White Coat Hypertension in Definition of Metabolic Syndrome

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SUMMARY

Although white coat hypertension (WCH) is believed to have an effect on health, there is no term defining WCH in metabolic syndrome.

Consecutive patients 20 years old or older who underwent a check-up were included. The study included 1068 cases. The prevalences of hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, impaired glucose tolerance (IGT), and WCH were similar to excess weight in that they increased significantly until the seventh decade of life and decreased thereafter significantly ($P < 0.05$ in most steps). On the other hand, the prevalences of hypertension (HT), diabetes mellitus (DM), and coronary heart disease (CHD) always increased significantly with age without any decrease ($P < 0.05$ in most steps), indicating their irreversibility in contrast to the reversibility of excess weight, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IGT, and WCH.

Metabolic syndrome is a reversible progression step between health and irreversible final diseases terminating with increased mortality and disabilities. Thus, the definition of metabolic syndrome should include reversible metabolic risk factors such as excess weight (overweight and obesity), hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IGT, and WCH, instead of irreversible diseases such as DM, HT, CHD, and stroke that have already developed and require drug therapy. After development of one of the final metabolic diseases, the term metabolic syndrome probably loses most of its significance, since from that point on, nonpharmaceutical approaches such as lifestyle changes, diet, and exercise will provide little benefit to prevent development of the others, most likely due to the cumulative effects of the risk factors on body systems over a long period of time. (Int Heart J 2008; 49: 449-457)

Key words: White coat hypertension, Metabolic syndrome, Excess weight, Dyslipidemia, Impaired glucose tolerance

AN association between certain metabolic parameters and hypertension (HT), type 2 diabetes mellitus (DM), coronary heart disease (CHD), stroke, and eventually an increased all-cause mortality has been known for many years and is

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Received for publication January 9, 2008.

Revised and accepted June 13, 2008.

defined as metabolic syndrome.^{1,2)} Metabolic syndrome is characterized by a group of metabolic risk factors, including obesity, dyslipidemia, elevated blood pressure (BP), insulin resistance, and a prothrombotic and proinflammatory state,³⁾ and is not a specific disease since it can be reversed completely with appropriate nonpharmaceutical approaches including lifestyle changes, diet, and exercise.⁴⁾ Therefore, it actually includes risk factors for the development of irreversible final diseases which decrease the duration and/or quality of normal life such as HT, DM, CHD, and stroke. Metabolic syndrome has become increasingly common in developed countries; for example, it is estimated that 50 million Americans have it.⁵⁾ On the other hand, white coat hypertension (WCH) is a well-known clinical entity defined as a persistently elevated BP in the doctor's office whereas normal in other conditions. It was reported in the Ohasama study⁶⁾ that WCH is a risk factor for development of home HT. Similarly, intima-media thickness and cross-sectional area of the carotid artery were found to be similar in patients with WCH and HT, which were significantly higher than in cases with sustained normotension (NT).⁷⁾ Additionally, plasma homocysteine levels were higher, and left ventricle mass index was greater in the WCH group compared to NT cases ($P < 0.001$ in both), but they were significantly lower in the WCH group than HT cases in another study ($P < 0.001$ and $P = 0.005$, respectively).⁸⁾ Although it is highly suspected that WCH has clinical significance for human health, there is no term defining WCH in metabolic syndrome. In the present study, we have attempted to determine the position of WCH in the definition of metabolic syndrome.

METHODS

The study was performed at the Internal Medicine Polyclinic of Dumlupinar University between August 2005 and March 2007. Consecutive patients 20 or older applying for a medical check-up were enrolled. Their medical histories including smoking habit, DM, dyslipidemia, and current medications were taken, and routine tests such as fasting plasma glucose (FPG), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and electrocardiography were performed. Current regular smokers, defined as those who had smoked for at least for the last 6 months, and cases with a previous smoking history of at least 5 pack-years were classified as smokers. Cigar or pipe smokers were excluded. Patients with devastating illnesses including type 1 DM, malignancies, acute and chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. The body mass index (BMI) of each case was calculated based on measurements taken by the physician. Weight in kilograms was

