The association between overweight/obesity and double diabetes in adults with type 1 diabetes; a cross-sectional study

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Research Article

Keywords: Type 1 Diabetes Mellitus, obesity, overweight, double diabetes, insulin resistance

DOI: https://doi.org/10.21203/rs.3.rs-256189/v1

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Abstract

Background: Double Diabetes (DD), type 1 diabetes (T1DM) + insulin resistance (IR), is associated with increased risk of micro/macro-vascular complications and mortality. Obesity can contribute to the development of DD. This study explored the prevalence of overweight/obesity and their association with DD in adults with T1DM.

Methods: Cross-sectional study of consecutive adults with T1DM attending diabetes clinics in a secondary care hospital (January-November 2019). Estimated glucose disposal rate (eGDR) was used as a marker of IR, and an eGDR < 8 was used to identify individuals with DD.

Results: 107 adults with T1DM were included; female/male: 51/56; age [median (inter-quartile range): 30.0 (23-51) years]; BMI 25.4 (22.8-30.0) kg/m². Overweight/obesity prevalence was 57/107 (53.3%) [overweight: 30/107 (28%); obesity: 27/107 (25.2%)]. Compared to those with normal BMI, individuals with T1DM and overweight/obesity had longer diabetes duration; higher total daily insulin dose; and higher DD prevalence: 48/57 (84.2%) vs 14/50 (28%) (p<0.01); with similar HbA1c. BMI correlated with total daily insulin dose (rho=0.55; p<0.01). Individuals with DD were older, had longer duration of diabetes, higher HbA1c, and more adverse lipid profile and microalbuminuria compared to those without DD.

Conclusions: Overweight/obesity is very common in adults with T1DM, and is associated with double diabetes. BMI is positively associated with total insulin dose. Double diabetes is associated with adverse cardiovascular risk profile and is also common in lean individuals with T1DM. Further research is needed to examine the impact of overweight/obesity in people with T1DM and whether weight loss in this population can improve diabetes-related outcomes.

Background

Obesity is a chronic disease that is closely associated with insulin resistance and significant morbidity1,2. The prevalence of obesity globally has tripled between 1975 and 20163. In England, the 2017 Health Survey (HSE) revealed that 64.3% of adults are overweight (35.6%) or have obesity (28.7%)4.

Type 2 Diabetes mellitus (T2DM) is typically linked to obesity with 90% of people with T2DM having a body mass index (BMI) in the overweight or obesity range5. In contrast, individuals with Type 1 diabetes mellitus (T1DM) are generally lean at diagnosis6. However, studies from North America suggest an increasing prevalence of overweight and obesity in people with T1DM6,7. Of note, in the Pittsburgh Epidemiology of Diabetes Complications study, 42% of adults with T1DM were overweight and 22.7% had obesity after 18 years of follow up5,8. Despite such studies, data on the prevalence of overweight and obesity in individuals with T1DM from other populations/cohorts remain limited.

Double diabetes (DD) is a term introduced to describe individuals with T1DM who also have features of insulin resistance9. Whilst there have been different definitions for DD, estimated glucose disposal rate (eGDR) has recently been proposed as a good marker of insulin resistance that is easy to measure in clinical practice9. As such, a cut-off eGDR value of < 8 in people with T1DM has been proposed to identify individuals with DD9. DD is associated with increased risk of micro- and macrovascular complications, as well as higher cardiovascular disease (CVD) and all-cause mortality9,10.

Given the paucity of relevant data, this study aimed to examine the prevalence of overweight and obesity in adult individuals with T1DM. A secondary study aim was to examine the associations between overweight/obesity and DD in this population.

Methods

We conducted a cross-sectional study examining consecutive adults with T1DM who attended the Young Adult Diabetes Clinic (individuals with age between 18 and 25 years) and the General Adult Diabetes Clinic (individuals > 25 years old) between 1st January and 25th November 2019 at Southmead Hospital, North Bristol NHS Trust, Bristol, UK. All investigations were performed as part of routine clinical care.

The Patient Safety, Assurance and Audit (PSAA) committee at North Bristol NHS Trust (the ethics committee at the trust which approves clinical audits) approved this audit (audit number: CA8757).

