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Time in range in children with type 1 diabetes using treatment strategies based on non-automated insulin delivery systems in the real-world

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Introduction

Continuous Glucose Monitoring (CGM) systems have been shown to reduce HbA1c levels (1), reduce hypoglycaemia (2), and provide essential glucose metric information (3) that is not available with traditional self-monitoring blood glucose systems (SMBG) in Type 1 Diabetes (TID). For these reasons, the use of CGM is rapidly increasing in many countries, despite the reported disparities in reimbursement (4). The term CGM includes rtCGM, which provides real-time numerical information about the current glucose level, glucose trends, alerts the user to lows and highs, and isCGM which provides the current glucose value only when the user chooses to scan the device, plus retrospective glucose data for a specified time period, without alarms for low or high glucose values. Even though these devices are often considered within the same category of CGM, recent clinically important differences were reported in the estimates of glycaemic indices (5).

Downloading and analysing CGM data remain a barrier for both people with diabetes (PWD) and clinicians to use these devices as a basis for improving glucose control. Wong et al. (6) reported that only 56% of caregivers of children with T1D ever downloaded device data and only 27% completing this task routinely. Despite the observed challenges in a real-world setting, there is increasing clinical evidence to support the importance of using CGM data for management of type 1 diabetes. A recent international consensus statement provided recommendations for CGM data utilization and reporting (7). There are four metrics from CGM that are of clinical value for people with diabetes and health care professionals as they are reflective of diabetes management in clinical practice. These metrics are: Time In Range (TIR), Time Below Range (TBR), Time Above Range (TAR), and coefficient of variation of glucose % CV. Specifically, the seven-point quarterly SMBG calculated TIR was strongly associated with diabetic complications in a new analysis of the data obtained from the diabetes control complications trial (8). Based on this evidence, TIR assumes a key role in clinical practice and it is necessary to have reference values to set the optimal therapeutic objectives. To date, there is a lack of information on TIR and other glucose metrics in the real-world setting for children with T1D. The aim of this study is to evaluate percentage of TIR in group of children under the age of 18 years, with T1D using glucose sensors with non-automated insulin delivery systems in a real-world setting.

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Methods

A multicentre study including children with T1D followed by 11 Italian centres for paediatric diabetes was conducted from January-May 2019. All centres have used CGM (9) and IP (10) technologies for the care of diabetes in children for more than 15 years and follow national recommendations on their use.

Inclusion criteria for the study were diagnosis of T1D and use of CGM for more than one year, age under 18 years, no changing of insulin administration (multiple daily injections, MDI or insulin pump, IP) within last three months, participants' willingness to enter study, centre's willingness to share anonymised clinical data and CGM downloaded information. We considered one year as a sufficient time to become confident with CGM as a tool to manage insulin therapy in clinical practice. Individuals with diabetes were excluded if they declared their unwillingness to participate, the centre could not share anonymised file data, and/or there was a lack of CGM downloaded data. The glucose sensors and insulin pumps are accessible to all children with T1D in Italy. The study was approved by the Local Ethics Committee of each centre. During a planned visit at the paediatric centre for diabetes care, children and their guardians were asked to participate in the study. Both children and their guardians provided written informed assent and consent.

For each participant, the following data were collected: date of birth, date of type 1 diagnosis, weight, height, number of weekly hours of physical activity, HbA1c, type of sensor used (rtCGM or isCGM), percentage of time CGM was active during the last two weeks, number of daily SBGM, type of therapy (MDI, or IP), type of IP, use of carbohydrate counting, number of severe hypoglycaemic episodes during the last 12 months, and number of DKA episodes requiring hospital admission during the last 12 months. The International Society for Paediatric and Adolescent Diabetes (ISPAD) guidelines state that hypoglycemia is an event associated with cognitive impairment, including coma or convulsions. Hypoglycemia was measured as blood glucose levels <70 mg/dl (11); DKA was defined as hyperglycaemia (> 200 mg/dl), venous pH <7.3 or serum bicarbonate <15 mmol/l (12). All centres used DCA Vantage® Analyzer to determine HbA1c.