divided by height in meters squared. Underweight was defined as a BMI below 18.5, normal weight as 18.5-24.9, overweight as 25-29.9, and obesity as a BMI of 30.0 kg/m² or greater.⁹⁾ Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already taking antidiabetic medications were defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 126 mg/dL, and cases with a 2-hour plasma glucose level of 200 mg/dL or higher were diagnosed with DM while 140-199 mg/dL was considered to indicate impaired glucose tolerance (IGT). Patients with dyslipidemia were identified and dyslipidemic subgroups were defined using the National Cholesterol Education Program Expert Panel's recommendations.⁹⁾ Dyslipidemia was diagnosed when LDL-C was 160 or higher and/or TG were 200 or higher and/or HDL-C was lower than 40 mg/dL. Stress electrocardiography was performed in cases with a history of angina pectoris or suspected of having angina pectoris on electrocardiography, and coronary angiography was only performed in stress electrocardiography positive cases. Thus, CHD was diagnosed either angiographically or based on a history of coronary artery bypass graft surgery. Office blood pressure (OBP) was checked after a 5-minute rest in a seated position with a mercury sphygmomanometer on 3 visits, and no smoking was permitted during the 2 preceeding hours. Home blood pressure (HBP) was measured twice daily for 10 days in all cases, even in normotensives in the office due to the risk of masked HT, after a 10-minute explanation about proper BP measurement techniques.¹⁰⁾ The patients were advised to perform upper arm measurements using a standard adult cuff with bladder sizes of 12 × 26 cm for arm circumferences up to 33 cm in length, and a large adult cuff with bladder sizes of 12 × 40 cm for arm circumferences up to 50 cm in length. They were also advised to rest for at least 5 minutes in the seated position before taking a measurement. The use of wrist and finger devices was discouraged. An additional 24-hour ambulatory blood pressure monitoring (ABP) was obtained only in cases with a higher OBP and/or HBP measurements and was performed with oscillometrical equipment (SpaceLabs 90207, Redmond, Washington, USA) set to take a reading every 10 minutes throughout a 24-hour period. Normal daily activities were allowed and the subjects were asked to keep the arm as relaxed as possible during measurements. HT is defined as a BP of 135/85 mmHg or greater during the daytime (between 10 AM to 8 PM) ABP.¹⁰⁾ WCH is defined as an OBP of 140/90 mmHg or greater with a mean daytime ABP of < 135/85 mmHg and sustained NT as an OBP of < 140/90 mmHg together with an average HBP of < 135/85 mmHg.¹⁰⁾ The prevalences of smoking, excess weight (overweight and obesity), hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IGT, DM, WCH, HT, and CHD were determined for each decade, and the prevalences were compared between the decades. The comparison of proportions method was

used in the statistical analyses.

RESULTS

The study included 1068 cases (628 females and 440 males). The characteristics of the study patients are presented in Table I. Due to the small number of cases in the ninth decade (only 20 cases), they were not included in the statistical comparisons. The prevalence of smoking showed a significant increase from the third to the fourth decade (11.0% versus 32.4%, $P < 0.001$), following which it remained almost stable at between 25% and 30%. As there were only 19 (1.7%) underweight cases and 307 (28.7%) normal weight cases, the prevalence of cases 20 years old or more with excess weight, 69.4% (742), was very high. The prevalence of excess weight increased gradually from 28.7% in the third decade to 87.0% in the seventh decade ($P < 0.05$ in most steps), and then decreased to 78.5% in the eighth decade ($P < 0.05$) and to 60.0% in the ninth decade of life. Interestingly, the prevalence of excess weight showed its most significant increase from the third to fourth decades (28.7% versus 63.6%, t -test value: 9.64,

Table I. Characteristics of the Study Cases

Variable	Third decade	<i>P</i>	Fourth decade	<i>P</i>	Fifth decade	<i>P</i>	Sixth decade	<i>P</i>	Seventh decade	<i>P</i>	Eighth decade
Number	181		157		246		249		108		107
Prevalence of smoking	11.0% (20)	***	32.4% (51)	ns†	28.8% (71)	ns	31.7% (79)	ns	23.1% (25)	ns	23.3% (25)
Prevalence of excess weight	28.7% (52)	***	63.6% (100)	***	78.4% (193)	ns	83.1% (207)	ns	87.0% (94)	*	78.5% (84)
Prevalence of hyperbetalipoproteinemia	1.6% (3)	***	12.7% (20)	ns	15.8% (39)	ns	19.6% (49)	ns	23.1% (25)	*	14.0% (15)
Prevalence of hypertriglyceridemia	5.5% (10)	***	15.2% (24)	*	20.3% (50)	*	25.7% (64)	ns	24.0% (26)	**	11.2% (12)
Prevalence of dyslipidemia	6.6% (12)	***	26.7% (42)	ns	31.7% (78)	*	38.9% (97)	ns	39.8% (43)	***	20.5% (22)
Prevalence of IGT‡	0.5% (1)	ns	1.2% (2)	***	10.1% (25)	***	19.6% (49)	ns	21.2% (23)	ns	15.8% (17)
Prevalence of diabetes mellitus	0.5% (1)	ns	1.9% (3)	***	11.7% (29)	***	21.6% (54)	ns	25.0% (27)	ns	26.1% (28)
Prevalence of white coat hypertension	23.2% (42)	ns	24.2% (38)	**	33.3% (82)	***	44.5% (111)	ns	40.7% (44)	**	25.2% (27)
Prevalence of hypertension	0.0% (8)	**	5.0% (8)	***	10.4% (26)	***	20.4% (51)	**	31.4% (34)	ns	38.3% (41)
Prevalence of CHD§	0.0% (9)	ns	0.0% (9)	*	3.6% (9)	***	12.8% (32)	**	22.2% (24)	ns	24.2% (26)

