Determinants of vascular complications in type 2 diabetic South Asians

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Waist-to-hip ratio is an independent predictor of cardiovascular events in South Asians with type 2 diabetes

A prospective study

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Abstract

Background and aims

South Asians have a high prevalence of diabetes and cardiovascular complications. Since traditional risk factors only partially explain this excessive risk, the identification of non-traditional risk factors is warranted. Among these, central obesity might be an important determinant of cardiovascular disease in this specific group.

Methods

We conducted a prospective observational study. A cohort consisting of 168 type 2 diabetic South Asians was followed for a median duration of 7.66 (IQR 7.48-8.1) years. The primary endpoint was the time to the first cardiovascular event, which was defined as the occurrence of either cardiovascular death, myocardial infarction, revascularization procedure, stroke, carotid artery desobstruction, peripheral artery revascularisation or amputation. To examine the effect of central obesity on cardiovascular events , Cox proportional hazards regression was performed.

Results

Out of 134 subjects for whom follow-up data were available, 30 subjects reached the primary endpoint. Waist-to-hip ratio was the principal predictor of cardiovascular events. Multivariate analysis for the occurrence of a cardiovascular event during follow-up revealed a hazard ratio of 3.77 (95% CI 1.09-13.1), P = 0.037) for the highest versus the lowest tertile of waist-to-hip ratio.

Conclusion

Waist-to-hip ratio is a principal predictor of future cardiovascular events in type 2 diabetic South Asians. The underlying pathophysiologic mechanism probably involves adipogenic inflammation, dyslipidemia and adipokine dysbalance. Our findings urges to explore the use of lifestyle intervention in this specific group.

Introduction

South Asians have a high incidence of diabetes and subsequent vascular complications [1]. Traditional risk factors do not fully explain this higher incidence [2], so non-traditional risk factors must be involved. Among these, research has focused on central obesity, which is highly prevalent in South Asians. At similar body mass index (BMI), South Asians have a higher percentage of body fat compared to Caucasian [3]. Moreover, fat distribution is different, with South Asians having a relatively high truncal fat mass [4]. Histomorphology of adipocytes in South Asians also differs from that in Caucasians [5], with South Asians having larger adipocytes which are considered dysfunctional compared to normal sized adipocytes [6].

Cross-sectional studies in South Asians demonstrate that central obesity is associated with several cardiovascular risk markers, such as increased C-reactive protein [7], insulin resistance and dyslipidemia [1], and urinary albumin/creatinine ratio [8]. Although these latter factors have been shown to be predictive for future cardiovascular events, prospective data on the role of central obesity itself in predicting cardiovascular events in diabetic South Asians are lacking.

We performed a prospective study in a cohort of 168 diabetic South Asians to examine the effect of central obesity on cardiovascular events.

Methods

Design of the follow-up study

We conducted a prospective follow-up study. All studied subjects were recruited from a previously published study [9]. The original study population comprised 465 South Asians. At baseline, subjects that were not known with diabetes underwent a 75 g oral glucose tolerance test. Diabetes was diagnosed based on the ADA 2003 criteria. Out of 465 subjects, 168 subjects had type 2 diabetes at baseline (122 already known with diabetes, 46 newly diagnosed), and from these subjects follow-up data were collected. The study protocol was approved by the Institutional Medical Ethics Committee. All subjects provided informed consent.

Study-patients were followed up by letter and subsequently by phone. When subjects could not be traced by address or phone number in our database, general practitioners or participating family members were involved.

Follow-up data consisted of medical history with regard to cardiovascular events. Subjects were sent a questionnaire and were invited for a visit to our out-patient clinic. During this visit the questionnaire was reviewed by the main investigator (M.A.S.). Subjects not willing to visit the out-patient clinic were asked permission to collect medical data from their general practitioner. For subjects who had died during the follow-up period, cause of death and cardiovascular history was retrieved from the general practitioner. All (self-) reported events were verified by contacting the hospital in which the event had occurred.

Measurements at baseline

Anthropometric measures at baseline included weight, height and waist- and hip circumference. Hip circumference was measured at the maximum hip circumference, waist circumference was measured at the point midway between the lower costal margin and the anterior superior iliac crest.

