Available online at www.sciencedirect.com

SciVerse ScienceDirect

Journal of the Chinese Medical Association 74 (2011) 442–447

www.jcma-online.com

Original Article

Clinical and biochemical indicators of homeostasis model assessment-estimated insulin resistance in postmenopausal women

Kuan-Hung Lin [a], Teh-Ling Liou [b], Li-Chuan Hsiao [c], Chii-Min Hwu [c,d,*]

[a] *Department of Medicine, Yang-Ming University Hospital, Yi-Lan, Taiwan, ROC*
[b] *Healthcare Center, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[c] *Section of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[d] *Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*

Received December 14, 2010; accepted June 15, 2011

Abstract

Background: Homeostasis model assessment of insulin resistance (HOMA-IR) is a surrogate estimate of directly measured insulin resistance that been robustly proven to be associated with diabetes and cardiovascular disease. The purpose of this study was to evaluate the use of several simple indicators to identify postmenopausal women with insulin resistance estimated by HOMA-IR.
Methods: We recruited 262 naturally postmenopausal women without overt diabetes for the study. HOMA-IR values were calculated from fasting glucose and insulin levels. Multiple linear regression analyses were carried out to detect determinants of HOMA-IR. Insulin resistance was conventionally defined as the upper quartile of the HOMA-IR values. The diagnostic power of clinical and biochemical markers for insulin resistance was assessed using receiver operating characteristic curves.
Results: Some 90% of the women with HOMA-IR $\geq$ 2.8 (75th percentile as cutoff) showed abnormal glucose metabolism and 45% of them had silent diabetes (odds ratio 6.09, 95% CI 3.17 − 11.73 vs. those with HOMA-IR $<$ 2.8). Results revealed that uric acid, body mass index, waist circumference, alanine aminotransferase, triglycerides, and high-density lipoprotein cholesterol were important determinants of HOMA-IR in these women. Using uric acid $\geq$ 5.0 mg/dL as a cutoff point, we could diagnose insulin resistance with 75.4% sensitivity and 73.1% specificity.
Conclusion: Postmenopausal women with HOMA-IR-estimated insulin resistance were at high risk of glucose abnormalities in this study. High HOMA-IR values were significantly associated with six clinical and biochemical indicators. Among these, high serum uric acid levels seemed to be a useful marker identifying postmenopausal women with insulin resistance. This study was registered at clinicaltrials.gov as NCT00945271.

Keywords: homeostasis model assessment; insulin resistance; menopause; uric acid; waist circumference

1. Introduction

Investigators in the Framingham study found that women had a four-fold higher risk for subsequent cardiovascular disease (CVD) in the 10 years following natural menopause.[1] The transition from pre- to postmenopause is associated with the emergence of many cardiovascular risk factors such as abdominal obesity, dyslipidemia, and insulin resistance.[2] Homeostasis model assessment of insulin resistance (HOMA-IR) is a surrogate estimate of directly measured insulin resistance based on measurements of fasting plasma glucose (PG) and insulin concentrations.[3] It has been robustly proven that HOMA-IR is associated with type 2 diabetes mellitus (DM) and CVD.[4] Lejsková et al recently reported that postmenopausal women with high HOMA-IR values had a three-fold increased risk of the metabolic syndrome compared to those with low HOMA-IR.[5] In the Bruneck study, Bonora et al found that women with high HOMA-IR values had a 2.0- to 2.5-fold higher risk of subsequent CVD after 15-year follow-up.[6]

* Corresponding author. Dr. Chii-Min Hwu, Section of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: chhwu@vghtpe.gov.tw (C.-M. Hwu).

1726-4901/$ - see front matter
doi:10.1016/j.jcma.2011.08.014

Rutter et al noted that more than two-thirds of incident DM and two-fifths of CVD events occurred in participants with HOMA-IR levels in the upper 25% in the Framingham Offspring Study.[7] Song et al showed that HOMA-IR is particularly useful in predicting the development of DM in individuals with fasting PG < 126 mg/dL compared to other markers such as fasting insulin in postmenopausal women.[8] Ausk et al analyzed data for 3511 participants with fasting PG < 126 mg/dL and without a known history of DM and found that individuals in the top HOMA-IR quartile had significantly greater mortality than those in the bottom quartile.[9] This compelling evidence indicates that individuals with HOMA-estimated insulin resistance warrant more medical attention with regard to prevention of DM, CVD and premature death.

