$ [19]. Of note, the study was conducted among hospitalised patients and, therefore, the results must be carefully interpreted when extrapolating to the general/outpatient population [19].

Guo et al. [20] investigated the relationship between TIR and sudomotor function among 466 in-patients at the Endocrinology Department of Jinling Hospital, Nanjing with T2DM. Sudomotor function was assessed using Sudoscan technology (SUDOSCAN Inc., San Diego, CA, USA). TIR was evaluated after 3 days of CGM (Meiqi Corp., Shenzhen, Guangdong, China) [20]. Overall, 135 participants exhibited sudomotor dysfunction (28.9%) and low TIR. A TIR value within the middle and the highest tertiles was associated with a lower prevalence of sudomotor dysfunction (20.51% and 21.94% vs. 44.52%, $p < 0.001$) [13]. Moreover, after adjustment for confounding factors, TIR appeared to be inversely and independently associated with the presence of sudomotor dysfunction (OR 0.979, 95% CI 0.971–0.987, $p < 0.001$) [20].

Interestingly, the association between subclinical diabetic polyneuropathy and GV has also been studied [21]. Among 509 subjects with T2DM (147 with DPN) admitted to the Endocrinology Department of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (Shanghai, China), a significant association was revealed between SDgluc and abnormal nerve function (OR 1.198, 95% CI 1.027–1.397). Moreover, the composite Z-score of NCV and response amplitude decreased witn increasing SDgluc ($p < 0.05$) [21]. Even after

adjustment for potential confounders (age, sex, BMI, HbA$_{1c}$ and diabetes duration), high SDgluc was independently associated with slower NCV ($b = -0.124$, $p = 0.021$) [21].

Finally, in an study of 281 outpatients with T2DM, as part of a multi-centre prospective cohort study (Hyogo Diabetes Hypoglycemia Cognition Complications [HDHCC] study, Japan), glucose was monitored with FreeStyle Libre Pro (Abbott Japan, Tokyo, Japan) during a 10-day period [22]. DPN was diagnosed by a combination of symptoms, signs, vibration perception threshold and NC parameters [22]. Multiple regression analyses revealed that DPN was associated with TIR deterioration (standard partial regression coefficient $\beta = -0.106$, $p = 0.033$) [22].

In conclusion, studies performed to date in subjects with T2DM have shown an association of GV with DPN and painful neuropathy. Of note, GV has been also associated with sub-clinical DPN. These findings are in accordance with data derived from other studies which showed that worsening glycaemic control and GV are associated with the development and progression of complications in diabetes [23, 24].

## CGM and DPN in Type 1 Diabetes Mellitus

Oyibo et al. [25] have examined the relationship between blood glucose excursions and painful diabetic neuropathy among 20 patients with type 1 DM (T1DM) and DPN randomly selected (10 with painful DPN and 10 with pain-free DPN). A CGM system (MiniMed system; Medtronic) was used for 3 days and MAGEs subsequently evaluated. Both groups, with and without pain, were similar in terms of age, T1DM duration, duration of neuropathy and CGM performance [25]. Mean glucose levels ($p = 0.02$) and M-values (as a measure of GV) ($p = 0.02$) were higher among T1DM subjects with painful neuropathy and, similarly, glucose excursions were more frequent among those subjects with painful DPN ($p < 0.01$); however, MAGE was similar between the two groups [25]. The authors suggested that reduced GV could contribute to the treatment of painful diabetic

neuropathy, but we should bear in mind that this was a small study and the results need confirmation [25].

Kwai et al. [26] investigated the role of GV on peripheral nerve function among 17 patients with T1DM using a CGM system (Enlite sensor; Medtronic) and nerve excitability techniques. Patients were recruited consecutively from the Prince of Wales Hospital in Sydney (Australia). MAGE was calculated to quantify GV [26]. There were significant correlations of MAGE with excitability markers of altered motor and sensory axonal function (superexcitability: $r = 0.54$; S2 accommodation: $r = -0.76$; minimum current/voltage (I/V) slope (expressed as rate of change per unit): $r = 0.71$; strength duration time constant: $r = 0.66$; latency: $r = 0.65$) ($p < 0.05$). Interestingly, there was no association between acute glucose levels and markers of axonal function [26].

