Insulin resistance and CGM-derived parameters in people with type 1 diabetes : are they associated?

Insulin resistance and CGM-derived parameters in people with type 1 diabetes: are they associated?

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Abstract

Background

Insulin resistance (IR) is increasingly more prevalent in people with type 1 diabetes (T1D). We investigated whether IR is associated with continuous glucose monitor (CGM)-derived parameters (glucometrics) such as time in range (TIR), time above range (TAR), time below range (TBR) and glycaemic variability (CV).

Methods

This is a retrospective analysis of two databases: IR was quantified according to the estimated glucose disposal rate (eGDR) (NCT04664036) and by performing a hyperinsulinaemic-euglycaemic clamp (HEC) (NCT04623320). All glucometrics were calculated over 28 days.

Results

A total of 287 subjects were included. Mean age was 46 ± 17 years, 55 % were male, TIR was 57 ± 14 % and eGDR was 7.6 (5.6 - 9.3) mg/kg min. The tertile of people with the lowest eGDR (highest level of IR) had a higher TAR compared to the tertile with the highest eGDR (39 ± 15 % versus 33 ± 14, $p = 0.043$). Using logistic regression, a higher eGDR was associated with a higher chance to fall in a higher TIR- (OR 1.251, $p < 0.001$), a lower TAR- (OR 1.281, $p < 0.001$) and a higher TBR-tertile (OR 0.893, $p = 0.039$),

adjusted for age, sex, diabetes duration, smoking status and alcohol intake. In the 48 people undergoing a HEC, no significant association between glucometrics and the HEC-determined glucose disposal rate (M-value) was observed.

Conclusion

In people with T1D, an association between IR, measured by eGDR, and worse CGM profiles was observed.

Introduction

Type 1 diabetes (T1D) is caused by an autoimmune destruction of pancreatic beta cells, leading to an absolute insulin deficiency and the need for lifelong insulin therapy. In type 2 diabetes (T2D), however, insulin resistance (IR), induced by excess weight, is one of the major features. However, people with T1D are not protected from overweight, and IR is becoming increasingly prevalent in people with T1D as well [1,2]. This combination of autoimmune-induced diabetes with clinical features of IR is referred to as 'double diabetes' [3-5]. The association between IR and the development of micro- and macrovascular complications in T1D has been demonstrated before, indicating the importance of identification of people with double diabetes [4,6-9].

Measuring IR in people with T1D is challenging. The hyperinsulinaemic-euglycaemic clamp (HEC) is the gold standard to quantify whole-body insulin sensitivity, but it is time-consuming and invasive, and thus unsuited to perform in large populations or in clinical practice. The estimated glucose disposal rate (eGDR) is a calculation based on a cluster of clinical variables (HbA1c, waist-to-hip ratio or waist circumference (WC) and hypertension) to estimate insulin sensitivity in people with T1D [7,10]. A low eGDR (indicating a higher level of IR) is associated with the presence of metabolic syndrome (MetS), and a higher prevalence of nephropathy, retinopathy and cardiovasculair disease (CVD), and this irrespective of HbA1c levels [4,7,9,11].

Nowadays, continuous glucose monitoring (CGM) is used in people with T1D to help achieve glucose targets. Derived from CGM, new parameters for glucose control have emerged such as time in range (TIR), time above range (TAR), time below range (TBR) and glycaemic variability assessed by coefficient of glucose variation (CV) [12,13]. The use of CGM is associated with improved glycaemic control, such as a lower HbA1c and less time spent in hypoglycaemia [14].

The association between IR and CGM-derived parameters (glucometrics) in people with T1D is scarcely studied. Previous studies were restricted to adolescents and used very short-term CGM data. The aim of this study is to assess whether IR is associated with glucometrics in adults with T1D. We hypothesize that IR in people with T1D is associated with a worse glycaemic control, as demonstrated by a lower TIR, higher TAR, higher TBR and higher CV.

Methodology and statistical plan

Research design

We conducted a retrospective, monocentric study of people with T1D (≥ 18 years of age) attending the outpatient clinic of the Antwerp University Hospital.

We analysed data collected from two different cohort studies. The first studied the prevalence, incidence and characteristics of non-alcoholic fatty liver disease (NAFLD) in T1D (NAFLDIA1, NCT04664036) [15]. The second study performed HEC tests to evaluate IR in people with T1D (BRECLAIR study, NCT04623320). Baseline characteristics were obtained from the corresponding datasets: age (years), sex (male/female), diabetes duration (years), WC (cm), BMI (kg/m²), systolic and diastolic blood pressure (mmHg), smoking status (yes/no), alcohol intake (yes/no), HbA1c (%) and daily insulin (dose per kg of bodyweight). Data were collected from September 2018 until December 2022. All subjects were actively questioned about symptoms of infection and all investigations were performed outside episodes of acute infection. There were no people with clinical hyperthyroidism at inclusion. All subjects were eligible if CGM data were available.

Glucometrics were retrieved using designated software: Libre View for Freestyle Libre (Abbott; Witney, Oxfordshire, UK), Carelink for Medronic (Medtronic, Northridge, California, USA), Clarity for Dexcom (Dexcom, Inc., San Diego, California). CGM data were used only if subjects were using their CGM device for at least 70 % of the time, based on the international consensus[12], to guarantee qualitative representation. All subjects had used their CGM device for at least 6 months. Glucometrics were calculated

over a standardized period of 28 days preceding the day on which all anthropometric and laboratory data were collected or prior to the HEC test. During the entire study period, people did not change their insulin preparation. Exclusion criteria were severe illness during study period as determined by hospitalisation > 3 days or discontinuation of CGM usage. Information regarding subject disposition is shown in Figure 1.