* $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$ † Nonsignificant ($P > 0.05$) ‡ Impaired glucose tolerance §Coronary heart disease

Table II. Mean Blood Pressure Values of the Study Cases

Variable	Sustained normotension (n = 551)	WCH* (n = 349)	Hypertension (n = 168)
Prevalence	51.5%	32.6%	15.7%
Mean age and range (year)	38.8 ± 12.3 (15-83)	48.2 ± 11.3 (15-79)	55.3 ± 10.3 (33-85)
Female ratio	57.1% (315)	63.3% (221)	65.4% (110)
Mean OBP†	117.3 ± 4.7/78.3 ± 5.1	153.3 ± 5.4/97.3 ± 9.3	167.5 ± 5.6/108.3 ± 5.7
Mean HBP‡	97.7 ± 13.3/73.1 ± 5.1	121.1 ± 5.5/74.1 ± 5.3	149.5 ± 6.3/97.3 ± 7.3
Mean ABP§	Not performed	123.7 ± 5.3/77.1 ± 5.3	150.7 ± 7.7/98.7 ± 7.3
Mean heart rate (beats/minute)	65.1 ± 11.5 (52-129)	75.3 ± 13.3 (61-149)	80.5 ± 11.3 (63-167)

*White coat hypertension †Office blood pressure ‡Home blood pressure §24-hour ambulatory blood pressure monitoring

$P < 0.001$), a pattern that was similar to that for smoking. The most significant finding of our study was that the prevalences of hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IGT, and WCH increased significantly until the seventh decade and then decreased significantly, which was similar to that for excess weight ($P < 0.05$ in most steps). On the other hand, the prevalences of HT, DM, and CHD always increased significantly with age and did not decrease ($P < 0.05$ in most steps), indicating the increases were irreversible as opposed to the reversible patterns of excess weight, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IGT, and WCH. On the other hand, 517 cases with WCH and HT were diagnosed based on both HBP and ABP, and no difference was observed between the two methods according to the total number of cases diagnosed. Mean systolic/diastolic OBP, HBP, and ABP values and mean heart rates of the groups are summarized in Table II.

DISCUSSION

Metabolic syndrome is a collection of metabolic risk factors for many terminal diseases. Although there is no universally accepted definition for the syndrome, it basically includes 5 features: obesity (high body weight, BMI, or waist circumference), high glucose and insulin levels, low HDL-C, high TG, and high BP.¹¹⁾ However, the currently used definitions of a BP of 135/85 or 140/90 mmHg or above and a FPG of 100 or 110 mg/dL or above also include patients with DM and HT. In actual fact, the syndrome is a collection of risk factors rather than a final disease or diseases, and the condition is reversible with appropriate non-pharmaceutical approaches. On the other hand, HT, DM, and symptomatic atherosclerosis are irreversible and final states that almost always require drug therapy to delay complications. For example, in our study, the prevalences of hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IGT, and WCH

increased significantly in parallel to excess weight until the seventh decade and then subsequently decreased ($P < 0.05$ in most steps). On the other hand, the prevalences of HT, DM, and CHD always continued to increase with age without any decrease ($P < 0.05$ in most steps), indicating they were irreversible conditions. Therefore, metabolic syndrome alone is a disadvantageous but reversible condition and not a final disease, and after the development of one of the final metabolic diseases, the term metabolic syndrome probably loses most of its significance since from that point on the nonpharmaceutical approaches will provide little benefit to prevent development of the others, most likely due to the cumulative effects of the risk factors on organ systems over a long period of time. Thus, the definition of metabolic syndrome should include reversible metabolic risk factors such as excess weight (overweight and obesity), hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IGT, and WCH, but not HT, DM, CHD, and stroke-like terminal diseases.

