# Relationship Between Insulin Resistance and End-Organ Damage in White Coat Hypertension

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**Background:** End-organ damage is seen in some patients suffering from white coat hypertension (WCH). It remains unclear which patients elude the risk of end-organ damage. A relationship between end-organ damage and insulin resistance was hypothesized.

**Methods:** This hypothesis was tested by comparing two groups of patients with WCH: those presenting with end-organ damage and those without end-organ damage. Both groups were tested for the presence of insulin resistance. The study was conducted in the outpatient clinics of the Internal and Family Medicine Departments of Cerrahpaşa Medical School, Istanbul University. In this study 290 patients were screened for WCH, of which 75 were included in the study. The WCH was defined as an office blood pressure (BP) ≥140/90 mm Hg and mean daytime BP <135/85 mm Hg. The patients were divided into two groups according to the presence of end-organ damage. All patients received 24-h ambulatory BP monitoring. End-organ damage was diagnosed by revealing left ventricular hypertrophy on echocardiographic examination or retinopathy with fundoscopic examination. The homeostasis model assessment insulin resistance index (HOMA-IR) was used to assess insulin resistance.

**Results:** Among 75 patients with WCH, hypertensive retinopathy was detected in 25 patients, left ventricular hypertrophy in 15 patients, and both retinopathy and left ventricular hypertrophy simultanously in 6 patients. There were no significant differences between the groups regarding age, sex, lipid profile, and glucose levels. The HOMA-IR values in the patients with WCH and end-organ damage (4.2 ± 1.7) were significantly higher ($P <$ .0001) than those determined in patients with WCH but without end-organ damage (2.6 ± 1.8). In patients with WCH with HOMA-IR values above 3 the risk of end-organ damage was found to be higher.

**Conclusions:** A possible relationship between end-organ damage and insulin resistance in patients with WCH exists. Am J Hypertens 2004;17:1011–1016 © 2004 American Journal of Hypertension, Ltd.

**Key Words:** White coat hypertension, insulin resistance, end-organ damage.

In recent years the scientific and clinical use of ambulatory blood pressure (BP) monitoring has increased markedly.[1,2] The definition of white coat hypertension (WCH) has been one of the major reasons for this increase. At present, there is a debate whether or not WCH is a benign condition. End-organ damage constituting the cause for this debate was displayed in some but not all series.[3–8]

In some patients with WCH definite end-organ damage has been shown.[9] However, the reason for this end-organ damage has not been clarified. In these patients, metabolic abnormalities have been shown as the cause of the condition.[10,11] Elevated blood insulin levels and the presence of insulin resistance could account for this.[12] Although it is known that insulin resistance is seen in patients with WCH, the relationship between insulin resistance and end-organ damage has not yet been studied.

The aim of this study is to clarify the presence of any association between insulin resistance and end-organ damage in patients with WCH.

## Methods

This study was conducted on subjects with office BP measurements >140 mm Hg systolic and 90 mm Hg diastolic who came to the outpatient clinics of the Departments of Internal Medicine and Family Medicine, Cerrahpaşa Medical School, Istanbul University. The hypothesis was tested by comparing two groups of patients with WCH: those presenting with end-organ damage and those

Received March 16, 2004. First decision July 6, 2004. Accepted July 7, 2004.

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Published by Elsevier Inc.

0895-7061/04/$30.00
doi:10.1016/j.amjhyper.2004.07.002

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without end-organ damage. Both groups were tested for the presence of insulin resistance. The main inclusion criteria were as follows: the absence of previous antihypertensive treatment or treatment withdrawn for at least the preceeding 4 weeks. Blood pressure was measured three times. The second and third measurements were conducted on subsequent visits after the first measurement. Those patients with mean BP values >140/90 mm Hg were admitted to the study. Patients suffering from organic diseases such as hyperthyroidism, fever, anemia, and diabetes were excluded from the study. Demographic parameters such as age, sex, height, weight, and body mass index (BMI) were recorded. All patients were subjected to 24-h ambulatory BP monitoring. Those patients who were diagnosed as having WCH were included in the study. To avoid interobserver variation, all cases received fundoscopic examination by the same ophthalmologist. Similarly, all echocardiographic examinations were done by the same cardiologist and left ventricular mass index was calculated. All patients with WCH were further investigated for insulin resistance by biochemical analysis. The homeostasis model assessment insulin resistance (HOMA-IR) index was used to determine insulin resistance.[13]

