RESEARCH: COMPLICATIONS

DIABETIC
Medicine

Body mass index, estimated glucose disposal rate and vascular complications in type 1 diabetes: Beyond glycated haemoglobin

Rebecca Helliwell[1] | Harriet Warnes[1] | Noppadol Kietsiriroje[2,3] | Matthew Campbell[4] | Rebecca Birch[5] | Sam M. Pearson[1,2] | Ramzi A. Ajjan[2]

[1]School of Medicine, University of Leeds, Leeds, UK

[2]Leeds Institute of Cardiovascular and Metabolic Medicine, Faculty of Medicine and Health, University of Leeds, Leeds, UK

[3]Endocrinology and Metabolism Unit, Internal Medicine Department, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

[4]Faculty of Health Sciences and Wellbeing, University of Sunderland, Sunderland, UK

[5]Division of Pathology and Data analytics, University of Leeds, Leeds, UK

Correspondence
Ramzi A. Ajjan, Leeds Institute of Cardiovascular and Metabolic Medicine Research, LIGHT Laboratories, Clarendon Way, LS2 9DA Leeds, UK
R.ajjan@leeds.ac.uk

Abstract

Aims: To understand the relationship between insulin resistance (IR), assessed as estimated glucose disposal rate (eGDR), and microvascular/macrovascular complications in people with type 1 diabetes.

Materials and methods: Individuals with a confirmed diagnosis of type 1 diabetes were included in this cross-sectional study. BMI was categorised into normal weight (18.0–24.9 kg m^{-2}), overweight (25.0–29.9 kg m^{-2}) and obese groups ($\geq$30.0 kg m^{-2}). We categorised eGDR into four groups: eGDR >8, 6–7.9, 4–5.9 and <4 mg kg^{-1} min^{-1}. Multiple logistic regression was used to identify associations with vascular complications, after adjusting for relevant confounders.

Results: A total of 2151 individuals with type 1 diabetes were studied. Median [interquartile range (IQR)] age was 41.0 [29.0, 55.0] with diabetes duration of 20.0 [11, 31] years. Odds ratio (OR) for retinopathy and nephropathy in obese compared with normal weight individuals was 1.64 (95% CI: 1.24–2.19; $p = 0.001$) and 1.62 (95% CI: 1.10–2.39; $p = 0.015$), while the association with cardiovascular disease just failed to reach statistical significance (OR 1.66 [95% CI: 0.97–2.86; $p = 0.066$]). Comparing individuals with eGDR $\geq$8 mg kg^{-1} min^{-1} and <4 mg kg^{-1} min^{-1} showed OR for retinopathy, nephropathy and macrovascular disease of 4.84 (95% CI: 3.36–6.97; $p < 0.001$), 8.35 (95% CI: 4.86–14.34; $p < 0.001$) and 13.22 (95% CI: 3.10–56.38; $p < 0.001$), respectively. Individuals with the highest eGDR category ($\geq$8 mg kg^{-1} min^{-1}) had the lowest complication rates irrespective of HbA$_{1c}$ levels.

Conclusions: Obesity is prevalent in type 1 diabetes and diabetes complications are not only related to glucose control. IR, assessed as eGDR, is strongly associated with both microvascular and macrovascular complications, regardless of HbA$_{1c}$ levels.

KEYWORDS
insulin resistance, obesity, type 1 diabetes, complications

Rebecca Helliwell and Harriet Warnes joint first authorship.

Sam M. Pearson and Ramzi A. Ajjan denotes joint senior authorship.

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1 | INTRODUCTION

According to the National Institute for Clinical Excellence, type 1 diabetes affects over 370,000 adults in the United Kingdom[1] and more than 1.6 million people are living with the condition in the United States.[2] Based largely upon the findings of the Diabetes Control and Complications Trial,[3] various guidelines recommend intensive insulin regimes to achieve a HbA_{1c} <6.5% or <7.0% (<48 or <53 mmol/mol), unless this target cannot be achieved due to disabling hypoglycaemia.[4] Obesity and insulin resistance (IR) are increasing in type 1 diabetes, partly related to lifestyle choices but also secondary to the condition itself. Subcutaneous insulin administration can induce peripheral IR both directly [5-7] and indirectly through weight gain[8] and treatment of repeated hypoglycaemia.[9] Consequently, this can lead to the challenging clinical scenario of escalating insulin doses, further weight gain and increasing IR creating a vicious cycle. The weight gain can have detrimental vascular effects through the development of an inflammatory and thrombotic milieu, typically associated with insulin-resistant states.[10-12]

It has been proposed that people with type 1 diabetes and IR constitute a clinical entity, termed 'double diabetes (DD).'[13] However, the exact definition of this group has been problematic with early studies labelling those with autoimmune diabetes and a family history of type 2 as having DD.[14,15] The definition of DD was subsequently refined to include type 1 diabetes individuals with features of the metabolic syndrome, a subpopulation that showed adverse clinical outcome compared with the rest of type 1 diabetes group.[16]

Estimated glucose disposal rate (eGDR) is a marker of IR, derived from data using euglycaemic–hyperinsulinemic clamps in 24 individuals with type 1 diabetes.[17] This is calculated according to a formula that uses standard clinical measures including waist–hip ratio (alternatively, waist circumference or BMI), HbA_{1c} and presence of hypertension. The strong correlation between eGDR and IR, using the gold standard clamp techniques, indicates this is a valuable marker to identify the presence of DD in those with type 1 diabetes.[17-19] Previous work has demonstrated a relationship between IR and vascular complications in people with type 1 diabetes while more recent prospective work linked eGDR with cardiovascular and all-cause mortality in this cohort.[18-26] However, the exact contribution of eGDR and its components to risk of complications is not entirely clear, particularly in patients on modern management strategies.

