Diabetic nephropathy in Surinamese South Asian subjects

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Studioportret van drie Indiase mannen met manden die op het hoofd worden gedragen, India, ca. 1875.

Chapter 6

Central obesity is an independent risk factor for albuminuria in non-diabetic South Asian subjects

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Published in Diabetes Care 2007;30:1840-4.

Abstract

Objective

South Asians have a high prevalence of central obesity. When the diagnosis diabetes is made, they have a very high risk of developing renal failure. In the current study, we explored the hypothesis that central obesity is associated with the development of renal injury, prior to the manifestation of diabetes mellitus.

Research design and methods

We invited first-degree non-diabetic relatives of South Asian type 2 diabetic patients for investigation of microalbuminuria and diabetes. Subjects who used antihypertensive or antidiabetic medication were excluded. We performed a glucose tolerance test according to the classic WHO-criteria; 205 subjects were normoglycemic; we excluded 25 because of impaired glucose tolerance, and 30 subjects were excluded because of de novo diabetes. Central obesity was measured by waist-to-hip ratio (WHR). Albuminuria was measured as albumin/creatinine ratio (ACR) in the early morning urine.

Results

Central obesity was independently related with albuminuria in the 205 normoglycemic subjects. We found no relation of fasting blood glucose or systolic blood pressure with albuminuria. Multivariate analysis for the presence of increased albuminuria (median ACR > 0.31 mg/mmol) showed a relative risk of 4.1 for the highest versus the lowest tertile of WHR ($p = 0.002$).

Conclusions

Central obesity is an early and independent risk factor for increased albuminuria in normoglycemic South Asian subjects. This could explain the high incidence of diabetic renal disease in South Asians, probably by the mechanism of insulin resistance and endothelial dysfunction in the pre-diabetic state.

Introduction

People of South Asian background (from India, Pakistan, Bangladesh and Sri Lanka) have a three times higher risk of developing diabetic nephropathy [1] and an almost 40-fold increased risk for end-stage diabetic nephropathy when compared to Caucasians. [2] The higher prevalence of diabetes only partially explains this high risk. [3-6] Also classical risk factors for nephropathy like hypertension, smoking, BMI, age, HbA1c or family history did not explain these renal complications in South Asians. [1;7] A population survey in the UK showed more microalbuminuria in South Asians when compared to Europeans. [8] After adjustment for age, hypertension and diabetes, urinary albumin excretion was still higher in South Asians than Europeans. So, the risk to develop renal injury appears to occur earlier in the course of the disease.

Central obesity reflected by a high waist-to-hip ratio (WHR) has only recently received more attention as a potential risk factor for renal disease in non-diabetic subjects. [9-10] The pathogenesis is unclear and could be mediated primarily by adipogenic inflammation and endothelial dysfunction giving microalbuminuria, or secondarily by hypertension and hyperglycemia which accompany central obesity.

Central obesity is known to be more common in South Asians compared to Caucasians. [11-12] Moreover, at the same level of WHR, South Asians seem to have increased abdominal visceral fat and greater insulin resistance compared to Caucasians. [12-13] It is not known whether this central obesity could explain the high risk for diabetic nephropathy in South Asian patients. Especially, we wanted to know whether central obesity is associated with the presence of renal injury (albuminuria) at a stage before the diabetes is diagnosed, independent of other risk factors as blood pressure and fasting blood glucose.

Research design and methods

The present study was part of the Hindustani Diabetic Nephropathy Study (HinDiNef), which is a population-based survey conducted in the Netherlands in the city The Hague. [14] The study was setup to detect a genetic susceptibility for nephropathy within the South Asian population, by assessing whether familial clustering of nephropathy occurs in families of South Asian type 2 diabetic patients with end-stage renal failure. For the recruitment of the diabetic index patients, we refer to our previously published study. [14] In the former published study, we compared nephropathy prevalence between

two groups of first-degree relatives of South Asian patients with type 2 diabetes; the first group (case-relatives) consisted of 169 relatives of patients with end-stage diabetic nephropathy; the second group (control-relatives) consisted of 161 relatives of diabetic patients who had no nephropathy. We did not find more nephropathy in relatives of South Asian type 2 diabetes patients with end-stage diabetic nephropathy in comparison with control-relatives. Diabetes was distributed equally in both family groups.

In the current study, we had 330 first degree family members. To prevent confounding by the antihypertensive or antidiabetic medication on the outcome of albuminuria, we excluded 70 patients. The remaining 260 relatives had glucose tolerance testing (GTT) using the classic WHO criteria. [15] A fasting blood glucose higher than 7.8 mmol/L or two-hour GTT value higher than 11.1 mmol/L, was classified as de novo-diabetes. If the fasting blood glucose was below the 7.8 mmol/L and two-hour GTT value was between 7.8-11.1 mmol/L, they were classified as impaired glucose tolerance. A two-hour GTT value below the 7.8 mmol/L, was classified as normoglycemic. After testing, 205 subjects were normoglycemic and eligible for our study. We excluded 25 subjects with impaired glucose tolerance and 30 subjects with de novo diabetes from further analysis.