Consent was not needed as this was a retrospective audit performed as part of a service evaluation, rather than a research study – this was approved by the PSAA committee.

Only clinically available data, as part of routine care, was included in the audit. The reporting of the study was carried out in accordance with STrengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines on observational studies.

The T1DM diagnosis was determined based on the age of diagnosis, presence of T1DM-related autoantibodies (GAD, IA-2, and zinc 8 transporter), the measurement of urinary or blood c-peptide, and history of diabetic ketoacidosis in accordance with the Association of British Clinical Diabetologists (ABCD) criteria for diagnosing T1DM11. Participants were included in the study if they fulfilled any of the following criteria: 1) low urine or blood c-peptide, regardless of age of diagnosis; 2) two or more positive T1DM-related autoantibodies, regardless of age of diagnosis; 3) one positive T1DM-related autoantibody, and diagnosed < 30 years of age; 4) history of diabetic ketoacidosis (DKA), and diagnosed < 30 years of age; 5) diagnosed < 20 years of age, regardless of T1DM-related autoantibody status. Participants with T2DM, maturity onset diabetes of the young (MODY), diabetes secondary to underlying medical conditions (e.g. due to pancreatitis or steroid induced diabetes), and individuals where the diabetes diagnosis was not clear or yet confirmed were excluded from this study.
Overweight was defined as a BMI of 25-29.9 kg/m\(^2\), and obesity as a BMI \(\geq 30\) kg/m\(^2\). For people of Asian ethnic background, BMI cut-offs of 23-27.4 kg/m\(^2\) and \(\geq 27.5\) kg/m\(^2\) were used to identify people with overweight and obesity, respectively\(^{12}\).

Participants’ data including height, weight, blood pressure, medications and past medical history, as well as biochemistry information including lipid profile and haemoglobin A1c (HbA1c – measured by high performance liquid chromatography) were collected from electronic Participants’ records. Hypertension was defined as recorded blood pressure > 140/90mmHg; use of blood pressure lowering medications; or a documented relevant diagnosis in the electronic Participant record\(^{13}\). Estimated glucose disposal rate (eGDR) was calculated as a validated proxy of insulin resistance based on the following formula:

\[ \text{eGDR} = 19.02 - (0.22 \times \text{BMI} \ [\text{kg/m}^2]) - (3.26 \times \text{hypertension status \ [yes = 1, no = 0]}) - (0.61 \times \text{HbA1c} \ \text{[converted from IFCC mmol/mol to NGSP %]}) \] \(^{9}\)

An eGDR value of < 8 was used to identify individuals with DD\(^{9}\). Data were collected, anonymised and stored on a secure NHS computer in line with data protection guidelines.

### Statistical analysis

Data are presented as median and interquartile range (IQR) or numbers (percentages), unless stated otherwise. Data were checked for normality using Histogram and Shapiro-Wilk test. Between groups comparisons, normal BMI vs. overweight/obesity, were assessed using the Mann-Whitney U test, or chi-square for frequencies. Correlations were assessed using Spearman rank-order correlation coefficient, as appropriate. A p-value of < 0.05, 2-tailed, was considered statistically significant. Data were analysed using PASW statistics 26 package (SPSS Inc., Chicago, USA)\(^{14}\).

### Results

In total, 198 individuals with diabetes were reviewed in the participating diabetes clinics during the study period. Of those, 107 were eligible for inclusion (Fig. 1). Table 1 summarizes demographics and pertinent clinical characteristics for the entire study cohort and by weight subgroup category (normal BMI, overweight, and obesity).
Table 1

Selected key study relevant demographic and clinical characteristics of the entire study cohort of adults with type 1 diabetes (T1DM), and by weight sub-group based on body mass index (BMI). Data are presented as median and interquartile range (IQ), and as percentages for frequencies. An estimated glucose disposal rate (eGDR) cut-off value of < 8 was applied to identify individuals with double diabetes (T1DM combined with insulin resistance). Microalbuminuria was defined as urine albumin/creatinine ratio > 3 mg/mmol. Hypertension was defined as blood pressure > 140/90 mmHg or a documented relevant diagnosis in the electronic Participant record. ACEI, angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blockers; BMI: body mass index; eGDR: estimated glucose disposal rate; HbA1c: haemoglobin A1c. *p-value < 0.05 for overweight/obesity vs. normal BMI.