We hypothesise that the risk of both microvascular disease and macrovascular complications in people with type 1 diabetes is not only determined by glycaemic control and IR has a key role. Therefore, the main aims of this study were to explore (i) relationship between obesity, assessed as BMI and diabetes-related microvascular and macrovascular complications, (ii) relationship between IR, measured as eGDR, and

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Novelty statement

In UK individuals with type 1 diabetes:

a. More than half of this population are overweight or obese, assessed using BMI.

b. While higher BMI showed an association with diabetes complications, estimated glucose disposal rate appeared to show an even stronger association with both microvascular and macrovascular disease.

c. Estimated glucose disposal rate may be a useful adjunct marker for risk stratification in routine clinical practice.

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diabetes complications and (iii) understand the association between vascular risk factors, obesity and IR.

2 | METHODS

For this study, a cross-sectional design was used with electronic patient data from November 2016 to February 2018, reviewed in Leeds Teaching Hospital Trust in England, UK. Data were collected on a single timepoint using the following inclusion criteria: (i) confirmed diagnosis of type 1 diabetes for over 1 year and current treatment with insulin. Diagnosis of type 1 diabetes was defined as being recorded in the medical records by a consultant physician or senior trainee in diabetes: (ii) availability of recent weight and height data, (iii) age over 18 years old and (iv) BMI $\geq$ 18.0 kg/m². Exclusion criteria were as follows: (i) diabetes aetiology is not confirmed or in doubt and (ii) having an established diagnosis of an eating disorder or a disorder related to body dysmorphia accompanied with a low BMI (<18.0 kg/m²). The study was classified as an audit and no ethical approval was deemed necessary as per local protocols. All data were anonymised before analysis.

2.1 | Outcome definitions

All outcomes were recorded from the most recent clinical information within the past 2 years preceding clinic attendance. BMI was categorised as healthy weight (18–24.9 kg/m²), overweight (25–30 kg/m²) and obese (>30 kg/m²). eGDR was used as a measure of IR and calculated using the formula; eGDRBMI = 19.02 − (0.22 × BMI, kg m⁻²) − (3.26 × hypertension, presence) − (0.61 × HbA_{1c}, %), whereby the presence of hypertension was defined by the actual blood pressures $\geq$140/90 mmHg or current use of any anti-hypertensive agents.[17,19] eGDR was categorised into four categories

(<4, 4–5.9, 6–7.9 and >8 mg kg^{-1} min^{-1}) based on previous work demonstrating a difference in mortality between these categories in a longitudinal observational study.[19]

Duration of diabetes was calculated using age at time of records review (years) − age at diagnosis (years). Retinopathy was defined as present if the observed abnormalities were more than simple background grade R1 alterations (R1 = mild non-proliferative changes and absence of macular disease) in at least one eye using retinal photography. Nephropathy was defined as estimated glomerular filtration rate < 60 ml min^{-1} m^{-2} and/or history of persistent albuminuria. Persistent albuminuria was defined as Urine Albumin:Creatinine Ratio > 3.0 mg mmol^{-1} on more than one occasion. Cardiovascular disease was defined as a history of myocardial infarction, angina, coronary revascularisation, documented ischaemic heart disease, stroke or transient ischaemic attacks.

2.2 | Statistical analysis

Descriptive data were presented in mean ± SD, median [IQR] or number (%). One-way ANOVA or Kruskal–Wallis and Chi-square tests were used to compare baseline characteristics among BMI categories for continuous and categorical variables, respectively. Generalised linear regression was used to estimate the mean difference of blood pressure or lipid parameters among BMI category with adjustment for age, sex, diabetes duration, the use of antihypertensive or statin (where relevant), and HbA$_{1c}$. To estimate mean differences of lipid parameters among eGDR category, the mean differences were adjusted for the same confounders as for BMI except for HbA$_{1c}$, which is part of eGDR calculation. Multiple logistic regression was used to evaluate the association between presence of microvascular or macrovascular complications and BMI or eGDR categories. BMI and eGDR categories were presented as crude and adjusted odd ratio (OR) with age, gender, diabetes duration and HbA$_{1c}$ adjusted for BMI category; and age, gender and diabetes duration adjusted for eGDR category. Further adjustment for treatment effect including statins, anti-hypertensives and adjunct oral hypoglycaemic agents was carried out for both BMI and eGDR categories. We added clinically relevant variables to the models while avoiding 'overfitting'. We also avoided including any variable with missing data $>10\%$ into adjusted models. The percentage of missing data of each variable is presented in Table 1. SPSS version 25.0 (IBM Incorporation) was used for all analyses.

