Diabetic nephropathy in Surinamese South Asian subjects

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“Life is what happens to you while you’re busy making other plans”

John Lennon

Ter herinnering aan mijn moeder

Contents

Benares aan de Ganges, India, ca. 1880.

Chapter 1

General introduction

Diabetic nephropathy is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli. It is characterized by nodular glomerulosclerosis. It is due to longstanding diabetes mellitus, and is the major cause for end-stage renal failure in many Western countries. [1] Besides these renal impacts, leading to dialysis, it is also associated with a high incidence of cardiovascular and eye complications due to concurrent angiopathy in these organs. [2] South Asian immigrants (East Indians) have a high incidence of type 2 diabetes and diabetic cardiovascular and renal complications compared to European persons. [3-11]

South Asian immigrants originally descend from the Indian Subcontinent, previously called British India. The social-scientific literature uses the term East-Indians to refer to immigrated Indians to the Caribbean. However, in the medical literature, immigrated Indians are referred by South Asians. In this thesis we will use the term South Asians because this is currently the most used term to refer to immigrated Indians in the medical literature.

The abolishment of slavery in the European colonies between 1834 and 1863 created the need for a new source of labour on the plantations. [12] In those days, Suriname was a prosperous Dutch Colony in South America. Indian natives (South Asians) were contracted by the Dutch government to work for five years in Suriname in exchange for a small wage, plus room and board. Between 1873 and 1916, about 34000 South Asians were brought to Suriname. [13] Although they had freedom of passage back to India, 22500 persons (66%) stayed in Suriname and has now grown to 300000 persons of whom 160000 live in the Netherlands. [14] Due to the independence of Suriname in 1975 and the political climate, a large group of Surinamese immigrants settled in the Netherlands. Most South Asians took residence in the surrounding of The Hague.

South Asians have a high prevalence of insulin resistance, obesity and type 2 diabetes mellitus. [3;15-19] The prevalence of type 2 diabetes is 7-8 times higher among South Asians than in Dutch European persons in The Hague. [20] This was previously noted in other South Asian immigrant populations worldwide in the UK, South Africa, Mauritius and Canada. [15;21-26] This high prevalence of diabetes is not only an immigration problem but also well-known in India due to the increasing living standards. [27]

Not only diabetes but also diabetic complications are more frequent among South Asians than in British European persons. This was first noted for cardiovascular disease, which is more common in the South Asian population, despite a lower prevalence of risk factors like advanced age, smoking, high blood pressure and dyslipidemia. [4;23;28] In the UK, the mortality from circulatory disease in South Asian persons is 1.5 times that

of the general British population. [29] Despite these lower prevalence of risk factors, South Asian diabetic patients have more renal complications. In comparison to British Europeans, the prevalence of microalbuminuria and end-stage diabetic nephropathy was more common in South Asians than in British Europeans. [8;9;30]

A population survey in the UK showed more microalbuminuria in South Asians than in Europeans. [31] After adjustment for age, hypertension and diabetes, South Asians had a higher urinary albumin excretion than Europeans. So, the risk to develop renal injury appears to occur earlier in the course of the disease. Also non-diabetic South Asians have a higher incidence of end-stage renal disease of undetermined cause than British Europeans. [32] Renal biopsy study showed an excess of hypertensive nephropathy, focal segmental glomerulosclerosis and idiopathic interstitial nephritis in non-diabetic South Asians. [33]

It is not clear if these renal problems are associated with the high rate of central obesity in the South Asian population. Central obesity reflected by a high waist-to-hip ratio (WHR) has only recently received attention as a potential risk factor for renal disease in non-diabetic subjects. [34;35] 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. [36-38]

Central obesity and insulin resistance are known to be more common in South Asians than in Europeans. [15;18] Moreover, at the same level of WHR, South Asians seem to have increased abdominal visceral fat and greater insulin resistance compared to Europeans. [17] The risk of insulin resistance seems to start early in life. Whincup et al. studied insulin resistance in South Asian children and compared them with white British children. [39] South Asian children were no more obese than those of European origin, but fasting and 30 minute post load insulin were about 50% higher. The SHARE study showed higher fasting blood glucose, cholesterol, systolic blood pressure in South Asians than in Europeans for the same body mass index (BMI) or WHR. [40;41] Even in the normal range, the metabolic markers were still higher in South Asians. It is not known whether this tendency for central obesity could lead to early renal injury and albuminuria before the manifestation of diabetes. This could preceed to early diabetic nephropathy and renal failure in the South Asian diabetic patients.

This thesis focuses on the incidence, risk factors and familial predisposition for nephropathy in diabetic and non-diabetic Surinamese South Asian immigrants living in the Netherlands.

Outline of this thesis

Chapter 2 describes the descent of the South Asian immigrants from India to Suriname and the Netherlands, leading to the selection of the study population for the thesis.
Chapter 3 investigates the incidence of end-stage diabetic nephropathy in Surinamese South Asian and the Dutch European population.
Chapter 4 investigates the incidence and progression of diabetic nephropathy in South Asian and Dutch European type 2 diabetic patients.
Chapter 5 investigates familial predisposition for diabetic nephropathy within the South Asian population.
Chapter 6 investigates early renal injury due to central obesity in non-diabetic South Asian subjects.

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Een dorp in de omgeving van Calcutta, India, ca. 1870.

Chapter 2

Study population

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Abstract

This chapter describes the recruitment, origins and selection process of the South Asian immigrant to Suriname and the Netherlands. Subsequently, we describe the two South Asian study cohorts used for this thesis: the HinDiNef (family study) and the HinDia project (out-patient clinic study).

Introduction

South Asian immigrants originally descend from the Indian Subcontinent, previously called British India (nowadays India, Pakistan and Bangladesh). The social-scientific literature uses the term East-Indians to refer to immigrated Indians to the Caribbean. However, in the medical literature, immigrated Indians are referred to as South Asians or Indo-Asians. In this thesis we will use the term South Asians because this is currently the most used term to refer to immigrated Indians in the medical literature.

Due to the abolishment of slavery the number of plantations in Suriname dropped dramatically from 452 to 131 during the years 1832-1873. [1] From 1835 to 1917, approximately 500000 British Indians were introduced into the Caribbean. About half of them (239000) went to British Guyana, the neighbour country of Suriname. Trinidad received 144000 Indians, and the remainder entered Jamaica, Guadeloupe, Martinique and Suriname. [2] The plantations in British-Guyana which suffered the same problems with the abolishment of slavery, flourished again. In agreement with a Dutch-British Treaty of September 8, 1870 immigration to Suriname from British India became organized. [3] From 1873 until 1916 some 64 ship transports were made. About 34000 South Asian people were shipped to Suriname. In that same period about 11000 contract workers returned when their 5 year contract was finished. [1]

The migration from India to Suriname

The recruitment of immigrants was only done in a circumscriptive area of North India called Uttar Pradesh , Uttarakhand and West-Bihar (see **figure 1**). This area was known for its overpopulation, poverty and shortage of employment and food. There was a large pressure of soil due to high population growth. According to the Registry of the immigration office in Paramaribo in Suriname, about 80% of the South Asian immigrants originally came from the Uttar Pradesh.

The main motive to migrate was the economic situation in North India. In those days, it was difficult to find an existence due to unemployment, food shortages and social structures like caste system, large(-scale) land ownership and usurers. [4;5]

The Dutch government established a medical selection of the South Asian immigrants because of a high mortality among the South Asian immigrants. [2] Following the agreement the first ship Lalla Rookh arrived on 5 June 1873 in Paramaribo and was followed by 7 more ships. The first two years were disastrous. More than 20% of the immigrants died during the voyage and at the plantations. [6] In June 1874 the British government became alarmed of the mortality rate and stopped the sea traffic

to Suriname and demanded the betterment of the conditions of the immigrants by giving better medical support. During 1877-78 the traffic was resumed but it was again interrupted in the years of 1879, 1886 and 1888. In later transports only 2% died during the journey. Because the South Asians stayed British Indian citizen, the Dutch government had to improve the medical and social circumstances. Therefore the South Asian immigrants had to pass five medical examinations before shipping to Suriname in order to prevent diseases and mortality. [2;7] South Asian contract laborers were examined on physical wellness, height, and fractures. They were also screened on venereal diseases, contageous diseases like cholera, tuberculosis and typhoid fever. Compared to the British Indian colonies like Mauritius and British Guyana, medical selection, supplies and life circumstances were better for Surinamese South Asian immigrants. [8]

Figure 1: *Circumscript area of recruitment of South Asian immigrants. (Adapted from C.J.M. de Klerk: "De immigratie der Hindostanen in Suriname", Amsterdam 1953: Urbi et Orbi.)*

South Asian population in Suriname

Upon arrival in Suriname the South Asian migrants worked on the plantations for 5 years as indentured labourers in agriculture and sugar cane fields. After 5 years, they had the option to go back to India with a free passage. About 34% of the South Asian immigrants went back to India. [1] Most of them stayed and received governmental farming land to stimulate the colonisation of Suriname. During and after the second World War most South Asians migrated from the rural areas to Paramaribo. This offered them better opportunities finding work, education and all the comforts of city living. After 1945, the means of higher education improved and more South Asians graduated from the university. Many South Asians were also attracted to politics. [9]

Migration to The Netherlands

In a short time a relatively young South Asian population went to the Netherlands. This was mainly due to the political climate in Suriname. There were two large migration waves. The first was around the independence of Suriname in 1975 and the second wave was around the revolution coup of Desi Bouterse in February 1980. See **figure 2**. After migration to the Netherlands most South Asians settled in the resident city The Hague and in Rotterdam. According to the records of the Statistics Netherlands (CBS statline 2002), The Hague and surroundings have about 35000 and Rotterdam has about 28000 South Asian inhabitants. [10]

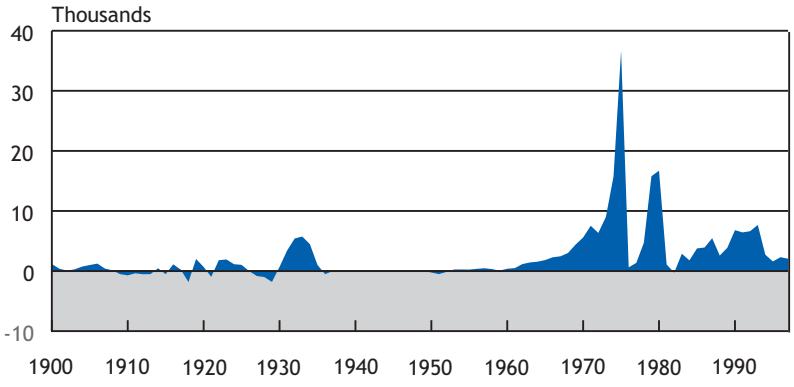

Figure 2: *Net migration from Suriname to the Netherlands.*

The immigrated Surinamese South Asians are much younger than the Native Dutch population. See **figure 3**.

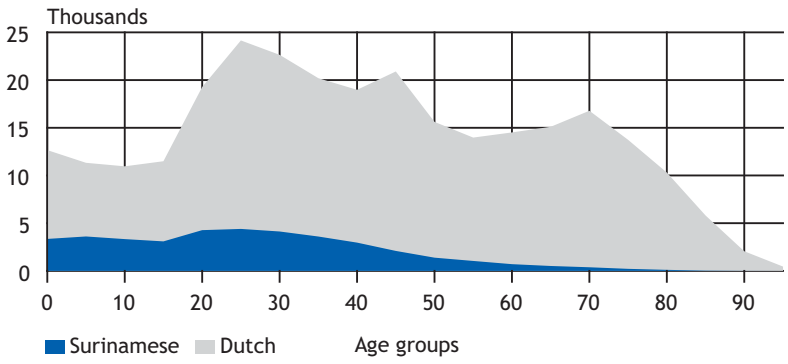

Figure 3: *Population composition of the city The Hague in the Netherlands. South Asians are relative young and older age groups are virtually absent.*

Selection of the study population for this thesis

In the subsequent paragraphs, we describe the different South Asian groups who were selected for this thesis. We used two study populations: a family cohort (chapter 3, 5 and 6) and a diabetic out-patient clinic cohort (chapter 4). See **figure 4**.

Chapter 3 We first performed a case-control study to determine the risk for end-stage diabetic nephropathy in the South Asian population, in comparison to Dutch European (native Dutch) persons. In the Netherlands patients are assigned to a regional dialysis centre based on the place of residence of the patient. The overall population figures per region are known and new patients are registered within three months after start of renal replacement therapy. This permitted us to determine the relative risk of end-stage diabetic nephropathy in these two ethnic groups. Because of the regional allocation of patients for renal replacement therapy, patients who live in The Hague are therefore treated in only three dialysis centres. In this case-control investigation, the case group is formed by dialysis patients with end-stage diabetic nephropathy. The control group comprises the general population in the city of The Hague. The investigated risk factor is South Asian ethnicity. If this ethnicity would be associated with a higher risk for end-stage diabetic nephropathy, this would result in an excess of South Asians in the dialysis wards in The Hague.

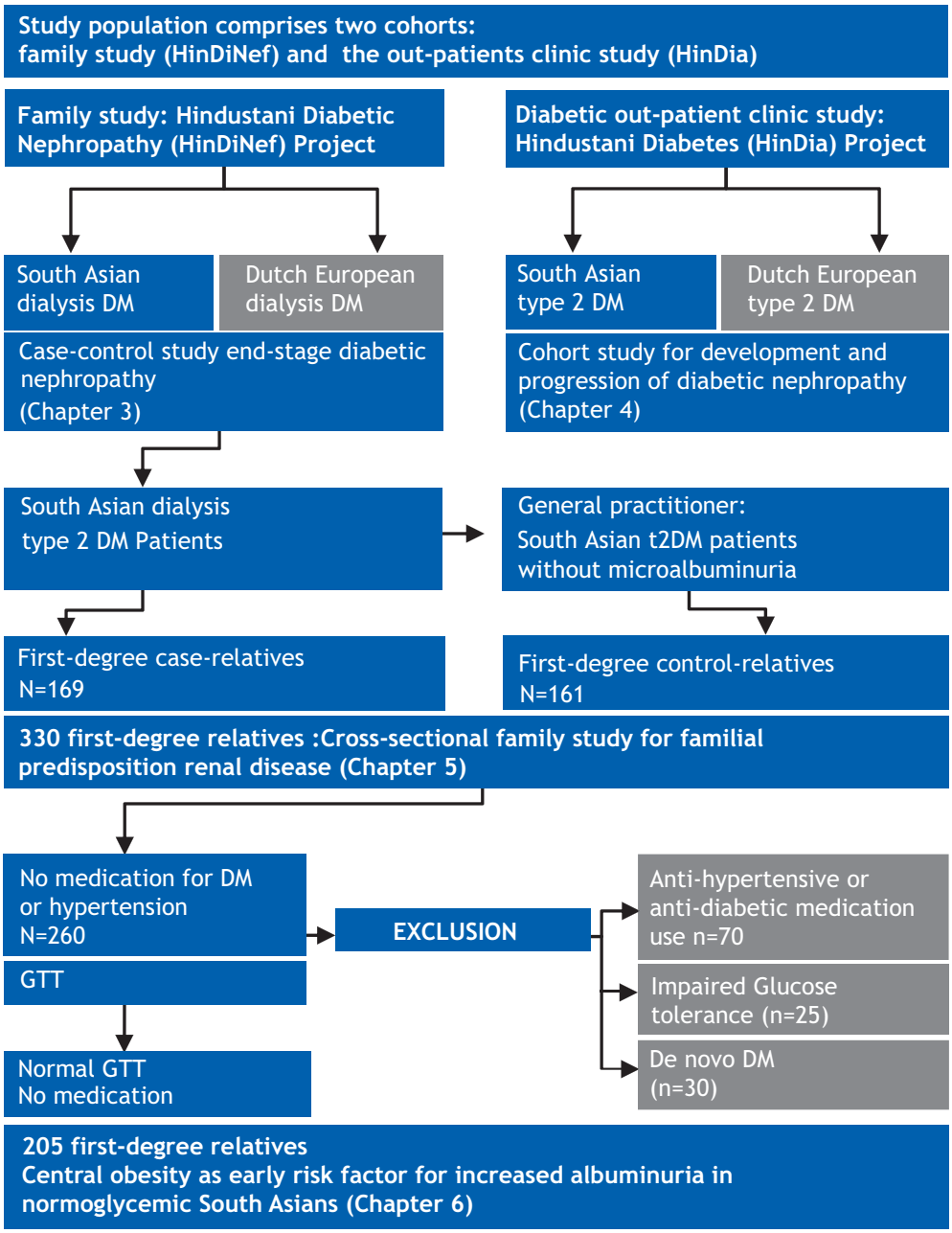

***Figure 4**: Description of the two study populations for this thesis.*

All newly started dialysis patients between 1990 and 1998 with end-stage diabetic nephropathy were identified through this registry. General population: this was based on the average population figures in the period 1995 to 1998 derived from the Central Bureau of Statistics. Patients were selected because they were coded by their nephrologist as having diabetic nephropathy. The medical records of all patients were examined for type of diabetes mellitus, presence of proteinuria, diabetic retinopathy and the absence of other causes of nephropathy like infections, tuberculosis, renal stones or obstructive nephropathy.