The authors of another study included 159 subjects with T1DM and examined whether optimised glycaemic control (measured by improved HbA$_{1c}$) could improve vibration perception thresholds (VPTs) [27]. The latter were measured at six frequencies (range: 4–125 Hz) at the heads of the first and fifth metatarsal bones using a VibroSense Meter (VibroSense Dynamics, Malmö, Sweden). Patients were being treated at the Department of Endocrinology, Skåne University Hospital, Malmö (Sweden) and were examined twice between 2015 and 2018. Among those participants whose HbA$_{1c}$ improved by $> 1$ mmol/mol (95 subjects), the mean Z-score, reflecting the combined effect of all VPTs, also improved and was lower at the follow-up compared with that at the baseline (0.2 [$-0.3$ to 1.2] vs. $-0.1$ [$-0.7$ to 0.8], $p = 0.00002$) [27]. In contrast, no difference in VPTs was observed among participants whose HbA$_{1c}$ was unchanged or deteriorated. The 4-Hz frequency was identified as the more sensitive frequency to detect improvements [27]. Unfortunately, GV was not measured in this study [27].

In a large U.S. population study that included 5936 participants with T1DM (T1D Exchange Clinic Registry), DPN was diagnosed by the Michigan Neuropathy Screening Instrument Questionnaire [28]. A CGM system was

used by 33% of the participants. The authors found no difference between the subjects with and without DPN [28].

More recently, Feng et al. [29] examined the association between TIR (including nocturnal TIR) and sudomotor dysfunction in 95 subjects with T1DM (74.41% male) hospitalised in the Endocrinology Department of the Jinling Hospital, the First School of Clinical Medicine, Southern Medical University (China) to improve glucose control. TIR was measured using a 72-h blind CGM system (Meiqi Corp.). Sudomotor dysfunction was assessed using Sudoscan technology (Impeto Medical, Paris, France). Patients with sudomotor dysfunction exhibited lower TIR and nocturnal TIR, as well as higher TAR and nocturnal TAR in comparison with those free from sudomotor dysfunction [29]. Multiple regression analysis showed an inverse association of both TIR and nocturnal TIR with the risk of sudomotor dysfunction after adjustment for confounding factors [29].

### CGM and DPN in Studies Including Subjects with Both T1DM and T2DM

Akaza et al. [30] examined the relationship between GV (estimated MAGE) and DPN in 40 outpatients of Shuuwa General Hospital (Saitama, Japan) with T1DM and T2DM (23 males and 17 females; age range: 34–79 years). Glucose levels were monitored with CGM, and DPN was diagnosed by NC study. In the multivariate linear regression analysis, MAGE was independently associated with a higher risk of medial plantar neuropathy ($\beta = -0.49$, $p = 0.007$) [30].

Yan et al. looked at the association between TIR and the prevalence and degree of painful diabetic neuropathy among 364 patients with this condition [31]. Individuals were recruited at the Department of Endocrinology and Metabolism of Henan Provincial People's Hospital (Zhengzhou, China). Based on a pain score, subjects were categorised into three groups: those who were pain-free and those with mild pain and moderate/severe pain, respectively. TIR was found to be associated with painful diabetic neuropathy, and was significantly lower among subjects with mild or moderate/severe pain than in those who reported no pain ($p < 0.05$) [31]. Moreover, the prevalence of pain decreased with increasing TIR ($p < 0.05$). Logistic regression analysis showed that lower TIR levels were significantly associated with an increasing risk of painful neuropathy ($p < 0.05$) [31].

In summary, GV has been associated not only with DPN but also with painful neuropathy. The pathogenesis of DPN involves several mechanisms. Of these, oxidative stress (induced by hyperglycaemia and acute glucose fluctuations) is receiving considerable attention [32]. Moreover, data support the possibility that GV could activate oxidative stress in a more intensive way than chronic hyperglycaemia [17, 33].

## CGM AND DIABETIC FOOT

Very limited data are available on TIR and clinical outcomes among patients with diabetic foot and diabetic foot ulcers (DFUs). The association of TIR with amputation and all-cause mortality was assessed retrospectively among 303 hospitalised patients with DFUs. The amputation rate and all-cause mortality was found to decline with increasing TIR [34]. Logistic regression analysis showed an inverse association of TIR with both amputation ($p = 0.034$) and all-cause mortality ($p = 0.013$) after controlling for multiple confounders [34].

