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Time in range, as measured by continuous glucose monitor, as a predictor of microvascular complications in type 2 diabetes: a systematic review

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ABSTRACT

Continuous glucose monitoring (CGM)-derived time in range (TIR) correlates with hemoglobin A1c (A1c) among patients with type 2 diabetes mellitus (T2DM); however, there is a paucity of data evaluating its association with microvascular complications. We conducted this systematic review to examine the association between TIR and microvascular complications of diabetic retinopathy (DR), diabetic nephropathy (DN), and diabetic peripheral neuropathy (DPN). We conducted a comprehensive literature search on PubMed, Scopus, and Web of Science online databases following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Full-text original articles that evaluated the association between CGM-derived TIR and risk of microvascular complications and were published between 2010 and June 2021 were included in our systematic review. The quality of the included studies was evaluated using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Data were analyzed using qualitative synthesis. Eleven studies on a total of 13987 patients were included in the systematic review. The median sample size, baseline A1c, and diabetes duration were 466 patients (range: 105–5901), 8.2% (SD 0.5%), and 11.3 years (1.0), respectively. Majority of the studies were conducted in Asia (10 out of 11). Four studies evaluated the relationship between CGM-derived TIR and DR and CGM-derived TIR and DN, while seven studies evaluated the relationship between CGM-derived TIR and DPN. A 10% increase in TIR was associated with a reduction in albuminuria, severity of DR, and prevalence of DPN and cardiac autonomic neuropathy. In addition, an association was observed between urinary albumin to creatinine ratio but not with estimated glomerular filtration rate. This review summarizes recent evidence supporting an association between CGM-derived TIR and microvascular complications among patients with T2DM. A larger-scale multicenter investigation that includes more diverse participants is warranted to further validate the utility of TIR as a predictor of diabetic microvascular complications.

INTRODUCTION

Hemoglobin A1c (A1c) is the primary tool for monitoring long-term glycemic control and assessing the risk of diabetes-related complications.[1 2] However, A1c has several limitations. A1c is affected by factors such as age, race/ethnicity, hemoglobinopathies, hemolytic anemia, recent blood transfusion, chronic kidney disease, and pregnancy, resulting in discrepancies between measured A1c and true glycemic control. Furthermore, A1c fails to provide information about extremes of hypoglycemia or hyperglycemia, glucose trends, and glycemic variability.[3] Intermittent self-monitored blood glucose (SMBG) is not influenced by conditions affecting red blood cell turnover and provides information beyond A1c; however, it is inconvenient and unpopular among patients of all age groups.

Continuous glucose monitoring (CGM) devices are increasingly popular, affordable, reliable in improving A1c, and overcome many of the limitations with A1c, and SMBG and CGM-derived metrics are now incorporated into the management of patients with diabetes.[4] CGM devices measure interstitial fluid glucose every 1–5 min and provide several metrics. Mean glucose from CGM has also been used to calculate glucose management indicator (GMI), also known as 'estimated A1C'.[5] Time in range (TIR) is another metric, defined as the percentage of time glucose between 70 mg/dL and 180 mg/dL (3.9–10.0 mmol/L). Over the last few years, TIR has become popular as a surrogate marker of glycemic control, which also correlates with A1c.[4] International consensus recommends TIR of 70% to align with A1c of ~7%, with a 0.5% decline in A1c per 10% increase in TIR.[4 6] Furthermore, a 5% increase in TIR was associated with significant clinical benefits among patients with type 2 diabetes mellitus (T2DM).[4]

While A1c remains the primary predictor of the development and progression of microvascular complications among patients with T2DM, there is growing evidence to support the association between TIR and diabetes-related microvascular complications.[7–9] In a

study by Sheng *et al*[9] on patients with T2DM, the authors calculated TIR from a 7-point SMBG and found lower TIR to have higher odds of having diabetic retinopathy (DR), diabetic nephropathy (DN), and diabetic peripheral neuropathy (DPN), suggesting a strong correlation between calculated TIR and risk of diabetes-related microvascular complications.

Although adoption of TIR in clinical practice is gradually increasing and becoming well established, its use as a predictor of long-term risk of diabetes-related microvascular complications is still growing and needs further validation. Therefore, we performed a systematic review to summarize the published literature evaluating CGM-derived TIR as a predictor of diabetes-related microvascular complications and discuss its implications on future clinical practice and research among patients with diabetes.

METHODS

This systematic review was performed using the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements.[10] For this study, a comprehensive literature search was done to identify original research articles in various databases. Before the literature screening process, a protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42021259988).

Selection criteria

Studies included in this systematic review met the following inclusion criteria: (1) cross-sectional/observational studies examining the association between CGM-derived TIR and microvascular complications among patients with T2DM, (2) full-text and (3) English-language articles, and (4) published between January 1, 2010 and June 5, 2021. We excluded the following studies: (1) review articles and (2) systematic review with or without meta-analysis.

Search strategy

On June 5, 2021, we conducted a comprehensive literature search in electronic databases (PubMed, Scopus, and Web of Science) for publications between 2010 and June 2021 with English language restrictions. The search strategy was designed and conducted by the principal investigator (RR), with input from the study's coinvestigators (RM, NJ, and VJ), using the following keywords: ((“Continuous glucose monitor” OR “Continuous glucose monitoring” OR “Dexcom” “Freestyle Libre” OR “Guardian” OR “Flash glucose monitoring” OR “Time in Range” OR “Time-in-range” OR “TIR”) AND (“Diabetes complications” OR “Microvascular complications” OR “Retinopathy” OR “Neuropathy” OR “Nephropathy” OR “Complication” OR “Microalbuminuria” OR “Albuminuria”)) AND (“Type II diabetes” OR “type 2 diabetes”). Next, the bibliographies of the selected articles were manually searched for any additional studies. After screening for duplicate studies, two reviewers (RM and NJ) independently reviewed the title and abstract of the identified publications. Studies were then excluded if they did not address our research question or meet our prespecified inclusion criteria. Finally, the full texts of the remaining articles were examined to determine the final exclusion for our systematic review. Any conflicts during the study selection process were resolved by the third reviewer (RR). Figure 1 shows the schematic diagram of the study selection process.

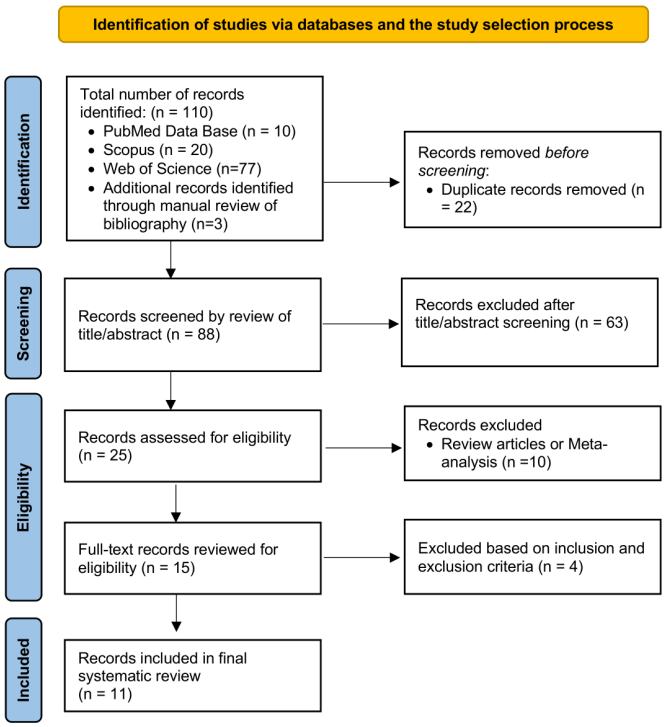

Figure 1 PRISMA method flow diagram of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data collection

A predefined Excel sheet was used for extraction of data from each study. The following data were extracted from each included study: (1) title, (2) primary author, (3) year of publication, (4) duration of study, (5) country of the study population, (6) study design, (7) aim of the study, (8) sample size, (9) pertinent variables measure, (10) results, (11) conclusion, and (12) limitations of the study.

Quality assessment

Two independent reviewers (RM and VJ) assessed the study quality and risk of bias in the included studies using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Study Quality Assessment Tools; https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).[11] Any disagreement was resolved by the other involved research reviewers (RR and VJ). Based on 14 questions, an overall rating was assigned as good,

fair, and poor for study quality, corresponding to low, moderate, or high risk of bias.

