Metabolic health and vascular complications in type 1 diabetes

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ABSTRACT

Aims: Optimal glycaemic control benefits risk of microvascular and macrovascular complications in type 1 diabetes (T1DM) but the importance of other components of metabolic health is less certain, particularly in the context of routine clinical practice.

Methods: Data for this cross-sectional analysis derived from a database covering inner North West London adult diabetes clinics. People with T1DM and with complete information for height, weight, blood pressure and serum high and low-density lipoprotein cholesterol (HDL-c and LDL-c) and triglyceride concentration measurements were included.

Results: Among the 920 participants, those with complications were older and had longer duration of diabetes but had similar HbA1c to people without complications. Systolic hypertension and low HDL-c were independently associated with complications. From having 0 risk factors, the prevalence of micro and macrovascular disease increased with increasing number of risk factors. Relative to those with ≥1 risk factor, those with 0 risk factors (n = 179) were at lower risk of retinopathy (OR 0.6 (0.4–0.9), *p* = 0.01) and nephropathy [OR 0.1 (0.04–0.3), *p* = 0.002], independent of individual characteristics.

Conclusions: In routine clinical management of T1DM, associations between lipid and blood pressure risk factors and prevalent micro and macrovascular disease remain, implying that more intensive risk factor management may be beneficial.

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1. Introduction

Type 1 diabetes mellitus (T1DM) is associated with microvascular and macrovascular complications. Among microvascular diseases, retinopathy is seen in 82–100% of people with T1DM,[1,2] and is a major cause of blindness.[2] Nephropathy, occurring in 20–40%, is a major cause of kidney disease[3] and neuropathy, in 23–29%, is implicated in most non-traumatic amputations.[4] Adults with T1DM are also at increased risk of macrovascular disease, including ischaemic heart disease (IHD), cerebrovascular accident (CVA) and peripheral vascular disease (PVD), with risks 10 times those of people without diabetes.[5]

There is abundant evidence that hyperglycaemia is important in micro and macrovascular complications of T1DM[6,7] and current guidelines have incorporated intensive glycaemic control into practice.[8] However, despite this, risk of complications remains significant, suggesting other factors may have a role.[9] Dyslipidaemia, an established risk factor for atherosclerotic disease in the general population and in type 2 diabetes, predicts worse cardiovascular outcomes and neuropathy in T1DM.[10,11] Increased adiposity may also be important[12,13] and hypertension has been linked to increased risk of mortality and end-stage complications.[14,15]

Both longitudinal studies and intervention trials have confirmed the relationship between risk factors and vascular disease in T1DM and risk factor management has become a well-established aspect of T1DM management. Successful risk factor management would be expected to eliminate or diminish associations between risk factors and prevalent vascular disease in T1DM but the extent to which this is the case in clinical practice requires investigation. We have, therefore, evaluated in cross-sectional data from an active clinical database, associations between glycaemia, adiposity, blood pressure and lipid risk factors and prevalent micro- and macrovascular disease in people with T1DM. For those risk factors for which management has been successful, we would expect only weak or non-existent associations between the risk

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factor and micro and macrovascular disease. On the other hand, where there are still opportunities for improved management we would expect marked associations to remain, with risk increasing according to increasing number of risk factor abnormalities.

2. Materials and methods

2.1. Study design

We undertook a cross sectional analysis based on clinic record information of risk factor status and the prevalence of microvascular and macrovascular disease in people with a clinician assigned diagnosis of T1DM. Participants were attending the adult diabetes outpatient clinics held at the Charing Cross Hospital and Hammersmith Hospital, covering areas of inner North West London, UK. Ethics committee approval was not sought for this study as the data were anonymised and assembled as clinical audit information.

2.2. Data collection

Data analysed in the present study had initially been entered on a dedicated clinical database implemented to support ongoing clinical audit. Data was recorded at each patient visit, either by a consultant diabetologist or specialist doctor in training under supervision, and included: date of birth, gender, ethnicity, type of diabetes, date of diagnosis, smoking and exercise status, alcohol consumption, family history, blood pressure, height and weight, and laboratory measurements of lipid profile, serum creatinine and glycated haemoglobin (HbA1c). Urine albumin: creatinine ratio was recorded only in 52% of participants and was not analysed as a risk factor in the present analysis. Clinical information including current medications, clinical examination findings and history of any medical problems including microvascular and macrovascular complications was recovered from the database as free text strings for subsequent classification.