| Selected study relevant characteristics | Entire study cohort (n = 107) | Sub-group | Normal BMI (n = 50) | Overweight (n = 30) | Obesity (n = 27) | Overweight/obesity (n = 57) |
|----------------------------------------|-------------------------------|-----------|---------------------|---------------------|-----------------|---------------------------|
| Age at clinic (years)                  | 30.0 (23.0-49.5)              | 26.0 (22.0-47.3)  | 30.5 (23.0-54.0)  | 38.0 (25.0-51.0)  | 34 (23.5-51.0)  |
| Age at diagnosis (years)               | 17.0 (11.0-27.0)              | 18.0 (11.0-27.5)  | 18.0 (11.8-28.3)  | 15.0 (7.0-25.0)   | 17.0 (9.0-27.5) |
| Diabetes duration (years)              | 12.0 (5.5-23.5)               | 9.5 (4.0-17.0)    | 12.0 (7.5-25.0)   | 19.0 (10.0-31.0)  | 15.0 (9.0-27.0)* |
| Female [n (%)]                         | 51 (48)                       | 22 (44)           | 15 (50)            | 14 (52)            | 29 (51)          |
| Body weight (kg)                       | 74.3 (63.6-87.4)              | 63.8 (60.1-73.7)  | 74.5 (68.5-81.9)  | 93.9 (87.4-111)   | 82.0 (74.0-95.7)* |
| BMI (kg/m²)                            | 25.4 (22.8-29.8)              | 22.8 (20.6-23.9)  | 26.3 (25.8-27.7)  | 34.4 (31.2-37.8)  | 29.4 (26.1-34.3)* |
| HbA1c (mmol/mol)                       | 70.0 (62.0-80.0)              | 70.0 (61.0-78.0)  | 70.5 (61.8-79.0)  | 70.0 (60.0-120.0) | 70.0 (63.0-79.5)  |
| Total Insulin dose (units)             | 49.0 (36.0-65.0)              | 42 (30.9-53.8)    | 51.5 (34.8-65.5)  | 78.0 (60.0-120.0) | 60 (46.0-83.0)*  |
| Insulin dose (unit/kg/day)             | 0.68 (0.53-0.89)              | 0.66 (0.48-0.76)  | 0.67 (0.51-0.86)  | 0.85 (0.56-1.1)   | 0.75 (0.56-0.95)* |
| Total Cholesterol (mmol/L)             | 4.3 (3.6-4.9)                 | 4.2 (3.5-4.9)     | 4.4 (3.6-4.9)     | 4.4 (3.8-5.0)     | 4.4 (3.5-6.0)    |
| Triglyceride (mmol/L)                  | 1.1 (0.7-1.7)                 | 1.0 (0.7-1.4)     | 1.2 (0.7-1.8)     | 1.3 (0.9-2.0)     | 1.3 (0.8-1.8)    |
| HDL Cholesterol (mmol/L)               | 1.4 (1.2-1.8)                 | 1.6 (1.3-1.9)     | 1.5 (1.2-1.9)     | 1.3 (1.1-1.5)     | 1.4 (1.1-1.7)*   |
| LDL Cholesterol (mmol/L)               | 2.3 (1.7-2.9)                 | 2.2 (1.6-2.6)     | 2.3 (2.0-3.0)     | 2.8 (1.8-3.4)     | 2.5 (1.9-3.1)    |
| Hypertension, [n (%)]                  | 20 (19)                       | 4 (8)             | 7 (23)            | 9 (33)             | 16 (28)*         |
| Statins [n (%)]                        | 33 (31)                       | 11 (22)           | 8 (27)            | 14 (52)            | 22 (39)          |
| ACEI/ARB [n (%)]                       | 22 (21)                       | 4 (8)             | 6 (20)            | 12 (44)            | 18 (32)*         |
| Metformin [n (%)]                      | 9 (8)                         | 2 (4)             | 1 (3)             | 6 (22)             | 7 (12)           |
| Microalbuminuria, [n (%)]              | 17 (16)                       | 5 (10)            | 5 (17)            | 7 (26)             | 12 (21)          |
| eGDR                                   | 7.4 (5.7-8.7)                 | 8.7 (7.4-9.7)     | 7.4 (6.0-8.2)     | 4.5 (3.7-6.8)     | 6.3 (4.5-7.6)*   |
| Double diabetes, [n (%)]               | 62 (58)                       | 14 (28)           | 21 (70)           | 27 (100)           | 48/57 (84)*      |

