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Cutoff Values of Surrogate Measures of Insulin Resistance for Metabolic Syndrome in Korean Non-diabetic Adults

We investigated the cutoff values of surrogate of insulin resistance for diagnosing metabolic syndrome in Korean adults. The data from 976 non-diabetic individuals (484 men and 492 women) aged 30-79 yr were analyzed. We determined the odds ratios for the prevalence of metabolic syndrome according to the quartiles of fasting insulin, homeostasis model for insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI) as independent variables, while adjusting for age, sex, and body mass index. The cutoff values of fasting insulin, HOMA-IR, and QUICKI were estimated by the areas under the receiver-operating characteristic (ROC) curves. The cutoff points for defining insulin resistance are a fasting insulin level of 12.94 μU/mL, HOMA-IR=3.04 as the 75th percentile value, and QUICKI=0.32 as the 25th percentile value. Compared with the lowest quartile, the adjusted odds ratios for the prevalence of metabolic syndrome in the highest quartiles of fasting insulin, HOMA-IR, and QUICKI were 1.95 (1.26-3.01), 2.27 (1.45-3.56), and 2.27 (1.45-3.56), respectively. The respective cutoff values for fasting serum insulin, HOMA-IR, and QUICKI by ROC analysis were 10.57 μU/mL (sensitivity 58.5%, specificity 66.8%), 2.34 (sensitivity 62.8%, specificity 65.7%), and 0.33 (sensitivity 61.2%, specificity 66.8%). Fasting insulin, HOMA-IR, and QUICKI can be used as surrogate measures of insulin resistance in Korean non-diabetic adults.

Key Words : *Insulin Resistance; Metabolic Syndrome X*

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INTRODUCTION

Metabolic syndrome was re-introduced in 1988 by Reaven, who suggested that insulin resistance and compensatory hyperinsulinemia underlie the clustering of cardiovascular risk factors, including glucose intolerance, hypertension, elevated serum triglycerides, low serum HDL cholesterol, and central obesity (1). Recently, the World Health Organization (WHO) (2) and the National Cholesterol Education Program (NCEP) expert panel (3) proposed working definitions for metabolic syndrome.

Insulin resistance is a reduced physiological response of the peripheral tissues to the action of insulin and is one of the major causes of type 2 diabetes (4). Many studies have reported that insulin resistance and hyperinsulinemia significantly increase cardiovascular disease (CVD) morbidity and mortality (5-7). Therefore, a reliable measure of insulin resistance is important for investigating the link between insulin resistance and metabolic syndrome. The most reliable reference methods for measuring insulin sensitivity in vivo are the hyperinsulinemic euglycemic clamp (8) and minimal-model analysis (MINMOD) of frequently sampled insulin levels during an intravenous glucose tolerance test (9, 10), but these methods are time-consuming, invasive, expensive, and technically difficult to apply in a clinical setting or for large populations.

For this reason, simpler, less-invasive techniques of determining insulin resistance, based on measuring fasting serum insulin and glucose, have been developed. The homeostasis model for insulin resistance (HOMA-IR) (11, 12) and the quantitative insulin sensitivity check index (QUICKI) (13) are the most commonly used surrogate measures and provide a reliable alternative to the glucose clamp. Many studies on reliable, simple, indirect methods for detecting insulin resistance in the general population have been reported (14-20).

Although the prevalence of metabolic syndrome in Korean adults has been investigated recently (21-26), no study has examined the cutoff values of surrogate measures of insulin resistance for increased metabolic syndrome in Korean adults. Therefore, we investigated the cutoff values of surrogate measures of insulin resistance for identifying metabolic syndrome in the Korean adults.