Huang et al. studied the association of TIR with postoperative wound healing among patients with DFUs [35]. The results showed that participants with TIR < 50% were more likely to undergo second surgery within 1 month ($p = 0.032$) and to stay longer in hospital ($p = 0.045$). In the multivariate analysis, TIR was also an independent risk factor for second surgery ($p = 0.034$), implying that high TIR should be sought in DFU patients undergoing surgery [35].

Additional prospective data on the role of CGM systems in improving outcomes among DFU patients are needed. Such outcomes might include wound healing, re-ulceration, amputation rates, quality of life, among others.

# DISCUSSION

In this review we discuss the associations of glycaemic control based on CGM measures and the prevalence of DPN among subjects with T1DM and T2DM (Table 1). Current evidence points to a potential association between GV or TIR and DPN. However, there are some caveats to this statement. First, the number of studies are limited, the majority of studies that have been performed involved mostly Asian populations and the vast majority of these studies are cross-sectional in design. Second, many participants were in-patients and, therefore, the findings cannot be applied to a general outpatient setting. Third, studies have used varying criteria for the assessment and definition of DPN, as well as various CGM systems. CGM has been used for limited time periods and various parameters (VG or TIR) have been assessed.

It is evident that the pathogenesis of DPN involves several mechanisms, with chronic hyperglycaemia being an established cardinal factor. It is interesting that not only hyperglycaemia per se but also acute glucose fluctuations induce oxidative stress, a relationship that has received considerable attention [25]. Some data support GV activating oxidative stress more than chronic hyperglycaemia [10, 26]. Intermittent high blood glucose exposure, rather than constant exposure to high blood glucose, has been shown to have deleterious effects in experimental studies [9].

The effect of GV on DPN has not been extensively studied. Possible mechanisms that are involved in the role of GV on DPN include the activation of protein kinase C-dependent NADPH oxidase, which leads to oxidative stress and GV-induced apoptosis of Schwann cells. Moreover, GV seems to significantly decrease the expression of superoxide dismutase and increase the levels of tumour necrosis factor alpha, interleukin-6, nuclear factor kappa B (NF-kB) and malondialdehyde. In summary, GV induces oxidative stress and inflammatory response by activating the NF-kB pathway, thereby causing DPN [36].

GV has also been associated with an increased incidence of hypoglycaemia.

Hypoglycaemia induces multiple inflammatory and endocrine responses (sympatho-adrenal response), including the release of inflammatory cytokines, the increase in platelet and neutrophil activation and increased adrenaline secretion, leading to endothelial dysfunction and thus decreased vasodilatation. Therefore, GV appears to play an important role in vascular damage [9].

Of note, an association between GV and the severity of autonomic neuropathy in T1DM has already been observed. In addition, reduced beta-cell function is a very important risk factor for GV. A negative association has been reported between C-peptide levels and GV in T1DM [37]. Reducing GV and optimising TIR using CGM systems might be a possible strategy to reduce the occurrence of DPN and other diabetes complications.

In this overall context, CGM systems can automatically measure glucose every 5 min, which is approximately 288 readings a day [13]. For an accurate interpretation of CGM readings, sufficient CGM data must be available. Minimum use of a CGM system is considered to be > 14 days, with the CSM system worn for at least 10 days (70%), to obtain reliable information [12]. Data on 14 days provide a good estimation of glucose metrics for a 3-month period [38]. Thus, longitudinal studies in large populations from various countries in which CGM systems are used for longer time periods are needed to establish a causal relationship among CGM measures and DPN.

Evidence presented in this review suggests that adequate glycaemic control according to CGM measures could be associated with DPN, as well as with subclinical DPN and, more interestingly, with symptoms of pain among patients with DPN. HbA$_{1c}$ is currently still the key surrogate marker for the development of long-term diabetes complications. However, HbA$_{1c}$ has several limitations, rendering CGM systems as an alternative very interesting [39]. Thus, it remains to be established whether, in comparison to HbA$_{1c}$, stringent glycaemic control defined by lower GV and higher TIR levels could be more efficiently correlated with the development of DPN and whether CGM could

