ORIGINAL ARTICLE doi: 10.1111/j.1463–1326.2004.00441.x

Abdominal obesity predicts declining insulin sensitivity in non-obese normoglycaemics: the Insulin Resistance Atherosclerosis Study (IRAS)

A. J. Karter,[1] R. B. D'Agostino Jr,[2] E. J. Mayer-Davis,[3] L. E. Wagenknecht,[2] A. J. G. Hanley,[4] R. F. Hamman,[5] R. Bergman,[6] M. F. Saad[7] and S. M. Haffner[8] for the IRAS investigators

[1]Kaiser Permanente, Division of Research, Northern California Region, Oakland, CA, USA
[2]Department of Public Health Sciences, Bowman Gray School of Medicine, Wake Forest University, Winston Salem, NC, USA
[3]Department of Epidemiology and Biostatistics and Center for Research in Nutrition and Health Disparities, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA
[4]Leadership Sinai Centre for Diabetes, Mt Sinai Hospital, Toronto, ON, Canada
[5]Department of Preventive Medicine/Biometrics, University of Colorado Health Sciences Center, Denver, CO, USA
[6]Department of Physiology and Biophysics, University of Southern California Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[7]Division of Endocrinology and Epidemiology, University of California Los Angeles School of Medicine, Los Angeles, CA, USA
[8]Division of Clinical Epidemiology, University of Texas Health Sciences Center at San Antonio, San Antonio, TX, USA

Aim: Cross-sectional studies have demonstrated a relationship between obesity and insulin sensitivity (S_I); however, there is a lack of evidence from longitudinal studies.

Methods: The Insulin Resistance Atherosclerosis Study (IRAS) estimated S_I ($\times 10^{-4}$/min·μU/ml) directly using a frequently sampled intravenous glucose tolerance test with minimal model analysis in 504 normoglycaemic subjects. Partial correlation coefficients (r) were calculated to compare the relationship of change in S_I from baseline to 5 years later (ΔS_I) with baseline waist circumference (waist) as a measure of abdominal obesity and body mass index (BMI) as a measure of overall obesity. Mean ΔS_I was -1.06 (SD = 1.85).

Results: Higher baseline waist ($r = -0.16$; $p = 0.0005$), but not BMI ($r = -0.005$; $p = 0.91$), was associated with (–) ΔS_I in models including sex, ethnicity, clinical centre and baseline S_I, BMI, waist, age and physical activity. The waist–ΔS_I relationship differed across the levels of baseline BMI, being significant only in normal weight ($r = -0.21$) and overweight subjects ($r = -0.16$), but not in obese subjects. ΔS_I was correlated with a 5-year change in either obesity measure (Δwaist: $r = -0.22$ and ΔBMI: $r = -0.20$; $p = 0.0001$).

Conclusions: Among non-diabetics, waist circumference was a strong predictor of declining S_I among lean subjects, a modest predictor among overweight subjects, but was not predictive among obese individuals. Waist circumference should be considered, in addition to BMI, when identifying individuals at high risk of diabetes or the insulin resistance syndrome.

Keywords: epidemiology, insulin sensitivity, obesity, visceral obesity
Received 8 April 2004; returned for revision 2 August 2004; revised version accepted 3 August 2004

Introduction

The insulin resistance syndrome (IRS) is characterized by insulin resistance accompanied by the clustering of cardiovascular disease (CVD) risk factors and the development of metabolic disorders [1–4]. Numerous

Correspondence:
Andrew J. Karter, PhD, 2000 Broadway, Oakland, CA 94612, USA.
E-mail:
andy.j.karter@kp.org

cross-sectional studies [5–8] have observed strong associations between IRS and body fat distribution, particularly abdominal obesity, independent of overall obesity, but longitudinal studies have been lacking.

Increasingly, clinical guidelines now specify lower treatment thresholds for CVD risk factors for patients with components of the IRS, including measures of abdominal obesity. For example, the National Cholesterol Education Program (NCEP) [9,10] employs abdominal obesity (waist circumference >102 cm in men and >88 cm in women) as one of the identifying factors for IRS and recognizes IRS as a secondary target for risk reduction after low-density lipoprotein (LDL) lowering. If predictors of prediabetes and progression to diabetes and IRS can be efficiently collected at low cost in clinical practice, this may facilitate effective risk stratification and targeting of individuals at the highest risk for interventions such as those which have been successfully demonstrated in the Diabetes Prevention Program [11,12].