Non-fasting blood samples were taken for routine laboratory measurement of serum triglycerides, HbA1c, serum creatinine and total, high- and low-density lipoprotein cholesterol (HDL-c and LDL-c) within 4 weeks of patient's appointment. On the day of the clinic visit, a clinic nurse measured height and weight and blood pressure using a standard sphygmomanometer in each attendee.

Based on clinical history, clinical notes and physical examination, diagnoses of complications were updated by attending clinicians at successive patient visits. Clinical history, annual eye screening assessment, monofilament and ankle reflex test, repeated abnormal urine albumin: creatinine ratio in those in whom it was measured and examination of peripheral arterial pulses all contributed to the diagnosis the clinicians recorded.

2.3. Data retrieval and organisation

Anonymised data were exported from the database and transcribed for subsequent analysis. Data validity was assessed by double-checking any uncharacteristic value against clinical records. People with T1DM who attended the clinic between 2003 (when data entry began), and 2016 were selected and data recorded at their most recent visit were selected for analysis. Only those with complete data for the risk factors: blood pressure, adiposity (based on height and weight), triglycerides, HDL-c and LDL-c were included.

BMI was calculated as weight/height^2 (kg/m^2). HbA1c measurements were recorded according to International Federation of Clinical Chemistry units (IFCC mmol/mol), or as DCCT- aligned percentage, which were converted to IFCC units for analysis. Exercise was categorised as: no exercise, mild exercise if patients reported being 'active' or 'walking' and moderate exercise if they described a regular exercise regime. Smoking, alcohol consumption, ethnicity and family history

were also categorised. Medications were reviewed and categorised as blood pressure, triglyceride or cholesterol-lowering medication.

2.4. Classification of complications

Using database records, complications were classed as 'present' or 'absent', based on any history of retinopathy, nephropathy, neuropathy or macrovascular disease. Each participant could, therefore, be represented in more than one vascular disease category. A diagnosis of retinopathy was subject to standardised, in-clinic grading and retinopathy was recorded as present if any history of retinopathy had been recorded, including background retinopathy, maculopathy, pre-proliferative, non-proliferative and proliferative retinopathy. Nephropathy was scored positive for evidence of microalbuminuria and proteinuria on repeat samples, chronic renal failure, renal impairment, end stage renal failure, haemodialysis or renal transplant. Neuropathy included any documented history of both peripheral and autonomic neuropathies, or clinical examination findings consistent with neuropathy. Patients with documented neuropathic pain, Charcot neuroarthropathy and diabetic cystopathy were also recorded positive for neuropathy.

Macrovascular disease was categorised as ischaemic heart disease (IHD: myocardial infarction, angina, or coronary revascularisation procedures), cerebrovascular accident (CVA: any history of stroke or transient ischaemic attack) or peripheral vascular disease (PVD: any history of intermittent claudication or amputation). Since prevalence of macrovascular disease was found to be low, these complications were combined for analysis into a single category of 'macrovascular complications'.

2.5. Risk factor definitions

As our analysis was oriented towards risk evaluation in clinical practice, we assigned cut-offs to each risk factor included in the analysis, above which an individual would, typically, be considered to have a risk factor abnormality. Risk factor cut-offs were assigned with reference to National Institute for Clinical Excellence (NICE) guidelines specific to patients with T1DM,[8] American Diabetes Association's (ADA) guidelines[17] and previously published criteria for the metabolic syndrome.[18–20] Additionally, a literature review evaluating the variables in metabolic health and the associations between metabolic health indices and micro and macrovascular disease in patients with T1DM was undertaken.[10,13,21] Based on our review, the following cut-offs were adopted for this analysis: BMI ≥ 30 kg/m^2; systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or use of blood pressure-lowering medication; triglycerides ≥ 1.7 mmol/L or use of fibrates; and, given that T1DM may compromise the advantage of high HDL-c concentration in women,[31] an HDL-c cut-off of ≪1.03 mmol/L was applied to both women and men. Although LDL-c measures were available, it was decided not to consider these in the present analysis as the NICE guideline recommends the use of statin to people with T1DM and that a statin be positively offered in T1DM over the age of 40 or with diabetes duration over 10 years, established nephropathy or other cardiovascular risk factors.[8] Therefore, whilst LDL-c levels will be significantly affected, prescription of statin may not be based on lipid level and could not be taken as an indication of an abnormal LDL-c level. For this analysis, waist circumference information was not available and glucose concentration was not included as all individuals had diabetes diagnosed and HbA1c measurements.