Data from CGM of the 2 weeks adjacent to the HbA1c measurement were downloaded at the each centre using a dedicated software or the open source Tidepool software. Data

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were anonymized at each centre and collected in a centralised database for the analysis. Four glucose metrics data were included for the analysis. Time in range (TIR) was defined as the percentage of time with blood glucose between 70 and 180 mg/dl (3.9-10.0 mmol/l), TBR and TAR as the percentage of time below and above target range and glucose variability was determined using the percentage coefficient of variation of glucose (%CV).

Statistical analysis

A non-parametric approach was used, since variables were not normally distributed to the Shapiro test. Children were subdivided into groups according to four treatment strategies, as the combinations of non-automated insulin-delivery systems (IP and MDI) and CGM (isCM and rt(CGM), i.e. MDI-isCGM, MDI-rtCGM, IP-isCGM, IP-rtCGM. The Kruskal-Wallis test was used to perform comparisons between treatment strategies on quantitative variables; medians and interquartile range (IQR, 1^{st} – 3^{rd} quartiles) were used to summarize data. Chi-square or Fisher exact test were applied to categorical variables and results were expressed as absolute and percent frequencies.

The absolute and percentage frequencies of children achieving CGM-based targets as suggested by recent international consensus recommendations (7) were evaluated according to treatment strategies; the Chi-square test was used to evaluate the association between CGM-based targets and treatment strategies.

Quantile regression analysis was performed to analyse the impact of insulin treatment strategies on TIR adjusted by personal and clinical characteristics collected on participants. Likelihood ratio test was used to identify the most parsimonious model. Quantile regression analysis allows the estimation of quantile-specific effects describing the impact of each independent variable (i.e. insulin-delivery system and subjects' personal and clinical characteristics) on each part of interest of the dependent variable (i.e. TIR). The nine deciles of the TIR distribution were considered in the analysis. Results were graphically summarized, the x-axis shows the values of the 9 deciles of the TIR distribution and the y-axis shows the effects of independent variables (regression coefficients) on TIR

for each decile (dotted lines) and 95% confidence bands (95%CI, grey area). If the zero line does not cross the grey area, the estimates significantly differ from 0.

All the analyses were performed using the R statistical package; a level of probability of 0.05 was used to assess the statistical significance.

Results

Overall, data from 666 children under the age of 18 years (51% males and 49% females) with T1D and disease duration more than one year, were analysed. Less than 2% of the total eligible participants were excluded due to the lack of all data downloaded from CGM. The median age and diabetes duration were respectively 12 years (IRQ: 10-15 years) and 5 years (IRQ: 3-7 years). The IP was used by 46% of participants, isCGM by 49%, rtCGM by 51%. All of the isCGM were Abbott FreeStyle Libre™ 1 (Abbott Diabetes Care, Inc, Alameda, CA); rtCGM were 2% Dexcom™ G4, 20% Dexcom™ G5, 19% Dexcom™ G6 (Dexcom, Inc, San Diego, CA), 10% Guardian™ Connect (Medtronic). Children on MDI were using basal bolus therapy with glargine or degludec insulin analogue and Lispro, Aspart or Glulisine rapid-acting insulin analogue. Insulin Pumps were 8.5% Roche Accu-check insight (Roche Diagnostic Deutschland GmbH), 16.7% Tandem t: slim X2™ (Tandem Diabetes Care®, San Diego, CA), 3.9% Ypsopump® (Ypsomed AG, Burgdorf, Switzerland), and 62.4% Omnipod® (Insulet Corporation, Billerica, MA). Severe hypoglycaemia and DKA requiring hospitalization during last 12 months occurred in eleven (1.6%) and nine (1.3%) subjects, respectively.

Table 1 and Figure 1 show subjects' personal and clinical characteristics according to the treatment strategies. Subjects on IP treatment used carbohydrate counting system more frequently and had a significant longer diabetes duration. Children using IP and rtCGM had significant lower HbA1c values than those on MDI and isCGM. Children on IP and rtCGM checked their capillary blood glucose values more frequently than all the other treatment strategies. Children using rtCGM, regardless of the insulin-delivery system, reported significant lower %CV values. In children using the IP the % time CGM active was higher than in those using MDI treatment. No significant differences between treatment

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strategies were found in the distribution of gender, number of severe hypoglycaemia and DKA requiring hospitalization during the last year (Table 1).