It is thought that abdominal obesity confers greater CVD risk [13] and greater deterioration of metabolic risk profile [14] than obesity alone. Increased abdominal adiposity has been cross-sectionally associated with elements of the IRS, including glucose intolerance [14], high triglyceride–low high-density lipoprotein cholesterol dyslipidaemic state [5], greater concentration of LDL particles (although no reduction in LDL particle diameter) [15], elevated C-reactive protein [14,16,17], increased plasminogen activator inhibitor 1 [18,19], elevated apolipoprotein B concentrations [14] and hypertension [20]. Prospective studies have previously demonstrated that abdominal obesity predicts future diabetes [21,22], hypertension [23], deterioration of lipid profile [24] and CVD events including myocardial infarction, angina pectoris, stroke and mortality [25,26].

It is thought that the relationship between abdominal obesity and these CVD risk factors is mediated through insulin resistance; however, the mechanisms linking abdominal adiposity and insulin resistance are not fully understood. Evidence suggests that the metabolically active, intra-abdominal (visceral) fat depot exerts the detrimental influence. A preponderance of enlarged fat cells in this type of adipose tissue increases the risk of glucose intolerance, hyperinsulinaemia and hypertriglyceridaemia [5,13,27,28]. These hypertrophied adipocytes [6] are resistant to insulin's antilipolytic action [28] and are more responsive to lipolytic hormones than the smaller fat cells from the gluteofemoral region. Resultant elevated levels of free fatty acids may induce insulin resistance in peripheral tissues as well as in the liver [29–32]. Alternatively, it has been suggested that elevated free testosterone and reduced sex hormone-binding globulin may play a central role in promoting increased upper body obesity and reducing fractional hepatic extraction of insulin [33,34]. Additionally, there is strong evidence that inflammatory markers increase with obesity and are also associated with insulin resistance [17].

We previously reported [35] a strong, positive association between waist circumference and insulin resistance, independent of overall obesity [body mass index (BMI)], using cross-sectional data from the baseline examination of the Insulin Resistance and Atherosclerosis Study (IRAS). We also demonstrated that this relationship was consistent in men and women, and across the three ethnic groups included in the study [African American, Hispanic and non-Hispanic White (White)]. With the follow-up examination (5 years after baseline) of the IRAS cohort, we were able to evaluate the longitudinal relationship between obesity and a direct measure of insulin sensitivity (S_I). Specifically, we studied the ability of baseline measures of overall (BMI) and abdominal (waist circumference) obesity to predict a 5-year change in S_I (ΔS_I) among 504 African American, Hispanic and White subjects with normal glucose tolerance (NGT). We also evaluated the correlation between 5-year change in these obesity measures and ΔS_I.

Methods

The Insulin Resistance Atherosclerosis Study

IRAS is a multicentre study of the relationship of insulin and insulin resistance to atherosclerosis and its risk factors in diabetic and non-diabetic African American, Hispanic and non-Hispanic White men and women. Participants, aged 40–69 years at baseline, were enrolled from clinical centres located in Oakland and Los Angeles, CA, and San Antonio, TX, and San Luis Valley, CO. Details of the IRAS study design have been published previously [36]. Institutional review boards from each clinical centre approved the study protocols, and participants gave informed consent. The baseline examinations occurred in 1992–94; the follow-up examinations were conducted approximately 5 years later (1998–99).

Sample Selection

Of the original cohort of 1624 IRAS participants, 1313 were seen in the follow-up examination (80.1%). Glucose tolerance was assessed at baseline and was based on World Health Organization (WHO) criteria for a 2-h,

75-g oral glucose tolerance test (OGTT) or use of oral hypoglycaemic agents. Prevalences were NGT 46%, impaired glucose tolerance 23% and (non-insulin taking) type 2 diabetes 31%. Six participants classified [37] as underweight (BMI $< 18.5\,kg/m^2$) were excluded due to insufficient power for stratified analyses for this metabolically unique group. This report focuses on the remaining subjects who completed a follow-up examination and were NGT at baseline (504 of 603 NGT subjects), including 119 African Americans from Oakland and Los Angeles, 179 Hispanics from San Luis Valley, CO, and San Antonio, TX, and 206 non-Hispanic Whites from all sites.

Variable Measurement

A 12-sample, insulin-enhanced, frequently sampled intravenous glucose tolerance test (FSIGT) was used to assess S_I. FSIGTs were performed with a glucose injection (0.3 g/kg body weight) at baseline and an insulin injection (0.03 U/kg) at 20 min. Blood samples were collected at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100 and 180 min for centralized determination of glucose and insulin levels (R. Bergman, University of Southern California, Los Angeles). S_I provides an estimate of insulin-mediated glucose disposal ($\times 10^{-4}$/min·μU/ml) based on Bergman's Minimal Model. S_I-values are bounded by zero and infinity, and they indicate an increasingly insulin-resistant state as they approach zero, and an increasing S_I as they increase. Prevalent and incident diabetes was assessed at baseline and 5-year examinations using the OGTT and WHO criteria. These methods have been described in detail previously [38].

