White coat hypertension may actually be an acute phase reactant in the body

Mehmet Rami Helvaci (1)
Orhan Ayyildiz (1)
Orhan Ekrem Muftuoglu (1)
Mehmet Gundogdu (1)
Abdulrazak Abyad (2)
Lesley Pocock (3)

(1) Professor of Internal Medicine, MD
(2) Middle-East Academy for Medicine of Aging, MD, MPH, MBA, AGSF
(3) medi-WORLD International

Correspondence:
Mehmet Rami Helvaci, MD
07400, ALANYA, Turkey
Phone: 00-90-506-4708759
Email: mramihelvaci@hotmail.com

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Abstract

Background: We tried to understand the significance of white coat hypertension (WCH), clinically.

Methods: We took consecutive underweight patients in the first phase, and age-matched consecutive patients with normal weight, overweight, and obesity in the second phase of the study.

Results: Although we were able to detect 50 cases in the underweight group with a mean age of 24.7 years, we were only able to detect nine age-matched cases in the obesity group, thus the obesity group was not taken for comparison. There were gradual and statistically significant increases in the prevalence of WCH beside the gradual and significant decreases in the sustained normotension (NT) from the underweight towards the normal weight and overweight groups. Eventually, only 31.8% of the overweight cases had sustained NT although they had very young mean age.

Conclusions: Due to the gradually increased prevalence of WCH from the underweight towards the normal weight and overweight groups and the very low prevalence of sustained NT in the overweight group despite their very young mean age and the already known increased prevalence of hypertension, impaired fasting glucose, impaired glucose tolerance, type 2 diabetes mellitus, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, coronary artery disease, chronic obstructive pulmonary disease, cirrhosis, chronic renal disease, and stroke and an increased all-cause mortality rate in the same direction, WCH may actually be an acute phase reactant, mainly alarming overweight and obesity and many associated health problems in future.

Key words: White coat hypertension, acute phase reactant, overweight, obesity

Introduction

In recent years, overweight and obesity have become major health problems particularly in developed countries. For example, 30% of adults in the United States can be classified as obese (1). Overweight and obesity are characterized by increased mass of adipose cells that result from a systemic imbalance between food intake and energy expenditure, and they are associated with increased levels of inflammatory parameters and many systemic disorders including white coat hypertension (WCH), hypertension (HT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), type 2 diabetes mellitus (DM), hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), cirrhosis, chronic renal disease (CRD), stroke, and an increased all-cause mortality rate (2-5). Additionally, obesity is highly correlated with dietary intake of increased calories and fat, both of which were linked to several types of cancers (6). For example, in a recent study performed among 900,000 people it was found that obese individuals were more likely to die from a number of cancers including breast, colon, and prostate (7). On the other hand, cardiovascular death, myocardial infarction, and stroke are the most common causes of deaths particularly in the developed countries again, and most of them are related with increased blood pressure (BP) (8). Therefore BP control is the mainstay for prevention of cardiovascular deaths. But diagnosis and management of HT is difficult due to the fact that BP varies greatly depending on physical and mental stresses. WCH is a well-known clinical entity defined as a persistently elevated BP in the doctor's office whereas normal in other conditions, and prognostic significance of it remains controversial (9, 10). For instance, it was reported in an Ohasama study that WCH is a risk factor for development of home HT (11). Similarly, 46.9% of cases with WCH versus 22.2% of cases with sustained normotension (NT) progressed to home HT in an eight-year follow up study (12). So the results demonstrated that WCH is a transitional condition eventually terminating with home HT. Additionally, intima-media thickness and cross-sectional area of carotid artery were found as similar in patients with WCH and HT, which were significantly higher than the sustained NT cases so authors concluded that there is target organ damage in WCH therefore it should not be considered as an innocent trait, clinically (13). Similarly, complication risks of WCH were different from subjects with sustained NT in another study (14). On the other hand, there was not any proof that WCH exhibits a clearly higher risk for cardiovascular events in the above 7.4-year follow up study (10). So most of the already performed studies about WCH have just focused on the progression to home HT in time or whether WCH causes any target organ damage or not. We therefore tried to understand some other possible clinical consequences of WCH in the present study.