MATERIALS AND METHODS

Subjects

This study was performed as a part of the Korean Metabolic Syndrome Study, which is evaluating the role of metabolic syndrome as a risk factor for cardiovascular disease in Korean adults (27). The study protocol was approved by the ethics committee of the Severance Hospital at Yonsei University, and informed consent was obtained from each participant. We measured the metabolic profile, cardiovascular risk factors, and carotid intima-media thickness (IMT) of 1,230 men and women aged 30 to 79 yr old. These measurements were made over a 3 month period (April to June, 2001) at a health screening center in Seoul, Korea. All the participants were healthy, independently functioning individuals who were at the health center to undergo screening tests. Of the 1,230 initial volunteers, 1,207 men and women completed anthropometric measurements, serum biochemistry, and carotid IMT measurements. Individuals who had diabetes (fasting serum glucose $\geq$126 mg/dL or currently using antidiabetic medication; n=115) or had a missing value for insulin (n=118) were excluded from the analysis. Ultimately, 976 subjects (484 men and 492 women) were used in the analyses.

Clinical and laboratory data

Trained nurses interviewed all the participants and obtained their medical history, family history of chronic disease, and information on life style factors, using a standardized questionnaire. The weight and height of each participant was measured while the subject was clothed only in a light gown, and the body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest; hip circumference was measured at the widest level over the greater trochanters in a standing position, by the same examiner. The participants were required to rest for at least 5 min before having their blood pressure checked twice at an interval of at least 1 min. The mean value of these two measurements was used for the analyses.

Fasting blood samples were collected from an antecubital vein in plain tubes early morning after an 8 hr fast. Blood glucose was estimated using a glucose oxidase method (747 automatic analyzer, Hitachi, Tokyo, Japan), and fasting glucose was evaluated according to the new criteria of the American Diabetes Association; the subjects were defined as having diabetes mellitus if the fasting serum glucose (FSG) was $\geq$7.0 mM/L, as impaired fasting glucose if the FSG was 6.1-6.9 mM/L, and as normal if the FSG was <6.1 mM/L (28). Serum total cholesterol, HDL-cholesterol, and triglycerides were determined by an enzymatic colorimetric method using an automatic analyzer (Au5200, Olympus, Tokyo, Japan), and LDL-cholesterol was calculated using Friedewald's equation.

Assessing insulin resistance

Serum insulin was estimated using a radioimmunoassay (Linco Research Inc., St. Louis, MO, U.S.A.) with a 4.0% interassay coefficient of variation; this method does not cross-react with proinsulin. Two indirect indices for assessing insulin resistance were calculated. HOMA-IR uses the formula described by Matthews et al.: fasting insulin (μU/mL) $\times$ fasting glucose (mM/L)/22.5 (11). The QUICKI index is based on the logarithmic transformation: 1/(log fasting insulin [μU/mL]+log fasting glucose [mg/dL]) (13).

Definition of metabolic syndrome

We used the NCEP Adult Treatment Panel (ATP) III definition of metabolic syndrome (3). We used the waist circumference criterion of the Asia-Pacific Region instead of the original criterion (29). The modified NCEP definition required at least three of the following: 1) increased waist circumference (>90 cm in men and >80 cm in women), 2) high triglycerides ($\geq$1.7 mM/L, [150 mg/dL], 3) low HDL cholesterol (<1.04 mM/L [40 mg/dL] in men and <1.29 mM/L [50 mg/dL] in women), 4) high blood pressure ($\geq$130/85 mmHg or current antihypertensive medications), and 5) high fasting glucose ($\geq$6.1 mM/L [110 mg/dL]).

Statistical analysis

The data in Table 1 are given as the mean (SD). The clinical and metabolic characteristics of the subjects according to gender were analyzed using an independent sample I-test. Multiple logistic regression analyses were used to estimate the

