REVIEW

ROLE OF CONTINUOUS GLUCOSE MONITORING IN DIABETIC NEUROPATHY

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ABSTRACT

Diabetes is a major health problem due to its high prevalence and chronic complications that lead to disability and reduced quality of life. Among the complications, diabetic neuropathy, with its many forms, is the most common. Glycemic control plays a crucial role in the occurrence of chronic complications. Recently, with the advent of new technologies for continuous glycemic monitoring, the role of glycemic variability in the occurrence, progression, evaluation and treatment of chronic complications is increasingly understood. The widespread use of these technologies in clinical practice will optimize the care of patients with diabetes.

KEYWORDS: *continuous glucose monitoring systems, diabetic neuropathy, glucose variability*

INTRODUCTION

Diabetes is a worldwide health problem causing significant disabilities, reducing life expectancy, and quality of life and increasing mortality. Due to its chronic complications, diabetes imposes a huge economic burden worldwide. Long term exposure to high blood sugar levels leads to nerve fibers damage and occurrence of diabetic neuropathy (DN). The simplest definition of DN is nerve damage caused by diabetes. DN is the most frequent chronic complication of diabetes and also the most common form of neuropathy. DN presents as a broad spectrum of clinical manifestations [1], with high morbidity and is more common with longer disease duration.

The present short review aims to describe, the role of glycemic variability in the occurrence, progression, evaluation and treatment of chronic complications and the implication of new technologies in clinical practice which can have an impact on lowering the incidence of these complications through continuous regulation of blood glucose levels.

MATERIALS AND METHOD

A literature review was conducted. The period researched spanned 01.01.2010-01.01.2020 regarding the role of continuous glucose monitoring in relation to diabetic neuropathy. The abstracts and the full texts of all relevant articles were examined. To conduct the search, we used the following words: "continuous glucose monitoring" AND "diabetes and complications" AND "diabetic neuropathy". The variables taken into consideration and discussed were: demographic information, diabetic peripheral neuropathy, blood glucose levels, diabetic autonomic neuropathy, and patient impaired awareness of hypoglycemia. The PubMed database was considered. The articles were manually evaluated using the P.I.C.O.S concept defined as Patient, Intervention, Comparator, Outcome, Study to construct the inquiries as to ensure clinical potency. After the articles were identified they were appraised using the PRISMA checklist. A number of 62 articles were identified. From these 8 were excluded due to fact that they were duplicates. Another 20 articles were excluded because the full text could not be accessed. From the remaining 34 articles, another 6 were eliminated as they were not written in English. After analysis of the 28 articles, 7 were excluded since the subject studied did not correspond with our aim of the review. Finally, 21 articles were used for detailed discussion in the main text.

RESULTS AND DISCUSSION

Glucose control and diabetic neuropathy

As the most common forms of DNs are distal symmetrical sensorimotor polyneuropathy (DSP) (among peripheral DNs - DPN), and cardiovascular autonomic neuropathy (CAN) (among autonomic neuropathies), these forms are also the most studied. The importance of glucose control on DN occurrence and outcomes is reviewed by Ang et al. [2]. Although in various observational or randomized trials DN definitions and used measurements are not always consistent, and although frequently DN was a secondary outcome, we can conclude from the observational studies that glucose control is essential for neuropathy prevention in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [2]. DCCT/EDIC study proved that intensive control is critical in order to prevent or slower the progression of DN (DSP and CAN) in T1DM [3]. Because in T2DM patients many other risk factors such as obesity, dyslipidemia and high blood pressure, or many other comorbidities are usually present, the effects of glucose control on DNs are less conclusive, but several studies reported risk reduction with intensive treatment [2]. The most important lesson is that intensive treatment is essential as early as possible in order to prevent neuropathy in T1DM and, possibly, T2DM [3]. HbA1c represents the golden-standard assay for glucose control, and it is used as the most important glucose control marker for the development of long-term diabetes complications in people with T1DM and T2DM, but in the recent years, glucose variability (GV) is gaining more and more recognition as complementary component needed to asses glycemic status. A comprehensive review of existing literature described the potential mechanism of GV involvement in chronic diabetes complications pathogeny [4]. Multiple mechanisms may be involved, as high

fluctuations of blood glucose increase both the risk of hyperglycemia and hypoglycemia. Consequently, inflammatory cytokines are released; oxidative stress and endothelial dysfunction are increased [4]. All these mechanisms are contributing to both macrovascular and microvascular diabetic complications. A bidirectional relationship might be also taken into consideration as GV can be aggravated in cases with advanced autonomic neuropathy.

