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Abstract

Aims: Optimal glycaemic control benefits risk of micro-vascular and macro-vascular 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.

Keywords	Type 1 diabetes; risk factors; metabolic health; microvascular complication; macrovascular complication
Taxonomy	Complications of Diabetes, Diabetes
Corresponding Author	Sandhya Bhattarai
Corresponding Author's Institution	Imperial college london
Order of Authors	Sandhya Bhattarai, Ian Godsland, Shivani Misra, Desmond Johnston, Nick Oliver
Suggested reviewers	Anna R Dover, Solomon Tesfaye, William Strain

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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
The data that has been used is confidential

Sandhya Bhattarai
Diabetes Endocrinology and Metabolic Medicine
Department of Medicine
Imperial College London
London W2 1PG, U.K

Date: 27/11/2018

Dear Dr Fonseca,

I am writing to submit our manuscript entitled, "Metabolic health and vascular complications in type 1 diabetes" for consideration for publication in Journal of Diabetes and its Complications.

In this paper, we evaluate in a type 1 diabetes clinic population, prevalent microvascular and macrovascular complications according to adiposity, blood pressure and lipid risk factors.

Our main finding is that in comparison to people with 1 or more risk factors, those with no risk factors are at significantly lower risk of retinopathy and nephropathy, independent of age, duration of diabetes, gender and glycaemic control. This suggests that more intensive management of metabolic risk factors in T1DM might further lower risk of microvascular complications. As vascular complications are major cause of morbidity and mortality in T1DM patients, we believe our findings would be of interest to readers of Journal of Diabetes and its Complications.

We confirm that this work is original and has not been published elsewhere, nor is it under consideration for publication in any other journal. We have no conflicts of interest to disclose and all authors approved the manuscript and its submission to the journal.

Please address all correspondence concerning this manuscript to me at sandhya.bhattarai@nhs.net .

Thank you for your consideration of this manuscript.

Sincerely,

Sandhya Bhattarai

Metabolic health and vascular complications in type 1 diabetes
Sandhya Bhattarai, Ian F Godsland , Shivani Misra , Desmond G Johnston , Nick Oliver

Responses to Reviewer's comments

We thank the reviewer for their thoughtful review and suggestions. Our responses are itemised below and in our revised manuscript changes have been highlighted.

Reviewer's Comment:

"Thank you for clarifying the data sources and the inherent weaknesses of the study. The conclusion about risk factor management in persons with T1DM carries an important message for clinicians. The lack of an association between vascular complications and HbA1c is problematic and deserves additional exploration."

Thank you. In our previous manuscript, we touched on this as follows: "*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*".

In our revised manuscript, we have given this point more prominence by adding the following to the introductory paragraph of the discussion: "*The absence of a relationship between HbA1c and diabetes-specific complications in our analysis is at odds with well-established data and reflects the 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.*"

Editor's Comment

1) Reviewer 1 continues to remain concerned about the lack of association between complications and A1c - which has been well established in the DCCT/ EDIC etc. Part of the problem appears to be somewhat loose use of terminology: Please draw a clear distinction between microvascular and macrovascular. You use the term "vascular" for both which is confusing.

Thank you for your comment. We have made changes to make distinction between microvascular and macrovascular complications.

2) To what extent are some of the changes in risk factors driven by the onset of nephropathy and CKD - it is well known that this may raise BP and change lipids.

In our previous manuscript, we mentioned this as a limitation of our analysis as follows: "*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"*]. In our revised manuscript, we have now expanded on this point by adding the following sentence: "*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.*"

4) The last bullet highlight - "Intensive management of metabolic risk factors in T1DM may reduce microvascular risk" is an overstatement. What you mean is that there is an association between lower microvascular risk among those who have better control of macrovascular risk factors. This may be related to a subpopulation with better self-care. You certainly have not shown a cause and effect relationship.