Given that HbA$_{1c}$, BMI and presence of hypertension are part of eGDR calculation, adjustments for these variables were not made when analysing the association between eGDR and complications. A similar methodology has been used in the past for the analysis of eGDR.[27]

3 | RESULTS

A total of 2375 individuals were identified for the study of whom 2151 met inclusion criteria. Reasons for exclusion are shown in Figure 1. Of 2151 individuals, median age was 41.0 [29.0, 55.0] years, 53.8% were men, mean BMI was 27.0 ± 4.9 kg m^{-2}, median duration of diabetes was 20.0 (11, 31) years and mean HbA$_{1c}$ was 69.1 ± 17.5 mmol mol^{-1}. Of 2094 individuals having HbA$_{1c}$ data, mean eGDR was 6.31 ± 2.32 mg kg^{-1} min^{-1}. A summary of data from the initial screening process of eligible participants is shown in Table 1.

3.1 | Obesity, IR and diabetes-related complications

3.1.1 | Retinopathy

Retinopathy, defined as any change higher than retinopathy grade R1, was present in 21.3% of the study cohort. For BMI, a significant increase in OR was seen with higher BMI category in an unadjusted model. After adjustment for age, gender, HbA$_{1c}$ and duration of diabetes, a similar pattern was observed, although less pronounced (Figure 2). When further adjustments were made for statins, anti-hypertensives and adjuvant anti-glycaemic therapies, obese individuals still showed an increased frequency of retinal complications (adjusted OR 1.38 [95% CI: 1.02–1.87; $p = 0.04$]) (Table S1).

When eGDR was used instead of BMI, large differences were seen in the unadjusted model and also in the model adjusted for age, gender and diabetes duration (Figure 3). These differences also remained significant after further adjustment for therapies other than insulin (adjusted OR 2.12, 2.02 and 4.07 for eGDR 6–7.9, 4–5.9 and <4 mg kg^{-1} min^{-1}, respectively; $p < 0.001$ for all) (Table S1).

3.1.2 | Nephropathy

Nephropathy was present in 18.6% of patients. Comparing across BMI categories, crude OR showed no difference in rates of nephropathy between normal weight and overweight groups but there was a significant increase in obese individuals (crude OR 1.93 [95% CI: 1.35–2.76; $p < 0.001$]). However, after adjusting for age, gender, HbA$_{1c}$ and diabetes duration, the degree to which obesity increased the odds was diminished (adjusted OR 1.62 (95% CI: 1.10–2.39; $p = 0.015$]) (Figure 2) and indeed after further adjustment to include non-insulin therapies, no significant differences were seen across BMI cohorts (Table S1).

When analysing the relationship between eGDR and nephropathy, a strong relationship was observed between falling

TABLE 1 Baseline characteristics by BMI category ($n = 2151$).

| Patient characteristic | Mean (SD), Median [25th, 75th percentiles], no (%) | | | | | |
	Normal weight ($n = 832$)	Overweight ($n = 819$)	Obese ($n = 500$)	*p* value	Missing data in total (%)	Missing data by group (%)
Median age, years	37.0 [26.0, 53.0]	43.0 [30.0, 55.0]	47.0 [35.0, 59.0]	<0.001	0	
Gender, men	425 (51.1%)	485 (59.2%)	248 (49.6%)	<0.001	0	
Median duration of diabetes, years	17.0 [9, 29]	20.0 [11.0, 31.0]	24.0 [15.0, 34.0]	<0.001	0	
BMI, kg m^{-2}	22.5 (1.7)	27.2 (1.4)	33.9 (3.7)	<0.001	0	
eGDR, mg kg^{-1} min^{-1}	7.66 (1.83)	6.27 (1.89)	4.15 (2.03)	<0.001	2.6	3.1, 2.6, 2.0
SBP, mmHg	128.8 (16.9)	133.7 (16.7)	138.4 (17.7)	<0.001	0.5	0.7, 0.5, 0.2
DBP, mmHg	75.9 (9.4)	77.4 (8.7)	78.9 (9.7)	<0.001	0.6	0.8, 0.6, 0.2
Presence of HTN, no	303 (36.7%)	421 (51.7%)	335 (67.3%)	<0.001	0.6	0.7, 0.6, 0.4
Number of anti-hypertensives, no.				<0.001	0.4	0.1, 0.5, 0.8
None	635 (76.4%)	535 (65.6%)	241 (48.6%)			
1 agent	127 (15.3%)	172 (21.1%)	123 (24.8%)			
2 agents	47 (5.7%)	77 (9.4%)	94 (19.0%)			
≥3 agents	22 (2.6%)	31 (3.8%)	38 (7.8%)			
.eGFR, ml min^{-1} m^{-2}				<0.001	10.1	9.4, 11.0, 8.4
>90	649 (86.5%)	578 (79.7%)	350 (76.4%)			
60–89.9	70 (10.5%)	116 (16.0%)	75 (16.4%)			
30–59.9	11 (1.5%)	24 (3.3%)	29 (6.3%)			
15–29.9	6 (0.8%)	4 (0.6%)	2 (0.4%)			
<15	5 (0.7%)	3 (0.4%)	2 (0.4%)			
Mode of insulin delivery				0.838	0	
MDI	64 (77.0%)	639 (78.0%)	398 (79.6%)			
CSII	126 (15.1%)	120 (14.7%)	65 (13.0%)			
Mixed insulin	65 (7.8%)	60 (7.3%)	37 (7.40%)			
Total daily insulin[i], U kg^{-1} day^{-1}	0.44 (0.31)	0.44 (0.27)	0.50 (0.40)	0.002	10.9	115, 9.5, 12.2
Use of adjuvant glycaemic therapy, no.	8 (1.0%)	34 (4.2%)	83 (16.6%)	<0.001	0	
Use of statin therapy, no	251 (30.2%)	346 (42.2%)	289 (57.8%)	<0.001	0	
HbA$_{1c}$, mmol mol^{-1}	69.9 (19.0)	67.5 (16.4)	70.1 (16.2)	0.006	2.0	2.4, 2.0, 1.6
HbA$_{1c}$, %	8.5 (1.7)	8.3 (1.5)	8.6 (1.5)	0.006	2.0	2.4, 2.0, 1.6
Total cholesterol, mmol L^{-1}	4.51 (0.86)	4.57 (1.03)	4.57 (0.98)	0.487	18.9	18.9, 19.5, 18.0
LDL-c, mmol L^{-1}	2.25 (0.71)	2.40 (0.78)	2.41 (0.83)	0.004	46.9	48.0, 45.3, 47.6
HDL-c, mmol L^{-1}	1.78 (0.54)	1.61 (0.54)	1.63 (1.16)	<0.001	37.9	39.5, 36.1, 38.0
Triglycerides, mmol L^{-1}	1.13 (0.82)	1.27 (0.79)	1.57 (0.97)	<0.001	33.1	33.2, 32.4, 34.4
Creatinine, mmol L^{-1}	73.6 (47.0)	78.1 (61.3)	80.6 (62.4)	0.085	9.7	9.3, 11.0, 8.4
Urine ACR[i]	6.1 (36.2)	4.9 (39.9)	6.4 (22.1)	0.808	39.0	36.8, 39.6, 41.8