Table 1. General characteristics of the study subjects

Characteristic	Men	Women	Total
Number of subjects	484	492	976
Age (yr)*	50.6 (10.6)	52.7 (9.5)	51.7 (10.1)
BMI (kg/m^2)†	24.5 (2.7)	24.9 (3.3)	24.7 (3.0)
Waist circumference (cm)*	86.2 (7.3)	82.1 (8.3)	84.1 (8.1)
Systolic blood pressure (mmHg)	129.5 (17.3)	130.8 (19.7)	130.2 (18.6)
Diastolic blood pressure (mmHg)	80.3 (11.7)	80.0 (12.8)	80.1 (12.3)
Total cholesterol (mM/L)*	5.15 (0.84)	5.34 (0.95)	5.24 (0.90)
Triglyceride (mM/L)*	2.11 (1.42)	1.63 (1.26)	1.87 (1.36)
HDL cholesterol (mM/L) *	1.13 (0.25)	1.32 (0.36)	1.22 (0.32)
Fasting serum glucose (mM/L)*	5.26 (0.54)	5.10 (0.51)	5.18 (0.53)
Fasting serum insulin (μU/mL)	10.9 (6.0)	11.0 (6.6)	11.0 (6.3)
HOMA-IR	2.59 (1.57)	2.52 (1.57)	2.55 (1.57)
QUICKI	0.34 (0.03)	0.34 (0.03)	0.34 (0.03)

Data are means (SD). *p<0.01, †p<0.05 between men and women.

odds ratios for the prevalence of metabolic syndrome according to the quartiles of fasting insulin, HOMA-IR, and QUICKI as independent variables, while adjusting for age, sex, and BMI. Pearson's correlation coefficients between the surrogate markers of insulin resistance (fasting insulin, HOMA-IR, and QUICKI) and the components of metabolic syndrome adjusted for age and sex were analyzed. The areas under the receiver-operating characteristic (ROC) curves for fasting insulin, HOMA-IR, and QUICKI for increased likelihood of metabolic syndrome were compared, and the cutoff values for fasting insulin, HOMA-IR, and QUICKI were estimated. The mean and SD of fasting insulin, HOMA-IR, and QUICKI were compared according to the number of components of metabolic syndrome using the modified NCEP criteria, while adjusting for age and sex. The statistical analysis was conducted using the program SPSS for Windows (version 11, SPSS Inc., Chicago, IL, U.S.A.), and $p<0.05$ was considered statistically significant.

Table 2. The prevalence and odds ratios (OR) of metabolic syndrome according to the quartiles of fasting serum insulin, HOMA-IR, and QUICKI

Parameter	No.	Interquartile range	Prevalence (%)	Crude		Adjusted*	
				OR	95% CI	OR	95% CI
Insulin							
1	244	-7.12	22.1	1.00		1.00	
2	244	7.12-9.58	22.1	1.00	0.65-1.53	0.84	0.53-1.32
3	244	9.58-12.94	37.3	2.09	1.41-3.12	1.55	1.01-2.38
4	244	12.94-	51.6	3.76	2.54-5.57	1.95	1.26-3.01
HOMA-IR							
1	244	-1.62	19.3	1.00		1.00	
2	244	1.62-2.19	23.0	1.25	0.81-1.93	1.05	0.66-1.66
3	244	2.19-3.04	39.3	2.72	1.81-4.09	2.12	1.37-3.28
4	244	3.04-	51.6	4.48	2.98-6.71	2.27	1.45-3.56
QUICKI							
1	244	-0.32	51.6	4.48	2.98-6.71	2.27	1.45-3.56
2	244	0.32-0.34	39.3	2.72	1.81-4.09	2.12	1.37-3.28
3	244	0.34-0.36	23.0	1.25	0.81-1.93	1.05	0.66-1.66
4	244	0.36-	19.3	1.00		1.00	

Data are given as the number, interquartile range, OR, and 95% confidence interval. *Adjusted for age, sex, and BMI.

RESULTS

The general characteristics of the 976 subjects, comprising 484 men and 492 women, are shown in Table 1 and Fig. 1. Women were older and had a higher BMI than men, but had a smaller waist circumference than men. Total cholesterol and HDL cholesterol were higher in women, while triglycerides were higher in men. Fasting insulin, HOMA-IR, and QUICKI were not significantly different between men and women.

