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Closer look at white-coat hypertension

Sipahioglu NT *et al*. Closer look at white-coat hypertension

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**Abstract**

This review aims to clarify novel concepts regarding the clinical and laboratory aspects of white-coat hypertension (WCHT). Recent studies on the clinical and biological implications of WCHT were compared with existing knowledge. Studies were included if the WCHT patients were defined according to the 2013 European Society of Hypertension guidelines, *i.e.*, an office blood pressure(BP) of ≥ 140/90 mmHg, a home BP of ≤ 135/85 mmHg, and a mean 24-h ambulatory BP of ≤ 130/80 mmHg. WCHT studies published since 2000 were selected, although a few studies performed before 2000 were used for comparative purposes. True WCHT was defined as normal ABPM and home BP readings, and partial WCHT was defined as an abnormality in one of these two readings. The reported prevalence of WCHT was 15%-45%. The incidence of WCHT tended to be higher in females and in non-smokers. Compared with normotensive (NT) patients, WCHT was associated with a higher left ventricular mass index, higher lipid levels, impaired fasting glucose, and decreased arterial compliance. The circadian rhythm in WCHT patients was more variable than in NT patient’s, with a higher pulse pressure and non-dipping characteristics. Compared with sustained hypertension (SHT) patients, WCHT patients have a better 10-year prognosis; compared with NT patients, WCHT patients have a similar stroke risk, but receive more frequent drug treatment. There are conflicting results regarding WCHT and markers of endothelial damage, oxidative stress and inflammation, and the data imply that WCHT patients may have a worse prognosis. Nitric oxide levels are lower, and oxidative stress parameters are higher in WCHT patients than in NT patients, whereas the antioxidant capacity is lower in WCHT patients than in NT patients. Clinicians should be aware of the risk factors associated with WCHT and patients should be closely monitored especially to identify target organ damage and metabolic syndrome.

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**Key words:** White-coat hypertension; Ambulatory blood pressure; Target organ damage; Glucose dysregulation

**Core tip:** There is contradictory information regarding the clinical presentations and prognosis of white-coat hypertension (WCHT). This review aims to summarize recent research and compare it to existing knowledge about WCHT. Published studies on the prevalence of WCHT, the associated target organ damage and cardiovascular markers, and WCHT patient prognosis were reviewed. WCHT may be a marker of future obesity and metabolic syndrome, is related to glucose dysregulation and left ventricular hypertrophy and may progress to sustained hypertension. Clinicians should be aware of the risk factors associated with WCHT, and patients should be closely monitored, especially to identify target organ damage and metabolic syndrome.

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**DEFINITION OF WHITE-COAT HYPERTENSION (WCHT)**

According to the 2013 guidelines published by the European Society of Hypertension and the European Society of Cardiology for the management of hypertension WCHT is defined for patients who are not taking medication as an office blood pressure(BP) of ≥ 140/90 on at least three occasions in the presence of a health care worker (particularly a physician),with normal 24-h ( ≤ 125-130/80 mmHg) and day ambulatory BP monitoring (ABPM) ( ≤ 130-135/85 mmHg) or a normal home BP (average of several readings, ≤ 130-135/85 mmHg)[1]. There were no changes in the definition of WCHT in the JNC8[2]. The American Heart Association (AHA) recommends home BP monitoring for patients with pre-hypertension (120-139/80-89 mmHg) and for patients diagnosed with hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg)[3].

It is recommended that at least two 24-h ABPM measurements be recorded to confirm WCHT[4]. WCHT can be divided into two subgroups: partial WCHT, where either the ABPM or the home BP readings are elevated; and true WCHT, in which both the ambulatory and home BP values are normal[5].

WCHT should be differentiated from the white coat effect, which is a rise in BP in response to the presence of a medical practitioner and may be observed in all types of patients, from normotensive (NT) persons to patients with sustained hypertension (SHT) in the presence or absence of therapy[6].

The prevalence of WCHT, its associations with other clinical conditions and vascular biomarkers, the risk of target organ damage and patient prognosis in comparison with other forms of hypertension will be discussed in this review.

