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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1708 – 1713
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

The association of low-grade inflammation, urinary albumin, and insulin resistance with metabolic syndrome in nondiabetic Taiwanese

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Received 2 April 2007; accepted 30 July 2007

Abstract

Metabolic syndrome, which involves different pathological mechanisms in associated disorders including inflammation, endothelial dysfunction, and insulin resistance, results in the development of cardiovascular diseases. The effect of the accumulative abnormalities of metabolic components and the relationship of each component to these associated disorders have not been clearly delineated. We therefore conducted a cross-sectional study to investigate the accumulative effect and the correlation of components of the metabolic syndrome to C-reactive protein (CRP), urinary albumin excretion (UAE), and the homeostasis model assessment for insulin resistance index (HOMA-IR). A total of 200 nondiabetic subjects received assessment of metabolic syndrome and measurements of serum CRP, UAE, and HOMA-IR. As the number of abnormalities of metabolic syndrome increased in subjects, the CRP, UAE, and HOMA-IR were significantly elevated (P value for trend less than .001, all). Waist circumference was an independent risk factor for CRP ($P = .012$); waist circumference and systolic blood pressure were independent risk factors for UAE ($P = .010$ and $P < .001$, respectively); and waist circumference, triglyceride, and glucose were independent risk factors for HOMA-IR ($P < .001$, all). More metabolic abnormalities were associated with higher risk of inflammation, urinary albumin, and insulin resistance. Waist circumference was the only independent risk factor for all 3 associated diseases in metabolic syndrome.

1. Introduction

Metabolic syndrome (MS), a clustering of metabolic factors, is associated with the development of cardiovascular disease; and the high prevalence makes it a serious public health problem [1-3]. The definition of the World Health Organization emphasized insulin resistance and included increased urinary albumin as one of the components of MS [4]. According to the *Third Report of the National Cholesterol Education Program* (NCEP), MS is also associated with inflammation and microalbuminuria [5-7]. However, abdominal obesity is considered a necessary component of MS by the new definition of the International Diabetes Federation; and the cutoff values vary according to ethnic differences [8,9]. Different physiological mechanisms such as inflammation, endothelial dysfunction, and insulin resistance are associated with various components of MS [10,11]. Abnormal glucose level is a necessary component by the World Health Organization definition, and high blood pressure was thought as the most important component by previous studies of MS [4,10,11]. It is not known whether central obesity is predominantly associated with an underlying pathophysiologic process of MS. We therefore conducted a cross-sectional study to investigate the relationship of each component of MS to the associated disorders, including inflammation, urinary albumin, and insulin resistance, in a group of nondiabetic Taiwanese.

2. Subjects and methods

2.1. Subjects

This study was conducted at an outpatient clinic of the Division of Endocrinology and Metabolism in Taichung

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doi:10.1016/j.metabol.2007.07.015

Veterans General Hospital, Taichung, Taiwan. The candidates, between 18 and 85 years of age, were screened. Exclusion criteria were as follows: (1) history of diabetes, taking antidiabetic medications, or fasting glucose of more than 125 mg/dL; (2) acute or chronic infectious disease; (3) severe systemic disease such as end-stage renal disease, liver cirrhosis, or immune disorder; and (4) change in medications for hypertension, hyperlipidemia, antiplatelet, or anti-inflammation in the past month. The participants were recruited from the patients or their family members in the outpatient department and volunteers of our hospital staff. The study was approved by the Institutional Review Board of Taichung Veterans General Hospital. The purpose and potential risks of the study were explained to the study subjects, and informed consents were obtained.

