# Diabetic nephropathy in Surinamese South Asian subjects

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3 Hindostaanse bezoekers tonen speciaal hun buik, Natuurpark Brownsberg, Suriname 2004.

# 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.

## References


1. Chandie Shaw PK, Vandenbroucke JP, Tjandra YI, Rosendaal FR, Rosman JB, Geerlings W et al. Increased end-stage diabetic nephropathy in Indo-Asian immigrants living in the Netherlands. Diabetologia 2002;453:337-341.
2. Middelkoop BJC, Kesarlal-Sadhoeram SM, Ramsaransing GN, Struben HWA. Diabetes mellitus among South Asian inhabitants of the Hague: high prevalence and an age-specific socioeconomic gradient. Int J Epidemiol 1999;28:1119-1123.
3. Mather HM, Keen H. The Southall Diabetes Survey: prevalence of known diabetes in Asians and Europeans. Br Med J (Clin Res Ed) 1985;291:1081-1084.
4. Simmons D, Williams DR, Powell MJ. The Coventry Diabetes Study: prevalence of diabetes and impaired glucose tolerance in Europids and Asians. QJM 1991;81:1021-1030.
5. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet 1991;337:382-386.
6. Simmons D. Parity, ethnic group and the prevalence of type 2 diabetes: the Coventry Diabetes Study. Diabet Med 1992;9:706-709.
7. Burden AC. Diabetes in Indo-Asian people. Practitioner 2001;245:445-451.
8. Chandie Shaw PK, Baboe F, van Es LA, van der Vijver JC, van de Ree MA, de Jonge N et al. South-asian type 2 diabetic patients have higher incidence and faster progression of renal disease compared with dutch-European diabetic patients. Diabetes Care 2006;29:1383-1385.
9. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1691.
10. Chandie Shaw PK, van Es LA, Paul LC, Rosendaal FR, Souverijn JH, Vandenbroucke JP. Renal disease in relatives of Indo-Asian Type 2 diabetic patients with end-stage diabetic nephropathy. Diabetologia 2003;46:618-624.
11. Chandie Shaw PK, Berger SP, Mallat M, Frolich M, Dekker FW, Rabelink TJ. Central obesity is an independent risk factor for albuminuria in nondiabetic South Asian subjects. Diabetes Care 2007;30:1840-1844.
12. Liese AD, Mayer-Davis EJ, Tyroler HA, Davis CE, Keil U, Duncan BB et al. Development of the multiple metabolic syndrome in the ARIC cohort: joint contribution of insulin, BMI, and WHR. Atherosclerosis risk in communities. Ann Epidemiol 1997;7:407-416.