Studies were included if the WCHT patients were defined according to the 2013 European Society of Hypertension guidelines. WCHT studies published since 2000 were selected, although a few studies performed before 2000 were used for comparative purposes

**THE PREVALENCE OF WHITE-COAT HYPERTENSION**

The Finn-Home study was performed on 1540 untreated participants with an age range of 44 to 75 years. Two hundred thirty-three patients had WCHT. The prevalence of WCHT was 15.1%. The home BP levels of the WCHT patients were higher than those of the NT individuals. The WCHT group was older and had a higher proportion of men; WCHT patients had more metabolic risk factors than NT individuals[7].

The PAMELA study was a population study performed in Monza, Italy. BP was measured in the office and, twice daily, by subjects at home. The investigators assessed the cardiovascular and all-cause mortality over 16 years (1992-2008) in 2051 patients with an age range of 25-74 years. The prevalence of WCHT among untreated hypertensive patients was estimated at 15%-45%, and WCHT was associated with non-smoking, female gender and increasing age. The prevalence of partial WCHT was 58%, whereas the prevalence of true WCHT was 42%[5].

Pickering *et al*[8] reported that the prevalence of WCHT was 21% in a 1988 study of 292 patients. WCHT patients tended to be female, be younger, and have a lower body weight.

**PREVALENCE OF WHITE-COAT HYPERTENSION IN PATIENTS WITH CHRONIC RENAL DISEASE**

The prevalence of WCHT was 15% among 355 long-term hemodialysis patients. When a pre-dialysis BP threshold of 140/90 mmHg was used to classify patients into BP categories, the prevalence of WCHT was 26%[9].

In a study by Bangash *et al*[10], the prevalence of WCHT was 18.3% in 980 patients with CKD. The threshold for identifying hypertension based on clinic and ambulatory BP measurements strongly influenced the risk of being diagnosed with masked hypertension (MHT) rather than WCHT. In studies of CRD patients with overt proteinuria, the lower threshold for WCHT (< 140/90 mm Hg) was responsible for the increased prevalence of WCHT.

**PREVALENCE OF WHITE-COAT HYPERTENSION IN TYPE 2 DIABETES MELLITUS (DM T2) PATIENTS**

In a Chinese study of 473 patients, the prevalence of WCHT was 7.36% in the overall population, 6.13% in male patients and 8.88% in female patients (*P <* 0.05). Age, etiology of Type 2 DM and male gender were dependent factors, whereas female gender, smoking and alcohol consumption were independent risk factors for WCHT in patients with Type 2 DM[11]. These findings are in accordance with previous studies, and the characteristics of WCHT in diabetic patients are similar to those in the general population.

**WHITE- COAT HYPERTENSION AND METABOLIC SYNDROME**

According to the 2009 Joint Statement on Metabolic Syndrome, metabolic syndrome is defined as the presence of abnormalities in three of the following five characteristics: waist circumference, triglyceride levels, high-density lipoprotein levels, BP and fasting blood glucose[12].

Helvaci *et al*[13,14] analyzed 955 patients (566 females and 389 males) and suggested that WCHT is not a predisposing factor for hypertension (HT) or atherosclerosis but rather it is an alarm signal. There was an increasing prevalence of obesity, impaired glucose tolerance (IGT) or DM, and coronary heart disease (CHD) between the WCHT and HT groups compared with the NT group. According to this study, the prevalence of dyslipidemia was the highest in the WCHT group (41.6%, *P <* 0.05), followed by 35.5% in the SHT group and 19.6% in the NTgroup.

In another study by Bjorklund *et al*[15], 602 male patients aged 50 years and older who had WCHT were followed for 20 years. Their baseline BMI values were similar to those of the individuals in the NT group (23.0 kg/m2 *vs* 23.8 kg/m2) at age 70. However, metabolic abnormalities (insulin sensitivity, elevated blood glucose, and increased serum insulin) and elevated heart rate (HR) developed over time in patients with WCHT and SHT. A lower BMI and a more favorable dietary fat composition predicted the development of WCHT as opposed to SHT.