Data synthesis

Before this systematic review, an initial literature search in the subject field revealed only a few studies with heterogeneous data points. Hence, we could not perform a meta-analysis, and a qualitative synthesis was performed.

RESULTS

Study selection

We identified 110 publications using our initial search of online databases: PubMed, Scopus, Web of Science, and manual review of the bibliography. Of these, 22 duplicate publications were removed. Of 88 records screened, 63 were excluded based on screening of the title/abstract and 10 were excluded being either review articles or meta-analysis. Fifteen eligible publications were retrieved in full text, of which four did not meet the inclusion criteria. Ultimately, we included 11 articles in our systematic review (figure 1).[12–22] There was complete agreement between authors regarding article inclusion, risk of bias assessment, and data extraction. Detailed characteristics of the included studies are summarized in online supplemental file 1.

Baseline characteristics

A total of 13 987 patients across 11 studies were included in our systematic review. The median sample size was 466 patients (range: 105–5901, IQR: 616). Ten studies were cross-sectional in design, while one study was an interim analysis of an ongoing prospective observational study.[20] The mean age of the participants was 59.3 years (SD 1.3), A1c at baseline 8.2% (SD 0.5%), and duration of diabetes 11.3 years (SD 1.0). For patients with retinopathy, nephropathy, and neuropathy, the mean duration of diabetes was 11.8, 13.1, and 11.0 years, the mean age was 62.1, 61.6, and 59.1 years, and the mean baseline A1c was 8%, 7.8%, and 8.1%, respectively. Five studies were conducted in China,[12–15 21] two in South Korea,[17 18] two in Japan,[20 22] one in India,[19] and one in the USA.[16] Five studies used Medtronic's CGM device,[12 15–18] four studies used Abbott's Freestyle Libre CGM (FLP-CGM) device,[19–22] one study used Meiqi CGM device,[14] while in one study both Medtronic and Meiqi CGM devices[13] were used. In all 11 studies, TIR was defined by the time per cent during 24 hours when the glucose was in the range of 70–180 mg/dL (3.9–10 mmol/L). The duration of use of CGM device varied in all studies and ranged between 3 and 14 days. Calibrations of the CGM device when applicable (in 6 of 11 studies) was done using two to four capillary blood glucose readings. In one study, the number of calibrations was not reported by the authors.[15] GMI values based on CGM data were available for only five studies and ranged between 7 and 7.5.[16–19 21] We have summarized the baseline characteristics of the included studies in table 1. On the study quality assessment tool, one study was rated 'good' and ten studies were rated 'fair'; none was rated 'poor', eliminating increased risk of bias in the studies included in our systematic review (online supplemental file 1).

Association between CGM-derived TIR and DR

Four cross-sectional studies evaluated the association between TIR and DR.[12 19 20 22] One study used Medtronic CGM over 72 hours,[12] while three studies used the FLP-CGM device to collect 14 days of data.[19 20 22] One study used FLP-CGM data over the middle 8-day period, excluding the first 2 days and the last 4 days.[20] The average prevalence of DR was 27.4% (range: 22.2%–30.1%). One study categorized participants into three groups based on glycemic profile ('TIR profile', 'hypo profile', and 'hyper profile') and showed higher odds of proliferative DR ('hypo profile': OR=2.84, 95% CI 1.65 to 4.88; 'hyper profile': OR=1.39, 95% CI 0.78 to 2.45) as well as non-proliferative DR ('hypo profile': OR=1.44, 95% CI 1.20 to 1.73; 'hyper profile': OR=1.33, 95% CI 1.11 to 1.58) compared with 'TIR profile'.[19] Two studies found a statistically significant association between a 10% increase in TIR and reduction in severity of DR,[12 20] while no significant association between TIR and DR was found in the study by Kuroda *et al*.[22] In both these studies, higher A1c was found to be associated with increased severity of DR ($p<0.01$),[12 20] while the relationship between A1c and DR was not assessed in the other two studies.[19 22]

In summary, a 10% increase in TIR is associated with reduction in severity of DR and higher time spent in target range is associated with decrease in severity of DR. In addition, CGM-derived TIR was found to be similar to A1c in predicting DR among patients with T2DM.

Association between CGM-derived TIR and DN

The association between TIR and nephropathy was evaluated in four studies.[17 19 20 22] In one study, CGM was done using Medtronic's CGM device for 3 days (GOLD) and 6 days (iPro2), respectively,[17] while in three studies FLP-CGM device was used to record data over 14 days.[19 20 22] In three studies, urinary albumin to creatinine ratio (UACR) >30 was used to define DN,[17 19 20] while in one study the authors used UACR and estimated glomerular filtration rate (eGFR) values to determine its association with TIR.[22] Participants were categorized into normoalbuminuria (UACR <30 mg/g), microalbuminuria (UACR 30–300 mg/g), or macroalbuminuria (UACR >300 mg/g) in two studies.[19 20] In one study, participants were grouped into with and without albuminuria.[17] The prevalence of albuminuria in these four studies was 32.67% (range 27%–36.6%), with a higher prevalence of microalbuminuria compared with macroalbuminuria (22.6% vs 8.5%, respectively). In another study, participants were categorized into three groups based on glycemic profile ('TIR profile', 'hypo profile', and 'hyper profile').[19] Compared with 'TIR profile', both 'hyper' and 'hypo' profiles had higher odds of macroalbuminuria ('hypo profile': OR=1.58, 95% CI 1.25 to 1.98; 'hyper profile': OR=1.37, 95% CI 1.10 to 1.71). Additionally, 'hyper' and 'hypo'

Table 1 Baseline characteristics of studies evaluating the association between CGM-derived TIR and microvascular complications among patients with T2DM

Characteristics	All included studies (N=11)	TIR and diabetic retinopathy (n=4)	TIR and diabetic nephropathy (n=4)	TIR and diabetic neuropathy (n=7)
Sample size, n (range)	466 (105–5901)	2315.5 (281–5901)	932.5 (281–5901)	349 (105–740)
Sex (%)				
Male	60.8	58.1	62.0	62.6
Female	39.2	41.9	38.0	37.4
Age, years, mean (SD)*	59.3 (1.3)	62.1 (0.99)	61.6 (0.4)	59.1 (2.8)
Baseline A1c, %, mean (SD)*	8.2 (0.5)	8.0 (0.6)	7.8 (0.4)	8.1 (0.6)
Duration of diabetes, years, mean (SD)†	11.3 (1.0)	11.8 (0.7)	13.1 (0.2)	11.0 (1.1)
Study location (n)				
China	5			
South Korea	2			
Japan	2			
India	1			
USA	1			
CGM device used (n)				
Medtronic	5			
Abbott Freestyle Libre	4			
Meiqi	1			
Medtronic+Meiqi	1			
Duration of CGM use (n)				
3 days	4			
14 days	4			
3 and 6 days for GOLD (Medtronic) and iPro2 (Medtronic), respectively‡	2			
Two 6-day periods, separated by 2 weeks§	1			
CGM device calibrations (n)				
Not applicable	4			
At least two times per day	3			
At least four times per day	3			
Not reported	1			

*Two studies (Yang *et al*[21] and Kuroda *et al*[22]) reported the median age and the median baseline A1c in their study and hence were not included in the final calculation of mean age and average baseline A1c of the participants.
†Four studies (Yang *et al*,[21] Kuroda *et al*,[22] Guo *et al*,[13] and Guo *et al*[14]) reported the median values for the duration of diabetes and hence were not included in the calculation of the mean duration of diabetes.
‡Yoo *et al*[17] and Kim *et al*[18] used GOLD (Medtronic) and iPro2 (Medtronic) CGM over 3 and 6 days, respectively.
§Mayeda *et al*[16] collected CGM data over two 6-day periods, separated by 2 weeks.
A1c, hemoglobin A1c; CGM, continuous glucose monitoring; T2DM, type 2 diabetes mellitus; TIR, time in range.

profiles also had higher odds of diabetic kidney disease, compared with 'TIR profile' ('hypo profile': OR=1.65, 95% CI 1.18 to 2.31; 'hyper profile': OR=1.88, 95% CI 1.37 to 2.58).[19] Two studies showed a statistically significant association between a 10% increase in TIR and reduction in severity of albuminuria.[17 20] In multiple regression analysis, Kuroda *et al*[22] found an association between TIR and UACR (β=−0.100, p=0.043) but not with eGFR (β=−0.011, p=0.824). Out of the four studies evaluating the relationship between TIR and DN, two studies found similar association between A1c and DN.[17 20] One study found higher A1c among patients with albuminuria compared with patients without albuminuria (8.5% vs 8.0%, p<0.01),[17] while in the second study the authors found a statistically significant association between severity of albuminuria and A1c (p<0.01).[20] In the rest of the two studies, the association between A1c and DN was not evaluated.[19 22]

In summary, two studies showed decrease in severity of albuminuria with a 10% increase in TIR, one study showed increased time spent in target range to be associated with lower risk of macroalbuminuria and diabetic kidney disease, while in one study increased TIR was associated with a decrease in UACR but not with eGFR. In limited studies evaluating the relationship between CGM-derived TIR and DN, it was found to be similar to A1c in predicting DN among patients with T2DM.