In addition to individual risk factors we also considered an inclusive index of 'metabolic health' quantified according to the number of risk factor abnormalities present. Previous studies of metabolic health in other contexts (primarily obesity) have allowed for the presence of 2[22], 1[23] or 0[24] metabolic risk factors in those classified as metabolically healthy. In the present analysis, we have evaluated risks of microvascular and macrovascular disease associated with having 1, 2, 3, or 4 risk factors relative to having 0 risk factors.

2.6. Statistical analysis

Statistical analysis was carried out using StataCorp. 2013 (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). As the majority of the variables were not normally distributed, median and inter-quartile range (IQR) were used to summarise continuous variables and between-group significances were tested using Mann Whitney U test. Variation in categorical variables was tested using Chi-square test. Proportions test was used to compare prevalence of vascular disease between groups. The odds ratio for a risk factor being associated with vascular disease was assessed in univariate logistic regression analyses. Independent associations, with adjustments for age and duration of diabetes and other demographic characteristics were explored in multivariable logistic regression analysis. Undue collinearity between age and duration of diabetes was excluded if the variance inflation factor on linear regression modelling was below 10. A significance level of $p \ll 0.05$ was adopted with no correction for multiple testing, choice of variables in each statistical test undertaken being strongly weighted by existing evidence, thus rendering the universal null hypothesis inapplicable.[32]

3. Results

3.1. Participant characteristics and their associations with micro and macrovascular complications

The database from which data for analysis were extracted comprised records for 1200 people with T1DM. Of these, 280 had incomplete information and were excluded from the analysis. Those excluded were significantly younger than the 920 included (median (IQR) age 33.9 (26.7–45.9) vs 43.8 (32.6–56.8) years, $p \ll 0.001$), had a shorter duration of diabetes (12.3 (4.4–21.4) vs 21.6 (11.4–33.5) years, $p \ll 0.001$), had a stronger family history of diabetes (T1DM 48 vs 26%; T2DM 29 vs 6%, $p \ll 0.001$) and had markedly fewer clinic appointment records (mean 3.4 vs 11.5). The age range among the 920 included in our analysis was 17.4–89.5 and median duration of T1DM was 28.5 years (range 0.3–63.8). Women comprised 49% and White European people 80%; 62% had never smoked, 19% were ex-smokers; 20% took no exercise; 51% were taking a statin and 43% took blood pressure-lowering medication. The absolute prevalence of retinopathy was 39%, nephropathy 17% and neuropathy 10%. Among those diagnosed with nephropathy, 43% had microalbuminuria, 13% had a renal transplant, 5% were on haemodialysis and the remainder had intermediate disease. One-hundred and four patients (11%) had one or more macrovascular complication with 70 having IHD, 43 PVD and 14 CVA. Seventeen percent of those included in the analysis were obese, 74% had hypertension or were taking blood-pressure-lowering medication, 16% had hypertriglyceridemia or were taking a fibrate and 11% had low HDL-c.

People with microvascular or macrovascular complications were generally older and had longer duration of diabetes than those without complications (Table 1). HbA1c tended to be higher among those with nephropathy or neuropathy. Gender did not differ according to presence of complications. Proportions of ex- but not current smokers were higher among those with complications. Non-drinkers and those taking no exercise were more highly represented among those with nephropathy, neuropathy and macrovascular disease. Family history of T1D was more highly represented among those with retinopathy. BMI was higher in those with macrovascular disease, as were blood pressure, triglycerides and use of blood pressure medication and statins; HDL-c was lower. Blood pressure was also higher among those with retinopathy and nephropathy, triglycerides were higher among those with nephropathy and neuropathy and use of blood pressure-medications and statins was higher among those with retinopathy, nephropathy and neuropathy. In accord with increased use of statins, LDL-c was generally lower among those with both micro and macrovascular disease.

3.2. Participant characteristics and risk factor abnormality associations with micro and macrovascular complications

Individual characteristics significantly associated with complications were identified in univariable logistic regression analysis. Both micro and macrovascular complications showed no associations with HbA1c. Retinopathy was associated with age, duration of diabetes, ex-smoking, no exercise and family history of type 1 diabetes; nephropathy with age, duration of diabetes, ex-smoking, no alcohol, no exercise, African ethnicity, and family history of type 1 diabetes; neuropathy with age, duration of diabetes, ex-smoking, no alcohol, no exercise; and macrovascular disease with age, duration of diabetes, ex-smoking, no alcohol, no exercise.

