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Obesity and the metabolic syndrome: the San Antonio Heart Study

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Obesity, especially visceral adiposity, is a major determinant of the development of type 2 diabetes. Both visceral adiposity and insulin resistance are strongly related to cardiovascular risk factors in diabetic and non-diabetic subjects. One of the areas where the correlation between visceral fat (upper body adiposity) and cardiovascular risk is most apparent is the prediabetic state. We have recently shown that only prediabetic subjects (those who later develop type 2 diabetes) who are insulin resistant and with upper body adiposity have increased triglycerides, decreased HDL cholesterol and high blood pressure.

Obesity: Metabolic syndrome: Type 2 diabetes: Prediabetic

Introduction

The concept of insulin-resistance syndrome (hypertension, dyslipidaemia, type 2 diabetes, insulin resistance and CHD) was initially developed by Professor Reaven (Reaven *et al*. 1993). The San Antonio Heart Study suggested that fasting insulin (a surrogate for insulin resistance) predicted the development of dyslipidaemia, hypertension and type 2 diabetes (Haffner *et al*. 1992; Table 1). Additionally, fasting insulin was significantly related prospectively to the number of metabolic disorders over 8 years (Haffner *et al*. 1992). However, in cross-sectional analysis from the Framingham Study (Meigs *et al*. 1997) the investigators found three factors for the metabolic syndrome, only one of which included insulin concentration. A number of reviews have discussed the insulin-resistance syndrome (Haffner & Miettinen 1997; Liese *et al*. 1998); the latter review specifically talks about the interactions of insulin and obesity in the metabolic syndrome.

A number of investigators have suggested that visceral fat may comprise a key component of the insulin-resistance syndrome (Despres *et al*. 1991; Pouliot *et al*. 1994). Some data are available from the San Antonio Heart Study on the influence of visceral fat (or anthropometric surrogates of visceral fat such as waist-to-hip ratio) as predictors of components of the metabolic syndrome, especially hypertension and type 2 diabetes (Haffner *et al*. 1990; Wei *et al*. 1999). In the current review we examine these issues of obesity and visceral fat as predictors of the metabolic syndrome.

Hypertension

The San Antonio Heart Study is a population-based study in Mexican Americans and non-Hispanic whites. The baseline examination was conducted in 1984–93, with a 7-year follow-up in 1991–94 (Haffner *et al*. 1990). In these analyses only non-diabetic, non-hypertensive subjects were included at baseline. Hypertension developed in 93 out of 1039 subjects. After adjustment for age, the BMI, waist-to-hip ratio, fasting glucose, triglyceride and fasting insulin predict the development of hypertension (Table 2; Haffner *et al*. 1990). Body mass index, fasting insulin and triglyceride levels predicted the development of hypertension in the Mexican Americans and non-Hispanic whites (Fig. 1). In addition, fasting insulin predicted the development of hypertension in both lean and obese subjects. In conclusion, a cluster of atherogenic changes may precede the development of hypertension, and both increased fasting insulin and overall adiposity predict the incidence of hypertension in important subgroups of patients.

Table 1. Eight-year incidence of metabolic disorders in subjects according to first and fourth quartile of fasting insulin at baseline

	Baseline insulin Quartile (%)			
Disorder	1	4	Relative risk	*P*
Hypertension	5·5	11·4	2·04	0·021
Hypertriglyceridaemia	2·6	8·9	3·46	<0·001
Low HDL-C	16·2	26·3	1·63	0·012
High LDL-C	16·4	20·1	1·23	0·223
Type 2 diabetes	2·2	12·2	5·62	<0·001

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Adapted from Haffner *et al.* (1992).

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Table 2. Anthropometric and clinical variables of non-diabetic normotensive subjects adjusted for age, gender and ethnicity by analysis of variance*

	Conversion status at follow-up		
Baseline variables	Hypertension	Normotension	*P*
Number of subjects†	93	946	–
Mexican Americans (%)†	80	75	0·32
Male (%)†	28	42	0·007
Age, *y*	46 (1·14)	41(0·35)	<0·001
Body mass index (kg/m^2)	31 (0·55)	28 (0·17)	<0·001
Waist-to-hip ratio	0·882 (0·008)	0·862 (0·002)	0·01
Triglycerides‡			
mmol/l	1·62 (1·45–1·79)	1·28 (1·24–1·32)	<0·001
mg/dl	143 (128–158)	113 (110–117)	
Glucose‡			
mmol/l	4·75 (4·63–4·88)	4·71 (4·67–4·75)	0·05
mg/dl	85·6 (83·4–87·9)	84·8 (84·1–85·6)	
Insulin (pmol/l)‡			
Fasting	85·9 (72·1–102·5)	57·0 (53·9–60·2)	<0·001

* Values are given as mean (±SE) or (95% CI) except where noted.
† Values are not adjusted for age, gender and ethnicity.
‡ Values are back-transformed from log transformation.
Adapted from Haffner *et al.* (1990).