Association between CGM-derived TIR and diabetic neuropathy

Seven studies examined the relationship between CGM-derived TIR and diabetic neuropathy.[13–16 18 21 22] Four studies evaluated the association of TIR with DPN,[14 16 21 22] two studies examined the association of TIR and cardiovascular autonomic neuropathy (CAN),[13 18] and in one study the association of TIR with peripheral nerve function was evaluated.[15] Three studies used Medtronic CGM,[15 16 18] two studies used Freestyle Libre,[21 22] while Meiqi[14] and both Meiqi and Medtronic[13] were used in one study each. The CGM data were collected for 3 days in three studies,[13–15] for 2 weeks in two studies,[21 22] for both 3 days (GOLD) and 6 days (iPro2) in one study,[18] and for two 6-day periods, separated by 2 weeks, in one study.[16]

Each of the studies evaluating DPN/CAN used different surrogates for examining neuropathy. Three studies used sudomotor function,[14] the Michigan Neuropathy Screening Instrument,[16] and the Numerical Rating Scale[21] to assess DPN. Kuroda *et al*[22] used the diagnostic criteria of the Japanese Study Group of Diabetes Neuropathy[23] to diagnose DPN. CAN was evaluated in two studies using a combination of five (three parasympathetic and two sympathetic) and four (three parasympathetic and one sympathetic) cardiovascular autonomic function tests.[13 18] Li *et al*[15] examined peripheral nerve function by electrophysiological measurement of motor and sensory nerves to calculate composite Z-score for conduction velocity, latency, and amplitude to assess peripheral nerve function.

The prevalence of DPN and CAN was 46.6% and 32.1%, respectively. Yang *et al*[21] showed a decline in TIR to be directly associated with increased prevalence of any painful DPN (OR=2.66, 95% CI 1.16 to 6.10, p<0.05), while Guo *et al*[14] found an increase in TIR to be inversely related to prevalence of sudomotor dysfunction (OR=0.979, 95% CI 0.971 to 0.987, p<0.001). In one study by Mayeda *et al*,[16] a 10% decrease in TIR was associated with increase in prevalence of DPN (OR=1.25, 95% CI 1.02 to 1.52, p<0.05) and that the rate of DPN was lower in participants with TIR >70% compared with participants with TIR <70% (43% vs 74%). Kuroda *et al*[22] found TIR to be weakly associated with presence of DPN (β=−0.106, p=0.033). Kim *et al*[18] showed the OR of CAN per 10% increase in TIR to be 0.894 (95% CI 0.81 to 0.99, p<0.05). Guo *et al*[13] found an increase in TIR quartiles to be inversely associated with prevalence of CAN (p<0.05). Li *et al*[15] assessed peripheral nerve function and found higher TIR to be associated with a higher composite Z-score of conduction velocity (b=0.230, p<0.001), higher composite Z-score of amplitude (b=0.099, p=0.010), and lower composite Z-score of latency (b=0.172, p<0.001). The authors further concluded the higher TIR tertile group to have lower risk of slowing conduction velocity (TIR medium: OR 0.44, p<0.001; TIR high: OR 0.26, p<0.001), lower risk of amplitude reduction (TIR high: OR 0.60, p<0.05), and higher rate of reduced latency (TIR medium: OR 1.57, p<0.05; TIR high OR 1.71, p<0.05) compared with the low tertile group.

Out of five studies evaluating DPN or peripheral nerve function, three studies evaluated the relationship between TIR and A1c,[14–16] while it was not examined in two studies.[21 22] There was no statistically significant relationship between TIR and A1c among patients with and without sudomotor dysfunction. One study found higher A1c in patients with sudomotor dysfunction compared with patients without sudomotor dysfunction; however, this association was not statistically significant (8.94 vs 8.6, p=0.118).[14] In another study, the authors did not find statistically significant relationship between A1c and severity of DPN (p=0.139).[16] Assessment of nerve function by Li *et al*[15] demonstrated A1c to be independently associated with composite Z-score of conduction velocity, latency, and amplitude (p<0.001). Compared with the relationship between A1c and DPN, the association between A1c and CAN was limited with only two studies examining this relationship. While one study showed higher A1c to be associated with greater prevalence of CAN (p=0.041),[18] in another study this association trended toward statistical significance (p=0.053).[13]

In summary, increase in TIR was associated with decrease in prevalence and severity of both DPN and CAN. TIR >70% was associated with significantly lower prevalence of DPN compared with TIR <70%. Additionally, based on limited studies, TIR was found to more closely correlate with DPN and CAN compared with A1c.

DISCUSSION

To our knowledge, this is the first systematic review examining the relationship between CGM-derived TIR and microvascular complication among patients with T2DM. The risk of microvascular complications and chronic hyperglycemia, as measured by A1c, has been well established in both patients with type 1 diabetes mellitus (T1DM) and patients with T2DM in landmark trials such as The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study.[24 25] CGM provides more comprehensive glucose data beyond A1c, is convenient for the patients,[26] and has shown promising evidence supporting improved glycemic control and quality of life among patients with diabetes.[27] Several studies have assessed the relationship between CGM-derived metrics and A1c. One study by Vigersky and McMahon[28] analyzing 18 randomized controlled trials found a strong correlation between A1c and TIR 70–180 mg/dL, while Beck *et al*[29] found that a 10% change in TIR of 70–180 mg/dL correlates with the mean A1c change by ~0.5%. Current international consensus recommends TIR of 70% to align with A1c of ~7%, with each 10% increase in TIR to correspond with ~0.5% A1c reduction.[4 6] In a previous work, Beck *et al*[7] validated a strong correlation between TIR derived from SMBG among patients in DCCT and risk of microvascular complications. With this association between

SMBG-derived TIR and microvascular complications, along with recent data validating the association of CGM-derived TIR with A1c, there is a growing interest in using CGM-derived TIR as a surrogate marker for assessment of various diabetes-related complications. This idea has been supported by many recent studies and the evidence is constantly growing. One study found a 6.4% reduction in risk of abnormal carotid intima-media thickness, a surrogate for cardiovascular disease, when TIR increased by 10%.[30] In a study by Ranjan *et al*[31] on patients with T1DM, improved TIR over 1 year was associated with reduced albuminuria (19% reduction in UACR per 10% increase in TIR). Lu *et al*[12] found an inverse correlation between TIR quartile and severity of DR. Yoo *et al*[17] reported albuminuria, a microvascular complication of diabetes, to be inversely related with TIR, while Mayeda *et al*[16] established an association between DPN among patients with T2DM and chronic kidney disease. The results of these studies further strengthen the potential of TIR as a tool for predicting the risk of development and progression of diabetes-related microvascular complications. In this systematic review of 11 original published articles, we found a strong correlation between CGM-derived TIR and microvascular complications.

Although CGM-derived TIR provides important information not captured by A1c, it is still insufficient in providing a complete description of glycemic control. Glycemic variability (measured by mean absolute glucose, SD, and coefficient of variation) has also been suggested to be an independent predictor of diabetes-related complications.[32] It results in oxidative stress[33] and endothelial dysfunction[34] and can lead to cardiovascular as well as microvascular complications.[35–37] Glycemic variability was not consistently assessed in the 11 studies included in our systematic review, and hence we did not evaluate its association with microvascular complications in our systematic review.

