Original Article

Adult height and proteinuria in type 2 diabetes

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Abstract

Background. Short stature has been shown to be associated with proteinuria in type 1 diabetes, but no data exist with respect to type 2 diabetes. The objective of the study was to investigate the relationship between final adult height and macroproteinuria in type 2 diabetic patients.

Methods. One hundred and forty-four consecutive type 2 diabetic patients (84 males, 60 females) with macroproteinuria were recruited into the study. For every patient, three diabetic controls matched for age, gender, and duration of diabetes were randomly selected. Height was measured in patients and controls to the nearest 0.5 cm.

Results. The mean height in men with macroproteinuria (n = 84) was 164.4 cm (SD 6.74) compared to 166.6 cm (SD 6.64) in controls (n = 252) (P < 0.01). The mean height in women with macroproteinuria (n = 60) was 150.6 cm (SD 5.20) compared to 152.5 cm (SD 5.78) in controls (n = 180) (P < 0.02).

Conclusion. Short stature is associated with an increased risk of macroproteinuria in type 2 diabetic patients. We postulate that common genetic or environmental factors that affect final adult height might also predispose to the development of nephropathy.

Keywords: adult height; birth weight; diabetic nephropathy; proteinuria

Introduction

Rossing et al. [1] previously reported that short stature is associated with diabetic nephropathy in type 1 diabetes. The Eurodiab investigators produced similar results although this was not the primary aim of the study [2]. Penfold et al. [3] also reported an association between short stature and microangiopathy in type 1 diabetes but they studied subjects with childhood-onset diabetes, in whom the association could be attributed to the common effect of antecedent poor glycaemic control on final adult height and microvascular complications. Short stature has also been associated with microalbuminuria in non-diabetic subjects [4]. There is no data on type 2 diabetes. The aim of the present study was to investigate whether there is an association between height and proteinuria in type 2 diabetes.

Subjects and methods

One hundred and forty-four type 2 diabetic patients with macroproteinuria (84 males, 60 females) were recruited. Patients who were dipstick positive for protein were randomly selected from a computer list of patients (in order of hospital number) attending the Diabetes Clinic at St Luke’s Hospital, Malta. These had 24-h urinary protein estimation (modified Coomassie brilliant blue test). Patients were given both verbal and written instructions on the method of urinary collection. The inclusion criterion was of two consecutive urinary protein excretion of ≥ 500 mg/24 h. Patients were excluded if they had haematuria, pyuria, a positive urine culture, or an abnormal ultrasound examination of the kidneys (other than increased renal size). Only three patients were excluded by these criteria: one with chronic pyelonephritis (pyuria and repeated positive urine cultures) and two with nephrolithiasis. The median (interquartile range) urinary protein excretion was 1153 (605–3995) mg/24 h in males and 910 (580–2498) mg/24 h in females. Fundoscopy was performed in all patients in a darkened room; fundal photographs were taken and examined by an independent ophthalmologist, who was unaware of the patients’ details other than that they were diabetic.

For every patient, three type 2 diabetic controls, matched for age (within 2 years), gender, and duration of diabetes (within 1 year) were randomly selected from a computer list of patients (in order of hospital number). All controls were dipstick negative for proteinuria on three consecutive tests. All cases and controls were of Maltese Caucasian descent. Adult height was taken to be that recorded at diagnosis of diabetes; this was done to avoid potential bias of the effect of nephropathy on height. Height was recorded in all patients to the nearest 0.5 cm. Blood pressure was measured in the supine position using a mercury sphygmomanometer.

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and, where necessary, a large cuff; the first and fifth Korotkoff sounds were used for systolic and diastolic blood pressures respectively. HBA1c was measured by high-performance liquid chromatography. Diagnosis of diabetes was made according to World Health Organisation criteria [5].

Statistical methods

Student’s t-test was used to assess the significance of differences between means of normally distributed data and the Wilcoxon rank sum test to assess the significance of differences between non-normally distributed data. A P value of <0.05 was taken as statistically significant.

Results

The mean height in men with macroproteinuria (n = 84) was 164.4 cm (SD = 6.74 cm) compared to 166.6 cm (SD = 6.64) in controls (n = 252) (P < 0.01). The mean height in women with macroproteinuria (n = 60) was 150.6 cm (SD = 5.20 cm) compared to 152.5 cm (SD = 5.78) in controls (n = 180) (P < 0.02). The median (interquartile range) urinary protein excretion of the third and first tertiles (by height) of macroproteinuric males was 899 (550–1255) mg/24 hr and 1742 (25–4940) mg/24 h respectively (P < 0.05). The corresponding figures for females were 796 (551–907) mg/24 hr and 915 (619–2382) mg/24 hr respectively (NS).