The PAMELA study demonstrated that patients with WCHT had similar baseline BMI values to patients with SHT(27 ± 4.3 kg/m2 *vs* 27.4 ± 5.2 kg/m2) but had higher fasting glucose levels compared with NT individuals (93.2 ± 20.9 mg/dL *vs* 85.5 ± 12.5 mg/dL, *P <* 0.05). At the end of the 10-year follow-up period, patients in the WCHT group were more likely to develop diabetes than those in the NT group (odds ratio: 2.9)[16].

A study conducted in Turkey by Afsar[17] revealed that the progression from sustained NT to SHT involves an increase in serum uric acid levels, impaired fasting glucose levels, and increases in BMI and waist circumference. The presence of metabolic syndrome was highest in people with SHT and lowest in those with sustained NT (*P <* 0.0001).This study concluded that the changes in these parameters were not as substantial in the WCHT group as they were when comparing the MHT and SHT groups to the NT group.

Several other studies have shown that the prevalence of impaired fasting glucose levels and abnormal glucose tolerance test results is higher in WCHT patients than in NT individuals. These findings suggest that WCHT is associated with glucose dysregulation and an increased riskfor diabetes[18,19].

Therefore, WCHT is an initial sign of deteriorating health. It commonly accompanies hyperlipidemia, elevated fasting glucose levels and a tendency toward being overweight.

**WHITE- COAT HYPERTENSION IN ELDERLY PATIENTS**

Two studies have analyzed WCHT in elderly people. In the first study, which was published by Hekman *et al*[20], elderly women (age range, 60-83 years; mean age, 69 ± 7 years) with WCHT had a higher SBP than NT elderly women between the hours of 8 am and 12 pm (133 ± 8.0 mmHg *vs* 123 ± 9.0 mmHg, *P <* 0.001). The BP variability was higher in the WCHT group only during the wakeful period (between 7 am and 11 pm, *P =* 0.02).

Age and BMI positively correlated with mean SBP at night. In the elderly women with WCHT, a higher SBP was associated with increasing age and BMI (*P =* 0.015 and *P =* 0.055, respectively). Elderly women with WCHT were more likely to smoke (*P =* 0.014) and snore (*P =* 0.046)[20].

In the second WCHT study on the elderly, Franklin SS. and colleagues analyzed 1168 untreated subjects with a mean age of 48.8 ± 16.6 years and with isolated systolic hypertension(ISH); 28.6% of the study participants had WCHT. The cardiovascular risk in untreated WCHT patients with ISH was similar to that in NT individuals (*P =* 0.63). Compared with the untreated NT individuals, individuals with WCHT undergoing treatment for ISH as well as treated NT individuals were at a higher cardiovascular risk (*P <* 0.01)[21]. The results suggested that age, BMI and the need for treatment increased the cardiovascular risk in elderly patients with WCHT.

**CIRCADIAN RHYTHMS IN PATIENTS WITH WHITE- COAT HYPERTENSION**

BP, HR, cardiac output and serum catecholamine levels increase during the day and decrease during the night. These changes enable an organism to adapt to the need for higher activity levels while awake. The decrease in BP at night is defined as “dipping,” and patients who fail to show this pattern are called “non-dippers”[22].

A study by Koroboki *et al*[22] determined that WCHT patients have the same circadian pattern as NT, MHT and untreated HT patients; however, the daytime and nighttime pulse pressures were higher in WCHT patients than in NT individuals, with nighttime pulse pressures reaching those in MHT patients. Circadian BP and HR profiles in MHT and WCHT patients have been compared with those in NT patients and in treated and untreated SHT patients using ambulatory BP measurements*.*

Pierdomenico *et al*[23] studied 12 NT, 12 WCHT and 12 SHT patients in 2000. The subjects underwent ABPM. Power spectral analyses of the R-R intervals were performed to obtain the low and high frequency components, concomitant with 24-hour urine testing for epinephrine and norepinephrine. This study demonstrated that patients with WCHT and SHT have similar circadian patterns based on ABPM; however, the other findings indicated sympathetic overactivity throughout the day in SHT patients but not in WCHT patients, suggesting that the two conditions may have different pathophysiological backgrounds[23].

Vyssoulis *et al*[24] classified WCHT patients according to the presence of accompanying metabolic syndrome traits and thus divided the patients into two groups based on the presence (*n =* 522) or absence (*n =* 1778) of metabolic syndrome. Patients with WCHT and a greater number of metabolic syndrome traits had non-dipping characteristics, along with elevated nighttime SBP levels that are indicative of an increased cardiovascular risk[24].