The study population was mainly of young adults with balanced numbers of men and women and long diabetes duration > 10 years. Ethnicity was documented in 72 participants (72/107; 67.3%); of those with documented ethnicity, one Participant was of Asian ethnic background (1/72; 1.4%), and the rest were White Caucasian (71/72; 98.6%). Participants with overweight/obesity were older, had higher total daily insulin dose, and higher prevalence of hypertension compared to normal BMI. HbA1c and lipid profile were similar between Participants with normal weight and those with overweight/obesity.

The prevalence of overweight/obesity was 57/107 (53.3%) [overweight: 30/107 (28%); and obesity: 27/107 (25.2%)]. A moderate association between increasing BMI and total daily insulin dose (rho = 0.55, p < 0.01) was noted (Table 2).

Table 2

Correlation between study pertinent variables by Spearman rank-order correlation coefficient (rho). BMI, body mass index; HbA1c, haemoglobin A1c. *P < 0.05 (2-tailed); **P < 0.01 (2-tailed).

| BMI (kg/m²) | Age at clinic (years) | Diabetes duration (years) | Total Insulin dose (units) | HbA1c (mmol/mol) |
|------------|-----------------------|---------------------------|---------------------------|-----------------|
| 0.22*      | 0.27**                | 0.55**                    | 0.12                      |
| Age at clinic (years) | 0.44**                | 0.02                      | 0.02                      |
| Diabetes duration (years) | 0.18                  | 0.01                      |                           |
| Total insulin dose (units) |                      |                           | 0.20*                    |
| HbA1c (mmol/mol) |                      |                           |                           |
The prevalence of DD in the study cohort was 62/107 (57.9%). There was a strong relationship between BMI and DD prevalence (Table 1), and all study participants with T1DM and obesity had DD (27/27, 100%). Individuals with DD were older, had longer duration of diabetes, higher HbA1c despite higher total insulin doses, more adverse lipid profile and more microalbuminuria compared to those without DD. A comparison between individuals with and without DD is summarised in Table 3.

| Selected study cohort characteristics | Double Diabetes |
|--------------------------------------|-----------------|
|                                     | No (n = 45)     | Yes (n = 62) |
| Age at clinic (years)                | 24.0 (21.5–38.5)| 37.0 (24.0–51.3)*|
| Age at diagnosis (years)             | 18.0 (11.0-25.5)| 16.5 (9.0–29.0) |
| Diabetes duration (years)            | 9.0 (2.0–17.0)  | 14.0 (8.8–26.5)*|
| Female [n (%)]                       | 22 (49)         | 29 (47)       |
| Body weight (kg)                     | 64.0 (61.1–74.3)| 80.5 (73.1–94.2)*|
| BMI (kg/m²)                          | 22.9 (20.7–24.3)| 29.1 (25.3–34.1)*|
| HbA1c (mmol/mol)                     | 63.0 (53.5–73.0)| 72.5 (66.8–87.0)*|
| Total Insulin dose (units)           | 42.0 (30.8–54.5)| 57.0 (42.3–80.5)*|
| Insulin dose (unit/kg/day)           | 0.65 (0.45–0.82)| 0.71 (0.56–0.93)*|
| Total Cholesterol (mmol/L)           | 4.1 (3.5–4.9)   | 4.4 (3.6-5.0) |
| Triglyceride (mmol/L)                | 0.9 (0.6–1.3)   | 1.3 (0.9–1.8)* |
| HDL Cholesterol (mmol/L)             | 1.6 (1.3–1.9)   | 1.4 (1.1–1.7)* |
| LDL Cholesterol (mmol/L)             | 2.0 (1.6–2.5)   | 2.5 (1.8–3.2)  |
| Hypertension, [n (%)]                | 0 (0)           | 20 (32)*       |
| Statins [n (%)]                      | 10 (22)         | 23 (37)        |
| ACEI/ARB [n (%)]                     | 3 (7)           | 19 (31)*       |
| Metformin [n (%)]                    | 5 (11)          | 9 (15)         |
| Microalbuminuria, [n (%)]            | 2 (4.4)         | 15 (24)*       |
| eGDR                                 | 8.9 (8.5–10.0)  | 6.1 (4.5–7.3)*|