All data were retrospectively collected from the above mentioned prospective studies (NAFLDIA1 and BRECLAIR). Both studies were carried out after approval by the institutional review board and ethics committee of Antwerp University Hospital (EC 18/32/361 and EC 20/40/515) and in accordance with Belgian legislation, the International Conference on Harmonization/Good Clinical Practice Guidelines and the Declaration of Helsinki. A written informed consent was obtained from all participants in both cohorts.

Parameters

Glucometrics

The parameters derived from CGM were TIR (the percentage of time the serum glucose level is spent between 70 and 180 mg/dL), TBR (percentage of time spent below 70 mg/dL) and TAR (percentage of time spent above 180 mg/dL). A TIR > 70 %, TBR < 4% and TAR < 25% is recommended [12,13]. Glucose variability is assessed using coefficient of variation, expressed as a percentage (% CV). A % CV of ≤ 36 % is considered to be indicative of stable glucose levels [12,14]. Glucose Management Indicator (GMI) is calculated from CGM-derived mean glucose and is an estimation of the HbA1c based on the CGM glucose levels [16]. GMI (%) = 3.31 + 0.02392 x [mean glucose in mg/dL].

Estimated glucose disposal rate (eGDR)

eGDR is originally derived from data of the HEC test of 24 people with T1D [10]. It quantifies insulin sensitivity, indicating that a lower eGDR correlates with a higher degree of IR. The eGDR (mg/kg/min) was calculated using the following formula: eGDR = 21.158 + (-0.09 × WC, cm) + (-3.407 × hypertension) + (-0.551 × HbA1c, %). Hypertension (1 assigned if present, 0 if absent) is defined as a systolic blood pressure ≥ 140 mmHg, a baseline diastolic blood pressure ≥ 90 mmHg or treatment with antihypertensive medication.

Hyperinsulinemic-euglycemic clamp (HEC)

The HEC was carried out after an overnight fast in a subgroup of 59 people. Closed-loop hybrid insulin pumps were disconnected prior to the HEC test when euglycemia was obtained. Intravenous catheters were placed in both arms for insulin and glucose infusion and for blood sampling. The insulin infusion was carried out with a 8 minute priming dose of insulin (80 mU/m2 body surface area/min) and then maintained at a rate of 40 mU/m2 body surface area/min for 240 min. We prolonged the total duration of insulin infusion in order to completely suppress endogenous glucose production (EGP) by the liver, despite the relatively low insulin infusion rate of insulin. Patients with elevated glycemia, without surpassing 180 mg/dL, were given a constant insulin infusion rate of 40 mU/m² body surface area/ minute, to obtain a glycemia of approximately 120 mg/dL, after which the infusion was halted, and blood glucose was monitored every 5 minutes until 90 mg/dL was reached. This point in time was declared T0 = 0 minutes. Blood glucose was clamped,

by variable glucose infusion, at a level of 90 mg/dL based on results from blood samples taken every 5 min. Serum glucose and insulin levels were measured at baseline and half-hourly thereafter. The M-value (in mg/kg/min) was based on the amount of glucose infused during the last 30 min of the study.

Statistical plan

Continuous variables are reported as mean ± standard deviation (SD) if normally distributed or as median and interquartile range (IQR) if not normally distributed. Nominal variables are reported as frequencies (n) and percentages (%).

To present the demographic characteristics of the study population, the cohort was divided in tertiles based on the eGDR or the M-value. Analysis of variance (ANOVA) was executed to compare the means of the tertiles. The Kruskal-Wallis test was used similarly when data were not normally distributed. Chi-squared statistics were used for categorical variables. In case of significant result, differences are further studied in pairwise post-hoc comparisons using t-test, Mann Whitney test or chi-squared test, depending on the nature of the data. Bonferroni correction for multiple test was applied on all analyses. If the assumption of normal distribution was not met, a logarithmic transformation was applied to obtain normality.

Linear regression was used to investigate the association between TIR/TAR (dependent variable) and IR (measured by eGDR and by M-value). Linear regression was not possible for TBR and CV due to violation of normality. A logistic regression analysis was applied to investigate the association between the different glucometrics as dependent variables

(TIR, TAR, TBR and CV) and IR. For these analyses, the population was divided in two groups, depending on whether or not the target for each glucometric variable was reached (TIR > 70%, TAR < 25%, TBR <4% and CV ≤ 36%). In addition, an ordinal logistic analysis was used: the population was divided in tertiles based on each glucometric variable separately, with the lowest group always containing the most unfavourable values (i.e. lowest TIR, highest TAR, highest TBR and highest CV) and the latter group containing the most favourable values. Age, sex, diabetes duration, smoking status and alcohol intake were selected as potential confounders, based on literature, clinical judgement and/or statistical significance [17,18] and added to all regression analyses of the first cohort (eGDR). Only age and sex were added to the analyses of the second cohort (HEC test) to avoid overfitting of the model. HbA1c, BMI and the presence of hypertension were not included as confounders in the analysis between eGDR and glucometrics, due to intrinsic collinearity with the eGDR. Odds ratios (ORs) and 95% confidence intervals are presented.

All statistical analyses were conducted using IBM SPSS statistics version 27 (Windows, Armonk, NY, USA). A two-tailed p-value < 0.05 was considered statistically significant.