Chapter 5 We subsequently performed a family study for familial predisposition of renal disease among first-degree family members of South Asian type 2 diabetic patients. We contacted first-degree family members of the South Asian dialysis patients who participated in the case-control study of chapter 3. We visited the general practitioners of the dialysis patients, and for every dialysis patient, a type 2 diabetic patient was randomly drawn from the registry of the general practitioner. The control diabetic patients had to be of South Asian origin, same sex as the dialysis patient without microalbuminuria. We subsequently contacted their first-degree relatives as control families. We compared nephropathy prevalence between these 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. A total of 330 case- and control-relatives were examined for diabetes, blood pressure, renal function, microalbuminuria and urine dipstick measurements.

Chapter 6 We explored the hypothesis that central obesity is associated with the development of renal injury, prior to the manifestation of diabetes mellitus. In the former family study of Chapter 5, 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 underwent glucose tolerance testing (GTT) using the classic WHO criteria. 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. Central obesity was measured by waist-to-hip ratio (WHR). Albuminuria was measured as albumin/creatinine ratio (ACR) in the early morning urine.

Chapter 4 We performed a cohort study in South Asian and Dutch European type 2 diabetic patients to compare the incidence of microalbuminuria and progression of renal failure between both ethnic groups. We used the registry of the out-

patient diabetic clinic of the Haga Teaching Hospital, during the period 1994-1996. The ethnicity was self-stated. Migrants who originally descended from the Indian subcontinent were reported as South Asian. Patients who were of Dutch descent were reported as European. We selected a cohort of 149 South Asian type 2 diabetic patients and matched them for sex and level of urinary albumin excretion with 155 European patients. Urinary albumin excretion and creatinine clearance were measured at inclusion and after 5 years follow-up.

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Pas gearriveerde immigranten uit toenmalig Brits-Indië staan voor het immigratiedepot nabij Paramaribo, Suriname, ca. 1915.

Chapter 3

Increased end-stage diabetic nephropathy in South Asian immigrants living in the Netherlands

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Abstract

Objective

To investigate the risk of end-stage diabetic nephropathy due to type 2 diabetes mellitus in South Asian immigrants from Suriname.

Research design and methods

A demographically based case-control study in Surinamese South Asians and Dutch European individuals. All newly started dialysis patients between 1990 and 1998 with end-stage diabetic nephropathy were identified through a national registry of all patients entering a renal replacement program in the Netherlands. The general population of native Dutch and Surinamese South Asians were taken as controls.

Results

Among South Asians, the age adjusted relative risk of end-stage diabetic nephropathy was 38 (95% confidence interval 16 to 91) in comparison with the native Dutch population. The duration of diabetes till start of dialysis treatment was similar in both ethnic groups, about 17 years.

Conclusion

South Asians had a nearly 40-fold increase in the risk for end-stage diabetic nephropathy due to type 2 diabetes mellitus, in comparison with the Native Dutch population. This was higher than expected on the basis of the eight-fold higher prevalence of diabetes the South Asian population. The similar diabetes duration until onset of the dialysis treatment in both ethnic groups supports the hypothesis of a higher incidence of diabetic nephropathy in the South Asian diabetic population. Early and frequent screening for diabetes and microalbuminuria is recommended in South Asians.

Introduction

Type 2 diabetes mellitus is frequently seen in immigrants of Asian Indian descent (South Asians). Three studies in Southall, Coventry and Leicester showed that diabetes occurs three to four times more frequent in those of South Asian origin than among the white UK population. [1-6] In the Netherlands, the increased prevalence of diabetes among Surinamese South Asian immigrants was recently investigated by the local Community Health Service in the city of The Hague. This survey revealed an eight times higher prevalence of diabetes in Surinamese South Asians when compared to the general Dutch population. [7]

Several hospital-based studies in the UK have shown a ten-fold higher incidence of end-stage renal failure due to diabetic nephropathy in South Asian immigrants, as compared to the European population. [2;8-11] Because a proportion of patients attended other centres, concerns arose about underestimation of the true incidence in these studies. Furthermore, specific studies on type 2 diabetes mellitus and end-stage renal failure are still lacking in the South Asian population. In several studies, microalbuminuria was more frequent in diabetic South Asians, which suggests that they are more prone to develop kidney disease. [12-14] There is no evidence that patients of South Asian origin have more often a high blood pressure or a poorer metabolic control explaining the early diabetic nephropathy. [2;4;15]

The national registry for renal replacement therapy in the Netherlands offered a unique possibility to study the relative risk of end-stage diabetic renal disease among Surinamese South Asians and Dutch European persons who are living in the city of The Hague. In the Netherlands patients are assigned to a regional dialysis center based on the place of residence of the patient. The overall population figures per region are known and new patients are registered within three months after start of renal replacement therapy. This permitted us to determine the relative risk of end-stage diabetic nephropathy in these two ethnic groups. In this article, we focus on end-stage renal failure due to type 2 diabetes mellitus, because specific incidence data on end-stage renal failure in type 2 diabetes are not known in the South Asian population.

Research design and methods

Clinical data from all patients who started with their dialysis treatment between Januari 1,1990 and December 31, 1997 were received from the Renal Replacement Registry Netherlands (a Dutch acronym: RENINE). These data were validated using the records of the dialysis centers.

Population

In this study, the case group is formed by dialysis patients with ESRF due to diabetes mellitus. The control group comprises the general population in the city of The Hague. The investigated risk factor is an South Asian ethnicity. If this ethnicity would have a higher risk for ESRF due to diabetes mellitus, this would result in an excess of South Asians in the dialysis wards in The Hague.

Case group: we identified all new South Asian and Dutch European dialysis patients with diabetic nephropathy who started their dialysis treatment in one of the three hospitals from 1990 until 1998. Patients living outside the city of The Hague were excluded. We adjusted for possible immigration for medical reasons, by excluding all South Asian patients who migrated to the Netherlands within two years before they started their dialysis treatment.

General population: this was based on the average population figures in the period 1995 to 1998 derived from the Statistics Netherlands (Central Bureau of Statistics). The term *"South Asians"* refers to all descendants of emigrants including the Indian subcontinent, like India, Pakistan, Nepal and Bangladesh. The white Dutch population is indicated with *"European"*. The Hague has 330000 inhabitants of whom 82% are European, 10% South Asians and 8% have another ethnicity. The Hague has about 189000 Dutch and 15000 Surinamese South Asian inhabitants *with an age of 30 years or older.*

Diagnosis of diabetic nephropathy: patients were selected because they were coded in the RENINE registry as having diabetic nephropathy by their nephrologist. The medical records of all patients were examined for type of diabetes mellitus, presence of proteinuria, diabetic retinopathy and the absence of other causes of nephropathy like infections, tuberculosis, renal stones or obstructive nephropathy. Diabetic retinopathy was defined by proliferative retinopathy necessitating laser treatment.

Type diabetes mellitus: patients who had used oral antidiabetic medication for more than one year or who had a high morning c-peptide level were coded as type 2 diabetic patients. Patients who used only insulin with a history of keto-acidosis were coded as type 1 diabetic patients.

Statistical analyses

By comparing both populations, we calculated crude odds-ratios as estimates of the relative risks with 95% confidence intervals for the risk factor of having a South Asian ethnicity. The South Asian population has a different age-distribution. Older age groups form a larger proportion of the native Europeans, than in the South Asian population: in the region, approximately 1700 South Asians were aged above the 60 years versus 76000 native Dutch inhabitants. Because this leads to an underestimation of the risk for end-stage diabetic nephropathy in the South Asians, we used age-stratification with the Mantel-Haenszel odds ratio in the population of 30 years and older. The following age-stratification was chosen: 30 to 49 years, 50 to 59 years and above the 59 years. The same age-stratification was used in a previous diabetes prevalence study done by the Municipal Health Service in The Hague to evaluate the higher prevalence of diabetes among the South Asian population. [7] The figures of the inhabitants were based on the census figures of the Statistics Netherlands (CBS) and the Municipal Health Services in the period 1995 to 1998.

The statistical significances in the difference of mean age, duration of the diabetes between the South Asian and Dutch European patients were calculated using the Student's t-test. Differences in type diabetes, dialysis treatment modalities were expressed as percentage difference with 95% confidence intervals.

Results

Study population

From January 1, 1990 to December 31, 1997, there were 94 new patients registered who started with dialysis treatment due to diabetic nephropathy. We excluded 25 patients because they had another ethnicity than Dutch European or South Asian. Eight patients were excluded because they lived outside the study region comprising The Hague and its surrounding suburbs. One European and two South Asian patients were incorrectly registered because they had no diabetes or diabetic nephropathy. Two patients (one European and one South Asian) had diabetes mellitus without proteinuria or a documented diabetic retinopathy. Because no renal biopsy had been done, we excluded these patients from the analysis to prevent misclassification of diabetic nephropathy. After the exclusion, 56 patients entered the study.

Basic characteristics

The basic characteristics of the study population are given in **Table 1**. There were 27 Dutch European and 29 South Asian patients who started with dialysis treatment due to diabetic nephropathy. The South Asians were slightly younger at the start of the dialysis treatment. The number of female patients predominated slightly in both ethnic groups. Type 2 diabetes mellitus was more present in the South Asian diabetic patients, 93% versus 67% in the European diabetic patients (difference 26% with 95% CI 6.4 to 46.5). About 74% of the Dutch European and 72% of the South Asian patients had a documented proliferative diabetic retinopathy. In about a quarter of the patients no report of an eye-examination could be found in the medical records. The prevalence of diabetic retinopathy did not differ between the European and the South Asian patient groups.

Table 1: *basic characteristics of the selected dialysis population*

	Dutch European	South Asians
Total number of patients	27	29
Mean age at onset of ESRF (yrs.)	58.8	53.3
Males number (%)	13 (48.1%)	14 (48.3%)
Type 2 diabetes mellitus (%)	18 (67%)	27 (93%)
Diabetic retinopathy		
No proliferative retinopathy (%)	0	1 (4%)
Proliferative retinopathy (%)	20 (74%)	21 (72%)
No documented visits (%)	7 (26%)	7 (24%)

Diagnosis diabetic nephropathy

The registered diagnoses were verified by reviewing the medical records of the patients (**Table 2**). No differences were observed in clinical criteria used to diagnose diabetic nephropathy. All patients had proteinuria. Thirteen patients underwent a renal biopsy: seven in the Dutch European patient group and six in the South Asian patient group. The histological results were consistent with diabetic nephropathy.

Type 2 diabetes mellitus

There were 18 Dutch European and 27 South Asian dialysis patients with type 2 diabetes mellitus. South Asian patients had an earlier age at onset of diabetes than Caucasians: 36 versus 50 years (difference 14 years with 95% confidence interval 6 to 20). Similarly, dialysis treatment started earlier: 67 versus 54 years (difference 13 years with 95%

confidence interval 7 to 21). The duration of the diabetes until the start of dialysis treatment was comparable in both ethnic groups: 16.7 and 17.6 years (difference -0.9 years with 95% confidence interval –6.2 to 4.6)

Table 2: *Diagnostic criteria for diabetic nephropathy in 56 patients with end-stage renal failure.*

	Europeans Number (%)	South Asians Number (%)
Diabetes, proteinuria and diabetic retinopathy	20 (74%)	21 (72%)
Diabetes, proteinuria	7 (26%)	8 (28%)

Relative risk of end-stage diabetic nephropathy

To calculate relative risks, we made a comparison with the population of *30 years and older* living in the city of The Hague. When looking at the relative risk for end-stage diabetic nephropathy, we excluded 12 patients because they lived in the suburbs of The Hague. For the final analysis two South Asians were excluded because they did not descent from Surinamese South Asian immigrants, and four South Asian patients were excluded because they had immigrated to the Netherlands within two years after start of dialysis therapy. Two patients were left out of the calculation because they were younger than 30 years at start of renal replacement therapy. A total of 16 European and 20 South Asian patients were included (**figure 1**). The crude and age-adjusted relative risks with 95% confidence intervals are given in **Table 3**. *The crude relative risk* for end-stage diabetic nephropathy overall was 16.2 for South Asians, with a 95%-confidence interval of 8.1 to 30.3. When looking at type 1 diabetes there was a slight increase, but the numbers are very small. The largest risk of nephropathy is caused by type 2 diabetes: 21.6-times higher incidence was noticed in the South Asian group. The *age-adjusted relative risk* using the Mantel-Haenszel method over the three age-strata showed an overall relative risk for end-stage diabetic nephropathy of 21.6 (95% confidence interval 10.1 to 42.7). This was mainly due to type 2 diabetes giving an age-adjusted relative risk of 37.7 (95% confidence interval 15.6 to 91.2).

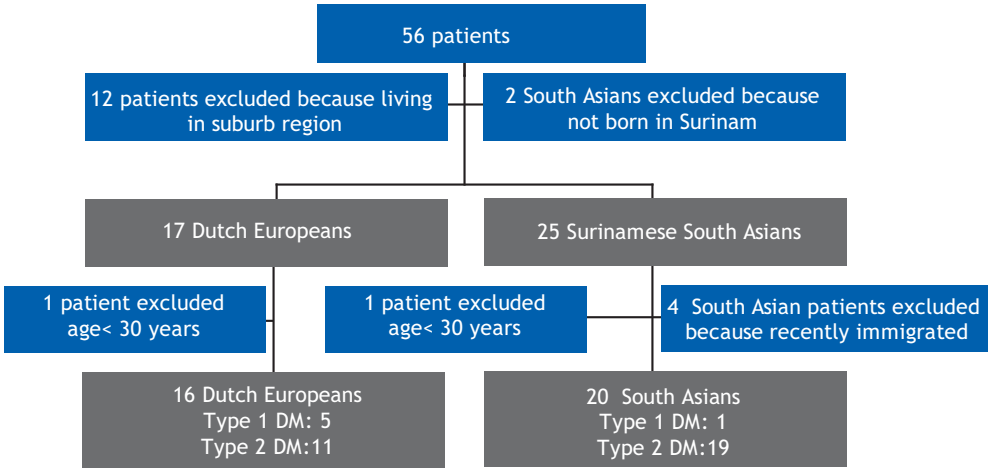

***Figure 1**: Flow diagram of the study population used for the incidence calculations.*

***Table 3**: Relative risk for end-stage diabetic nephropathy in Dutch European and South Asian inhabitants above the age of 30 years. Age corrected relative risk was calculated using the Mantel-Haenszel method. (95% confidence intervals are given in brackets).*

	Crude relative risk	Age-corrected relative risk
Overall risk ESRF due to diabetes mellitus	16.2 (95%-CI 8.1 to 30.3)	21.7 (95%-CI 10.1 to 42.7)
Relative risk in type 1 diabetes	2.52 (95%-CI 0.3 to 21.6)	Not given because of small numbers
Relative risk in type 2 diabetes	21.6 (95%-CI 10.3 to 45.7)	37.7 (95%-CI 15.6 to 91.2)

Discussion

We determined the relative risk of end-stage renal failure (ESRF) due to diabetes mellitus between Surinamese South Asian immigrants and native Dutch European persons older than 30 years, who are living in the city of The Hague. The Surinamese South Asians, originally descended from the Indian subcontinent. Due to the former colonial bounds with the Netherlands, a relatively young South Asian migrant population settled in the Netherlands. In this population, the age-adjusted relative risk for ESRF due to both types of diabetes was 22-times increased. ESRF due to type

2 diabetes was almost 40-fold increased in the South Asian population. Also a slight increase in type 1 diabetes was noted in this population but the numbers were too small to draw conclusions.

