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Anthropometrical measures are easily obtainable sensitive and specific predictors of insulin resistance in healthy individuals

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Summary
Background: The objective of this study was to investigate whether user-friendly anthropometrical variables, i.e., waist circumference (WC) and body mass index (BMI) can properly identify insulin resistance (IR) in healthy subjects.
Methods: A cross-sectional study was carried out with 164 disease-free subjects (78 males and 86 females aged 22—50 years) recruited from hospital staff in Barcelona (Spain) over a period of one year. BMI, WC, blood pressure, total cholesterol, triglycerides, HDL-cholesterol, glucose and insulin were measured by standard methods. IR was defined as homeostasis model assessment (HOMA)-IR equal to or greater than 3,8.
Results: The prevalence of IR was 29.9% (males 39.5%, females 21.8%; $P = 0.017$). Multiple stepwise linear regression analysis identified WC ($r^2 = 0.496$; $P < 0.0005$) as the only independent predictor of IR in the whole group. WC ($r^2 = 0.499$; $P < 0.0005$) was the only variable that predicted IR in men and BMI ($r^2 = 0.506$; $P < 0.0005$) in women. WC above 88 cm for women and 102 cm for men predicted IR with a sensitivity of 90.9% and 100%, and a specificity of 71.7% and 51.6%, respectively.

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However, receiving operator characteristics (ROC) curve analysis showed optimal WC values of 106.5 and 97.5 cm for men and women, respectively.
Conclusions: WC is a simple, non-invasive and efficient tool for the screening of IR in the general population. Finally, taking into account that cut-off points of WC are population-specific, it will be of considerable interest to establish the relationship of WC with metabolic complications in all ethnic groups in order to generate useful critical values.

Introduction

The measurement of insulin resistance (IR) has received considerable attention in recent years because IR plays a key role in the pathophysiology of the metabolic syndrome and is currently accepted as one of the underlying causes of type 2 diabetes mellitus [1,2]. Identifying individuals with IR is therefore important in primary care settings to select the best preventive and therapeutic interventions. IR is currently being evaluated by the hyperinsulinemic euglycemic glucose clamp technique [3] which, although disclosing high sensitivity and reproducibility, is expensive, cumbersome and time consuming. The homeostasis model assessment (HOMA) [4] is based on feedback dependence between fasting serum insulin and glucose, correlates very well with classic steady state hyperinsulinemic clamps [5,6] and has been widely applied in epidemiological studies; nevertheless, it is not affordable for most primary care practitioners. Some clinical (Obesity indexes) or laboratory (fasting triglycerides and HDL-cholesterol) markers, among others, are known to correlate with IR [7—12]. As laboratory measurements needed even for indirect assessment of IR are costly, the objective of our study was to search for the most appropriate, non-costly, non-invasive, simple and efficient clinical tool to predict IR in a group of apparently healthy participants.

Methods

A total of 164 healthy Caucasian individuals (78 men and 86 women) participated in this study. This population was selected out of a convenience sampling of disease-free volunteers. Eligibility criteria included absence of any familial or personal history of diabetes (WHO criteria), hypertension and dyslipidemia as well as not taking medications known to affect carbohydrate or lipid metabolism. Written informed consent was obtained from each patient according to the standards established by the Hospital's ethics committee. All anthropometrical measurements were performed by the same trained observer (J.Y.) during the initial visit after participants had removed their shoes and heavy clothing. Weight (digital scales: Seca, Germany) and height (portable stadiometers: Holtain, Crymych, UK) were obtained and body mass index (BMI), defined as weight (kg) divided by the square height (in meters) was calculated. Waist circumference (WC) was measured at the end of gentle expiration using a single plastic tape, mid-way between the lowest rib and the iliac crest with the participant standing.

After an overnight fast (10—12 h), blood was drawn. Both plasma glucose and insulin were measured three times at 5 min intervals according to the original HOMA methodology description [3]. A HOMA index 3.8 was considered diagnostic of insulin resistance based on our own database ($N = 80$) of healthy individuals without clinical and biological criteria for IR, obesity or diabetes (unpublished data). Indeed, HOMA index $\geqslant 3.8$ paralleled fasting plasma insulin levels $\geqslant 17$ μIU/L (90th percentile of a reference, non-diabetic population). Insulin was measured using an immunocheminoluminometric assay (IMMULITE Diagnostic Products Corporation, Los Angeles, CA). The intra and inter-assay imprecision was 3% and 7%, respectively. Cross-reactivity with pro-insulin was less than 0.01%. Otherwise, in basal blood samples cholesterol and triglycerides were measured by enzymatic methods. LDL-cholesterol was calculated by Friedwald's formula and HDL-cholesterol after precipitation of apo B containing lipoproteins.