Results

Population characteristics

The characteristics of the study population are presented in Table 1. The mean age was 46 ± 17 years, 55 % were male, the median diabetes duration was 26 [14 – 36] years. The population had a median HbA1c of 7.3% [6.8 - 7.9], the mean TIR was 57 ± 14 % and the median eGDR was 7.6 [5.6 - 9.3] mg/kg/min. Twenty seven percent were on continuous subcutaneous insulin infusion therapy, of which 74% used insulin aspart and 15% used insulin lispro. In the group of multiple daily injections (73%), insulin aspart as short acting (76%) and insulin glargine as long acting (60%) were mostly used. Thirteen people (5%) had an eGFR below 60 ml/min/1.73m² (CKD-EPI), of which 4 had a clearance below 30 ml/min/1.73m². Eight percent of the study population (n = 23) used metformin, 5 patients used a GLP-1 analogue and 3 used a SGLT-2 inhibitor. Thirty-eight percent were on statin treatment, 2% used fibrates and 4% used ezetimibe. Seventeen percent were had hypothyroidism (n = 48). There were no differences in eGDR in people with versus without autoimmune thyroid disease (7.1 ± 2.8 mg/kg/min and 7.4 ± 2.5 mg/kg/min respectively, p = 0.388).

The cohort was divided in tertiles, based on their eGDR. Tertile 1 was the most insulin sensitive group, tertile 3 the most insulin resistant. The most insulin sensitive group was younger, had a lower proportion of males, had a shorter disease duration, a smaller WC, a lower BMI, and had less hypertension than the most insulin resistant group. HbA1c, mean glucose level and GMI were lower and they spent less TAR. A tendency towards a

higher TIR in the most insulin sensitive group was seen, but did not reach statistical significance. There were no significant differences in smoking status and alcohol intake, insulin dose per kg bodyweight, TBR and CV. Half of our study population (53%) already developed micro- and/or macrovascular complications. All complications were significantly more present in the most insulin resistant group (Supplemental Table 1 [19]).

Association between eGDR and glucometric variables

In linear regression analysis, TIR was positively associated (β = 0.016, 95% CI 0.008 - 0.024, p < 0.001) and TAR was negatively associated with eGDR (β = -0.021, 95% CI –(0.029 - 0.012), p < 0.001), and this adjusted for age, sex, diabetes duration, smoking status and alcohol intake. When performing a comparable analysis with waist circumference instead of eGDR, a similar result was found: TIR was negatively and TAR was positively associated with WC (β = -0.002, 95% CI –(0.003 - 0.001), p 0.002 and β = 0.003, 95% CI 0.001 - 0.004, p < 0.001 respectively).

Table 2 shows the results of the logistic regression analyses between glucometrics and eGDR. The glucometrics were analysed both binary (reaching the goal for TIR/TAR/TBR/CV) and by tertiles (for each glucometric separately, the lowest group always containing the most unfavourable values). All associations were adjusted for age, sex, diabetes duration, smoking status and alcohol intake. When dividing the study population in reaching the target for TIR, TAR, TBR or CV (TIR > 70%, TAR < 25%, TBR <4% and CV ≤ 36%), there was no significant association between TIR, TBR or CV and

IR measured by eGDR. A significant association was found between reaching the target for TAR (< 25%) and eGDR (OR 1.214, 95% CI 1.053 - 1.400, p 0.008). Dividing the study population in tertiles by TIR, TAR, TBR and CV, a higher eGDR was associated with a higher chance to be in the more favourable group of TIR (OR 1.251, 95% CI 1.120 - 1.399, p < 0.001) and of TAR (OR 1.281, 95% CI 1.146 - 1.443, p < 0.001). When looking at the analysis with TBR, a higher eGDR was associated with a higher chance to be in a more unfavourable tertile (higher TBR) (OR 0.893, 95% CI 0.801 - 0.994, p 0.039). There was no association between eGDR and CV. Interactions between eGDR and each of the confounders were added to the model to check for effect modification. An interaction was found between eGDR and diabetes duration in all analysis with TIR and TAR (linear, binary logistic and ordinal logistic regression). The association between TIR/TAR and eGDR became weaker the longer one had diabetes. All coefficients of the linear regression with TIR and TAR are shown in Supplemental Table 2[19]. No effect modification was found in analysis with TBR or CV.

Population characteristics in the study population with HEC

Table 3 shows the characteristics of the 48 people who underwent a HEC. Their mean age was 47 ± 15 years, 63 % were male, the median diabetes duration was 24 years [17 - 40], the mean TIR was 63 ± 15 % and the median M-value was 5.0 mg/kg/min [0.9 - 15.6]. Except for 1 person (eGFR 33 ml/min/1.73m²), everyone had a renal function above 60 ml/min/1.73m². This group had a larger WC, higher BMI, a higher proportion of people with hypertension, lower alcohol intake, higher daily insulin need (dose per kg bodyweight), spent more time in range and less below range, and were more insulin

resistant (lower eGDR) compared to the first cohort (n = 287), but age, diabetes duration, HbA1c, sex and smoking status were comparable.

The cohort was divided in tertiles, based on their M-value (Table 3). The most insulin resistant group (with the lowest M-value) had a larger WC, a higher BMI, higher proportion of people with hypertension and used a higher insulin dose ($p < 0.05$) compared to the most insulin sensitive group. No significant differences were found when looking at glucometrics (TIR, TAR, TBR or CV) and at age, sex, diabetes duration, smoking status, alcohol intake, HbA1c, mean glucose and mean time in hypoglycaemia.

A significant correlation was found between eGDR and M-value (Spearman rho = 0.625, $p < 0.001$).

Association between M-value (HEC) and glucometric variables

Neither TIR nor TAR were significantly associated with M-value in linear regression analysis, with or without adjusting for age and sex.