Laboratory measurements at baseline included lipids, creatinin, fasting glucose, fasting insulin, high-sensitivity C-reactive protein (hsCRP), adiponectin and serum complement factor 3 (C3) Lipids, creatinin, glucose an insulin were measured according to standard methods. High-sensitivity C-reactive protein was measured with a fully automated Cobas Integra 800, according to the manufacturers proceedings (Roche, Almere, the Netherlands). The variation coefficients (VC) were below 3 %. Adiponectin was measured with a radio-immunoassay after dilution. The interassay VC's ranged from 6.9 to 9.2 % at different levels (Millipore Corporation, Billerica, MA 01821, USA). Serum C3 concentration was quantified using radial immunodiffusion according to Mancini, using a polyclonal rabbit anti-human C3 anti-serum as described earlier [10]. Homeostatic model assessment for assessing insulin resistance (HOMA-IR) was performed as follows: [fasting insulin concentration (mU/L) x fasting glucose concentration (mmol/L)] / 22.5 [11].

Definition of endpoint

Cardiovascular events were defined as the occurrence of either a myocardial infarction, Percutaneous Transluminal Coronary Angioplasty (PTCA), Coronary Artery Bypass Grafting (CABG), stroke, Carotid Artery Desobstruction, peripheral vascular angioplasty, bypass or amputation, or sudden cardiac death. The latter was defined as a witnessed sudden circulatory arrest. The primary end-point was the time to the first cardiovascular event.

Statistical analysis

Normally distributed variables are expressed as mean ± 1 standard deviation and skewed distributed variables as median and interquartile range. Differences between two groups were assessed by Student's t-test or Mann-Whitney-U test as appropriate. Differences between more than two groups were assessed by analysis of variance, adjusting for multiple comparisons according to Bonferroni. Correlations were assessed using Pearson's correlation, skewed distributed variables being log-transformed. To identify predictors of cardiovascular events and to adjust for potential confounding factors, Cox proportional hazards regression was performed. Survival curves were compared using the Log-Rank test. All test were two-sided and the level of significance was set at 0.05. All analyses were performed using SPSS for windows, version 17.

Results

Out of 168 type 2 diabetic subjects at baseline, 21 could not be traced and 13 subjects refused to participate. Eighty-six subjects visited the out-patient clinic, 31 subjects did not visit the out-patient clinic but medical information was retrieved from the general practitioner, and 17 subjects had died (see below). The median duration of follow-up was 7.66 (IQR 7.48-8.10) years. Participants lost to follow-up did not differ in baseline characteristics from participants in whom follow-up data were available (table 1).

During follow-up, 39 cardiovascular events occurred in 30 subjects (16 men, 14 women): 3 sudden cardiac deaths, 2 fatal and 5 non-fatal myocardial infarction, 13 percutaneous coronary interventions, 8 coronary artery bypass graft procedures, 2 fatal and 5 non-fatal strokes, 1 lower extremity amputation. Eleven of these 30 subjects had already experienced a cardiovascular event at baseline. Ten subjects died due to non-cardiovascular causes. Two of these subjects reached the primary end-point before they died, the other 8 were censored.

The characteristics of the 134 subjects in whom follow-up data were available are shown in relation to waist-to-hip ratio (WHR) tertile in table 2. As expected, there were more women in the lowest WHR tertile and more men in the highest WHR tertile. Compared to subjects in the lowest WHR tertile, subjects in the highest WHR tertile had higher fasting triglycerides, lower HDL cholesterol levels, higher urinary albumin/creatinine ratio, and a higher prevalence of baseline cardiovascular events. Men and women differed only with respect to