Material and methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and August 2006 in two phases. In the first phase, we took consecutive underweight patients between the ages of 15 and 70 years to be able to see the possible consequences of weight on BP and to avoid debility induced weight loss in elders. In the second phase, age-matched consecutive cases with normal weight, overweight, and obesity were detected. Their medical histories including smoking habit and medications were learnt, and a routine check up procedure was performed. Current regular smokers at least for the last 6 months and cases with a previous smoking history of at least five pack-years were accepted as smokers, and cigar or pipe smokers were excluded. Insulin using diabetics and patients with devastating illnesses including malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Body mass index (BMI) of each case was calculated by the measurements of the Same Physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared, and underweight is defined as a BMI of lower than 18.5, normal weight between 18.5-24.9, overweight between 25–29.9, and obesity as a BMI of 30.0 kg/m(2) or higher (15). Office blood pressure (OBP) was checked after a 5-minute rest in seated position with the mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases even in normotensives in the office due to the risk of masked HT after a 10-minute education session about proper BP measurement techniques (16). The education included recommendation of upper arm while discouraging wrist and finger devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest at least for a period of 5 minutes in the seated position before measurement. An additional 24-hour ambulatory blood pressure monitoring (ABP) was not required due to the equal effectiveness of the ABP and HBP measurement techniques for the diagnosis of WCH and HT (17, 18). Eventually, HT is defined as a BP of 135/85 mmHg or greater on mean HBP values (16). WCH is defined as an OBP of 140/90 mmHg or greater, but a mean HBP value of lower than 135/85 mmHg, sustained NT as an OBP of lower than 140/90 mmHg together with an average HBP of lower than 135/85 mmHg, and masked HT as an OBP of lower than 140/90 mmHg but a mean HBP of 135/85 mmHg or greater (16). Prevalence of smoking, sustained NT, WCH, and HT were detected in each group, and results were compared in between. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 417 cases (217 females), totally. The first and second phases took periods of eight and four months, respectively. During the first phase, we were able to detect 50 cases (31 females) with underweight. On the other hand, we were able to detect just nine cases (six females) in the obesity group during the second phase therefore the obesity group was not taken for comparison. Despite the nonsignificant differences according to age in between, female ratios were detected as 62.0% (31 cases), 53.9% (149 cases), and 40.6% (37 cases) in the underweight, normal weight, and overweight groups, respectively (Table 1). So there was a statistically significant ($p<0.05$) male predominance in the overweight group. Beside that there were nonsignificant differences according to the prevalence of smoking between the three groups. There were gradual and statistically significant increases in the prevalence of WCH beside the gradual and significant decreases in the sustained NT from the underweight towards the normal weight and overweight groups. Eventually, the prevalence of WCH reached 68.1% (62 cases) in the overweight group. In other words, only 31.8% (29 cases) of the overweight group had sustained NT despite the very young mean age of the patients. Probably due to the very young mean age, there was only one case of HT among the study cases.

Table 1: Blood pressure variability of the study cases

Variables	Underweight (n= 50)	*p*-value	Normal weight (n= 276)	*p*-value	Overweight (n= 91)
Mean age (year)	24.7 ± 9.1 (15-63)	Ns*	24.3 ± 4.3 (15-39)	Ns	24.7 ± 5.2 (15-33)
Female ratio	62.0% (31)	Ns	*53.9% (149)*	*<0.05*	*40.6% (37)*
Smoking	14.0% (7)	Ns	15.2% (42)	Ns	17.5% (16)
Sustained NT†	*80.0% (40)*	*<0.05*	*64.1% (177)*	*<0.001*	*31.8% (29)*
WCH‡	*20.0% (10)*	*<0.05*	*35.5% (98)*	*<0.001*	*68.1% (62)*
HT§	0% (0)	Ns	0.3% (1)	Ns	0% (0)

*Nonsignificant ($p>0.05$) †Normotension ‡White coat hypertension §Hypertension

Table 2: Comparison of the previous study cases

Variables	Sustained NT* (n= 54)	*p*-value	WCH† (n= 66)	*p*-value	HT‡ (n= 49)	*p*-value§
Female ratio	*38.8%*	*<0.001*	*65.1%*	Ns‖	55.1%	*<0.05*
Mean age (year)	57.3 ± 11.0 (36-80)	Ns	55.3 ± 8.6 (36-75)	Ns	53.0 ± 9.3 (38-76)	Ns
Smoking	*44.4%*	*<0.001*	*13.6%*	*<0.05*	*24.4%*	*<0.01*
Overweight	31.4%	Ns	31.8%	Ns	24.4%	Ns
Obesity	*20.3%*	*<0.05*	*31.8%*	*<0.001*	*55.1%*	*<0.001*
*IGT***	*1.8%*	*<0.05*	*6.0%*	Ns	*8.1%*	*<0.01*
*DM****	*14.8%*	Ns	*18.1%*	*<0.01*	*34.6%*	*<0.001*
Hyperbetalipoproteinemia	*5.5%*	*<0.001*	*19.6%*	Ns	*12.2%*	*<0.05*
Hypertriglyceridemia	*7.4%*	*<0.001*	*21.2%*	Ns	*18.3%*	*<0.01*
Dyslipidemia	*12.9*	*<0.001*	*33.3%*	Ns	*28.5%*	*<0.01*

*Normotension †White coat hypertension ‡Hypertension §Value as a result of the comparison between the sustained NT and HT cases ‖Nonsignificant ($p>0.05$) **Impaired glucose tolerance ***Diabetes mellitus