The association between TIR and microvascular complications was adjusted for A1c. The association was independent of A1c for severity of neuropathic pain,[21] sudomotor dysfunction,[14] conduction velocity,[15] CAN,[13] severity of DR,[12] and albuminuria.[20] Varghese *et al*[19] also observed an A1c independent association between TIR and retinopathy as well as nephropathy parameters among hypo and hyper profiles versus TIR profiles. In three studies, the association between TIR and CAN,[18] albuminuria,[17] and DR[20] was found to be dependent on A1c. Additionally, Mayeda *et al*[16] did not observe any association between A1c and DPN. Parameters, although non-uniformly defined among 11 studies, were consistently applied to the study subjects.

There are some limitations to our systematic review which need to be noted. The small number of available studies evaluating the association of CGM-derived TIR and microvascular complications and the quality of the studies included in the review are the most significant limitations of our systematic review. We included keywords to search various databases instead of using medical subject headings or MeSH terms, resulting in limited search results. Even with broader terms the results were the same articles. However, we addressed this limitation of the study by manually searching the bibliographies of included articles to look for any additional studies. The involved studies were primarily cross-sectional in design, and in the absence of prospective studies a direct causal relationship cannot be established between TIR and microvascular complications. Majority of the studies were conducted in Asia (10 out of 11 studies) and study participants were predominantly Asian (13 882 out 13 987), affecting the generalizability of our findings to other populations. There were significant methodological differences among various studies included in our systematic review. The studies differed in the type of CGM device used (Medtronic vs Freestyle Libre vs Meiqi), duration over which CGM data were collected (72 hours to 14 days), and calibration of CGM devices (two to four times per day). These differences could significantly impact the TIR.[38] Additionally, there was no study involving the Dexcom CGM device, one of the most used CGM devices, owing to its ability to integrate into hybrid-close loop systems. Furthermore, each study used different surrogates for assessment of neuropathy, retinopathy, and nephropathy. For DR, participants were classified into mild non-proliferative DR, moderate non-proliferative DR, and vision-threatening DR by Lu *et al*,[12] versus simple DR, preproliferative DR, and proliferative DR by Wakasugi *et al*,[20] versus non-proliferative DR and proliferative DR by Varghese *et al*.[19] To evaluate DN, patients were categorized into those with microalbuminuria and macroalbuminuria in one study versus microalbuminuria, diabetic kidney disease, and macroalbuminuria by Varghese *et al*,[19] versus with and without albuminuria in the third study. Similarly, for defining DPN, different criteria like sudomotor dysfunction, Michigan Neuropathy Screening Instrument, and Numerical Rating Scale were used in three different studies. To evaluate for CAN, one study used five cardiac reflex tests, while only four cardiac reflex tests were used in another study. This heterogeneity in outcomes assessed prevented quantitative analysis in our systematic review. A subgroup analysis between studies with more than 10–14 days of CGM data versus less than 10 days of CGM data could not be performed owing to lack of consistency in the duration of CGM data analyzed, low number of studies in each group, and heterogeneity in outcomes assessed in each study. Moreover, only in a few studies (6 out of 11) the authors evaluated the association of microvascular complications to a 10% change in TIR. In contrast, the other studies did not report these data and only assessed the outcomes for different TIR quartiles.

CONCLUSION

In summary, our study affirms the significant association between CGM-derived TIR and microvascular complications of DN, DR, and DPN among patients with T2DM.

However, heterogeneity in the CGM data reported a lack of uniformity in methodology and outcomes measured, limited race/ethnicity of the population evaluated in the included studies, and restricted generalization of the findings from our systematic review. Therefore, a larger-scale multicenter investigation that includes more diverse participants is warranted to further validate the association between CGM-derived TIR and microvascular complications among patients with T2DM.

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Supplementary Appendix

Contents

Appendix 1. Details of Search strategy

DATABASE	TIMESPAN	SEARCH STRATEGY
Pubmed	2010 to June 2021	(("Continuous glucose monitor" OR "Continuous glucose monitoring" OR "Dexcom" "Freestyle Libre" OR "Guardian" OR "Flash glucose monitoring" OR "Time in Range" OR "Time-in-range" OR "TIR") AND ("Diabetes complications" OR "Microvascular complications" OR "Retinopathy" "Neuropathy" OR "Nephropathy" OR "Complication" OR "Microalbuminuria" OR "Albuminuria")) AND ("Type II diabetes" OR "type 2 diabetes")
Scopus	2010 to June 2021	(("Continuous glucose monitor" OR "Continuous glucose monitoring" OR "Dexcom" "Freestyle Libre" OR "Guardian" OR "Flash glucose monitoring" OR "Time in Range" OR "Time-in-range" OR "TIR") AND ("Diabetes complications" OR "Microvascular complications" OR "Retinopathy" "Neuropathy" OR "Nephropathy" OR "Complication" OR "Microalbuminuria" OR "Albuminuria")) AND ("Type II diabetes" OR "type 2 diabetes")
Web of Science	2010 to June 2021	(("Continuous glucose monitor" OR "Continuous glucose monitoring" OR "Dexcom" "Freestyle Libre" OR "Guardian" OR "Flash glucose monitoring" OR "Time in Range" OR "Time-in-range" OR "TIR") AND ("Diabetes complications" OR "Microvascular complications" OR "Retinopathy" "Neuropathy" OR "Nephropathy" OR "Complication" OR "Microalbuminuria" OR "Albuminuria")) AND ("Type II diabetes" OR "type 2 diabetes")

Raj R, *et al. BMJ Open Diab Res Care* 2022; 10:e002573. doi: 10.1136/bmjdrc-2021-002573

Appendix 2. Characteristics of the Studies Investigated

Study ID	Varghese et al. (Varghese JS, Ho JC, Anjana RM, Pradeepa R, Patel SA, Jebarani S, Baskar V, Narayan KMV, Mohan V. Profiles of Intraday Glucose in Type 2 Diabetes and Their Association with Complications: An Analysis of Continuous Glucose Monitoring Data. Diabetes Technol Ther. 2021 Aug;23(8):555-564. doi: 10.1089/dia.2020.0672. Epub 2021 May 11. PMID: 33720761)
Country/Year	India/2021
Study Design	Cross Sectional; Single Centre
Aim Of Study	To identify profiles of type 2 diabetes from continuous glucose monitoring (CGM) data using ambulatory glucose profile (AGP) indicators and examine the association with prevalent complications.
Methods	PARTICIPANTS: • Sample Size: 5901 • SEX (Male % / Female %): 64.8%/ 35.2% • AGE (mean): 55.4 years • ETHNICITY : Asians (Indian) • DURATION OF DIABETES (mean (SD) years): 8.1(6.8) • Duration during which subjects were recruited:4 years • HbA1c at baseline: 9 INCLUSION CRITERIA: ● age between 18 and 80 years, having at least 75% of CGM data recorded over 14-day period, with valid HbA1c measurements within 30 days of CGM. EXCLUSION CRITERIA: ● participants with other forms of diabetes
Interventions	• CGM Devices Used: Abbott FreeStyle Libre Pro- CGM data for two weeks was collected • Duration of CGM use:14 days • Calibration of CGM: NA • % of time CGM device active OR Time wearing CGM :>99% (during 14 days data)
Outcomes/ Result	• Participants were categorised into three groups based on glycemic profile (‘‘TIR Profile’’, ‘‘Hypo Profile’’, and ‘‘Hyper Profile’’) • Urinary albumin-to-creatinine ratio (UACR) > 30 was used to define DN. Participants were categorized into normoalbuminuria (UACR <30 mg/g), microalbuminuria (UACR 30-300 mg/g) or macroalbuminuria (UACR >300 mg/g). Retinopathy was classified as NPDR and PDR. • Among the participants, 30.1% had retinopathy and 35.5% had nephropathy. • Mean TIR% = 78.4 ASSOCIATION OF CGM PROFILES WITH EXISTING COMPLICATIONS ● Both Hypo and Hyper profiles had higher odds of nonproliferative diabetic retinopathy (“Hypo”: 1.44, 1.20–1.73; “Hyper”: 1.33, 1.11–1.58), macroalbuminuria (“Hypo”: 1.58, 1.25–1.98; “Hyper”: 1.37, 1.10–1.71), and diabetic kidney disease (“Hypo”: 1.65, 1.18–2.31; “Hyper”: 1.88, 1.37–2.58), compared with “TIR profile. Also, higher odds of PDR (‘‘Hypo profile’’: 2.84, 1.65–4.88 and ‘‘Hyper profile’’: 1.39, 0.78–2.45) as well as NPDR (‘‘Hypo profile’’:1.44, 1.20-1.73 and ‘‘Hyper profile’’:1.33, 1.11-1.58) compared to ‘‘TIR profile’. ● The study observed an A1C independent association between TIR and retinopathy and as well as nephropathy parameters among hypo and hyper profiles versus TIR profiles.
Publication details	COMMERCIAL FUNDING: No NON-COMMERCIAL FUNDING: No.