2.2. Methods

Overnight fasting blood samples for measurement of serum glucose, lipoprotein profiles, insulin, and C-reactive protein (CRP) levels were collected. Fasting glucose levels were measured by the glucose oxidase-peroxidase method (Wako Diagnostics, Tokyo, Japan). Serum cholesterol and triglyceride levels were assayed using commercial test kits (Merck, Darmstadt, Germany). High-density lipoprotein (HDL) cholesterol concentration was determined after the precipitation of apolipoprotein B–containing lipoproteins by phosphotungstic acid and magnesium chloride reagent [12]. Low-density lipoprotein (LDL) cholesterol level was calculated according to the method of Friedewald et al [13] once fasting serum triglyceride levels were less than 400 mg/dL. Otherwise, the LDL cholesterol level was determined after separation of very low-density lipoprotein from serum by ultracentrifugation and precipitation of apolipoprotein B–containing particles with phosphotungstic acid and magnesium chloride reagent. Serum insulin was determined by commercially available assay kit (IMMULITE, I-2000; EURO/Diagnostic Products, Gwynedd, United Kingdom) for a quantitative evaluation of insulin resistance according to the homeostasis model assessment (HOMA) described by Matthews et al [14]. The HOMA insulin resistance (HOMA IR) index = [fasting insulin (in micro–international units per milliliter) * fasting glucose (in millimoles per liter)]/22.5. C-reactive protein was measured by immunochemical assay using purified duck immunoglobulin Y antibodies (Good Biotech, Taichung, Taiwan) [15]. Urinary spot samples were collected after rest for analysis of urinary albumin and creatinine. The urinary albumin excretion (UAE) was expressed by 1000*albumin/creatinine. Based on the modified NCEP criteria, there were 5 components of MS, as follows: (1) waist circumference more than 90 cm in men or 80 cm in women [8,9,16], (2) triglycerides equal to or more than 150 mg/dL, (3) HDL cholesterol less than 40 mg/dL in men or 50 mg/dL in women, (4) blood pressure equal to or more than 130/85 mm Hg or using antihypertensive medications, and (5) fasting glucose between 100 and 125 mg/dL [8,16,17]. Metabolic syndrome was diagnosed if 3 or more of the above components were present [5].

2.3. Statistical analyses

The subjects were divided into 5 groups—0, 1, 2, 3, and 4/5 factors—according to the number of abnormal components of MS each subject had [5,6]. All descriptive data were presented as mean ± SEM. The nonparametric Kruskal-Wallis test was conducted to detect the difference among the 5 groups. The χ^2 test was used to assess the differences in sex in the groups. Multivariate logistic regression analyses were used to analyze the relationship of associated disorders, including CRP, UAE, and HOMA-IR, to MS. The relationships between the components of MS and the associated disorders were determined by Pearson correlation. Multivariate linear regression analyses were used to assess the standardized coefficient of each component of MS to the associated disorders. Because

Table 1
Clinical data of study subjects categorized by the number of positive components in MS based on the modified NCEP criteria

	0	1	2	3	4/5	*P*
Patient number	15	51	51	48	35	
Sex (male/female)	9/6	32/19	32/19	29/19	18/17	.845
Age (y)	60 ± 2	64 ± 2	64 ± 1	65 ± 2	63 ± 2	.362
Smoking (pack-y)	14 ± 7	7 ± 3	10 ± 3	8 ± 2	8 ± 2	.558
Body mass index (kg/m^2)	21.6 ± 0.7	23.0 ± 0.5	24.7 ± 0.4	25.7 ± 0.5	26.5 ± 0.5	<.001
Waist (cm)	78.5 ± 1.7	84.5 ± 1.0	88.7 ± 1.2	93.2 ± 1.0	92.9 ± 1.2	<.001
Systolic BP (mm Hg)	111 ± 3	121 ± 3	126 ± 3	136 ± 3	132 ± 4	<.001
Diastolic BP (mm Hg)	67 ± 3	70 ± 2	72 ± 1	75 ± 2	74 ± 2	.075
Fasting glucose (mg/dL)	84 ± 2	90 ± 1	96 ± 1	100 ± 2	103 ± 2	<.001
Triglyceride (mg/dL)	85 ± 7	102 ± 6	130 ± 11	142 ± 10	220 ± 15	<.001
HDL cholesterol (mg/dL)	71 ± 8	57 ± 2	50 ± 2	50 ± 3	41 ± 1	<.001
Total cholesterol (mg/dL)	179 ± 9	192 ± 6	186 ± 5	185 ± 5	195 ± 5	.485
LDL cholesterol (mg/dL)	91 ± 15	115 ± 5	109 ± 3	106 ± 4	110 ± 5	.641
CRP (mg/L)	1.1 ± 0.3	1.4 ± 0.2	1.7 ± 0.3	2.2 ± 0.3	2.7 ± 0.7	.026
UAE (mg/g)	5 ± 1	21 ± 9	50 ± 22	64 ± 34	71 ± 39	<.001
HOMA-IR	1.1 ± 0.2	1.5 ± 0.1	2.2 ± 0.2	2.6 ± 0.3	3.1 ± 0.3	<.001

BP indicates blood pressure.

of skewed distribution, CRP and UAE were logarithm-transformed (log) in analyses. Statistical analysis was performed by SPSS 10.0 (SPSS, Chicago, IL).