Although HOMA-IR may be a potential tool for identifying individuals at risk of adverse outcomes, its use is limited at present because fasting levels of insulin are not measured routinely, partly owing to the cost of measurement and a lack of assay standardization.[10] Given the apparent clinical importance of identifying postmenopausal women with high HOMA-IR values, an investigation of the utility of simple indicators, including anthropometric measurements and routine biochemistry tests, in accomplishing this task seems worthwhile. Our aim was to evaluate the use of several simple indicators in identifying postmenopausal women with insulin resistance estimated by HOMA-IR. Our results may provide clinicians with clues for identifying postmenopausal women who are susceptible to DM and CVD.

2. Methods

2.1. Participants

From October 2009 to July 2010, 262 naturally postmenopausal women who had not menstruated within the last 12 months were recruited from a hospital-based research clinic. The women were volunteers for health surveys and participants in observational studies. Those who had undergone hysterectomy and/or oophorectomy before or within 12 months of natural menopause were excluded. Women with a known history of DM or fasting PG > 126 mg/dL were excluded from the study. The participants did not have liver, kidney, blood, heart or neurological diseases. None of them had experienced acute illness in the previous 6 months. Concomitant use of anti-lipid agents, glucose modification agents, or hormone replacement was not allowed during the study. The study protocol was approved by the institutional review board of the hospital, and written informed consent was obtained from all participants before they entered the study.

2.2. Clinical examination

The participants underwent anthropometric measurement at 8.00 AM after an overnight fast of 8–10 hours. Weight was measured to the nearest 0.1 kg. Height was measured to the nearest millimeter. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference (WC) was measured at the level of the umbilicus to the nearest millimeter after expiration using an anthropometric tape while the participant breathed quietly.[11] Blood pressure (BP) was measured using an automated oscillometric BP recorder (Dinamap 1864SX, Critikon, Tampa, FL, USA) after the individual had rested quietly for 10 minutes. Fasting blood samples were collected for measurement of PG, insulin, lipids, and other biochemical parameters. Then 75 g of glucose monohydrate (in 300 mL of water) was administered to each participant to drink over 5 minutes.[11] Blood samples were taken 120 minutes after glucose loading for an oral glucose tolerance test. The samples were centrifuged as soon as possible and stored at −20 °C until assay. Participants were interviewed during the oral glucose tolerance test regarding demographic characteristics and medical history. If an individual was taking antihypertensive medication or had diastolic BP > 90 mmHg or systolic BP > 140 mmHg, she was classified as hypertensive.

2.3. Measurements

PG was measured by a glucose oxidase method using a glucose analyzer (model 2300, YSI, Yellow Springs, OH, USA). Plasma insulin was measured using an automated chemiluminescence system (ADVIA Centaur Immunoassay System, Siemens Healthcare Diagnostics, Deerfield, IL, USA). The intra- and inter-assay coefficients of variation (CV) for insulin measurement were 3.7% and 4.4%, respectively. Serum lipids and biochemical parameters were measured using commercial assay kits (Roche Diagnostics, Basel, Switzerland) on an automatic blood chemistry analyzer (Roche-Hitachi 7180, Roche Diagnostics, Basel, Switzerland). Serum high-density lipoprotein cholesterol (HDL-C) was determined using a polyethylene glycol-modified enzymatic cholesterol assay after dextran sulfate precipitation. The intra-assay CVs for total cholesterol (TC), total triglyceride (TG), and HDL-C assays were 2.1%, 1.1%, and 1.4%, and inter-assay CVs were 3.1%, 2.6%, and 3.0%, respectively.