Anthropometric measures were taken with the standing participant in lightweight clothing with shoes removed. Height and weight were measured in duplicate and recorded to the nearest 0.1 cm and 0.1 kg, respectively. BMI was classified by 1998 National Heart, Lung, and Blood Institute (NHLBI) cut points [37] ('normal' if BMI was 18.5–24.9 kg/m^2; 'overweight' if BMI was 25.0–29.9 kg/m^2; 'obese' if BMI $\geq 30.0\,kg/m^2$). Minimum waist circumference (waist) was used as the measure of abdominal obesity, as it is generally considered the most predictive of abdominal visceral adiposity [39] and accounted for up to 37% of the variance in cross-sectional measures of S_I [40]. Waist circumference was based on average of duplicate readings, measured during mid-respiration, using a flexible steel tape measure at the natural indentation or at a level midway between the iliac crest and the lower edge of the rib cage if no natural indentation was present. Waist circumference was recorded to the nearest 0.5 cm and the mean of two measurements within 1 cm of each other. 'Abdominal obesity' was classified by 1998 NHLBI [37] cut points for waist [>102 cm (>40 inches) in men; >88 cm (>35 inches) in women].

Statistical Analysis

We calculated age-adjusted partial correlation coefficients and least square mean estimates from multiple correlation and generalized linear models. The dependent variable, 5-year change in S_I (ΔS_I) was calculated by subtracting S_I at baseline from that of follow up [i.e. $\Delta S_I = S_{I\ (follow\text{-}up)} - S_{I\ (baseline)}$]. Although both baseline S_I and follow-up S_I have right-skewed distributions, the distribution of their difference is more normally distributed and therefore no further transformation was made on this outcome, because the methods employed are robust to minor departures from normality. Multivariate models were used to test hypotheses for main effects ($\alpha = 0.05$) including effects of baseline BMI and waist circumference on the primary outcome, ΔS_I. Interactions terms ($\alpha = 0.05$) were modelled to test whether the slope of the ΔS_I–waist varied by overall obesity status, whether the slope of the ΔS_I–BMI varied by abdominal obesity status, and whether the ΔS_I–waist and ΔS_I–BMI relationships varied as a function of ethnicity or gender. To account for regression to the mean, these models included baseline S_I. The models also adjusted for potential confounding by demographic variables (age, gender, ethnicity and clinical site) and physical activity ('sedentary' if subject reported on a 5-level scale 'rarely' or 'never' participating in vigorous activities over the past year). Other behavioural indicators were shown to have little or no impact in previous analyses.

Results

Subject Characteristics

The age distribution was similar across levels of obesity (table 1). Women were more likely to be normal weight or obese and more likely to have abdominal obesity. African Americans and Hispanics were more likely to be overweight or obese than White subjects. The mean waist circumference was similar for all ethnic-clinic groups, and the proportion with abdominal obesity was similar among African American, Hispanic and White subjects. Obese and abdominally obese individuals were more likely to be sedentary. There was little discordance in obesity measures. All non-obese individuals (based on BMI) had normal waist circumference. While a few obese individuals had normal waist circumference, the

Table 1 Subject characteristics (n = 504) by obesity status

	Overall obesity (BMI)*				Fat distribution†		
	Normal (n = 158)	Overweight (n = 240)	Obese (n = 106)	p-Value	Normal waist circumference (n = 397)	Abdominal obesity (n = 107)	p-Value
Age	54.1 (8.9)	53.4 (8.1)	52.4 (8.3)	NS	53.6 (8.4)	52.8 (8.4)	NS
Sex (% women)	53	45	61	‡	46	71	§
Race (%)							
Whites	51	37	34		42	36	
African Americans	16	27	28		23	25	
Hispanics	33	36	38	‡	35	38	NS
Sedentary (%)	20	25	33	NS	22	36	‡
Overall obesity (%)*							
Normal	100	0	0		40	0	
Overweight	0	100	0		54	23	
Obese	0	0	100	§	6	77	§
Abdominal obesity† (%)	0	10	77	§	0	100	§
Waist (cm)	79.3 (7.7)	89.0 (7.6)	100.9 (0.1)	§	85.0 (9.0)	101.3 (9.3)	§
BMI (kg/m^2)	22.9 (1.6)	27.4 (1.4)	34.5 (4.1)	§	25.8 (3.0)	33.7 (4.7)	§
Weight change (%)¶							
Lost $\geq$ 5 lb	2	10	18		7	15	
Stable ($\pm$ <5 lb)	78	67	49		70	53	
Gained $\geq$ 5 lb	20	24	33	§	23	32	**
Incident diabetes (%)	4	7	15	**	6	14	**
Baseline S_I ($\times 10^{-4}$/min·μU/ml) (median with interquartile range)	3.5 (2.0)	2.4 (1.8)	1.6 (2.0)	§	2.9 (2.1)	1.3 (1.1)	§
ΔS_I¶	−1.4 (2.1)	−1.0 (1.7)	−0.8 (1.7)	**	−1.2 (2.0)	−0.5 (0.8)	§