Discussion

WCH is a condition characterized by elevated BP in medical settings combined with normal ABP or self-measured HBP. As already detected in some other studies (17, 18), both methods were equally effective for the diagnosis of WCH and HT. Similarly, recent HT guidelines propose self-measurement of HBP as an important technique to evaluate response to antihypertensive therapy, to improve compliance with therapy, and as an alternative to ABP to confirm or refute the WCH (19). In the above study (17), we observed very high prevalence of WCH in society, 33.3% in the second, 46.6% in the third, 50.0% in the fourth, 48.9% in the fifth, 36.9% in the sixth, 19.2% in the seventh, and 8.3% in the eighth decades of life, and prevalence of HT initially started to be higher than 40% in the sixth decade, and it reached up to 75% in the eighth decade of life. On the other hand, the prevalence of HT was detected as just 3% in the third, 8% in the fourth, and 21% in the fifth decades of life (17). The high prevalence of WCH in society was also shown in some other reports (20, 21). So as a hypothesis, we come to the result that all HT cases, 75% in the eighth decade of life (17), may arise from the previously WCH cases but WCH may actually be an acute phase reactant for several consequences other than HT alone. Although it was postulated in a recent review (22) that patients with WCH are characterized by absence of target organ damage induced by HT, absence of risk of future cardiovascular disease related to HT, and absence of lowering of BP from antihypertensive treatment, we evaluated WCH not as a cause of HT or atherosclerosis alone but as an acute phase reactant mainly alarming overweight and obesity and many associated disorders in the future, in the present study. When we compared the underweight, normal weight, and overweight groups according to BP variability, beside the significantly decreased prevalence of sustained NT from the underweight towards the normal weight and overweight groups, the prevalence of WCH increased in the same direction, significantly. Eventually, the prevalence of WCH reached up to 68.1% in the overweight group, and only 31.8% of the overweight group have sustained NT although their very young mean. Similarly, in the above study (17), we detected the prevalence of WCH as 33.3% even in the second, and 46.6% in the third decades of life (17), despite the lower prevalence of overweight and obesity in these age groups. On the other hand, when we compared the sustained NT, WCH, and HT groups in another study (18), WCH cases were found in between according to the frequencies of almost all of the following disorders including obesity, IGT, DM, hypertriglyceridemia, hyperbetalipoproteinemia, and dyslipidemia, and nearly all of the disorders showed a gradual and significant progression in frequencies from the sustained NT towards the WCH and HT cases (Table 2). As a surprising result of the above study (18), the prevalence of smoking significantly decreased from the sustained NT towards HT and WCH groups, but actually 38.8% of the sustained NT, 65.1% of the WCH, and 55.1% of the HT cases were female and we totally studied 45 smokers, 39 of those were males. So the highest female ratio of the WCH group showed the lowest smoking ratio and the lowest female ratio of the sustained NT group showed the highest smoking ratio. On the other hand, 20% and 35.5% of WCH cases in the underweight and the normal weight groups, respectively, may indicate that WCH may be an acute phase reactant influenced by several factors instead of BMI alone (23-25).

Authors in the Adult Treatment Panel III reported that some people may be classified as overweight just due to the larger muscular mass that may also explain the significant male predominance of the overweight group in the present study (59.3%, $p<0.05$). But actually most of them have excess body fat tissue, too, and both overweight and obesity predispose to CAD, stroke, dyslipidemia, DM, HT, and numerous other pathologies (15). Similarly, the differences between the normal weight and overweight groups according to the decreasing prevalence of sustained NT and increasing prevalence of WCH were significant in the present study ($p<0.001$ for both). So the larger muscular mass of the males probably does not protect them from the definition of excess weight according to the BMI.

Relationship between excess weight and HT is well-described under the heading of metabolic syndrome, and clinical manifestations of the syndrome include overweight and obesity, dyslipidemia, HT, insulin resistance, and proinflammatory as well as prothrombotic states. Overweight and obesity lead to both structural and functional abnormalities of the cardiovascular system. In general, overweight and obese individuals will have an increased circulating blood volume as well as an increased volume of cardiac output, thought to be the result of increased oxygen demand of the extra body tissue. The prolonged increase in circulating blood volume can lead to myocardial hypertrophy and decreased compliance, in addition to the common comorbidity of HT. In addition to HT, the prevalence of high fasting plasma glucose, high serum total cholesterol, and low high density lipoprotein cholesterol, and their clustering all raised parallel to the increased BMI value (26). Combination of these cardiovascular risk factors will eventually lead to an increase in left ventricular stroke work with a higher risk of arrhythmias, cardiac failure, and sudden cardiac death. The prevalence of CAD and stroke, especially ischemic stroke, increased parallel to the increased BMI values (27). The above prospective cohort study showed that the BMI was one of the independent risk factors of stroke and CAD (26). Eventually, the risk of death from all causes including cardiovascular diseases, cancers, or other diseases increases throughout the range of moderate and severe weight excess for both genders in all age groups (2).

As a conclusion, due to the gradually increased prevalence of WCH from the underweight towards the normal weight and overweight groups and the very low prevalence of sustained NT in the overweight group although the very young mean age of them and the already known increased prevalence of HT, IFG, IGT, DM, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, CAD, COPD, cirrhosis, CRD, and stroke and an increased all-cause

mortality rate in the same direction, WCH may actually be an acute phase reactant mainly alarming overweight and obesity and many associated health problems in future.

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