Surprisingly, a quarter of lean individuals with T1DM had evidence of DD. A comparison between lean individuals with and without DD is summarised in Table 4. Lean individuals with DD, compared to those without, took similar total daily insulin dose, but were older, had higher HbA1c, and more microalbuminuria (Table 4).
Table 4
A comparison between lean participants (normal BMI; n = 50) with and without double diabetes. Data are presented as median and interquartile range (IQ), and as percentages for frequencies. ACEI, angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blockers; BMI: body mass index; eGDR, estimated glucose disposal rate; HbA1c: haemoglobin A1c. *p-value < 0.05.

| Selected study cohort characteristics | Double diabetes in participant with normal BMI |
|-------------------------------------|-----------------------------------------------|
|                                    | No (n = 36)                                   | Yes (n = 14)        |
| Age at clinic (years)              | 24.5 (21.0-35.8)                              | 39.0 (23.0-63.8)*  |
| Age at diagnosis (years)           | 18.0 (11.0-24.5)                              | 17.0 (11.3–51.8)   |
| Diabetes duration (years)          | 9.0 (2.0–17.0)                                | 9.5 (5.8–18.8)     |
| Female [n (%)]                     | 16 (44)                                       | 6 (43)             |
| Body weight (kg)                   | 63.4 (60.3–73.1)                              | 67.3 (59.6–75.0)   |
| BMI (kg/m²)                        | 22.6 (20.1–23.5)                              | 23.2 (22.0-24.6)   |
| HbA1c (mmol/mol)                   | 65.0 (55.0-74.8)                              | 88.5 (70.8-105.3)* |
| Total Insulin dose (units)         | 42.0 (30.6–50.3)                              | 41.5 (31.5–58.3)   |
| Insulin dose (unit/kg/day)         | 0.65 (0.47–0.77)                              | 0.68 (0.50–0.76)   |
| Total Cholesterol (mmol/L)         | 3.8 (3.4–4.9)                                 | 4.3 (3.7–5.4)      |
| Triglyceride (mmol/L)              | 0.9 (0.7–1.3)                                 | 1.3 (0.8–1.6)      |
| HDL Cholesterol (mmol/L)           | 1.6 (1.3–1.9)                                 | 1.6 (1.4-2.0)      |
| LDL Cholesterol (mmol/L)           | 2.0 (1.6–2.5)                                 | 2.2 (1.9-3.0)      |
| Hypertension, [n (%)]              | 0 (0)                                         | 4 (29)*            |
| Statins [n (%)]                    | 7 (19)                                        | 4 (29)             |
| ACEI/ARB [n (%)]                   | 2 (6)                                         | 2 (14)             |
| Metformin [n (%)]                  | 4 (11)                                        | 3 (21)             |
| Microalbuminuria, [n (%)]          | 0 (0)                                         | 5 (36)*            |
| eGDR                               | 9.0 (8.6–10.0)                                | 7.1 (5.6–7.4)*     |

Discussion

This study highlights the high prevalence of overweight and obesity in adults with T1DM. The prevalence of overweight/obesity in our study sample (53.3%, median age of 30 years) is close to the prevalence of overweight/obesity within the 25–34 year age group in the general population in England (54.0%)³. Furthermore, the proportion of adults with T1DM who had obesity in our cohort (25.7%) is similar to that reported by Conway et al. in North America (22.7%)⁷. This suggests that people with T1DM are at similar risk to obesity as the general population. This requires more attention, and highlights the need for more research to better understand the clinical consequences of overweight/obesity in T1DM and the impact of treatment strategies.