**Table 1** Studies assessing the relationship between continuous glucose monitoring and diabetic peripheral neuropathy

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/ TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Oyibo, 2002 [25] | 20 With DPN | *Inclusion:* T1DM with DPN *Exclusion:* non-diabetic cause of neuropathy; other cause for pain in the feet (e.g. peripheral arterial disease, foot ulcers, infection, arthritis) | T1DM | VPT > 2 SD of the age adjusted value and Neuropathy Disability Score > 4/ 10 | MiniMed system (Medtronic, Northridge, CA, USA) | 3 days | Spearman's rank correlation coefficient to test for correlation between measures of glycaemic stability and painful episodes | No | Patients with painful neuropathy have greater glucose flux and possibly poorer diabetes control, compared with patients with painless neuropathy | Observational |
| Xu, 2014 [7] | 90 45 inpatients with DPN (from a total of 312) 45 controls (outpatients with no DPN) | *Inclusion:* HbA$_{1c}$ < 7% *Exclusion:* acute diabetes complications, hyperthyroidism, non-diabetic neuropathic deficits (e.g. peripheral vascular disease, arthritis, malignancy, alcohol abuse, vitamin B deficiency, spinal stenosis) | T2DM | Presence of a symptom or symptoms or a sign or signs of neuropathy and an abnormality on NC tests | MiniMed system (Medtronic) | 72 h | Univariate analysis to estimate the contribution of clinical risk factors to DPN using OR and 95% CI, and multivariate logistic regression analysis to identify independent risk factors for DPN | Yes | GV evaluated by MAGE was the most significantly independent risk factor for DPN | Cross-sectional |

**Table 1** continued

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Kwai, 2016 [26] | 17 | *Inclusion:* T1DM; no sensory or motor symptoms; normal NCS | T1DM | Median motor and sensory excitability assessments | Enlite sensor (Medtronic) | 6 days | Spearman Rho correlations between MAGE and excitability parameters | No | GV may be an important mediator of axonal dysfunction in T1DM and a contributing factor in development of diabetic neuropathy | Cross-sectional |
| Akaza, 2018 [30] | 40 Outpatients | *Inclusion:* DM; age 34–79 years; *Exclusion:* age > 80 years; severe renal impairment eGFR < 15 mL/min/1.73 m²; renal replacement therapy; severe hepatic function; other peripheral neuropathies | T1DM + T2DM | NCS | IPro2® sensor (Medtronic) | 7 days | Pearson correlation coefficient or Spearman's rank correlation coefficient to evaluate correlations between variables. Multiple linear regression analyses to determine the independent factors associated with NCS parameters, using covariates: MAGE, gender, age, DM type and duration, HbA$_{1c}$, BMI, SBP, LDL-C | Yes | GV may be an independent risk factor for DPN | Cross-sectional |

**Table 1** continued

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/ TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Hu, 2018 [17] | 982 (197 with DPN) | *Inclusion:* T2DM; age 25–75 years; current antidiabetic treatments for at least 3 months *Exclusion:* T1DM; acute diabetic complications; previous use of drugs that affect glucose, (i.e. steroids); folate/ vitamin B12 deficiency; alcohol abuse; thyroid function disorders; previous malignancy; chronic renal failure or chronic liver disease; connective tissue diseases; spinal stenosis | T2DM | Presence of both neuropathic symptoms/ signs and an abnormality on NC test | Minimed Gold system (Medtronic) | 3 days | Univariate logistic regression analysis to select the risk factors associated with DPN Multivariate logistic regression analysis to identify independent contributors to DPN. ROC curve to explore the cut-off value of GV for predicting DPN | Yes | Increased GV assessed by MAGE is a significant independent contributor to DPN | Cross-sectional observational |

**Table 1** continued

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/ TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Mayeda, 2019 [18] | 105 (81 with eGFR < 60 mL/min/ 1.73 m$^2$) and 24 controls (with eGFR ≥ 60 mL/ min/1.73 m$^2$) | *Inclusion:* T2DM under treatment with insulin or sulfonylurea *Exclusion:* age < 18 years; history of kidney transplant; dialysis treatment; treatment with erythropoietin; current use of clinical CGM; pregnancy; current therapy for cancer; no knowledge of English language | T2DM | MNSI questionnaire | Enlite sensor (Medtronic) | Two 6-day periods | Linear regression with robust Huber-White SEs to test differences in MNSI score by CKD status, adjusting for age, sex and race Logistic regression to test differences in the prevalence of DPN by CKD status, TIR, GMI and other metrics and clinical characteristics | Yes | For every 10% lower TIR there is a 25% increased risk of DPN | Prospective observational |