We were in an unique position to perform a demographically and geographically defined population study. In the Netherlands, patients with end-stage renal failure are assigned to a dialysis facility based on their place of residence. All patients with ESRF who live in the city of The Hague are therefore treated in only three dialysis centers. We could identify them by using the national registry for renal replacement therapy (RENINE). This registry also contains the diagnosis of end-stage renal failure (ESRF). Throughout the years a nearly 100% response rate was obtained in the registry. We verified the diagnosis of diabetic nephropathy by reviewing the medical charts. Most patients had proteinuria and diabetic retinopathy. In only a few patients a renal biopsy was performed. There were no differences in the criteria used to diagnose diabetic nephropathy in both ethnic groups. It might be argued that we missed some patients with diabetic nephropathy because of incorrect registration of the renal diagnosis. We therefore performed a crosscheck with the hospital registries, which revealed no missed patients. We choose the period until 1998, to ensure that the nephrologist's diagnosis of diabetic nephropathy was not influenced by the study hypothesis. We carefully corrected for immigration for medical reasons by excluding all South Asian patients who immigrated to the Netherlands within two years before onset of renal replacement therapy. The South Asian population had a different age-distribution. Older age groups, which form a large section in Dutch European population are almost absent in the South Asian population. Because this underestimates the risk for end-stage diabetic nephropathy in South Asians, we performed an age correction using the Mantel-Haenszel method. The age-corrected relative risk for ESRF due to type 2 diabetes was 38 compared to Dutch European. We calculated a similar diabetes duration of about 17 years in both ethnic groups. South Asians were 13 years younger at the onset of the dialysis treatment. This age difference could be explained by the younger age at which the diabetes started in the South Asian population, but might also be a reflection of the younger age distribution in the South Asian population. We cannot exclude that more South Asians died from cardiovascular disease before startingdialysis treatment than in the European group. This would underestimate the risk in the South Asian population.

In two hospital-based studies done in the UK, the centre-specific incidence was a tenfold higher for end-stage diabetic nephropathy in the migrant South Asian population. [8;10] The difference with our study is explained by the study design.

Firstly, our study was a demographically and geographically defined population study. This prevented underestimation of the risk by missing patients which were treated in other hospitals. Furthermore, the studies performed in the UK, calculated the risk in the population above the age of 15 while we used only persons aged 30 and above, since the risk of end-stage diabetic nephropathy is neglectible below that age. When we calculated the risk in our population also from the age of 15 years and older the relative risk was similar. Finally, there are differences in disease patterns of South Asian immigrants originating from different parts of the Indian subcontinent. [16] Unlike the South Asians in the UK, Surinamese South Asians originally descend from a restricted area in Northern India, the West-Bihar and formerly United Provinces. So the South Asian population of the Netherlands is probably more homogeneous than in other studies.

The increased risk of end-stage diabetic nephropathy could be explained in part by the increased prevalence of type 2 diabetes in the South Asian population. A recent survey done by the Municipal Health Service showed an eightfold higher prevalence of diabetes among the South Asian population in The Hague. [7] In addition, large population studies in the UK show a three to four times increased risk for diabetes among the South Asian migrant population. [1-6] However, this higher prevalence of diabetes does not fully explain the close to 40-times increased risk for end-stage type 2 diabetic nephropathy among South Asians. Additional factors should therefore be considered such as a more aggressive course of diabetic disease or a higher incidence of nephropathy in the South Asian type 2 diabetic population. The similar diabetes duration until onset of the dialysis treatment in both ethnic groups supports the hypothesis of a higher incidence of diabetic nephropathy in the South Asian diabetic population.

Conclusion

We found a close to 40-fold higher risk of end-stage diabetic nephropathy due to type 2 diabetes mellitus in Surinamese South Asian immigrants when compared to native Dutch individuals. The eight-times higher prevalence of diabetes in the South Asian general population only partially explains the increased risk of end-stage diabetic nephropathy in South Asians. The similar diabetes duration until onset of the dialysis treatment in both ethnic groups supports the hypothesis of a higher incidence of

diabetic nephropathy in the South Asian diabetic population. Early and frequent screening for diabetes and microalbuminuria is recommended in South Asians.

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Brits-Indische immigranten aan boord van een schip op de Surinamerivier bij Paramaribo, dat hen terug brengt naar Brits-Indië, Suriname, ca. 1890.

Chapter 4

South Asian type 2 diabetic patients have higher incidence and faster progression of renal disease in comparison with Dutch European diabetic patients

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Abstract

Objective

In the Netherlands, South Asians older than 30 years have a nearly 40-fold higher risk for end-stage diabetic nephropathy than Europeans. This higher risk is only partially explained by the reported eightfold higher prevalence of diabetes in the South Asian population. We therefore compared the incidence of microalbuminuria and the progression of renal failure between South Asian and Dutch European type 2 diabetic patients.

Research design and methods

We selected a cohort of 149 South Asian patients who were matched with 155 Dutch European type 2 diabetic patients, by using the registry of an out-patient diabetic clinic. Urinary albumin excretion and creatinine clearance were measured at inclusion and after nearly 5 years follow-up. In each group, about 7% of the patients were lost-to-follow-up and 11% had incomplete follow-up data for final analysis.

Results

Complete follow-up was acquired in 107 South Asian and 94 European diabetic patients. After correction for the younger age of the South Asian patients (12 years), the odds ratio for developing microalbuminuria or macroalbuminuria was nearly 4 in the South Asian type 2 diabetic group. After 5 years follow-up, the loss in glomerular filtration rate was 1.45 times higher (10 ml/min/1.73 m^2) in the South Asian group.

Conclusions

At a much younger age, South Asian type 2 diabetic patients develop more nephropathy and have faster progression of renal failure in comparison to Dutch European diabetic patients.

Introduction

Surinamese South Asian migrants, living in the Netherlands and older than 30 years, have a nearly 40-fold increased age-adjusted risk for end-stage diabetic nephropathy in comparison to their European Dutch counterparts. [1] Several studies in the UK also showed a higher incidence of ESRF in South Asian diabetic patients. [2-6]

There is no clear explanation for the increased risk in South Asian migrants, who originally descend from the Indian subcontinent. Our previous family study in South Asian dialysis patients with type 2 diabetes showed no familiar predisposition for renal disease within the South Asian migrant population. [7] In an earlier study, an eightfold higher prevalence of type 2 diabetes was reported for South Asian migrants living in the Netherlands. [8] However, this higher prevalence of diabetes only partially explains the nearly 40-fold increased risk for end-stage diabetic nephropathy in the South Asian migrants. [1] This gap could be explained by either a higher incidence of nephropathy in the Asian diabetic patients and/or faster progression to end-stage renal disease. A cross-sectional study performed in the UK, showed 1.5 times higher prevalence of microalbuminuria in South Asian diabetic patients compared to native British diabetic patients. [9] This could be an indication for higher incidence of microalbuminuria in the South Asian diabetic patients. Previous follow-up studies revealed conflicting results in the rate of progression of diabetic nephropathy in South Asians versus Europeans. [10,11]

We performed a cohort study in South Asian and native Dutch European type 2 diabetic patients to compare differences in the incidence and progression of microalbuminuria and the progression of renal failure between both ethnic groups.

Research Design and Methods

Patients

All participants took part in a registry of 1705 diabetic patients who visited the diabetic out-patient clinic of the Haga Teaching Hospital, during the period 1994-1996. After excluding the type 1 diabetic patients, we had 222 South Asian patients and 1201 Dutch European patients with type 2 diabetes. In the registry, we found urinary albumin excretion results in 149 patients of South Asian and, 611 patients of Dutch origin. Among these 611 patients, we performed a matched random sampling of 155 Dutch European patients, matched to the 149 South Asian patients for gender and

level of urinary albumin excretion. The local Medical Ethics Committee of the Haga Teaching Hospital approved the study, and the participants gave informed consent.

Follow-up of the study population

The study population consisted of 149 South Asian and 155 Dutch European type 2 diabetic patients, in total 304 patients. Incomplete follow-up data were obtained in 39 South Asians and 60 Dutch Europeans (see **figure 1**). In each ethnic group, about 11% of the patients had no follow-up investigation done, and in about 2% of the patients the original hospital records could not be retrieved. About 7% of the patients were lost-to-follow-up. At the end of the investigation 10 of the 149 South Asian diabetic patients died (6.7%) versus 30 of the 155 Dutch European patients (19.3%). Three South Asian patients were later excluded; one patient gave no informed consent; one patient became pregnant and one patient had a urine collection date after the inclusion deadline. Of the Dutch European patients, one was excluded because of a missing urine collection date. After exclusion, there were 107 South Asian and 94 Dutch European diabetic patients eligible for analysis. In these patients albuminuria was equally distributed in each ethnic patient group at time of inclusion: about 61% had no microalbuminuria, 28% had microalbuminuria and 11% had macroalbuminuria.

Procedures

The baseline characteristics of the patients were assessed from the medical record at the inclusion date. Follow-up was completed if the patient had at least four years of follow-up and all required data were present. If values were missing or the patient had not completed the four years follow-up, the investigation was scheduled at the next visit to the out-patient clinic. If patients were deceased before the end date (July 1, 2001) of the investigation, they were stated as such, and otherwise reported as alive. Patients who were discharged from the out-patient clinic were traced by contacting the general practitioner (GP). If the patient was unknown to the GP, we tried to locate the patient by using the registry office or financial records of the hospital. If this was unsuccessful, patients were stated as lost-to-follow-up.

At inclusion we collected from the medical records: date, length, weight, blood pressure, age, gender, ethnicity, first referral date and reason of referral to the out-patient clinic, duration of diabetes, type of diabetes, retinopathy, smoking habits, glycohemoglobin (HbA1c), serum cholesterol, laboratory results for urinary albumin excretion, serum creatinine and creatinine clearance, as well as antidiabetic and/or antihypertensive medication. Acquired cardiovascular disease at start of investigation was registered from the medical records.

At follow-up we collected laboratory test results for urinary albumin excretion (the type of urinary albumin excretion test, spot urine or 24-hour sample was specified), serum creatinine, HbA1c, serum cholesterol, weight, blood pressure and antihypertensive medication. Furthermore, the occurrence of cardiovascular complications during follow-up was registered.

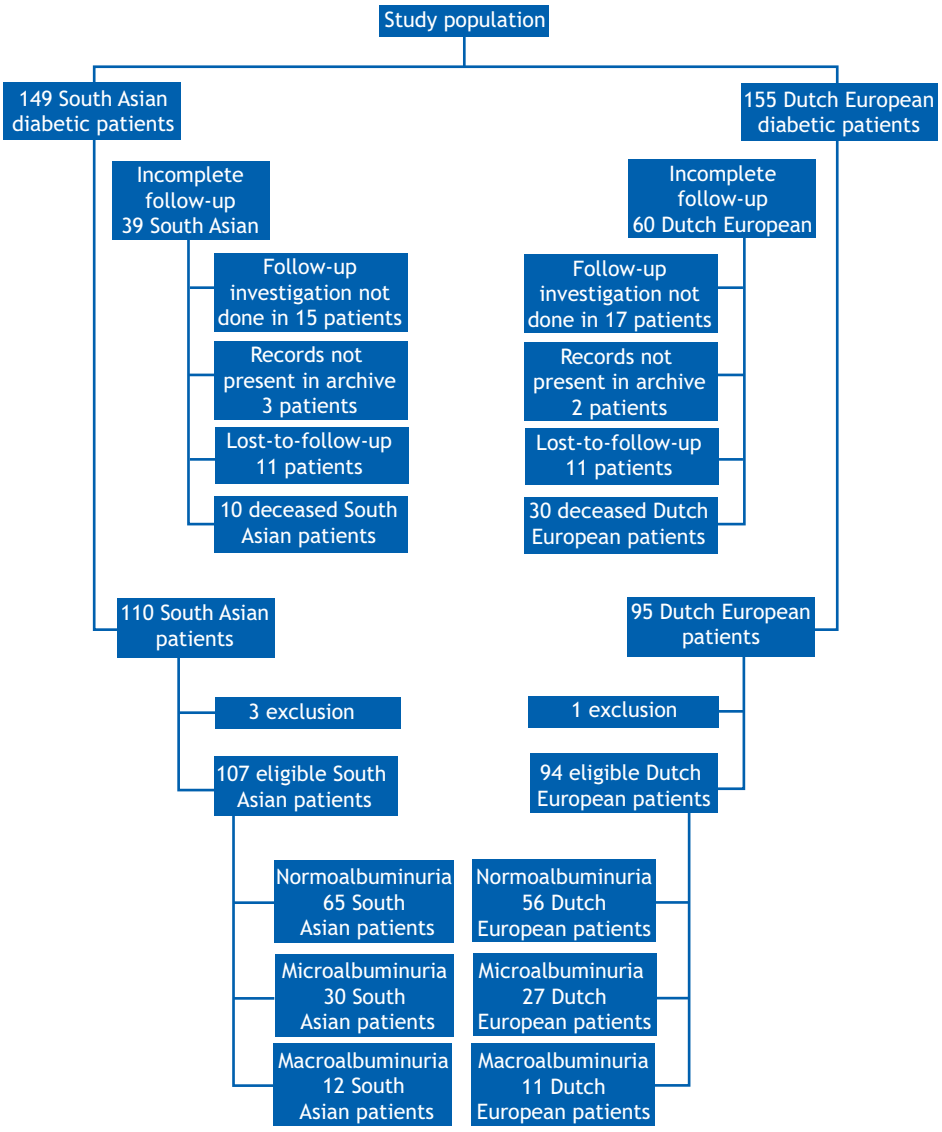

Figure 1: *Follow-up of 149 South Asian and 155 Dutch European type 2 diabetic patients.*

Definitions

Microalbuminuria was defined as albuminuria above 30 mg in a 24-hour urine collection or when using a spot urine collection, an albumin/creatinine ratio above the 2.5 g/mol creatinine in males and above the 3.5 g/mol creatinine in females. *Macroalbuminuria* was defined as albuminuria above 300 mg in the 24-hour urine collection or when using a spot urine collection, an albumin/creatinine ratio above the 36 g/mol in males and above the 40 g/mol in females. The *ethnicity* was self-stated. Patients who were of Dutch native descent were reported as European patients. Migrants who originally descend from the Indian subcontinent (India, Pakistan or Bangladesh) were reported as South Asian patients. If the patient had another ethnicity than South Asian or Dutch European, the patient was excluded for follow-up. *Type diabetes mellitus*: patients who had used oral antidiabetic medication and/or diet for more than one year were coded as type 2 diabetic patients. Patients who used only insulin with a history of keto-acidosis were coded as type 1 diabetic patients. *First referral* was defined as the first presentation of the patient to the out-patient clinic. The *date and reason* of first *referral* to the out-patient clinic was also noted to detect differences in referral for renal disease in the South Asian and Dutch diabetic groups. *Antidiabetic medication* was reported as oral or insulin in combination or alone. *Retinopathy* was defined as proliferative retinopathy necessitating laser coagulation or operation; if no report of the ophthalmologist could be found within one year of inclusion retinopathy was stated as missing report. *Blood pressure, length and weight* were recorded by the treating physician. *Antihypertensive medication* and blood pressure were recorded within 1 month before or after the inclusion date and at the end of follow-up. *Smoking* was classified as never or ever smoked. Loss of renal function during follow-up was compared between the ethnic groups using the creatinine clearance. *Creatinine clearance* was calculated from the 24-hour urine per 1.73 m^2. *Cardiovascular disease* was defined as: coronary heart disease (documented myocardial infarction, PTCA, CABG), cerebrovascular event (TIA, documented stroke, intracranial bleeding) and peripheral vascular complications (documented amputation, re-vascularisation operation)

Laboratory procedures

Laboratory results were taken within one month before or after inclusion date of urinary albumin excretion determination. The urinary albumin excretion at inclusion of the investigation was determined in the 24-hour urine. At follow-up, in the patients without a 24-hour urine collection, spot-urine albumin/creatinine ratio was performed. Urinary albumin and protein were measured by immunoturbidimetric assay on a

clinical chemistry analyzer. Glucose, creatinine, cholesterol and triglycerides and HDL-cholesterol were measured on a clinical chemistry analyzer. HbA1c was measured using the HPLC method with a Variant analyzer (Biorad, Hercules, CA, USA). Variance Coefficient 1.5% at different levels. The reference values for HbA1c are between 4.3 and 6.3%. All the laboratory results at inclusion and most follow-up investigations were done in clinical chemistry laboratory of the Haga Teaching Hospital. Patients who where treated by the GP had their follow-up investigations done in other laboratories. However, an extensive regional interlaboratory comparison study, in which the above mentioned analyses were compared, did not show a clinical relevant difference for the accuracy of the analyses (dr. F. Hudig, personal communication).

