RENAL INVOLVEMENT IS RELATED TO BODY HEIGHT IN NEWLY DIAGNOSED DIABETIC WOMEN AGED 40 YEARS OR OVER

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SUMMARY
- We scrutinized the relation between body height and renal involvement in a large population-based sample of newly diagnosed diabetic patients aged 40 years or over. The urinary albumin concentration (UAC) was measured in freshly voided morning urine in 1,284 newly diagnosed diabetic patients. The course of insulin treatment showed that at least 97.6% of the patients could be regarded as Type 2 diabetic. Linear regression analyses were done with log UAC as dependent variable, and height, age, HbA1c, smoking habits, education, occupation, body weight and systolic blood pressure as independent variables. Median age was 65.3 years. In bivariate analyses UAC increased with decreasing height for women (R (S) = – 0.090, p = 0.028), but not for men (R (S) = – 0.049, p = 0.20). After backwards elimination in the regression models, height remained in the model for women only (p = 0.041). Our finding of a relationship between short stature and renal involvement in Type 2 diabetic female patients adds to existing evidence from studies with non-diabetic and Type 1 diabetic subjects.

Key-words: diabetic nephropathies, body height, type 2 diabetes mellitus, family practice, epidemiology.

RE´ SUME´
- L’atteinte rénale est liée à la taille chez les femmes diabétiques type 2 récemment diagnostiquées et âgées de 40 ans ou plus. Nous avons étudié la relation entre la taille et l’atteinte rénale dans une large population de diabétiques récemment diagnostiqués et âgés de 40 ans ou plus. L’excrétion urinaire d’albumine (EUA) a été mesurée sur des urines fraîches matinales chez 1 284 diabétiques récemment diagnostiqués. Le besoin d’insulinothérapie montre que 97,6 % d’entre eux peuvent être considérés comme diabétiques type 2. Les analyses en régression linéaire furent réalisées avec le logarithme de l’EUA comme variable dépendante et la taille, l’âge, l’HbA1c, le tabagisme, le niveau éducatif, l’activité professionnelle, le poids corporel et la pression artérielle systolique comme variables indépendantes. La médiane pour l’âge était de 65,3 ans. En analyse bivariée l’EUA augmente avec la diminution de la taille chez la femme (R (S) = – 0,090, p = 0,028), et pas chez l’homme (R (S) = – 0,049, p = 0,20). Après ajustement dans les modèles de régression, la taille demeure significative dans le modèle chez les femmes uniquement (p = 0,041). Ces données en faveur d’une relation entre petite taille et atteinte rénale dans le type 2 chez la femme s’ajoutent à celles déjà disponibles pour ce qui concerne le diabète type 1 et les sujets non-diabétiques.

Mots-clés : néphropathies diabétiques, taille corporelle, diabète type 2, médecine générale, épidémiologie.

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Low birth weight has been described as a risk factor for the development of Type 2 diabetes in men [1] and for cardiovascular disease in non-diabetic subjects [2]. Adult height has been shown to be inversely related to microalbuminuria in non-diabetic men [3] and to the severity of albuminuria in Type 1 diabetic patients [4]. Short stature was also related to excess cardiovascular morbidity in both genders [5,6] and to increased cardiovascular mortality in women [7].

We scrutinized the relation between body height and renal involvement in a large population-based sample of newly diagnosed middle-aged and elderly diabetic patients taking into account possible confounders of this relationship.

**PATIENTS AND METHODS**

**Study population** – At the end of 1988, 477 general practitioners (GPs) volunteered to take part in the Danish study, Diabetes Care in General Practice. Before the study started, the GPs were randomized to an intervention and a non-intervention group. All GPs were to include all patients on their practice list who fulfilled the following criteria:

1) diabetes mellitus diagnosed from 1 March 1989 to 28 February 1991 (71 doctors volunteered for a 1-year extension of this period); patients who were hospitalized when the diagnosis was established were also considered for inclusion,

2) based on hyperglycaemic symptoms and/or raised blood glucose values measured in general practice, the diagnosis was established with a single fasting whole blood/plasma glucose 7.0/8.0 mmol/l or over measured at a major laboratory,

3) age 40 years or over at diagnosis. A total of 1,381 diabetic patients were included in the study. The GPs were instructed not to alter diagnostic practice during the inclusion period. The inclusion activity was constant over time. Besides the 1,381 diabetic patients, 162 diabetic patients (10.5% out of a total of 1,543 patients) were suspected of having diabetes, but they were excluded by the GPs according to three exclusion criteria stipulated in the study synopsis: severe somatic disease (31%), psychiatric disease (31%) and unwillingness to participate (38%). Forty-six diabetic patients who were being treated with steroids at the time of diagnosis were excluded from the present analysis. Twelve non-Caucasian patients were excluded because there were so few. Of the remaining 1,323 subjects, 39 (3.0%) patients did not provide any usable urine sample, primarily because of persistent haematuria in at least four consecutive urine samples, so the final study population was 1,284 newly diagnosed diabetic patients.