In bivariable analysis with age and duration of diabetes as independent variables, logistic regression identified duration of diabetes as independently associated with retinopathy and nephropathy (both $p \ll 0.001$, there being no independent association with age ($p \gg 0.05$). However, neuropathy was independently associated with both age ($p \ll 0.001$) and duration of diabetes ($p = 0.01$) as was macrovascular disease (both age and duration of diabetes $p \ll 0.001$). Linear regression analysis confirmed no undue co-linearity between age and duration of diabetes in these associations, the variance inflation factor remaining below 2 for all models.

Univariable associations between complications and risk factors were explored with the risk factors expressed as continuous (BMI, systolic blood pressure, and serum triglyceride and HDL-c concentrations) variables and as categorical variables, with categorisation as described above, in 'Section 2.5 Risk factor definitions'. Significant associations differed hardly at all whether continuous or categorical variables were entered in the model. The only exception was for nephropathy and triglycerides, for which there was a significant association if triglycerides were entered as a log-transformed continuous variable ($p = 0.004$) and no significant association for triglycerides as a continuous ($p = 0.2$) or categorical variable ($p = 0.1$). Further analyses were undertaken with the clinically familiar risk factor categorisations.

Independent associations between micro and macrovascular complications and risk factors were explored in multivariable logistic regression models for each risk factor with those individual characteristics identified as significantly associated with each complication in univariable logistic regression included as potential confounders (Table 2).

3.3. Numbers of risk factor abnormalities and micro and macrovascular complications

There were 179 patients with 0 risk factors, 478 had 1 risk factor, 193 had 2, 56 had 3 and 14 had all 4 risk factors present. The prevalence of micro- and macrovascular disease increased with increasing number of risk factors present (Fig. 1).

Comparison of proportions showed that for each category of micro and macrovascular disease, there was a significantly higher proportion of cases among those with 1 risk factor than those with none (all $p \ll 0.001$) and this was confirmed in logistic regression analysis, with odds ratios for each number of risk factor abnormalities expressed relative to those with no risk factor abnormalities (Table 3).

Since risk of having a complication increased significantly with the presence of a single risk factor abnormality, participants were distinguished as metabolically healthy if they had no abnormal risk factors and metabolically unhealthy if they had one or more risk factor abnormalities. Compared with people with T1DM with ≥1 risk factor, those with 0 risk factors were younger, had shorter duration of diabetes and a lower serum creatinine concentration, a lower proportion of men and of statin use and a higher proportion taking exercise (Supplementary Table 1). HbA1c, total cholesterol, family history, ethnicity distribution and patient's smoking and alcohol habit did not differ.

Table 1

Characteristics of patients with or without each complication. Data are expressed as median (IQR) for continuous variable and % (n) for categorical variables.