3. Results

A total of 211 subjects were screened, and 11 subjects were excluded because of criteria or incomplete data. There were 200 subjects enrolled in this study. There were no significant differences in age or sex among these 5 groups. The data of all the subjects are shown in Table 1. Waist circumference was significantly different among these 5 groups ($P < .001$). The systolic blood pressure ($P < .001$), but not diastolic blood pressure ($P = .075$), was significantly different. Fasting serum concentrations of triglyceride and HDL cholesterol were significantly different ($P < .001$, both), but not total or LDL cholesterol ($P = .485$ and $P = .641$, respectively). The fasting glucose levels were also significantly different among these 5 groups ($P < .001$) (Table 1).

There were significantly progressive increases of CRP (as index of low-grade inflammation), UAE (as index of endothelial dysfunction), and HOMA-IR (as index of insulin resistance) as the number of components of MS accumulated ($P = .026$, $P < .001$, and $P < .001$, respectively) (Table 1). All the P values for the test of trend were less than .001 (Fig. 1). After sex and medications, including angiotensin-converting enzyme inhibitors (and/or angiotensin II receptor blockers), β-blockers, antiplatelet drugs, statins, and fibrates, were adjusted by multivariate logistic regression, the CRP was significantly higher in subjects with MS than in those without (odds ratio = 3.012, $P = .003$). Similar results were also found in assessment of UAE (odds ratio = 4.099, $P < .001$) and HOMA-IR (odds ratio = 1.758, $P = .001$) (Table 2).

Table 3 shows the relationship of associated disorders and each component of MS. The CRP was significantly correlated to waist circumference ($r = 0.231$, $P = .001$) and triglyceride ($r = 0.164$, $P = .021$). The UAE was significantly correlated to waist circumference ($r = 0.237$, $P = .001$), systolic blood pressure ($r = 0.319$, $P < .001$), and glucose ($r = 0.199$, $P = .007$). The HOMA-IR was significantly correlated to waist circumference ($r = 0.401$, $P < .001$), triglyceride ($r = 0.344$, $P < .001$), HDL cholesterol ($r = -0.221$, $P = .002$), and glucose ($r = 0.268$, $P = .002$) (Table 3). Among these 5 components of MS, only waist circumference was an independent risk factor for CRP. Waist circumference and systolic blood pressure were independent risk factors for UAE. Waist circumference, triglyceride, and glucose were independent risk factors for HOMA-IR (Table 4).