Table 1 baseline characteristics of the study population

	Follow-up (n=134)	Lost to follow-up (n=34)	P-value
Age (years)	50.7 ± 11.2	48.9 ± 11.2	0.392
% male sex	46	45	0.886
Diabetes duration (years)	7.0 (0-13)	5.0 (0-11)	0.519
HOMA-IR*	7.4 (4.8-12.3)	7.7 (5.3-12.1)	0.841
HbA1c (%)	7.7 ± 1.8	7.7 ± 2.0	0.976
Systolic blood pressure (mm Hg)	138 ± 24	140 ± 27	0.638
Diastolic blood pressure (mm Hg)	84 ± 11	84 ± 11	0.937
Urinary albumin/creatinine ratio (mg/mmol)	1.0 (0.4-4.6)	1.0 (0.4-5.0)	0.991
High-sensitivity C-reactive protein (mg/L)	3.5 (1.8-8.0)	4.8 (1.7-8.4)	0.851
Cockroft-Gault creatinine clearance (ml/min)	86 ± 27	93 ± 20	0.205
Total cholesterol (mmol/L)	5.1 ± 1.0	5.0 ± 0.9	0.666
Fasting triglycerides (mmol/L)	1.59 (1.16-2.32)	1.46 (1.24-2.13)	0.869
HDL-cholesterol (mmol/L)	1.23 ± 0.3	1.28 ± 0.3	0.954
Ratio total cholesterol: HDL-cholesterol	4.14 (3.45-5.05)	4.20 (3.10-5.0)	0.432
Body Mass Index	28.0 ± 4.7	28.4 ± 4.0	0.551
Waist-to-hip ratio	0.97 (0.93-1.03)	0.99 (0.95-1.04)	0.223
Adiponectin (mg/L)	7.6 (5.3-10.6)	6.8 (4.6-9.4)	0.124
Serum C3 (μg/ml)	871 ± 100	895 ± 78	0.226
% previous cardiovascular event	14	11	0.663
% current or previous smoker	45	39	0.528

*HOMA-IR = Homeostatic model assessment for assessing insulin resistance

HDL cholesterol level (mean 1.11 ± 0.25 versus 1.32 ± 0.34 mmol/L in men and women, respectively, P<0.001). All other parameters were not different between men and women (data not shown).

Waist-to-hip ratio correlated weakly with adiponectin concentration (r = -0.213, P = 0.016), HDL cholesterol (r = -0.248, P = 0.004), HOMA-IR (r = 0.180, P = 0.040), fasting triglycerides (r = 0.211, P = 0.016) and urinary albumin/creatinine ratio (r = 0.180, P = 0.039) but not with hsCRP, C3, total cholesterol and BMI.

Table 2 baseline characteristics of 134 type 2 diabetic South Asians according to WHR tertile

WHR tertile	1	2	3
Age (years)	48.9 ± 12.2	50.8 ± 10.2	52.5 ± 11.0
% male sex	16	55*	64*
Diabetes duration (years)	6.0 (0.7-13.0)	4.0 (0.0-10.0)	10.5 (0.0-16.3)
HOMA-IR‡	6.26 (4.38-9.93)	7.73 (4.33-10.46)	8.6 (6.0-11.8)
HbA1c (%)	7.3 ± 1.6	7.7 ± 2.2	8.0 ± 1.6
Systolic blood pressure (mm Hg)	138 ± 27	133 ± 16	145 ± 27
Diastolic blood pressure (mm Hg)	85 ± 10	81 ± 11	87 ± 13
Urinary albumin/creatinine ratio (mg/mmol)	0.80 (0.34-2.76)	0.73 (0.33-3.20)	2.74 (0.7-14.9)*†
High-sensitivity C-reactive protein (mg/L)	3.9 (2.2-9.3)	3.5 (1.7-9.4)	3.2 (1.3-5.9)
Cockroft-Gault creatinine clearance (ml/min)	92 ± 31	90 ± 27	94 ± 37
Total cholesterol (mmol/L)	5.22 ± 0.98	5.13 ± 1.02	5.10 ± 0.97
Fasting triglycerides (mmol/L)	1.28 (1.03-1.61)	1.70 (1.10-2.63)	1.79 (1.37-2.61)*
HDL-cholesterol (mmol/L)	1.36 ± 0.37	1.17 ± 0.25*	1.16 ± 0.29*
Ratio total cholesterol: HDL-cholesterol	4.04 ± 1.24	4.57 ± 1.41	4.51 ± 0.92
Body Mass Index	28.3 ± 5.0	26.0 ± 3.6	28.6 ± 5.1
Adiponectin (mg/L)	8.8 (6.5-13.0)	7.0 (4.8-9.3)*	7.6 (5.7-11.7)
Serum C3 (µg/ml)	887 ± 83	869 ± 90	859 ± 124
% previous cardiovascular event	5	7	27*†
% current or previous smoker	39	48	52
Follow-up duration (years)	7.7 (7.5-8.1)	7.8 (7.5-8.1)	7.7 (7.3-8.2)