Table 4 shows the results of the logistic regression analyses between M-value and the glucometrics, both binary and by tertiles. No significant associations were found between TIR/TAR and the M-value. There was a tendency towards an association between a higher M-value and a higher chance to be in a more unfavourable tertile (higher TBR) (OR =0.835, 95% CI 0.389 - 1.013, p = 0.068). All associations were adjusted for age and sex.

Discussion

Overweight and obesity are increasingly prevalent in people with T1D [20]. Consequently, metabolic comorbidities related to underlying IR such as the MetS, NAFLD and vascular complications are increasingly observed in this population as well [4,21,22]. In this study, we aimed to investigate whether IR is associated with worse glucometrics.

Our study showed that an increasing eGDR, thus a higher insulin sensitivity, was independently associated with a higher TIR, lower TAR and a higher TBR, and this adjusted for age, sex, duration of diabetes, smoking status and alcohol intake. In the sub-analysis, studying the association between IR, using the gold standard e.g. the HEC-derived M-value, and glucometrics, a tendency towards association between M-value and TBR was observed. An association between TIR/TAR and M-value was not observed.

Only a limited number of studies investigated the link between IR and glucometrics in T1D. Chan et al. performed a HEC in 100 adolescents with T1D [23]. In contrast to our results, they found a paradoxical association between hyperglycaemia and improved insulin sensitivity, and between longer time in hypoglycaemia and higher IR. However, the conclusions of Chan et al. were based on just 48-hour CGM data and they did not adjust for covariates. Their population was younger, had a shorter diabetes duration and worse glycaemic control, reflected by the HbA1c (8.4 % versus 7.2 % in our study population). Guo et al. found no differences in TIR, TAR and TBR when comparing T1D with and without MetS (n = 207) [24], although there was a trend (not significant) towards less people

with the MetS reaching a TIR ≥ 70 % and a TAR < 25 %. No differences were found in TBR and number of people achieving TBR < 4 %. Their study population was comparable in age, but had a shorter diabetes duration (6 versus 26 years respectively). Their subjects also had a worse HbA1c (8.3% versus 7.3% in our study), but comparable TIR (58% versus 57% respectively), which can be explained by less TBR and more TAR in their study. Glucometrics were calculated over only a one-week period. The two above-mentioned studies were thus limited by using only a short time period of CGM, in contrast to the recommendation that CGM data from at least 10-14 days are needed [25]. Infrequent measurements might lead to erroneous data on TIR and GV. Our study took CGM data from a 28-day time window, reducing the possibility of incorrect representation of the overall glycaemic variation of each individual. Furthermore, by only including data from people with 70% usage, we further reduced the chance of inaccurate findings.

The exact pathophysiology of how people with T1D develop clinical IR is not yet fully understood, but originates probably from an interaction between multiple factors such as genetic predisposition and lifestyle. It is still troublesome to identify people with T1D and IR, as standardized criteria are lacking [26]. Different cut-off values for eGDR have been proposed (ranging between 7 - 8 mg/kg/min) [7,27,28], but no validated cut-off value has been determined. Chillaron et al. found a 100 % sensitivity for the diagnosis of MetS with an eGDR < 8.77 mg/kg min [7]. Ferreira-Hermosillo et al. suggested a cut-off value of < 7.32 mg/kg/min with a sensitivity of 85 % and specificity of 84 % for the detection of MetS [28]. A cohort study, performed in Sweden, found that people with an eGDR < 8 mg/kg/min showed an increased mortality risk compared to an age- and sex-matched background

population, further increasing within lower eGDR categories [27]. The median eGDR of our study was 7.6 mg/kg/min, meaning half of our study population would have IR based upon the above-mentioned cut-offs. However, despite not having an exact definition for the diagnosis of IR in T1D, eGDR is an easily applicable tool in practice, which could be useful in screening of people with T1D who are at risk of IR.

Having co-existing IR is not trivial for people with T1D. IR not only contributes to a worse glycaemic control, as we have shown, but also confers an increased risk of micro- and macrovascular complications [4,6-9,29]. The increased risk of CVD was even shown to be independent of glycaemic control reflected by HbA1c [9,30]. Incorporating targeting IR in the treatment strategies of T1D would thus not only contribute to a better glycaemic control, but might eventually also reduce the risk of long-term complications. Data linking TIR to (microvascular or macrovascular) complications in T1D are rather limited [31]. In the study of El Malahi et al., people who spent ≤ 70 % TIR had a higher prevalence of microvascular complications, such as retinopathy and peripheral neuropathy and were more likely to be hospitalized for hypoglycaemia or diabetic ketoacidosis.

The main pillars of the management of IR are exercise and diet. Lifestyle changes are the first-line treatment for people with T2D, but are sometimes underappreciated in the treatment of T1D [32]. Applying the measurement of IR in practice may shift the focus from isolated management of glucose levels, to a more holistic and personalised treatment plan focusing on a healthier lifestyle alongside reaching glycaemic targets [33]. Glucose-lowering

agents, such as metformin, SGLT-2 inhibitors and GLP-1 analogues, are known to improve insulin sensitivity in T2D. However, at present their use in T1D is not guideline-recommended [34]. The limited use of metformin, GLP-1 analogues and SGLT2-inhibitors in our study population prohibited further comparisons. The potential benefits of metformin on HbA1c and BMI in people with T1D have been shown in different studies, however, these effects were inconsistent and usually short-lived (<1 year) [35,36]. Different RCT's and real world data showed a modest weight reduction with SGLT-2 inhibitors in T1D, ranging between 1.5 - 3.2 kg depending on the exact dose, drug and treatment duration [34,37]. However, due to higher rates of diabetic ketoacidosis in people with T1D using SGLT-2 inhibitors, the question arises whether the benefits outweighs the disadvantages. In real world data, GLP-1 analogues showed a mean weight reduction of 5 kg after use of at least 90 days [38]. Preliminary data on the use of semaglutide in T1D showed promising results, with a mean body weight reduction of 8.5 ± 7.8 kg, but further research is necessary [39].