Significant differences were found in the CGM metrics among the four treatment strategies (Figure 1). The group treated with IP & rtCGM had significantly higher median value of TIR (61, IQR: 50-71) than MDI and isCGM (49, IQR: 40-60), MDI and rtCGM (56, IQR: 39-66), and IP and isCGM (56, IQR: 42-65). The group treated with MDI and isCGM had a significantly higher median value of TBR (5, IQR: 2-8) than MDI and rtCGM (2, IQR: 1-4) and IP and rtCGM (3, IQR: 1-6); group MDI and rtCGM had lower median value of TBR (2, IQR: 1-4) than IP and isCGM (5, IQR: 3-7) and IP and rtCGM (3, IQR; 1-6), and IP and isCGM had higher median value of TBR than IP and rtCGM. The groups treated by MDI and isCGM and MDI and rtCGM had significantly higher median values of TAR (44, IQR: 33-56; 42, IQR: 30-61, respectively) than IP and rtCGM group (35, IQR; 24-46). Subjects treated with IP and isCGM reported median value of TAR of 38 (IQR: 30-54).

Table 2 shows children and adolescents achieving CGM-based targets as suggested by recent international consensus recommendations (7) according to treatment strategies. All of the targets were achieved more frequently by subjects using rtCGM independently from the insulin-delivery system.

Figure 2 shows the results of quantile regression analysis, with TIR as dependent variable. Age, diabetes duration, treatment strategies, use of carbohydrate counting, percentage of time CGM was active during the last two weeks, were found significantly associated with TIR. A positive effect of age was found from the second decile of TIR distribution, while higher diabetes duration significantly decreased TIR and this effect was observed in all the 9 deciles of TIR distribution. The treatment strategy MDI-isCGM was considered as reference category and all the other strategies significantly increased TIR: MDI-rtCGM and IP-isCGM in the second part of TIR distribution, while IP-rtCGM in all the deciles of TIR distribution. The use of carbohydrate counting and the high percentage of time CGM was active during the last two weeks were significantly associated with high percentage of TIR in almost all the deciles of the distribution.

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Discussion

To the best of our knowledge there are no previous studies examining differences in glucose metrics in children and adolescents with T1D recorded in the real-world using different treatment strategies based on non-automated insulin-delivery systems. In this large cohort of children with T1D under 18 years of age, using CGM and non-automated insulin-delivery systems, the simultaneous use of rtCGM and IP was associated with higher percent values of TIR, lower TAR, and lower HbA1c values. Independently from the insulin-delivery system, lower values of TBR were associated with the use of rtCGM. Our study highlights the positive effect of rtCGM on TIR distribution compared to isCGM when associated to MDI, or IP compared to MDI when associated to isCGM and suggests that the combination of more advanced technological non-automated systems (IP-rtCGM) offers the best results in achieving time in range in the real-world. The Diamond study (13), that analysed TIR in a randomized control study of adults with diabetes using MDI, reported an improvement of TIR, reaching a median value of 52% after 6 months of the use of rtCGM. At the same time, TAR and TBR reduced to 44% and 2.7% respectively.

In our study, similar values were reported by children using isCGM and MDI, while rtCGM and MDI allowed them to obtain median TIR, TAR and TBR values of 56%, 42% and 2%, respectively. In a randomized study performed during a summer-camp (14), children using isCGM and IP reported TIR of 50.9%, TAR 45.2%, and TBR 1.3%. The 2014 Italian Society of Paediatric Endocrinology and Diabetes (ISPED) recommendations for self-monitoring blood glucose, including CGM, explicitly state that paediatric diabetologists must encourage and provide ongoing education for PWD and families on the importance of the use of CGM and download data to enhance self-management (9). These recommendations are widely applied throughout Italy, since coverage for CGM is provided by the National Health System and most paediatric centres are equipped with multidisciplinary teams. Thus, the better results on glucose metrics reported in our study could be related to education programs on the use of CGM for children and their parents, having involved paediatric centres with long-lasting experience on the use of technology for diabetes care. The HypoDE study (15) reported a median TBR value of 1.6% (IQR: 0.9-3.7) in a trial of adults with T1D treated with MDI and rtCGM for 6 months, with impaired

hypoglycaemia awareness, receiving instructions on optimal use of rtCGM. In our cohort of children using the same treatment strategy (n=119), the median TBR was comparable (2%, IQR: 1-4).