Table 2 shows the odds ratios for the prevalence of metabolic syndrome according to the quartiles of fasting insulin, HOMA-IR, and QUICKI as independent variables. The cutoff point defining insulin resistance was a fasting insulin level of 12.94 μU/mL, HOMA-IR=3.04 as the 75th percentile value, and QUICKI=0.32 as the 25th percentile value. Compared with the lowest quartile of fasting insulin level, the crude and adjusted odds ratios for the prevalence of metabolic syndrome in the highest quartile were 3.76 (2.54-5.57) and 1.95 (1.26-3.01), respectively, which were significantly increased according to the increased quartile of fasting insulin. Similarly, the crude and adjusted odds ratios for the prevalence of metabolic syndrome among the highest quartile of HOMA-IR were 4.48 (2.98-6.71) and 2.27 (1.45-3.56),

Table 3. Correlation between surrogate markers of insulin resistance and the components of metabolic syndrome

Component	Insulin		HOMA-IR		QUICKI	
	Univariate (r)	Multivariate (beta)	Univariate (r)	Multivariate (beta)	Univariate (r)	Multivariate (beta)
Fasting glucose	0.172*	0.114*	0.334*	0.283*	-0.340*	-0.285*
Systolic blood pressure	0.102†	-0.059	0.117*	-0.053	-0.168*	-0.057
Diastolic blood pressure	0.109†	0.067	0.117*	0.057	-0.181*	-0.131†
Triglyceride	0.238*	0.158*	0.235*	0.151*	-0.233*	-0.149*
HDL cholesterol	-0.094†	0.031	-0.104†	0.032	0.098†	-0.030
Waist circumference	0.377*	0.337*	0.381*	0.315*	-0.372*	-0.291*

Data are Pearson's correlation (r) coefficients adjusted for age and sex and standardized coefficients (beta) using multivariate regression analysis. *$p<0.001$, †$p<0.005$.

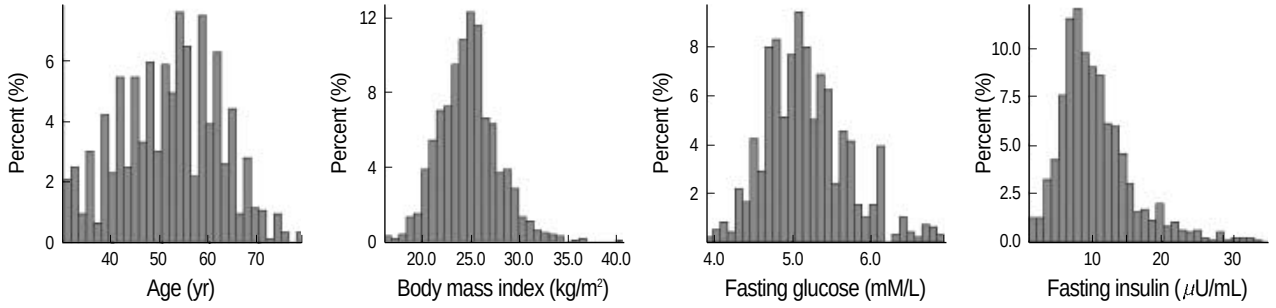

Fig. 1. Distribution of age, body mass index, fasting glucose and fasting insulin of study subjects.

