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Body Mass Index's influence on arterial hypertension in Type 1 diabetes – A brief report from IMI-SOPHIA study

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ABSTRACT

Information on BMI and risk of developing hypertension in type 1 diabetes (T1D) is scarce, and it comes mostly from cross-sectional analyses. This study underscores a risk of developing hypertension in T1D individuals with high BMI, and this risk appears to be higher than in those with type 2 diabetes.

1. Introduction

Obesity is reported to have increased adverse cardiometabolic consequences in people with T1D.[1–3]However, the extent of the association between increased BMI and cardiovascular complications, especially hypertension, in T1D patients remains unclear. To address this knowledge gap, we conducted a study to estimate the risk of developing arterial hypertension in a large cohort of T1D individuals based on their BMI.

2. Methods

In a retrospective follow-up study, we included people with T1D aged over 18 at diagnosis from Tayside/Fife (Scotland, UK). We anonymously linked to The Scottish Care Information – Diabetes Collaboration database, biochemistry, demography, Scottish Morbidity Records, prescriptions, and General Registrar Office records on patient deaths. The period of follow-up for the analysis was from 1995 to 2019.

The study population inclusion criteria comprised clinician-assigned diagnosis of T1D with at least one post-diagnosis BMI measurement and at least one insulin prescription.[4] The last available BMI measurement within 3 years post-T1D diagnosis and the first measurement of HbA1c, blood pressure, and non-fasting cholesterol within 3–12 months after diagnosis were collected as the baseline data. Each patient was stratified on BMI at baseline and those with BMI < 25 Kg/m^2 (i.e., unexposed cohort) were compared to those with BMI ≥ 25 Kg/m^2 (i.e., exposed cohorts).

The clinical outcome (i.e., arterial hypertension) was incident and it was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg on at least 3 occasions and/or the use of antihypertensive medications during the follow-up.[5] Other covariates considered were age, sex, social deprivation as measured by the Scottish Index of Multiple Deprivation (SIMD), smoking history, and baseline blood pressure, HbA1c and serum cholesterol.

As a comparator, we repeated the study in an independent cohort of clinician-assigned diagnosis of type 2 diabetes (T2D) from the same population of Tayside/Fife, and who were followed-up during the same period.

2.1. Statistical analyses

Survival analyses with Kaplan-Meier and Cox proportional hazards procedures were used to accommodate varying follow-up durations among patients. Adjusted Cox models were also stratified by the year of diabetes diagnosis, and the proportional hazards assumption was tested based on Schoenfeld residuals. BMI was coded both as binary and as

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dummy variables to account for three exposure levels (normal: BMI < 25, overweight: BMI = 25–29, and obese: BMI ≥ 30 Kg/m^2) following WHO BMI cut-offs. Competing risk regression models were used to test robustness, where death was the competing event. Extended Cox models allowed for time-varying covariates. Data analysis was performed using STATA/MP® version 15.1 software, with statistical significance set at $P < 0.05$.

2.2. Statement on ethics

The study was approved by the East of Scotland Research Ethics Service- EoSRES (HIC datasets V2, REC ref. 18/ES/0126, IRAS ID 143637). All analyses were performed on anonymised datasets that are not publicly available.

3. Results

The study identified 1973 patients with T1D (42 % being female and mean age at diagnosis of 34.3 years), and 18.9 % were obese at baseline (Table 1). During a mean follow-up of 8.5 years (range 1–25 years) the Kaplan-Meier estimates revealed a lower survival probability of remaining free of hypertension over time for those overweight and obese at baseline (Fig. 1). After 15 years of follow-up, this probability was 47 % for those with overweight and 35 % for those obese, compared to 61 % for those with normal BMI. Adjusted Cox models, with a time at risk of 9905 person-years and 465 clinical outcomes, showed that overweight patients had an increased hazard ratio (HR) for developing hypertension (HR = 1.66, 95%CI 1.12–2.45) which nearly doubled in obese patients (HR = 3.18, 95%CI 1.93–5.24). Competing risk regression models showed similar results (HR = 1.35, 95%CI 1.03–1.76 for overweight and HR = 2.98, 95%CI 2.17–4.10 for obese). Considering BMI as a time-varying covariate in an extended Cox model yielded a baseline HR of 1.20 (95%CI 1.09–1.32), showing that for every increased unit (i.e., 1 Kg/m^2) of BMI the risk of developing arterial hypertension increased by 20 %.