**Table 1** continued

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Li, 2020 [19] | 740 Hospitalised | *Inclusion:* T2DM *Exclusion:* progressive malignancy; diseases that could affect nerve conduction function (e.g. chronic inflammatory demyelinating polyneuropathy, carpal tunnel syndrome); life-shortening medical conditions | T2DM | NCS | Medtronic | 72 h | Multivariate linear regression analysis to assess the independent associations of HbA$_{1c}$/TIR with NCS parameters after adjusting for covariates. The composite Z-scores of the NCS parameters were divided into 2 groups with the median as the cut point. Association of TIR tertiles and low composite Z-scores of the NCS parameters through binary logistic regression. ROC analysis to predict probabilities of NC function | Yes | Higher TIR tertiles are independently associated with better peripheral nerve function | Cross-sectional |

**Table 1** continued

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Dahlin, 2020 [27] | 159 | *Inclusion:* T1DM<br>*Exclusion:* hypoglycaemia at the time of the visit; chemotherapy | T1DM | VPT | 109 FGM<br>19 CGM<br>30 SMBG | 1–3 years | Mean Z-score for each observation was calculated from all individual Z-scores and gave an estimate of all VPT frequencies together<br><br>Wilcoxon signed-rank test to compare VPTs at the baseline and at follow-up visit | No | Lower HbA$_{1c}$ was associated with improved VPT | Observational |

**Table 1** continued

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Guo, 2020 [20] | 466 Inpatients | *Inclusion:* T2DM *Exclusion:* severe illness or acute stress (heart failure, liver failure, acute/chronic inflammatory disorders, malignant diseases, surgery); history of oral medications that may affect the nervous system; recent history of alcoholism; other metabolic disorders (e.g. vitamin B12 depletion) | T2DM | Sudomotor function (Sudoscan, Impeto Medical, Paris, France) | Meiqi Corp. (Shenzhen, Guangdong, China) | 3 days | Binary logistic regression analysis to explore the link between TIR (as a continuous or categorical variable) and sudomotor dysfunction after adjusting for clinical conditions, including age, diabetes duration, sex, BMI, SBP, DBP, smoking, TG, TC, HbA$_{1c}$, and GV metrics | Yes | TIR is inversely and independently linked with the prevalence of sudomotor dysfunction | Cross-sectional |

**Table 1** continued

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Feng, 2021 [29] | 95 Inpatients to better control their glucose | *Inclusion:* T1DM *Exclusion:* acute condition requiring intervention (ketoacidosis, hypoglycaemic coma); secondary neurological impairment from drugs; alcoholism; vitamin B12 deficiency or thyroid disease | T1DM | Sudomotor testing (Sudoscan, Impeto Medical, Paris, France) | Meiqi Corp. | 72 h blind-CGM | Binary logistic regression analysis and linear regression analysis with FESC as a categorical variable or a continuous variable to examine the independent correlation between TIR and sudomotor function ORs and 95% CI were listed | Yes | TIR is negatively correlated with sudomotor dysfunction | Retrospective |

**Table 1** continued

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/ TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Pan, 2021 [21] | 509 (147 with DPN) | *Inclusion*: age 25–75 years; valid and available data of NCS; current antidiabetic medication for at least 3 months. *Exclusion*: Lack of data on sex, age, HbA$_{1c}$ diabetes duration, neurological diseases that could influence NC; severe kidney or liver disease; mental disorder; malignancy; symmetrical distant neuropathy symptoms/signs; use of vitamins B1 or B12 or folic acid in the previous 6 months; acute diabetic complications | T2DM | NCV | Medtronic | 3 days | Five binary logistic regression models for HbA1c, SDgluc, MAGE, CVgluc, average glucose after controlling for: age, sex, BMI and diabetes duration. Multiple linear regression analysis to investigate associations between GV parameters and the continuous composite Z-score of nerve conduction parameters (NCV, distal latency, response amplitude) as dependent variables. Five multivariate linear regression models for HbA1c, HbA1c and SDgluc, HbA1c and MAGE, HbA1c and CVgluc and HbA1c and average glucose. Covariates: age, BMI, diabetes duration, HbA1c, CVgluc, SDgluc, MAGE, average glucose as continuous variables; sex as categorical variable | Yes | SDgluc is a significant independent contributor to subclinical diabetic polyneuropathy | Cross-sectional observational |