Assessment of glycemic variability

Glucose variations may be observed in time and described as a phenomenon that has two dimensions, respectively amplitude and duration [5]. The glycemic excursions may be noticed traditionally by using self-monitoring of blood glucose, which reflects blood glucose fluctuations on the timescale of hours or days, or more recently and accurately by using the new devices continuous glucose monitoring (CGM) or intermittent (flash) glucose monitoring (i-CGM). CGM systems measure the concentration of glucose in the interstitial fluid. A small, sterile, flexible electrode is inserted just under the skin to determine the glucose content in the interstitial fluid. Glucose from the interstitial fluid penetrates the semi permeable membrane of the sensor and reacts with a reagent (usually glucosidase) found in the sensor, this reaction producing electrons measured in an input signal. Then, this measurement is converted to a glucose value at the sensor level, usually using a calibration. There are various metrics currently recommended to asses GV.

In 2019 an international panel of experts issued a consensus endorsed by the most important professional diabetes organizations where recommendations are made for the most relevant aspects of CGM data utilization and reporting [6]. GV may be reported on long-term basis, analyzing serial measurements over a longer period of time (usually between consequent visits), and short-term basis, analyzing within-day and between-day GV [4]. The most common metrics for GV, recommended by the international consensus [6] are further described in association with DN. The glucose levels may be analyzed along the amplitude axis, and along time axis. The main measurements for the amplitude are: standard deviation (SD), coefficient of variation (CV), mean amplitude of glycemic excursions (MAGE). The temporal characteristics are: time spent within target range (TIR), time spent in hypoglycemia - time below target glucose range (TBR) or hyperglycemia - time above target glucose range (TAR) [7]. SD describes variation around the mean blood glucose (intra-day or inter-day). CV is calculated as SD/mean and gives the magnitude of variability relative to mean blood glucose and it is the recommended amplitude measure by the international consensus [6]. Mean amplitude of glycemic excursions (MAGE) is mainly use to reveal mealtime-related glucose excursions, and is calculated as arithmetic mean of the differences between consecutive peaks and nadirs [6]. The time spent by the patient in the various glucose ranges is expressed as the percentage of the readings spent in each range per day. TIR complete the whole image of the level of glycemic control [6].

CGM evaluated glycemic variability and diabetic peripheral neuropathy

We will further discuss the data from studies that assessed the association between GV and DNP both in T1DM and T2DM.

In 17 T1DM patients, aged 28.60±1.47 years, with a mean HbA1c of 8.14±0.34%, without sensory or motor symptoms and with normal nerve conduction parameters, GV was assessed by GCM-MAGE, and neurophysiological tests were performed. In these patients without nerve damage, using nerve excitability techniques in order to obtain information on axonal ion channel function and membrane potential, the authors investigated several motor and sensory nerve excitability parameters and the results indicated greater abnormality with higher MAGE values, leading to the conclusion that GV may be an important mediator of axonal dysfunction in T1DM and a contributing factor in development of diabetic neuropathy [8].

The nerve conduction study of Akaza and collaborators was the first to quantify the relation between GV (assessed by CGM) in 23 males and 17 females with T1DM and T2DM, aged 34 to 79 years, and axonal loss of the medial plantar nerve. In their study, MAGE had a significantly positive correlation with disease duration and

low-density lipoprotein cholesterol level, and significantly negative correlation with BMI and medial plantar compound nerve action potential amplitude. Using multivariate linear regression analysis, after adjustment for clinical background, the study found that MAGE was independently associated with a higher risk of medial plantar neuropathy [9].