Statistical analyses

Qualitative variables are expressed as sample size (number of cases) and percentage (%), and quantitative variables are expressed as mean and standard error of the mean (SEM). Ninety-five percent confidence limits of HOMA and the metabolic values

were evaluated in men and women to assess the power and selectivity of these indexes. The relationship between two qualitative variables was assessed using χ^2 test with a continuity correction whenever necessary. ANOVA was used to assess the differences between variables (HOMA indexes, WC, etc.). Pearson's coefficient was employed to assess the correlation between quantitative variables.

Stepwise multiple regression analysis was used to determine the dependence of the HOMA over several other (independent) variables for both sexes. Multiple stepwise logistic regression analysis was used to examine the independent relationship between the anthropometrical indexes, age and insulin resistance estimates. Then, a receiving operator characteristics (ROC) curve was drawn for the selection of the optimal cut-off points determining the sensitivity and specificity for the WC and BMI's critical ranges. $P < 0.05$ was considered statistically significant. Data were analysed using the SPSS 10.0 statistical package (SPSS Inc.).

Results

Characteristics of the participants are given in Table 1. Men had significantly higher values of BMI and WC, fasting basal glucose, triglyceride and serum insulin concentrations (17.0 ± 1.3 μIU/L vs. 12.7 ± 0.9 μIU/L; $P = 0.008$), HbA1c (%) and HOMA index values (4.09 ± 0.35 vs. 2.90 ± 0.25; $P = 0.006$) Men showed lower HDL-cholesterol concentrations than women.

According to a HOMA index cut-off point of 3.8, the IR prevalence was 29.9%. (39.5% in men vs. 21.8% in women; $P = 0.017$). Obesity (BMI > 30 kg m^{-2}) was more prevalent in men ($P = 0.022$) while overweight was so in women (25.0 > BMI < 30 kg m^{-2}) ($P = 0.022$). Abdominal obesity (AO) (WC $\geqslant$ 102/88 for men/women, respectively) was more prevalent in men (68% vs. 40%; $P = 0.004$). The prevalence of IR was 2.0% in subjects with normal WC and 52.5% in the group with AO ($P < 0.0005$).

Univariate analysis showed that the variables most strongly related to HOMA index were WC (0.71—0.73) and BMI (0.47—0.52) in the whole group and also in men and women whereas HDL, LDL and total-cholesterol and triglyceride concentrations showed weaker associations ($r = 0.22$—0.48) in all the analysed groups (Table 2a).

Multiple stepwise linear regression analysis was therefore performed to predict the variables' independent contribution to predict HOMA index (Table 2b). Considering the whole group, HOMA index was strongly predicted by WC ($r^2 = 0.496$; $P < 0.0005$) as well as in men, WC ($r^2 = 0.499$; $P < 0.0005$) whereas the most predictive value was BMI ($r^2 = 0.506$; $P < 0.0005$) in women. The rest of variables, including WC in women, did not contribute significantly to the regression model.

Accordingly, the sensitivity and specificity of both anthropometric variables to predict HOMA index, and hence, IR was analysed using ROC curve. As shown in Table 3, WC above 88 cm for women and 102 cm for men predicted IR with a sensitivity of 90.9% and 100%, and a specificity of 71.7% and