2.4. Statistical analysis

Data are expressed as mean (S.D.) or *n* (%). The HOMA-IR index was calculated according to the formula: HOMA-IR = fasting PG (mmol/L) × fasting insulin (mU/L)/22.5.[3,4] The participants were divided into four groups according to HOMA-IR value quartiles. Individuals with HOMA-IR ≥ 2.8 (75th percentile cutoff) were considered to be insulin-resistant according to European Group for the Study of Insulin Resistance recommendation.[12] Because of their skewed distributions, fasting TG, alanine aminotransferase (ALT), and HOMA-IR were analyzed after logarithmic transformation. Clinical and biochemical characteristics were compared using χ^2 tests and one-way analysis of variance with a post-hoc Duncan test for categorical and continuous variables, respectively. Pearson correlation procedures were used to test the correlation of log HOMA-IR with clinical and biochemical indicators. The relative contributions of significant correlates to log HOMA-IR were then evaluated by multiple linear

regression analyses. Receiver operating characteristic (ROC) curves were applied to determine optimal cutoff values for clinical and biochemical markers for the diagnosis of insulin resistance (estimated by HOMA-IR $\geq$ 2.8 in this study). For each marker tested, sensitivity and specificity were calculated for the diagnosis of HOMA-estimated insulin resistance.[13] The area under the ROC curve (AROC) for each marker was calculated from a plot of sensitivity versus 1 − specificity. Accuracy was determined from sensitivity and specificity, because the true positive rate (prevalence) of HOMA-IR $\geq$ 2.8 was known, using the equation: accuracy = (sensitivity × prevalence) + [specificity × (1 − prevalence)]. The positive likelihood ratio (LR) was calculated as sensitivity/(1 − specificity).[13] A positive LR > 1 indicates that the probability of a positive test for an individual with the disease is greater than the probability of a positive test for an individual without the disease. The negative LR was calculated as (1 − sensitivity)/specificity.[13] A negative LR < 1 indicates that the probability of a negative test for an individual with the disease is less than the probability of a negative test for an individual without the disease. Analyses were performed using the SPSS program (Version 16.0, SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

3. Results

The clinical characteristics of the participants by HOMA-IR quartiles are shown in Table 1. The four groups were comparable in age, height, diastolic BP, total cholesterol, and low-density lipoprotein cholesterol. There were significant differences in weight, BMI, WC, uric acid (UA), systolic BP, fasting PG, log ALT, log TG and HDL-C among the four groups. Women with high HOMA-IR (in the fourth quartile, Q4) were heavier and had higher BMI, WC, systolic BP, and serum UA, fasting TG and ALT than those in the first quartile (Q1) group (compared by post hoc Duncan test, all $p < 0.05$). Women in the Q4 group also had significantly lower HDL-C concentrations than women in the Q1 group ($p < 0.05$). More than 30% of the women with HOMA-IR $\geq$ 2.8 already had hypertension. Some 90% of the women with HOMA-IR $\geq$ 2.8 exhibited abnormal glucose metabolism: 45% had silent DM (i.e. fasting PG < 126 and 2-h PG $\geq$ 200 mg/dL), and 43% had impaired glucose tolerance (IGT, 140 $\leq$ 2-h PG < 200 mg/dL) (Fig. 1). The odds ratio of silent DM for women with HOMA-IR $\geq$ 2.8, compared with those with HOMA-IR < 2.8, was 6.09 (95% confidence interval, 3.17–11.73).

There were significant correlations between log HOMA-IR and several clinical and biochemical indicators, including BMI, WC, systolic BP, UA, log ALT, log TG and HDL-C (all $p < 0.05$). Multiple linear regression results revealed that BMI, WC, UA, log ALT, log TG, and HDL-C were important determinants of log HOMA-IR in these women (Table 2). The regression model explained 50.4% of the variance of log HOMA-IR. We used ROC curve analysis to assess the diagnostic power of the above indicators for the diagnosis of insulin resistance (estimated by HOMA-IR $\geq$ 2.8). The cutoff values and AROC for UA, TG, ALT, BMI, WC, and HDL-C for HOMA-IR $\geq$ 2.8 are listed in Table 3. Using UA $\geq$ 5.0 mg/dL as a cutoff point, we could diagnose HOMA-

Table 1
Descriptive characteristics of the study participants by HOMA-IR quartiles