The subjects were not classified according to the type of diabetes, but 19 of the 711 patients in the intervention group commenced insulin treatment within 180 days of the diabetes diagnosis. Insulin treatment was discontinued for two of these patients during the observation period. Thus, at least 694 (97.6%) subjects could be regarded as Type 2 diabetic. Informed consent was obtained from all participants. The protocol was in accordance with the Helsinki declaration and was approved by the ethics committee of Copenhagen and Frederiksberg.

**Clinical and self-reported information** – When the patient was enrolled in the study, the GP recorded height and body weight without shoes and outer garments, and blood pressure was measured by routine methods after a 10-minute rest in a sitting position. The GP also handed out a questionnaire including a modified London School of Hygiene smoking questionnaire and a question concerning education and occupation, or former occupation if the patient was a pensioner or unemployed.

**Laboratory methods** – The participants produced a freshly voided morning urine sample as soon as possible after the day of diagnosis. The urine sample was sent by post in a polystyrene test tube without cooling to Århus Kommunehospital to be analysed. Urinary albumin was measured by a polyethylene glycol radioimmuno assay. Fasting blood samples were drawn from the study participants at their first visit to the practice clinic after the diagnosis was confirmed. A blood sample for Haemoglobin A1c (HbA1c) was sent by post without cooling in an EDTA-prepared test tube to Odense University Hospital. HbA1c values measured more than 1 year after the diabetes diagnosis were excluded from the following analyses. HbA1c was determined by HPLC with ion-exchange column-chromatography, reference interval: 0.054–0.074 fract.

**Statistical analysis** – UAC was log transformed for distributional purposes, but normal distribution was not obtained. Correlations of UAC with continuous variables were assessed by Spearman’s rank correlation coefficient, R(S). Linear regression analysis with backwards reduction of non-significant variables was used. Analyses were stratified according to gender. The nominal level of statistical significance for all analyses was p < 0.05 (two-sided). Smoking habits were scored in three categories: current smoker, former smoker and non-smoker (i.e. a person who never smoked). Education was classed in three categories: basic school education only, vocational upper secondary education, and higher education. Employment was classed in salaried employee, skilled wage-earner, unskilled wage-earner, self-employed or assisting spouse (agriculture only), and self-employed or assisting spouse (excluding agriculture).
RESULTS

In the final sample of 1,284 newly diagnosed diabetic patients, the median age was 65.2 years: 63.5 years for men and 67.3 years for women at the time of diagnosis. The male/female ratio was 1.15 (688/596). The median diagnostic fasting plasma glucose was 13.7 mmol/l. UAC increased with decreasing height, but the association reached statistical significance only for women (Fig. 1 and Table I). However, there was a marked reduction in height with age at diabetes diagnosis for both men and women (Table I). Three multivariate models were tested. All were linear regression models with log UAC as dependent and height, age at diagnosis and HbA1c as independent variables. In model 1 smoking habits, education and occupation were added to these independent variables. Only HbA1c remained in the final model for men. For women this was the case for both height and HbA1c (Table II). As colinearity between age and height may have influenced the results, the step in the backwards elimination procedure just before the final model for women emerged was examined. At this point, age (p = 0.19) was removed to leave only height and HbA1c in the final model. From the model with age to the model without age, the estimate of the coefficient for height changed 19%. This relatively large change is an argument for keeping age in the model. However, when height, although statistically significant (p = 0.049), was removed instead of age, a model was obtained with age (p = 0.051) and HbA1c. Therefore, the final model 1 in table II seems to be valid, although the possibility of colinearity between age and height cannot be ruled out completely.

Model 2 included both body weight and systolic blood pressure as supplementary independent variables (Table I). A third model with all eight independent variables gave identical results with height remaining in the model for women only. In these models age was still not statistically significant when height was removed before age in the elimination procedure.