In a larger study that included 740 T2DM patients, the authors evaluated nerve conduction velocity, latency, and amplitude after dividing patient into tertiles according to the CGM-derived TIR. A better diabetes control as evaluated by higher TIR was associated with better peripheral nerve function. The risk of TIR tertiles for low composite Z-score of conduction velocity was significant and remained significant even after adjustment of HbA1c [10]. Mayeda and collaborators also found in T2DM patients that lower TIR was associated with DPN symptoms. Even more, for every 10% lower TIR there is a 25% increased risk of DPN [11].

Another cross-sectional study that included 982 T2DM patients, 20.1% with DPN noticed higher values for MAGE, MODD, and SD in those with DPN than in those without DPN [12]. Increased GV (as assessed by MAGE) represents a significant independent factor to DPN. The authors succeeded to quantify the risk, as they described 4.57-fold increased mean risk of DPN for each 1 mmol/L increase in MAGE [12]. Besides significantly lower TIR in patient with DPN, Yang et al. described a negative correlation between TIR and NRS score. A decreasing TIR was associated with an increasing risk of any pain and moderate/severe pain even after adjusting for other GV metrics [13].

CGM evaluated glycemic variability and diabetic autonomic neuropathy

CAN is the most common form of autonomic neuropathy studied in relationship with GV. A study in 20 T1DM patients described increased GV (assessed by SD, MAGE, CONGA derived from CGM) in a close relationship with advanced CAN [14]. An independent association between CAN and CGM-defined GV was also described by Jun et al. in adults with type 1 diabetes, with most significant contributors to this association of those parameters describing the degree of level 2 hypoglycemia (glucose < 54 mg/dL) [15].

Heart rate variability (HRV) was inversely associated with the standard deviation of the mean interstitial tissue glucose, and the correlations were stronger for the night recordings in 50 T2DM patients treated with oral antidiabetic agents [16]. This inverse correlation of HRV with GV might be interpreted as a sign of causality between GV and CAN [16]. Another study in T2DM inadequately controlled patients requiring CGM found CV assed by CGM to be independently associated with the presence of CAN assessed by standard Ewing cardiovascular reflex tests [17]. An increased TIR was significantly inversely associated with the presence of advanced CAN in the study of Kim et al. The researchers also found time above range (TAR) of greater than 180 mg/dL to be independently correlated with the presence of definite CAN [18].

Baroreflex sensitivity (BRS) is a sensitive measure of CAN in T2DM, being associated with cardiovascular disease events. The study of Matsutani et al. found higher GV (increased CGM values for SD, CV, and MAGE) significantly related to low levels of BRS [19]. After multiple regression analysis, CV and MAGE were predictors of BRS independent of other risk factors like age, gender, hypertension, dyslipidemia, heart rate, estimated glomerular filtration rate, and CGM-mean glucose, suggesting that GV is an important risk contributor to altered BRS [19].

Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycemia

A randomized controlled crossover trial in 52 adult patients with T1DM and impaired awareness of hypoglycemia was designed to determine if the intervention with CGM may improve the time spent by the patients in the normal glycemic range. Usage of CGM significantly improved TIR, also reducing the time spent in hypoglycemia and hyperglycemia, compared with self-monitoring of blood glucose. Additionally, when using CGM the frequency of severe hypoglycemic events was lower [20]. A recent review of the current literature discusses the effects of CGM technologies in T1DM patients with impaired awareness of

hypoglycemia. The authors conclude that CGM is an effective instrument to reduce hypoglycemia and severe hypoglycemic episodes in T1D patients, even in those with impaired awareness of hypoglycemia [21].

CONCLUSION

With the new glucose monitoring technologies, GV is becoming a more meaningful assessment of glycemic control. As these technologies gain availability and usage, and as far as research progresses, more evidences are gathering about of the role and mechanisms of GV in various forms of DN. Incorporating new GV metrics into clinical practice may be a promising approach to DN, helping clinicians to better understand, screen, asses and manage DN.

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