Survival analyses of T2D cohort included 10,252 people (42 % female and a mean age at diagnosis of 58 years) with a mean follow-up of 4.4 years that showed an increased risk of developing hypertension for overweight (HR = 1.24, 95%CI 1.12–1.38) and obese subgroups (HR = 1.53, 95%CI 1.39–1.68). After 15 years of follow-up, the probability of remaining free of hypertension was 26 % for those with overweight and 23 % for those obese, compared to 35 % for those with normal BMI. Therefore, over time, this probability was closer among the BMI subgroups in this cohort, compared to the T1D cohort (Fig. 2).

Table 1
Description of patients at diagnosis of Type 1 Diabetes by exposure status (normal, overweight, or obese). Baseline data (n = 1973).

Characteristic	Normal (n = 953)	Overweight (n = 646)	Obese (n = 374)	P
N (%)				
Sex – female	406 (42.6)	237 (36.7)	184 (49.2)	<0.001
Arterial hypertension	85 (8.9)	98 (15.2)	98 (26.2)	<0.001
Smoking	626 (66.8)	398 (62.4)	218 (58.8)	<0.05
SIMD				
1 most deprived	198 (22.3)	113 (18.7)	73 (20.9)	
2	169 (19.0)	120 (19.9)	77 (22.1)	
3	175 (19.7)	119 (19.7)	71 (20.3)	
4	215 (24.2)	145 (24.1)	84 (24.1)	
5 least deprived	132 (14.9)	106 (17.6)	44 (12.6)	=0.515
Mean (SD)				
Age at diagnosis (years)	32.2 (12.6)	36.0 (31.1)	36.9 (13.9)	=0.078
BMI (kg/m^2)	22.0 (2.1)	27.1 (1.4)	34.1 (4.3)	<0.001
Systolic Blood Pressure (mmHg)	122.0 (15.4)	126.7 (15.8)	131.5 (15.6)	<0.001
Diastolic Blood Pressure (mmHg)	73.8 (10.4)	76.9 (10.3)	80.4 (11.3)	=0.111
HbA1c (mmol/mol)	66, 8.2 % (2.3)	62, 7.8 % (1.9)	62, 7.8 % (2.1)	<0.05
Median (IQR)				
Serum Cholesterol (mml/L)*	4.6 (3.9–5.4)	4.8 (4.1–5.8)	5.0 (4.2–6.1)	<0.001
Serum HDL-cholesterol (mml/L)*	1.4 (1.1–1.7)	1.3 (1.1–1.5)	1.2 (1.0–1.4)	<0.001

BMI=Body mass index. IQR = Interquartile range. SD = standard deviation. SIMD = Scottish Index of Multiple Deprivation. Average age at diagnosis = 34.3 (±13.2) years. (*) Sample size: serum total cholesterol n = 1123, serum HDL-cholesterol n = 1097. Smoking refers to any time during follow-up.

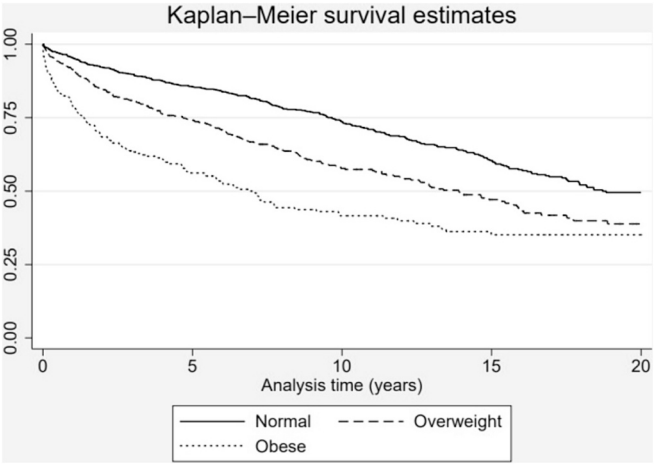

Fig. 1. Probability of remaining free of arterial hypertension for people with Type 1 diabetes by Body Mass Index at diabetes diagnosis (normal, overweight, or obese) over 20 years of follow-up.

4. Discussion

This study demonstrates that excess weight heightens the risk of hypertension in T1D patients. Given T1D's association with higher CVD rates and related fatalities,[6] effective blood pressure control becomes paramount in this patient group.