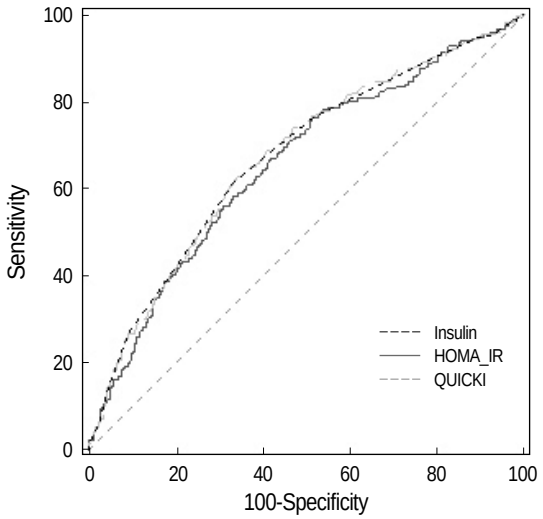

Fig. 2. Receiver-operating characteristic (ROC) curves for fasting serum insulin, HOMA-IR, and QUICKI for increased metabolic syndrome. The cutoff values for fasting serum insulin, HOMA-IR, and QUICKI are 10.57 μU/mL (sensitivity 58.5%, specificity 66.8 %), 2.34 (sensitivity 62.8%, specificity 65.7%), and 0.33 (sensitivity 61.2%, specificity 66.8%) (p<0.001, respectively). The areas under the ROC curves (95% CI) for the parameters are 0.656 (0.625-0.685), 0.672 (0.641-0.701), and 0.671 (0.641-0.701), respectively.

respectively, which were also significantly increased according to the increased quartile of HOMA-IR. The odds ratio for QUICKI was the same as that for HOMA-IR, which was higher than that for fasting insulin.

Table 3 shows the relationship between the surrogate markers of insulin resistance (fasting insulin, HOMA-IR, and QUICKI) and the components of metabolic syndrome adjusted for age and sex. All the values of the components of metabolic syndrome were significantly related to fasting insulin, HOMA-IR, and QUICKI. HOMA-IR was most strongly correlated with waist circumference and HDL cholesterol. The areas under the ROC curves for fasting insulin, HOMA-IR, and QUICKI are shown as Fig. 2. The areas under the ROC curves (95% CI) for the three parameters were 0.656 (0.625-0.685), 0.672 (0.641-0.701), and 0.671 (0.641-0.701), respectively. The cutoff values for fasting serum insulin, HOMA-IR, and QUICKI were 10.57 μU/mL (sensitivity 58.5%, specificity 66.8%), 2.34 (sensitivity 62.8%, specificity 65.7%), and 0.33 (sensitivity 61.2%, specificity 66.8%) (p<0.001), respectively.

DISCUSSION

In this study, we demonstrated that fasting insulin, HOMA-IR, and QUICKI are simple, yet reliable, methods for detecting insulin resistance in the Korean non-diabetic general population. Insulin resistance was strongly associated with metabolic syndrome. We also proposed cutoff values for fasting insulin, HOMA-IR, and QUICKI for predicting an increased likelihood of metabolic syndrome in Korean non-diabetic adults. The cutoff values for insulin resistance can be adopted for epidemiological studies, as well as in clinical practice.

The gold standard test for evaluating insulin resistance is the euglycemic hyperinsulinemic clamp, but its use is limited to clinical practice owing to the time and cost involved (8). Many studies have reported on several simple methods for evaluating insulin resistance that can reduce time and cost and are relatively accurate (11-13).

Fasting insulin levels are one of the simplest indirect indices for diagnosing insulin resistance. Yeni-Komshian et al. reported that the fasting plasma insulin concentration was significantly correlated with the estimated insulin action (r=0.61, p< 0.001) (16), and Strumvoll et al. reported that the correlation coefficient between fasting insulin and the insulin sensitivity index (ISI) was remarkably similar to that between ISI and the 120 min insulin (-0.59 vs. -0.62) (30), suggesting that fasting insulin is a simple predictor of insulin resistance. McAuley et al. suggested that fasting insulin alone was as accurate at predicting insulin resistance in the normoglycemic population and that a fasting insulin level ≥12.2 μU/mL in normoglycemic individuals was a reliable test for insulin resistance (17). In our study, the cutoff value of fasting insulin for defining insulin resistance was 12.94 μU/mL as the 75th percentile in Korean non-diabetic adults, which is similar to the 12 μU/mL of Ascaso et al. (19). The cutoff value of fasting insulin for increased metabolic syndrome in our study was 10.57 μU/mL, which is lower than the cutoff for insulin resistance. Our cutoff value is similar to the results of Park et al. (10.15 μU/mL in men, 9.53 μU/mL in women) for a sample of 7,057 healthy Korean adults (21).