**Table 1** continued

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Yang, 2021 [31] | 364 | *Inclusion*: age > 18 years. *Exclusion*: other causes of neuropathy (osteoarthritis, cervical/lumbar diseases; connective tissue disease; peripheral vascular disease; tumours; herpes zoster infection; abnormal thyroid function; severe malnutrition; vitamin B12 deficiency; major psychiatric disorders; severe pain from a cause other than DPN; central nervous system lesions; pregnancy) | Unspecified | (1) Typical symptoms (2) Abnormal Toronto Clinical Scoring System scores and/or (3) Abnormality on NC test | FreeStyle Libre (Abbott Diabetes Care, Witney, UK) | 2 weeks | Multiple linear regression analysis to estimate the association between TIR and the NRS score. Multinomial logistic regression analysis to evaluate the independence of association of TIR with different stages of PDN after controlling for risk factors: sex, age, BMI, DM duration, $HbA_{1c}$, fasting C-peptide, TC, LDL-C, eGFR, smoking status, drinking status, TCSS score, NCS, antidiabetic agents, GV metrics. The independence of association between TIR and the presence of any PDN was assessed by binary logistic regression analysis | Yes | TIR is correlated with painful diabetic neuropathy | Cross-sectional |

Table 1 continued

| First author of study, year | Number of subjects (N) | Criteria of recruitment | DM type | Assessment of DPN | CGM system | Time of CGM | Statistical tests used | Adjustment for known risk factors of DPN | Association between GV/TIR and DPN | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|
| Kuroda, 2021 [22] | 281 Outpatients | Inclusion: T2DM; age 40–75 years; regular visits as outpatient to hospitals or clinics. Exclusion: patients unable to regularly visit a hospital or clinic; T1DM; dementia; severe hepatic and/or renal dysfunction; cancer; ineligibility for the study | T2DM | Presence of ≥ 2 of 3 of following items: (1) Symptoms (2) Decrease of bilateral Achilles tendon reflexes (3) Decreased vibration sense of bilateral medial malleolus OR, abnormality ≥ 1 on test (NCV, amplitude, latency) in ≥ 2 nerves | FreeStyle Libre Pro (Abbott Japan, Tokyo, Japan) | 10 days | Multiple regression analysis using variables: age, sex, disease duration, BMI, HbA$_{1c}$, eGFR, UACR, the presence or absence of DPN and diabetic retinopathy, use of drugs with a high risk for hypoglycaemia (sulfonylurea, glinide, insulin), as explanatory variables | Yes | DPN was associated with TIR deterioration | Prospective |

BMI Body mass index, CGM continuous glucose monitoring, CI confidence interval, CKD chronic kidney disease, DBP diastolic blood pressure, DM diabetes mellitus, DPN diabetic peripheral neuropathy, eGFR estimated glomerular filtration rate, FGM flash glucose monitoring, GV glycaemic variability, HbA$_{1c}$ glycated haemogobin, LDL-C low-density lipoprotein cholesterol, MAGE mean amplitude of glycaemic excursions, MNSI Michigan Neuropathy Screening Instrument, NC nerve conduction, NCS nerve conduction study, NCV nerve conduction velocity, OR odds ratio, ROC receiver-operating characteristic analysis, SBP systolic blood pressure, SD standard deviation, SDglu standard deviation of glucose, SE standard error, SMBG self-monitoring of blood glucose, T1DM type 1 diabetes mellitus, T2DM type 2 diabetes mellitus, TC total cholesterol, TG triglycerides, TIR time-in-range, TCSS Toronto Clinical Scoring System scores, UACR urine albumin-creatinine ratio, VPT vibration perception threshold

provide new therapeutic targets for the prevention of DPN.

# CONCLUSIONS

Stringent glycaemic control is crucial in order to prevent the development and progression of DPN. Emerging evidence suggests that GV (MAGE) may be a novel factor in the pathogenesis of diabetic complications, and significant associations have been reported between CGM-derived data (TIR and GV) and DPN. However, the number of studies are currently limited. Most of the studies carried out to date are cross-sectional and have used different methodologies for the assessment of DPN, while the duration of CGM use has also been very limited. Therefore, the causal relationship between CGM-derived data and the development of DPN cannot be firmly established at this time. It also remains to be elucidated whether CGM measures could be considered the new therapeutic targets for DPN management.

# ACKNOWLEDGEMENTS

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