Table 1 Characteristics of the study population

	Men	Women	*P*
N = 164	78 (47%)	86 (53%)	NS
Age (years)	41.8 ± 1.6	41.6 ± 1.5	NS
BMI (kg/m^2)	30.7 ± 0.7	28.7 ± 0.7	0.035
% Overweight	29.7%	37.2%	0.022
% Obese	55.4%	34.9%	0.022
Waist (cm)	106.2 ± 2.0	88.8 ± 2.2	<0.0005
% WC $\geqslant$ 102 cm (M)/88 cm (W)	68%	40%	0.004
Glucose (mg/dl)	93.4 ± 1.5	89.0 ± 1.3	0.028
HbA1c (%)	5.50 ± 0.07	5.22 ± 0.08	0.010
Insulin (μIU/L)	17.0 ± 1.3	12.7 ± 0.9	0.008
HOMA index	4.08 ± 0.34	2.90 ± 0.25	0.006
% HOMA index $\geqslant$ 3.8	39.5%	21.8%	0.017
Cholesterol (mg/dl)	195.1 ± 4.8	201.5 ± 3.9	NS
HDL cholesterol (mg/dl)	44.3 ± 1.1	57.0 ± 1.6	<0.0005
LDL cholesterol (mg/dl)	123.2 ± 4.1	125.0 ± 3.5	NS
Triglycerides (mg/dl)	133.0 ± 7.9	102.4 ± 7.9	0.007
Blood pressure (mmHg)	130/74	128/74	NS

Table 2a Univariate correlation matrix between HOMA index, anthropometrical and biochemical variables

	BMI	WC	Total cholesterol	HDL-cholesterol	LDL-cholesterol	Triglycerides
All						
HOMA (r)	0.509***	0.715***	0.218**	−0.303***	0.188**	0.434***
Women						
HOMA (r)	0.471***	0.728***	0.326***	−0.360***	0.329**	0.482***
Men						
HOMA (r)	0.521***	0.709***	0.172*	−0.086*	0.079*	0.330***

* P = NS.
** $P < 0.005$.
*** $P < 0.0005$.

Table 2b Multivariate stepwise regression analysis

Coefficients[a]	β	P
All (excluded variables:[b] age, BMI, gender, HDL, TG (all P = NS))		
Constant	−6.224	<0.0005
WC (R^2 = 0.496)	9.738E − 02	<0.0005
Coefficients[a]	**β**	**P**
Men only (excluded variables:[b] age, BMI, HDL, TG (all P = NS))		
Constant	−10.855	<0.0005
WC (R^2 = 0.499)	0.140	<0.0005
Coefficients[c]	**β**	**P**
Women only (excluded variables:[b] age, WC, HDL, TG (all P = NS))		
Constant	−2.569	0.001
BMI (R^2 = 0.506)	0.174	<0.0005

[a] Predictive variables of the model: (constant), WC.
[b] Dependent variable: HOMA index.
[c] Predictive variables of the model: (constant), BMI.

Table 3 Sensitivity and specificity of two waist circumference cut-offs (88 cm for women) and (102 cm for men) vs. obesity (BMI $\geqslant$ 30 kg m^{-2}) for predicting HOMA index

	Waist circumference			BMI		
	Cut-off $\geqslant$ 88 cm (Women) and $\geqslant$102 cm (Men)			Cut-off $\geqslant$ 30 kg m^{-2}		
	Sensitivity	Specificity	Likelihood ratios	Sensitivity	Specificity	Likelihood ratios
Women	90.9	71.7	$P < 0.0005$	72.1	61.1	$P = 0.010$
Men	100	51.6	$P < 0.0005$	89.7	65.9	$P < 0.0005$

51.6%, respectively. However, the optimal WC and BMI critical values for predicting IR corresponded to those values at which the sensitivity and specificity were maximal in the ROC curves shown in Fig. 1. Although different than the values recommended by the NCEP-ATP III [13], when the WC of 97.5 cm for women and 106.5 cm for men were applied to the multiple stepwise regression analysis, no further improvement of IR prediction was observed (data not shown).

Discussion

The aim of the study was to investigate whether anthropometrical parameters, more readily available than insulin levels or other laboratory tests, can adequately identify IR in healthy subjects. The major finding in the present study was that BMI and particularly WC, both overall and abdominal adiposity indexes, are reliable surrogate markers of IR in healthy subjects.