BMI, body mass index; ΔS_I, change in insulin sensitivity (S_I); NS, statistically non-significant. Data are measured at baseline, unless indicated as a measure of change, and when not given as percentages or medians (interquartile range), data are means (SD).
*'Normal' if BMI < 25 kg/m^2; 'Overweight' if 25 $\geq$ BMI > 30 kg/m^2; 'Obese' if BMI $\geq$ 30 kg/m^2.
†'Abdominally obese' if waist circumference >102 cm in men and >88 cm in women.
‡p-Value: 0.01–0.05.
§p-Value: <0.001.
¶Longitudinal change (follow-up examination – baseline examination values).
**p-Value: 0.001–0.01.

majority of obese individuals also had abdominal obesity. Compared to their less obese counterparts, the majority of the obese subjects and the majority of the abdominally obese subjects did not remain weight stable (i.e. more likely to have lost or gained $\geq$5 lb during follow-up). On average, S_I declined by −1.06 (SD 1.85; range −12.35 to 7.8) over the 5-year period, with similar declines in the three ethnic groups. Greater overall and abdominal obesity were associated with greater incidence of diabetes and more insulin resistance (lower S_I), but smaller declines in measures of S_I. The greatest longitudinal decline in S_I (ΔS_I) was observed in the strata with the highest baseline values of S_I.

Relationships between Obesity and Change in S_I

Overall, baseline waist circumference (r = −0.16; p = 0.0004), but not baseline BMI (r = −0.005; p = 0.9), was independently correlated with a decline in S_I in models further adjusted for baseline S_I, age, sex, clinic, race, height and physical activity. The relationship between ΔS_I and waist varied significantly by levels of BMI, as well as the other way around (ΔS_I–BMI varied by waist), but neither relationship differed significantly across gender or ethnic-clinic groups (table 2). Therefore, we pooled men and women across ethnic groups and clinics, while stratifying subsequent analyses by overall obesity and fat distribution (table 3). Because baseline S_I was the strongest predictor of ΔS_I (floor effect and/or regression to the mean), all models were adjusted for baseline S_I. In models of waist circumference stratified by overall obesity, the correlation between waist and ΔS_I was strongest in the normal weight (r = −0.21; p = 0.01), intermediate in the overweight (r = −0.16; p = 0.01) and absent in the obese subjects (r = −0.04; p = 0.7). In models stratified by abdominal obesity, the

Table 2 p-Values for interaction terms in Generalized Linear Models of change in insulin sensitivity (ΔS_I) regressed on waist, body mass index (BMI), age, sex, clinic, race, height and physical activity

	Oakland/Los Angeles		San Antonio/San Luis	
Interaction terms	**African Americans**	**Non-Hispanic Whites**	**Hispanics**	**Non-Hispanic Whites**
Waist × gender*	0.13	0.32	0.45	0.12
BMI × gender*	0.85	0.48	0.08	0.37
Waist × race†	0.39	0.39	0.75	0.75
BMI × race†	0.42	0.42	0.44	0.44
BMI × waist‡	0.0007	0.0007	0.0007	0.0007

*Models stratified by race and clinic.
†Models stratified by clinic only.
‡Models not stratified (pooled).

correlation between BMI and ΔS_I was not statistically significant among subjects with normal waist ($r = -0.07$; $p = 0.18$), while positive in abdominally obese subjects ($r = 0.20$; $p = 0.054$). In the counter-intuitive latter correlation, there was one abdominally obese individual with a very large BMI whose S_I improved from 1.91 to 2.54 during the study. When this person was removed from the analysis, the correlation dropped to 0.10 ($p = 0.3$). We did not remove this individual from the analyses, because the data did appear to be correct, although puzzling.

Relationships between Change in Obesity and Change in S_I

Additionally, we specified 'change–change' models correlating ΔS_I and change in BMI (ΔBMI) and change in waist (Δwaist), while partialling out age, sex, race, centre, baseline S_I, height, physical activity and baseline values for the other obesity measure. The ΔS_I was significantly correlated with change in both obesity measures, with Δwaist ($r = -0.22$; $p = 0.0001$) and ΔBMI ($r = -0.20$; $p = 0.0001$).