	HOMA-IR quartile (range)				p
	Q1 (0.48–1.18)	Q2 (1.19–1.73)	Q3 (1.74–2.78)	Q4 (≥ 2.8)	
n	65	66	66	65	
Age (y)	59.2 (4.7)	59.7 (5.1)	60.2 (5.2)	59.0 (5.1)	0.55
Weight (kg)	52.6 (7.1)	55.6 (6.8)	58.5 (6.2)	63.3 (8.6)	<0.0001
Height (cm)	155.8 (6.0)	156.2 (4.5)	155.6 (5.9)	157.0 (5.0)	0.42
BMI (kg/m^2)	21.6 (2.4)	22.8 (2.3)	24.2 (2.9)	25.7 (3.3)	<0.0001
WC (cm)	76.5 (7.1)	80.9 (7.4)	84.4 (7.6)	88.8 (9.0)	<0.0001
Systolic BP (mmHg)	112 (20)	118 (16)	119 (20)	124 (17)	0.008
Diastolic BP (mmHg)	67 (10)	68 (9)	68 (10)	71 (9)	0.14
UA (mg/dL)	4.3 (0.8)	4.7 (0.9)	4.7 (0.8)	5.6 (1.2)	<0.0001
ALT (U/L)	19 (21)	20 (114)	20 (80)	28 (105)	—
Log ALT	1.29 (0.11)	1.33 (0.17)	1.32 (0.15)	1.46 (0.19)	<0.0001
Fasting PG (mg/dL)	91 (6)	95 (6)	100 (7)	104 (9)	<0.0001
Total cholesterol (mg/dL)	212 (43)	214 (33)	209 (34)	216 (36)	0.69
LDL-C (mg/dL)	123 (36)	127 (30)	122 (31)	134 (32)	0.14
TG (mg/dL)	60 (309)	80 (406)	96 (291)	118 (374)	—
Log TG	1.82 (0.19)	1.93 (0.21)	2.00 (0.26)	2.10 (0.18)	<0.0001
HDL-C (mg/dL)	74 (18)	68 (17)	64 (18)	54 (11)	<0.0001
Hypertensive (n, %)	7 (10.8%)	9 (13.6%)	19 (28.8%)	22 (33.8%)	0.002

Data are expressed as mean (S.D.) or n (%). The median (range) for ALT and TG values is also presented. One-way analysis of variance or a χ^2 test was used to compare differences among the four groups.

ALT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; log ALT = logarithmic transformation of ALT (in U/L); log TG = log transformation of fasting TG (in mg/dL); PG = plasma glucose; Q1 = first quartile for HOMA-IR; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile; TG = total triglycerides; UA = uric acid; WC = waist circumference.

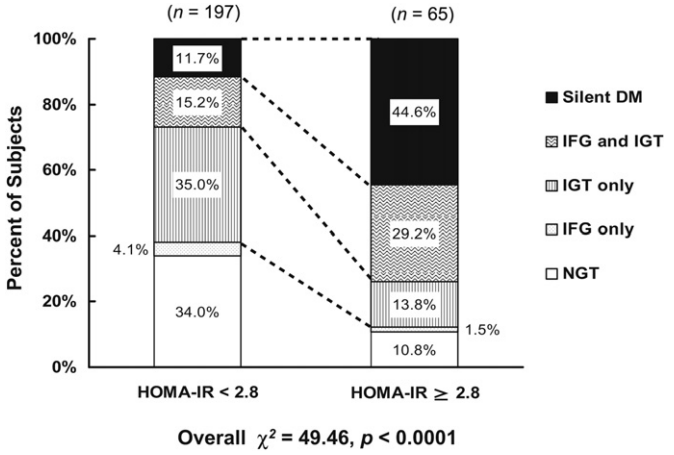

Fig. 1. Distribution of glucose abnormalities in the study participants. We used the following criteria to define glucose abnormalities in the study: silent DM, fasting PG $<$ 126 mg/dL and 2-h PG $\geq$ 200 mg/dL; combined IFG and IGT, 100 $\leq$ fasting PG $<$ 126 mg/dL and 140 $\leq$ 2-h PG $<$ 200 mg/dL; IGT only, fasting PG $<$ 100 mg/dL and 140 $\leq$ 2-h PG $<$ 200 mg/dL; IFG only, 100 $\leq$ fasting PG $<$ 126 mg/dL and 2-h PG $<$ 140 mg/dL; NGT, fasting PG $<$ 100 mg/dL and 2 h PG $<$ 140 mg/dL. There were significant differences in glucose abnormalities between women with HOMA-IR $\geq$ 2.8 and those with HOMA-IR $<$ 2.8 according to χ^2 tests. DM = diabetes mellitus; HOMA-IR = homeostasis model assessment of insulin resistance; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NGT = normal glucose tolerance; PG = plasma glucose.