(Continues)

TABLE 1 (Continued)

| Patient characteristic | Mean (SD), Median [25th, 75th percentiles], no (%) | | | | | |
	Normal weight (n = 832)	Overweight (n = 819)	Obese (n = 500)	p value	Missing data in total (%)	Missing data by group (%)
ALT, U L^{-1}	20.7 (12.6)	22.6 (16.5)	26.1 (16.7)	<0.001	23.5	23.3, 24.4, 22.4
Retinopathy >grade 1, no	144 (17.3%)	176 (21.5%)	139 (27.8%)	<0.001	0	
Nephropathy, no.	80 (15.9%)	80 (16.6%)	77 (26.6%)	<0.001	40.7	39.5, 41.0, 42.0
Cardiovascular disease, no	31 (3.7%)	33 (4.0%)	34 (6.8%)	0.022	0	

Abbreviations: ACR, albumin: creatinine ratio; ALT, alaninine aminotransferase; BMI, body mass index; CSII, continuous subcutaneous insulin injection; DBP, diastolic blood pressure; eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; HDL-c, high-density liporotein cholesterol; HTN, hypertension; LDL-c, low-density lipoprotein cholesterol; MDI, multiple daily dose insulin; SBP, systolic blood pressure.

eGDR and the presence of nephropathy. After adjusting for age, gender and duration of diabetes, this strong relationship persisted (adjusted OR 1.98, 3.82 and 8.35 for eGDR 6–7.9, 4–5.9 and <4 mg kg^{-1} min^{-1}, respectively; $p < 0.05$ for all) (Figure 3) as it did when adjusting for therapeutic agents other than insulin (adjusted OR 1.71, 2.64 and 5.56 for eGDR 6–7.9, 4–5.9 and <4 mg kg^{-1} min^{-1}; $p = 0.07$, 0.001 and <0.001, respectively) (Table S1).

3.1.3 | Macrovascular complications

In an unadjusted model, differences in rates of cardiovascular events were seen in those whom were obese (crude OR 1.88 [95% CI: 1.14–3.11; $p = 0.01$]) but not in those whom were overweight ($p = 0.75$). However, the association found in obese individuals showed only a trend after adjusting for age, gender, HbA$_{1c}$ and diabetes duration (adjusted OR 1.66 [95% CI: 0.97–2.86; $p = 0.07$]) (Figure 2).

Lower eGDR, on the other hand, was markedly associated with the presence of macrovascular disease in the unadjusted model. After adjustment for age, gender and duration of diabetes, adjusted OR for eGDR <4 mg kg^{-1} min^{-1} remained highly significant (adjusted OR 13.22 [95% CI: 3.10–56.38; $p < 0.001$]) and a similar pattern was seen for those with eGDR 4–5.9 mg kg^{-1} min^{-1} (adjusted OR 6.57 [95% CI: 1.54–28.00; $p = 0.01$]) (Figure 3). Even after further adjustment for therapies other than insulin, the
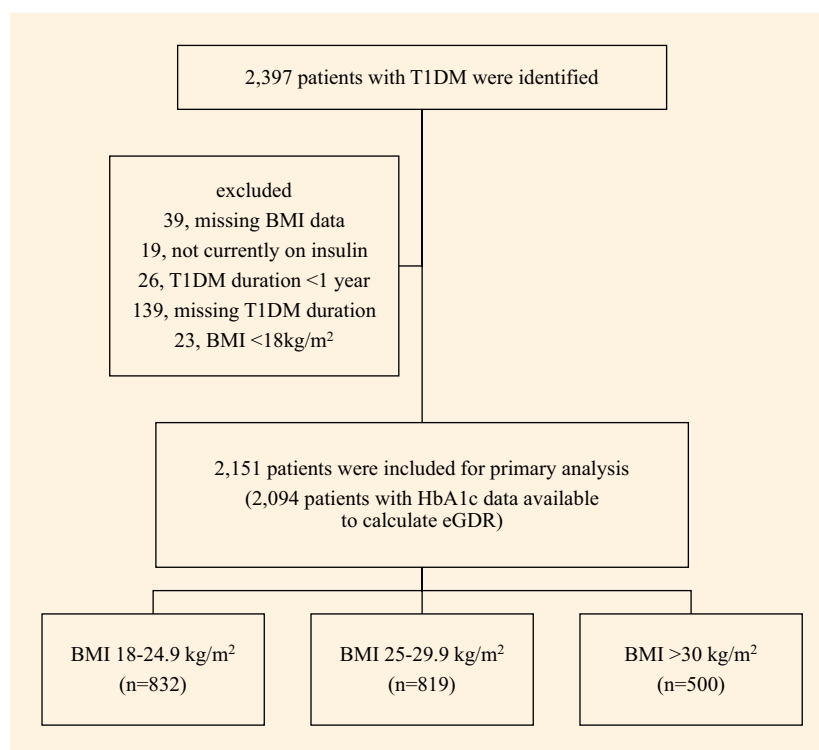

