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doi:10.3748/wjg.15.5598

World J Gastroenterol 2009 November 28; 15(44): 5598-5603
World Journal of Gastroenterology ISSN 1007-9327

BRIEF ARTICLE

A better parameter in predicting insulin resistance: Obesity plus elevated alanine aminotransferase

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Received: July 11, 2009 Revised: September 7, 2009
Accepted: September 14, 2009
Published online: November 28, 2009

Abstract

AIM: To investigate the association of obesity and elevated alanine aminotransferase with insulin resistance and compare these factors with metabolic syndrome.

METHODS: We enrolled a total of 1308 male workers aged from 22 to 63 years. Data was extracted from the workers' periodic health check-ups in hospitals. All cases were from the community of northern Taiwan. This was a cross-sectional observational study from July to September in 2004. We grouped all cases into four groups, based on the quartile of homeostasis model assessment. The top fourth quartile group was defined as the group with insulin resistance. We performed multivariate logistic regression analysis for the odds ratio of the risk factors for insulin resistance.

RESULTS: Compared with metabolic syndrome, the coexistence of both factors had a 4.3-fold (95% CI: 2.7-6.8) increased risk, which was more than metabolic syndrome with a 3.6-fold (95% CI: 2.6-5.0) increased risk. The two factors had a synergistic effect. The synergistic index of obesity and elevated alanine aminotransferase (ALT) was 2.1 (95% CI: 1.01-4.3).

CONCLUSION: Obesity and elevated ALT are associated with insulin resistance. The effects are synergistic. Coexistence of them is better than metabolic syndrome in predicting insulin resistance.

Key words: Alanine aminotransferase; Transaminase; Overweight; Obesity; Insulin resistance

Peer reviewer: Yasuji Arase, MD, Department of Gastroenterology, Toranomon Hospital, 2-2-2 Toranomonminato-ku, Tokyo 105-8470, Japan

Chen PH, Chen JD, Lin YC. A better parameter in predicting insulin resistance: Obesity plus elevated alanine aminotransferase. *World J Gastroenterol* 2009; 15(44): 5598-5603 Available from: URL: http://www.wjgnet.com/1007-9327/15/5598.asp DOI: http://dx.doi.org/10.3748/wjg.15.5598

INTRODUCTION

Insulin resistance is a key feature of type 2 diabetes mellitus and it plays an important role in cardiovascular diseases[1]. Predicting insulin resistance is useful in preventing diabetes or cardiovascular disease. Insulin resistance can be directly measured with a hyperinsulinemic euglycemic clamp[2]. In addition, several parameters from less invasive methods have been demonstrated to be related to, or to predict, insulin resistance, such as obesity[3-5], alanine aminotransferase (ALT) level[6], metabolic syndrome, chronic inflammation status[5], nonalcoholic fatty liver disease (NAFLD)[7,8], and adiponectin level[9]. Some of these factors are easily measured (e.g. body weight and ALT) and the others are more complex (e.g. metabolic syndrome), not available in most laboratories (e.g. adiponectin), or are technique-dependent (e.g. sonographic NAFLD).

In Taiwan, the national health program provides a periodic examination for every adult older than forty. The program includes measurements of body height/weight, and ALT level. Measurement of insulin resistance, however, is not included in the program because of its inconvenience, although it is important for preventing cardiovascular disease.

Obesity is a ongoing problem in Taiwan and world-

wide[10,11]. It is associated with several conditions, of which insulin resistance might be the most important[12].

Alanine aminotransferase (ALT) is a widely used laboratory test and abnormal ALT levels are common[13,14]. Elevated ALT has also been noted to be related to insulin resistance.

Besides being non-invasive, both obesity and ALT measurements are easily obtained and are inexpensive. Our purpose was to confirm the belief that that obesity and elevated ALT are important parameters of insulin resistance. We reported that the coexistence of both factors has a synergistic effect and the coexistence might be better than metabolic syndrome for predicting insulin resistance. The possible mechanism will be explored in the article. This result is helpful for preventing cardiovascular disease in public health.