To date, research has focused on glucose metrics analysis comparing non-automated insulin-delivery systems, that are usually referred to as sensor augmented pump (SAP), and automated systems, commonly known as predictive low glucose management (PLGM), hybrid closed-loop (HCL), and full-closed loop (FCL) or artificial pancreas (16). A published randomised study (17), that analysed the effects of at-home use of the Tandem Control-IQ artificial pancreas in young children, reported a mean TIR of 52.8%, TBR of 2.1%, TAR of 44.7% with SAP, and mean TIR of 71.2%, TBR of 2.1%, TAR of 26.2% with Control-IQ system. In our study glucose metrics of children using SAP, showed a slightly higher median TIR of 56% or 61% if the IP was associated with the isCGM or rtCGM, respectively; at the same time, TAR was lower reaching median values of 38% and 35% with isCGM and rtCGM, respectively; TBR was superimposable. A systematic review and meta-analysis of outpatients randomised controlled trials evaluating efficacy of artificial pancreas systems (18) reported a weighted mean of TIR of 58.21% with SAP and 12.59% higher with artificial pancreas systems.

A recent consensus recommendation provided guidance (7) on targets for assessment of glycaemic control for people with T1D. These targets are goal values of TIR>70%, TBR<4%, TAR<25% for adults, and goal value of TIR> 60% for age <25years, if the HbA1c goal is 7.5%. In our analysis, performed on children under 18 years, the percentage of participants meeting TIR>70% was 8.3% with MDI-isCGM (Table 2) and 28.1% with IP-rtCGM. The percentage of participants with TIR>60% was 24.2% with MDI-isCGM and 52.5% with IP-rtCGM. Interestingly, the percentage of children reaching a TBR<4% was higher for both the treatment strategies using rtCGM.

High glucose variability is considered a possible risk factor for diabetic vascular complications and is associated with increased risk of hypoglycaemic events. A threshold for % CV of 36% indicates which PWD had stable or unstable glucose homeostasis (19), with the lower values associated to low glucose variability. In our study, the lower %CV

values were obtained by participants using rtCGM, suggesting that its use is the best choice in non-automated insulin-delivery system to reduce the risk of hypoglycaemia.Beyond treatment strategy, the carbohydrate counting and the percentage of time CGM was active were modifiable factors associated with TIR. This observation demonstrates the impact of education in improving glucose control in children with T1D.

There were several limitations to this study. The variation in different CGM systems, could contribute to the differences in the accuracy of CGM-based glucose metrics. The recruitment methods included only participants of the paediatric centres with specialized expertise in the use of technologies that could contribute to an overestimation of device use in comparison to the entire population of all Italian youth with type 1 diabetes. It is also assumed that recruited children have received education on the use of those devices, and that education resulted in a higher proportion of those reaching their targets for glucose metrics than the national population. Both of these factors impact generalizability of the results.

We did not collect information on the number of participants downloading data. We do not know if this activity is associated to TIR variation and this remains a gap in knowledge and a crucial challenge for PWD, nurses, educators and physicians when providing diabetes care. Systematically gathering information on downloaded and analysed data from PWD and health care providers could be useful to interpret the TIR variation in the real-world. In addition, we did not analyse socio-economic factors of the study population. Therefore, we do not know if these factors impacted CGM-based targets. Despite these limitations, the large sample of participants and the inclusion of many centres evenly distributed in North, Centre and South areas offer a country-wide picture of glucose results in the real-world.