Discussion

We studied the ability of baseline measures of overall (BMI) and abdominal (waist circumference) obesity to predict 5-year ΔS_I among 504 African American, Hispanic and White subjects with NGT. In models adjusted for demographic and behavioural factors, larger baseline waist circumference predicted declining S_I independent of baseline BMI, while BMI failed to predict ΔS_I independently of waist circumference. The increase in S_I among abdominally obese patients with overall obesity is a counter-intuitive finding which may be type 1 error, regression to the mean or the result of true behavioural changes (e.g. dietary or physical activity changes) made by these very high-risk individuals. Regardless, the finding has no public health relevance, as the risks associated with having both overall and abdominal obesity clearly outweigh this observed benefit. The relationships between these measures of obesity and ΔS_I did not differ significantly across ethnic groups or between men and women. However, the relationship between ΔS_I and either measure of obesity differed across levels of (i.e. interacted with) the alternative measure of obesity.

Table 3 Pearson's partial correlation coefficients for five models*correlating change in insulin sensitivity (ΔS_I) and baseline measures of waist and body mass index (BMI)

	ΔS_I and baseline BMI		ΔS_I and baseline waist	
	Partial correlation coefficient	**p-Value**	**Partial correlation coefficient**	**p-Value**
Fat distribution				
Normal waist	−0.07	0.18	Not applicable	Not applicable
Abdominally obese	0.20	0.05	Not applicable	Not applicable
Overall obesity				
Normal	Not applicable	Not applicable	−0.21	0.01
Overweight	Not applicable	Not applicable	−0.16	0.01
Obese	Not applicable	Not applicable	−0.04	0.70

*Models adjusted for age, sex, race, centre, baseline S_I, height, physical activity and baseline values for the other obesity measure. Models are stratified by levels of fat distribution (normal waist vs. abdominally obese) and overall obesity status (normal, overweight and obese).

Waist circumference predicted the largest decline in S_I among lean subjects, smaller decline among overweight subjects, but was not predictive among obese individuals. Surprisingly, BMI predicted increasing S_I among abdominally obese individuals, perhaps due to lifestyle changes in efforts to restrict further weight gains [41,42]. These counter-intuitive findings are consistent with those reported by the Hoorn Study, suggesting that large hip and thigh circumferences (measures of peripheral obesity) were associated with a lower risk of developing diabetes, whereas larger waist circumference was associated with an increased risk [43]. However, in our study, increases over time in either measure of obesity resulted in significant declines in S_I. In this racially and ethnically mixed population, there was a low prevalence of discordant abdominal and overall obesity status. Of the total subjects in the study, all patients who were abdominally obese were also classified as having overall obesity (based on BMI) and only 6% with overall obesity had a normal waist circumference. However, it is possible that this rare discordant obesity status may be of greater public health relevance in other populations, e.g. Asians.

Our findings are consistent with the wealth of existing literature suggesting the importance of visceral adiposity in metabolic disorders and CVD, including recent comprehensive analyses of the third National Health and Nutrition Examination Survey (NHANES III) [44,45]. Waist circumference was previously shown in IRAS to be one of the best predictors of incident metabolic syndrome using NCEP Adult Treatment Panel (ATP) III criteria [46]. No other longitudinal studies have examined race/ethnic differences. However, a cross-sectional study using exact measures of overall (using dual-energy X-ray absorptiometry measured per cent fat) and visceral [using computerized tomographic (CT) scans] adiposity and fasting insulin from the Coronary Artery Risk Development in Young Adults Study reported significant associations between fasting insulin and waist circumference and exact measures of visceral adiposity in non-Hispanic White men and women, and African American women, but not in African Americans men [8]. The authors proposed that the findings might have been due to the lack of variability in obesity in African American male subjects. Similar to our findings, the authors reported a stronger relationship between insulin and central obesity than with overall obesity. It has been hypothesized that in the ageing process, increasing insulin resistance and its associated negative impact on health is primarily precipitated by increasing accumulation of visceral adiposity rather than ageing *per se* [14,47–52]. This is further supported by experimental studies involving the removal of visceral fat in Zucker Diabetic Fatty rats and longitudinal follow up [53]. The most noteworthy longitudinal studies (12 and 13 years of follow-up) also reported a stronger relationship between abdominal adiposity and the incidence of cardiovascular events, diabetes and death than overall obesity (BMI), and found abdominal adiposity to have the strongest effect among lean individuals [21,25,26].