All subjects included in the study underwent physical examination, blood chemistry, urine analysis, and 24-h urine collection for microalbuminuria. Body mass index was calculated by dividing the body weight (in kilograms) by the square of the height (in meters squared). The HOMA-IR index was calculated as fasting glucose (in millimoles per liter) x fasting insulin (in milliunit per milliliter)/22.5.[14]

### Office BP and 24-Hour BP

The office BP measurements of the subjects were done by a mercury manometer according to World Health Organisation–International Society of Hypertension standards after 10 min of rest and in the sitting position.[15] The 24-h ambulatory BP monitoring (ABPM) was performed with the A&D TM-2421 (A&D Medical, Milpitas, CA), which uses a microphone to detect Korotkoff sounds. This device was previously validated by the British Hypertension Society[16] (see the webpage: http://www.hyp.ac.uk/bhs/bp-_monitors/ambulatory.htm).

The procedures used for the application of the device have been described elsewhere.[17] During the recordings subjects were asked to follow their ordinary daily activities and to keep a diary of them. Blood pressure was measured every 15 min during the daytime (6 AM to midnight) and every 30 min during the nighttime (midnight to 6 AM). The WCH was defined as an office BP ≥140/90 mm Hg and mean daytime BP <135/85 mm Hg.[18]

### Echocardiography

The echocardiographic methods to measure left ventricular mass, internal end-diastolic and end-systolic diameters, and septal and posterior wall thicknesses of the left ventricle used in this study have been described elsewhere.[19–21] To correct for differences in body size, left ventricular mass index (LVMI) was calculated by dividing the LVM by the body surface area. A LVMI >125 g/m$^2$ in men and 110 g/m$^2$ in women indicated left ventricular hypertrophy.[21]

### Fundoscopic Evaluation

The presence, type, and extent of hypertensive retinopathy (HTRP) were investigated in a darkened room after dilating the pupils. The fundus was evaluated by a single ophthalmologist who was unaware of the patients' clinical data. Retinal lesions were classified according to the Keith-Wagener-Barker classification as hypertensive retinopathy grade I, II, and III.[22]

### Statistical Analysis

All calculations were performed using the SPSS (SPSS Inc, Chicago, IL) for Windows 11.05 software package. The differences between the groups were tested by Student *t* test and Mann-Whitney U test. The data are given as the mean ± standard deviation. A *P* value of < .05 was accepted as statistically significant. To analyze the association of HOMA-IR with other metabolic parameters, Pearson and Spearman correlation coefficient analyses were applied. A cutoff point for insulin resistance was determined by the receiver operating characteristics (ROC) curve method. Multivariate stepwise logistic regression analysis was used to determine possible associations between insulin resistance and other parameters.

## Results

Among 290 patients (mean age 48 ± 11 years) who were found to be hypertensive according to their office BP measurements and were further screened by 24-h ambulatory BP monitoring, 75 subjects were then diagnosed as having WCH. The mean age of the participants with WCH was 49.9 ± 12.0 years, and their mean office BP at entry was 157 ± 22.1/99 ± 11.5 mm Hg.

The WCH was detected in 123 cases and sustained hypertension in 167 cases. Those with sustained hypertension as well as the 15 patients with hyperthyroidism, 13 with anemia, 4 with fever, and 16 with diabetes were excluded from the study. This left 75 patients with WCH who were evaluated in this study. Among these patients 25 had hypertensive retinopathy and 15 left ventricular hypertrophy. In 6 patients both hypertensive retinopathy and left ventricular hypertrophy were seen simultanuously. According to the presence of end-organ damage, the patients were then divided into two groups: group 1 consisted of 41 cases without end-organ damage and group 2 consisted of 34 cases with end-organ damage.