The limitations of our study are its retrospective and cross-sectional design, which prevents us from drawing conclusions about causality. Furthermore, this is a tertiary care centre study, and the results observed might not be applicable to all patients with T1D. Thirdly, the sub-analysis of HEC-derived M-value and glucometrics had a small sample size, and therefore association between M-value and glucometrics needs to be very strong to be significant. In addition, our main analyses were done with eGDR, which is an estimate of IR, but no gold standard. As mentioned above, there is no validated cut-off value for diagnosing clinically relevant IR. In our population, the correlation factor with the M-value was r = 0.625. This is lower than the correlation factor found in the original article

by Williams et al. (r = 0.79) [10]. Their analyses were based on data of only 24 people with T1D and their study population had an higher BMI and worse metabolic control (Hb1Ac between 8.6 - 10.3 %) compared to ours. The difference in correlation factors is probably due to the difference in baseline characteristics. The association between TIR/TAR and insulin resistance, measured by eGDR, could not be confirmed in the second cohort (HEC-test). This could be explained by the fact that eGDR is not a perfect representation of the M-value, as illustrated by the above mentioned correlation factor. Indeed, we must take into account that eGDR is based on clinical factors, i.e. hypertension, WC and HbA1c, meaning that insulin resistant people with a well-controlled Hba1c or no hypertension (often still absent in younger people with T1D and possible IR) may have a falsely high eGDR. The clinical factors are also static, and acute changes in IR, will not reflect quickly into the eGDR. Thirdly, the eGDR is no direct measurement of insulin sensitivity. Therefore we propose to look at the eGDR as a continuum rather than applying absolute cut-off values. Focusing on improving eGDR, rather than reaching a certain cut-off, could be more meaningful. To conclude, we realize that there is collinearity between HbA1c (incorporated in the formula of eGDR) and glucometrics. We are nevertheless convinced that the above analyses are valuable, given eGDR has been tested against the gold standard HEC test (showing a correlation factor of r = 0.79 in the original paper [10]) and the eGDR formula has been shown to be a good marker of increased risk for micro- and macrovascular complications and mortality in T1D [7,11,27]. In addition, sensitivity analyses (linear regression with waist circumference instead of eGDR as independent variable) showed comparable significant results, showing that the association between glucometrics and eGDR cannot be explained by collinearity alone.

The strengths of our study are the detailed characterisation of the patient population and the reasonably large number of HEC tests. In addition, our study included high-quality CGM data: the sensor had already been used for at least 6 months, was active for at least 70 % time and data were calculated over a representative 28-day period. This was the first study to investigate the association between glucometrics and IR in adult people with T1D using high-quality CGM data, in accordance with the clinical guidelines of CGM interpretations [12].

Conclusion

To conclude, our study found that a lower IR, measured by eGDR, was independently associated with a higher TIR, lower TAR and a higher TBR and this adjusted for age, sex, duration of diabetes, smoking status and alcohol intake. A higher TBR showed a tendency towards association with more insulin sensitivity (higher M-value) in analyses with the HEC test. These findings support the role of IR as a determinant of glycaemic control in people with T1D and suggests that indirect methods to quantify insulin sensitivity might be worthwhile to be explored.

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Data Availability

Restrictions apply to the availability of some or all data generated or analysed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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Legends for figures and tables

Table 1: demographic characteristics of the study population and by eGDR categories

[a]19% missing data

[b]22% missing data

estimated glucose disposal rate (eGDR), waist circumference (WC), body mass index (BMI), time in range (TIR), time above range (TAR), time below range (TBR), coefficient of variation (CV), Glucose Management Indicator (GMI)

Table 2: Association of glucometrics and eGDR*, logistic regression

estimated glucose disposal rate (eGDR), time in range (TIR), time above range (TAR), time below range (TBR), coefficient of variation (CV)

all odds are formulated for higher order tertiles:

[a] TIR divided into tertiles, from unfavourable to favourable: 20 - 52 %, 53 - 62 % and 63 - 97 %

[b] TAR divided into tertiles, from unfavourable to favourable: 43 - 80 %, 28 - 42 % and 3 - 27 %

[c] TBR divided into tertiles, from unfavourable to favourable: 8 - 36 %, 4 - 7 % and 0 - 3 %

[d] CV divided into tertiles, from unfavourable to favourable: 43.5 - 72.1 %, 37.4 - 43.0 % and 22.2 – 37.3 %

*all associations were adjusted for age, sex, diabetes duration, smoking and alcohol intake

Table 3: demographic characteristics of the study population and by M-value

waist circumference (WC), body mass index (BMI), time in range (TIR), time above range (TAR), time below range (TBR), coefficient of variation (CV), Glucose Management Indicator (GMI), estimated glucose disposal rate (eGDR)

Table 4: Association of glucometrics and M-value*, logistic regression

time in range (TIR), time above range (TAR), time below range (TBR), coefficient of variation (CV)

All odds are formulated for higher order tertiles

[a] *TIR divided into tertiles, from unfavourable to favourable: 33 - 56 %, 57 - 67 % and 68 - 88 %*

[b] *TAR divided into tertiles, from unfavourable to favourable: 40 - 65 %, 27 - 38 % and 11 - 26 %*