FIGURE 1 Patient enrolment and reasons for exclusion

association between cardiovascular events and those with eGDR <4 mg kg^{-1} min^{-1} remained significant (adjusted OR 5.87 [95% CI: 1.21–28.50; $p = 0.03$]) (Table S1).

3.2 | Obesity, IR and metabolic parameters

In overweight and obese individuals, systolic and diastolic blood pressures were significantly higher when compared to normal weight patients (Table 1). These differences remained significant after adjusting for age, sex, duration of diabetes and HbA$_{1c}$ as well as use of antihypertensive agents (Figure S1). HbA$_{1c}$ in normal weight, overweight and obese individuals were 69.9 ± 19.0, 67.5 ± 16.4 and 70.1 ± 16.2 mmol mol^{-1}, respectively (post-hoc Bonferroni, $p = 0.16$ for normal weight vs. overweight and $p = 0.27$ for obese vs. overweight). Total daily insulin requirement in normal weight, overweight and obese individuals were 0.44 ± 0.31, 0.44 ± 0.27 and 0.50 ± 0.40 U kg^{-1} day^{-1}, respectively ($p = 0.002$).

Obese individuals were found to have adverse lipid profiles compared to normal weight patients including an increase in total cholesterol, triglycerides and LDL-cholesterol together with a decrease in HDL-cholesterol. The estimated mean difference of each lipid parameter remained significant after adjusting for age, gender, HbA$_{1c}$, duration of diabetes and statins ($p = 0.03$ for total cholesterol, and $p < 0.001$ for other lipid parameters). The effect of IR (assessed by eGDR category) on lipid parameters resembled that of obesity, whereby individuals with lower eGDR had less desirable lipid profile including higher levels of total cholesterol, triglyceride and LDL-cholesterol as well as lower levels of HDL-cholesterol (Figure S2).

3.3 | Use of hypoglycaemic therapies other than insulin

Of the 125 individuals receiving adjuvant anti-hyperglycaemic therapy, 113 individuals were taking Metformin/Metformin modified release, 1 patient received a sodium glucose co-transporter-2 (SGLT2) inhibitor, and 11 individuals were prescribed glucagon-like peptide-1 receptor agonist (GLP1-RA).

Patients receiving adjuvant hypoglycaemic therapies were older (47.5 ± 16.3 vs. 43.2 ± 16.6; $p = 0.005$), yet had a trend towards shorter duration of type 1 diabetes (20.1 ± 12.2 vs. 22.2 ± 14.5; $p = 0.072$) with a female predominance (female 64% vs. male 36%; $p < 0.001$). The odds ratio (OR) for receiving adjuvant anti-hyperglycaemic therapy was significantly higher in both overweight (OR 4.85, 95% CI: 2.22–10.60, $p < 0.001$) and obese individuals (OR 21.09, 95% CI: 10.02–44.38, $p < 0.001$) compared to healthy weight patients after adjusting for age, gender, HbA$_{1c}$ and duration of diabetes.

3.4 | The relative contribution of HbA$_{1c}$ and eGDR components to diabetes-related complications

We further evaluated the association of diabetes-related complications and eGDR in the context of various levels of HbA$_{1c}$. Individuals with the highest eGDR category (≥ 8 mg kg^{-1} min^{-1}) had the lowest complication rates regardless of HbA$_{1c}$ levels (Figure 4), indicating that HbA$_{1c}$ is not the sole predictor of microvascular and macrovascular complications in people with type 1 diabetes. The highest complication rate was demonstrated in those with low eGDR and high HbA$_{1c}$. We also analysed the association between