**WHITE-COAT HYPERTENSION AND TARGET ORGAN DAMAGE**

In 2003, Karter *et al*[25]studied 50 NT, 90 WCHT and 101 SHT subjects and reported that WCHT patients had a higher BMI and a greater left ventricular mass index (LVMI) than NT individuals(*P <* 0.001). Urinary albumin excretion was similar in WCHT patients and in those with SHT. No difference in renal function between WCHT and HT patients was noted by Pierdomenico[26].

In the PAMELA study, Cardillo, Weber, Mancia and Mulè reported that LVMI was increased in WCHT patients compared with NT patients (*P <* 0.01), whereas Pierdomenico and Hoeghelm found no difference in LVMI[5,26-31].

Arterial compliance was lower in WCHT patients than in the NT group in studies by Karter’s (*P <* 0.001) and Gomez[25,32]. Turfaner *et al*[33] analyzed 47 dipper and 43 non-dipper WCHT patients and determined, that non-dipping in WCHT patients was related to decreased arterial compliance and that the global risk load for target organ damage was higher in non-dipper WCHT subjects.

The carotid artery intimal media thickness (IMT), which is used to measure the progression of atherosclerosis in WCHT patients, has been reported to be similar in NT and WCHT individuals (see studies by Pierdomenico, Karter, Roman and Gariepy[25,34-36]).

In contrast*,* the HARVEST study by Puato *et al*[37] compared the baseline and follow-up IMT values in 35 WCHT, 20 NT and 39 SHT patients over five years. The baseline (*P =* 0.004) and follow-up (*P <* 0.01) IMT values were significantly higher and increased faster in WCHT patients than in NT controls. There was no significant difference between patients with WCHT and those with SHT (*P =* 0.27). This increase in IMT was associated with triglyceride levels, age and mean arterial pressure at ABPM, as determined by multivariate regression analysis[37]*.*

In a cross-sectional survey that included 2915 Japanese patients aged ≥ 40 years, the carotid IMT was significantly thicker in WCHT patients than in NT patients (0.73mm *vs*0.67 mm, *P =* 0.001)[38].

**WHITE-COAT HYPERTENSION AND BIOVASCULAR MARKERS**

Studies on endothelial damage and angiogenesis, which indicate an increased risk for a poor prognosis in WCHT patients, have suggested that WCHT is associated with significantly higher endothelin-1 and vascular endothelial growth factor (VEGF) levels[39].

There is controversy regarding the amount of Nitric xide(NO) in WCHT patients. Karter observed higher NO levels in WCHT patients compared with NT patients (*P <* 0.001). Karter *et al*[39], Pierdomenico *et al*[40] andGüven *et al*[41] showed no significant differences in NO levels in WCHT and NT patients. Pierdomenico *et al*[40] andGüven *et al*[41] demonstrated that NO levels were higher in WCHT patients than in SHT patients (*P <* 0.05). The difference was more significant in the Karter study (*P <* 0.001). In the Karter study, the threshold for clinical WCHT was defined as a DBP > 85 mmHg; in other studies, the threshold was defined as a BP ≥ 140/90 mmHg, which may result in a difference in endothelial dysfunction parameters.

Homocysteine and asymmetric dimethylarginine (ADMA) levels were examined in two different studies with contradictory results. Pierdomenico found no significant differences in homocysteine levels among WCHT patients and NT patients, whereas Curgunlu *et al*[42,43] showed significantly higher homocysteine levels in WCHT patients (*P <* 0.001). Homocysteine levels were significantly higher in SHT patients than in WCHT patients, with *P* values of 0.0003 and *P <* 0.001 in the studies performed by Pierdomenico *et al*[44] and Curgunlu *et al*[42,43], respectively. Regarding inflammation, only one of three WCHT studies on C-reactive protein found a significant difference between the WCHT and NT groups[41,45,46].