Statistics

For statistical comparison of the difference of means, e.g. age, duration of the diabetes, laboratory values between the case - and control group, the Student's t-test was used; the measured difference of the means were expressed with 95% confidence intervals and P-values. Differences of categorical variables like microalbuminuria, medication use, retinopathy, referral reasons were expressed as percentage difference with 95% confidence intervals and as Chi-Square P-values. We used multivariate analysis for correction of differences in risk factors for development of microalbuminuria/ macroalbuminuria, reporting the odds ratio Exp(B) with 95% CI. The decline in creatinine clearance (delta GFR) was calculated per patient. The mean delta GFR was compared between the ethnic groups using the Student's t-test.

Results

Incidence of microalbuminuria

In the 65 South Asian and 56 European patients without microalbuminuria (normoalbuminuria) at inclusion, the unadjusted odds ratio for development of micro- or macroalbuminuria in South Asian diabetic patients relative to the European Dutch patients was 2.1 (95% CI 0.84 to 5.1). (**Figure 2**) After correction for the lower age and higher HbA1c values, the adjusted odds ratio for developing micro- or macroalbuminuria increased from 2.1 to 3.9. Without adjustment for higher HbA1c value in the South Asians, the odds ratio for micro- or macroalbuminuria increased to 4.7 (95% CI 1.4 to 16; p-value 0.013) Introduction of other risk factors for microalbuminuria as gender, duration of diabetes showed no significant changes in the adjusted odds ratio. (Table 1)

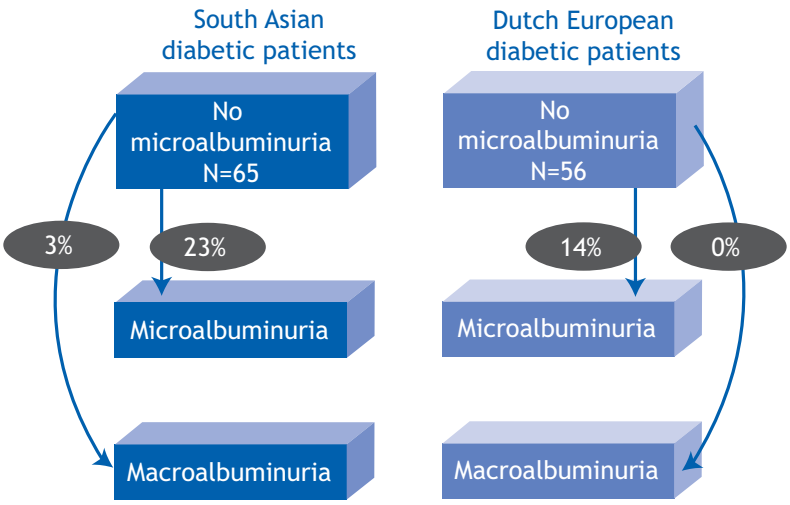

Figure 2: *Incidence of microalbuminuria and macroalbuminuria in South Asian and Dutch European type 2 diabetic patients after 5 years follow-up. The solid arrows show the progression percentage of albuminuria in patients with no microalbuminuria at inclusion.*

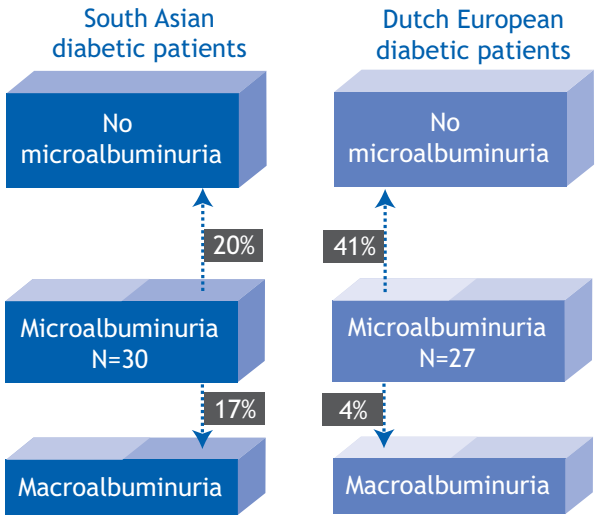

Figure 3: *Evolution of microalbuminuria in 30 South Asian and 27 Dutch European diabetic patients after 5 years follow-up. The dashed arrows show the progression or regression of albuminuria.*

Table 1: *Multivariate analysis for the end-point microalbuminuria/macroalbuminuria in 65 South Asian and 56 Dutch European patients who had no microalbuminuria at inclusion of investigation.*

Model	Exp(B)	95% CI for Exp(B)	P-value
Ethnicity	3.9	1.1 to 14	0.03
Gender	0.9	0.35 to 2.3	0.83
Age	1.05	1.01 to 1.1	0.04
HbA1c	1.2	0.9 to 1.6	0.19
Diabetes duration	0.98	0.9 to 1.05	0.51
Constant	36		0.008

Evolution of microalbuminuria

In the 30 South Asian and 27 European diabetic patients who had microalbuminuria at inclusion of the study, the progression of microalbuminuria to macroalbuminuria was also higher in the South Asian patients. (**Figure 3**) The odds ratio for progression to macroalbuminuria was 5.2 (95% CI 0.56 to 47). European diabetics had a higher tendency for regression to normoalbuminuria. Because of small numbers, we did not include the 12 South Asian patients and 11 European patients with macroalbuminuria in figure 3.

The baseline values for demographic, clinical and biochemical variables are summarised in **Table 2** for the patients who had no microalbuminuria at inclusion of the study. **Table 3** summarises the baseline values for the patients who had microalbuminuria or macroalbuminuria at the start of the study. The age at which the diabetes was diagnosed was 12 years lower in South Asian diabetic patients than in the European group. The diabetes duration was equal and about 12 years. Patients with microalbuminuria or microalbuminuria at inclusion were relatively older than their ethnic counterparts without microalbuminuria. South Asian patients were shorter but had an equal body mass index (BMI). The urinary albumin excretion rate at inclusion was uniformly distributed between both ethnic groups. Mean serum cholesterol, antihypertensive medication, mean systolic blood pressure values and smoking were lower in de South Asian group. (**Table 4**) Despite the lower cardiovascular risk factors and the younger age in South Asian diabetic patients, there were no differences in cardiovascular complications during follow-up. Renine-Angiotensin System (RAS) blocker usage was higher at the end of the study. There were no differences in RAS-blocker usage between both ethnic groups.

Progression of renal failure

The glomerular filtration rate (GFR) estimated with the creatinine clearance was almost equal at start of the investigation. (**Table 2** and **3**) In the analysis, we excluded 14 South Asian and 14 Dutch European patients because of a missing 24-hour creatinine clearance determination.The duration of follow-up was 5.1 years in the South Asian group and 5.0 years in the European group (difference of 0.1 years with 95% CI -0.21 to 0.35; p-value 0.62).

Table 2: *Normoalbuminuric patients baseline values in 65 South Asian and 56 Dutch European type 2 diabetic patients without microalbuminuria at inclusion.*

	Asian	European	Difference (95% CI)	P-value
Males (%)	41.5	41.1	0.4 (-13.1 to 18.1)	0.95
Age (yrs.)	50.6	63.8	-13.2 (-17 to -9.7)	0.0001
Reasons referral (%) Diabetes	75	61.5	13.5 (-29.8 to 2.9)	0.28
Proteinuria	1.5	1.8		
Follow-up (yrs.)	5.2	5.0	0.2 (-0.23 to 0.47)	0.5
Years after first presentation	4.1	3.2	0.9 (-0.23 to 0.43)	0.5
Known duration of diabetes (yrs.)	9.4	9.2	0.2 (-2.4 to 2.9)	0.85
Age at diagnosis of DM	41.1	54.6	-13.5 (-17 to -9.7)	0.0001
Insulin treatment (%)	60	57.1	2.9 (-14.7 to 20.5)	0.84
HbA_{1c} (%)	8.3	7.4	0.9 (0.43 to 1.5)	0.0001
Proliferative retinopathy (%)	20	14.3	5.7 (-7.6 to 19.1)	0.7
Unknown	10.7	10.8		
Weight (kg)	78.1	77.2	0.9 (-6.0 to 7.9)	0.78
Height (cm)	162	169	7 (-8.6 to -1.4)	0.006
Body mass index (kg/m^2)	29.3	27.9	1.4 (-0.5 to 3.3)	0.148
Body square area (m^2)	1.81	1.86	-0.05 (-0.13 to 0.02)	0.13
Urinary AER (mg/24 h)	11.4	10.8	0.6 (-2.0 to 3.4)	0.62
Urinary creatinine excretion($ml/min/1.73m^2$)	9.3	10.6	-1.3 (-2.7 to 0.16)	0.08
Serum creatinine (µmol/l)	68.7	77.1	-8.4 (-16 to -0.6)	0.03
Creatinine clearance ($ml/min/1.73m^2$)	96	93	3 (-11 to 16)	0.7
Serum-total cholesterol (mmol/l)	5.5	5.7	0.2 (-0.6 to 0.09)	0.16
Ever smoked (%)	16.9	17.9	-1 (-14 to 13)	0.31
Unknown	6.2	14.3		
Antihypertensive treatment (%)	29.2	53.6	-24.4 (-41 to -7.2)	0.007
Systolic blood pressure (mmHg)	135	145	10 (-18 to -3.4)	0.004
Diastolic blood pressure (mmHg)	80.1	80.4	0.3 (-3.4 to 4.2)	0.83

The decline in renal function was 1.45 times higher in South Asian diabetic patient group. (**Figure 4**) After 5 years follow-up, South Asian diabetic patient lost 32 ml/min of their GFR versus 22 ml/min loss in the European patients group (difference of 10 ml/min/1.73 m^2 with 95% CI 0.04 to 20; p-value 0.049).

Table 3: *Microalbuminuric/macroalbuminuric patients baseline values in 42 South Asian and 38 Dutch European type 2 diabetic patients.*

	Asian	European	Difference(95% CI)	P-value
Males (%)	45.2	39.5	5.7 (-16 to 27)	0.65
Age (yrs.)	54.4	63.7	-9.3 (-14 to -4.5)	0.0001
Reasons referral (%) Diabetes	61.9	78.9	-17 (-37 to 2.5)	0.16
Proteinuria	7.1	5.3		
Follow-up (yrs.)	5.2	5.1	0.1 (-4.2 to 0.5)	0.87
Years after first presentation	4.6	4.3	0.3 (-1.6 to 2.3)	0.73
Known duration DM (yrs.)	11.9	12.3	0.4 (-4.0 to 3.1)	0.56
Age at diagnosis of DM	42.6	51.2	-8.6 (-14 to -3.6)	0.0001
Insulin treatment (%)	64.3	63.2	1.1 (-20 to 22)	0.76
HbA_{1c} (%)	8.9	8.4	0.49 (-0.4 to 1.4)	0.3
Proliferative retinopathy (%)	19.0	13.2	5.9 (-10 to 21.9)	0.56
Unknown	7.1	13.2		
Weight (kg)	83.1	85.8	-2.7 (-15 to 9.6)	0.66
Height (cm)	161	167	-6 (-10 to -1.7)	0.006
Body mass index (kg/m^2)	29.8	30.1	-0.32 (-2.8 to 2.1)	0.79
Body square area (m^2)	1.82	1.93	-0.11 (-0.2 to -0.02)	0.002
Urinary AER (mg/24 h)	431	694	257 (-775 to 249)	0.31
Urinary creatinine excretion (mmol/24 h)	10.8	11.1	-0.3 (-2.1 to 1.5)	0.75
Serum creatinine (µmol/l)	76.3	78.9	-2.6 (-13 to 8.2)	0.63
Creatinine clearance (ml/min/1.73 m^2)	103	94.5	9.1 (-10 to 28.4)	0.35
Serum-total cholesterol (mmol/l)	5.8	6.1	-0.37 (-0.85 to 0.1)	0.12
Ever smoked (%)	19.0	42.1	-23.1 (-43 to -0.03)	0.04
Unknown	7.1	5.3		
Antihypertensive treatment (%)	54.8	76.3	-21.5 (-42 to -1.3)	0.04
Systolic blood pressure (mmHg)	144	159	-15 (-25 to -3.2)	0.01
Diastolic blood pressure (mmHg)	85.5	88.5	-3.0 (-8.5 to 2.4)	0.27

Table 4: *Risk factors for progression of renal failure, antihypertensive usage and cardiovascular complication at the inclusion in 107 South Asian and 94 Dutch European patients with type 2 diabetes mellitus. The values represents means, unless otherwise stated.*