We agree that our previous final bullet point was too general. Our key observations actually relate not to lower microvascular risk in those with better control, but to higher microvascular risk in those who, despite adequate glycaemic control, still have multiple metabolic risk factors. We have, therefore, revised our final bulleted highlight as follows: "*In people with type 1 diabetes and two or more metabolic risk factors, more intensive risk factor management could benefit microvascular risk.*"

- Despite attentive glycaemic control in T1DM, variation in vascular risk remains

- In T1DM HbA1c did not vary with incidence of complications

- Adiposity, blood pressure, triglycerides and HDL cholesterol showed relationships

- Metabolically healthy people with T1DM have lower risk of retinopathy and nephropathy

- In people with type 1 diabetes and two or more metabolic risk factors, more intensive risk factor management could benefit microvascular risk

Metabolic health and vascular complications in type 1 diabetes

Sandhya Bhattarai [a], Ian F Godsland [a], Shivani Misra [a], Desmond G Johnston [a], Nick Oliver [a]

a. Diabetes Endocrinology and Metabolic Medicine, Faculty of Medicine, Imperial College London, U.K

Sandhya Bhattarai: Sandhya.bhattarai@nhs.net

Ian F Godsland: i.godsland@imperial.ac.uk

Shivani Misra: s.misra@imperial.ac.uk

Desmond G Johnston: d.johnston@imperial.ac.uk

Nick Oliver: nick.oliver@imperial.ac.uk

Corresponding author:

Sandhya Bhattarai MBBS BSc (Hons)

Diabetes Endocrinology and Metabolic Medicine,

Department of Medicine, Imperial College London,

St Mary's Campus, Norfolk Place,

London W2 1PG, U.K

Tel: + 44 (0)20 7594 2429

Email address: sandhya.bhattarai@nhs.net

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.

Keywords: Type 1 diabetes; risk factors; metabolic health; microvascular complication; macrovascular complication.

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 factor and micro and macrovascular disease. On the other hand,

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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 mm Hg 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.

2.7 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<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<0.001), had a shorter duration of diabetes (12.3 (4.4-21.4) vs 21.6 (11.4-33.5) years, p<0.001), had a stronger family history of diabetes (T1DM 48 vs 26%; T2DM 29 vs 6%, p<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.

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Seventeen per cent 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.

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 $^{<0.001}$ (39.9-60.0)	42.4 (32.0-55.8)	51.2 $^{<0.001}$ (40.2-62.6)	42.6 (32.0- 55.5)	54.8 $^{<0.001}$ (44.4-64.3)	41.1 (31.6-54.2)	60.0 $^{<0.001}$ (51.7-70.9)
Duration of T1DM (yr)	15.0 (7.35-25.5)	30.7 $^{<0.001}$ (21.9-41.4)	19.3 (9.75-31.0)	31.0 $^{<0.001}$ (21.9-41.7)	20.5 (10.8- 31.9)	30.7 $^{<0.001}$ (20.4- 41.4)	19.7 (10.8-30.8)	37.8 $^{<0.001}$ (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) $^{<0.001}$	18 (144)	35 (30) $^{<0.001}$	17 (135)	39 (39) $^{<0.001}$
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 $^{<0.001}$ (124-143)	130 (120-140)	137 $^{<0.001}$ (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 $^{<0.001}$ (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 $^{<0.001}$ (1.05-1.65)
Anti-hypertensives	30 (170)	62 (223) $^{<0.001}$	35 (266)	84 (127) $^{<0.001}$	40 (333)	67 (60) $^{<0.001}$	37 (303)	87 (90) $^{<0.001}$
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) $^{<0.001}$	46 (355)	76 (115) $^{<0.001}$	49 (404)	73 (66) $^{<0.001}$	46 (374)	92 (96) $^{<0.001}$

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.

3.1 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 $p<0.001$, there being no independent association with age ($p>0.05$). However, neuropathy was independently associated with both age ($p<0.001$) and duration of diabetes ($p=0.01$) as was macrovascular disease (both age and duration of diabetes $p<0.001$). 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 '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)

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	1.87	0.89	0.91
	$(0.81\text{-}1.86)^{0.3}$	$(1.24\text{-}2.80)^{0.003}$	$(0.58\text{-}1.37)^{0.5}$	$(0.55\text{-}1.53)^{0.7}$
Nephropathy	1.17	5.88	1.24	2.24
	$(0.72\text{-}1.91)^{0.5}$	$(2.63\text{-}13.1)^{<0.001}$	$(0.76\text{-}2.05)^{0.3}$	$(1.31\text{-}3.83)^{0.003}$
Neuropathy	0.81	2.02	1.47	1.29
	$(0.43\text{-}1.53)^{0.5}$	$(0.92\text{-}4.43)^{0.07}$	$(0.83\text{-}2.46)^{0.1}$	$(0.66\text{-}2.52)^{0.4}$
Macrovascular disease	1.20	2.82	1.64	2.71
	$(0.67\text{-}2.19)^{0.5}$	$(1.05\text{-}7.56)^{0.03}$	$(0.91\text{-}2.95)^{0.09}$	$(1.44\text{-}5.10)^{0.002}$