The reports on oxidative stress markers in WCHT are conflicting. Among the oxidative stress parameters, paraoxonase (PON-1) levels were significantly lower (*P <* 0.001) and malondialdehyde (MDA) levels were higher (*P <* 0.026) in WCHT patients compared with NT patients, whereas ox-LDL was not significantly different between the NT, WCHT and SHT groups[47].

A study by Caner *et al*[48] on other oxidative stress parameters, such as protein carbonyl(PCO) and antioxidant capacity, showed that PCO was higher (*P <* 0.001) and that antioxidant markers(plasma thiol, plasma CuZn-SOD and erythrocyte glutathione) were lower (*P <* 0.01)in WCHT patients compared with the NT group. Plasminogen activator 1(PAI-1) and von Willebrand factor levels were not different between the WCHT and NT groups[45].

**PROGNOSIS AND STROKE RISK IN PATIENTS WITH WHITE-COAT HYPERTENSION**

Verdecchia *et al*[49]reported that the cumulative hazard for stroke in WCHT patients (based on ABPM) tended to increase after 6 years of follow-up and exceeded that of ambulatory hypertensive patients after 9 years of follow-up.

In Japan, 1332 subjects (872 females and 460 males, age ≥ 40 years) who were representative of the Japanese population were followed for 10 years to monitor stroke risk as part of the OHASAMA study. There was no significant difference in outcome between WCHT and NT patients (daytime B*P <* 135/85 mmHg based on ambulatory BP)[**50].**

Pierdomenico *et al***[51]** compared the cardiac and cerebrovascular risks in SHT and WCHT individuals, which were reported to be RR = 4.16, 95%CI: 1.48-11.6, *P =* 0.007, and RR = 4.12, 95%CI: 1.62-10.5, *P =* 0.003, respectively. There was no significant difference between the NT and WCHT individuals in this study, which followed 1732 subjects (1333 SHT, 399 WCHT, and 305 NT) for 6 years**.**

In another study, Pierdomenico *et al*[52]compared the cardiovascular risk in NT and WCHT patients and found no statistically significant differences, regardless of the NT population type or the follow-up duration. They noted that the WCHT patients were more likely to be receiving drug treatment when compared with the NT patients**.**

The PAMELA study reported that in partial WCHT patients with either ABPM or home BP monitoring abnormalities, the incidence of fatal events was markedly increased, with a 60% higher fully adjusted risk of cardiovascular and all-cause mortality compared with NT controls; however, the risks of cardiovascular and all-cause mortality were not significantly different from those in NT subjects with true WCHT[5,29].

**TREATMENT**

Subjects with WCHT frequently have dysmetabolic risk factors and asymptomatic organ damage, which increase the cardiovascular risk. In these higher-risk individuals with WCHT, drug treatment may be considered in addition to appropriate lifestyle changes. Both lifestyle changes and drug treatment may also be considered when normal ambulatory BP values are accompanied by abnormal home BP values (or vice versa) because this condition is also characterized by increased cardiovascular risk. In the absence of additional cardiovascular risk factors, intervention may be limited to lifestyle changes but should include meticulous follow-up (including periodic out-of-office BP monitoring) because the out-of-office BP is often higher in WCHT patients than in truly NT individuals, and people with WCHT have a greater risk of developing organ damage or progressing to diabetes and SHT[1,2].

**CONCLUSION**

WCHT is a sign of deteriorating health. It is often accompanied by hyperlipidemia, elevated fasting glucose levels and a tendency toward being overweight. Based on the clinical and laboratory features, WCHTcan be placed on a spectrum of BP disorders that extends between NT and SHT. Commonly, WCHT progresses to SHT, obesity and metabolic syndrome. In the elderly, the cardiovascular risk associated with WCHT increases with age, BMI and the need for treatment[53].

Patients with WCHT should be assessed for the presence of target organ damage and for the development of cardiovascular risk factors. These assessments should include an oral glucose tolerance test. Patients should be educated regarding increased cardiovascular and diabetes risks, with a special emphasis on maintaining or losing weight. Patients should limit salt intake and should not consume processed food. Patients with WCHT should be monitored for conversion to SHT (ABPM every six months or yearly and/or regular home monitoring).

In the future, with the increased use of ABPM or home monitoring, patients with WCHT will be identified more often and more easily; it may become possible to protect these patients from developing target organ damage[54].

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