	Asian	European	Difference (95% CI)	P-value
Risk factors				
Age (yrs.)	52.1	63.8	-11.7 (-15 to -8.7)	0.0001
Males (%)	43.0	40.4	2.6 (-11 to 16)	0.71
HbA1c (%)	8.6	7.8	0.8 (0.3 to 1.3)	0.003
Duration of DM (yrs.)	10.4	10.4	0 (-2.2 to 2.1)	0.97
Serum-total cholesterol (mmol/l)	5.6	5.9	-0.3 (-0.58 to -0.02)	0.03
Ever smoked (%)	17.8	27.7	-9.9 (-21 to 1.7)	0.1
Smoking unknown	6.5	10.6		
Antihypertensive usage (%)	39.3	62.8	-23.5 (-36 to -9.7)	0.001
Systolic bloodpressure (mmHg)	138	150	-12 (-19 to -6.0)	0.0001
Diastolic bloodpressure (mmHg)	83	84	-1 (-4.3 to 2.2)	0.52
Antihypertensive medication at inclusion (%)				
RAS-inhibition	27.1	27.7	-0.6 (-13 to 12)	0.64
ß-blockers	12.1	21.3	-9.2 (-20 to 1.2)	0.1
Calcium-blockers	7.5	16.0	-8.5 (-18 to 0.5)	0.08
Alpha-blockers	0.9	1.1	-0.2 (-4.9 to 9.1)	0.4
Diuretics	11.2	30.9	-19.7 (-31 to -8.4)	0.001
Antihypertensive medication at endpoint (%)				
RAS-inhibition	51.4	47.9	3.5 (-10 to 17)	
ß-blockers	16.8	31.9	-15.1 (-27 to -3.2)	0.012
Calcium-blockers	15.0	19.1	-4.1 (-15 to 6.2)	0.43
Alpha-blockers	2.8	3.2	-0.4 (-6.5 to 5.1)	0.87
Diuretics	33.6	43.6	-10 (-23 to 3.4)	0.15
Cardiovascular complications at inclusion (%)				
Ischemic heart disease	14	16	-2 (-12 to 8.0)	0.7
Cerebrovascular accident	7.5	8.5	-1 (-9.3 to 6.7)	0.8
Peripheral vascular disease	0	5.3	-5.3 (-12 to -0.7)	0.02
Cardiovascular complications during follow up (%)				
Ischemic heart disease	12.1	11.7	0.4 (-9.0 to 9.5)	0.92
Cerebrovascular accident	7.5	3.2	4.3 (-1.8 to 10)	0.18
Peripheral vascular disease	0.9	4.3	-3.4 (-7.8 to 1.1)	0.13

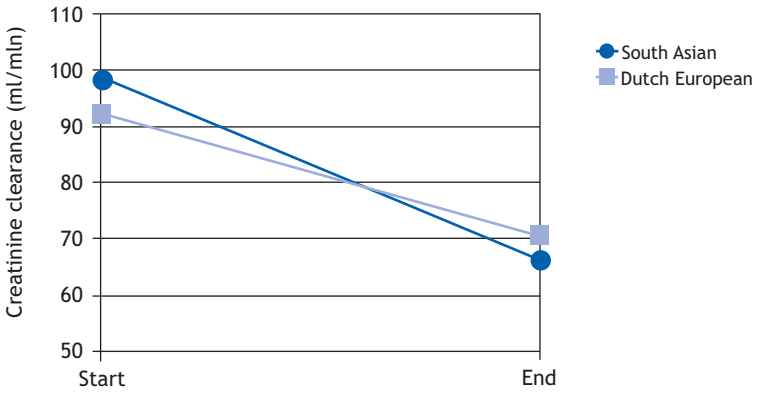

***Figure 4**: Creatinine clearance GFR loss in South Asian (circles) and Dutch European (squares) diabetic patients. Values are shown as mean creatinine clearance, clustered by ethnic group measured at beginning and at end of follow-up period. The GFR declined from 99 ml/min to 67 ml/min for South Asian patients and from 92 ml/min to 70 ml/min for Dutch European patients.*

Discussion

Diabetic South Asian patients have an ethnic susceptibility for developing nephropathy. We found a twice higher incidence of nephropathy and faster loss of renal function in South Asian diabetic patients compared to European Dutch diabetic patients. After correction for the 12 years age difference, the adjusted odds ratio for developing nephropathy increased to nearly 4 for the South Asian type 2 diabetic group. After 5 years follow-up, the loss in glomerular filtration was 1.45 times higher in the South Asian group.

The South Asian population in our study is different from the European Dutch population because at the start of follow-up they were younger and had less cardiovascular complications and used less antihypertensive medication than the European group. Duration of diabetes, time of first referral and reasons of referral were the same in both ethnic groups. Despite the lower blood pressure values, the lesser use of antihypertensive drugs, lower serum total cholesterol and after correction for the higher HbA1c values, we found a 4 times increased odds ratio for developing microalbuminuria or macroalbuminuria in the South Asian diabetic group. The adjusted odds ratio derived after multivariate analysis slightly overestimates the true relative

risk because of the high frequency of microalbuminuria. [12] After correction for the overestimation, the relative risk is still higher in the South Asian group: 2.8 (95% CI 1.08 to 4.9). The higher risk for microalbuminuria was not attributed to differences in RAS blocker usage between the two ethnic groups. However, the use of diuretics was higher in European patients. This could conceal microalbuminuria at inclusion in the European diabetic group, giving in fact an underestimation of the increased risk for microalbuminuria.

In an earlier study, we found a nearly 40-fold increased risk for end-stage diabetic nephropathy in the South Asian population living in the Netherlands. [1] Our study explains the gap between the reported 8-times higher prevalence of diabetes [8] and the 40-fold higher risk of end-stage diabetic nephropathy in the South Asian population. Our previous reported family study in South Asian dialysis patients showed no familiar predisposition for renal disease within the South Asian population. [7] The lack of familial clustering of renal disease in South Asian diabetic patients points to an universal genetic or environmental susceptibility for nephropathy in this population. We assume that the nearly 40-fold higher risk of end-stage diabetic nephropathy in South Asian migrants is caused by several factors: first the 8-times higher prevalence of diabetes in South Asians, secondly more development of nephropathy and finally, a faster progression of renal failure in the South Asian group.

Our findings could have been confounded by the higher mortality in the European population, probably explained by the older age. The same phenomenon was described earlier by Mather et al. [13] After 11 years follow-up 33% of the South Asian patients died (mean age 55 years) versus 57% of the older European diabetic patients (mean age 67 years). Since microalbuminuria is an independent risk factor for cardiovascular mortality, [14,15] this could give lower microalbuminuria levels in the studied population at the end. Nevertheless, during the follow-up, cardiovascular disease was equal in both ethnic groups. Furthermore, we matched the European patients for urinary albumin excretion and gender at start of the investigation. Finally, after age-adjustment, the higher risk for microalbuminuria still persisted. Other limitations of our study concern the patient group who was discharged from the out-patient clinic and taken into the care of the general practitioners. First, follow-up measurements for urinary albumin excretion and creatinine clearance were not frequently done by the GP. Another problem we encountered was that the follow-up measurements of the discharged patients were done in different laboratories. However, the patients of both ethnic groups were equally distributed over the laboratories and also the method of albuminuria testing was equally distributed over the South Asian and European diabetic patients groups.

Our cohort study complements the cross-sectional studies performed by Mather et al. [9] and Chowdhury et al. [16] Both studies found higher prevalence rates of microalbuminuria in South Asian diabetic patients versus British European diabetic patients. Two studies showed conflicting results with regard to renal loss in South Asian migrants. The study of Koppiker et al. [10] showed no difference in loss of renal function. However, another study of Earle et al. [11] found a higher progression of renal failure in South Asians versus British diabetic patients. The conflicting results of the previous studies are understandable, because both studies could only utilize the serum creatinine values as determinant for renal function loss, making these studies less sensitive for detecting differences in renal failure. We therefore used creatinine clearance in the 24-hour urine, which is a better estimate of renal function. Using serum creatinine value alone is especially hazardous in migrant populations because of the differences in muscle mass. We did not use calculated GFR method, like Cockcroft-Gault estimation or simplified MDRD-formula because these have not been validated South Asian patients. [17] The results calculated by Cockcroft-Gault or simplified MDRD formula revealed also a high progressive loss in GFR in the South Asian diabetic group. (data not given).

What could be the pathophysiologic mechanism leading to more nephropathy in South Asian diabetic patients?

Higher microalbuminuria does not always implies renal disease, but can also be a marker for endothelial damage. One of the hypothesis could be a common ethnic susceptibility for endothelial dysfunction within the South Asian population, leading to more microalbuminuria and ischemic heart disease. We therefore took cardiovascular complications into account, which were not different between the groups. This was observed despite the younger age, less hypertension and lower serum cholesterol values in the South Asians. McKeigue et al. reported unusually high coronary heart disease rates in people originating from the Indian subcontinent. [18,19] In a cross-sectional study in the UK, Cappuccio et al. showed that the classical Framingham risk equations underestimate the risk for myocardial infarction. [20] It is difficult to prove this hypothesis because our study was not designed to detect differences in endothelial dysfunction.

Conclusion

South Asian type 2 diabetic patients develop more nephropathy and have faster progression of renal failure in comparison to European diabetic patients. Classic risk factors for development of microalbuminuria and progression of renal failure do not explain this higher risk in South Asian diabetic patients. Our study confirms the hypothesis of a general genetic or environmental susceptibility for nephropathy among South Asian diabetics. As South Asian patients develop these complications insidiously at a much younger age, we recommend general practitioners to screen for diabetes and renal failure in every South Asian migrant above the age of 30 years.

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Een Hindostaanse arbeider voor zijn huis met gezin en buren, Suriname, ca. 1930.

Chapter 5

Renal disease in relatives of South Asian type 2 diabetic patients with end-stage diabetic nephropathy

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Abstract

Objective

South Asian immigrants in The Hague, The Netherlands, have a nearly 40-fold higher risk of end-stage diabetic nephropathy compared to the Dutch European population. To detect a genetic susceptibility for nephropathy within the South Asian population, we assessed whether familial clustering of nephropathy occurs in families of South Asian type 2 diabetic patients.

Research design and methods

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. The case- and control-relatives were examined for diabetes, blood pressure, renal function, microalbuminuria and urine dipstick measurements.

Results

The mean age was 41 years and similar in the case- and control-relatives. Diabetes was distributed equally in both family groups. We did not find more nephropathy in first-degree relatives of South Asian type 2 diabetes patients with end-stage diabetic nephropathy in comparison with control-relatives.

Conclusions

We could not detect a genetic susceptibility for diabetic nephropathy within the South Asian population. The lack of familial clustering of renal disease in South Asian diabetic patients points to a general genetic or environmental susceptibility for diabetic nephropathy in this population.

Introduction

Familial clustering of diabetic nephropathy was first described in type 1 diabetic patients. [1] Later, clustering was also observed in type 2 diabetic patients. A familial predisposition for diabetic nephropathy was observed in different ethnic groups like the American Pima Indians, Afro-Americans, Brazilian and Italian type 2 diabetic patients. [2-7] These observations are consistent with the hypothesis of a genetic susceptibility in the pathogenesis of diabetic nephropathy.

South Asian persons from Suriname originally descent from the Indian subcontinent, including India, Pakistan, and Bangladesh. In a recent study, South Asian patients were found to have a close to 40-fold increased risk for end-stage diabetic nephropathy in comparison to native Europeans. [8] Studies performed in the UK showed comparable results. [9-10] This is higher than expected since the prevalence of type 2 diabetes was only eight times higher in the South Asian population, again in comparison with the Dutch European native population. [11] An explanation for this relatively higher incidence of diabetic nephropathy could be an additional genetic susceptibility to develop nephropathy within the South Asian population. This might be detected by the presence of familial clustering of nephropathy in relatives of patients with diabetic nephropathy, but specific family studies for nephropathy are lacking in the South Asian population. However, a small case-control family study in South India showed higher rates of proteinuria in siblings of type 2 diabetic patients with nephropathy in comparison with age, sex and diabetic duration matched siblings of control patients without diabetic nephropathy. [12]

The aim of our study was to investigate whether familial clustering of nephropathy occurs in first degree relatives of type 2 diabetic South Asian patients with and without nephropathy. We tried to prevent selection bias by a population-based study design and the testing of all non-diabetic relatives, with an oral glucose tolerance test.

Research design and methods

Study Design

In this study, we evaluated the predisposition for nephropathy among South Asian first degree relatives of type 2 diabetic patients with end-stage renal failure (**case-relatives**). They were compared with first-degree relatives of South Asian type 2 diabetic patients who had no clinical signs of diabetic nephropathy (**control-relatives**).

The case- and control-relatives were invited for an assessment (see below) between September 1, 1998 and December 31, 2000.
The study protocol was approved by the Institutional Medical Ethics Committee in accordance with the Declaration of Helsinki.

Subjects

Case-families

The case-index patients were recruited from the records of the dialysis units of three regional hospitals, which together represent the total dialysis capacity in the town of The Hague. Included were all patients first registered between 1990 and 1999 for dialysis because of end-stage renal failure attributed to type 2 diabetes; patients were considered to have type 2 diabetes if they used oral antidiabetic medication prior to dialysis, or if their fasting C-peptide levels were indicative of type 2 diabetes. South Asian dialysis patients were initially identified by their surnames. If the patients were alive, we visited them in the dialysis unit and confirmed their ethnic origin. A standardized interview was taken with respect to diabetes and family history as well as demographic parameters. After informed consent, we contacted their first-degree relatives living in the Netherlands (parents, siblings and children). If the case-index patient had died, we contacted the relatives with the help of the general practitioner (GP) of the deceased patient.

Control-families

Control-index patients with type 2 diabetes were selected with the help of general practitioners (GP) of the included case-index patients. For each case-index patient included, one South Asian control-index was chosen at random among the patients with type 2 diabetes from the records of the GP; control-index patients were eligible if they were of the same sex as the case-index and had no microalbuminuria. To ensure random sampling, we went through all the records of that GP, and made a numbered list of all eligible South Asian type 2 patients. Subsequently, control-index patients were drawn from this list by use of a random number table. Another source of control-index patients were the spouses of the investigated relatives. If the spouse had type 2 diabetes mellitus and no microalbuminuria, we invited the siblings and parents of the spouse for the investigation. The control-index patients were also invited through a letter for a visit at our outpatient's research unit. A few days later they were contacted by phone for informed consent and an appointment at our research outpatient clinic.

Inclusion of the family relatives

All first-degree relatives (father, mother, siblings, and children) of the case- and control-index patients living in the Netherlands were invited as part of a family investigation for diabetes and renal disease. We invited the case- and control-relatives randomly throughout the investigation period. Relatives who were pregnant were invited later on, three months after they gave birth. Patients younger than 16 years were not included. We tried to avoid appointments during the menstrual period of women.

Procedures and Measurements

The family relatives came during the morning hours, after fasting for at least 8 hours. Fasting venous blood samples were drawn for hemoglobin, creatinine and lipid profile. The relatives brought an early morning urine sample for quantitative measurements of albuminuria and dipstick urine analysis. 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, a large cuff was used. The weight and height were recorded in underwear. Also the circumference measurements of the waist and hip were performed. If the relatives did not use antidiabetic medication, an oral glucose tolerance test was done with 75 gram glucose and the fasting glucose as well as two hour glucose was measured. The renal function was estimated using the Cockcroft-Gault estimation. [13] We used a questionnaire to obtain data on general demographic variables (age, sex, educational level and marital status) family history of diabetes mellitus in first-degree relatives (age of onset, duration, treatment), 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 1.5% at different levels. The reference values for HbA1c are between 4.3 and 6.3%. Urine dipstick investigation for leukocyturia and hematuria was performed with patch test strips using reflectance photometry with a Miditron photometer (Boehringer Mannheim-Roche, diagnostics). [14]

Outcome measurements

Patients who currently used oral antidiabetics or insulin were classified as known diabetics. All other patients had a glucose tolerance testing (GTT) using the classic WHO criteria. [15] If the fasting blood glucose was higher than 7.8 mmol/L or two-hour GTT value was higher than 11.1 mmol/L, patients were coded as de novo-diabetic patients. 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 coded as impaired glucose tolerance. If the two-hour GTT value was below the 7.8 mmol/L, patients were classified as normoglycemic. Urine albumin concentration was measured in relation to the creatinine and expressed as ratio of albumin/creatinine in mg/mmol. Microalbuminuria was defined according to the diabetic standards. Normoalbuminuria was present if the albumin/creatinine ratio was < 2.5 in males and < 3.5 in females. Microalbuminuria was present if the ratio was between 2.5 and 36 for males and between 3.5 and 40 for females. Proteinuria was defined if the ratio was above 36 for males and 40 for females. The renal function was estimated using the Cockcroft-Gault formula and normalized for BSA of 1.73 m^2. The results of the urine dipstick were measured using qualitative test strips which were coded using an automated photometric reader. Leukocyturia was registered as absent, trace or positive; hematuria was registered as absent, trace or positive. During this visit, patients showed their medications. In case the patient forgot to bring the prescribed medication or medication card, the GP was contacted for the exact medication. Patients who did not use antihypertensive medication were coded as normotensive if the average blood pressure was below the 160 mmHg systolic and below the 90 mmHg diastolic. Borderline hypertensive profile was defined as diastolic blood pressure between 90 to 95 mmHg and systolic blood pressure below the 160 mmHg. If patients used antihypertensive medication or had average blood pressure above the 160 mmHg systolic or 95 mmHg diastolic, they were registered as hypertensive profile.