	Retinopathy		Nephropathy		Neuropathy		Macrovascular event	
	Absent (n = 559)	Present n = 361	Absent (n = 768)	Present (n = 152)	Absent (n = 830)	Present (n = 90)	Absent (n = 816)	Present (n = 104)
Age (yr)	38.7 (30.0–53.5)	50.9$^{\ll0.001}$ (39.9–60.0)	42.4 (32.0–55.8)	51.2$^{\ll0.001}$ (40.2–62.6)	42.6 (32.0–55.5)	54.8$^{\ll0.001}$ (44.4–64.3)	41.1 (31.6–54.2)	60.0$^{\ll0.001}$ (51.7–70.9)
Duration of T1DM (yr)	15.0 (7.35–25.5)	30.7$^{\ll0.001}$ (21.9–41.4)	19.3 (9.75–31.0)	31.0$^{\ll0.001}$ (21.9–41.7)	20.5 (10.8–31.9)	30.7$^{\ll0.001}$ (20.4–41.4)	19.7 (10.8–30.8)	37.8$^{\ll0.001}$ (24.9–47.5)
HbA1C (mmol/mol [%])	64 (55–74) [8.0 (7.2–8.9)]	65 (56–74)$^{0.3}$ [8.1(7.3–8.9)]	64 (55–74) [8.0(7.2–8.9)]	67 (57–77)$^{0.06}$ [8.2(7.4–9.2)]	64 (55–74) [8.0 (7.2–8.9)]	67 (59–78)$^{0.01}$ [8.3 (7.5–9.3)]	65 (55–75) [8.1 (7.2–9.0)]	65 (57–73)$^{0.9}$ [8.1 (7.4–8.8)]
Male	51 (286)	49 (178)$^{0.5}$	52 (395)	46 (69)$^{0.1}$	52 (425)	44 (39)$^{0.1}$	49 (403)	59 (61)$^{0.06}$
Never smoked	62 (343)	55 (198)	61 (463)	51 (78)	61 (500)	46 (41)	61 (492)	47 (49)
Ex-smoker	19 (107)	25 (91)$^{0.02}$	20 (150)	32 (48)$^{0.002}$	21 (169)	32 (29)$^{0.004}$	21 (166)	31 (32)$^{0.006}$
Non-drinker	22 (119)	25 (85)$^{0.6}$	21 (155)	33 (49)$^{0.001}$	22 (172)	37 (31)$^{0.005}$	22 (171)	33 (33)$^{0.05}$
No exercise	17 (94)	23 (80)$^{0.1}$	17 (126)	32 (48)$^{\ll0.001}$	18 (144)	35 (30)$^{\ll0.001}$	17 (135)	39 (39)$^{\ll0.001}$
Family history								
T1DM	24 (136)	30 (110)$^{0.03}$	26 (196)	33 (50)$^{0.1}$	27 (228)	20 (18)$^{0.2}$	27 (219)	26 (27)$^{0.2}$
T2DM	8 (44)	4 (15)	6 (49)	7 (10)	7 (56)	3 (3)	7 (55)	4 (4)
Both	2 (11)	1 (5)	2 (12)	3 (4)	2 (14)	2 (2)	1 (12)	4 (4)
Ethnicity								
White	78 (437)	82 (295)$^{0.4}$	81 (620)	74 (112)$^{0.03}$	79 (657)	83 (75)$^{0.2}$	79 (645)	84 (87)$^{0.3}$
African	8 (44)	6 (21)	6 (47)	12 (18)	7 (57)	9 (8)	7 (57)	8 (8)
Asian/Indian	6 (34)	6 (23)	6 (44)	9 (13)	6 (52)	6 (5)	6(51)	6 (6)
BMI (kg·m^{-2})	25.3 (22.6–28)	25.5$^{0.1}$ (23–28.7)	25.3 (22.7–28.1)	25.9$^{0.06}$ (23.2–29.1)	25.4 (22.8–28.1)	25.4$^{0.9}$ (22.9–29)	25.2 (22.9–28)	26.8$^{0.02}$ (22.6–29.9)
Systolic BP (mmHg)	129 (118–139)	133$^{\ll0.001}$ (124–143)	130 (120–140)	137$^{\ll0.01}$ (125–151)	130 (120–141)	132$^{0.1}$ (122–147)	130 (120–140)	136$^{0.002}$ (125–148)
Diastolic BP (mmHg)	75 (69–83)	74 (68–80)$^{0.03}$	75 (69–82)	75$^{0.6}$ (69–82)	75 (69–81)	75$^{0.9}$ (69–83)	75 (69–82)	71$^{0.01}$ (65–80)
Triglycerides (mmol/L)	0.94 (0.69–1.40)	0.9$^{0.1}$ (0.67–1.33)	0.9 (0.68–1.35)	1.03$^{0.004}$ (0.74–1.49)	0.91 (0.68–1.36)	1.02$^{0.03}$ (0.74–1.62)	0.9 (0.68–1.35)	1.12$^{0.001}$ (0.78–1.66)
LDL chol (mmol/L)	2.5 (2.0–3.0)	2.4$^{0.06}$ (2.0–3.0)	2.5 (2.0–3.0)	2.3$^{0.01}$ (1.8–2.9)	2.5 (2.0–3.0)	2.3$^{0.1}$ (1.8–3.0)	2.5 (2.0–3.1)	2.1$^{\ll0.001}$ (1.6–2.6)
HDL chol (mmol/L)	1.45 (1.2–1.76)	1.47$^{0.6}$ (1.21–1.76)	1.47 (1.21–1.77)	1.43$^{0.05}$ (1.16–1.71)	1.47 (1.21–1.76)	1.47$^{0.9}$ (1.2–1.8)	1.47 (1.22–1.78)	1.32$^{\ll0.001}$ (1.05–1.65)
Anti-hypertensives	30 (170)	62 (223)$^{\ll0.001}$	35 (266)	84 (127)$^{\ll0.001}$	40 (333)	67 (60)$^{\ll0.001}$	37 (303)	87 (90)$^{\ll0.001}$
Fibrates	0.5 (3)	1.1 (4)$^{0.3}$	0.7 (6)	0.7 (1)$^{0.8}$	0.7 (6)	1.1 (1)$^{0.6}$	0.6 (5)	1.9 (2)$^{0.1}$
Statins	39 (220)	69 (250)$^{\ll0.001}$	46 (355)	76 (115)$^{\ll0.001}$	49 (404)	73 (66)$^{\ll0.001}$	46 (374)	92 (96)$^{\ll0.001}$