Retinopathy was independently associated with hypertension (p=0.003, Nephropathy with hypertension (p<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)

3.1 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 (Figure 1).

Figure1 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.
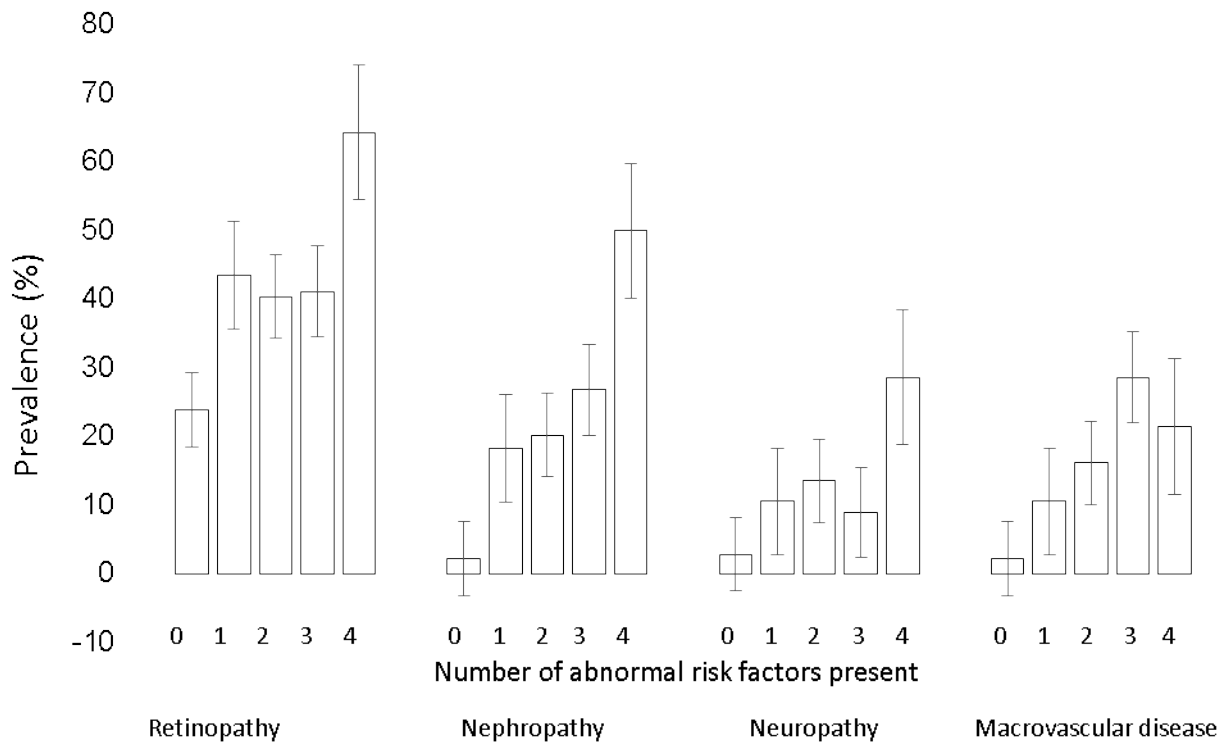
Comparison of proportions showed that for each category of micro and macrovascular disease, there was a significantly higher proportion of cases among those with 1 risk factor than those with none (all p<0.001) and this was confirmed in logistic regression analysis, with odds ratios for each number of risk factor abnormalities expressed relative to those with no risk factor abnormalities (Table 3).