Statistical Analysis

The calculations for the study size were based on a minimally detectable relative risk of 3 for microalbuminuria in relatives of South Asian diabetics with renal failure versus South Asian diabetics without renal failure, with a type 1 error of 0.05 and a power of 0.90. Based on studies in the United Kingdom [9] and the Netherlands, [11] we assumed the diabetes mellitus prevalence in South Asian families at 20-30 percent). Assuming a prevalence of microalbuminuria in the family members of the controls at 7 percent, 150 relatives have to be included in each family group (of whom about

40 would expect to suffer from diabetes mellitus). For statistical comparison of the difference of means, e.g. age, duration of the diabetes, laboratory values between the case- and control-group, the Student's t-test was used; the measured difference of the means were expressed with 95% confidence intervals and P-values. Differences of categorical variables like glucose tolerance, urine dipstick measurements were expressed as percentage difference with 95% confidence intervals and as Chi-Square P-values.

Results

Recruitment of Index-patients

The recruitment of the index patients is shown in **Table 1.** We contacted 57 index patients with type 2 diabetes mellitus and end-stage diabetic nephropathy. Of these patients 20 were not eligible: 4 could not be reached by telephone or by mail, 1 had no potential relatives for investigation, and 15 patients did not give permission to contact their relatives, leaving 37 case-index patients.

Table 1: *Recruitment and drop-out reasons of the Index patients.*

	Case-index patients	Control-index patients
Contacted Index patients	**57**	**132**
Not reached index patients	4 (7.0%)	26 (19.7%)
No potential family members	1 (1.8%)	15 (11.3%)
No Informed consent	15 (26.3%)	31 (23.5%)
Microalbuminuria (control-index patient)	NA	17 (12.9%)
Eligible index patients	**37 (64.9%)**	**43 (32.6%)**

We contacted 132 control-index patients with type 2 diabetes mellitus and no microalbuminuria according to the records of the GP's. We could not reach 26 patients because they did not respond on our invitation and could not be reached by phone. Fifteen patients had no first-degree relatives living in the Netherlands and 31 control-index patients did not approve to contact their relatives. We therefore investigated 60 index control patients. Seventeen index control patients were excluded afterwards because they had microalbuminuria, leaving 43 eligible control-index patients for the study

Basic characteristics of the case- and control-index patients are given in **Table 2.** The age at inclusion for our investigation was slightly higher in the case-index patients group than in the control-index group. The case-index patients with end-stage diabetic nephropathy also had a longer duration of diabetes disease than the control-index patients who had no nephropathy (difference 4.6 years with 95% CI 0.9 to 8.4). The index patients with diabetic nephropathy were more often treated with insulin therapy.

Table 2: *Basic characteristics of the eligible index patients with type 2 diabetes mellitus.*

	Case-index patients	Control-index patients	Difference (95 % CI)
Number	37	43	
Males n (%)	43%	42%	1 (-20 to 23)
Age at inclusion investigation (years)	56.1	52.5	3.6 (-1,2 to 8.5)
Age at diagnosis diabetes (years)	38.7	39.0	-0.3 (-5.64 to 5.1)
Mean diabetes duration (years)	17.2	12.6	4.6 (0.9 to 8.4)
Insulin treated (%)	62.2	48.8	13.4 (8.3 to 34.9)

Recruitment of first-degree relatives

The recruitment of the 330 first-degree (siblings, children, parents) relatives was similar in families of index-case and index-control patients. Recruitment was done in 37 case families and 43 control families. The reasons and numbers of patients who did not participate in the study were distributed equally between the case- and control-group. In the case-group 234 relatives were approached; 65 patients (27.8%) declined or were unreachable, giving 169 case-relatives for our investigation. In the control-group 221 relatives were approached; 60 patients (27.2%) declined or were unreachable, giving 161 control-relatives for the present investigation.

Characteristics of the relatives

The basic characteristics are displayed in **Table 3.** Mean age was similar in the case and control families, about 41 years. There was a female preponderance in both family groups. Mean body mass index, body surface area, waist-hip ratio measurements and lipid profiles were equal in the case and control-relatives. In the case-family members, 19 (11.2%) were known diabetic patients. The amount of known diabetic relatives in the control-family members was higher (n = 28; 17.4%). The results of the glucose

tolerance testing according to the WHO criteria among the remaining relatives were similar.

Table 3: *Basic characteristics of first-degree relatives of diabetic index patients with and without nephropathy. The characteristics are expressed as means, unless otherwise stated.*

	Case-relatives	Control-relatives	Difference (95 % CI)	P-value
Age	41.5	40.7	0.8 (-1.8 to 3.3)	0.55
Male (%)	37.9%	44.7%	-6.8 (-17.5 to 3.7)	0.21
Body mass index (kg/m^2)	26.56	26.63	-0.07(-1.1 to 0.9)	0.89
Body surface area (m^2)	1.76	1.80	-0.04 (-0.1 to 0.06)	0.09
Waist-Hip ratio	0.92	0.93	-0.01 (-0.03 to 0.2)	0.39
Cholesterol	5.2	5.1	0.1 (-0.13 to 0.3)	0.45
HDL-Chol/Cholesterol ratio	4.21	4.24	-0.03 (-0.3 to 0.2)	0.85
Triglycerides	1.51	1.68	-0.17 (-0.5 to 0.1)	0.29
HbA1c (%)	5.59	5.75	-0.16 (-0.5 to 0.2)	0.31
Glucose tolerance testing (GTT)				
De novo DM	**13%**	**8.1%**	4.9 (-1.6 to 11.5)	0.22
Impaired GT	**8.9%**	**10.6%**	-1.7 (-8.1 to 4.7)	
Normoglycemia	**66.9%**	**64.0%**	2.9 (-7.4 to 13.2)	
Known DM	**11.2%**	**17.4%**	-6.2 (-13.7 to 1.4)	
Age (years)	53.8	52.9	-0.1 (-5.8 to 7.6)	
Insulin usage (%)	52.6	17.9	34.7 (8.2 to 61.3)	
Diabetes duration (years)	10.5	10.0	0.5 (-4.6 to 5.5)	
HbA1c (%)	8.26	8.01	0.25 (-0.7 to 1.2)	

Life style characteristics of the 330 relatives are shown in **Table 4**. There were no differences in numbers of smokers between the case- and control-relatives. There were slightly more subjects with vegetarian eating habits and Muslim religious attitudes in the control families. The level of education distributed equal in both case- and control relative family groups. The number of divorced persons was significant higher in the case group.

Blood pressure profiles and treatments are given in **Table 5**. The mean blood pressure measurements were equal in both the case and control-relatives. Antihypertensive medical treatment was used in 13% of the case-relatives and 15% of the control-relatives. The distribution of the type of antihypertensive medication was not different in both groups, especially for the ACE-inhibitor and Angiotensin 2 receptor blockers usage.

Table 4: Life style in 330 first degree family relatives.

	Case-relatives	Control-relatives	Difference (95 % CI)	P-Value
Smoking (%)				
Never	63.9	59.7	4.2 (-6.4 to 14.7)	0.32
Stopped	7.1	11.9		
Yes	29.0	28.3		
Vegetarian eating pattern (%)				
No	95.9	84.3	11.6 (5.2 to 18.0)	0.004
Only no meat or fish	4.1	14.5		
No meat, fish, dairy products or eggs	0.0	1.3		
Religion (%)				
Hindu	75.7	63.5	12.2 (2.3 to 22.1)	0.033
Muslim	20.1	27		
Christian	1.8	1.9		
Other or no religion	2.4	7.5		
Education (%)				
Primary school	23.7	19.3	4.4 (-4.4 to 13.3)	0.24
Lower general/vocation	17.8	13.6	4.2 (-2.4 to 13.0)	
Intermediate and higher general/vocation	48.4	54.1	-6.0 (-16.3 to 5.3)	
Higher vocation/University	10.1	13.0	-2.9 (-9.9 to 3.9)	
Marital Status (%)				
Maried	41.4	52.8	-11.4 (-22.1 to -0.6)	0.086
Unmarried	23.7	25.5	-1.8 (-11.1 to 7.5)	
Widowed	5.9	5.0	0.9 (-3.9 to 5.8)	
Divorced	23.1	12.4	10.7 (2.5 to 18.8)	
Unknown	5.9	4.3	1.6 (-3.1 to 6.3)	

Table 5: Blood pressure and treatment of hypertension in 330 family relatives.

	Case-relatives	Control-relatives	Difference (95 % CI)	P-value
Systolic blood pressure (mean, mmHg)	127.1	126.6	0.5 (-4.1 to 5.1)	0.83
Diastolic blood pressure (mean, mmHg)	79.3	79.7	-0.4 (-2.84 to 2.1)	0.75
Blood pressure profile (%)				
Normotensive profile	73.4	73.3	0.1 (-9.5 to 9.6)	0.64
Borderline hypertensive profile	4.1	5.6	1.8 (-4.8 to 9.6)	
Hypertensive profile	9.5	6.2		
Antihypertensive use	13.0	14.9	-1.9 (-9.4 to 5.6)	
Antihypertensive medication use (%)				
ACE-inhibitors	23.9	20.0	3.9 (-13.6 to 21.4)	0.65
AII-antagonists	0.0	5.0	-5.0 (-11.8 to 1.7)	
Diuretics	26.1	17.5		
ß-blockers	23.9	20.0	1.1 (-17.1 to 19.3)	
Ca- antagonists	21.7	27.5		
Other	4.4	10.0		

Clinical features of renal disease in first-degree relatives

The features of renal disease are given in **Table 6**. No differences were detected in the distribution of microalbuminuria and proteinuria among the case- and control-relatives. Subgroup analysis for diabetic state according to the WHO-criteria also showed no differences for microalbuminuria between the two family groups. Also serum creatinine values and estimated renal clearances were equal in both groups.

In general, there was no difference in dipstick readings between the case- and control-relatives.

***Table 6**: Clinical features of renal disease in 330 first-degree relatives of Type 2 diabetic patients with and without diabetic nephropathy.*

		Case-relatives	Control-relatives	Difference (95 % CI)	P-value
Albuminuria distribution (%)					
Normoalbuminuria		88.7	88.8	0.1 (-6.7 to 6.9)	0.81
Microalbuminuria		7.7	8.7		
Proteinuria		3.6	2.5		
Renal function creatinine (µmol/l)		83.7	82.7	1.0 (-3.1 to 5.0)	0.63
Cockcroft-Gault renal clearance/1.73 m^2		92.6	94.5	-1.9 (-6.4 to 2.5)	0.39
Urine dipstick readings					
Hematuria (%)	Absent	82.8	80.1	2.7 (-5.7 to 11.1)	0.02
	Trace	10.1	5.6	4.5 (-1.3 to 10.2)	
	Positive	7.1	14.3	-7.2 (-13.8 to -0.53)	
Leukocyturia (%)	Absent	63.9	68.3	-4.4 (-14.6 to 5.8)	0.42
	Trace	23.7	18.6	5.1 (-3.7 to 13.8)	
	Positive	12.4	13.1	-0.7 (-7.8 to 6.6)	

Discussion

In this population-based family study, we found no difference in the prevalence of nephropathy in family members of South Asian type 2 diabetes patients with and without nephropathy.

Recently, we reported a close to 40-fold higher risk of end-stage nephropathy due to type 2 diabetes mellitus in Surinamese South Asian immigrants when compared to native Dutch individuals. [8] This is much higher than the eight-time higher prevalence of diabetes [11] in this population. This supports the hypothesis of a higher susceptibility to develop diabetic nephropathy in the South Asian diabetic population. Another

possibility is faster progression of diabetic nephropathy towards end-stage renal failure in South Asian diabetic patients. Earlier studies for progression of nephropathy in South Asian diabetics were not conclusive. [16-17] An ethnic predisposition for renal diseases can emerge in two ways: a general susceptibility of the entire South Asian population or a familial predisposition for renal diseases within certain South Asian families. The latter would point towards shared environmental risk factors in these families or could indicate susceptibility genes for nephropathy which are inherited independently from diabetes mellitus.

In the present study, we investigated nephropathy in first-degree relatives of South Asian type 2 diabetic patients who had end-stage diabetic nephropathy necessitating dialysis treatment or in whom preparations for dialysis were made. As controls we invited first degree relatives of South Asian type 2 diabetic patients who did not have microalbuminuria. Despite the fact that we took the most pronounced renal disease patients as case-index patients, we did not detect differences in renal disease in their relatives, defined by micro-albuminuria, glomerular filtration rates and blood pressures. The familial predisposition for type 2 diabetes measured by GTT was similar in both the case- and control-relatives. There were no differences in the prevalence of newly discovered diabetics and impaired glucose tolerance test. Diabetic state, blood pressure profiles, antihypertensive treatment were the same in both groups. Urine dipstick measurement for leukocyturia and hematuria were similar in the case- and control-relatives. A difference was noted in religions. The control group had somewhat more Muslims than Hindu's which could explain the slightly higher percentage of vegetarians in the control group. However, this could only lead to less proteinuria in the control group.

The main advantage of our study is the investigation of all the diabetic family members, including previously unidentified diabetic family relatives. This appeared to be important because for every known diabetic relative, a new diabetic relative was discovered. Diabetes was the strongest risk factor for renal disease in both family groups. To prevent bias we randomly selected the control-index patients using the records of GP's of our case-index patients. Furthermore, we invited the relatives of the case families and control families in the same way.

The findings in our study are different from other studies in other ethnic populations with type 2 diabetic patients. In American Pima Indians, there is a higher risk of diabetic nephropathy in diabetic siblings and offspring if the index patient had diabetic nephropathy. [3] This was also found in families of Afro-American, Italian and Brazilian patients with type 2 diabetes. [4-7] However, the results of these studies cannot

be extrapolated directly to the South Asian population living in the Netherlands. Firstly, most studies were done with relatives of known diabetic patients only as controls. To study the hypothesis of familial nephropathy, we also took the results of newly discovered diabetic family members into account. Secondly, nearly all studies used proteinuric diabetics as case-index patients. We investigated relatives of case-index patients on dialysis treatment, giving a stronger contrast with the relatives of control-index patients. It could be argued that the number of diabetics in our study was not large enough to have sufficient power for detecting a clustering of diabetic nephropathy. However, given perfect equality in the degree of albuminuria and the prevalence of nephropathy patients in both groups, it is difficult to imagine that this would dramatically change with a larger sample size.

Conclusions

In the present investigation we did not find familial clustering of renal disease in families of type 2 diabetic patients with end-stage diabetic nephropathy. In an earlier study the much higher incidence of diabetic nephropathy in South Asians is not simply due to the higher incidence of diabetes. The “gap” between the 40-fold increase in diabetic nephropathy and the only 8-fold increase of diabetes itself may mean that all persons of South Asian descent are especially vulnerable to develop nephropathy once they have developed diabetes mellitus. Another possibility is faster progression of nephropathy towards end-stage diabetic nephropathy in this population. Future investigations should focus on the development and progression of diabetic nephropathy in South Asian type 2 diabetics.