The clinical characteristics are given in Table 1. Both systolic and diastolic blood pressure were higher in the proteinuric patients than in control subjects and this reached statistical significance for diastolic measurements. Other clinical parameters including age, duration of diabetes (and hence age at diagnosis) and glycosylated haemoglobin were similar in both groups, although serum creatinine was higher in patients than in healthy subjects.

Discussion

Our data show that men with proteinuria and type 2 diabetes were on average 2.2 cm shorter whilst women with proteinuria were 1.9 cm shorter. This compares to a difference of 1.7 cm reported in men with type 1 diabetes by Rossing et al. [1]. Furthermore, we found that short stature was associated with a higher urinary protein excretion even in macroproteinuric males; this strengthens the validity of our findings. It is noteworthy that both Rossing et al. [1] and the Eurodiab investigators [2], who studied type 1 diabetic patients, did not attain statistical significance in females.

Renal biopsies were not performed because of ethical considerations. However, it is likely that proteinuria in our patients was due to diabetic nephropathy. Firstly, it has been shown that most cases of proteinuria occurring in type 2 diabetic patients are due to diabetic renal disease [6,7]. Furthermore, we were careful to exclude other causes of proteinuria. The
fact that almost all proteinuric patients also had diabetic retinopathy also strongly suggests diabetic nephropathy.

Because of ethical considerations, antihypertensive treatment was not stopped, even though it is known that it can affect protein excretion. It is unlikely that this affected our results, as the proportion on antihypertensives was similar in macroproteinuric patients and controls. The fact that controls and macroproteinuric patients were matched for duration of diabetes resulted in some controls having a short disease duration, some of which might progress to macroproteinuria. If anything, this could have led to underestimation of the difference in height between the two groups.

The difference in height observed in our study is likely to be a genuine association with diabetic nephropathy. Our patients and controls were well matched for age and duration of diabetes (and hence for age at diagnosis of diabetes). Duration of diabetes is a major determinant of diabetic nephropathy. We were only able to calculate disease duration from the date of diagnosis. It is impossible to exclude the possibility that the patients with nephropathy did not have a longer duration of undiagnosed diabetes or more severe hyperglycaemia pre-diagnosis. Even if this were the case, it should not have altered adult height.

The reason for the difference in adult height observed in our study is unclear and merits further investigation. It is unlikely to be due to adult environmental factors, but could be a result of an unidentified environmental factor(s) operating early in life, possibly in utero. As low birth-weight has been associated with the later development of hypertension [8,9] and of diabetic nephropathy [10], and to be correlated to adult height [10,11], the latter could be acting as a surrogate marker for birth-weight. Birth-weight records were not available for these subjects, which meant we were not able to test this hypothesis. It is possible that the association of short stature with proteinuria in diabetic patients could be mediated, at least in part, through high blood pressure. In our study there was a small but significant difference in diastolic blood pressure of patients and controls. There was a similar trend in systolic blood pressure, but his did not reach statistical significance.

One of the major determinants of adult height is childhood nutrition. The association between adult height and proteinuria could therefore be explained by undernutrition or malnutrition in childhood predisposing to both renal disease and short final adult height. However, data on infants exposed to starvation during the siege of Leningrad have failed to show any association between nutrition in infancy and the later development of microalbuminuria [12].

Adult height is also under strong genetic control. An alternative explanation to our data could therefore be that common genetic factors predispose to both short stature and to diabetic renal disease. There is evidence of familial clustering of renal disease in type 2 diabetes both from data on Pima Indians [13] and from our own work on subjects of Maltese descent [14], suggesting that genetic factors may be involved in the aetiology of type 2 diabetic renal disease. It has recently been proposed that genes that predispose to insulin resistance may reduce insulin-related growth in utero as well as being associated with hypertension and type 2 diabetes in adult life [15]. Diabetic nephropathy has been shown to be associated with insulin resistance [16,17]. It is interesting to hypothesize that a genetic predisposition to insulin resistance might explain the association of short stature and proteinuria by predisposing to low birth-weight and short stature as well as to renal disease.

Finally, low birth-weight has been associated with a reduction in nephron number [18]; it has been suggested that such a congenital oligonephropathy can predispose to renal disease and to hypertension [19,20]. We have shown that diabetic nephropathy is associated with short stature in type 2 as well as in type 1 diabetes [1]. This suggests that similar genetic and/or environmental factors predispose to renal disease in both major types of diabetes. The further investigation of aetiology of this observation may give important insights into diabetic nephropathy.

References


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