MATERIALS AND METHODS

Data from a total of 1308 male workers' health check-up records were analyzed. Data were collected *via* a questionnaire, including age (years), smoking status (packs per day), and alcohol consumption status (times per week). Anthropometrical data collected included systolic and diastolic blood pressure (mmHg), body weight (kg), height (cm), calculated body mass index, BMI (kg/m^2), and waist circumference (cm). The laboratory measurements were conducted by Beckman Coulter auto-analyzer (model DxC 800 Synchron), and included triglyceride (mg/dL), high-density lipoprotein (HDL, mg/dL), aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), and fasting plasma glucose (mg/dL). The insulin level (U/mL) was measured by the Abbott autoanalyzer (model AxSym). Insulin resistance was defined as the top quartile of $HOMA_{IR}$ (homeostasis model assessment)[2]. Obesity was defined as BMI $\geqslant$ 27 according to the modified criteria in Taiwan[11]. Abdominal obesity (or central obesity) was defined as a waist circumference $\geqslant$ 90 cm in men, according to the modified criteria from ATPⅢ for Asia subjects[15]. Elevated blood pressure, elevated triglyceride, low high-density lipoprotein, and elevated fasting glucose were defined based on previous ATPⅢ criteria for metabolic syndrome as systolic blood pressure $\geqslant$ 130 mmHg or diastolic blood pressure $\geqslant$ 85 mmHg, triglyceride $\geqslant$ 150 mg/dL, high density lipoprotein $<$ 40 mg/dL, and fasting glucose $\geqslant$ 100 mg/dL. Elevated ALT was defined as ALT $>$ 40 U/L (according to our laboratory and any cause, such viral hepatitis or alcoholism, was not ruled out). Smoking was defined as smoking more than one pack per day. Alcohol consumption was defined as drinking more than once per week. The Student's *t* test and chi-square test were used for analyzing continuous variables and categorical variables, respectively. Multivariate logistic regression was used to evaluate the relationship between insulin resistance and the risk factors. We introduced three models for multivariate logistic regression analysis for the odds ratio of the risk factors for insulin resistance. Model 1 showed the odds ratio of the risk factors among which metabolic syndrome is regarded as five separate components. Metabolic syndrome is regarded as a single factor in model 2. Elevated ALT and obesity are regarded as two separate risk factors in model 1 and model 2. The coexistence of the two factors is regarded as a single factor and is compared with metabolic syndrome in model 3. To understand the synergistic effect of the risk factors, we introduced the synergistic index to see if the synergistic effect of obesity and elevated ALT was statistically significant[16]. This analytical study, limited to health check-up data, followed all the ethical criteria for human research[17]. The study protocol (TYGH09702108) was reviewed and approved by the Ethics Committee of the Taoyuan General Hospital.

RESULTS

A total of 1308 male examinees were enrolled in the present study. The baseline characteristics of the study population stratified by $HOMA_{IR}$ are presented in Table 1. The mean age of the total population was 38.7 years (ranging from 22-63 years); increasing age with the higher $HOMA_{IR}$ was noted. A similar increasing trend was also presented in the other parameters except that a decreasing trend was noted in the HDL parameter. We also examined the significance of the trend of the increasing ALT level with insulin resistance through ANOVA analysis.

The abnormality prevalence of the four stratified categories according to the HOMA quartile, and the whole samples, are shown in Table 2. Similarly, the abnormality prevalence rates of all parameters (except smoking and drinking) increase with the higher $HOMA_{IR}$.

In Table 3, after controlling for age, metabolic syndrome, hypercholesterolemia, elevated low-density lipoprotein, drinking, and smoking status, obesity has a 2.5-fold (95% CI: 1.7-3.6) and elevated ALT has a 2.1-fold (1.4-3.0) increased risk of insulin resistance in model 1. Each of these is more than at least three components of metabolic syndrome (abdominal obesity, elevated blood pressure, and hypo-HDL cholesterolemia). In model 2, obesity has a 3.0-fold (2.1-4.2) and elevated ALT has a 2.1-fold (1.5-2.9) increased risk of insulin resistance. Metabolic syndrome has a 2.6-fold (1.8-3.7) increased risk. On their own, both risk factors are similar to, or even more significant than metabolic syndrome. In model 3, we compared the coexistence of obesity and elevated ALT with metabolic syndrome. The coexistence of the two factors has a 4.3-fold (2.7-6.8) increased risk, far more than metabolic syndrome that has a 3.6-fold (2.6-5.0) increased risk. To examine the relationship between obesity and elevated ALT, we presented the synergistic effect of both factors in Table 4. It showed the synergistic index is 2.1 and it is statistically significant (95% CI: 1.0-4.3). Different odds ratios of obesity and elevated ALT in Tables 3 and 4 were noted due to different controlling factors.