Several study limitations and strengths are important to consider. Although the prospective observational design allows evaluation of many classical criteria for causality (e.g. temporal sequence and strength of association) and results from such studies are most often comparable to findings from randomized clinical trials [54,55], the design be can faulted for potential selection or confounding bias. Although modest in magnitude, the correlations observed in this study are impressive given (1) correlations relied on a single measurement of baseline obesity, (2) S_I is an imperfectly measured variable (i.e. a model-based estimate), and (3) the outcome, ΔS_I, was measured over a 5-year interval with no intervening measurements. Also, given these metabolic changes are processes that occur gradually over the life course, the statistical significance of our estimates further supports their prognostic value. Also, because the lower end of the distribution of S_I is bounded by zero, there is a 'floor effect' resulting in greatly diminished or absent ΔS_I among insulin-resistant subjects, i.e. those starting with S_I close to zero at baseline. However, because baseline S_I was the strongest predictor of change in sensitivity, models were adjusted to minimize the effect of regression to the mean. Anthropometric measures of obesity do not distinguish between visceral and subcutaneous abdominal adipose tissue, and provide less accurate measures of intra-abdominal fat compared to measures using magnetic resonance imaging or axial CT scan. A previous study reported nearly identical correlations between fasting insulin and waist circumference vs. fasting insulin and an exact measure of intra-abdominal fat based on CT scans, suggesting that waist circumferences was a reasonable surrogate for visceral fat (correlation between waist circumference and visceral fat $r \approx 0.80$) [8]. Similarly, BMI is an imprecise surrogate for overall obesity, as it confounds body fat with other body compartments such as muscle and skeletal mass [56,57]. This measurement imprecision may vary by ethnicity and could introduce residual confounding and potential biases. In particular, given the growing importance of measures of obesity in risk stratification for guidelines (e.g. NCEP), low-tech measures such as waist circumference and BMI are considerably more practical for population-level screening in a clinical (non-research)

setting than the expensive high-tech measures mentioned above.

The major strength of this study is that it is the first longitudinal evaluation of the relationship between overall or abdominal obesity and ΔS_I using a direct measure of S_I. This direct measure of S_I (i.e. Bergman's S_I) is distinct from indirect measures (e.g. fasting insulin), as it estimates an index of insulin-dependent glucose disappearance that is distinct from glucose effectiveness (insulin-independent glucose disappearance) [38,58]. The IRAS cohort includes a large tri-ethnic sample of men and women with a wide range of obesity. The absence of significant differences by ethnicity or gender suggests that these findings might be generalizable to other glucose-tolerant populations.

Study findings suggest a simple public health message: the presence of abdominal obesity predicts future declines in S_I especially in non-obese individuals, thereby increasing their risk of diabetes and CVD. In addition, increases either in overall or in abdominal obesity over time also signal risk of declining S_I. The simplicity and low cost of measuring waist circumference suggests its potential as a practical screening criterion for insulin resistance, a risk stratifier for CVD treatment guidelines, and a variable that complements and is likely superior to BMI as criteria of a patient's medical risk profile [59,60]. The prevalence of discordant obesity measures (e.g. abdominal obesity in a lean individual) is exceedingly low. Thus, defining risk as those with either abdominal or overall obesity has the most clinical value and conveys a simpler message than trying to risk stratify by the distinct cross-tabulated (overall $\times$ abdominal obesity) categories. These data support the inclusion of waist circumference cut points in the NCEP ATP III definition of the metabolic syndrome and suggest the importance of measuring it in clinical practice. These findings confirm the importance of identifying and exploring modifiable behavioural correlates to waist circumference, and assessing whether behavioural interventions that reduce abdominal adiposity (and its associated risks and endpoints) also slow the increasing insulin resistance associated with ageing [57].

Acknowledgements

This study was supported by grants U01-HL47887, U01-HL47889, U01-HL47890 and U01-HL47892 from the NHLBI, and M01-RR-43 from National Center for Research Resources.

References

1 Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; **37:** 1595–1607.
2 DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991; **14:** 173–194.
3 Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 1992; **41:** 715–722.
4 Hanley AJ, Karter AJ, Festa A *et al.* Factor analysis of metabolic syndrome using directly measured insulin sensitivity: The Insulin Resistance Atherosclerosis Study. Diabetes 2002; **51:** 2642–2647.
5 Kissebah AH, Vydelingum N, Murray R *et al.* Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982; **54:** 254–260.
6 Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. J Clin Invest 1983; **72:** 1150–1162.
7 Evans DJ, Hoffmann RG, Kalkhoff RK, Kissebah AH. Relationship of body fat topography to insulin sensitivity and metabolic profiles in premenopausal women. Metabolism 1984; **33:** 68–75.
8 Sidney S, Lewis CE, Hill JO *et al.* Association of total and central adiposity measures with fasting insulin in a biracial population of young adults with normal glucose tolerance: the CARDIA study. Obes Res 1999; **7** (3): 265–272.
9 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA 2001; **285:** 2486–2497.
10 Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003; **52** (5): 1210–1214.
11 Knowler WC, Barrett-Connor E, Fowler SE *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; **346** (6): 393–403.
12 The Diabetes Prevention Program (DPP). Description of lifestyle intervention. Diabetes Care 2002; **25:** 2165–2171.
13 Peiris AN, Sothmann MS, Hoffmann RG *et al.* Adiposity, fat distribution, and cardiovascular risk. Ann Intern Med 1989; **110:** 867–872.
14 Pascot A, Despres JP, Lemieux I *et al.* Deterioration of the metabolic risk profile in women. Respective contributions of impaired glucose tolerance and visceral fat accumulation. Diabetes Care 2001; **24:** 902–908.