In addition, we found an association between the duration of T1DM and overweight/obesity. This is probably caused by similar factors that contribute to weight gain with increasing age, including reduced basal metabolic rate, fat free mass, and physical activity with ageing; and to hormonal changes that occur during the ageing process.¹⁵ Moreover, we also noted that people with T1DM and overweight/obesity required higher doses of insulin to achieve similar glycaemic control to those with normal BMI. As insulin treatment may promote weight gain in people with T2DM and T1DM¹⁶,¹⁷, this creates a vicious cycle in this population; where overweight/obesity will result in the need for more insulin to overcome insulin resistance, whilst injecting more insulin would promote weight gain. Subsequently, the relationship between insulin treatment and weight gain in people in T1DM is probably bi-directional, and adds further challenges to the management of diabetes in this population. Indeed, diabulimia, an eating disorder where a Participant with T1DM does not inject insulin in order to lose weight, is a serious problem in those affected with significant risk of DKA and mortality.¹⁸ Therefore, further research is needed to better understand the pathophysiology and consequences of overweight/obesity in people with T1DM⁹.¹⁹

Overall, three quarters of adults with T1DM who were at least overweight in our study had DD. This finding was even stronger in the study Participants with obesity, with all these individuals having DD. Interestingly, a quarter of lean adults with T1DM also had DD. This could be due to age, lean individuals with DD who older than lean individuals without DD, while total daily insulin dose doesn't seem to be a factor. It could also be related to other unmeasured factors, for example, waist circumference, ethnicity, family history of insulin resistance, and physical activity. Notably, large observational studies suggest that individuals with DD have a higher risk of micro-/macro-vascular complications and mortality compared to people with T1DM without insulin resistance.² Our study also showed that DD was associated with microalbuminuria, hypertension and adverse lipid profile suggesting increased CVD risk. Subsequently, overweight/obesity is an extra burden on the health of people with T1DM, and, thus, interventions aiming to prevent weight gain and/or that
promote weight loss might be beneficial in reducing the risk of diabetes complications in this population. However, there is a lack of data on interventions that are effective in promoting weight loss/weight maintenance in people with T1DM. Interventions such as very-low carbohydrate diet, glucagon-like peptide-1 (GLP-1) analogues, sodium–glucose cotransporter 2 (SGLT2) inhibitors, and bariatric surgery have been suggested by some research groups, but the evidence behind their effectiveness and safety remains limited for this population.\textsuperscript{20, 21} In that respect, our study highlights the need for more research to identify effective weight management interventions for people with T1DM.

**Study Limitations**

Certain study limitations should be acknowledged, including the cross-sectional nature of the study that does not allow to ascertain causation. Moreover, there was no available precise information on the socio-economic status of the study participants. Finally, another study limitation is that because the study involved adults attending the general diabetes clinics, Participants on insulin pump therapy were not included.

**Conclusions**

Overweight/obesity is very common in adults with T1DM, and is associated with double diabetes. BMI is positively associated with total daily insulin dose in this population. Double diabetes is associated with adverse cardiovascular risk profile and is also common in lean individuals with T1DM. Further research is needed to examine the impact of overweight/obesity in people with T1DM and whether weight loss in this population can improve diabetes-related outcomes.

**Declarations**

**Ethics approval**

The study was part of an audit assessing the diabetes service in Southmead Hospital, North Bristol NHS Trust approved by the Patient Safety, Assurance and Audit (PSAA) committee at North Bristol NHS Trust (audit number: CAB757). The need for consent was also waived by the approving committee. The reporting of the study was carried out in accordance with "STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)" guidelines on observational studies.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Competing interest**

There are no competing interests to declare

**Funding**

No funding was received to conduct this work

**Authors contribution**

NC, contributed to the study design, data collection, analysis and interpretation, and writing of manuscript; KL, contributed to the study design, interpretation of data and writing of manuscript; IK and AAT contributed to data interpretation, and writing of manuscript; HK contributed to the research idea, study design, data collection, analysis and interpretation, and writing of manuscript. All authors contributed to and authorised the final version of the manuscript.

**Acknowledgements**

Not applicable

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