estimated insulin resistance with 75.4% sensitivity and 73.1% specificity in these women. Furthermore, this diagnostic test (UA $\geq$ 5.0 mg/dL for HOMA-IR $\geq$ 2.8) yielded the highest AROC and the highest accuracy among the parameters tested in the study (Table 3). All the markers except for HDL-C showed small increases in association with HOMA-IR $\geq$ 2.8 (positive LR of 2–5) (Table 3). All the markers except for ALT had negative LR values in the range 0.2–0.5 (Table 3). Thus, the probability of a negative test result for an individual with HOMA-IR $\geq$ 2.8 is less than the probability of a negative test for an individual without the disease.

4. Discussion

In this cohort of postmenopausal women, we demonstrated that approximately 45% of the women with high HOMA-IR values had silent DM (Fig. 1). Silent DM, also known as isolated post-challenge hyperglycemia, is a form of DM with fasting PG $<$ 126 mg/dL but 2-h PG $\geq$ 200 mg/dL.[14] Long-term studies have shown that individuals with silent DM have equivalent CVD and total mortality risks as those with known DM.[14] Qiao et al urged health professionals to detect silent DM in high-risk individuals for the prevention of adverse outcomes.[15] Our research provides a clue to identification of silent DM cases among postmenopausal women. The odds of silent DM for women with HOMA-IR $\geq$ 2.8 were six-fold greater than the odds for women with HOMA-IR $<$ 2.8. It seems that high HOMA-IR was a good marker for silent DM in these women. Moreover, the women with high HOMA-IR values also had an increased cardiovascular risk profile, including high BP and dyslipidemia (Table 1). Together, these findings suggest that insulin resistance (estimated by high HOMA-IR values in our study), although generally under-recognized in clinical practice, may have important health consequences for postmenopausal women.[2,8,16]

Given the apparent importance of insulin resistance as a marker of silent DM, it would seem useful to identify insulin-resistant individuals in clinical practice. Unfortunately, the HOMA-IR value used in the current study to define insulin resistance cannot be translated to other situations unless the insulin concentrations are measured in the same laboratory.[17] Reaven suggested that identification of metabolic variables closely related to insulin resistance, and for which standardized laboratory measurements are available, might be useful in determining individuals with insulin resistance.[18] With this approach, we demonstrated that high UA levels, as well as five other parameters, can identify postmenopausal women who are insulin-resistant. Our data show that UA was a major determinant of HOMA-IR (Table 2), and using UA $\geq$ 5.0 mg/dL as a cutoff point, we could diagnose HOMA-estimated insulin resistance in postmenopausal women with 75.4% sensitivity and 73.1% specificity. Several epidemiologic studies have demonstrated that serum UA levels are positively associated with insulin resistance and its corresponding hyperinsulinemia.[19,20] Facchini and colleagues explained that insulin resistance decreases urinary UA clearance, which leads to an increase in serum UA concentrations.[21] Individuals with insulin resistance might also have impairment in the glycolytic pathway, which would result in an increase in the flux of glucose-6-phosphate to the hexose monophosphate shunt and accumulation of substrates for UA production, leading to hyperuricemia.[22] However, evidence also shows that hyperuricemia may actually promote or worsen insulin resistance owing to its detrimental effects on endothelial dysfunction.[22] Recently, the Rancho Bernardo Study suggested that serum UA can independently predict CVD mortality, especially in older adults with glucose abnormalities.[23] If our goal is to identify insulin-resistant women at risk of CVD, serum UA may offer advantages beyond the need to identify insulin resistance.

Nilsson et al recruited 223 elderly Swedish women representative of a general population to study the associations between WC and insulin resistance.[24] The investigators reported that the optimal WC cutoff for insulin resistance

Table 2
Results of the multiple regression analyses with log HOMA-IR as the dependent variable (n = 262)

Variable entered	Estimate	SE	p
BMI	0.016	0.007	0.021
WC	0.006	0.002	0.009
Systolic BP	0.001	0.001	0.54
Diastolic BP	0.0001	0.002	0.78
UA	0.046	0.012	<0.0001
Log ALT	0.314	0.073	<0.0001
Log TG	0.143	0.067	0.033
HDL-C	−0.003	0.001	0.004

Abbreviations as for Table 1.