Study ID	Wakasugi et al. (Wakasugi S, Mita T, Katakami N, Okada Y, Yoshii H, Osonoi T, Nishida K, Shiraiwa T, Torimoto K, Kurozumi A, Gosho M, Shimomura I, Watada H. Associations between continuous glucose monitoring-derived metrics and diabetic retinopathy and albuminuria in patients with type 2 diabetes. BMJ Open Diabetes Res Care. 2021 Apr;9(1):e001923. doi: 10.1136/bmjdrc-2020-001923. PMID: 33879513; PMCID: PMC8061826)
Country/Year	Japan/2021
Study Design	Exploratory cross-sectional analysis of an ongoing 5year follow up prospective study; Multicentric in 34 institutions
Aim Of Study	To investigate the relationships between glucose fluctuations evaluated with CGM and the incidence of composite cardiovascular events over a 5-year follow-up period
Methods	• Sample Size: 999 • AGE (mean (SD) years): 64.6 (9.6) • ETHNICITY : Asians (Japanese) • DURATION OF DIABETES (mean (SD) years): 28.6 (10.8). • Duration during which subjects were recruited: 11 months • HbA1c at baseline: 7 INCLUSION CRITERIA: • age ≥30 years and ≤80 years, regardless of gender; • receiving treatment for type 2 diabetes at one of the participating outpatient clinics; • no changes (including new prescriptions) in antidiabetic medications for 6 months prior (insulin dosage changes were allowed); • No anticipated changes in antidiabetic medications from the time of enrolment until a CGM device was applied on the back of the upper arm EXCLUSION CRITERIA: • type 1 or secondary diabetes • presence of severe infectious disease preoperatively, postoperatively, or associated with severe trauma; • history of myocardial infarction, angina pectoris, cerebral stroke, cerebral infarction, or arteriosclerosis obliterans; current treatment with artificial dialysis; moderate liver dysfunction defined as aspartate aminotransferase ≥100IU/L; moderate or severe heart failure (New York Heart Association stage III or worse); pregnancy, lactation, possible pregnancy, or plans to become pregnant during the study period; present or history of a malignant tumor; • use of a sensor-augmented insulin pump; • type 2 diabetes diagnosis within the past year;
Interventions	• CGM Devices Used: FreeStyle Libre Pro • Duration of CGM use:14 days; analyzed FLP-CGM data over the middle 8-day period, excluding the first 2 days and last 4 days. • Calibration of CGM: NA • % of time CGM device active OR Time wearing CGM :Analysis of CGM data was done on middle 8-day period during 14 days use
Outcomes/ Results	• The presence and severity of DR were determined by trained ophthalmologists and grouped into four: no diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), pre-proliferative diabetic retinopathy (PPDR), or proliferative diabetic retinopathy (PDR). • DN was defined according to the level of UAE: <30mg/g creatinine was defined as normoalbuminuria, 30–299mg/g creatinine was defined as microalbuminuria, and ≥300mg/g creatinine was defined as macroalbuminuria. • The prevalence of microalbuminuria and macroalbuminuria was 20.3% and 6.7%, respectively. The overall prevalence of diabetic retinopathy was 22.2%; Prevalence of SDR was 13.3%, PPDR 5% and PDR was 3.9%. • Mean TIR% = 78.90 RELATIONSHIP BETWEEN FLP-CGM-DERIVED METRICS AND DR SEVERITY • Statistically significant association between a 10 % increase in TIR and reduction in severity of DR (OR= 0.85, 95% CI 0.78-0.93, p <0.001) • No significant associations between FLP-CGM-derived metrics and DR severity after adjusting for HbA1c. RELATIONSHIP BETWEEN FLP-CGM-DERIVED METRICS AND ALBUMINURIA SEVERITY • Showed statistically significant association between a 10 % increase in TIR and reduction in severity of albuminuria (OR=0.81, 95% CI 0.72- 0.90, p<0.001).The association was independent of A1c for albuminuria.
Publication details	FUNDING: This study was financially supported by the Japan Agency for Medical Research and Development (AMED) under Grant Number JP20ek0210105 (to HW) and the Manpei Suzuki Diabetes Foundation (to HW). TO and HW have received research funds from Abbott Japan. HW is a member of the advisory board of Abbott Japan.

Study ID	Kim et al. (Kim MY, Kim G, Park JY, Choi MS, Jun JE, Lee YB, Jin SM, Hur KY, Kim JH. The Association Between Continuous Glucose Monitoring-Derived Metrics and Cardiovascular Autonomic Neuropathy in Outpatients with Type 2 Diabetes. Diabetes Technol Ther. 2021 Jun;23(6):434-442. doi: 10.1089/dia.2020.0599. Epub 2021 Apr 5. PMID: 33523771)
Country/Year	South Korea/2021
Study Design	Cross Sectional Study; Single Center
Aim of Study	Associations between CGM-derived TIR, hyperglycemia, and hypoglycemia metrics and cardiovascular autonomic neuropathy (CAN) in patients with type 2 diabetes
Methods	● Sample: 284 ● SEX (Male % / Female %): 58.5/ 41.5 ● AGE (mean (SD) years): 57.4(10.5) ● ETHNICITY : Asians (Korean) ● DURATION OF DIABETES (mean (SD) years): 12(8.5) ● Duration during which subjects were recruited: 10 years ● HbA1c at baseline: 8.30 INCLUSION CRITERIA: ● Those who underwent CGM and autonomic function testing at the same time or within 3 months EXCLUSION CRITERIA: ● Patients with type 1 or gestational diabetes mellitus ● Cancer ● History of thyroid dysfunction, myocardial infarction, revascularization, stroke, severe liver disease , GFR <30 mL/min/1.73 m2
Interventions	● CGM Devices Used: CGM using GOLD™ (Medtronic MiniMed) for 3 days or iPro™2 (Medtronic MiniMed) for 6 day ● Duration of CGM use: 3-days for GOLDTM(Medtronic MiniMed, North Ridge, CA) and 6-days for iProTM2 (Medtronic MiniMed) ● Calibration of CGM: 2 ● % of time CGM device active OR Time wearing CGM :3 days(GOLD™) or 6 days (iPro™2) (T=77±23.7h; C=76.9±19.2)
Outcomes/ Results	● Patient were classified in to group with and without cardiovascular autonomic function testing: the cardiovascular autonomic neuropathy (CAN) group (n = 84, 29.6%) and the non-CAN group ● Mean TIR %=CAN 57±27; No CAN 62.7 ± 26.8 ASSOCIATIONS BETWEEN TIR 70–180 MG/DL AND CAN ● CAN was evaluated using a combination of five (3-parasympathetic and 2-sympathetic) cardiovascular autonomic function tests. CAN -defined as abnormal result in ≥2 parasympathetic test and severity estimated as sum of scores of 5 Cardiac autonomic function Tests ● OR of presence of CAN was 0.876 [95% confidence interval (CI): 0.79–0.98] per 10% increase in the TIR 70–180 mg/dL after adjusting for age, sex, diabetes duration, any medications, and glycemic variability. There is inverse association of severity of CAN with 10% increase in TIR (OR: 0.89, 95% CI: 0.81–0.98)
Publication details	FUNDING: This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HI19C0543). This research was funded by the Korea Disease Control and Prevention Agency (grant number 2020-ER6402-00).