Several authors reported that WCH is associated with some features of metabolic syndrome,¹²⁾ and more than 85% of cases with metabolic syndrome have elevated BP levels.⁴⁾ On the other hand, we observed very high prevalences of WCH even in younger subjects in the early decades of life; 23.2% in the third decade and 24.2% in the fourth decade. The high prevalences of WCH in society were also shown in other studies.¹³⁻¹⁵⁾ When we compared the sustained NT, WCH, and HT groups in another study,¹⁶⁾ the prevalences of nearly all of the health problems including obesity, IGT, DM, and CHD showed significant progression from the sustained NT group towards the WCH and HT groups, with the WCH group being found to be an intermediate step in between. It is interesting that the prevalence of dyslipidemia was the highest in the WCH group; 41.6% versus 19.6% ($P < 0.001$) in the sustained NT group and 35.5% in the HT group ($P < 0.05$).¹⁶⁾ Similar results indicating the higher prevalences of dyslipidemia in WCH cases were also observed in one of our previous studies,¹⁷⁾ which is in direct contrast to another study indicating serum TG and cholesterol levels did not differ significantly between NT, WCH, and sustained HT cases in males.¹⁸⁾ The relatively lower prevalence of dyslipidemia in the HT group may be explained by the already increased amount of adipose tissue per taken fat in the HT cases, since the prevalence of obesity was significantly higher in the HT group than in the WCH group ($P < 0.01$).¹⁶⁾ Therefore, the detected higher prevalences of WCH even in early decades, despite the lower prevalences of excess weight in these age groups, may indicate a trend towards weight gain and many final diseases. Most if not all of these relationships are closely related with the metabolic syndrome since WCH and dyslipidemia are two significant components of the syndrome, at least according to our opinion. On the other hand, we accept WCH as a different entity from borderline/mild HT due to the completely normal HBP and ABP values of

WCH, whereas they are abnormal in mild HT cases. However, both kinds of patients can benefit from lifestyle modification including exercise, weight loss, and a diet low in animal products and high in fresh fruits and vegetables.

It is already known that excess weight leads to both structural and functional abnormalities in many systems of the body, as well as a higher risk of death from all causes, including cardiovascular diseases and cancers, and increases parallel to the range of moderate to severe weight excess in all age groups.¹⁹⁾ The effects of body weight on BP were also demonstrated previously by us when we found that the prevalence of sustained NT was significantly higher in underweight cases (80.3%) than normal weight (64.0%) and overweight cases (31.5%)²⁰⁾ ($P < 0.05$ for both), and in another study that 55.1% of cases with HT were obese compared to 26.6% of cases with NT ($P < 0.001$).²¹⁾ Thus, the dominant underlying risk factor of the metabolic syndrome appears to be already existing excess weight⁴⁾ or a trend towards excess weight, which is probably the main cause of insulin resistance, dyslipidemia, IGT, and WCH. Even prevention of the accelerating trend of body weight with diet or exercise, even in the absence of prominent weight loss, will probably result with resolution of many parameters of the metabolic syndrome.²²⁻²⁴⁾ However, it is our opinion that limitation of excess weight as excessive fat tissue in and around the abdomen under the heading of abdominal obesity is meaningless, and instead should be defined as excess weight including overweight and obesity via BMI, since adipocytes function as an endocrine organ that produces a variety of cytokines and hormones anywhere in the body.⁴⁾ The resulting hyperactivity of the sympathetic nervous system and renin-angiotensin-aldosterone system is most likely associated with insulin resistance, endothelial dysfunction, and elevated BP. Similarly, the Adult Treatment Panel III reported⁹⁾ that although some people are classified as overweight due to a large muscular mass, most of them also have excess fat tissue, and being overweight and obese do not only predispose a person to CHD, stroke, and numerous other conditions, they also have a high burden of other CHD risk factors including type 2 DM, HT, and dyslipidemia.

In conclusion, metabolic syndrome is a reversible progression step between physical health and irreversible final diseases terminating with increased mortality and disabilities. Thus, the definition of metabolic syndrome should include reversible metabolic risk factors such as excess weight (overweight and obesity), hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, IGT, and WCH, instead of irreversible diseases such as DM, HT, CHD, and stroke that have already developed and require drug therapy. After development of one of the final metabolic diseases, the term metabolic syndrome probably loses most of its significance, since from now on, nonpharmaceutical approaches such as lifestyle changes, diet, and exercise will provide little benefit to prevent development of

the others, most likely due to the cumulative effects of the risk factors on body systems over a long period of time.

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