[c] *TBR divided into tertiles, from unfavourable to favourable: 6 - 12 %, 3 - 5 % and 0 - 2 %*

[d] *CV divided into tertiles, from unfavourable to favourable: 41.1 - 49.6 %, 34.9 - 40.9 % and 28.1 - 34.6 %*

*all associations were adjusted for age and sex

Figure 1: flowcharts depicting the study design

PANEL A: data obtained from the database NAFLDIA1

Continuous glocse monitoring (CGM), time in range (TIR), time above range (TAR), time below range (TBR)

PANEL B: data obtained form the database BRECLAIR

Hyperinsulinaemic-euglycaemic clamp (HEC) test, continuous glucose monitoring (CGM)

Tables

Table 1. Demographic characteristics of the study population and by eGDR categories

Characteristics	Mean (SD), Median (25-75th percentiles), no (%)				p-value	Post hoc p-value group 1 vs 2	Post hoc p-value group 1 vs 3
	Total study population	eGDR tertile 1 (9.2 – 12.1 mg/kg/min)	eGDR tertile 2 (6.1 – 9.1 mg/kg/min)	eGDR tertile 3 (1.1 – 6.0 mg/kg/min)			
n	287	96	95	96			
Age (years)	46 ± 17	36 ± 14	45 ± 15	57 ± 13	*< 0.001*	*< 0.001*	*< 0.001*
Male (n, %)	158 (55)	42 (43)	51 (54)	65 (68)	*0.002*	*0.387*	*< 0.001*
Diabetes duration (years)	26 [14 – 36]	17 [10 – 29]	27 [15 – 36]	34 [24 - 46]	*< 0.001*	*< 0.001*	*0.004*
WC (cm)	89 [80 – 101]	79 [73 – 84]	92 [84 – 100]	101 [95 – 113]	*< 0.001*	*< 0.001*	*< 0.001*
BMI (kg/m²)	25.4 [22.6-28.5]	22.9 [21.0 - 24.8]	26.1 [23.9 - 28.9]	28.2 [25.4 - 31.4]	*< 0.001*	*< 0.001*	*< 0.001*
Hypertension (n, %)	124 (43)	0 (0)	32 (34 %)	92 (96)	*< 0.001*	*< 0.001*	*< 0.001*
Active smoking (n, %)	27 (9)	8 (8)	11 (12)	6 (6)	*0.421*	*1.000*	*1.000*
Alcohol intake (n, %)	201 (70)	72 (75)	65 (68)	64 (67)	*0.414*	*0.939*	*0.612*
HbA1c (%)	7.3 [6.8 - 7.9]	7.1 [6.6 - 7.7]	7.4 [6.9 - 7.9]	7.6 [6.9 - 8.2]	*< 0.001*	*0.043*	*< 0.001*
Insulin (dose per kg)	0.57 [0.45 - 0.72][a]	0.55 [0.45 - 0.65]	0.61 [0.46 - 0.73]	0.56 [0.44 - 0.74]	*0.149*	*0.120*	*1.000*
TIR (%)	57 ± 14	59 ± 14	56 ± 15	56 ± 14	*0.138*	*0.355*	*0.193*
TAR (%)	36 ± 15	33 ± 14	37 ± 16	39 ± 15	*0.047*	*0.355*	*0.043*
TBR (%)	5 [3 – 10]	5 [2 – 11]	6 [3 – 10]	4 [2 – 8]	*0.182*	*1.000*	*0.621*
TIR > 70% (n, %)	50 (17)	20 (21)	17 (18)	13 (14)	*0.407*	*1.000*	*0.543*
TAR < 25% (n, %)	69 (24)	25 (26)	25 (26)	19 (20)	*0.489*	*1.000*	*0.909*

TBR < 4% (n, %)	106 (37)	38 (40)	31 (33)	37 (38)	*0.593*	*0.951*	*1.000*
CV ≤ 36% (n, %)	61 (27)	21 (27)	17 (22)	23 (32)	*0.370*	*1.000*	*1.000*
CV (%)	40.0 [35.6 - 45.5][b]	40.1 [35.0-45.3]	40.3 [36.6 - 45.7]	39.4 [34.3 - 45.6]	*0.501*	*1.000*	*1.000*
Time in hypoglycaemia (min)	104 [81 – 127]	106 [86-130]	102 [79 – 132]	104 [81 – 123]	*0.684*	*1.000*	*1.000*
Mean glucose (mg/dl)	161 [144 – 180]	155 [143 – 176]	161 [143 – 183]	167 [149 – 184]	*0.048*	*0.397*	*0.045*
GMI (%)	7.2 [6.7 - 7.7]	7.0 [6.7 - 7.5]	7.3 [6.7 - 7.7]	7.3 [6.9 - 7.8]	*0.050*	*0.910*	*0.044*
eGDR (mg/kg min)	7.6 [5.3 - 9.6]	10.0 [9.6 - 10.5]	7.6 [6.8 - 8.6]	4.5 [3.7 - 5.3]			

[a]19% missing data

[b]22% missing data

estimated glucose disposal rate (eGDR), waist circumference (WC), body mass index (BMI), time in range (TIR), time above range (TAR), time below range (TBR), coefficient of variation (CV), Glucose Management Indicator (GMI)