Table 1 Basic characteristics of subjects, stratified by HOMA$_{IR}$ (mean ± SD)

	The four sub-groups stratified by HOMA$_{IR}$[1]				Total
	Q1 (327, 25%)	Q2 (326, 25%)	Q3 (328, 25%)	Q4 (327, 25%)	(1308, 100%)
Age (yr)	38.1 ± 10.0	38.5 ± 9.7	38.7 ± 10.0	39.7 ± 10.3	38.7 ± 10.0
Systolic blood pressure (mmHg)	124.4 ± 13.9	125.8 ± 14.7[a]	128.0 ± 15.1[a]	132.5 ± 16.0[a]	127.7 ± 15.2
Diastolic blood pressure (mmHg)	77.3 ± 10.0	77.6 ± 10.4[a]	79.6 ± 11.2[a]	82.1 ± 11.7[a]	79.1 ± 11.0
Body mass index (kg/m^2)	22.8 ± 2.5	23.7 ± 2.5[a]	25.1 ± 2.7[a]	27.0 ± 3.4[a]	24.7 ± 3.3
Waist circumference (cm)	83.6 ± 6.6	85.8 ± 6.1[a]	88.9 ± 6.7[a]	92.6 ± 7.5[a]	87.7 ± 7.5
ALT (U/L)	22.4 ± 16.1	25.5 ± 18.1[a]	36.1 ± 48.4[a]	40.2 ± 26.4[a]	31.0 ± 31.0
AST (U/L)	23.9 ± 11.1	24.2 ± 16.0[a]	27.6 ± 20.2[a]	28.0 ± 11.5[a]	25.9 ± 15.3
Fasting glucose (mg/dL)	95.1 ± 7.6	97.9 ± 7.9[a]	99.4 ± 7.9[a]	102.5 ± 8.5[a]	98.7 ± 8.4
Fasting insulin (U/mL)	3.6 ± 1.0	6.1 ± 0.9[a]	8.9 ± 1.1[a]	15.8 ± 6.5[a]	8.6 ± 5.7
HOMA$_{IR}$	0.8 ± 0.2	1.5 ± 0.2[a]	2.1 ± 0.2[a]	3.9 ± 1.7[a]	2.1 ± 1.5
Triglyceride (mg/dL)	113.9 ± 86.8	127.6 ± 86.2[a]	157.9 ± 105.7[a]	202.8 ± 156.9[a]	150.6 ± 117.6
HDL (mg/dL)	52.8 ± 12.5	50.2 ± 9.8[a]	47.4 ± 10.7[a]	44.4 ± 8.9[a]	48.7 ± 11.0

[1]The subjects were stratified into four groups according to HOMA$_{IR}$; Q1 means the 1st quartile, Q2 means the 2nd, *etc.* ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HDL: High-density lipoprotein; HOMA$_{IR}$: Insulin resistance assessed by homeostasis model assessment = fasting insulin (U/mL) × glucose (mmol/L)/22.5. [a]$P < 0.05$ *vs* Q1.

Table 2 Abnormality prevalence distribution, stratified by HOMA$_{IR}$ *n* (%)

	The four sub-groups stratified by HOMA$_{IR}$				Total
Abnormality[1]	Q1 327 (25)	Q2 326 (25)	Q3 328 (25)	Q4 327 (25)	1308 (100)
Obesity	20 (6.1)	29 (8.9)	81 (24.7)[a]	153 (46.8)[a]	283 (21.6)
Elevated ALT	25 (7.6)	36 (11.0)	74 (22.6)[a]	118 (36.1)[a]	253 (19.3)
Metabolic syndrome components					
Abdominal obesity	45 (13.8)	74 (22.7)[a]	126 (38.4)[a]	188 (57.5)[a]	433 (33.1)
Elevated blood pressure	110 (33.6)	118 (36.2)	136 (41.5)[a]	187 (57.2)[a]	551 (42.1)
Elevated fasting glucose	16 (4.9)	22 (6.7)	37 (11.3)[a]	62 (19.0)[a]	137 (10.5)
Elevated triglyceride	58 (17.7)	83 (25.5)[a]	132 (40.2)[a]	195 (59.6)[a]	468 (35.8)
Hypo-HDL cholesterolemia	39 (11.9)	47 (14.4)	71 (21.6)[a]	108 (33.0)[a]	265 (20.3)
Alcohol consumption	83 (25.4)	56 (17.2)	74 (22.6)	73 (22.3)	286 (21.9)
Cigarette smoking	122 (37.3)	118 (36.2)[a]	108 (32.9)	109 (33.3)	457 (34.9)