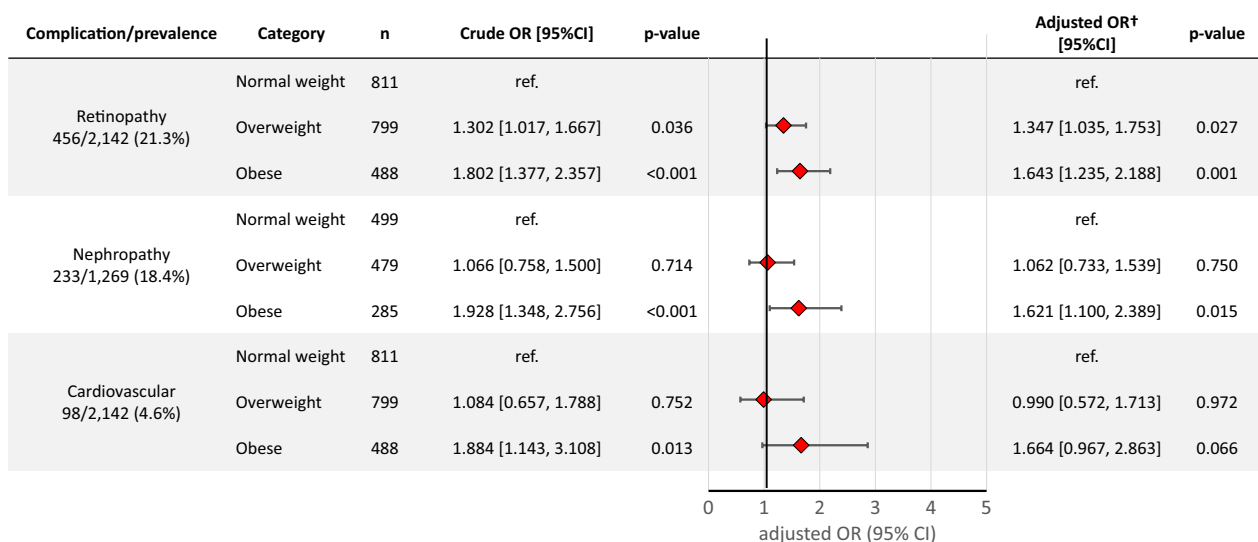| Complication/prevalence	Category	n	Crude OR [95%CI]	p-value		Adjusted OR† [95%CI]	p-value
Retinopathy 456/2,142 (21.3%)	Normal weight	811	ref.			ref.	
	Overweight	799	1.302 [1.017, 1.667]	0.036		1.347 [1.035, 1.753]	0.027
	Obese	488	1.802 [1.377, 2.357]	<0.001		1.643 [1.235, 2.188]	0.001
Nephropathy 233/1,269 (18.4%)	Normal weight	499	ref.			ref.	
	Overweight	479	1.066 [0.758, 1.500]	0.714		1.062 [0.733, 1.539]	0.750
	Obese	285	1.928 [1.348, 2.756]	<0.001		1.621 [1.100, 2.389]	0.015
Cardiovascular 98/2,142 (4.6%)	Normal weight	811	ref.			ref.	
	Overweight	799	1.084 [0.657, 1.788]	0.752		0.990 [0.572, 1.713]	0.972
	Obese	488	1.884 [1.143, 3.108]	0.013		1.664 [0.967, 2.863]	0.066

adjusted OR (95% CI)

FIGURE 2 Multiple logistic regression analysis showing odd ratio [95% CI] of retinopathy (>R1), nephropathy and cardiovascular disease by BMI category. †Adjusted for age, sex, diabetes duration and HbA$_{1c}$. BMI, body mass index
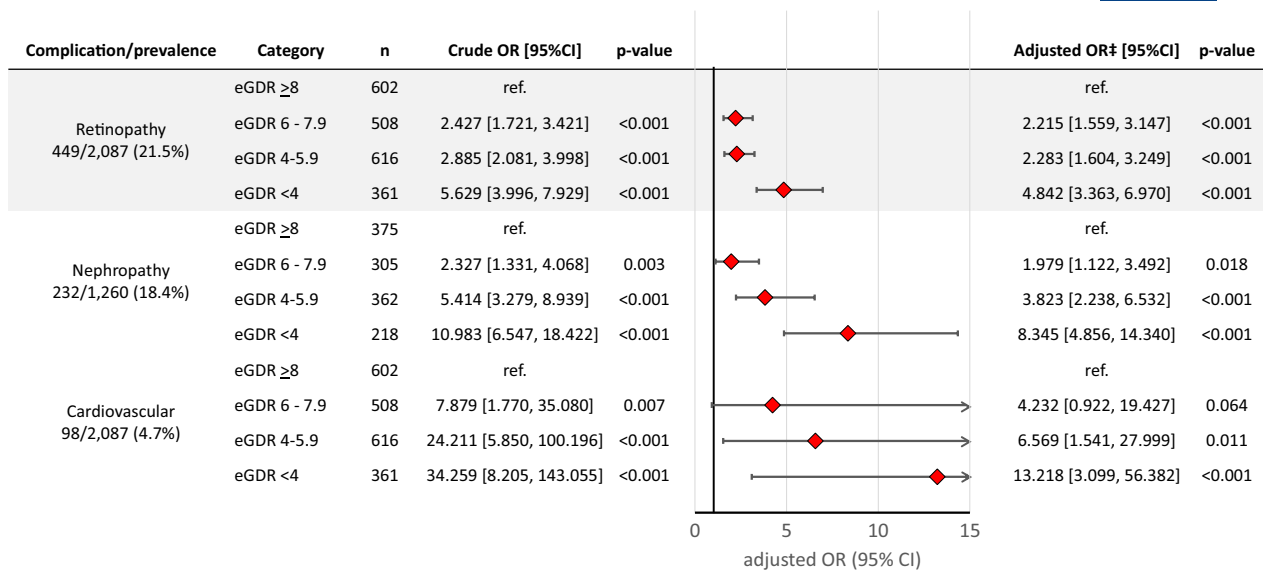
Complication/prevalence	Category	n	Crude OR [95%CI]	p-value		Adjusted OR‡ [95%CI]	p-value
Retinopathy 449/2,087 (21.5%)	eGDR ≥8	602	ref.			ref.	
	eGDR 6 - 7.9	508	2.427 [1.721, 3.421]	<0.001		2.215 [1.559, 3.147]	<0.001
	eGDR 4-5.9	616	2.885 [2.081, 3.998]	<0.001		2.283 [1.604, 3.249]	<0.001
	eGDR <4	361	5.629 [3.996, 7.929]	<0.001		4.842 [3.363, 6.970]	<0.001
Nephropathy 232/1,260 (18.4%)	eGDR ≥8	375	ref.			ref.	
	eGDR 6 - 7.9	305	2.327 [1.331, 4.068]	0.003		1.979 [1.122, 3.492]	0.018
	eGDR 4-5.9	362	5.414 [3.279, 8.939]	<0.001		3.823 [2.238, 6.532]	<0.001
	eGDR <4	218	10.983 [6.547, 18.422]	<0.001		8.345 [4.856, 14.340]	<0.001
Cardiovascular 98/2,087 (4.7%)	eGDR ≥8	602	ref.			ref.	
	eGDR 6 - 7.9	508	7.879 [1.770, 35.080]	0.007		4.232 [0.922, 19.427]	0.064
	eGDR 4-5.9	616	24.211 [5.850, 100.196]	<0.001		6.569 [1.541, 27.999]	0.011
	eGDR <4	361	34.259 [8.205, 143.055]	<0.001		13.218 [3.099, 56.382]	<0.001