All first-degree relatives (father, mother, siblings, and children) of the South Asian diabetic patients, living in the Netherlands, were invited as part of a family investigation for diabetes and renal disease. We invited the relatives at random during the investigation period. Relatives who were pregnant were invited later on, three months after they gave birth. Subjects younger than 16 years were not included. We tried to avoid appointments during the menstrual period of women. The study protocol was approved by the Institutional Medical Ethics Committee in accordance with the Declaration of Helsinki.

Procedures and measurements

The family relatives came during the morning hours, after fasting for at least 8 hours. Fasting venous blood samples were drawn. An oral glucose tolerance test was done with 75 gram glucose and the fasting glucose as well as two hour glucose was measured. The relatives brought an early morning urine sample for quantitative measurements of albuminuria. They stayed in a quiet room and the blood pressure was measured three times after 5 minutes rest in sitting position using an OMRON 705CP automatic oscillometric blood pressure device. The cuff was placed at the right upper arm. If the circumference of the arm exceeded 32 cm, we used a large cuff. The weight

and height were recorded in underwear, just as the circumference measurements of the waist and hip. A questionnaire was used to obtain data on age, sex, diabetes, hypertension, smoking and medication.

Laboratory measurements

Urinary albumin and protein were measured by immunoturbidimetric assay on a Hitachi 911, as was the HDL-cholesterol in serum. Glucose, creatinine, cholesterol and triglycerides were measured on a Hitachi-747 (Hitachi Tokyo, Japan). HbA1c was measured using the HPLC method with a Variant analyzer, Biorad, Hercules, CA, USA. Variance Coefficient was 1.5% at different levels. The reference values for HbA1c were between 4.3 and 6.3%. C-reactive protein (CRP) was measured on a fully automated P 800 analyzer (Roche/Hitachi, Tokyo, Japan) with an immunoturbidimetric assay. The interassay Variance Coefficient was < 2.5% at different levels. Albuminuria was measured in relation to the creatinine and expressed as ratio of albumin/creatinine ratio (ACR) in mg/mmol. The renal function was estimated using the adjusted 4-variable MDRD-formula. [16]

Statistical Analysis

The relation of albuminuria with tertiles waist-to-hip ratio (WHR), blood glucose and systolic blood pressure was studied in the non-diabetic normoglycemic subjects (n = 205). Continuous variables were expressed as mean ± SD unless otherwise specified. Student's t test was used for continuous variables and the Chi-square test for categorical variables to compare differences between albuminuria groups. The tertiles of WHR were stratified for sex, to abolish sex specific differences in WHR. For comparing differences in median ACR and CRP between the lowest versus the highest tertile of WHR, the Mann-Whitney test was used. Multivariate logistic regression analysis was performed for increased albuminuria as dependent variable. We defined "increased" albuminuria as ACR higher than the median value of the analyzed study group: > 0.31 mg/mmol. We used systolic blood pressure, two-hour blood glucose, BMI and age as continuous variables and used smoking, sex, and tertiles of WHR as categorical variables. Current smokers and subjects who stopped smoking less than five years ago were classified as smokers; all others were classified as non-smokers.

Results

The characteristics of the 205 normoglycemic subjects are shown in relation to low or increased albumin/creatinine ratio (ACR) in **Table 1**. The mean ACR was 0.17 mg/mmol in the low albuminuria versus 0.96 in the increased albuminuria group. The subjects had a mean age of about 37 years, 44% was male. Subjects with increased albuminuria had a slightly higher WHR and blood pressure. The mean BMI and CRP were lower in the increased albuminuria group. There were no differences in age, sex, smoking, and familial renal disease between the groups. Renal function measured by MDRD formula was slightly higher in the increased albuminuria group.

Table 1: *Basic characteristics of 205 normoglycemic South Asians. The subjects represented as total group , low albuminuria (ACR ≤ 0.31 mg/mmol) and "increased" albuminuria (ACR > 0.31 mg/mmol). Values represent means ± SD unless otherwise stated.*