[1]Obesity: Body mass index ⩾ 27 kg/m^2; Elevated ALT: ALT > 40 U/L; Abdominal obesity: waist circumference ⩾ 90 cm in male adults; Elevated blood pressure: blood pressure ⩾ 130/85 mmHg; Elevated fasting glucose: fasting glucose ⩾ 100 mg/dL; Elevated triglyceride: triglyceride ⩾ 150 mg/dL; Hypo-HDL cholesterolemia: HDL cholestero1 < 40 mg/dL; Hypercholesterolemia: total cholesterol ⩾ 200 mg/dL; Elevated LDL: LDL cholesterol ⩾ 130 mg/dL; Alcohol consumption: more than once per week; Cigarette smoking: more than one pack per day. [a]$P < 0.05$ *vs* Q1 (χ^2 test).

Table 3 OR of risk factors, presented as OR (95% CI)

Model[1]	Model 1	Model 2	Model 3
Both obesity and elevated ALT	-	-	4.3 (2.7-6.8)
Obesity	2.5[2] (1.7-3.6)	3.0[2] (2.1-4.2)	-
Elevated ALT	2.1[2] (1.4-3.0)	2.1[2] (1.5-2.9)	-
Metabolic syndrome	-	2.6[2] (1.8-3.7)	3.6 (2.6-5.0)
Abdominal obesity	1.6[2] (1.2-2.2)	-	-
Elevated blood pressure	1.7[2] (1.2-2.4)	-	-
Elevated fasting glucose	2.8[2] (1.8-4.4)	-	-
Elevated triglyceride	2.2[2] (1.6-3.1)	-	-
Hypo-HDL cholesterolemia	1.6[2] (1.1-2.2)	-	-
Alcohol consumption	1.2 (0.8-1.7)	1.2 (0.8-1.6)	1.2 (0.9-1.7)
Cigarette smoking	0.9 (0.7-1.2)	0.9 (0.6-1.2)	0.9 (0.6-1.2)

[1]Risk factors of metabolic syndrome were regarded as five individual factor in model 1 and as a single factor in model 2; both obesity and elevated ALT were regarded as a single factor in model 3; [2]Significant odds ratio (OR), adjusted for age.

Table 4 Synergistic effect of obesity and elevated ALT on insulin resistance[1]

	OR	(95% CI)	SI	95% CI
Neither obesity nor elevated ALT	1.0	Reference	No risk	-
Obesity only	2.3	(1.5-3.5)	One risk only	-
Elevated ALT only	1.8	(1.1-2.9)	One risk only	-
Obesity plus elevated ALT	5.5	(3.2-9.3)	2.1	(1.01-4.3)

[1]Insulin resistance is defined as the 4th quartile of the HOMA$_{IR}$. SI: Synergistic index.

DISCUSSION

Obesity is a worsening problem in Taiwan and worldwide[10]. Due to the variety of definition criteria, the prevalence rate varies. In Taiwan, the prevalence rate of obesity (defined as BMI ⩾ 27 in this article), surveyed in 2000-2001 were 15.9% and 10.7% in men and women separately, and the rate has progressively increased[11]. The prevalence rate of obesity in our study, which was conducted after 2001, is higher and is compatible with the trend of increasing prevalence. Obesity is associated with several comorbidities[10], including coronary heart disease, stroke, NAFLD, and type 2 diabetes mellitus. Insulin resistance is present and important in the above clinical problems.

In our study, obesity alone is an important risk factor of insulin resistance. Similar results have also been published in other studies[3-5]. In contrast, weight reduction improves insulin resistance[18,19], even if it is achieved by surgery[20]. However, not all obese subjects have insulin resistance[12]. Although the exact mechanism is still not fully understood, many factors have been found to induce insulin resistance through different pathways, such as increased non-esterified fatty acids (NEFAs), adipocyte dysfunction, leptin, adiponectin, chronic inflammatory status, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and fat distribution[10,12,21]. Among these factors, NEFAs, released from dysfunctional adipocytes, might be the single most critical factor in modulating insulin sensitivity[10,12,21].