adjusted OR (95% CI)

FIGURE 3 Multiple logistic regression analysis showing odd ratio [95% CI] of retinopathy (>R1), nephropathy and cardiovascular disease by eGDR category. ‡With adjustment for age, sex and duration of type 1 diabetes mellitus
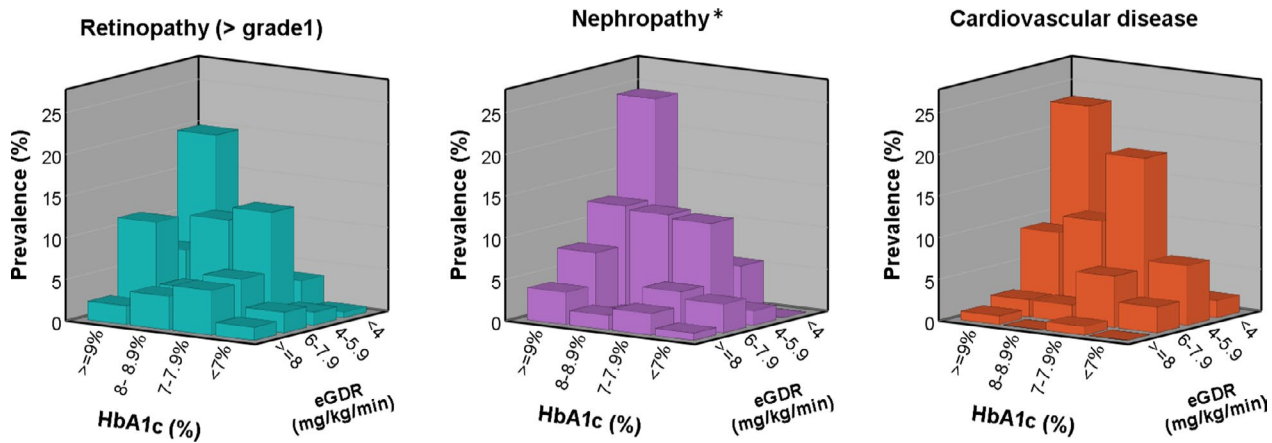

FIGURE 4 The prevalence rates of diabetes-related complications by HbA_{1c} and eGDR categories ($n = 2094$). Left panel, retinopathy grade > R1; middle panel, nephropathy; right panel, cardiovascular disease. *Nephropathy, $n = 1270$

components of eGDR and complications with results demonstrating that eGDR as a whole shows the strongest association with complications (Table S2).

4 | DISCUSSION

This study aimed to explore the clinical impact of obesity and IR on metabolic parameters and prevalence of vascular complications in people living with type 1 diabetes.

Glycaemic control, measured as HbA_{1c}, is a key predictor of future microvascular disease in individuals with type 1 diabetes.[3] However, we found that BMI may also determine predisposition to microvascular complications, particularly in relation to retinopathy, suggesting that weight also has a role. However, the association between BMI and microvascular

disease was relatively modest. In contrast, eGDR showed a stronger association with microvascular disease even after correcting for age and diabetes duration. These findings indicate that microvascular disease in type 1 diabetes is not only modulated by glycaemic control but also IR. Moreover, our data demonstrate that eGDR is more strongly linked to the development of microvascular complications than BMI. A largely similar pattern was observed for macrovascular disease; obese individuals had increased prevalence of cardiovascular disease but the association between BMI and macrovascular complications lost significance after adjusting for relevant confounders. On the other hand, eGDR was associated with the presence of macrovascular disease with or without adjustment for confounders. It should be noted that previous work has shown a J-shaped or U-shaped association between BMI and mortality in type 1 diabetes individuals,[28]

which may have played a role in the stronger association of eGDR with complications in our study. However, this J-like effect of BMI would have been minimised in the current work by excluding individual with BMI<18 kg m^{-2} from the study.