Baseline characteristics of both groups are shown in Table 1. Age, sex, and BMI distribution were similar in

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**Table 1.** Baseline characteristics of patients

| | White Coat Hypertensive Without End-Organ Damage (group 1) ($n$ = 41) | White Coat Hypertensive With End-Organ Damage (group 2) ($n$ = 34) |
|---|---|---|
| Age (y) | 48 ± 10.6 | 53 ± 9.8 |
| Sex (M/F) | 8/33 | 5/29 |
| Body mass index (kg/m$^2$) | 28.6 ± 4.3 | 29.6 ± 4.7 |
| Office SBP (mm Hg) | 156.2 ± 21.1 | 154.8 ± 20.6 |
| Office DBP (mm Hg) | 98.2 ± 11.3 | 97.4 ± 11.6 |
| Heart rate (beats/min) | 75.4 ± 11.7 | 74.9 ± 9.2 |
| 24-h SBP (mm Hg) | 117.1 ± 6.4 | 117.5 ± 6.9 |
| 24-h DBP (mm Hg) | 72.5 ± 4.8 | 72.8 ± 4.9 |
| Daytime SBP (mm Hg) | 121.2 ± 5.8 | 120.8 ± 6.9 |
| Daytime DBP (mm Hg) | 74.8 ± 5.0 | 74.2 ± 6.3 |
| Nighttime SBP (mm Hg) | 109.9 ± 9.5 | 109.0 ± 9.5 |
| Nighttime DBP (mm Hg) | 65.7 ± 6.9 | 64.0 ± 8.4 |

DBP = diastolic blood pressure; SBP = systolic blood pressure; $P$ = not significant.

both groups. Similarly when considering office BP measurements, heart rate, 24-h BP measurement, daytime and nighttime BP measurements, there were no significant differences between the two groups. This indicated a succesful matching.

## Echocardiographic Findings

The echocardiographic characteristics of both groups are reported in Table 2. No significant differences in left ventricular end-diastolic diameter, left ventricular end-systolic diameter, relative wall thickness, left ventricular early-to-atrial peak filling rate, and ejection fraction were observed between them. Interventricular septum thickness, left ventricular posterior wall thickness, and LVMI were significantly greater in group 2 than in group 1 ($P \leq .001$).

## Hypertensive Retinopathy

In group 2, 25 subjects had hypertensive retinopathy. Stage I hypertensive retinopathy was detected in 19 cases and stage II in 6 cases. Six subjects of this group also had left ventricular hypertrophy.

## Insulin Resistance and Metabolic Findings

The metabolic parameters of the study population are shown in Table 3. There were no significant differences between the two groups in the measurements of blood glucose, creatinine, uric acid, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride levels, and microalbuminuria. The HOMA-IR was significantly lower in group 1 than in group 2 (2.6 ± 1.8 $v$ 4.2 ± 1.7; $P \leq .0001$).

There were no significant correlations between the HOMA-IR and the following parameters: glucose, creatinine, uric acid, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and microalbuminuria. A valid correlation was detected between HOMA-IR and BMI ($r_s = 0.28$, $P = .02$), LVM ($r_s = 0.25$, $P = .05$), LVMI ($r_s = 0.23$, $P = .05$), and the presence of hypertensive retinopathy ($r_s = 0.34$, $P = .005$).

For the presence of a correlation between HOMA-IR and HTRP versus LVMI, which are determinants of end-organ damage, a cutoff value for HOMA-IR was