ALT level is a widely used laboratory test in Taiwan. Elevated ALT is a common laboratory abnormality in a healthy population. The statistical database from the healthy population in the United States in 2003 showed the prevalence rate of abnormal transaminase was 20.8%, similar to previous findings (19.3%)[13]. Another study showed the prevalence rate in the male adolescent population was 12.4%, which was lower, but the population was younger[14].

Our results show elevated ALT is a risk factor of insulin resistance, independent of metabolic syndrome. This conclusion has been also proposed in previous articles[6,22,23]. In Pima, in Indians with normal glucose tolerance, elevated ALT was associated with a decline in clamp-derived whole body insulin sensitivity, according to longitudinal analysis, and it predicted the development of type 2 diabetes in a prospective analysis[6]. This was extended to those with impaired glucose tolerance in another study[22], in which a population of African-Americans and white subjects were analyzed. Burgert *et al*[23] also noted a relationship between elevated ALT and reduced insulin sensitivity in obese children. Our study showed a similar result in Taiwanese adult males using community-based data. A semi-quantified result was also noted in a previous article[22]. Our study also showed the trend of a significantly increasing level of ALT in the more severe insulin-resistant group.

The causes of elevated ALT may be NAFLD, viral hepatitis, alcohol, or medications[24]. NAFLD is also a common clinical problem, and it has been proven to cause elevated ALT[25]. NAFLD was regarded as an explanation of the association between elevated ALT and insulin resistance in previous studies[6,26]. It has also been reported that hepatitis C induced insulin resistance[27]. This might be a partial explanation of the relationship between elevated ALT and insulin resistance. In contrast, alcohol intake in sufficient amounts can improve insulin resistance[8,28]. Many kinds of medication can induce elevated ALT, but there is a lack of evidence that medication leads to insulin resistance. One study in 1983 reported aspirin induced insulin insensitivity, but there were only eight subjects in the study[29]. The C-reactive protein (CRP) level might provide another explanation. A previous study indicated that the CRP level was higher in subjects with elevated ALT than those with normal ALT[30]. Another study showed a high CRP level was related to insulin resistance[31]. From these studies, we might conclude that subjects with elevated ALT have a higher CRP level and further, are more insulin-resistant. The exact mechanism is, however, not well-understood. Further evidence is required.

Interestingly, there is a dramatically higher risk of insulin resistance in subjects with both elevated ALT and obesity. This result has seldom been discussed in the literature.

There are several studies concerning the association between obesity and elevated ALT, but the role of insulin resistance had not been identified in these studies[32,33]. In studies on the association between ALT level and insulin resistance, there was no analysis identifying the effect of obesity, but a significant relationship between body weight and ALT level were shown in the data[6,22]. Elevated ALT was associated with insulin resistance in obese subjects in previous studies, but it lacked comparative analysis between obese and non-obese subjects[23,30].

What mechanism leads to the synergistic effect of obesity and elevated ALT? As discussed earlier, adipocyte dysfunction is regarded as the link between obesity and insulin resistance[21], and its associated release of NEFAs (or free fatty acids) was regarded as the single most critical factor modulating insulin sensitivity[1,10,12,21]. In the model, adipocyte dysfunction results in increased circulating NEFAs, which further mediates insulin resistance. The excessive build-up of NEFAs in the liver leads to NAFLD, of which elevated ALT level is the best marker even within the reference interval[34]. Obesity coexisting with elevated ALT points to excessive NEFAs release and adipocyte dysfunction. This shows the existence of the link "from obesity to insulin resistance". Besides, in the cell module, TNF-α, and its effects on down-regulation of the nuclear hormone receptor peroxisome proliferator activated receptor-γ (PPARγ) strongly contributed to the effects of inflammatory cytokines on adipocytes[21]. Thus the inflammatory status results in adipocyte dysfunction. As elevated ALT is a reflection of systemic inflammation[6], we concluded that coexistence of elevated ALT and obesity means the existence of inflammatory status, the excessive release of NEFAs, and their result: adipocyte dysfunction connecting obesity to insulin resistance.