Study ID	Kuroda et al. (Kuroda N, Kusunoki Y, Osugi K, Ohigashi M, Azuma D, Ikeda H, Makino S, Otsuka A, Tamada D, Watanabe N, Washio K, Tsunoda T, Matsuo T, Konishi K, Katsuno T, Koyama H; Hyogo Diabetes Hypoglycemia Cognition Complications (HDHCC) study group. Relationships between time in range, glycemic variability including hypoglycemia and types of diabetes therapy in Japanese patients with type 2 diabetes mellitus: Hyogo Diabetes Hypoglycemia Cognition Complications study. J Diabetes Investig. 2021 Feb;12(2):244-253. doi: 10.1111/jdi.13336. Epub 2020 Aug 2. PMID: 32594655; PMCID: PMC7858127)
Country/Year	Japan/2021
Study Design	Multicentre, Prospective Cohort Study
Aim Of Study	To assess the relationships between TIR, glycemic variability and patient characteristics in patients with type 2 diabetes mellitus
Methods	● Sample: 300 ● SEX (Male % / Female %): 61.9/ 38.1 ● AGE (mean (SD) years): 68 Median, IQR (62-71) ● ETHNICITY : Asians (Japanese) ● DURATION OF DIABETES (mean (SD) years): 13 Median; IQR 7-23 ● HbA1c at baseline: 6.90 ● Duration during which subjects were recruited: 2 years INCLUSION CRITERIA: ● Included patients with type 2 diabetes mellitus, aged between 40 and 75 years, who regularly visited outpatient hospitals or clinics. EXCLUSION CRITERIA: ● Type 1 diabetes; ● Dementia; ● Severe hepatic and/or renal dysfunction; ● Cancer
Interventions	● CGM Devices Used: FreeStyle Libre Pro ● Duration of CGM use: 10 d (>70% over 14days) ● Calibration of CGM: N/A ● % of time CGM device active OR Time wearing CGM : 10 d (>70% over 14days) ● Mean TIR % = 78.9 (66.9–90.4)
Outcomes/ Results	ASSOCIATION BETWEEN TIR AND RETINOPATHY ● No statistically significant association between TIR and DR (β = 0.091, P = 0.086) ASSOCIATION BETWEEN TIR AND NEPHROPATHY ● UACR and EGFR was used ● Association was seen between TIR and UACR (β = −0.100, P = 0.043) but not with eGFR (β = −0.011, P = 0.824). ASSOCIATION BETWEEN TIR AND NEUROPATHY ● Diagnostic criteria of the Japanese Study Group of Diabetes Neuropathy was used to diagnose DPN. ● Presence of DPN to be associated with TIR (β = −0.106, P = 0.033)
Publication details	FUNDING: This research was funded by the faculty research grant of Hyogo College of Medicine (No. 210790). The authors of the present study thank Drs Hiroyuki Konya (Ashiya Municipal Hospital), Hideki Ifuku (Amagasaki Chuo Hospital), Takeshi Fukui (Fukui Clinic), Isao Hayashi (Hayashi Clinic), Satoru Katayama (Hyogo College of Medicine, Sasayama Medical Center), Masataka Kanyama, Masaru Usami (Ikeda Hospital), Tadahiro Inagaki (Inagaki Medical Clinic), Tomoya Hamaguchi, Chikako Inoue (Itami City Hospital), Akinori Kanzaki (Kawasaki Hospital), Shogo Kurebayashi (Kurebayashi Clinic), Kenji Kusunoki (Kusunoki Clinic), Minoru Kubota (Kwansei Gakuin University, Health Care Center), Takeharu Sasaki (Nishinomiya Watanabe Hospital), Mariko Naka, Sachie Hirose (Osaka Gyoumeikan Hospital), Mitsuyoshi Namba (Takarazuka City Hospital), Tetsuhiro Kitamura (Tamada Clinic) and Hidenori Taniguchi (Taniguchi Medical Clinic). The authors of this study also thank the patients who participated in this study.

Study ID	Guo et al. (Guo QY, Lu B, Guo ZH, Feng ZQ, Yuan YY, Jin XG, Zang P, Gu P, Shao JQ. Continuous glucose monitoring defined time-in-range is associated with sudomotor dysfunction in type 2 diabetes. World J Diabetes. 2020 Nov 15;11(11):489-500. doi: 10.4239/wjd.v11.i11.489. PMID: 33269061; PMCID: PMC7672791)
Country/Year	China/2020
Design	Cross Sectional Study; Single Center
Aim of Study	To explore the relationship between TIR obtained from CGM and sudomotor function detected by SUDOSCAN in subjects with type 2 diabetes.
Method	• Sample size: 466 inpatients with T2DM. • SEX (Male % / Female %): 69.9/ 30.1 • AGE (mean (SD) years): 54.5(8.76) • ETHNICITY : Asians (Chinese) • DURATION OF DIABETES (mean (SD) years): 8 Median (range 3-13) • HbA1c at baseline: 8.70 • Duration during which subjects were recruited: October 2017 to May 2019. INCLUSION CRITERIA: • Diagnosed according to the 1999 WHO diagnostic criteria for diabetes EXCLUSION CRITERIA: • Severe illness or acute stress such as heart failure, liver failure, acute or chronic inflammatory disorders, malignant diseases, and surgery; • History of using oral medications that may affect the nervous system and a recent history of alcoholism; and • Subjects with other metabolic disorders like the lack of vitamin B12.
Interventions	• CGM Devices Used: CGM (Meiqi Corporation) • Duration of CGM use: 3 days • Calibration of CGM: 4 times • % of time CGM device active OR Time wearing CGM : 3 days • Sudoscan assessment was done using HESC and FESC (sudomotor dysfunction (+) = average FESC <60 µS).
Outcomes/ Result	• Mean TIR % =SuD+ 72.82 (53.06, 86.79); SuD- 53.12 (28.36, 79.69) ASSOCITATION BETWEEN TIR and SUDOMOTOR FUNCTION • Increase in TIR to be inversely related to prevalence of sudomotor dysfunction (OR 0.979, 95% CI: 0.971-0.987, P < 0.001). • The association was independent of A1c.
Publication details	FUNDING: By National Natural Science Foundation of China, No.81774134 and No. 81873174; Natural Science Foundation of Jiangsu Province of China, No.BK20150558 and No. BK20171331; Postdoctoral Foundation of Jiangsu Province of China, No. 1501120C; Jiangsu Province 333 Talent Funding Project, No. BRA2017595; and Young Medical Key Talents Project of Jiangsu Province, No.QNRC2016902.

Study ID	Yoo et al. (Yoo JH, Choi MS, Ahn J, Park SW, Kim Y, Hur KY, Jin SM, Kim G, Kim JH. Association Between Continuous Glucose Monitoring-Derived Time in Range, Other Core Metrics, and Albuminuria in Type 2 Diabetes. Diabetes Technol Ther. 2020 Oct;22(10):768-776. doi: 10.1089/dia.2019.0499. Epub 2020 Apr 13. PMID: 32167394)
Country/Year	South Korea/2021
Study Design	Cross Sectional Study; Multicentric; 2 Centres
Aim of Study	To assess the relationship between TIR and other CGM parameters and the risk of albuminuria in type 2 diabetes
Methods	• Sample size: 866 • SEX (Male % / Female %): 67.3/ 32.7 • AGE (mean (SD) years): 53 (46-60) • ETHNICITY : Asians(Korean) • DURATION OF DIABETES (mean (SD) years): 8 median (range 3-14) • Duration during which subjects were recruited: 10 years • HbA1c at baseline: 8.20 INCLUSION CRITERIA: • type 2 diabetes patients EXCLUSION CRITERIA: • Subjects with missing data for urine albumin-to creatinine ratio (ACR) (n = 182), subjects with malignancy (n = 5) or severe liver disease defined by a Child-Pugh score of greater than 7 (n = 19), or subjects with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m2 when calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (n = 26) were excluded. Subjects with other missing data or with a history of diabetic ketoacidosis or hyperosmolar hyperglycaemic syndrome were also excluded.
Interventions	• Continuous glucose monitoring was done using Medtronic CGM device for 3 days (GOLD^{TM}) and 6 days (iPro^{TM2}). • Duration of CGM use: 3 or 6 days • Calibration of CGM: 2 times a day • % of time CGM device active OR Time wearing CGM :T (with albuminuria) =79.9±22.3 hours; C (without albuminuria) =77.5±21.7 h
Outcomes/ Result	• Urinary albumin-to-creatinine ratio (UACR) > 30 was used to define DN. participants were grouped into with-and without-albuminuria. • Mean TIR% = 78.9 • Prevalence of albuminuria was 36.6%. ASSOCIATION BETWEEN TIR AND ALBUMINURIA • Subjects who achieved the target of TIR of 70-180 mg/dL ≥ 70%, TAR (>180 mg/dL) < 25%, and TAR (>250 mg/dL) < 5% had a lower prevalence of albuminuria than subjects who did not achieve those targets (all $p < 0.001$). • Mean amount of CGM data was 77.5 ± 21.7 hours in subjects without albuminuria and 79.9 ± 22.3 hours in subjects with albuminuria, which were comparable ($p = 0.128$). Subjects with albuminuria were observed to have significantly lower mean TIR of 70-180 mg/dL and higher TAR > 180 mg/dL , TAR > 250 mg/dL than those without albuminuria.
Publication details	FUNDING: none