	Total	Albumin / creatinine ratio		
		≤ 0.31	> 0.31	P-value
Number	205	105	100	
Waist-to-hip ratio (WHR)	0.90±0.08	0.89±0.08	0.91±0.08	0.15
Albumin/creatinine ratio (mg/mmol)	0.55±1.36	0.17±0.09	0.96±1.9	<0.001
Age (years)	37.3±9.4	36.9±9.4	37.0±9.5	0.92
Male sex (%)	43.9	44.8	43.0	0.80
BMI (kg/m^2)	25.4±4.2	25.7±4.3	25.1±4.1	0.32
Fasting glucose	5.1±0.54	5.1±0.55	5.1±0.54	0.46
Two-hour blood glucose	5.4±1.21	5.4±1.18	5.4±1.25	0.97
Total cholesterol	5.17±0.99	5.2±0.97	5.1±1.01	0.45
HDL-cholesterol	1.3±0.36	1.3±0.38	1.3±0.35	0.69
Triglycerides	1.3±0.70	1.2±0.63	1.4±0.77	0.26
C-reactive protein (CRP)	4.2±6.1	4.7±6.1	3.6±6.0	0.19
Smoking (%)	34.8	35.2	34.3	0.89
Systolic blood pressure (mmHg)	120±15.6	119±12.6	120±18.2	0.51
Diastolic blood pressure (mmHg)	76±10.0	75±8.9	77±11.0	0.10
MDRD clearance (ml/min/1.73 m^2)	85±13.0	83±13.1	87±12.6	0.027
Family history of renal failure (%)	53.7	53.3	54.0	0.92

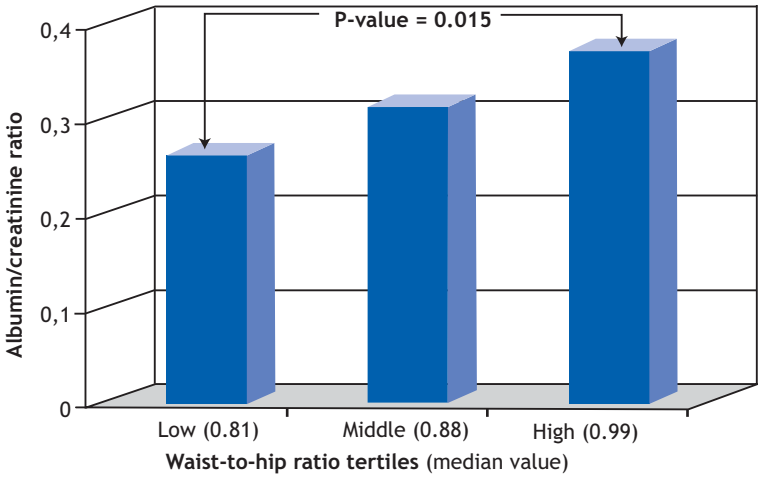

Figure 1: *Shows the median albumin/creatinine ratio (ACR) in the urine in relation to tertiles of central obesity (WHR). The median ACR rose simultaneous with increasing tertiles of WHR. The difference in median ACR between the lowest versus the highest tertile WHR was 0.16 mg/mmol; p = 0.015.*

The median CRP also correlated with the increase of the WHR tertiles. The difference in CRP between the lowest versus the highest tertile was 2 mg/L; p = 0.02.

Univariate and multivariate analysis

The results of the univariate analysis for having an increased albuminuria (ACR > 0.31 mg/mmol) are shown in **Table 2** (univariate OR). There was a significant relation between urinary albumin excretion above 0.31 mg/mmol with WHR. No relation could be found for age, BMI, weight, fasting and two-hour blood glucose, triglycerides, smoking, blood pressure, CRP and family history in the univariate analysis.

After adjustment for only age and sex, we found a twice higher risk for increased albuminuria (ACR > 0.31 mg/mmol) for the higher versus the lower tertile of WHR: OR 2.2 (95 % CI 1.06 to 4.4); p = 0.03. Separate multivariate analysis stratified for sex or BMI subsets revealed no different conclusions. There was no relation of sex and BMI with increased albuminuria. The results of the adjusted multivariate analysis for sex, age, smoking, systolic blood pressure, CRP, two-hour blood glucose and BMI are shown in **Table 2** (multivariate OR). After multivariate adjustment, the OR for increased albuminuria went up to 4.1 for the highest WHR tertile (p = 0.002).

Table 2: *Univariate and multivariate analysis for "increased" albuminuria (ACR > 0.31 mg/mmol) as dependent variable, expressed as odds ratio (OR) with 95 % CI and p-value.*

		Odds Ratio of increased albuminuria (95 %CI)			
		Univariate OR	**P-value**	**Multivariate OR***	**P-value**
Waist-to-hip ratio tertiles	Low	1 (ref.)		1 (ref.)	
	Middle	1.5 (0.75 to 2.9)	0.26	2.2 (1.0 to 4.7)	0.05
	High	2.0 (1.03 to 4.0)	0.04	4.1 (1.6 to 10.0)	0.002
Female sex		1.1 (0.62 to 1.9)	0.80	1.5 (0.80 to 3.0)	0.20
Age		1.0 (0.97 to 1.03)	0.92	0.97 (0.94 to 1.01)	0.15
Smoking		0.96 (0.54 to 1.71)	0.89	1.04 (0.55 to 1.96)	0.90
BMI		0.97 (0.91 to 1.03)	0.32	0.91 (0.83 to 0.99)	0.03
Systolic blood pressure (per 10 mmHg)		1.06 (0.89 to 1.27)	0.51	1.17 (0.93 to 1.47)	0.17
C-reactive protein (CRP)		0.97 (0.92 to 1.02)	0.19	0.96 (0.91 to 1.01)	0.16
Two-hour glucose		1.0 (0.8 to 1.26)	0.97	0.99 (0.77 to 1.28)	0.94