Based on the models, most subjects with both obesity and elevated ALT should have insulin resistance. In our study, the actual prevalence rate of insulin resistance in the sub-group with both obesity and elevated ALT was almost 70% (not shown in table). This is compatible with our hypothesis.

The limits of this study deserve mention. First, insulin resistance was defined as the top quartile of $HOMA_{IR}$ (homeostasis model assessment), instead of a direct measurement. This might be less representative of insulin resistance, but more cases are available because of the more simple classification. Secondly, although our results showed a trend of increasing

ALT level with more severe insulin resistance, it still lacks an exact quantified relationship. More evidence is needed to confirm if there is a better cutoff value of ALT level or quantified relationship between ALT level and insulin resistance. Thirdly, cigarette smoking and alcohol consumption were recorded as more than one pack per day/once per week, instead of exact quantified data; therefore, it cannot be concluded that there was no relationship between smoking/drinking and insulin resistance based on our results.

In conclusion, obesity and elevated ALT have been shown to be associated with insulin resistance. The coexistence of both factors points to the existence of a linking mechanism between obesity and insulin resistance. The results suggest a synergistic effect on insulin resistance. The coexistence of these parameters might be better than metabolic syndrome for evaluating insulin resistance in clinical practice.

COMMENTS

Background

Insulin resistance is a key feature of type 2 diabetes mellitus and it plays an important role in cardiovascular diseases. Direct measurement of insulin resistance with hyperinsulinemic euglycemic clamp is invasive and inconvenient. For public health, less invasive methods are required. Many parameters have been proposed. Metabolic syndrome is one of the most popularly-used parameter.

Research frontiers

This study proposed that obesity plus elevated alanine aminotransferase (ALT) might be better than metabolic syndrome for predicting insulin resistance due to its being non-invasive and convenience. This article also explored the mechanism linking obesity, elevated ALT, and insulin resistance.

Applications

This study highlights the applications on public health since the measurements of obesity and ALT are easily obtained.

Peer review

The content of the article will be interesting not only for the gastroenterologists, but also for other specialists. For understanding the quantified relationship between body weight or ALT level and insulin resistance, further investigations are required.