Study ID	Yang et al. (Yang J, Yang X, Zhao D, Wang X, Wei W, Yuan H. Association of time in range, as assessed by continuous glucose monitoring, with painful diabetic polyneuropathy. J Diabetes Investig. 2021 May;12(5):828-836. doi: 10.1111/jdi.13394. Epub 2020 Sep 29. PMID: 32885597; PMCID: PMC8089011)
Country/Year	China/2021
Study Design	Cross Sectional study; Single Center
Aim of Study	To assess association between TIR and the prevalence and degree of painful diabetic neuropathy (PDN)
Methods	• Sample size 364 • SEX (Male % / Female %): 67.3/ 32.7 • AGE (mean (SD) years): 53 (46-60) • ETHNICITY : Asians (Chinese) • DURATION OF DIABETES (mean (SD) years): 8 median (range 3-14) • Duration during which subjects were recruited: 10 months • HbA1c at baseline: 7.35 INCLUSION CRITERIA: • age>18 years with DPN EXCLUSION CRITERIA: • other causes of neuropathy, such as osteoarthritis, cervical and lumbar diseases, connective tissue disease, peripheral vascular disease, tumors, herpes zoster infection, abnormal thyroid function, and severe malnutrition or vitamin B12 deficiency; • coexisting major psychiatric disorders; • severe pain from a cause other than DPN; • central nervous system lesions; • pregnancy.
Interventions	• CGM Devices: Free Style Libre • Duration of CGM use: 14 days • Calibration of CGM: NA • % of time CGM device active OR Time wearing CGM :2 weeks
Outcomes/ Result	• The Pain measurement was done using 11 step- numerical rating scale(NRS) and patients were classified into pain free (NRS=0), mild pain (1-3), and moderate/severe pain(4-10) groups • Mean TIR %= 78.90 • Prevalence of painful diabetic neuropathy was 51.92% ASSOCIATION OF TIR WITH PAINFUL DIABETIC NEUROPATHY • Compared with the pain-free group, the level of TIR decreased significantly in the mild pain and moderate/severe pain groups ($P < 0.05$). • The prevalence of mild pain and moderate/severe pain decreased with increasing TIR quartiles (all $P < 0.05$). • Decline in TIR was directly associated with increased prevalence of any painful DPN (OR 2.66, 95 % CI: 1.16–6.10, $p < 0.05$). • Multiple linear regression analysis showed that TIR was significantly negatively correlated with the numerical rating scale score after adjustment for glycated hemoglobin, glycemic variability indicators and other risk factors ($P < 0.05$). • Logistic regression analysis showed decreasing level of TIR was significantly associated with increasing risk of any pain and moderate/severe pain ($P < 0.05$). • The association was independent of A1c
Publication details	FUNDING: This study was supported by the National Natural Science Foundation of China (81970705); Central Plains Thousand Talents Plan (204200510026); the Overseas Research and Study Program for Talents in Health Science and Technology of Henan Province (2018078, 2018098).

Study ID	Li et al. (Li F, Zhang Y, Li H, Lu J, Jiang L, Vigersky RA, Zhou J, Wang C, Bao Y, Jia W. TIR generated by continuous glucose monitoring is associated with peripheral nerve function in type 2 diabetes. Diabetes Res Clin Pract. 2020 Aug;166:108289. doi: 10.1016/j.diabres.2020.108289. Epub 2020 Jun 29. PMID: 32615278)
Country/Year	China/2020
Study Design	Cross Sectional Study Single Center
Aim of Study	To assess "Association between TIR and nerve conduction study parameters."
Methods	● PARTICIPANTS: 740 ● SEX (Male % / Female %): 50.95/ 49.05 ● AGE (mean (SD) years): 60.24(12.81) ● ETHNICITY : Asians (Chinese) ● DURATION OF DIABETES (mean (SD) years): 10.66(7.49) ● Duration during which subjects were recruited; 1 year and 5 months ● HbA1c at baseline: 8.55 INCLUSION CRITERIA: ● Patients with T2DM who had undergone screening for diabetic neuropathy with NCS and were monitored by a CGM system at the inpatient department of Shang-hai Jiao Tong University Affiliated Sixth People's Hospital between April 2013 and August 2014. EXCLUSION CRITERIA: ● Progressive malignancy, ● Diseases affecting nerve conduction function (such as chronic inflammatory demyelinating polyneuropathy or carpal tunnel syndrome, etc.), o ● Other life-shortening medical conditions
Interventions	● CGM Devices Used: Medtronic CGM device readings were obtained for 3 consecutive days. ● Duration of CGM use: 3 days. ● Calibration of CGM: NA ● % of time CGM device active OR Time wearing CGM : NA ● Mean TIR % = not described ● Electrophysiologic measurement of motor and sensory nerve was used to calculate composite Z-score for conduction velocity (CV), latency, and amplitude to assess peripheral nerve function. ● Parameter for motor nerve studies included (median, ulnar and tibial nerves) - Conduction velocity (CV), compound muscle action potential amplitude (CMAP), distal latency. ● Parameter for sensory nerve studies included (median, ulnar, and sural nerves) - Onset latency, sensory nerve action potential amplitude (SNAP), and CV.
Outcomes/ Result	ASSOCIATION BETWEEN TIR AND NERVE FUNCTION ● Higher TIR was associated with a higher composite Z-score of CV (b = 0.230, P < 0.001), higher composite Z-score of amplitude (b = 0.099, P = 0.010), and lower composite Z-score of latency (b = 0.172, P < 0.001). ● Higher TIR tertile group was found to have lower risk of slowing conduction velocity (TIR medium: OR 0.44, P < 0.001; TIR high: OR 0.26, P < 0.001), lower risk of amplitude reduction (TIR high: OR 0.60, P < 0.05), and higher rate of reduced latency (TIR medium: OR 1.57, P < 0.05; TIR high OR 1.71, P < 0.05) compared to low tertile group
Publication details	FUNDING: This study was financially supported by National Key Research and Development Programme of China (grant no. 2017YFC0906903), the Municipal Human Resources Development Programme for Outstanding Leaders in Medical Disciplines in Shanghai (grant no. 2017BR045), and the National Human Genetic Resources Sharing Service Platform (grant no. YCZYPT [2017]02), Shanghai Major Clinical Disease Clinical Sample Pool of Professional and Technical Services Platform (18DZ2294100).

Study ID	Guo et al. (Guo Q, Zang P, Xu S, Song W, Zhang Z, Liu C, Guo Z, Chen J, Lu B, Gu P, Shao J. Time in Range, as a Novel Metric of Glycemic Control, Is Reversely Associated with Presence of Diabetic Cardiovascular Autonomic Neuropathy Independent of HbA1c in Chinese Type 2 Diabetes. J Diabetes Res. 2020 Feb 6;2020:5817074. doi: 10.1155/2020/5817074. PMID: 32090120; PMCID: PMC7026737)
Country/Year	China/2020
Design	Cross Sectional Study
Aim of Study	To explore the relationship between TIR obtained from CGM and sudomotor function detected by SUDOSCAN in subjects with type 2 diabetes.
Method	• Sample size: 466 inpatients with T2DM. • SEX (Male % / Female %): 69.9/ 30.1 • AGE (mean (SD) years): 54.5(8.76) • ETHNICITY : Asians (Chinese) • DURATION OF DIABETES (mean (SD) years): 8 Median (range 3-13) • HbA1c at baseline: 8.70 • Duration during which subjects were recruited: October 2017 to May 2019. INCLUSION CRITERIA: • Diagnosed according to the 1999 WHO diagnostic criteria for diabetes EXCLUSION CRITERIA: • Severe illness or acute stress such as heart failure, liver failure, acute or chronic inflammatory disorders, malignant diseases, and surgery; • History of using oral medications that may affect the nervous system and a recent history of alcoholism; and • Subjects with other metabolic disorders like the lack of vitamin B12.
Interventions	• CGM Devices Used: CGM (Meiqi Corporation) • Duration of CGM use: 3 days • Calibration of CGM: 4 times • % of time CGM device active OR Time wearing CGM : 3 days • Sudoscan assessment was done using HESC and FESC (sudomotor dysfunction (+) = average FESC <60 μS).
Outcomes/ Result	• Mean TIR % =SuD+ 72.82 (53.06, 86.79); SuD- 53.12 (28.36, 79.69) ASSOCITATION BETWEEN TIR and SUDOMOTOR FUNCTION • Increase in TIR to be inversely related to prevalence of sudomotor dysfunction (OR 0.979, 95% CI: 0.971-0.987, P < 0.001). • The association was independent of A1c.
Publication details	FUNDING: By National Natural Science Foundation of China, No.81774134 and No. 81873174; Natural Science Foundation of Jiangsu Province of China, No.BK20150558 and No. BK20171331; Postdoctoral Foundation of Jiangsu Province of China, No. 1501120C; Jiangsu Province 333 Talent Funding Project, No. BRA2017595; and Young Medical Key Talents Project of Jiangsu Province, No.QNRC2016902.