Significances are for comparison between complications present and absent, derived by Mann-Whitney test for continuous variables and by chi square test for categorical variables, are shown in superscript adjacent to summary statistics for the complications present group.

The odds ratios for having a microvascular or macrovascular complication in people categorised as metabolically healthy relative to people categorised metabolically unhealthy were significantly lower for all complications: retinopathy ($p \le 0.001$–0.001). These associations were independent of gender, serum creatinine and exercise. With age and duration of diabetes entered as covariates, the odds ratios (95%CI) were: retinopathy 0.59 (0.39–0.91), $p = 0.01$; nephropathy 0.12 (0.04–0.32), $p \ll 0.001$; neuropathy 0.35 (0.14–0.90), $p = 0.03$; macrovascular disease 0.38 (0.13–1.11), 0.06.

4. Discussion

In the cross-section of clinic attendees with T1DM we studied, significant independent associations were apparent between micro and macrovascular complications and hypertension, low HDL-c and the number of risk factor abnormalities present in an individual. These observations draw attention to the continuing need for improvements in the risk factor profile in people with T1DM. Interestingly, glycaemia, assessed by HbA1c concentrations, showed no associations with complications. The median level of HbA1c in our study group was 65 mmol/mol, which is somewhat higher than recommended targets. Nevertheless, the contrast between the lack of association between complications and HbA1c and the strong associations apparent for hypertension, low HDL-c and number of risk factors does suggest that a greater focus on the management of risk factors other than glycaemia, especially blood pressure and lipids, might be beneficial. The absence of a relationship between HbA1c and diabetes-specific complications in our analysis is at odds with well-established data and reflects the

Table 2

Multiple logistic regression odds ratios for independent associations between micro and macrovascular complications and risk factors. Individual characteristics significantly associated with complications in univariable logistic regression were included as potential confounding variables.

	Obesity	Hypertension	Hypertriglyceridemia (TG ≥ 1.70)	Low HDL-c
Retinopathy	1.22 (0.81–1.86)$^{0.3}$	1.87 (1.24–2.80)$^{0.003}$	0.89 (0.58–1.37)$^{0.5}$	0.91 (0.55–1.53)$^{0.7}$
Nephropathy	1.17 (0.72–1.91)$^{0.5}$	5.88 (2.63–13.1)$^{\ll0.001}$	1.24 (0.76–2.05)$^{0.3}$	2.24 (1.31–3.83)$^{0.003}$
Neuropathy	0.81 (0.43–1.53)$^{0.5}$	2.02 (0.92–4.43)$^{0.07}$	1.47 (0.83–2.46)$^{0.1}$	1.29 (0.66–2.52)$^{0.4}$
Macrovascular disease	1.20 (0.67–2.19)$^{0.5}$	2.82 (1.05–7.56)$^{0.03}$	1.64 (0.91–2.95)$^{0.09}$	2.71 (1.44–5.10)$^{0.002}$