Table 3. Odds ratio and 95% confidence intervals for the presence of each complications 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)	2.4 (1.6-3.6) $^{<0.001}$	9.7 (3.5-26.9) $^{<0.001}$	4.1 (1.6-10.4) $^{0.003}$	5.1 (1.8-14.4) $^{0.002}$
2 (n=478)	2.1 (1.4-3.6) $^{0.001}$	11.1 (3.9-31.7) $^{<0.001}$	5.4 (2.0-14.4) $^{0.001}$	8.4 (2.9-24.2) $^{<0.001}$
3 (n=193)	2.2 (1.2-4.2) $^{0.01}$	16.0 (5.0-50.8) $^{<0.001}$	3.4 (1.0-12.2) $^{0.06}$	17.5 (5.6-55.2) $^{<0.001}$
4 (n=56)	5.7 (1.8-17.9) $^{0.003}$	43.7 (10.3-185) $^{<0.001}$	13.9 (3.2-60.0) $^{<0.001}$	11.9 (2.4-60.1) $^{0.003}$

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.

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= <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<0.001; neuropathy 0.35 (0.14-0.90), p=0.03; macrovascular disease 0.38 (0.13-1.11), 0.06.

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 levels 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 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, more than 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-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, mis-diagnosis 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.

References

(1) Stephenson J, Fuller JH, EUROBIAB IDDM Complications Study Group. Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. *Diabetologia.* 1994;37(3): 278-285.

(2) Fong DS, Aiello L, Gardner TW, et al. Retinopathy in diabetes. *Diabetes care.* 2004;27 Suppl 1: S84-7.

(3) American Diabetes Association. Standards of medical care in diabetes--2010. *Diabetes care.* 2010;33 Suppl 1S11-61.

(4) Abbott CA, Malik RA, van Ross ER, et al. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes care.* 2011;34(10): 2220-2224.

(5) de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Diabetes Care.* 2014;130(13): 1110-1130.

(6) Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl j Med.* 1993;329(14): 977-986.

(7) The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes.* 1995;44(8): 968-983.

(8) The National Institute for Health and Care Excellence. *Type 1 diabetes in adults: diagnosis and management.* Available from: https://www.nice.org.uk/guidance/ng17 [Accessed 20/6/2018].

(9) Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group, Nathan DM, Zinman B, Cleary PA, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). *Arch Intern Med.* 2009;169(14): 1307-1316.

(10) Soedamah-Muthu SS, Chaturvedi N, Toeller M, et al. Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. *Diabetes care.* 2004;27(2): 530-537.

(11) Tesfaye S, Chaturvedi N, Eaton SE, et al. Vascular risk factors and diabetic neuropathy. N Engl J Med. 2005;352(4): 341-350.

(12) Price SA, Gorelik A, Fourlanos S, et al. Obesity is associated with retinopathy and macrovascular disease in type 1 diabetes. *Obes Res Clin Pract.* 2014;8(2): e178-e182.

(13) 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(7): 1649-1655.

(14) Mühlhauser I, Overmann H, Bender R, Jörgens V, et al. Predictors of mortality and end-stage diabetic complications in patients with Type 1 diabetes mellitus on intensified insulin therapy. *Diabetic Medicine.* 2000;17(10): 727-734.

(15) Nathan D, Bebu I, Braffett H B, et al. Risk Factors for Cardiovascular Disease in Type 1 Diabetes. *Diabetes.* 2016 May;65(5): 1370-1371-1379.

(16) Chillarón JJ, Flores-Le-Roux JA, Goday A, et al. Metabolic syndrome and type-1 diabetes mellitus: prevalence and associated factors. *Rev Esp Cardiol (English Edition).* 2010;63(4): 423-429.

(17) Haffner SM. American diabetes association. Dyslipidemia management in adults with diabetes. 2004.

(18) Alberti, Kurt George Matthew Mayer, Zimmet Pf. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabetic Medicine.* 1998;15(7): 539-553.

(19) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *Jama.* 2001;285(19): 2486-2497.

(20) International Diabetes Federation. *IDF Worldwide Definition of the Metabolic Syndrome.* Available from:
https://www.idf.org/component/attachments/attachments.html?id=705&task=download [Accessed 20/6/2018].

(21) Orchard TJ, Forrest KY, Pittsburgh Epidemiology of Diabetes Complications Study,et al. Lipid and blood pressure treatment goals for type 1 diabetes: 10-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes care.* 2001;24(6): 1053-1059.