Table 3
Diagnostic power of clinical and biochemical indicators for homeostasis model assessment-estimated insulin resistance in postmenopausal women

Variable	AROC	Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive LR	Negative LR
UA (mg/dL)	0.777	≥5.0	75.4	73.1	73.7	2.80	0.34
TG (mg/dL)	0.763	≥100	78.5	69.5	71.8	3.28	0.31
ALT (U/L)	0.753	≥25	60.0	77.7	73.3	2.69	0.51
BMI (kg/m^2)	0.748	≥23.2	78.5	64.0	67.6	2.18	0.34
WC (cm)	0.747	≥86	63.1	75.6	72.5	2.59	0.49
HDL-C (mg/dL)	0.260	<66	86.2	54.3	62.2	1.89	0.25

AROC = area under the receiver operating characteristic curve; LR = likelihood ratio; other abbreviations as for Table 1.

estimated by HOMA-IR in these women was 88 cm. Women with WC > 88 cm had a relative risk of 5.6 of being insulin-resistant compared to those with WC ≤ 88 cm in their study.[24] Although it has been suggested that Asians might have a lower WC cutoff than Europeans at equivalent risk,[25] surprisingly, the WC cutoff for insulin resistance in our study was close to that for the Nilsson study (Table 3). Bao et al used magnetic resonance imaging to measure visceral fat area in 615 middle-aged Chinese women and found that the optimal WC cutoff for abdominal obesity was 85 cm.[26] Considering the significant contribution of visceral fat accumulation to the features of insulin resistance, the current WC cutoff for Chinese women according to the new international harmonization criteria[27] may not be appropriate in term of diagnosis of insulin resistance. More studies are needed to clarify this issue.

Our study has some limitations. First, the study cohort was naturally postmenopausal women without a history of DM. The ability of the same indicators or cutoffs to identify high HOMA-IR conditions in other populations is unproven. Second, insulin resistance is distributed continuously throughout the general population, and there is no consensus on criteria to classify individuals as being insulin-resistant or insulin-sensitive. If alternative thresholds for high HOMA-IR values were selected, there might be widely disparate results in the performance of clinical markers for identifying insulin resistance. Finally, because a common reference system for insulin measurements is not finalized, the absolute HOMA-IR values used in this study cannot be translated to other samples measured using a different insulin assay. Of course, the use of simple indicators to identify individuals who are insulin-resistant is not ideal. The major virtue of this approach is that these parameters are determined by a clinically routine method, and the sensitivity and specificity for the diagnosis of HOMA-estimated insulin resistance are reasonable. However, our findings also emphasize the need for better efforts to identify insulin-resistant individuals than the use of these simple markers. A standardized insulin assay would help to close the gap between epidemiological research and real-world practice in finding cases of insulin resistance.[18] Until that day arrives, our ability to identify insulin-resistant individuals will rely heavily on the use of simple clinical markers.

In conclusion, our study demonstrated that postmenopausal women with HOMA-estimated insulin resistance were at high risk of silent DM. High HOMA-IR values were significantly associated with components of the metabolic syndrome, as well as with serum UA concentrations. High UA levels (≥ 5.0 mg/dL) seem to be a useful indicator for identifying postmenopausal women with insulin resistance.

Acknowledgments

The study was supported by grants from the National Science Council ROC (NSC98-2314-B-075-001-MY3) and the Taipei Veterans General Hospital (V99C-153, VN99-02).