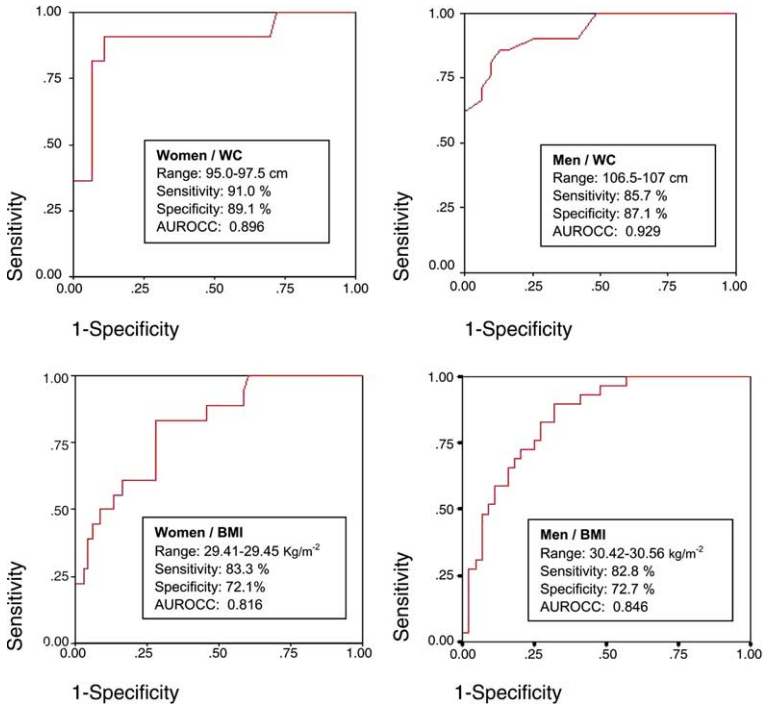

Figure 1 Receiver operating characteristics (ROC) curves for WC and BMI in the prediction of HOMA index. AUROCC: area under the ROC curves.

Euglycemic hyperinsulinemic clamp technique is generally considered to be the gold standard for the in vivo measurement of IR [3]. Thus, the major limitation of this study was the use of the HOMA index, a surrogate measure of IR, as the gold standard of such an abnormality. However, HOMA index closely mirrors euglycemic insulin clamp results [5,6] and has been widely applied in prospective clinical and epidemiological studies and currently stands as an accepted, clinically applicable, surrogate of insulin resistance [10,16—23].

Other limitations of our study included the somewhat narrow ranges of age, BMI and WC. Hence, the study population is unfiltered and their data are depicted as such.

The HOMA index $\geqslant$3.8 we obtained in our reference population stands as an intermediate value between the index reported by Haffner et al. [16] in the Mexican population (HOMA index = 3.3) and Kashiwabara et al. [21] (HOMA index = 4.0) in the Japanese population. Additionally, it is practically identical to that reported by Ascaso et al. [14] (N = 3.8) in a closely geographically related population. The latter can be attributed to the similar age and gender distribution of both reported populations. The prevalence of IR observed in the present study is similar to that reported in southern European metropolitan communities [14,15] and was lower in women than in men.

It is well known that WC and BMI are statistically related to age, blood pressure, plasma triglycerides, glucose, insulin values, and HOMA index, and inversely related to the plasma concentration of HDL-cholesterol [20]. Moreover, these results have been replicated in closely geographically related populations [15]. However, studies that specifically evaluate how these variables, without including insulin levels, can predict IR are few [24].

In agreement with previous studies [12,14,15, 19,20], BMI, WC and fasting triglycerides concentrations were the only variables which correlated significantly with the HOMA index in both men and women in the univariate analysis. However, the multiple stepwise regression analysis depicted in Table 2b discloses WC itself explaining almost 50% of the variability of IR in the whole group, in agreement with Ascaso et al. [15]. WC in men and BMI in women were the only independent predictors of IR. This gender difference has, to the best of our knowledge, not been described elsewhere and might be related to the significantly higher prevalence of abdominal obesity in the men of our series (68% vs. 40%; P = 0.004) (Table 1). Additionally, HDL-cholesterol and triglyceride levels were not found to be independent parameters of risk of IR and thus, were excluded from the model in contrast with the results of other authors on similar southern European populations [15].

Our findings not only support the relationship between obesity indexes and IR but also add information about the accuracy in predicting IR using WC and BMI. Overall (BMI) and specifically abdominal (WC) obesity indexes accurately predicted IR in healthy subjects. The optimal critical range of BMI for predicting IR concurs with the WHO definition of obesity, while for the optimal WC range, the values were higher than those considered as indicative of increased health risk in Caucasian men and women (97.5 and 106.5 cm for women and men, respectively), mainly when referred to NCEP-ATP III guidelines (88 and 102 cm for women and men, respectively) [13,25—27]. These differences could be related mainly to the fact that the critical values of abdominal obesity may be affected by ethnicity [26]. In both genders, WC critical range was more sensitive and specific than BMI critical range in the prediction of IR.