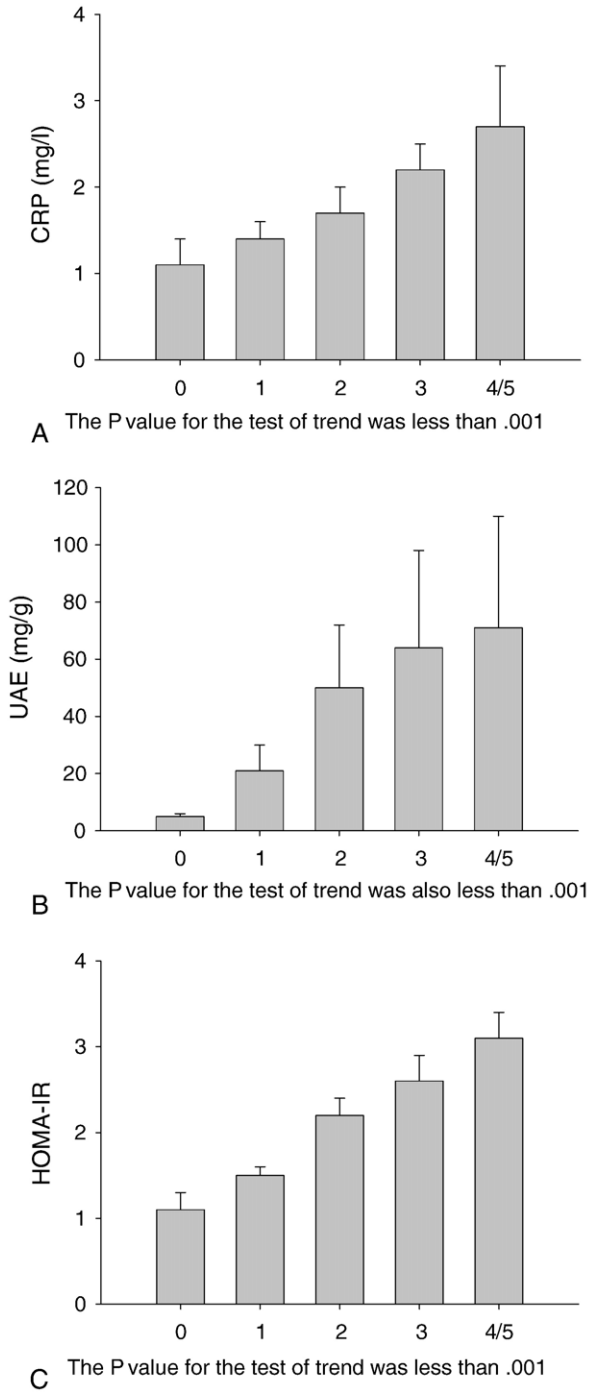

Fig. 1. The more components of MS exist, the more common are the associated laboratory abnormalities. A, C-reactive protein (in milligrams per liter). B, Urinary albumin excretion (in milligrams per gram). C, Homeostasis model assessment for insulin resistance index.

4. Discussion

Metabolic syndrome is an important condition consisting of multiple risk factors for the development of cardiovascular disease. In addition, based on NCEP criteria, when the accumulative abnormal components are increased, the risks of cardiovascular disease are also increased [6]. Recently, it was suggested that the diagnostic thresholds of the components of MS be revised for ethnic differences and fasting glucose level [8,9,16,17]. Inflammation, urinary

Table 2
Logistic regression analysis for MS and the associated disorders

Variable	Odds ratio	95% CI	P
CRP (mg/L)			
No MS	1.000		
MS	3.012	1.445-6.276	.003
UAE (mg/g)			
No MS	1.000		
MS	4.099	1.951-8.609	<.001
HOMA-IR			
No MS	1.000		
MS	1.758	1.263-2.447	.001

Adjusted for age, sex, and medications, including angiotensin-converting enzyme inhibitors (and/or angiotensin II receptor blockers), β-blockers, antiplatelet drugs, statins, and fibrates. No MS means subjects with less than 3 components of MS; MS means subjects with equal to or more than 3 components of MS. C-reactive protein and UAE were logarithm-transformed. CI indicates confidence interval.

albumin, and insulin resistance levels showed a trend toward increase in the number of components by the criteria in our study.

The 5 components of MS may not be related to the same physiological pathway [10]. Wang et al [11] demonstrated that UAE may be thought of as a complication of diabetes and hypertension rather than MS. In a previous National Health and Nutrition Examination Survey III study, greater waist circumference, elevated blood pressure, and high glucose level were independent risk factors for microalbuminuria [7]. Except for diabetes, in an Australian study, hypertension and abdominal obesity, rather than dyslipidemia or impaired glucose intolerance, were independent risk factors for UAE [18]. In our study, we also found that only waist circumference and systolic blood pressure were independent risk factors for UAE; on the other hand, waist circumference, triglyceride, and glucose were independent risk factors for insulin resistance. Consistent with the results of our study, several reports indicated that greater waist circumference and hypertriglycemia of MS were most associated with hyperinsulinemia [19-21].

C-reactive protein is associated with the development of macrovascular disease in subjects with MS [6,22]. Hoekstra et al [23] demonstrated that the effects of MS on inflammation were dependent on body fat. In our study, waist circumference in MS was the most powerful independent risk factor for CRP. In agreement with our

Table 3
The correlation coefficient (r) between the components of MS and the associated disorders

	CRP	UAE	HOMA-IR
Waist	0.231 *	0.237 *	0.401 *
Systolic BP	0.021	0.319 *	0.042
Triglyceride	0.164 *	0.062	0.344 *
HDL cholesterol	−0.108	−0.103	−0.221 *
Fasting glucose	0.116	0.199 *	0.456 *

* $P < .05$.