Study ID	Mayeda et al. (Mayeda L, Katz R, Ahmad I, Bansal N, Batacchi Z, Hirsch IB, Robinson N, Trence DL, Zelnick L, de Boer IH. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. BMJ Open Diabetes Res Care. 2020 Jan;8(1):e000991. doi: 10.1136/bmjdrc-2019-000991. PMID: 31958307; PMCID: PMC7039577)
Country	USA/2020
Design	Cross Sectional Study; Multicentric
Aim of Study	To assess "describe the prevalence of DPN symptoms among participants with type 2 DM and moderate-to severe CKD and 2) examine the association of glycemia (as measured by CGM) with DPN symptoms among our target population"
Methods	● Sample Size: 105 [81 participants with moderate-to-severe CKD and 24 control participants] ● SEX (Male % / Female %): 63.8/ 36.2 ● AGE (mean (SD) years): 67.08(10.09) ● ETHNICITY : White, Black, Hispanic, Others ● DURATION OF DIABETES (mean (SD) years): 19.08(10.19) ● Duration during which subjects were recruited: 2 years ● HbA1c at baseline: 7.84 INCLUSION CRITERIA: ● Moderate-to-severe CKD (estimated glomerular filtration rate (eGFR) <60mL/ min/1.73m2). EXCLUSION CRITERIA: ● age <18 years, history of kidney transplant, dialysis treatment, treatment with erythropoietin, current use of clinical CGM, pregnancy or current therapy for cancer and inability to speak English.
Interventions	● CGM Devices Used: Medtronic ● Duration of CGM use: Two 6-day periods, separated by 2 weeks. ● Calibration of CGM: 2 times a day ● % of time CGM device active OR Time wearing CGM : Two 6-day periods, separated by 2 weeks. ● DPN symptoms was evaluated using MNSI (Michigan Neuropathy Screening Instrument) questionnaire, (Positive if MNSI ≥2 Symptoms)
Outcomes/ Result	● Mean TIR % =78.90 ● DPN prevalence was 74% ASSOCIATION BETWEEN TIR AND DPN ● Rate of DPN was higher in participants with TIR >70 % compared to participants with TIR <70 % (43 % vs 74%). ● DPN prevalence was inversely correlated with TIR (OR 1.25 (95% CI 1.02 to 1.52) per 10% lower TIR). ● Lower TIR and higher glucose monitoring indicators (GMI) were associated with DPN symptoms. ● 10 % increase in TIR was found to be inversely associated with prevalence of DPN (OR 1.25, 95% CI: 1.02 - 1.52, p <0.05). ● Authors did not observe any association between A1c and DPN.
Publication details	FUNDING: The CANDY Study was primarily supported by American Diabetes Association grant #4-15-CKD-20. Additional funding came from grants R01DK088762, R01DK087726 and T32DK007247 from the National Institute of Diabetes and Digestive and Kidney Diseases; a grant from Puget Sound Veterans Affairs Health Care System and an unrestricted grant from Northwest Kidney Centres.

Study ID	Lu et al. (Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, Lu W, Zhu W, Bao Y, Vigersky RA, Jia W. Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. Diabetes Care. 2018 Nov;41(11):2370-2376. doi: 10.2337/dc18-1131. Epub 2018 Sep 10. PMID: 30201847)
Country/Year	China/2018
Study Design	Cross Sectional study; Single Center
Aim of Study	To assess "Association between TIR assessed by CGM and DR"
Methods	• Sample size: 3262 • SEX (Male % / Female %): 50.95/ 49.05 • AGE (mean (SD) years): 60.24 (11.2). • ETHNICITY : Asians (Chinese) • DURATION OF DIABETES (mean (SD) years): 28.6 (12.81). • Duration during which subjects were recruited: 7 years • HbA1c at baseline: 8.90 INCLUSION CRITERIA: ● age 18 years, presence of type 2 diabetes, and a stable glucose-lowering regimen over the previous 3 months. EXCLUSION CRITERIA: ● diabetic ketoacidosis; a hyperglycemic hyperosmolar state or severe and recurrent hypoglycemic events within the previous 3 months; and a history of malignancy, mental disorders, or severe kidney or liver dysfunction.
Interventions	● CGM Devices Used: Medtronic CGM device readings over 3 days ● Duration of CGM use: 3 days ● Calibration of CGM: 4 times a day ● % of time CGM device active OR Time wearing CGM :72h ● Participants were classified into mild NPDR, moderate NPDR, and vision threatening DR
Outcomes	● Mean TIR %= 78.90 ● Overall prevalence of DR was 23.9%. The prevalence of mild NPDR, moderate NPDR, and VTDR were 10.9%, 6.1%, and 6.9%, respectively. ASSOCIATION BETWEEN TIR and DR ● Multinomial logistic regression revealed significant associations between TIR and all stages of DR (mild NPDR, P = 0.018; moderate NPDR, P = 0.014; VTDR, P = 0.019) after controlling for age, sex, BMI, diabetes duration, blood pressure, lipid profile, and HbA1c. ● All of the patients were stratified according to quartiles of TIR (quartile 1 [Q1]: #51%; quartile 2 [Q2]: 51–71%; quartile 3 [Q3]: 71–86%; quartile 4 [Q4]: .86%). In general, the prevalence of DR by severity decreased with ascending quartiles of TIR (all P for trend ,0.001). the highest TIR quartile was independently associated with all stages of DR, compared with the lowest quartile (mild NPDR: odds ratio [OR] 0.56, P = 0.010; moderate NPDR: OR 0.48, P = 0.009; VTDR: OR 0.53, P = 0.023) ● An inverse correlation between TIR quartile and severity of diabetic retinopathy with statistically significant association between a 10 % increase in TIR and reduction in severity of DR was found.
Publication details	FUNDING: This work was funded by the National Natural Science Foundation of China (grant no.81100590), the Shanghai United Developing Technology Project of Municipal Hospitals (grant nos. SHDC12006101 and SHDC12010115), and the Shanghai Municipal Education Commission Gaofeng Clinical Medicine grant support (grant no. 20161430).

Appendix 3. Study Quality Assessment

	Major Outcomes	**Varghese et. al. 2021**	**Wakasugi et. al. 2020**	**Kim et. al. 2021**	**Kurodа et. al. 2021**	**Guo et. al. 11/2020**	**Yoo et. al. 2020**	**Yang et. al. 2020**	**Li et. al. 2020**	**Guo et. al. 02/2020**	**Mayeda et. al. 2019**	**Lu et. al. 2018**
1	Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Were all the subjects selected or recruited from the same or similar populations? Were inclusion and exclusion criteria prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	Yes	No	No	No	No	No
6	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	No	No	No	No	No	Yes	No	No	No	Yes	No
7	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
8	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome ?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Was the exposure(s) assessed more than once over time?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
11	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Were the outcome assessors blinded to the exposure status of participants?	No	No	No	N/A	No	Yes	N/A	N/A	No	No	No
13	Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Overall Quality Rating	Fair	Fair	Fair	Fair	Fair	Good	Fair	Fair	Fair	Fair	Fair