Noteworthy, the high sensitivity levels achieved with the NCEP recommended WC cut-offs were accompanied by a modest specificity. However, the high sensitivity level is indeed of paramount importance since the key issue of this test is not to miss at-risk individuals (false negatives) and indeed we are mostly interested in maximizing sensitivity using clinical criteria, even if specificity suffers.

Moreover, over-diagnosis and over-treatment are not major concerns since diet and physical exercise are the cornerstones of prevention [27—29].

It is known that obesity is a risk factor for the development of the metabolic syndrome, type 2 diabetes mellitus and cardiovascular disease [30] and that this association is not only related to the degree of obesity, but also appears to be critically dependent on body fat distribution [25,31—38]. The higher metabolic impact of central versus peripheral body fat distribution has been firmly established and, although the importance of the site of abdominal fat accumulation is a matter of some debate, intra-abdominal fat has been proposed as the most important determinant of IR and other obesity-related metabolic abnormalities [7,8,10—12]. BMI does not provide information on the distribution of body fat while intra-abdominal fat can be crudely identified on the basis of an increased WC, the variable considered the simplest and best correlate of visceral adiposity in men and women [37,38] and the best indicator of changes in intra-abdominal fat during weight loss [38]. On the contrary, the waist-to-hip ratio alone has a limited ability to predict visceral fat deposition [8,9,35—39].

We conclude that application of WC provides a simple surrogate marker of IR that may be used as a screening test both in general and high risk populations. Finally, although no differences in IR prediction were observed when using cut-off points derived from ROC curves or NCEP-ATP III recommendations, it will be of considerable interest to establish the relationship of WC with metabolic complications in all ethnic groups in order to generate useful critical values. Larger population series could disclose significantly different IR predictive capacity when using WC cut-off points derived from specific populations.

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References

[1] Reaven GM. Insulin resistance, compensatory hyperinsulinemia and dyslipidemia in syndrome X. In: Jacocot B, Mathe J-C, Fruchart J-C, editors. *Atherosclerosis XI*. Singapore: Elsevier; 1998. p. 259—65.

[2] Reaven GM. Banting lecture: role of insulin resistance in human disease. *Diabetes* 1988;**37**:1596—607.

[3] DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979;**237**:E214—223.

[4] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher RL, Turner RL. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentration in man. *Diabetologia* 1985;**28**:412—9.

[5] Katz A, Nambi SS, Mather K, et al.. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 2000;**85**:2402—10.

[6] Bonora E, Targher G, Alberich M, et al.. Homeostasis model assessment mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies on subjects with various degrees of glucose intolerance and insulin sensitivity. *Diabetes Care* 2000;**23**:57—63.

[7] Ho SC, Chen YM, Woo JL, Leung SS, Lam TH, Janus ED. Association between simple anthropometric indices and cardiovascular risk factors. *Int J Obes Relat Metab Disord* 2001;**25**:1689—97.

[8] Seidell JC, Perusse L, Despres JP, Bouchard C. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. *Am J Clin Nutr* 2001;**74**:315—21.

[9] Dobbelsteyn CJ, Joffres MR, MacLean DR, Flowerdew G. A comparative evaluation of waist circumference, waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. The Canadian Heart Health Surveys. *Int J Obes Relat Metab Disord* 2001;**25**:652—61.

[10] McAuley KA, Williams SM, Mann JI, et al.. Diagnosing insulin resistance in the general population. *Diabetes Care* 2001;**24**:460—4.

[11] Lemieux I, Pascot A, Couillard C, et al.. Hypertriglyceridemic waist: a marker of the atherogenic (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? *Circulation* 2000;**102**:179—84.