15 Lemieux I, Pascot A, Tchernof A *et al.* Visceral adipose tissue and low-density lipoprotein particle size in middle-aged versus young men. Metabolism 1999; **48:** 1322–1327.
16 Lemieux I, Pascot A, Prud'homme D *et al.* Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. Arterioscler Thromb Vasc Biol 2001; **21:** 961–967.
17 Festa A, D'Agostino R Jr, Williams K *et al.* The relation of body fat mass and distribution to markers of chronic inflammation. Int J Obes Relat Metab Disord 2001; **25** (10): 1407–1415.
18 Vague P, Juhan-Vague I, Chabert V, Alessi MC, Atlan C. Fat distribution and plasminogen activator inhibitor activity in nondiabetic obese women. Metabolism 1989; **38:** 913–915.
19 Janand-Delenne B, Chagnaud C, Raccah D, Alessi MC, Juhan-Vague I, Vague P. Visceral fat as a main determinant of plasminogen activator inhibitor 1 level in women. Int J Obes Relat Metab Disord 1998; **22:** 312–317.
20 Blair D, Habicht JP, Sims EA, Sylwester D, Abraham S. Evidence for an increased risk for hypertension with centrally located body fat and the effect of race and sex on this risk. Am J Epidemiol 1984; **119:** 526–540.
21 Ohlson LO, Larsson B, Svardsudd K *et al.* The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes 1985; **34:** 1055–1058.
22 Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L. Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. Diabetes Care 2000; **23:** 465–471.
23 Cassano PA, Segal MR, Vokonas PS, Weiss ST. Body fat distribution, blood pressure, and hypertension. A prospective cohort study of men in the normative aging study. Ann Epidemiol 1990; **1:** 33–48.
24 Couillard C, Lemieux S, Moorjani S *et al.* Associations between 12 year changes in body fatness and lipoprotein-lipid levels in men and women of the Quebec Family Study. Int J Obes Relat Metab Disord 1996; **20:** 1081–1088.
25 Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. Br Med J (Clin Res Ed) 1984; **289:** 1257–1261.
26 Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. Br Med J (Clin Res Ed) 1984; **288:** 1401–1404.
27 Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 1987; **36:** 54–59.
28 Salans LB, Knittle JL, Hirsch J. The role of adipose cell size and adipose tissue insulin sensitivity in the carbohydrate intolerance of human obesity. J Clin Invest 1968; **47:** 153–165.
29 Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle: Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963; **1:** 785–789.
30 Ferrannini E, Barrett EJ, Bevilacqua S, DeFronzo RA. Effect of fatty acids on glucose production and utilization in man. J Clin Invest 1983; **72:** 1737–1747.
31 Kissebah AH, Peiris AN, Evans DJ. Mechanisms associating body fat distribution to glucose intolerance and diabetes mellitus: window with a view. Acta Med Scand Suppl 1988; **723:** 79–89.
32 Bevilacqua S, Bonadonna R, Buzzigoli G *et al.* Acute elevation of free fatty acid levels leads to hepatic insulin resistance in obese subjects. Metabolism 1987; **36:** 502–506.
33 Evans DJ, Murray R, Kissebah AH. Relationship between skeletal muscle insulin resistance, insulin-mediated glucose disposal, and insulin binding. Effects of obesity and body fat topography. J Clin Invest 1984; **74:** 1515–1525.
34 Evans DJ, Hoffmann RG, Kalkhoff RK, Kissebah AH. Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. J Clin Endocrinol Metab 1983; **57:** 304–310.
35 Karter AJ, Mayer-Davis EJ, Selby JV *et al.* Insulin sensitivity and abdominal obesity in African-American, Hispanic, and non-Hispanic white men and women. The Insulin Resistance Atherosclerosis Study. Diabetes 1996; **45:** 1547–1555.
36 Wagenknecht LE, Mayer EJ, Rewers M *et al.* The Insulin Resistance Atherosclerosis Study (IRAS) objectives, design, and recruitment results. Ann Epidemiol 1995; **5:** 464–472.
37 Pi-Sunyer XF. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. National Institutes of Health, National Heart, Lung, and Blood Institute, 1998: 1–178.
38 Saad MF, Anderson RL, Laws A *et al.* A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. Insulin Resistance Atherosclerosis Study. Diabetes 1994; **43:** 1114–1121.
39 Rankinen T, Kim SY, Perusse L, Despres JP, Bouchard C. The prediction of abdominal visceral fat level from body composition and anthropometry: ROC analysis. Int J Obes Relat Metab Disord 1999; **23:** 801–809.
40 Weidner MD, Gavigan KE, Tyndall GL, Hickey MS, McCammon MR, Houmard JA. Which anthropometric indices of regional adiposity are related to the insulin resistance of aging? Int J Obes Relat Metab Disord 1995; **19:** 325–330.