13. Bonnet F, Marre M, Halimi JM, Stengel B, Lange C, Laville M et al. Waist circumference and the metabolic syndrome predict the development of elevated albuminuria in non-diabetic subjects: the DESIR Study. J Hypertens 2006;24:1157-1163.
14. Yudkin JS. Adipose tissue, insulin action and vascular disease: inflammatory signals. Int J Obes Relat Metab Disord 2003;27 Suppl 3:S25-8.
15. Yudkin JS, Eringa E, Stehouwer CD. "Vasocrine" signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. Lancet 2005;365:1817-1820.
16. Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J et al. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nat Med 2005;11: 183-190.
17. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421-426.
18. Wachtell K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Ann Intern Med 2003;139:901-906.
19. Arnlov J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation 2005;112:969-75.
20. Ruggenenti P, Remuzzi G. Time to abandon microalbuminuria? Kidney Int 2006;70:1214-1222.
21. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J Clin Invest 1996;97:2601-2610.
22. Mittal S, Kher V, Gulati S, Agarwal LK, Arora P. Chronic renal failure in India. Ren Fail 1997;19: 763-770.
23. Jafar TH, Schmid CH, Levey AS. Serum creatinine as marker of kidney function in South Asians: a study of reduced GFR in adults in Pakistan. J Am Soc Nephrol 2005;16:1413-1419.
24. Dowse GK, Gareeboo H, Zimmet PZ, Alberti KG, Tuomilehto J, Fareed D et al. High prevalence of NIDDM and impaired glucose tolerance in Indian, Creole, and Chinese Mauritians. Mauritius Noncommunicable Disease Study Group. Diabetes 1990;39:390-396.
25. Simmons D, Williams DR, Powell MJ. The Coventry Diabetes Study: prevalence of diabetes and impaired glucose tolerance in Europids and Asians. Q J Med 1991;81:1021-1030.
26. Dowse GK, Zimmet PZ, Alberti KG, Brigham L, Carlin JB, Tuomilehto J et al. Serum insulin distributions and reproducibility of the relationship between 2-hour insulin and plasma glucose levels in Asian Indian, Creole, and Chinese Mauritians. Mauritius NCD Study Group. Metabolism 1993;42:1232-1241.
27. Snehalatha C, Ramachandran A, Vijay V, Viswanathan M. Differences in plasma insulin responses in urban and rural Indians: a study in southern-Indians. Diabet Med 1994;11:445-448.
28. Tai ES, Lim SC, Chew SK, Tan BY, Tan CE. Homeostasis model assessment in a population with mixed ethnicity: the 1992 Singapore National Health Survey. Diabetes Res Clin Pract 2000;49: 159-168.
29. Ramachandran A. Epidemiology of diabetes in India--three decades of research. J Assoc Physicians India 2005;53:34-38.
30. Bhatnagar D, Anand IS, Durrington PN, Patel DJ, Wander GS, Mackness MI et al. Coronary risk factors in people from the Indian subcontinent living in west London and their siblings in India. Lancet 1995;345:405-409.

31. Singh RB, Niaz MA, Agarwal P, Beegum R, Rastogi SS, Singh NK. Epidemiologic study of central obesity, insulin resistance and associated disturbances in the urban population of North India. Acta Cardiol 1995;50:215-225.
32. McKeigue PM, Miller GJ, Marmot MG. Coronary heart disease in south Asians overseas: a review. J Clin Epidemiol 1989;42:597-609.
33. Wild S, McKeigue P. Cross sectional analysis of mortality by country of birth in England and Wales, 1970-92. BMJ 1997;314:705-710.
34. Fischbacher CM, Bhopal R, Povey C, Steiner M, Chalmers J, Mueller G et al. Record linked retrospective cohort study of 4.6 million people exploring ethnic variations in disease: myocardial infarction in South Asians. BMC Public Health 2007;7:142.
35. Balarajan R, Bulusu L, Adelstein AM, Shukla V. Patterns of mortality among migrants to England and Wales from the Indian subcontinent. Br Med J (Clin Res Ed) 1984;289:1185-1187.
36. Balarajan R. Ethnic differences in mortality from ischaemic heart disease and cerebrovascular disease in England and Wales. BMJ 1991;302:560-564.
37. Bhopal R. What is the risk of coronary heart disease in South Asians? A review of UK research. J Public Health Med 2000;22:375-385.
38. Mohan V, Deepa R, Rani SS, Premalatha G. Prevalence of coronary artery disease and its relationship to lipids in a selected population in South India: The Chennai Urban Population Study (CUPS No. 5). J Am Coll Cardiol 2001;38:682-687.
39. Gupta R, Gupta VP, Sarna M, Bhatnagar S, Thanvi J, Sharma V et al. Prevalence of coronary heart disease and risk factors in an urban Indian population: Jaipur Heart Watch-2. Indian Heart J 2002;54:59-66.
40. Cappuccio FP, Oakeshott P, Strazzullo P, Kerry SM. Application of Framingham risk estimates to ethnic minorities in United Kingdom and implications for primary prevention of heart disease in general practice: cross sectional population based study. BMJ 2002;325:1271.
41. Bhopal R, Unwin N, White M, Yallop J, Walker L, Alberti KG et al. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: cross sectional study. BMJ 1999;319:215-220.
42. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49: 289-297.