In the analysis of variance, skewed distributed variables were log-transformed.
*/† Significant difference (P < 0.05) compared to tertile 1 (*) or tertile 2 (†)
‡HOMA-IR = Homeostatic model assessment for assessing insulin resistance

Cox proportional hazard regression

In univariate analysis an increased waist-to-hip ratio was a predictor of cardiovascular events (hazard ratio 6.4 (95% CI 1.9-21.9), P = 0.003 for the highest versus the lowest WHR tertile, see table 3). In figure 1, the event-free survival curves for the lowest and the highest WHR tertile are shown for 8

Table 3 predictors of cardiovascular events

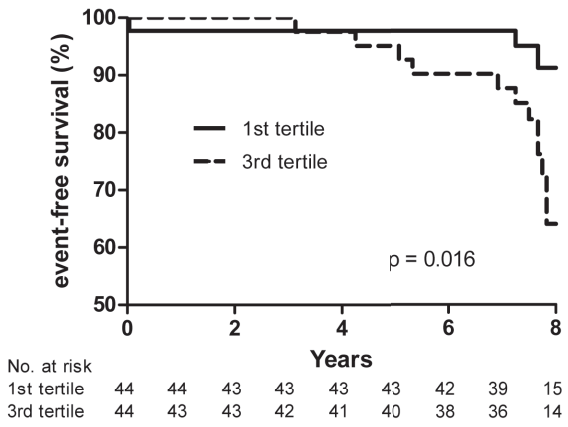
	Hazard ratio for future cardiovascular events (95%CI)	
	Univariate	**Multivariate***
Waist-to-hip ratio tertiles		
Lowest tertile	1.0 (reference)	1.0 (reference)
Middle tertile	2.46 (0.6-9.6)	2.3 (0.6-9.6)
Highest tertile	6.4 (1.9-21.9)	4.87 (1.25-18.93)
Age (years)	1.02 (0.99-1.06)	1.0 (0.95-1.05)
Male sex	1.51 (0.74-3.12)	0.88 (0.37-2.13)
Systolic blood pressure per 10 mm Hg	1.14 (0.98-1.32)	1.01 (0.98-1.03)
HbA1c (%)	1.22 (1.02-1.46)	1.17 (0.91-1.51)
Diabetes duration (years)	1.03 (0.995-1.07)	1.0 (0.94-1.06)
Total cholesterol (mmol/L)	1.20 (0.81-1.80)	1.33 (0.86-2.05)
Current or former smoker	1.27 (0.61-2.62)	1.08 (0.44-2.63)
Cardiovascular event at baseline	5.1 (2.3-11.1)	
urinary albumin/creatinine ratio (mg/mmol)#	1.97 (1.36-2.83)	
plasma adiponectin concentration (mg/L)#	4.96 (0.73-33.72)	
Body Mass Index	1.0 (0.91-1.08)	
HOMA-IR†#	0.93 (0.26-3.27)	
high-sensitivity C-reactive protein (mg/L)#	1.37 (0.60-3.13)	
fasting triglycerides (mmol/L)#	1.84 (0.37-9.19)	
HDL-cholesterol (mmol/L)	1.85 (0.57-6.03)	
Ratio total cholesterol:HDL-cholesterol	0.93 (0.69-1.27)	
Cockroft-Gault creatinine clearance (ml/min)	0.99 (0.98-1.01)	
Serum C3 (μg/ml)	1.002 (0.997-1.006)	

* Included as covariates are waist-to-hip ratio, age, sex, systolic blood pressure, HbA1c, diabetes duration, total cholesterol, and smoking status.

skewed distribuited variables were log-transformed

† HOMA-IR = Homeostatic model assessment for assessing insulin resistance

Figure 1



Unadjusted Kaplan-Meier survival curves according to waist-to-hip-ratio tertile (solid line = first / lowest WHR tertile, dashed line = third / highest WHR tertile). The highest WHR tertile has a worse event-free survival compared to the first WHR tertile (Log rank test P = 0.016).

years of follow-up. In addition to WHR, urinary albumin/creatinine ratio, a cardiovascular event at baseline and HbA1c were associated with the occurrence of cardiovascular events.