References

1. Lerner DJ, Kannel WB. Pattern of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J* 1986;**111**:383−90.
2. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab* 2003;**88**:2404−11.
3. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;**28**:412−9.
4. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004;**27**:1487−95.
5. Lejsková M, Alušík S, Suchánek M, Žecová S, Piťha J. Menopause: clustering of metabolic syndrome components and population changes in insulin resistance. *Climacteric* 2011;**14**:83−91.
6. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Meigs JB, et al. Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in Caucasian subjects from the general population. The Bruneck Study. *Diabetes Care* 2007;**30**:318−24.
7. Rutter MK, Wilson PWF, Sullivan LM, Fox CS, Sr D'Agostino RB, Meigs JB. Use of alternative thresholds defining insulin resistance to predict type 2 diabetes mellitus and cardiovascular disease. *Circulation* 2008;**117**:1003−9.
8. Song Y, Manson JE, Tinker L, Howard BV, Kuller LH, Nathan L, et al. Insulin sensitivity and insulin secretion determined by homeostasis model assessment and risk of diabetes in a multiethnic cohort of women. The women's health initiative observational study. *Diabetes Care* 2007;**30**:1747−52.
9. Ausk KJ, Boyko EJ, Ioannou GN. Insulin resistance predicts mortality in nondiabetic individuals in the U.S. *Diabetes Care* 2010;**33**:1179−85.
10. McLaughlin TL, Reaven GM. Beyond type 2 diabetes: the need for a clinically useful way to identify insulin resistance. *Am J Med* 2003;**114**:501−2.
11. Hwu CM, Fuh JL, Hsiao CF, Wang SJ, Lu SR, Wei MC, et al. Waist circumference predicts metabolic cardiovascular risk in postmenopausal Chinese women. *Menopause* 2003;**10**:73−80.
12. Balkau B, Charles MA, Drivsholm T, Borch-Johnsen K, Wareham N, Yudkin JS, et al. Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. *Diabete Metab* 2002;**28**:364−76.
13. Kramer MS. *Clinical epidemiology and biostatistics: a primer for clinical investigators and decision-makers*. New York: Springer-Verlag; 1988.
14. Shaw JE, Hodge AM, de Courten M, Chitson P, Zimmet PZ. Isolated post-challenge hyperglycaemia confirmed as a risk factor for mortality. *Diabetologia* 1999;**42**:1050−4.

15. Qiao Q, Tuomilehto J, Borch-Johnsen K. Post-challenge hyperglycaemia is associated with premature death and macrovascular complications. *Diabetologia* 2003;**46**(suppl):M17−21.
16. McFarlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. *J Clin Endocrinol Metab* 2001;**86**:713−8.
17. Manley SE, Stratton IM, Clark PM, Luzio SD. Comparison of 11 human insulin assays: implications for clinical investigation and research. *Clin Chem* 2007;**53**:922−32.
18. Reaven G. Wanted! A standardized measurement of plasma insulin concentration. *Arterioscler Thromb Vasc Biol* 2011;**31**:954−5.
19. Chou P, Lin KC, Lin HY, Tsai ST. Gender differences in the relationships of serum uric acid with fasting serum insulin and plasma glucose in patients without diabetes. *J Rheumatol* 2001;**28**:571−6.
20. Bonora E, Capaldo B, Perin PC, Del Prato S, De Mattia G, Frittitta L, et al. Hyperinsulinemia and insulin resistance are independently associated with plasma lipids, uric acid and blood pressure in non-diabetic subjects. The GISIR database. *Nutr Metab Cardiovasc Dis* 2008;**18**: 624−31.
21. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *J Am Med Assoc* 1991; **266**:3008−11.
22. Tsouli SG, Liberopoulos EN, Mikhailidis DP, Athyros VG, Elisaf MS. Elevated serum uric acid levels in metabolic syndrome: an active component or an innocent bystander? *Metabolism* 2006;**55**:1293−301.
23. Kramer CK, von Mühlen D, Jassal SK, Barrett-Connor E. A prospective study of uric acid by glucose tolerance status and survival: the Rancho Bernardo Study. *J Intern Med* 2010;**267**:561−6.
24. Nilsson G, Hedberg P, Jonaon T, Lönnberg I, Tenerz Å, Forberg R, et al. Waist circumference alone predicts insulin resistance as good as the metabolic syndrome in elderly women. *Eur J Intern Med* 2008;**19**:520−6.
25. Lear SA, James PT, Ko GT, Kumanyika S. Appropriateness of waist circumference and waist-to-hip ratio cutoffs for different groups. *Eur J Clin Nutr* 2010;**64**:42−61.
26. Bao Y, Lu J, Wang C, Yang M, Li H, Zhang X, et al. Optimal waist circumference cutoffs for abdominal obesity in Chinese. *Atherosclerosis* 2008;**201**:378−84.
27. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome. A joint interim statement of the International diabetes federation task force on epidemiology and prevention; National heart, Lung, and blood institute; American heart association; World heart federation; International atherosclerosis society; and International association for the study of obesity. *Circulation* 2009;**120**:1640−5.