Sex differences in vascular stiffness and relationship to adiposity and the risk of renal functional decline in patients with type 2 diabetes

Kenneth A Earle MD1,3, Lauren Ng 2, Sarah White3, Karima Zitouni PhD2

1 St Georges Healthcare NHS Trust, Thomas Addison Unit, London, UK

2 St. Georges University of London, London, UK

3 St. Georges University of London, Population Health Research Institute, London, UK

4 St. Georges University of London, Cardiovascular Sciences Division, London, UK

Corresponding author:

Kenneth A Earle

St George’s University Hospitals NHS Trust, Blackshaw Rd, London SW 17 0RE, UK

Email: kearle@sgul.ac.uk

Tel: +44 208 672 1255

Fax:+44 208 7253270

Background

The current obesity epidemic is associated with the rising incidence of type 2 diabetes. Although improvements in glycaemic control are associated with a reduction in incidence of some complications of diabetes, it remains the leading cause of end-stage kidney disease world-wide. Chronic kidney disease affects around 18-30% of patients with type 2 diabetes in the United Kingdom (UK) compared to 6.9% of the general population (1,2). Moreover, CKD is an independent risk factor for hospitalization, and major cause of premature death from cardiovascular disease (CVD). These data imply that obesity not only drives the emergence of diabetes but may be necessary for the progression of renal disease and CVD which develops more readily in sub-groups of patients. The risk of death from CVD in patients with diabetes is reportedly higher among women than in men. Furthermore, in patients of non-Caucasian heritage, CKD appears to be a stronger risk factor for all-cause mortality and CVD than in patients of Caucasian heritage. The mechanism(s) by which obesity promotes both renal- and cardiovascular disease in patients with diabetes is unclear.

Vascular stiffness is increasingly recognized as predictor for CVD that could impact kidney function through the transmission of systemic pressures to the renal vascular bed. Studies in adults without diabetes, have shown that vascular stiffness is related to measures of general and central adiposity and it has an inconsistent association with gender. Non-diabetic patients, of non-Caucasian heritage have demonstrably less vasodilatory function compared to matched Caucasian patients after adjustment for traditional CVD risk factors. A recent study has shown that in patients with type 2 diabetes, arterial stiffness was related to obesity independently of blood pressure, hyperlipidaemia and blood glucose regulation. In this study, we investigate how vascular stiffness relates to sex, adiposity and the risk of progressive renal dysfunction in adult patients with type 2 diabetes, who do not have clinical evidence of CVD.

Materials and Methods

Patients with type 2 diabetes, not in receipt of renal replacement therapy were recruited from general practices in South West London, UK. Those with at least 2 of the following characteristics: a history of hypertension (3 consecutive sitting blood pressure readings >140 systolic and/or diastolic 90 mmHg without treatment or receiving treatment for known hypertension), a urinary albumin:creatinine ratio >3 mg/mmol or a family history of hypertension, cardiovascular or end-stage renal disease occurring in a first-degree relative < 65 years old, were considered at increased risk of progressive renal disease. Patients assigned themselves to an ethnic group by choosing from the classification list used by the Office of Population Surveys, UK. We assigned patients selecting either, White British, White Irish or other White group as being of Caucasian heritage and those selecting either Black Caribbean, Black African, Black other, Indian, Pakistani, Bangladeshi, Chinese, or other Asian as being of non-Caucasian heritage.

Patients were excluded if they had a history of malignancy or any other life threatening illness, current pregnancy, systolic blood pressure >200mmHg, diastolic blood pressure >160 mmHg, end-stage renal disease, nephrotic range proteinuria excretion (total protein excretion rate >3 g/day or albumin creatinine ratio >300 mg/mmol or a history of CVD. Cardiovascular disease was defined as having a clinical record of ischaemic heart disease (angina, myocardial infarction, coronary artery revascularization and or heart failure), peripheral vascular disease (intermittent claudication or peripheral artery revascularization) or cerebrovascular disease (transient ischaemic episodes or stroke), a positive response to the modified Rose questionnaire instrument (17) or an abnormal 12-lead electrocardiogram performed at rest (Seca CardioConcept 5.6, Seca United Kingdom). These data including the treatment histories, and the clinical and biochemical measurements were collected at the in-person visit and recorded on an electronic proforma.