*Adjusted for WHR, sex, age, smoking, BMI, blood pressure, CRP, glucose

Discussion

The current study demonstrates that central obesity is the single most important risk factor for increased urinary albumin excretion in non-diabetic South Asian subjects. This relationship was even strengthened after correction for body mass index underscoring the critical role of visceral fat in this relationship. With the increasing central obesity, other components of the metabolic syndrome such as higher blood glucose, CRP, triglycerides and a higher blood pressure emerged. However, none of these factors could independently predict the occurrence of increased urinary albumin excretion. The albumin/creatinine ratios (ACR) in our study are below the conventional definitions of microalbuminuria. Recent studies indicate that comparable levels of albuminuria well below the traditional threshold are a continuous risk factor for cardiovascular morbidity and mortality. [17-20] Due to the lack of a threshold value for increased cardiovascular risk we defined "increased" albuminuria as an ACR higher than the median value of the analyzed study group: > 0.31 mg/mmol. These findings suggest that the observed increase of urinary albumin excretion associated with an increased WHR is an important predictor of cardiovascular morbidity in this high risk South Asian population.

In the current study we used first degree relatives of South Asian type 2 diabetic patients. We previously reported no familial predisposition for nephropathy in this group. [14] Also the environmental factors are homogenous throughout the population. Therefore the current results most likely can be related to the South Asian ethnicity. It is of interest that such a specific independent relation between visceral obesity and increased albumin excretion has not been described in South Asians. Several studies in Caucasians found a relation between metabolic syndrome, obesity and microalbuminuria [10;21-26] and renal insufficiency. [27-28] Studies in non-Caucasian populations revealed conflicting results. For example in Hispanics no relationship was found, [29] while in Korean persons a relationship between central obesity and microalbuminuria could be found. [30] We found a clear independent relation with central obesity in non-diabetic South Asians, emphasizing this mechanism in this population. The SHARE study showed higher fasting blood glucose, cholesterol, systolic blood pressure in South Asians in comparison to Europeans for the same BMI or WHR. Even in the normal range, the metabolic markers were still higher. The reference value of WHR and BMI in South Asians has to be adjusted downwards, and further studies are warranted to address this issue. [31]

These findings have major implications for the public health in this ethnic group. South Asians are very prone to obesity and type 2 diabetes. [12-13] This susceptibility for central obesity and insulin resistance could explain the higher rates of end-stage diabetic nephropathy in migrant South Asians. [2] Apparently by the time the diagnosis type 2 diabetes mellitus is made, the subjects may have already developed renal injury. [7] Our observation may help explain the high prevalence of diabetic nephropathy in this ethnic group. We cannot deduce the exact mechanisms involved in the link between visceral obesity and the development of nephropathy from our current study. Most likely this involves a multi-factorial complex pathogenesis, including the release of adipokines and pro-inflammatory cytokines from the visceral adipose tissue, sympathetic activation and activation of the renin-angiotensin system by adipocytes. [32-34] Irrespective of the pathogenic mechanisms involved, the current study strongly argues for early intervention strategies aimed at reducing visceral obesity in South Asians. Life style intervention has proven to be very effective in prevention of the development of type 2 diabetes in other ethnic populations [35] and evaluation of such interventions are warranted in this population with regards to their potential prevention of organ damage as well.

One of the limitations of our study is the cross-sectional family design. We therefore cannot make correlations with development of diabetic nephropathy. However, in a

recent follow-up study, South Asians had a higher incidence of diabetic nephropathy and a faster decline in renal function as compared to European type 2 diabetic patients. [1]

Conclusion

In relative young non-diabetic South Asians, we were able to show a clear relation of albuminuria with central obesity, independent of blood glucose, blood pressure and renal function. This could explain the higher rates of microalbuminuria and end-stage diabetic nephropathy in the South Asian population. Screening for central obesity in South Asians with a simple measure tape could identify persons at risk for developing renal organ damage in the “normal” glucose range.

Acknowledgements

We like to express our gratitude to the Dutch Diabetes Research Foundation for supporting our study. We thank Mrs. Sylvana Kadir and Mrs. Jozé Krol for their valuable and indispensable assistance in this project.

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