In multivariate analysis with age, sex, systolic blood pressure, HbA1c, diabetes duration, total cholesterol and smoking as covariates, only waist-to-hip ratio remained independently associated with the occurrence of cardiovascular events (multivariate HR 3.77(95% CI 1.09-13.1), P = 0.037 for the highest versus the lowest WHR tertile). The association remained after adjusting for a cardiovascular event at baseline (HR 4.84 (95%CI 1.36-17.2) for the highest versus the lowest WHR tertile). When only subjects without a prior cardiovascular event were analyzed, the association remained significant (univariate HR 8.04, 95% CI 1.79-36.04. P = 0.006, multivariate HR 7.1, 95% CI 1.24-40.9, P = 0.028). When men and women were analyzed separately, WHR above the median was associated with cardiovascular events (univariate HR 5.9 (95%CI 1.32-26.7, P = 0.02) and 3.6 (95%CI 1.0-13.0, P = 0.05), in men and women respectively. Multivariate HR with age, HbA1c, diabetes duration, systolic blood

pressure, smoking status and total cholesterol was not statistically significant (multivariate HR 4.56 (95%CI 0.89-23.3, P = 0.069) and 2.9 (95%CI 0.71-12.0, P = 0.137), in men and women respectively.
To identify possible mediators by which central obesity might influence cardiovascular risk, we separately adjusted for adiponectin concentration, hsCRP, complement C3, HOMA-IR, fasting triglycerides, total cholesterol, and HDL-cholesterol. However, the association of WHR and cardiovascular events was not attenuated by any of these covariates (data not shown).

Discussion

The current study demonstrates that waist-to-hip ratio, as a measure of central obesity, is a principal predictor of cardiovascular events in type 2 diabetic South Asians. Studies from different parts in the world report an increased prevalence of insulin resistance and diabetes in South Asians. South Asians develop diabetes 10 years earlier than Caucasians and therefore are exposed to a greater degree of cumulative glycemic damage to the vasculature [12]. Indeed, cardiovascular complications are more frequent in South Asians [13]. We previously studied South Asians living in the Netherlands, showing that central obesity is associated with albuminuria, even in the non-diabetic state [8]. These findings underscore the importance of developing effective preventive strategies for this specific population.
Instead of being an inert energy storage pool, visceral adipose tissue is an active regulator of metabolism [14]. Central obesity is associated with insulin resistance and dyslipidemia [15,16]. In addition, adipose tissue produces cytokines, complement factors and over 30 so-called adipokines [6]. Adipose tissue, as a source of pro-inflammatory cytokines, might drive chronic-vascular-inflammation ("adipogenic inflammation") [17]. Several studies show increased CRP levels in South Asians compared to Caucasians [7,18,19], indicating that an increased pro-inflammatory state is present in this ethnic group. However, so far, data on the predictive role of hsCRP for cardiovascular events in this specific group were lacking. In our type 2 diabetic South Asians, hsCRP was not a predictor of cardiovascular events.
Complement factor C3, which is also produced by adipose tissue [20], is the central molecule in the complement cascade. Compared to Caucasians, South Asians have increased levels of complement C3 [21,22]. As the complement

system is involved in atherogenesis [23], enhanced complement activation might contribute to increased atherogenicity in South Asians [21]. However, while in South Asians serum C3 is strongly associated with the metabolic syndrome [24], we did not find such a relationship with cardiovascular events in our study.

A previous cardiovascular event and a high urinary albumin/creatinine ratio were both associated with future cardiovascular events. In contrast to WHR, which likely has a pathophysiological link to cardiovascular events, this association likely reflects established end-organ damage. In addition, diabetes duration and HbA1c predicted cardiovascular events, pointing at the importance of cumulative glycemic damage to the vasculature.

Adjustment for hsCRP, complement C3, adiponectin, HOMA-IR, and various lipid parameters did not attenuate the strong predictive value of WHR for cardiovascular events. This suggests that neither insulin resistance, dyslipidemia, increased inflammation, complement or adiponectin levels alone can explain the association between central obesity and cardiovascular events. These factors likely act in concert.

A limitation of our study is the relatively small sample size which may limit the detection of predictors with smaller effects in this ethnic group.

In conclusion, we show that in patients with type 2 diabetes of South Asians descent living in a western society, waist-to-hip ratio is a principal predictor of future cardiovascular events. This warrants interventions aimed at weight loss and reduction of central abdominal fat mass to determine whether this will lead to a decline in cardiovascular events.

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