Clinical assessments

Patients were invited to attend a clinical research facility where all measurements were carried out by trained research nurses under the same conditions. Anthropometric measures included height in metres, weight in kilogrammes, and waist circumference in centimetre. Body mass index (BMI) was calculated from the weight in kilogrammes divided by the square of height in metres. Body composition was determined using a bioimpedance foot-to-foot analyser (Tanita BF-350, Tanita Corporation, Japan). Patients were asked to stand with bare feet on the analyser footpads and percentage body fat was automatically calculated after correcting for gender, age, and height. Sitting blood pressure was measured by digital oscillometry (Omron 705IT, OMRON Healthcare Europe, Netherlands) according to the National Institutes of Health and Care Excellence guidance (http://www.nice.org.uk/guidance/cg127).

Arterial Stiffness

Pulse wave amplitude was analysed using infra-red finger plethysmography (PulseTrace PCA2, CareFusion UK 232 Ltd, Basingstoke). The measurements were made in room-assisted temperature conditions. The contour of the finger pulse was automatically analysed to determine a stiffness index (SI). The readings were made over 10 minutes and the SI computed from the mean of 3 readings was adjusted for age, sex, height, and body weight.

Biochemical assessments

Venous blood was sampled after a 12 hour fast. Plasma creatinine was measured by the Jaffe reation (Cobas 8000 module c702, Roche Diagnostics, Germany), urinary albumin was measured by immunoturbidimetry (Cobas 6000 module c50, Roche Diagnostics, Germany) . Renal function was calculated as the eGFR from the plasma creatinine using the CKD-EPI equation. Glycosylated Haemoglobin (HbA1C) was measured by immunoturbidimetry (ADVIA® 2400, Siemens Diagnostics, Germany). Total triglycerides, total- and HDL-cholesterol were estimated using a colorimetric enzymatic assay (Cobas 8000 module c702, Roche Diagnostics, Germany). LDL-cholesterol concentration was calculated using the Friedewald formula: LDL cholesterol = total cholesterol-(triglyceride (mmol/L)/(2.19) − HDL-cholesterol (mmol/L).

The study was approved by the local ethics research committee and all patients provided written informed consent.

Statistics

Data were analysed using parametric and non-parametric tests according to their distribution (Stata 14 Chicago, US) and expressed as mean and standard deviation unless stated otherwise. Regression analysis was performed with SI as the dependent variable for gender and for heritage groups.

Results

A total of 252 patients were screened at the clinical research facility and of these 166 (49.41% female) met the inclusion criteria. The male and female groups were of similar chronological age and duration of diabetes and there were no significant differences in body mass index, waist circumference and blood pressure. Percentage body fat, fasting total- , HDL- and LDL cholesterols were significantly higher and eGFR significantly lower in women compared with men (Table 1). The proportion of the female and male groups receiving blood glucose lowering treatment with insulin, the incretins (glucagon-like polypepetide-1 and dipeptidyl peptidase inhibitor-4), metformin and sulphonylurea was similar. There were no differences in the use of renin-angiotensin system modulators (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), calcium channel blockers and/or loop or thiazide diuretics for the management of hypertension. HMGCoA reductase inhibitor (statin) usage was significantly less in women (Table 2). The proportion of men with a positive current and/or past history of smoking tobacco was more than 2-fold greater than in women (59 vs 29%; p=0.0005).

Women and men of Caucasian and non-Caucasian heritage were of similar age (61.4 (7.6) vs 60.42 (8.2) years; p=0.6299 and 61.8 (6.5) vs 59.5 (8.4) years;p=0.1316) and duration of diabetes (8.8 (7.7) vs 8.6 (7.6) years; p=0.8783 and 10.2 (7.0) vs 13.1 (8.0) years; p=0.088). There were no gender differences in waist circumference or body mass index within each group, but both measures were significantly lower in the non-Caucasian group (Fig 1). The Caucasian group had a significantly lower haemoglobin Alc level and a higher proportion of current and/or ex-smokers compared with the non-Caucasian group respectively (53.9 (16.6) vs 60.(18.3) mmol/mol; p=0.0320 and 66 vs 30%;p=0.0000). There were no statistically significant differences in cholesterol and triglyceride levels, renal function, urinary albumin excretion rates, the usage of statins or non-insulin blood glucose lowering and blood pressure lowering treatment regimens between these heritage groups.

The mean (95% confidence interval) vascular stiffness index (VSI) was significantly higher in the Caucasian than in the non-Caucasian group. In univariate analysis body mass index correlated significantly with VSI in women but not in men of both heritage groups (Fig 2).

A linear regression model with SI as the outcome variable including age, blood pressure, HbA1c, eGFR and bioimpedance was significant in women (R-squared =0.20; p=0.026). There was a positive correlation with bioimpedance (0.309; p=0.007) and negative correlation with eGFR (-0.172; p=0.004).