REFERENCES

1 **Eckel RH**, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; **365**: 1415-1428
2 **Liu CM**, Tung TH, Tsai ST, Liu JH, Tsai YK, Chen VT, Tam TN, Lu HF, Wang KK, Hsu CT, Shih HC, Chan DC, Chou P. Serum insulin, insulin resistance, beta-cell dysfunction, and gallstone disease among type 2 diabetics in Chinese population: a community-based study in Kinmen, Taiwan. *World J Gastroenterol* 2005; **11**: 7159-7164
3 **Viner RM**, Segal TY, Lichtarowicz-Krynska E, Hindmarsh P. Prevalence of the insulin resistance syndrome in obesity. *Arch Dis Child* 2005; **90**: 10-14
4 **Ludvik B**, Nolan JJ, Baloga J, Sacks D, Olefsky J. Effect of obesity on insulin resistance in normal subjects and patients with NIDDM. *Diabetes* 1995; **44**: 1121-1125
5 **Shoelson SE**, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology* 2007; **132**: 2169-2180
6 **Vozarova B**, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C, Tataranni PA. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes* 2002; **51**: 1889-1895
7 **Utzschneider KM**, Kahn SE. Review: The role of insulin resistance in nonalcoholic fatty liver disease. *J Clin Endocrinol Metab* 2006; **91**: 4753-4761
8 **Greenfield JR**, Samaras K, Hayward CS, Chisholm DJ, Campbell LV. Beneficial postprandial effect of a small amount of alcohol on diabetes and cardiovascular risk factors: modification by insulin resistance. *J Clin Endocrinol Metab* 2005; **90**: 661-672
9 **Kadowaki T**, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest* 2006; **116**: 1784-1792
10 **Eckel RH**, York DA, Rössner S, Hubbard V, Caterson I, St Jeor ST, Hayman LL, Mullis RM, Blair SN. Prevention Conference VII: Obesity, a worldwide epidemic related to heart disease and stroke: executive summary. *Circulation* 2004; **110**: 2968-2975
11 **Chu NF**. Prevalence of obesity in Taiwan. *Obes Rev* 2005; **6**: 271-274
12 **Kahn SE**, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006; **444**: 840-846
13 **Patt CH**, Yoo HY, Dibadj K, Flynn J, Thuluvath PJ. Prevalence of transaminase abnormalities in asymptomatic, healthy subjects participating in an executive health-screening program. *Dig Dis Sci* 2003; **48**: 797-801
14 **Fraser A**, Longnecker MP, Lawlor DA. Prevalence of elevated alanine aminotransferase among US adolescents and associated factors: NHANES 1999-2004. *Gastroenterology* 2007; **133**: 1814-1820
15 **Tan CE**, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 2004; **27**: 1182-1186
16 **Lundberg M**, Fredlund P, Hallqvist J, Diderichsen F. A SAS program calculating three measures of interaction with confidence intervals. *Epidemiology* 1996; **7**: 655-656
17 **Portaluppi F**, Touitou Y, Smolensky MH. Ethical and methodological standards for laboratory and medical biological rhythm research. *Chronobiol Int* 2008; **25**: 999-1016
18 **Goodpaster BH**, Kelley DE, Wing RR, Meier A, Thaete FL. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. *Diabetes* 1999; **48**: 839-847
19 **Petersen KF**, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* 2005; **54**: 603-608
20 **Halverson JD**, Kramer J, Cave A, Permutt A, Santiago J. Altered glucose tolerance, insulin response, and insulin sensitivity after massive weight reduction subsequent to gastric bypass. *Surgery* 1982; **92**: 235-240
21 **Guilherme A**, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nat Rev Mol Cell Biol* 2008; **9**: 367-377
22 **Hanley AJ**, Wagenknecht LE, Festa A, D'Agostino RB Jr, Haffner SM. Alanine aminotransferase and directly measured insulin sensitivity in a multiethnic cohort: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2007; **30**: 1819-1827
23 **Burgert TS**, Taksali SE, Dziura J, Goodman TR, Yeckel CW, Papademetris X, Constable RT, Weiss R, Tamborlane WV, Savoye M, Seyal AA, Caprio S. Alanine aminotransferase levels and fatty liver in childhood obesity: associations with insulin resistance, adiponectin, and visceral fat. *J Clin Endocrinol Metab* 2006; **91**: 4287-4294
24 **Pratt DS**, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med* 2000; **342**: 1266-1271
25 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231
26 **Bloomgarden ZT**. Nonalcoholic fatty liver disease and insulin resistance in youth. *Diabetes Care* 2007; **30**: 1663-1669
27 **Hui JM**, Sud A, Farrell GC, Bandara P, Byth K, Kench JG, McCaughan GW, George J. Insulin resistance is associated with

chronic hepatitis C virus infection and fibrosis progression [corrected]. *Gastroenterology* 2003; **125**: 1695-1704

28 **Kiechl S**, Willeit J, Poewe W, Egger G, Oberhollenzer F, Muggeo M, Bonora E. Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study). *BMJ* 1996; **313**: 1040-1044

29 **Newman WP**, Brodows RG. Aspirin causes tissue insensitivity to insulin in normal man. *J Clin Endocrinol Metab* 1983; **57**: 1102-1106

30 **Quirós-Tejeira RE**, Rivera CA, Ziba TT, Mehta N, Smith CW, Butte NF. Risk for nonalcoholic fatty liver disease in Hispanic youth with BMI > or =95th percentile. *J Pediatr Gastroenterol Nutr* 2007; **44**: 228-236

31 **McLaughlin T**, Abbasi F, Lamendola C, Liang L, Reaven G, Schaaf P, Reaven P. Differentiation between obesity and insulin resistance in the association with C-reactive protein. *Circulation* 2002; **106**: 2908-2912

32 **Ioannou GN**, Weiss NS, Boyko EJ, Kahn SE, Lee SP. Contribution of metabolic factors to alanine aminotransferase activity in persons with other causes of liver disease. *Gastroenterology* 2005; **128**: 627-635

33 **Park HS**, Han JH, Choi KM, Kim SM. Relation between elevated serum alanine aminotransferase and metabolic syndrome in Korean adolescents. *Am J Clin Nutr* 2005; **82**: 1046-1051

34 **Chang Y**, Ryu S, Sung E, Jang Y. Higher concentrations of alanine aminotransferase within the reference interval predict nonalcoholic fatty liver disease. *Clin Chem* 2007; **53**: 686-692

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