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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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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

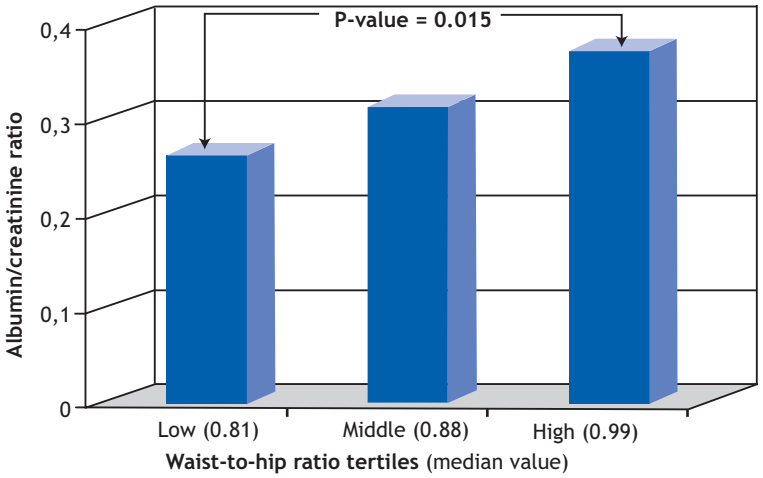

Figure 1: *Shows the median albumin/creatinine ratio (ACR) in the urine in relation to tertiles of central obesity (WHR). The median ACR rose simultaneous with increasing tertiles of WHR. The difference in median ACR between the lowest versus the highest tertile WHR was 0.16 mg/mmol; p = 0.015.*

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.

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Chapter 7

Discussion

This thesis focuses on the incidence, risk factors and familial predisposition for nephropathy in diabetic and non-diabetic Surinamese South Asians. The Surinamese South Asians, originally descended from the North-East India. Due to the former colonial bounds with the Netherlands, a relatively young South Asian migrant population settled in the Netherlands.

In **chapter 2**, the descent of the South Asian immigrants is described and their migration to Suriname and the Netherlands. Unlike the South Asians in the United Kingdom, Surinamese South Asian persons originally descended from a restricted area in Northern India. The selection of contract labourers (indentured labourers) for working in Suriname was very strict: there were at least five medical examinations. Only healthy persons with a good physical condition and certain height were accepted. Only one third of the 34000 migrated South Asians went back to India. So the South Asian population of the Netherlands is probably more homogeneous than those in other migrant studies. We described the structure and selection of the South Asian immigrants, for the studies mentioned below, in a flow diagram.

In **chapter 3**, we determined the relative risk of end-stage diabetic nephropathy between Surinamese South Asian immigrants and native Dutch European persons older than 30 years, who are living in the city of The Hague. [1] In this population, the age-adjusted relative risk for end-stage diabetic nephropathy was 22-times increased. End-stage diabetic nephropathy due to type 2 diabetes was 38-fold increased in the South Asian population. We were in an unique position to perform a demographically and geographically defined population study. In the Netherlands, patients with end-stage renal failure are assigned to a dialysis facility based on their place of residence. We could identify them by using the national registry for renal replacement therapy (RENINE). This registry also contains the diagnosis of end-stage renal failure (end-stage diabetic nephropathy). We reviewed the medical charts to verify the diagnosis of diabetic nephropathy. The diagnostic criteria were similar in both ethnic groups. Most patients had proteinuria and diabetic retinopathy. We corrected for immigration for medical reasons by excluding all South Asian patients who immigrated to the Netherlands within two years before onset of renal replacement therapy. The 38-fold increased risk for end-stage diabetic nephropathy could partially be explained by the increased prevalence of type 2 diabetes in the South Asian population. A survey done by the Municipal Health Service of The Hague showed an eightfold higher prevalence of diabetes among the South Asian population than in the general Dutch population. [2]

In addition, large population studies in the UK showed a three to four times increased risk for diabetes among the South Asian migrant population. [3-7] However, this higher prevalence of diabetes does not fully explain the close to 40-times increased risk for end-stage type 2 diabetic nephropathy among South Asians. Additional factors should therefore be considered such as a more aggressive course of diabetic disease or a higher incidence of nephropathy in the South Asian type 2 diabetic population. The similar diabetes duration of 17 years until onset of the dialysis treatment in both ethnic groups supports the hypothesis of a higher incidence of diabetic nephropathy in the South Asian diabetic population. Furthermore, we cannot exclude differences due to cardiovascular death before starting dialysis treatment because the Dutch European dialysis patients were 13 years older than the South Asians.

In **chapter 4**, we described a cohort investigation among South Asian and Dutch European type 2 diabetic patients for development of nephropathy. [8] As earlier mentioned, the eight times higher prevalence of diabetes among South Asians only partially explains the nearly 40-fold increased risk for end-stage diabetic nephropathy. We therefore compared the incidence of microalbuminuria and the progression of renal failure between South Asian and Dutch European type 2 diabetic patients. After correction for the younger age of the South Asian patients (12 years), the odds ratio for developing microalbuminuria or macroalbuminuria was nearly 4 in the South Asian type 2 diabetic group. After 5 years follow-up, the loss in glomerular filtration rate was 1.45 times higher (Δ GFR loss 10 ml/min/1.73 m2) in the South Asian group. The higher risk for diabetic nephropathy in the South Asian population was not explained by differences in classic risk factors: South Asians were younger and had less cardiovascular complications and lower blood pressure values with less antihypertensive medication than the Dutch European group. We also adjusted our analysis for HbA1c levels in the South Asian diabetic patients. The higher risk for microalbuminuria in South Asians was not attributed to differences in RAS blocker or diuretic usage between the two ethnic groups. The adjusted odds ratio, derived after multivariate analysis, slightly overestimates the true relative risk because of the high frequency of microalbuminuria. After correction for the overestimation, [9] the relative risk was still higher in the South Asian group: 2.8 (95% CI 1.1 to 4.9). Our findings points to an genetic or environmental susceptibility factor within the South Asian population.

In **chapter 5**, we investigated familial predisposition for diabetic nephropathy within

the South Asian population. [10] 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 diabetic patients with end-stage diabetic nephropathy; the second group (control-relatives) consisted of 161 relatives of diabetic patients without nephropathy. We could not detect a genetic susceptibility for diabetic nephropathy within the South Asian population. The lack of familial clustering of renal disease in South Asian diabetic patients points to a general ethnic or environmental susceptibility for diabetic nephropathy in this population. This could be due to the high prevalence of obesity and insulin resistance among South Asians.

In **chapter 6**, we explored the hypothesis that central obesity is associated with the development of renal injury, prior to the manifestation of diabetes mellitus. [11] 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. [12-13] 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. [14-16] We studied first-degree non-diabetic relatives of South Asian type 2 diabetic patients for investigation of albuminuria and diabetes. Subjects who used antihypertensive or antidiabetic medication were excluded. Subjects who had an abnormal glucose tolerance test were also excluded. Central obesity was independently related with low level albuminuria in normoglycemic South Asian subjects. With increasing central obesity, other components of the metabolic syndrome such as body mass index, blood pressure, glucose, CRP, triglycerides also increased. 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. However, 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. 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.

Conclusion

Central obesity is an early and independent risk factor for increased albuminuria in normoglycemic South Asian subjects. This could not only explain the high prevalence of type 2 diabetes, but also explains 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. [14;15;21] We did not find familial predisposition for renal disease in South Asian diabetic patients. We assume that the nearly 40-fold higher risk of end-stage diabetic nephropathy in South Asian migrants [1] is primarily caused by central obesity which leads to:

a. Early renal injury in the pre-diabetic state. [11]
b. Eight-times higher prevalence of type 2 diabetes mellitus. [2]
c. More diabetic nephropathy and faster decline in renal function. [8]

Can our findings be generalised to the current Indian and other migrant South Asian populations?

In this thesis, we reveal that renal disease is increased in diabetic and non-diabetic South Asian migrants. Can our findings in Suriname South Asians living in the Netherlands be generalised to other migrant South Asian populations like in the United Kingdom, or in 800 million Indian Asians living in the Indian subcontinent?

There are no large comparative studies done in the origin of the Surinamese South Asian population in North-East India. [22] However in urban Pakistan, a high prevalence of chronic renal disease with reduced glomerular filtration rate (GFR < 60ml/1.73 m^2) was shown by Jafar et al. [23] They found a low GFR in about 30% of a population-based sample. The risk factors were the same as in our study: older age, lower body weight, lower BMI, higher blood pressure and diabetes.

Although comparative studies are lacking for renal disease between Indian Asians and their migrant population, there are clear signs for heterogeneity in other correlated diseases like diabetes and coronary heart disease. South Asian migrants worldwide have a high risk for insulin resistance, obesity and type 2 diabetes mellitus. [2;3;24-28] The prevalence of diabetes is much higher in migrant South Asian populations than in their original Indian population. [7;29;30] However the prevalence of diabetes is rising rapidly, especially in the urban population in India. Between 1971 to 2000, the prevalence rose from 1.2 to 12.1%. [29] Improved socioeconomic status, increased family income, educational status, and a sedentary life-style are contributing factors.

The risk for diabetes is four times higher in the urban areas than in the rural parts. [31] The same applies to the prevalence of coronary heart disease risk factors. [30;32-39] Bhatnagar et al. showed the impact of migration from India to the UK in South Asian migrants versus their siblings living in India. [30] Insulin resistance and cholesterol was higher in the migrated siblings in the UK. Furthermore, South Asians have a high risk for coronary heart disease despite lower Framingham risk scores.[40] Bhopal et al. showed a large difference in the prevalence of coronary heart risk factors between the different population of the Indian subcontinent. [41] For instance Bangladeshi and Pakistani were poorer and had more diabetes than Indians (22.4 versus 24.6%). Bangladeshi men smoked more and had higher levels of glucose and dyslipidemia. However, their blood pressure was lower than in other Indian groups. Renal disease is one of the strongest risk factors for cardiovascular death and correlated with cardiovascular risk factors.[17-19] The heterogeneity in the prevalence of coronary risk factors and diabetes could also hold true for renal risk factors.

Another difference in Surinamese South Asians is their area of descent. More than 80% of the migrants come from one area: The United Provinces of Agra and Oudh, mainly referred to simply as the United Provinces. It corresponds approximately to the modern-day Indian states of Uttar Pradesh and West-Bihar. The Dutch government chose this area of recruitment hoping for more recruitment of immigrants because of the food shortage and overpopulation in this part of India. In this food and resources shortage, they selected South Asian migrants who were physically fit by medical examinations. Due to this selection process the mortality among the South Asians migrants went down from 20 to 2%.

In summary, although comparative studies for differences in renal disease between the Indian population and migrant South Asian population are still lacking, there is evidence of a chronic renal burden in the Indian subcontinent. Looking at the differences in diabetes prevalence, coronary risk factors between the different populations on the Indian subcontinent and their migrant descent, we cannot generalize our findings straightly to other South Asian and Indian populations. Due to more urbanisation, higher income and selection of the migrant population, diabetes, obesity and renal disease seems to be exaggerated in Surinamese South Asians than in India. However, the rapid rise in urbanisation and welfare in India will probably equalize the differences within a few decades.

Implications in clinical practice

Screening for central obesity in South Asians with a simple measure tape could identify persons at risk for developing renal organ damage already in the "normal" glucose range. Since one out of three South Asian persons will develop diabetes in life, prevention strategies should be employed starting at primary school. Progression of impaired glucose tolerance to diabetes is high in Indian Asians and South Asians and can be reduced by life-style programs or metformin. [42] Life style prevention programs could not only prevent the complications of diabetes and obesity, but also be cost-effective, because the diabetic complications start at a younger age in South Asians with less cardiovascular death and continuously increasing medical consumption.

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Demonstratie aan de Waterkant te Paramaribo, Suriname, 1948.

Chapter 8

Nederlandse samenvatting

Dit proefschrift gaat over het optreden van nierbeschadiging (nefropathie) ten gevolge van suikerziekte en overgewicht bij Surinaamse Hindostanen die in Nederland wonen. Surinaamse Hindostanen zijn oorspronkelijk afkomstig uit Noord-Oost India. Door het koloniale verleden met Suriname heeft een grote groep van ongeveer 170.000 Hindostaanse migranten zich gevestigd in Nederland.

In **hoofdstuk 2** wordt de migratie van de Hindostanen beschreven, vanuit India naar Suriname en vervolgens naar Nederland. In tegenstelling tot Hindostaanse migranten in Groot-Brittannië, zijn Surinaamse Hindostanen grotendeels afkomstig uit een afgebakend gebied in Noord-Oost India, namelijk West-Bihar en Uttar Pradesh. De Surinaamse Hindostanen in Nederland zijn daardoor waarschijnlijk meer homogeen dan elders in de wereld levende Hindostaanse migranten. De gemigreerde Hindostanen waren geselecteerd als contractarbeiders om zwaar lichamelijk werk te kunnen verrichten op de plantages in Suriname. Alvorens zij definitief werden ingescheept, werden zij minimaal vijfmaal medisch gekeurd. Alleen gezonde personen met een goede lichamelijke conditie en een geschikte lichaamsbouw werden geaccepteerd. Slechts 1/3 deel van de ongeveer 34.000 gemigreerde Hindostanen ging vanuit Suriname terug naar India. In hoofdstuk 2 beschrijven wij hoe de selectie en opbouw van de studiepopulatie heeft plaatsgevonden.

In **hoofdstuk 3** hebben wij de kans berekend om aan de nierdialyse te raken door suikerziekte bij Hindostanen en Nederlanders die ouder zijn dan 30 jaar. Wanneer de nieren nauwelijks meer functioneren is nierfunctie vervangende behandeling noodzakelijk om in leven te blijven. Deze behandeling wordt in de volksmond “nierdialyse” genoemd. Hierbij wordt het bloed gezuiverd van overtollige afvalstoffen en vocht door middel van een machine of door buikvliesspoelingen. Hoewel deze behandeling over het algemeen goed wordt verdragen, is het op de lange termijn voor de patiënt een zware lichamelijke en psychische belasting. Patiënten die dialyseren ten gevolge van suikerziekte hebben bovendien een sterk verkorte levensverwachting. De behandeling en begeleiding van dialyse patiënten vindt plaats in speciale dialyse centra, omdat het een medisch ingewikkelde en kostbare behandeling is. Wij waren in de unieke positie om regionaal onderzoek te verrichten, doordat in Nederland een landelijk register bestaat voor de gegevens van de dialyse patiënten (Stichting RENINE). Patiënten worden op grond van hun woonplaats bij een bepaald dialysecentrum behandeld. Verder bevat het register de oorzaak van nierfalen, in ons geval nierfalen ten gevolge van suikerziekte (ofwel diabetische nefropathie). Tevens werden de

medische statussen bekeken en gecontroleerd op welke manier de nierbeschadiging was vastgesteld. De gebruikte diagnostische criteria werden op dezelfde manier toegepast bij Hindostaanse en Nederlandse suikerpatiënten. Hindostaanse patiënten die om medische redenen naar Nederland geëmigreerd zijn, werden buiten beschouwing gelaten. Hindostanen hadden 22-maal meer kans op dialyse door suikerziekte dan Nederlanders. Wanneer we een leeftijdscorrectie uitvoeren, omdat de Hindostanen veel jonger zijn als de suikerziekte begint, dan stijgt het risico naar 38-maal meer kans op dialyse. Hoewel suikerziekte 8-maal vaker voorkomt onder de Hindostaanse bevolking in Den Haag, bleek het risico op dialyse in de algemene bevolking bijna 40-maal hoger te zijn voor een Hindostaan dan voor een persoon van Nederlandse afkomst. Deze toename, ten opzichte van personen van Nederlandse afkomst, zou kunnen berusten op het vroeger ontstaan van nierbeschadiging bij Hindostaanse patiënten met suikerziekte. Een andere mogelijkheid zou een agressiever beloop zijn, waardoor de nierbeschadiging eerder zou kunnen leiden tot dialyse bij Hindostaanse suikerpatiënten. Wat we verder niet goed konden uitsluiten, waren verschillen in sterfte tussen Hindostaanse en Nederlandse suikerpatiënten nog voordat ze met de dialyse behandeling konden starten.