Retinopathy was independently associated with hypertension ($p = 0.003$, nephropathy with hypertension ($p \ll 0.001$) and low HDL-c ($p = 0.003$), neuropathy with hypertension at borderline significance ($p = 0.07$) and macrovascular disease with hypertension ($p = 0.03$), hypertriglyceridemia at borderline significance ($p = 0.09$) and low HDL-c ($p = 0.002$).
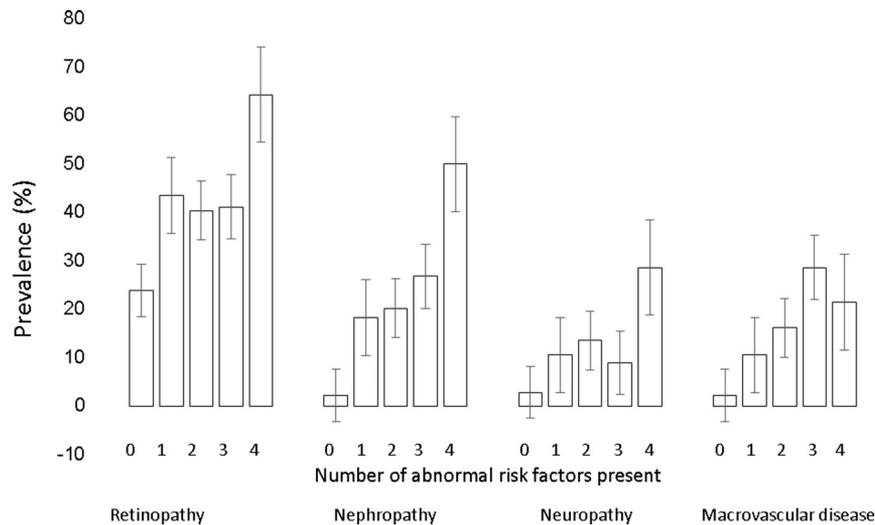
Fig. 1. Prevalence of microvascular and macrovascular complications with increasing number of risk factors. Prevalence shown in percentage out of number of people in the risk factor number group with error bars representing SEM.

relative contribution of risk factors to micro- and macrovascular disease in a clinic population with HbA1c values close to target. It does not necessarily suggest that HbA1c is not an important risk factor but emphasises that, where HbA1c is addressed, blood pressure emerges as the dominant risk factor.

With regard to individual risk factor abnormalities, we found elevated blood pressure to be consistently associated with all complications and low HDL-c with neuropathy and macrovascular disease (despite HDL-C being generally higher in people with T1DM), but elevated BMI and triglycerides showed no independent associations. In accord with our findings, previous cross-sectional studies have shown increased blood pressure but not BMI to be independently related to retinopathy and neuropathy[13] and blood pressure and low HDL-c to CHD.[10] There has, nevertheless, been evidence for the importance of BMI in neuropathy[11] and retinopathy.[12] A prospective analysis from the Diabetes Control and Complication Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study confirmed blood pressure as important for macrovascular disease and also noted that BMI was not a strong risk factor in people with T1DM but, in contrast to our findings, triglycerides was positively associated with macrovascular disease.[15] Also in longitudinal analysis, the Joslin Medallists (people with T1DM for 50 years with markedly slow progression of microvascular complications) had high HDL-c, low blood pressure and low triglycerides.[25,26] Increased exercise was another factor suggested to play a role in protecting the Medallists from complications, which accords with our observations of a significant negative

association between increased exercise and presence of macrovascular complications.

Our result showed a general pattern of increasing prevalence of complications with increasing number of risk factors, similar to a smaller analysis ($n = 91$) of metabolic syndrome and microvascular complications.[16] We observed that the prevalence of complications could be relatively high among those with 4 risk factors but, with small group sizes, this was only significant for neuropathy. Although BMI showed no independent effect on risk of complications, increased adiposity can promote the emergence of the other risk factors we evaluated. Its underlying mechanistic influences could then have been expressed in other risk factor disturbances and it should not be concluded that increased BMI is not important. Importantly, 19% of people with T1DM, were metabolically healthy, with levels of BMI, blood pressure, triglycerides and HDL-c risk factors below the cut-offs for normality we used and their risks of prevalent microvascular diseases, especially retinopathy and nephropathy, were reduced relative to those with one or more risk factors.

It is also noteworthy that despite, on average, ≫20 years of diabetes in our sample, the prevalence of microvascular complications was appreciably lower than reported in previous studies: retinopathy in 32% of our participants compared with 82–100% previously reported[1,2]; neuropathy in 10% compared with 23–29%[4]; and nephropathy in 17% compared with 20–40%,[3] despite inclusion of all severities of retinopathy and both autonomic and peripheral neuropathy. Given that the prevalence of complications showed no significant variation according to HbA1c, we might speculate that gains to be made by optimising glycaemic control were fully expressed in our sample, with the remaining variation in risk of micro and macrovascular disease being that associated with other risk factors.