Table 4
Assessment of the risk factors of the associated disorders by linear regression

	B [a]	β [b]	95% CI	P
Risk factor of CRP (mg/L)				
Waist (cm)	0.01061	0.190	0.002 to 0.019	.012
Systolic BP (mm Hg)	0.00014	0.006	−0.003 to 0.003	.927
Triglyceride (mg/dL)	0.00068	0.112	0.000 to 0.002	.125
HDL cholesterol (mg/dL)	−0.00072	−0.026	−0.005 to 0.003	.727
Glucose (mg/dL)	0.00161	0.042	−0.004 to 0.007	.571
Risk factor of UAE (mg/g)				
Waist (cm)	0.01330	0.195	0.003 to 0.023	.010
Systolic BP (mm Hg)	0.00813	0.308	0.005 to 0.012	<.001
Triglyceride (mg/dL)	−0.00006	−0.009	−0.001 to 0.001	.905
HDL cholesterol (mg/dL)	−0.00036	−0.011	−0.005 to 0.005	.885
Glucose (mg/dL)	0.00570	0.118	−0.001 to 0.013	.108
Risk factor of HOMA				
Waist (cm)	0.00776	0.249	0.004 to 0.012	<.001
Systolic BP (mm Hg)	0.00005	0.004	−0.001 to 0.001	.939
Triglyceride (mg/dL)	0.00080	0.234	0.000 to 0.001	<.001
HDL cholesterol (mg/dL)	−0.00053	−0.034	−0.002 to 0.001	.582
Glucose (mg/dL)	0.00760	0.349	0.005 to 0.010	<.001

[a] B = linear regression coefficient, meaning change in log-transformed CRP, UAE, or HOMA per unit change in the components of metabolic syndrome.

[b] β = standardized coefficient, meaning the power of change in log-transformed CRP, UAE, or HOMA.

study results, several studies demonstrated that waist circumference was an independent risk factor for CRP [24,25]. In the study by Piche et al [26], visceral adipose tissue was thought to be the determining factor for high CRP in MS. In a Korean study, an increased trend in the serum CRP levels and HOMA-IR was found as the number of the components of MS increased [27]. In our study, we demonstrated that not only CRP and HOMA-IR but also UAE had a tendency to increase, as indicated by the number of metabolic abnormalities. Furthermore, we found that waist circumference was the only independent risk factor for UAE, HOMA-IR, and CRP; it also showed significant correlation with UAE, HOMA-IR, and CRP.

Hypertension is a major risk factor for cardiovascular disease, and treatment of blood pressure dose not remove all of the cardiovascular risk; therefore, treated hypertension is still a risk factor for cardiovascular disease [5,28]. Diagnosed hypertension treated by hypertensive medications is also counted as a component of MS by the International Diabetes Federation definition [8]. Therefore, the treated hypertension was included as the component of elevated blood pressure in our study because elevated blood pressure, even for a short period before treatment, will result in endothelial dysfunction [29].

In our study, systolic blood pressure showed significant difference between groups, but not diastolic blood pressure. There was a greater difference between systolic and diastolic blood pressure in subjects with MS (59 ± 2 mm Hg) than in those without MS (51 ± 1 mm Hg) ($P < .001$). However, the association between MS and uncontrolled

isolated systolic hypertension was not confirmed in large-scale studies [30,31].

This cross-sectional study demonstrated that central obesity was involved in inflammation, urinary albumin, and insulin resistance. However, obesity is a more difficult issue for clinical practice than other risk factors [32,33]. The effect of treatment of obesity, as compared with other risks, should be assessed in a long-term prospective study.

In conclusion, the low-grade inflammation, urinary albumin, and insulin resistance revealed a trend toward an increase in the number of metabolic abnormalities according to the modified NCEP criteria. Our study also revealed the relatively more powerful association of central obesity, as compared with other components of MS, on CRP, UAE, and HOMA-IR.

Acknowledgment

This study was supported by a grant from Taichung Veterans General Hospital, Taichung, Taiwan, ROC (TCVGH-953503A).

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