The HOMA-IR is a useful, validated method for evaluating insulin resistance (11, 12). Bonora et al. suggested that the top quintile of the HOMA-IR, i.e., a value ≥2.77, had isolated insulin resistance in subjects with no metabolic disorders (14). In the Botnia study, Tripathy et al. found that subjects with impaired fasting glucose were more insulin resistant than subjects with normal glucose tolerance (HOMA-IR, 2.64 vs. 1.73) (15). Yeni-Komshian et al. suggested that the cutoff of HOMA-IR in 490 healthy non-diabetic volunteers based on determining the steady-state plasma glucose was 2.7 (16). Ascaso et al. reported that the 75th percentile value as the cutoff point for defining insulin resistance was HOMA-IR=2.6 (19). In our study, the HOMA-IR was a more reliable index of insulin resistance than the fasting insulin level in Korean non-diabetic adults. The 75th percentile value of HOMA-IR was 3.04, and the cutoff of the HOMA-IR for increasing metabolic syndrome was 2.34. Other studies of Korean populations have found that the mean HOMA-IR in metabolic syndrome, impaired glucose tolerance, or type 2 diabetes was 3.0-3.5 (23, 31, 32) and that the cutoff value of HOMA-IR for increased metabolic syndrome in healthy Korean adults was 2.78 in men and 2.48 in women (21), which

is similar to our result.

The recently developed QUICKI by Katz et al. may be a better surrogate measure of insulin resistance than HOMA-IR (13). They reported that the overall correlation between the gold standard SI_{clamp} and QUICKI (r=0.78) was significantly better than the overall correlation between SI_{clamp} and HOMA-IR (r=0.6). Hrebicek et al. found that adult patients with QUICKI <0.357, which is the lower limit of the 95% confidence limits in healthy persons, formed a group with typical manifestations of metabolic syndrome (18). Ascaso et al. found that the 25th percentile of QUICKI was 0.33 (19). Brady et al. suggested that the revised QUICKI based on fasting insulin, glucose, and free fatty acids is most strongly correlated with insulin sensitivity (Si) using the minimal model, compared with QUICKI or HOMA-IR (r=0.67 vs. 0.51 vs. 0.50) (20). In our study, the 25th percentile value of QUICKI was 0.32, and the cutoff of QUICKI for increased metabolic syndrome was 0.33.

Recently, the International Diabetes Federation suggested the new criteria for metabolic syndrome with necessity of the diagnostic standard that could be used commonly worldwide (33). Using this new criteria, the cutoff values of fasting insulin, HOMA-IR, and QUICKI are 10.58 μU/ mL, 2.38, and 0.33, which are similar to the results of NCEP criteria.

Insulin resistance is an important risk factor for type 2 diabetes and cardiovascular disease. Yip et al. reported that, during a 5 yr follow-up, 18% of the most insulin-resistant group developed either high blood pressure or had a CVD event and that insulin resistance or compensatory hyperinsulinemia predicted CVD events (6). In a 6 yr prospective follow-up study of 208 healthy adults, Facchini et al. reported that one-fifth of insulin-resistant individuals developed age-related diseases, such as hypertension, coronary artery disease, cerebral ischemia, cancer, and type 2 diabetes mellitus, while none of the insulin-sensitive group developed any of these diseases (7). They also stated that insulin resistance is a very important factor for predicting the future occurrence of age-related diseases, even in healthy adults. Huh et al. found that strict therapy with a low-fat, low-calorie diet in patients with coronary artery disease for 1 yr resulted in weight reduction, improved lipid profiles and insulin resistance, and ultimately improved coronary diameter stenosis (34). Therefore, they suggested that improving insulin resistance reduced risk factors and reversed coronary atherosclerosis.