[12] Cnop M, Lanchild MJ, Vidal J, et al.. The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations: distinct metabolic effect of two fat components. *Diabetes* 2002;**51**:1005–15.
[13] 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 Adult (Adult Treatment Panel III). JAMA 2001;285:2486–97.
[14] Ascaso JF, Romero P, Real JT, Priego A, Valdecabres C, Carmena R. Cuantificación de la insulinorresistencia con los valores de insulina basal e índice HOMA en una población no diabética. *Med Clin (Barc)* 2001;**117**:530–3.
[15] Ascaso JF, Romero P, Real JT, Lorente RI, Martínez-Valls J, Carmena R. Abdominal obesity, insulin resístance, and metabolic syndrome in a Southern European population. *Eur J Intern Med* 2003;**14**:101–6.
[16] Haffner SM, Kennedy E, Gonzalez C, Stern MP, Miettinen H. A prospective analysis of the HOMA model. The Mexico City Diabetes Study. *Diabetes Care* 1996;**19**:1138–41.
[17] Haffner SM, Mykkanen L, Festa A, Burke JP, Stern MP. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. *Circulation* 2000;**101**:975–80.
[18] Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. *Diabetes Care* 2002;**25**:1177–84.
[19] Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean SM, Haffner SM. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. *Diabetes Care* 2002;**25**:2016–21.
[20] Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. *Diabetes Care* 1997;**20**:1087–92.
[21] Kashiwabara H, Inaba M, Maruno Y, et al.. Insulin levels during fasting and the glucose tolerance test and HOMA's index predict subsequent development of hypertension. *Hypertension* 2000;**191**:83–8.
[22] Laakso M. How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 1993;**137**:959–65.
[23] Mykkanen L, Haffner SM, Ronnemaa T, Bergman R, Laakso M. Low insulin sensitivity is associated with clustering of cardiovascular disease risk factors. *Am J Epidemiol* 1997;**146**:315–21.
[24] Williams KV, Erhey JR, Becker D, Arslanian S, Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 2000;**494**:626–32.
[25] Lakka HM, Lakka TA, Tuomilehto J, Salonen JT. Abdominal obesity is associated with increased risk of acute coronary events in men. *Eur Heart J* 2002;**23**:706–13.
[26] Molarius A, Seidell JC, Visscher TL, Hofman A. Misclassification of high-risk older subjects using waist action levels established for young middle-aged adults-results from the Rotterdam Study. *J Am Geriatr Soc* 2000;**4812**:1638–45.
[27] Mayer-Davis EJ, Levin S, Bergman RN, D'Agostino Jr RB, Karter AJ, Saad MFInsulin Resistance Atherosclerosis Study (IRAS). Insulin secretion, obesity, and the potential behavioral influences: results from the Insulin Resistance Atherosclerosis Study (IRAS). *Diabetes Metab Res Rev* 2001;**172**:137–45.
[28] Tuomilehto J, Lindstrom J, Eriksson JG, et al.. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;**334**:1343–50.
[29] Knowler WC, Barrett-Connor E, Fowler SE, et al.Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;**346**:393–403.
[30] Felber JP, Golay A, Jequier E, et al.. The metabolic consequences of long-term human obesity. *Int J Obes* 1988;**12**:377–89.
[31] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. I. Diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. *Diabetic Med* 1998;**15**:539–53.
[32] Grinker JA, Tucker KL, Vokonas PS, Rush D. Changes in patterns of fatness in adult men in relation to serum indices of cardiovascular risk: the Normative Aging Study. *Int J Obes Relat Metab Disord* 2000;**24**:1369–78.
[33] Bjorntop P. Classification of obese patients and complications related to the distribution of surplus fat. *Am J Clin Nutr* 1987;**45**:1120–5.
[34] Dennis KE, Goldberg AP. Differential effects of body fatness and body fat distribution on risk factors for cardiovascular disease in women. *Arterioscler Thromb* 1993;**13**:1487–94.
[35] Kanaley JA, Andersen-Reid ML, Oenning L, Kottle BA, Jensen MD. Differential health benefits of weight loss in upper-body and lower-body obese women. *Am J Clin Nutr* 1993;**57**:20–6.
[36] Lemieux S. Contribution of visceral obesity to the insulin resistance syndrome. *Can J Appl Physiol* 2001;**26**:273–90.
[37] Pouliot MC, Despres JP, Lemieux S, et al.. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;**73**:460–8.
[38] Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP. A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. *Am J Clin Nutr* 1996;**64**:685–93.
[39] Lemieux S, Prud'homme D, Tremblay A, Bouchard C, Despres JP. Anthropometric correlates to changes in visceral adipose tissue over 7 years in women. *Int J Obes Relat Metab Disord* 1996;**20**:618–24.