Table 2. Association of glucometrics and eGDR*, logistic regression

	TIR >70%		**TIR tertiles[a]**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
eGDR	1.121 (0.961 - 1.308)	0.147	1.258 (1.126 - 1.406)	< 0.001
	TAR <25%		**TAR tertiles[b]**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
eGDR	1.214 (1.053 - 1.400)	0.008	1.281 (1.146 - 1.443)	< 0.001
	TBR < 4%		**TBR tertiles[c]**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
eGDR	0.957 (0.847 - 1.082)	0.484	0.893 (0.801 - 0.994)	0.039
	CV ≤ 36%		**CV tertiles[d]**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
eGDR	1.120 (0.960 - 1.305)	0.149	1.044 (0.926 - 1.178)	0.477

estimated glucose disposal rate (eGDR), time in range (TIR), time above range (TAR), time below range (TBR), coefficient of variation (CV)

all odds are formulated for higher order tertiles:

[a] TIR divided into tertiles, from unfavourable to favourable: 20 - 52 %, 53 - 62 % and 63 - 97 %

[b] TAR divided into tertiles, from unfavourable to favourable: 43 - 80 %, 28 - 42 % and 3 - 27 %

[c] TBR divided into tertiles, from unfavourable to favourable: 8 - 36 %, 4 - 7 % and 0 - 3 %

[d] CV divided into tertiles, from unfavourable to favourable: 43.5 - 72.1 %, 37.4 - 43.0 % and 22.2 – 37.3 %

**all associations were adjusted for age, sex, diabetes duration, smoking and alcohol intake*

Table 3. Demographic characteristics of the study population and by M-value

Characteristics	Mean (SD), Median (25-75th percentiles), no (%)				p-value	Post hoc p-value group 1 vs 2	Post hoc p-value group 1 vs 3
	Total study population	m-value tertile 1 (6.2 - 15.6 mg/kg/min)	m-value tertile 2 (4.4 - 6.0 mg/kg/min)	m-value tertile 3 (0.9 - 4.4 mg/kg/min)			
n	48	16	16	16			
Age (years)	47 ± 15	46 ± 11	50 ± 17	44 ±15	*0.399*	*1.000*	*1.000*
Male (%)	30 (63)	8 (50)	12 (75)	10 (63)	*0.344*	*0.432*	*1.000*
Diabetes duration (years)	24 [17 – 40]	27 [14 – 42]	24 [17 – 40]	25 [20 – 35]	*0.876*	*1.000*	*1.000*
WC (cm)	96 ± 17	81 ± 11	97 ± 12	109 ± 15	*< 0.001*	*0.002*	*< 0.001*
BMI (kg/m^2)	27.7 ± 5.1	23.8 ± 4.1	27.2 ± 3.5	32.0 ± 4.1	*< 0.001*	*0.060*	*< 0.001*
Hypertension (%)	30 (63)	7 (44)	10 (63)	13 (81)	*0.091*	*0.864*	*0.084*
Active smoking (%)	5 (10)	3 (19)	1 (6)	1 (6)	*0.433*	*0.825*	*0.825*
Alcohol intake (%)	15 (3)	7 (44)	5 (31)	3 (19)	*0.312*	*1.000*	*0.381*
HbA1c (%)	7.2 [6.0 - 9.8]	6.9 [6.4 - 7.3]	7.5 [6.5 - 8.1]	7.3 [6.8 - 7.7]	*0.319*	*0.465*	*0.758*
Insulin (dose per kg)	0.64 [0.40 - 1.65]	0.46 [0.43 - 0.59]	0.66 [0.24 – 0.49]	0.99 [0.69 - 1.31]	*< 0.001*	*0.018*	*< 0.001*
TIR (%)	63 ± 15	66 ± 14	60 ± 15	60 ± 15	*0.432*	*0.847*	*0.741*
TAR (%)	31 [11 – 65]	27 [20 – 36]	33 [24 - 49]	35 [26 – 49]	*0.237*	*0.579*	*0.339*
TBR (%)	3 [2 – 8]	5 [3 – 9]	4 [2 – 6]	2 [1 – 5]	*0.086*	*0.609*	*0.090*
TIR > 70% (%)	15 (31)	6 (38)	5 (31)	4 (25)	*0.748*	*1.000*	*1.000*
TAR < 25% (%)	14 (29)	7 (44)	4 (25)	3 (19)	*0.270*	*0.792*	*0.381*
TBR < 4% (%)	27 (56)	7 (44)	8 (50)	12 (75)	*0.169*	*1.000*	*0.216*
CV ≤ 36% (%)	17 (35)	6 (38)	6 (38)	5 (31)	*0.913*	*1.000*	*1.000*
CV (%)	39.2 [28.1 - 49.6]	40.3 [31.8 - 42.5]	39.0 [32.5 - 42.1]	37.0 [34.2 - 40.0]	*0.842*	*1.000*	*1.000*
Time in hypoglycaemia (min)	103 ± 35	109 ± 33	108 ± 47	92 ± 21	*0.410*	*1.000*	*0.726*

Mean glucose (mg/dl)	157 [131 – 221]	147 [138 – 161]	156 [149 – 187]	161 [150 – 180]	*0.137*	*0.327*	*0.210*
GMI (%)	7.1 [6.2 - 8.6]	6.9 [6.6 - 7.2]	7.1 [6.9 - 7.8]	7.2 [6.9 - 7.6]	*0.126*	*0.288*	*0.201*
eGDR (mg/kg min)	5.6 [4.2 - 9.5]	8.5 [5.8 - 10.7]	5.4 [4.2 - 8.7)	4.2 [3.1 - 6.1]	*< 0.001*	*0.034*	*< 0.001*
M-value (mg/kg min)	5.0 [0.9 - 15.6]	8.3 [7.4 - 10.1]	5.0 [4.6 - 5.3]	2.8 [2.3 - 3.6]			

waist circumference (WC), body mass index (BMI), time in range (TIR), time above range (TAR), time below range (TBR), coefficient of variation (CV), Glucose Management Indicator (GMI), estimated glucose disposal rate (eGDR)