In this study, we found that insulin resistance was strongly associated with metabolic syndrome and its components, especially with central obesity (waist circumference) and hypertriglyceridemia. In addition, we found that metabolic syndrome in Korean non-diabetic adults was increased at a lower level of insulin resistance than the 75th percentile of fasting insulin and HOMA-IR or the 25th percentile of QUICKI. Consequently, we must be concerned with the early detection of insulin resistance and metabolic syndrome in clinical and epidemiological settings and with the prevention of type 2 diabetes, dyslipidemia, hypertension, and cardiovascular diseases.

This study has some limitations. First, the diagnosis of insulin resistance was made based only on single test of fasting blood glucose and insulin. Hyperinsulinemic-euglycemic clamp were not performed to confirm the diagnosis of insulin resistance. However, WHO recommended this method for epidemiological study (2). Second, there were selection bias and thus limitation of representative of Korean adults in this study subjects. Third, although plasma glucose assay is highly reproducible in different laboratories, insulin assay can vary considerably, especially if antibodies cross-reacting with proinsulin are used (35). In our study, we used an human insulin-specific radioimmunoassay with no significant cross-reactivity with proinsulin, thereby minimizing the interference on surrogate measures by proinsulin.

In conclusion, fasting insulin, HOMA-IR, and QUICKI can be used as surrogate measures of insulin resistance in Korean non-diabetic adults. We suggest that the cutoff values of these simple methods can be applied to evaluate insulin resistance and to predict metabolic syndrome in Korean non-diabetic adults. Furthermore, we should monitor the healthy insulin-resistant population to prevent ongoing cardiovascular diseases. Prospective follow-up data are needed to refine the correlations of insulin resistance to metabolic syndrome

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REFERENCES

1. Reaven GM. *Banting lecture 1988: Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-607.*
2. Alberti KG, Zimmer PZ. *Definition, diagnosis and classification of diabetes mellitus and its complications: Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO Consultation. Diabet Med 1998; 15: 539-53.*
3. 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 (Adult Treatment Panel III). JAMA 2001; 285: 2486-97.*
4. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR. *Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. Lancet 1992; 340: 925-9.*
5. Després JP, Lamarche B, Mauriège P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ. *Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 1996; 334: 952-7.*
6. Yip J, Facchini FS, Reaven GM. *Resistance to insulin-mediated glu-*

cose disposal as a predictor of cardiovascular disease. J Clin Endocrinol Metab 1998; 83: 2773-6.