DISCUSSION

The main finding in this large group of newly diagnosed middle-aged and elderly diabetic patients was the inverse relationship between body height and renal involvement in women only. The association remained after adjustment for confounders, including proxy variables of socioeconomic status. To our knowledge this has not before been described in Type 2 diabetic patients, but it confirms findings in several other groups of patients and populations. The strengths of our study lie primarily in the patient sampling. The study was based on a well-defined background population in each general practice. The unchanged inclusion activity during the inclusion period and the few exclusions all indicate that the patient material in the present study is a representative sample of newly diagnosed diabetic patients in this age group in Denmark. As estimated from the proportion of patients receiving insulin at 1-year follow-up, more than 97.6% were Type 2 diabetic patients. Such a population-based patient sample has the advantage over clinic-based samples of giving a more precise description of the relationship between the diabetic complications and their possible determinants [8]. Poor glycaemic control predicts the development of

![Urinary albumin concentration, mg/l](image)

FIG. 1. Urinary albumin concentration according to height in newly diagnosed diabetic patients aged 40 years or over. Median (bold line), upper and lower quartiles (thin lines) and 5 % and 95 % centiles (broken lines) are shown. Number of patients (height range in cm, n); men: < 165, n = 73; 165-169, n = 139; 170-174, n = 193; 175-179, n = 159; 180-184, n = 96; 185+, n = 27; women: < 150, n = 17; 150-154, n = 73; 155-159, n = 154; 160-164, n = 192; 165-169, n = 124; 170+, n = 36; total = 1283. Height is missing for one male patient.
Microalbuminuria. As glycaemic control deteriorates over time, the duration of diabetes is possibly a confounder of the relationship between short stature and albuminuria. This bias is negligible in our study of newly diagnosed diabetic patients. It is well-known that urinary albumin excretion declines with treatment [9]. Although this treatment effect is expected to be independent of individual height, the fact that most measurements were done immediately after diabetes diagnosis may have contributed to the results. Determinants of adult height are genetic and environmental, including social class [10]. For this reason occupation and education were included in our multivariate analyses.

In our analyses, age was the most difficult confounder to handle because height declines with age [11]. The generation effect on height is an unlikely explanation for the observed inverse relationship between height and urinary albumin concentration in the present study because of the wide age spectrum of patients involved. Our results rest, however, on a rather strict interpretation of p-values, which are only just over or below 5%. We cannot completely rule out the possibility that age and height are so closely correlated that it is impossible to separate the effect of age and height on urinary albumin concentration in our data.

### Table I. Body height and age according to urinary albumin concentration in newly diagnosed diabetic patients aged 40 years or over.

<table>
<thead>
<tr>
<th>Urinary albumin concentration, mg/l</th>
<th>R(S)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15</td>
<td>15– &lt; 40</td>
<td>40– &lt; 200</td>
</tr>
<tr>
<td>Body height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>men</td>
<td>173.5</td>
<td>172.3</td>
</tr>
<tr>
<td>women</td>
<td>161.1</td>
<td>160.4</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>men</td>
<td>61.9</td>
<td>64.7</td>
</tr>
<tr>
<td>women</td>
<td>65.4</td>
<td>67.1</td>
</tr>
</tbody>
</table>

Data are means. R (S) = Spearman’s rank correlation coefficient.

### Table II. Results from linear regression analyses with log of urinary albumin concentration as dependent variable. Final models after backwards elimination.

<table>
<thead>
<tr>
<th>Independent variables, besides height, age at diagnosis and HbA1c, in full model</th>
<th>MEN</th>
<th>WOMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Independent variables in final model</td>
<td>Estimate of coefficient</td>
</tr>
<tr>
<td>Model 1</td>
<td>HbA1c</td>
<td>10.47</td>
</tr>
<tr>
<td>smoking habits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>HbA1c</td>
<td>10.65</td>
</tr>
<tr>
<td>body weight</td>
<td>systolic BP</td>
<td>0.013</td>
</tr>
<tr>
<td>systolic BP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Newly diagnosed diabetic patients aged 40 years or over. Data are maximum likelihood estimates of coefficients with p-values based on the F-test. Intercept not shown.
Our finding of an inverse relationship between height and UAC is of special interest because microalbuminuria is a risk marker for several diseases and increased mortality. Furthermore, both birth weight and birth length are predictors of adult height [12]. This is why our results add to the ongoing discussion about the predictive value of birth weight [13].

An inverse association between height and diabetic nephropathy has also been found in Type 1 diabetic men [14]. In non-diabetic subjects increased risk of cardiovascular disease [5] and mortality from cardiovascular disease was found in shorter women compared to taller [7]. In a cross-sectional study, non-diabetic, microalbuminuric men were shorter than normalalbuminuric, whereas no association was found in women [3]. Another group did not find any association between height and urinary albumin excretion in a similar, but larger study [15]. Some of the studies however did not control for social class [3, 5, 14]. In the NHANES I study, the inverse relation between height and cardiovascular disease disappeared when the analysis was adjusted for age and years of education [16].

In conclusion, we found an inverse relation between height and urinary albumin concentration in newly diagnosed predominantly Type 2 diabetic women, which has not been described before. The relation persisted after adjustment for adult confounders, including social class. Our results add to existing evidence of a relationship between short stature and cardiovascular disease [17]. In a cross-sectional study, non-diabetic, microalbuminuric women born 1915-29. BMJ, 1998, 317, 241-245.


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REFERENCES