The relationship between IR, measured as eGDR, and presence of both microvascular and macrovascular complications in this work is well-aligned with previous studies in this area.[23-26] Advantages of our study include the contemporary and relatively large cohort of patients analysed as well as the in-depth investigation of eGDR and its metabolic components. Overall, our data suggest that eGDR measurement can be useful clinically to further help stratify risk of complications in people with type 1 diabetes. Indeed, a recent nation-wide prospective study from Sweden, including 17,050 individuals with type 1 diabetes, demonstrated an inverse correlation between eGDR and both cardiovascular and all-cause mortality over a 7.1-year follow-up period.[19] This study also showed that survival in individuals with eGDR ≥ 8 mg kg^{-1} min^{-1} was similar to people without diabetes. In keeping with this, we found that those with eGDR $\geq$8 mg kg^{-1} min^{-1} had the lowest prevalence of macrovascular complications. The same also applied to microvascular disease, suggesting that eGDR may also be a useful marker to predict the development of these complications.

Just like HbA$_{1c}$, a key advantage of eGDR is the continuous nature of this variable, making assessment of future vascular risk relatively simple. Unlike HbA$_{1c}$ however, eGDR includes other key measures that are implicated in vascular pathology and influenced by IR. Therefore, eGDR is an IR marker that helps to better stratify the risk of diabetes complications in those with type 1 diabetes than separately using each of its components. Taken together, a reduction in HbA$_{1c}$ may seem protective but this is not necessarily the case if the drop in HbA$_{1c}$ is associated with a significant decrease in eGDR (and hence an increase in IR). In support of this, our data show that high HbA$_{1c}$ per se was not associated with complications in the presence of high eGDR. In contrast, the combination of high HbA$_{1c}$ and low eGDR showed clear associations with complications, emphasising the importance of IR in predisposition to microvascular and macrovascular disease.

Future prospective studies are required to answer a number of clinically relevant questions, including (1) what is the optimal cut-off of eGDR that should be implemented in routine clinical practice? (2) what are the best management strategies to modify eGDR and crucially, (3) is eGDR a measure that people with type 1 diabetes connect to and understand? While a multifactorial intervention in type 1 diabetes is routine practice, this is not always the case in the younger age group where the focus is on glycaemia. Incorporating eGDR into routine practice may help healthcare professionals and patients appreciate the importance of risk factors other than glucose levels, potentially improving long-term outcome in

people with type 1 diabetes, particularly those whom are insulin resistant. Also, this will potentially help to explore the effects of adjuvant therapies such as SGLT2 inhibitors and GLP1-RA on the development of complications by monitoring changes in eGDR.[29] A large proportion of patients were overweight/obese in our study but there was relatively little use of adjunctive glycaemic therapies (other than metformin), despite data showing weight loss and/or glycaemic improvement with GLP-1RA and sGLT2 inhibitors.[29]

This study has several strengths. First, it was conducted with real-world data and using a contemporary cohort of patients, reflecting routine clinical practice and making results more generalisable. Second, it is a single-centre study with uniform data collection and relatively large sample size. Third, there was a good spread of ages with high rate of microvascular complications, consistent with the real-world nature of the data. Finally, our results show that eGDR is a strong marker of both microvascular and macrovascular complications, suggesting it can be used to predict risk and monitor response to a specific management strategy.

There are several limitations to this work. First, data were collected using a cross-sectional study design, which can only establish associations and is unable to demonstrate a causal relationship. Second, data analysis employed different adjustments for BMI and eGDR but this is due to the inability to adjust for components of eGDR. Also, caution should be exercised with data interpretation given testing for associations on multiple covariates and the use of a number of models. Third, information on current/previous smoking was lacking and as such we were unable to ascertain if there was any pattern in smoking habits observed and thus were unable to adjust for this important confounder. Fourth, the limited ethnic diversity of the group studied makes generalisability of the results questionable and larger studies involving multiple centres and different countries are warranted to fully understand the potential role of eGDR in routine clinical practice. Fifth, the validity of eGDR in conditions associated with changes in HbA$_{1c}$, such as haemoglobinopathies and advanced renal failure, remains unknown. Finally, it is important to note that not all studies have found strong correlation between IR determined by clamp techniques and eGDR.[30] However, eGDR correlates well with diabetes complications and as such it has the potential to serve as a vascular risk marker, and future longitudinal studies are required to investigate this possibility.

In conclusion, this study, in a contemporary group of people with type 1 diabetes, shows that eGDR is strongly associated with the presence of both microvascular and macrovascular complications, regardless of HbA$_{1c}$. This indicates that eGDR may be a useful adjunct marker for risk stratification in routine practice. Future prospective studies are warranted to evaluate the role of modulating eGDR in preventing vascular complications in people with type 1 diabetes, which

will help to fully establish the role of this variable in daily clinical management of type 1 diabetes.

CONFLICT OF INTEREST
None to declare in relation to this work (all authors).

AUTHORS' CONTRIBUTION
Harriet Warnes and Rebecca Helliwell collected the majority for data for the study. Noppadol Kietsiriroje and Rebecca Birch performed the statistical analysis and were involved in manuscript creation. Matthew Campbell critically appraised the work and was involved in editing of the final manuscript. Sam M. Pearson was involved in data collection, statistical analysis and manuscript creation. Ramzi A. Ajjan had overall oversight of the work and formulated the hypothesis for investigation.

ORCID
Sam M. Pearson https://orcid.org/0000-0002-4943-6759

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.