7. Facchini FS, Hua N, Abbasi F, Reaven GM. *Insulin resistance as a predictor of age-related diseases. J Clin Endocrinol Metab 2001; 86: 3574-8.*
8. DeFronzo RA, Toin JD, Andres R. *Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol 1979; 237: 214-23.*
9. Bergman RN, Phillips LS, Cobelli C. *Physiological evaluation of factors controlling glucose tolerance in man. J Clin Invest 1981; 68: 1456-67.*
10. Finegood DT, Hramiak IM, Dupre J. *A modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin-dependent diabetes. J Clin Endocrinol Metab 1990; 70: 1538-49.*
11. 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 concentration in man. Diabetologia 1985; 28: 412-9.*
12. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. *Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity. Diabetes Care 2000; 23: 57-63.*
13. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ. *Quantitative insulin-sensitivity check index: A simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000; 85: 2402-10.*
14. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G, Alberiche M, Bonadonna RC, Muggeo M. *Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. Diabetes 1998; 47: 1643-9.*
15. Tripathy D, Carlsson M, Almgren P, Isomaa B, Taskinen MR, Tuomi T, Groop LC. *Insulin secretion and insulin sensitivity in relation to glucose tolerance: lessons for the Botnia study. Diabetes 2000; 49: 975-80.*
16. Yeni-Komshian H, Carantoni M, Abbasi F, Reaven GM. *Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 490 healthy nondiabetic volunteers. Diabetes Care 2000; 23: 171-5.*
17. McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, Duncan AW. *Diagnosing insulin resistance in the general population. Diabetes Care 2001; 24: 460-4.*
18. Hrebicek J, Janout V, Malincikova J, Horakova D, Cizek L. *Detection of insulin resistance by simple quantitative insulin sensitivity check index QUICKI for epidemiological assessment and prevention. J Clin Endocrinol Metab 2002; 87: 144-7.*
19. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. *Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care 2003; 26: 3320-5.*
20. Brady LM, Gower BA, Lovegrove SS, Williams CM, Lovegrove JA. *Revised QUICKI provides a strong surrogate estimate of insulin sensitivity when compared with the minimal model. Int J Obesity 2004; 28: 222-7.*
21. Park SH, Lee WY, Rhee EJ, Jeon WK, Kim BI, Ryu SH, Kim SW. *Relative risks of the metabolic syndrome according to the degree of insulin resistance in apparently healthy Korean adults. Clin Sci 2005; 108: 553-9.*
22. Jeong SK, Nam HS, Rhee JA, Shin JH, Kim JM, Cho KH. *Metabolic syndrome and ALT: a community study in adult Koreans. Int J Obesity 2004; 28: 1033-8.*
23. Kim ES, Han SM, Kim YI, Song KH, Kim MS, Kim WB, Park JY, Lee KU. *Prevalence and clinical characteristics of metabolic syndrome in a rural population of South Korea. Diabet Med 2004; 21: 1141-3.*
24. Song J, Kim E, Shin C, Kim SS, Lee HK, Jung M, Jung SC, Jo SA, Jo I. *Prevalence of the metabolic syndrome among South Korean adults: the Ansan study. Diabet Med 2004; 21: 1154-5.*
25. Oh JY, Hong YS, Sung YA, Barrett-Connor E. *Prevalence and factor analysis of metabolic syndrome in an urban Korean population. Diabetes Care 2004; 27: 2027-32.*
26. Park HS, Oh SW, Cho SI, Choi WH, Kim YS. *The metabolic syndrome and associated lifestyle factors among South Korean adults. Int J Epidemiol 2004; 33: 328-36.*
27. Kim HJ, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, Lim SK, Kim KR, Lee HC, Huh KB, Cha BS. *Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch Intern Med 2004; 164: 2169-75.*
28. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997; 20: 1183-97.*
29. Western Pacific Regional Office of the World Health Organization, The International Obesity Task Force. *The Asia-Pacific perspective: redefining obesity and its treatment. Sydney, Health Communications Australia, 2000.*
30. Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Jarvinen H, Van Haeften T, Renn W, Gerich J. *Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. Diabetes Care 2000; 23: 295-301.*
31. Kim DJ, Lee MS, Kim KW, Lee MK. *Insulin secretory dysfunction and insulin resistance in the pathogenesis of Korean type 2 diabetes mellitus. Metabolism 2001; 50: 590-3.*
32. Choi KM, Lee J, Kim YH, Kim KB, Kim DL, Kim SG, Shin DH, Kim NH, Park IB, Choi DS, Baik SH. *Relation between insulin resistance and hematological parameters in elderly Koreans-Southwest Seoul (SWS) Study. Diabetes Res Clin Pract 2003; 60: 205-12.*
33. IDF Press Conference: *The IDF consensus worldwide definition of the metabolic syndrome. Available from: URL: http://www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf. [Accessed 3 February 2006].*
34. Huh KB, Lee HC, Cho SY, Lee JH, Song YD. *The role of insulin resistance in Korean patients with coronary atherosclerosis. Diabetes 1996; 45 (Suppl 3): 59-61.*
35. Robbins DC, Andersen L, Bowsher R, Chance R, Dinesen B, Frank B, Gingerich R, Goldstein D, Widemeyer HM, Haffner S, Hales CN, Jarrett L, Polonsky K, Porte D, Skyler J, Webb G, Kallagher K. *Report of the American Diabetes Association's task force on standardization of the insulin assay. Diabetes 1996; 45: 242-56.*