**Table 2.** Echocardiographic characteristics of patients

| | White Coat Hypertensive Without End-Organ Damage (group 1) ($n$ = 41) | White Coat Hypertensive With End-Organ Damage (group 2) ($n$ = 34) | $P$ |
|---|---|---|---|
| IV septum thickness (mm) | 10 ± 0.1 | 11.1 ± 0.1 | <.0001 |
| LV posterior wall thickness (mm) | 9.8 ± 0.1 | 11.1 ± 0.1 | <.0001 |
| LV end diastolic diameter (mm) | 45 ± 0.4 | 45 ± 0.5 | NS |
| LV end systolic diameter (mm) | 24 ± 5.2 | 27 ± 6.3 | NS |
| LV mass (g/m) | 156 ± 31.8 | 181 ± 55.8 | .006 |
| LV mass index (g/m$^2$) | 87.0 ± 16.4 | 103.3 ± 30.9 | .0001 |
| Relative wall thickness (%) | 40.8 ± 8.0 | 41.7 ± 7.0 | NS |
| E/A | 1.09 ± 0.2 | 1.09 ± 0.3 | NS |
| LV ejection fraction (%) | 63.8 ± 0.7 | 64.1 ± 0.8 | NS |

E/A = LV early to atrial peak filling rate; IV = interventricular; LV = left ventricular; NS = not significant.

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**Table 3.** Metabolic parameters of patients

| | White Coat Hypertensive Without End-Organ Damage (group 1) | White Coat Hypertensive With End-Organ Damage (group 2) | *P* |
|---|---|---|---|
| Glucose (mg/dL) | 101 ± 18 | 100 ± 12 | NS |
| Creatinine (mg/dL) | 0.8 ± 0.2 | 0.7 ± 0.1 | NS |
| Uric acid, (mg/dL) | 5.0 ± 4.1 | 4.6 ± 2.9 | NS |
| Total cholesterol (mg/dL) | 217 ± 44 | 228 ± 37 | NS |
| HDL-cholesterol (mg/dL) | 45.8 ± 19.7 | 54.7 ± 31.8 | NS |
| LDL-cholesterol (mg/dL) | 140 ± 44 | 146 ± 38 | NS |
| Triglycerides (mg/dL) | 143 ± 58.8 | 146 ± 62 | NS |
| Microalbuminuria (mg/d) | 25.6 ± 35.6 | 32.2 ± 47 | NS |
| HOMA-IR | 2.6 ± 1.8 | 4.2 ± 1.7 | <.0001 |

HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment insulin resistance; LDL = low-density lipoprotein; NS = not significant.

calculated by using the ROC curve method. In patients with WCH with HOMA-IR values above 3, the risk of end-organ damage was found to be higher. The sensitivity of this cutoff value was 91% and the specificity 81%. These results clearly indicated a higher risk of end-organ damage in patients with WCH whose HOMA-IR levels are above 3.

Multivariate stepwise logistic regression analysis showed that HOMA-IR was associated with the presence of retinopathy and LVMI ($P = .012$ and $P = .04$, respectively). No correlation was found between other parameters and HOMA-IR.

After the conversion of HOMA-IR, logistic regression analysis was done. The HTRP (B = 1.7, SE 0.596, $P = .004$) and LVMI (B = 0.02, SE 0.013, $P = .04$) were found to be the predictors affecting HOMA-IR. The risk prediction of these parameters was 15.1 (3.9–58.1) and 20.4 (2.5–165.7), respectively. The risk of an incidence of HTRP and LVMI increased with the elevation of HOMA-IR level. This was stronger in cases where HOMA-IR was greater than 3.

## Discussion

The results of this study reveal that patients with WCH suffering from end-organ damage were found to be more insulin resistant.

Both subject groups (white coat hypertensive without end-organ damage and white coat hypertensive with end-organ damage) were highly comparable with respect to sex, age, and BP. All were unmedicated or had not been receiving any antihypertensive treatment for at least 4 weeks before study entry. Increased body weight is an important variable in patients being evaluated metabolically, as it causes increases both in blood insulin levels and insulin resistance.[23,24] In our study all subjects were overweight, which might be assumed as a factor for developing end organ damage. Furthermore, in other studies end-organ damage and metabolic alterations were demonstrated in patients with WCH. Zakopoulos et al[9] and Muldoon et al[25] reported that atherosclerosis of the carotid arteries is an another example of end-organ damage. In their studies intimal medial thickness of the common carotid arteries (CCA-IMT) in the WCH group was significantly higher than that of the normotensive group, but did not differ from that of the hypertensive group. Body weight differed significantly between the groups in the study by Zakopoulos et al.[9] Those subjects with WCH were more obese than the normal subjects and had body weight measurements resembling those of the hypertensive group. On the basis of these findings Pickering and Kario[26] proposed that the CCA-IMT of obese subjects being higher than that of normal individuals could be related to BMI.[26] Yet in our study, the BMI of both groups—those with end-organ damage and those without—were similar and thus being overweight appears to be not responsible by itself for end-organ damage.