Incidence of diabetes

The correlations for anthropometric variables at baseline in the San Antonio Heart Study are shown in Table 3 (Wei *et al.* 1999). A cohort of 721 Mexican Americans aged 25–64 years who were free of type 2 diabetes at baseline were followed for an average of 7·2 years; 105 new cases of type 2 diabetes were diagnosed. Body weight, BMI, waist circumference and waist-to-hip ratio (WHR) were all positively predictive of type 2 diabetes independent of age and sex (Table 4). Waist circumference was the strongest predictor of type 2 diabetes (Table 4). The predictive power of a single measurement of waist circumference was at least equal to that of WHR and BMI combined (Table 5). The risk of type 2 diabetes for those in the highest quartile of waist circumference was 11 times greater than for those in the lowest quartile (95% CI = 4·2–28·8). The waist–type 2 diabetes relation was stronger in subjects with BMI ⩽ 27 kg/m^2 (adjusted odds ratio, OR = 6·0 for a 1 SD difference) than in subjects with BMI > 27 kg/m^2 (OR = 1·7 for a 1 SD difference). In multivariate analysis, waist circumference was the only significant predictor of type 2 diabetes in models that

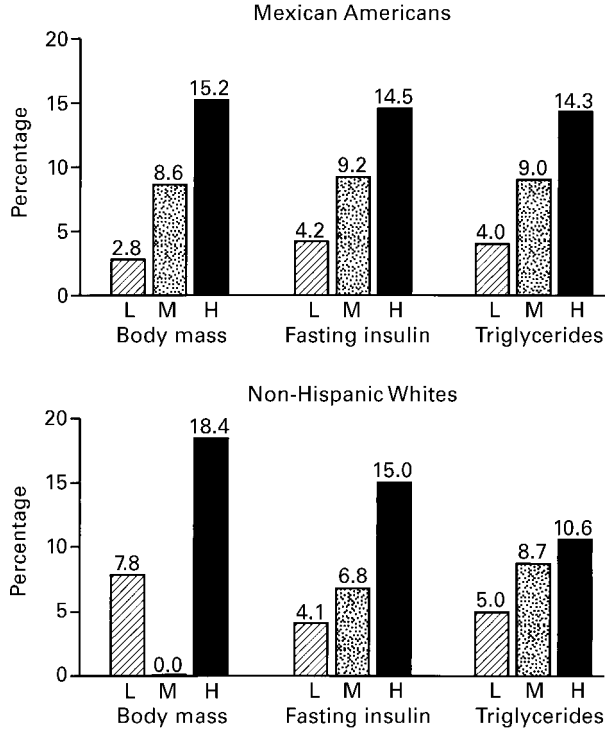

Fig. 1. Univariate relation of incidence of hypertension to BMI category (L, low, <25·2; M, medium, 25·2–29·6; H, high, ⩾29·6); insulin tertile (L, <44·4; M, 44·4–85·8; H, >85·8 pmol/l); triglyceride tertile (L, <1·03 mmol/l [<91 mg/dl]; M, 1·03–1·60 [91–142]; H, >1·60 [>142] in Mexican Americans and non-Hispanic whites. The *P* values were computed for test for trend. Adapted from Haffner *et al.* (1990).

Table 3. Spearman correlation analyses of selected anthropometric variables

Variable	BMI	WHR	Waist
Men			
WHR	0·50	–	0·86
Waist	0·86	0·73	–
Women			
WHR	0·41	–	0·72
Waist	0·87	0·72	–

Adapted from Wei *et al.* (1999).

Table 4. The age-adjusted odds ratio for developing type 2 diabetes for a 1 SD difference at baseline in selected anthropometric variables according to gender

	Women		Men	
Variable	OR 95%	CI	OR 95%	CI
BMI (SD = 5·7 kg/m^2)	1·51	1·21–1·90	1·69	1·07–2·65
Waist (SD = 14·4 cm)	1·80	1·40–2·33	1·84	1·13–3·00

OR, adjusted odds ratio.
Adapted from Wei *et al.* (1999).