Based on the glucose metrics reported with the four therapeutic strategies, few children with type 1 diabetes are able to reach a TIR> 70% while the number increases substantially if the target is considered at TIR> 60%. These results pose the question of what is the best clinical suggestion in this situation. Is it to settle for a lower TIR to avoid frustration for children and parents or discuss with them the reasons for not reaching the target and

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accept the challenge of improving glucose metrics? We suggest the latter as the DCCT dataset analysed by Beck and co-authors (8) showed that TIR, calculated on the basis of quarterly seven-point glucose tests, has a strong association with the risk of developing retinopathy and microalbuminuria. In particular, the frequency of retinopathy was 9% with a TIR between 60 and 70% and 5% with a TIR> 70%; the frequency of microalbuminuria was 2% with TIR between 60 and 70% and 3% with TIR> 70%. Therefore, even with a TIR above 60%, the risk of chronic complications remains limited, however there is no doubt that the higher the TIR, the lower the risk of complications and the CGM-based target for TIR should be> 70% for all children with type 1 diabetes. These topics should be discussed with children and parents and, where there are no barriers, the use of a more advanced therapeutic strategy to improve glucose metrics should be considered. CGM-based goal setting in clinical practise is hard to establish and the stepwise approach suggested by the international consensus group (7) is deemed the best way to support children and families to achieve outcomes closest to suggested goals. We consider the third quartile of each treatment strategy of our analysis as a reasonable result that can be reached as first step for TIR and the first quartile for TBR and TBR. Therefore, for children using isCGM-MDI, rtCGM-MDI, isCGM-IP, TIR could be >60%, TBR<3%, TAR <30%; for children using rtCGM-IP as non-automated modality TIR could be >70%, TBR<3%, TBR<25%.

The study results showed that the best glucose metrics were achieved with the combination of rtCGM and the IP. Until automatic insulin-delivery systems are available on the market, the most advanced non-automated system and diabetes education services should be available to all children with type 1 diabetes. If there are no barriers, an upgrade of the treatment strategy with a higher performing technology should be offered to all children who do not achieve blood glucose metrics within the suggested range.

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Author Disclosure Statement

No competing financial interest exist. This study has been previously presented as poster at the 45th ISPAD Annual Conference in Boston, Massachusetts, USA

Authors' contribution

VC designed the study, contributed to data interpretation and writing the article. RG analysed the data, contributed to data interpretation and writing the article. RB, AC, EDN, AI, FL, GM, MM, MB, NM, EM, IR, NR, AR, GS, AS, RS, DT, ST, LZ, SZ, and CM researched data and contributed to data interpretation. VC is the guarantor of this work, and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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Table 1. Patients' clinical characteristics according to treatment strategy

		Treatment strategy				
		MDI-isCGM (G_1) n=240	MDI-rtCGM (G_2) n=119	IP-isCGM (G_3) n=85	IP-rtCGM (G_4) n=221	p
Gender*	M	122 (50.8)	64 (53.8)	42 (49.4)	114 (51.6)	0.932
Use of Carbo Counting System*	Yes	79 (33.1)	38 (31.7)	51 (60)	144 (65.2)	<0.001
Severe Hypoglycaemia (last 12 months)*	Yes	6 (2.5)	1 (0.8)	2 (2.4)	2 (0.9)	0.462
DKA requiring hospital admission (last 12 months)*	Yes	1 (0.4)	1 (0.8)	2 (2.4)	5 (2.3)	0.213
Age#	Year	12.9 (10.2-15.3)	12.2 (8.9-14.6)	12.4 (11.4-14.4)	12.1 (9-15.1)	0.110
Diabetes duration#	Year	4.4 (2.3-6.7) G_1 vs G_3 and vs G_4	3.5 (1.8-6) G_2 vs G_3 and vs G_4	5.5 (3.8-9.4)	5.1 (3.5-7.4)	<0.001
BMI#	kg/m^2	19.6 (17.5-22)	19.1 (16.7-21.3)	19.2 (17.5-21.5)	19.2 (16.9-21.5)	0.432

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Physical activity[#]	hours/ week	3 (2-4)	3 (0.5-5)	4 (2-5)	3.5 (2-5)	0.110
HbA1c[#]	%	7.6 (6.9-8.1) G_1 vs G_4	7.5 (6.7-8.2)	7.3 (6.9-7.7)	7.3 (6.7-7.8)	0.002
SMBG/day[#]	n°	1 (0.8-2) G_1 vs G_4	1 (0-2) G_2 vs G_4	1 (0.5-2) G_3 vs G_4	2 (1-3)	<0.001
CV[#]	%	39.4 (37.1-43.4) G_1 vs G_2 and vs G_4	36.2 (32.8-40.8) G_2 vs G_3	40.5 (37.4-45.1) G_3 vs G_4	36.8 (34-39.9)	<0.001
% time CGM active in the past 2 weeks[#]		91 (84.5-96) G_1 vs G_3 and vs G_4	92.1 (81.6-96.9) G_2 vs G_3	95.6 (89.5-99)	94.1 (87.6-97)	<0.001