41 Mayer-Davis EJ, Kirkner GJ, Karter AJ, Zaccaro DJ. Metabolic predictors of 5-year change in weight and waist circumference in a triethnic population: the Insulin Resistance Atherosclerosis Study. Am J Epidemiol 2003; **157:** 592–601.
42 Mayer-Davis EJ, Levin S, Bergman RN, D'Agostino JR, Karter AJ, Saad MF. Insulin secretion, obesity, and potential behavioral influences: results from the Insulin Resistance Atherosclerosis Study (IRAS). Diabetes Metab Res Rev 2001; **17:** 137–145.
43 Snijder MB, Dekker JM, Visser M *et al.* Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. Am J Clin Nutr 2003; **77** (5): 1192–1197.
44 Zhu S, Wang Z, Heshka S, Heo M, Faith MS, Heymsfield SB. Waist circumference and obesity-associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. Am J Clin Nutr 2002; **76** (4): 743–749.
45 Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. Arch Intern Med 2002; **162** (18): 2074–2079.
46 Palaniappan L, Carnethon MR, Wang Y *et al.* Predictors of the incident metabolic syndrome in adults: the Insulin Resistance Atherosclerosis Study. Diabetes Care 2004; **27:** 788–793.
47 Imbeault P, Prins JB, Stolic M *et al.* Aging per se does not influence glucose homeostasis: in vivo and in vitro evidence. Diabetes Care 2003; **26:** 480–484.
48 Boden G, Chen X, DeSantis RA, Kendrick Z. Effects of age and body fat on insulin resistance in healthy men. Diabetes Care 1993; **16:** 728–733.
49 Pascot A, Despres JP, Lemieux I *et al.* Contribution of visceral obesity to the deterioration of the metabolic risk profile in men with impaired glucose tolerance. Diabetologia 2000; **43:** 1126–1135.
50 Pascot A, Lemieux S, Lemieux I *et al.* Age-related increase in visceral adipose tissue and body fat and the metabolic risk profile of premenopausal women. Diabetes Care 1999; **22:** 1471–1478.
51 Kohrt WM, Kirwan JP, Staten MA, Bourey RE, King DS, Holloszy JO. Insulin resistance in aging is related to abdominal obesity. Diabetes 1993; **42:** 273–281.
52 Lemieux S, Prud'homme D, Nadeau A, Tremblay A, Bouchard C, Despres JP. Seven-year changes in body fat and visceral adipose tissue in women. Association with indexes of plasma glucose-insulin homeostasis. Diabetes Care 1996; **19:** 983–991.
53 Gabriely I, Ma XH, Yang XM *et al.* Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? Diabetes 2002; **51** (10): 2951–2958.
54 Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med 2000; **342** (25): 1878–1886.
55 Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000; **342** (25): 1887–1892.
56 Michels KB, Greenland S, Rosner BA. Does body mass index adequately capture the relation of body composition and body size to health outcomes? Am J Epidemiol 1998; **147:** 167–172.
57 Stern MP, Haffner SM. Body fat distribution and hyperinsulinemia as risk factors for diabetes and cardiovascular disease. Arteriosclerosis 1986; **6:** 123–130.
58 Bergman RN. Lilly lecture 1989. Toward physiological understanding of glucose tolerance. Minimal-model approach. Diabetes 1989; **38:** 1512–1527.
59 Egger G. The case for using waist to hip ratio measurements in routine medical checks. Med J Aust 1992; **156:** 280–285.
60 Haffner SM, Mitchell BD, Stern MP, Hazuda HP, Patterson JK. Public health significance of upper body adiposity for non-insulin dependent diabetes mellitus in Mexican Americans. Int J Obes Relat Metab Disord 1992; **16:** 177–184.