Information on BMI and risk of developing hypertension in T1D is scarce, and it comes mostly from cross-sectional analyses. Our findings align with available cohort studies,[5,7] that examined the effects of intensive insulin therapy in the development of hypertension and reported a HR = 1.11 associated with covariate BMI in relation to

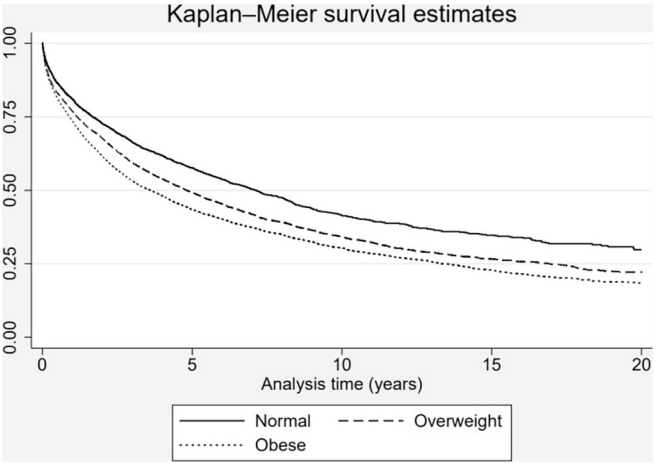

Fig. 2. Probability of remaining free of arterial hypertension for people with Type 2 diabetes by Body Mass Index at diabetes diagnosis (normal, overweight, or obese) over 20 years of follow-up.

hypertension.[5]

We acknowledge certain limitations in our study. BMI was evaluated at baseline and weight fluctuations in T1D patients due to medications were not fully accounted for. We did not consider other autoimmune diseases associated with hypertension (i.e., Graves' disease), and even though our entire study T1D cohort was normotensive at baseline (i.e., any patient with hypertension was excluded), we cannot completely rule out some potential impact in our results because these diseases were not recorded throughout the follow-up. Although we did not include a non-diabetic comparator group as our data were limited to those with diabetes, we included a comparator cohort of T2D. The risk of hypertension appears to be higher for T1D than for T2D, and for the general population. Kivimaki et al. found that obese individuals in the general UK population had a HR = 1.98 (95 % CI 1.77–2.21) for developing hypertension during a mean follow-up of 11.8 years.[8] The results of our study provide support for the potential use of GLP-1 agonists that show promise in individuals with obesity and Type 1 diabetes by aiding in weight management.[9]

In conclusion, the results of the present study underscore a significant risk of developing hypertension in T1D patients with high BMI. Furthermore, the impact of BMI in developing hypertension is much stronger in T1D than other groups. To implement weight management effectively in clinical practice, further prospective studies assessing the safety and efficacy of weight loss in T1D patients are warranted.

CRediT authorship contribution statement

Laurence D. Petty: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Enrique Soto-Pedre:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rory J. McCrimmon:** Writing – review & editing, Validation, Methodology. **Ewan R. Pearson:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no potential conflict of interest relevant to this article.

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References

1. Polsky S, Ellis SL. Obesity, insulin resistance, and type 1 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes*. 2015;22:277–282.
2. De Block CE, De Leeuw IH, Van Gaal LF. Impact of overweight on chronic microvascular complications in type 1 diabetic patients. *Diabetes Care*. 2005;28:1649–1655.
3. Karamanakos G, Kokkinos A, Dalamaga M, Liatis S. Highlighting the role of obesity and insulin resistance in type 1 diabetes and its associated cardiometabolic complications. *Curr Obes Rep*. 2022;11:180–202.
4. McGurnaghan SJ, McKeigue PM, Read SH, et al. Development and validation of a cardiovascular risk prediction model in type 1 diabetes. *Diabetologia*. 2021;64:2001–2011.
5. de Boer IH, Kestenbaum B, Rue TC, et al. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. *Arch Intern Med*. 2008;168:1867–1873.
6. Livingstone SJ, Looker HC, Hothersall EJ, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. *PLoS Med*. 2012;9, e1001321.
7. Purnell JQ, Hokanson JE, Marcovina SM, Steffes MW, Cleary PA, Brunzell JD. Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. Diabetes Control and Complications Trial. *Jama*. 1998;280:140–146.
8. Kivimäki M, Strandberg T, Pentti J, et al. Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study. *Lancet Diabetes Endocrinol*. 2022;10:253–263.
9. Popoviciu MS, Păduraru L, Yahya G, Metwally K, Cavalu S. Emerging role of GLP-1 agonists in obesity: a comprehensive review of randomised controlled trials. *Int J Mol Sci*. 2023;24.