We are not aware of any studies that have explored micro and macrovascular risks in T1DM patients according to successive numbers of risk factors. However, multiple studies have categorised T1DM according to presence or absence of metabolic syndrome, whether defined by WHO, IDF or NCEP-ATPIII criteria.[27,28] Most studies found an increased risk of macrovascular complications in groups with metabolic syndrome and there is evidence for increased risk of nephropathy and neuropathy.[27,28] Discrepancies with our findings could be due to metabolic syndrome criteria allowing for participants, considered free of metabolic syndrome, to have one risk factor, while we restricted 'metabolically healthy' status to those with 0 risk factors.

Complications were clinician-diagnosed in our study, therefore offering potentially more reliable information compared to self-

Table 3

Odds ratio and 95% confidence intervals for the presence of each complication according to increasing number of risk factor in logistic regression analysis. Significances are shown in superscript.

n risk factors	Retinopathy (n = 361)	Nephropathy (n = 152)	Neuropathy (n = 90)	Macrovascular (n = 104)
0	1	1	1	1
1 (n = 179)	5.1 (1.8–14.4)$^{0.002}$	2.4 (1.6–3.6)$^{<0.001}$	9.7 (3.5–26.9)$^{<0.001}$	4.1 (1.6–10.4)$^{0.003}$
2 (n = 478)	8.4 (2.9–24.2)$^{<0.001}$	2.1 (1.4–3.6)$^{0.001}$	11.1 (3.9–31.7)$^{<0.001}$	5.4 (2.0–14.4)$^{0.001}$
3 (n = 193)	17.5 (5.6–55.2)$^{<0.001}$	2.2 (1.2–4.2)$^{0.01}$	16.0 (5.0–50.8)$^{<0.001}$	3.4 (1.0–12.2)$^{0.06}$
4 (n = 56)	13.9 (3.2–60.0)$^{<0.001}$	5.7 (1.8–17.9)$^{0.003}$	43.7 (10.3–185)$^{<0.001}$	11.9 (2.4–60.1)$^{0.003}$

administered questionnaires used in some studies.[26,29] Moreover, our sample was selected from a clinical database, which includes everyone attending a large diabetes clinic in the West London area and is, therefore, representative of an extensive population group.

Limitations of our study include its cross-sectional design, with prevalence of complications rather than incidence evaluated, thus limiting conclusions regarding causality. Prevalent complications can have a reverse impact on metabolic health parameters; for example, nephropathy is associated with low HDL cholesterol, can affect blood pressure via the renin angiotensin system and can be an independent risk factor for cardiovascular disease.[30] The marked prevalence of low HDL cholesterol and hypertension in those with nephropathy could be secondary to the disease process, but the associations of the other complications with hypertension and number of risk factors are less readily explained. It should also be noted that the data were collected from a clinical database with some diagnostic information recorded as free text fields, which limited our ability to stratify complications according to type and severity. With regard to lifestyle variables, diagnosis of complications may be expected to modify behaviour, and this could account for the significant associations we observed between complications and ex-smoking, no alcohol and no exercise. These lifestyle factors can influence risk factor levels; nevertheless, the associations we observed between complications and risk factor abnormalities were independent of smoking, alcohol and exercise habits. In a T1DM clinic population, misdiagnosis is possible; however, a generally young age at diagnosis and careful case reviews in this population would have minimised this possibility. Twenty-three percent of those in the source database had to be excluded due to missing information. Those excluded were younger, had a shorter duration of T1DM and fewer clinic visits, perhaps biasing our sample in favour of those with complications. It should be acknowledged that a clear definition of metabolic health markers specifically for T1DM is needed since the complex metabolic changes due to insulin administration substantially alters the metabolic profile and cut-offs derived from population studies may not be applicable.

Despite these limitations, our findings, nevertheless, support the possibility that more intensive management of risk factors abnormalities could be of benefit in reducing T1DM complications. Hypertension was a particularly prominent associate of increased risk and more attention could readily be given to blood pressure normalisation. Nevertheless, the increasing risks we observed with increasing numbers of risk factors suggest more attention should be given not only to blood pressure but adiposity and lipid profile as well.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2019.05.026.

Declaration of Competing Interest

None declared.

Contribution statement

S.B. collated and analysed the data, drafted the manuscript and contributed to discussion and review. I.F.G. contributed to the concept and planning of the study as well as writing and review of the manuscript. N.O. contributed to the concept, discussion and review of the manuscript. S.M. and D.G.J. reviewed the manuscript and contributed to discussions. S.B. is the guarantor of this work and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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