1

Table 4. Association of glucometrics and M-value*, logistic regression

	TIR >70%		**TIR tertiles[a]**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
M-value	1.025 (0.828 - 1.270)	0.819	1.054 (0.880 - 1.261)	0.569
	TAR <25%		**TAR tertiles[b]**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
M-value	1.128 (0.912 - 1.396)	0.266	1.113 (0.926 - 1.337)	0.253
	TBR < 4%		**TBR tertiles[c]**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
M-value	0.834 (0.671 - 1.036)	0.101	0.835 (0.389 – 1.013)	0.068
	CV ≤ 36%		**CV tertiles[d]**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
M-value	1.034 (0.830 - 1.289)	0.763	0.900 (0.747 - 1.083)	0.267

time in range (TIR), time above range (TAR), time below range (TBR), coefficient of variation (CV)

All odds are formulated for higher order tertiles

[a] TIR divided into tertiles, from unfavourable to favourable: 33 - 56 %, 57 - 67 % and 68 - 88 %

[b] TAR divided into tertiles, from unfavourable to favourable: 40 - 65 %, 27 - 38 % and 11 - 26 %

[c] TBR divided into tertiles, from unfavourable to favourable: 6 - 12 %, 3 - 5 % and 0 - 2 %

[d] CV divided into tertiles, from unfavourable to favourable: 41.1 - 49.6 %, 34.9 - 40.9 % and 28.1 - 34.6 %

**all associations were adjusted for age and sex*

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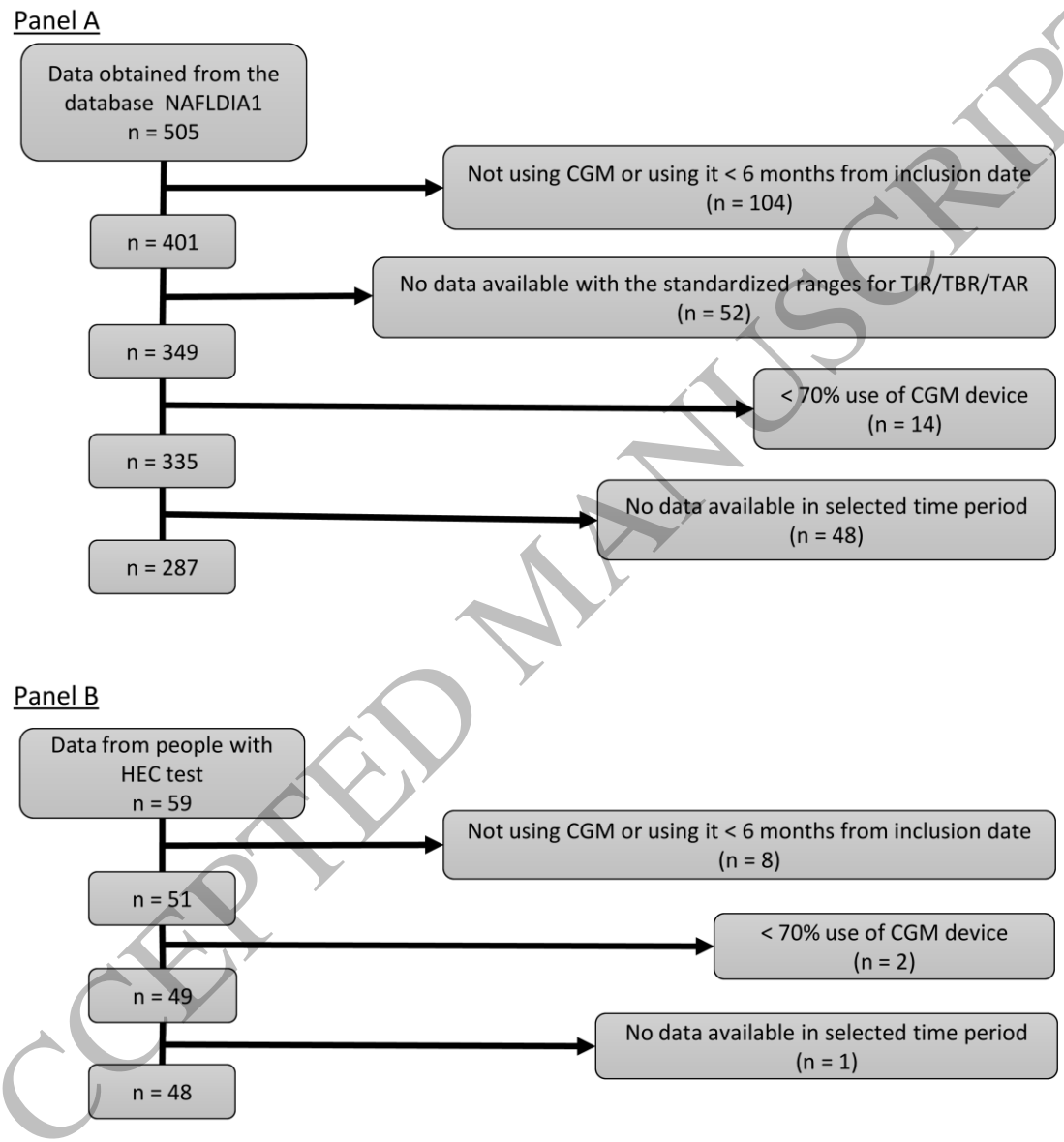
3

1 **Figure 1**



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