(22) Durward C, Hartman TJ, Nickols-Richardson SM. All-cause mortality risk of metabolically healthy obese individuals in NHANES III. *J Obes.* 2012;2012.

(23) Hinnouho GM, Czernichow S, Dugravot A, et al. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? *Diabetes care.* 2013;36(8): 2294-2300.

(24) Vukovic R, Milenkovic T, Mitrovic K, et al. Preserved insulin sensitivity predicts metabolically healthy obese phenotype in children and adolescents. *Eur J Pediatr.* 2015;174(12): 1649-1655.

(25) Bain S, Gill G, Dyer P, et al. Characteristics of type 1 diabetes of over 50 years duration (the Golden Years Cohort). *Diabetic Medicine.* 2003;20(10): 808-811.

(26) Keenan HA, Costacou T, Sun JK, Doria A, et al. Clinical factors associated with resistance to microvascular complications in diabetic patients of extreme disease duration: the 50-year medalist study. *Diabetes care.* 2007;30(8): 1995-1997.

(27) Metascreen Writing Committee, Bonadonna R, Cucinotta D, et al. The metabolic syndrome is a risk indicator of microvascular and macrovascular complications in diabetes: results from Metascreen, a multicenter diabetes clinic-based survey. *Diabetes care.* 2006;29(12): 2701-2707.

(28) Thorn LM, Forsblom C, Fagerudd J, et al. Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control (the FinnDiane study). *Diabetes care.* 2005;28(8): 2019-2024.

(29) Weisman A, Rovinski R, Farooqi MA, et al. Commonly Measured Clinical Variables Are Not Associated With Burden of Complications in Long-standing Type 1 Diabetes: Results From the Canadian Study of Longevity in Diabetes. *Diabetes care.* 2016;39(5): e67-8.

(30) Rabelink TJ. Cardiovascular risk in patients with renal disease: treating the risk or treating the risk factor? *Nephrol Dial Transplant.* 2004;19(1): 23-26.

(31) Costacou T, Evans RW, Orchard TJ. High-density lipoprotein cholesterol in diabetes: is higher always better? *Journal of clinical lipidology*. 2011 Sep 1;5(5):387-94.

(32) Perneger TV. What's wrong with Bonferroni adjustments. *BMJ.* 1998 Apr 18;316(7139):1236-8.

Supplementary Table 1. Characteristics of metabolically healthy and unhealthy patients with type 1 diabetes shown as median (IQR) for continuous data and % (n) for categorical where % is out of total number in the metabolic health category.

	Metabolically healthy (n=179)	Metabolically unhealthy (n=741)	p
Age (years)	33.8 (27.7-42.5)	47.4 (34.6-58.9)	<0.001
Duration of T1DM	14.7 (6.5-23.8)	22.7 (12.9-35.2)	<0.001
Male Gender	39.3 (70)	53.2 (394)	0.001
Non-smoker	82 (142)	81 (597)	0.5
Non-drinker	43 (72)	40 (283)	0.3
No exercise	13 (23)	21 (151)	0.01
FH T1DM	22 (40)	28 (206)	
FH T2DM	6 (11)	6 (48)	0.4
Both	2(4)	2 (12)	
White	80 (143)	79 (589)	
African Caribbean	5 (9)	8 (56)	0.2
Asian/ Indian	5 (9)	6 (48)	
HbA1C (% [mmol/mol])	8.0 (7.1-8.9) [64 (54-74)]	8.1 (7.3-8.9) [65 (56-74)]	0.4
Serum Creatinine	74 (68-81)	79 (69-93)	<0.001
UACR	1 (0.6-1.8)	1.6 (0.7-5.6)	<0.001
Total Cholesterol	4.5 (3.9-5.1)	4.5 (3.9-5.1)	0.6
On Statin	21.2 (38)	58.3 (432)	<0.001

Author Agreement Form

Title: Metabolic health and vascular complications in type 1 diabetes

Authors: Sandhya Bhattarai, Ian F Godsland, Shivani Misra, Desmond G Johnston, Nick Oliver

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Corresponding author:

Sandhya Bhattarai   Date: 27/11/2018

Co-authors:

Ian F Godsland   Date: 14/12/2018

Shivani Misra   Date: 14/12/2018

Desmond G Johnston   Date: 10/12/8

Nick Oliver   Date: 14/12/18