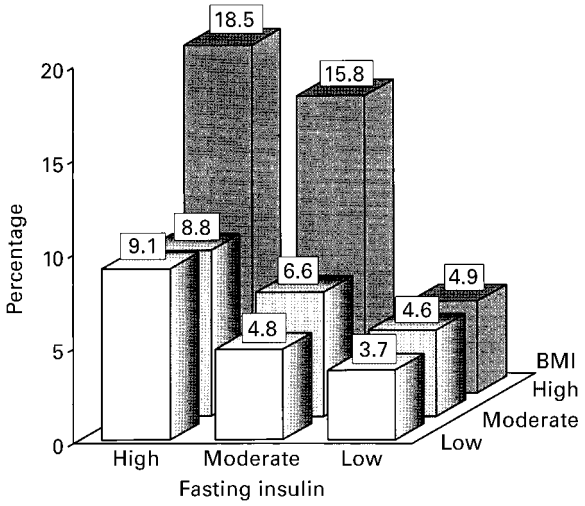

Fig. 2. Incidence of hypertension stratified by BMI. Values for BMI categories and insulin tertiles are explained in the legend to Fig. 1. Adapted from Haffner *et al.* (1990).

included other anthropometric variables either separately or simultaneously (Table 6). The WHR and BMI were independent predictors of type 2 diabetes after adjustment for each other; however their predictive abilities disappeared after adjustment for waist circumference.

The data indicate that waist circumference is the best obesity-related predictor of type 2 diabetes. This finding suggests that the distribution of body fat, especially abdominal localization, is a more important determinant than the total amount of body fat in the development of type 2 diabetes in Mexican Americans. Similar data for non-Hispanic whites were presented at the present symposium (unpublished results).

Conclusions

We have shown that obesity and adverse body-fat distribution predict the development of both hypertension and type 2 diabetes. For hypertension, BMI is the strongest predictor. Our data thus suggest different measures of overall body-fat distribution on overall adiposity, as associated with different

Table 5. Likelihood-ratio test for comparison of waist circumference, BMI and WHR as predictors of type 2 diabetes in logistic model*

Model†	2×ln likelihood	χ^2	d.f.	*P*
Model I for waist and BMI				
Waist (0·72) + BMI (–0·13)‡	–540·8	–	–	–
Waist (0·60)	–541·2	0·4	1	0·53
BMI (0·44)	–552·6	11·8	1	0·0006
Model II for waist and WHR				
Waist (0·49) + WHR (0·21)‡	–539·6	–	–	–
Waist (0·60)	–541·2	1·6	1	0·21
WHR (0·55)	–552·1	12·5	1	0·0004
Model III for BMI and WHR				
BMI (0·34) + WHR (0·42)	–542·7	–	–	–
BMI (0·44)	–552·6	9·9	1	0·0017
WHR (0·55)	–552·1	9·4	1	0·0021
Model IV for waist, BMI, and WHR				
Waist (0·47) + BMI (0·001)‡ + WHR (0·21)‡	–539·6	–	–	–
Waist (0·60)	–541·2	1·6	2	0·45
BMI (0·34) + WHR (0·42)	–542·7	3·1	1	0·08

* β presented for a 1 SD difference in the predictor variable at baseline.
† All models include age and sex.
‡ $P > 0{\cdot}05$, otherwise $P < 0{\cdot}05$.
Adapted from Wei *et al.* (1999).

Table 6. Adjusted odds ratio (OR) of selected variables (1 SD difference) for type 2 diabetes in models with or without waist circumference

			Model 3			
Main variable	Model 1 Adjusted for age and sex OR for main variable		Adjusted for age, sex, and waist OR for main variable		Adjusted for age, sex, and main variables OR for waist	
Waist (cm) (SD = 14·4)	1·82	<0·0001*	–	–	–	–
WHR (SD = 0·091)	1·73	<0·0001	1·23	0·200	1·63	<0·001
BMI (kg/m^2) (SD = 5·7)	1·51	0·0003	0·88	0·420	2·05	<0·001

* *P* value for odds ratio.
Adapted from Wei *et al.* (1999).

metabolic outcomes. It will be important to explore whether these findings can be replicated in other populations. Most previous studies of clustering of cardiovascular risk factors have dealt with clustering of insulin resistance rather than obesity.

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