*Values are n (%), p-value refers to Fisher exact test

#Values are median (1^{st} – 3^{rd} quartiles); p-value refers to Kruskal-Wallis test

Significant multiple comparisons are indicated as G_i vs G_j, with i, j=1,…,4 and i≠j

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Table 2. Children achieving CGM-based targets

Recommended CGM-based targets	MDI-isCGM (n=240) n (%)	MDI-rtCGM (n=120) n (%)	IP-isCGM (n=85) n (%)	IP-rtCGM (n=221) n (%)	p
TBR<4%	102 (42.5)	87 (72.5)	24 (28.2)	136 (61.5)	<0.001
TIR>60%	58 (24.2)	51 (42.5)	29 (34.1)	116 (52.5)	<0.001
TIR>70%	20 (8.3)	17 (14.2)	11 (12.9)	62 (28.1)	<0.001
TAR<25%	25 (10.4)	20 (16.7)	17 (20)	58 (26.2)	<0.001

p-values refer to Chi-square test

* as suggested by recent international consensus recommendations according to technology treatment.

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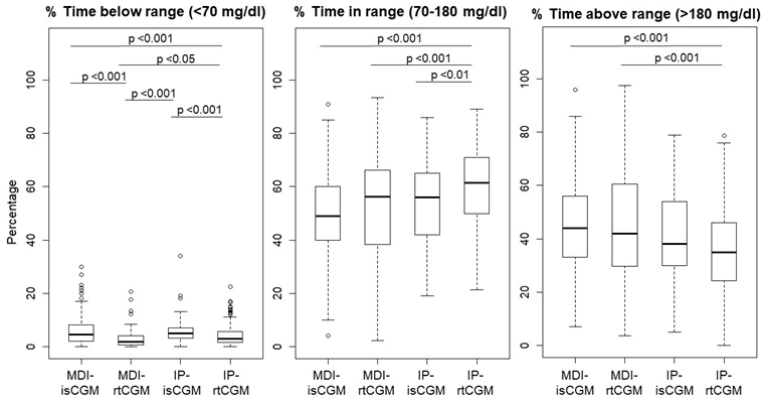

Figure 1. Time Below Range (TBR), Time in Range (TIR), Time Above Range (TAR) by treatment strategy

p-values refer to Kruskal-Wallis test

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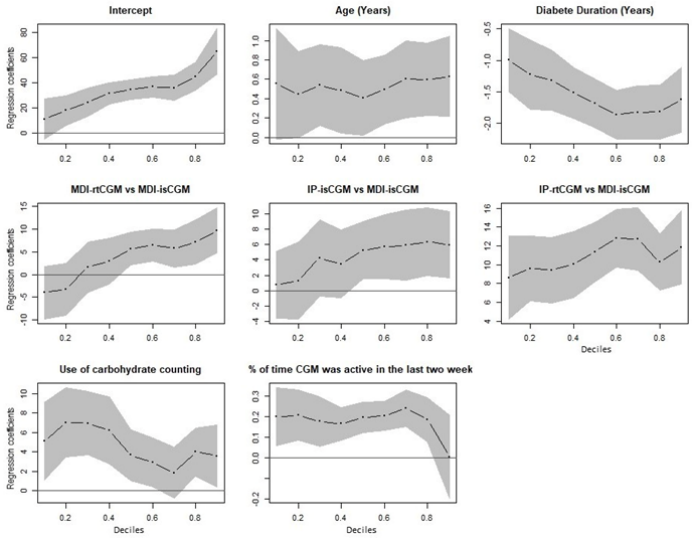

Figure 2. Factors associated to TIR, results of quantile regression analysis

y-axis shows the regression coefficients, i.e., the effects of independent variable on TIR deciles;

grey area shows 95%CI