In **hoofdstuk 4** hebben wij een groep Hindostaanse en Nederlandse suikerpatiënten met type 2 diabetes met elkaar vergeleken met betrekking tot het ontstaan van nierbeschadiging en het verlies van hun nierfunctie. Nierbeschadiging ten gevolge van suikerziekte kan geconstateerd worden door toegenomen uitscheiding van kleine hoeveelheden eiwit in de urine, dit heet microalbuminurie. Hindostaanse suikerpatiënten kregen sneller microalbuminurie dan Nederlandse suikerpatiënten. Ook de nierfunctie ging bijna anderhalf keer sneller achteruit bij de Hindostaanse suikerpatiënten. Na vijf jaar hadden zij 10% meer nierfunctie verlies dan Nederlandse suikerpatiënten. Het verhoogde risico op nierbeschadiging en verlies van nierfunctie werd niet verklaard door bekende risicofactoren: Hindostanen waren juist jonger, hadden minder hoge bloeddruk en minder bloeddruk verlagende medicijnen nodig. Zelfs na statistische correcties, zoals de iets slechtere suikerregulatie (HbA1c), bleef het risico op nierbeschadiging bijna driemaal hoger. Dit kan wijzen op een erfelijke factor of op een omgevingsfactor voor nierbeschadiging binnen de Hindostaanse bevolking.

In **hoofdstuk 5** hebben wij onderzoek gedaan naar aanleg voor nierbeschadiging door suikerziekte binnen de Hindostaanse bevolking. We hebben daarvoor de families van

twee groepen Hindostaanse suikerpatiënten onderzocht. De eerste groep familieleden was afkomstig van Hindostaanse suikerpatiënten die leden aan zeer ernstige nierbeschadiging ("nierdialyse" patiënten). Deze werden vergeleken met familieleden van Hindostaanse suikerpatiënten die geen tekenen hadden van nierbeschadiging. Hindostaanse eerste graads familieleden van nierdialyse patiënten hadden geen hoger risico op nierbeschadiging, hoge bloeddruk of suikerziekte. Het ontbreken van een familiaire aanleg voor nierbeschadiging binnen de Hindostaanse bevolking kan wijzen op een algemeen etnische factor of een omgevingsfactor voor nierbeschadiging binnen de Hindostaanse bevolking. Hindostanen hebben een sterk verhoogd risico op het krijgen van overgewicht (obesitas) en problemen met hun insuline stofwisseling. Patiënten met overgewicht hebben meer risico op nierbeschadiging. Dit zou dus een verklaring kunnen zijn voor het verhoogde risico op nierproblemen in de Hindostaanse populatie.

In **hoofdstuk 6** hebben wij onderzocht of centrale obesitas (vetophoping in de buik) gepaard gaat met nierschade bij Hindostaanse personen die geen suikerziekte hebben. Centrale obesitas kan gemeten worden door de verhouding van de taille en heupomvang. Een verhoogde taille-heupomvang verhouding geeft niet alleen een verhoogd risico op hart- en vaat ziekten, maar is ook een potentiële risicofactor voor nierziekten bij niet-diabeten. De oorzaak is onduidelijk en men vermoedt dat door het buikvet ontstekingsstoffen (cytokines) en hormonen worden gemaakt. Deze zouden dan de wand van de bloedvaten in de nieren kunnen laten ontsteken, waardoor er eiwit in de urine kan vrijkomen. Gezonde familieleden van Hindostaanse suikerpatiënten werden onderzocht op eiwituitscheiding (albuminurie) in de urine en suikerziekte (glucose tolerantie test in bloed). De familieleden mochten geen enkele vorm van suikerziekte hebben of medicatie gebruiken voor hoge bloeddruk. Na meting van de taille-heupomvang verhouding werden de familieleden ingedeeld in drie oplopende groepen van buikvet. Personen met veel buikvet hadden meer eiwit (albuminurie) in hun urine dan personen met weinig buikvet. Verder hadden personen met veel buikvet een hoger vetgehalte (triglyceriden), een hogere bloeddruk, een hogere ontstekingseiwit (CRP) en een hogere bloedsuikerwaarde dan personen met minder buikvet. De gemeten hoeveelheid eiwit in de urine (albuminurie) is veel lager dan de grenswaarde die we normaliter gebruiken voor meting van nierbeschadiging ten gevolge van suikerziekte (microalbuminurie). Toch blijken dit soort licht verhoogde eiwituitscheidingen gepaard te gaan met toegenomen sterfte door hart- en vaatziekten. Toegenomen buikvet is een groot probleem onder de Hindostaanse bevolking in de

westerse wereld. Het zou de explosieve toename van hartinfarcten en nierproblemen bij Hindostanen kunnen verklaren.

Conclusie

Centrale obesitas is een vroege en onafhankelijke risico factor voor toegenomen eiwit uitscheiding (albuminurie) bij Hindostaanse personen, reeds voordat problemen door suikerziekte zijn begonnen. De centrale obesitas verklaart niet alleen de 8-maal hogere prevalentie van suikerziekte in de Hindostaanse bevolking, maar ook het hoge risico op nierschade ten gevolge van suikerziekte. Wij denken dat, reeds voor de ontwikkeling van suikerziekte, de eerste beschadiging van de nieren optreedt door het toegenomen buikvet. Wanneer vervolgens de suikerziekte ontstaat, gaan deze reeds beschadigde nieren eerder achteruit. De bijna 40-maal hogere risico op nierfalen bij Hindostaanse migranten wordt ons inziens voornamelijk bepaald door de hoge kans op centrale obesitas welke leidt tot:

a. Een vroege nierbeschadiging reeds voordat de suikerziekte is ontstaan.
b. Het 8-maal vaker voorkomen van type 2 suikerziekte.
c. Meer diabetische nierbeschadiging en snellere achteruitgang van de nierfunctie na het ontstaan van suikerziekte.

Zijn onze bevindingen ook toepasbaar bij elders levende Hindostaanse migrant groepen en in de huidige Indiase bevolking?

In dit proefschrift rapporteren wij dat nierbeschadiging verhoogd is bij Hindostanen in Nederland. Gelden onze bevindingen ook voor de miljoenen Hindostanen wereldwijd? Om deze belangrijke vraag te beantwoorden zullen we in deze paragraaf de vergelijking maken met andere Hindostaanse migrant groepen en de huidige bevolking in India. Er zijn helaas geen grote vergelijkende studies verricht naar nierinsufficiëntie in het oorspronkelijke gebied waar de Hindostanen vandaan komen (Noord-Oost-India). Een grote populatie studie verricht in Pakistan liet zien dat 30% van de bevolking een gestoorde nierfunctie had (GFR < 60 ml/min/1.73 m^2). De klassieke risicofactoren waren hetzelfde als in onze studie: leeftijd, suikerziekte, hoge bloeddruk en een lage Quetelet Index. Overgewicht werd in deze studie niet gemeten met behulp van de buikomvang, maar met de body mass index (BMI), ook wel Quetelet Index genoemd. De BMI is een index voor het gewicht in verhouding tot lichaamslengte. Patiënten met een gestoorde nierfunctie hadden een lagere BMI en gewicht, maar waren óók

kleiner. De BMI is een algemene maat voor overgewicht, maar is geen goede maat voor centrale obesitas (buikvetophoping) bij Hindostanen. In onze studie was een lage BMI ook een risicofactor voor nierschade.

Hoewel vergelijkende populatie studies naar nierziekten ontbreken tussen Hindostaanse migranten en hun oorspronkelijke populatie in India, zijn er wel duidelijke aanwijzingen voor populatieverschillen bij andere ziekten zoals suikerziekte en hartinfarcten. Wereldwijd hebben Hindostaanse migrant groepen een sterk verhoogd risico op centrale obesitas en suikerziekte. Suikerziekte komt vaker voor bij Hindostaanse migranten dan onder de oorspronkelijke bevolking in India. Opvallend is echter, dat de verschillen ieder jaar kleiner worden door de snel stijgende prevalentie van suikerziekte in India, met name in de stedelijke gebieden. Deze prevalentie is sinds 1971 tot 2000 toegenomen van 1.2 naar 12.1%. Het gaat samen met een verbeterde sociaal-economische status, een hoger gezinsinkomen, een hoger opleidingsniveau en een meer passieve levensstijl. Het risico op suikerziekte is viermaal hoger in de stedelijke gebieden dan op het platteland. Soortgelijke bevindingen zijn gedaan voor risicofactoren voor het krijgen van een hartinfarct. Vermeldenswaardig is het onderzoek van Bhatnager e.a. in Groot-Brittannië (GB), waarbij Hindostaanse migranten in GB werden vergeleken met hun in India wonende broers of zusters. Na migratie steeg het cholesterol en overgewicht. Andere studies toonden een verhoogd risico op een hartinfarct bij Hindostanen, welke onvoldoende wordt voorspeld door klassieke risicofactoren, zoals roken, geslacht en cholesterol (Framingham risicoscore). Tot slot zijn er op het Indiaas subcontinent grote verschillen in prevalentie van risicofactoren voor hartziekten: personen uit Bangladesh en Pakistan zijn armer en hebben vaker suikerziekte. Mannen uit Bangladesh roken meer en hebben vaker hogere suikers en vetgehalte van het bloed, terwijl hun bloeddruk lager is dan bij andere Hindostaanse bevolkingsgroepen. Nierziekte is een zeer sterke voorspeller van sterfte door hart- en vaatziekten en is bovendien gecorreleerd met de risicofactoren voor deze aandoeningen. De heterogeniteit in de prevalentie van deze risicofactoren en de suikerziekte kan daarom ook voor nieraandoeningen bij Hindostanen gelden.

Er is nog een ander verschil met Hindostaanse migrant groepen elders in de wereld; Surinaamse Hindostanen zijn voor meer dan 80 % van de gevallen afkomstig uit hetzelfde gebied, de United Provinces (Uttar Pradesh en West-Bihar). De Nederlandse regering koos voor dit rekruteringsgebied vanwege de overbevolking en de grote economische malaise, waardoor rekrutering succesvoller was. In dit gebied, geteisterd

door hongersnood, overstromingen en ziekte, werden migranten geselecteerd die fysiek in goede conditie waren om op de plantages in Suriname te werken. Door medisch onderzoek en selectie daalde de mortaliteit onder de gemigreerde groep Hindostanen van 20% naar 2%.

Samenvattend zijn er duidelijke aanwijzingen voor toegenomen chronische nierziekten op het Indiaas subcontinent, echter goede vergelijkende studies ontbreken. Er zijn duidelijke verschillen in prevalentie van suikerziekte, risicofactoren voor hartinfarcten tussen de verschillende Hindostaanse populaties op het Indiaas subcontinent en andere Hindostaanse migrant groepen wereldwijd. We kunnen daardoor onze bevindingen niet rechtstreeks toepassen op andere Indiase personen of migrant groepen. Door de verstedelijking, een hoger inkomen en selectie van de gemigreerde populatie, komen buikvetophoping, suikerziekte en nierziekte vaker voor bij Surinaamse Hindostanen dan in India. Helaas is India bezig met een inhaalrace, veroorzaakt door de snel stijgende verstedelijking en welvaart. Wij verwachten daardoor, dat binnen enkele decennia de verschillen met Westerse Hindostaanse migranten zullen zijn verdwenen.

Implicaties voor de klinische praktijk

Het screenen van de Hindostaanse bevolking op buikvetophoping met behulp van een gewoon meetlint, kan personen identificeren die een verhoogd risico hebben op nierschade, reeds voor het stadium van suikerziekte. Aangezien één op de drie Hindostanen suikerziekte zal ontwikkelen gedurende het leven, dienen er vanaf de basisschool preventiecampagnes te worden gestart. Deze zogenaamde leefstijl-interventie programma's kunnen de ontwikkeling van overgewicht en suikerziekte effectief remmen in de Hindostaanse populatie. De complicaties ten gevolge van suikerziekte starten bij Hindostanen op jongere leeftijd en gaan gepaard met meer sterfte ten gevolge van hart- en vaatziekten. Dit leidt ertoe dat er een explosieve toename van medische consumptie zal optreden. Het instellen van leefstijl-interventie programma's zullen waarschijnlijk kosteneffectief zijn, doordat bij afname van complicaties ook een afname van medische kosten wordt teweeggebracht.

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Dankwoord

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Sylvana, mi goedoe....
Je weet wat ik wil zeggen.... woorden schieten mij namelijk tekort....
De tijd is nu eindelijk aangebroken voor onze andere “projecten”.

Curriculum vitae

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De schrijver van dit proefschrift werd geboren op 23 augustus 1964 in Amsterdam. In 1982 deed hij eindexamen VWO aan het Spaarne Scholengemeenschap te Haarlem. Vervolgens startte hij met zijn studie geneeskunde aan de Universiteit van Amsterdam. Na het behalen van het doctoraal examen in augustus 1986, begon hij met zijn co-schappen aan de Rijksuniversiteit Leiden. Na het behalen van zijn artsexamen in februari 1989 was hij werkzaam als arts-assistent interne geneeskunde in het Militaire Hospitaal Dr. A. Mathijsen te Utrecht (hoofd: kolonel-arts dr. M. van Zoeren) en vanaf september 1990 in het Onze Lieve Vrouwe Gasthuis te Amsterdam (hoofd: dr. J. Silberbusch). In januari 1991 startte hij met zijn opleiding tot internist in het Rode Kruis Ziekenhuis te 's-Gravenhage (opleider: dr. D. Overbosch, internist). Vanaf mei 1994 continueerde hij zijn specialisatie tot internist in het Leids Universitair Medisch Centrum (opleider: prof. dr. A.E. Meinders). Na zijn specialisatie tot internist in mei 1997 was hij kortdurend werkzaam op de afdeling Intensive Care en Beademing in het Leids Universitair Medisch Centrum (LUMC) (hoofd: dr. J.G. van der Hoeven). In september 1997 startte hij zijn opleiding tot nefroloog in het LUMC (opleiders: prof. dr. L.A. van Es en prof. dr. L.C. Paul) In deze periode werd ook een begin gemaakt met dit proefschrift onder leiding van prof. dr. L.A. van Es, prof. dr. J.P. Vandenbroucke en later prof. dr. L.C. Paul. Na het overlijden van prof. dr. Leen Paul op 16 juli 2004 werd het promotie onderzoek voortgezet onder leiding van prof. A.J. Rabelink. Sinds januari 2003 is de schrijver werkzaam als internist-nefroloog in het Medisch Centrum Haaglanden te 's-Gravenhage.

Colofon bronvermelding illustraties Tropenmuseum, Amsterdam.

Hoofdstuk 1: Benares aan de Ganges, India, ca. 1880.
Collectienr. 60003879.

Hoofdstuk 2: Een dorp in de omgeving van Calcutta, India, ca. 1870.
Collectienr. 60003662.

Hoofdstuk 3: Pas gearriveerde immigranten uit toenmalig Brits-Indië staan voor het immigratiedepot nabij Paramaribo, Suriname, ca. 1915.
Collectienr. 60006155.

Hoofdstuk 4: Brits-Indische immigranten aan boord van een schip op de Surinamerivier bij Paramaribo, dat hen terug brengt naar Brits-Indië, Suriname, ca. 1890.
Collectienr. 60012353.

Hoofdstuk 5: Een Hindostaanse arbeider voor zijn huis met gezin en buren, Suriname, ca. 1930.
Collectienr. 60006195.

Hoofdstuk 6: Studioportret van drie Indiase mannen met manden of korven die op het hoofd worden gedragen, India, ca. 1875.
Collectienr. 60003920.

Hoofdstuk 8: Demonstratie aan de Waterkant te Paramaribo, Suriname, 1948.
Collectienr. 10020461.