End-organ damage, particularly hypertensive retinopathy and left ventricular hypertrophy, had been observed in patients with WCH.[27,28] Fundoscopic changes, which are observed as a complication in hypertension, and insulin resistance were strongly correlated in our subjects with WCH. The importance of this finding was reinforced further by the finding that retinopathy may develop especially in those patients with WCH who are insulin resistant.

In recent years, the importance of insulin resistance has come to the fore after its role in the pathogenesis of many metabolic disorders had been clarified. The insulin resistance syndrome includes hypertension, changes in atherogenic lipoproteins, diabetes, and hypercoaguability.[29] The presence of insulin resistance in patients with WCH has also been reported in many studies. Muldoon et al[25] reported that the patients with WCH were more insulin resistant than normal subjects. Insulin is a hormone with trophic properties and thus may cause cardiovascular hypertrophy and atherosclerosis. It stimulates growth factor receptors, cell proliferation, and lipid storage, increasing sympathetic activity and indirectly causing BP elevation.[30–32] Cardiovascular morbidity and mortality are increased in hypertensive patients with left ventricular hypertrophy.[33] Lind et al[34] and Paslisso et al[35]

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found a correlation between left ventricular mass and insulin resistance in patients with sustained hypertension. Our study results show this to be valid even in patients with WCH. Those patients with end-organ damage also tend to be more insulin resistant.

The HOMA-IR method was used to determine insulin resistance, although it has some limitations. Euglycemic clamp and intravenous glucose tolerance test (IVGTT) are accurate but difficult and expensive to perform in an outpatient setting. Furthermore, it has been demonstrated that HOMA-IR has higher correlation with the euglycemic clamp and IVGTT in individuals, like our subjects, with normoglycemia than in those with impaired glucose tolerance and diabetes.[13]

The presence of end-organ damage in patients with WCH is an important finding, because it clarifies factors contributing to subclinic vascular disease. It is also important to know which patients with WCH will develop end-organ damage. Our present study suggests an answer. A patient with WCH with a HOMA-IR higher than 3 has a higher risk of developing end-organ damage. These patients can be regarded as candidates for more aggressive treatment modalities. Another finding of this study is the correlation between insulin resistance and retinopathy is stronger than the correlation between insulin resistance and the elevation of LVMI as a consequence of end-organ damage. Retinopathy may develop secondarily to hypertension as well as to atherosclerosis, where lipid abnormalities and diabetes play an important role. The exclusion of diabetic patients from the study prevented a misinterpretation of the effect of diabetes on the development of end-organ damage. The possible effect of lipid abnormalities were also nonsignificant because the results of lipid parameters did not differ between the two groups.

In conclusion, this study suggests a correlation between end-organ damage and insulin resistance in patients with WCH. Therefore, in the management of patients with WCH it will be appropriate to determine the presence of insulin resistance in addition to the recommendation of appropriate lifestyle changes to decrease the risk for end-organ damage.

## References


1. Pickering T, American Society of Hypertension Ad Hoc Panel: Recommendations for the use of home (self) and ambulatory blood pressure monitoring. Am J Hypertens 1996;9:1–11.
2. Mallion JM, Baguet JP, Siche JP, Tremel F, De Gaudemaris R: Clinical value of ambulatory blood pressure monitoring. J Hypertens 1999;17:585–595.
3. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G: Relationship of 24-hour blood pressure mean and variability to severity of target organ damage in hypertension. J Hypertens 1987;5:93–98.
4. Cardillo C, De Felice F, Campia U, Folli G: Psychophysiological reactivity and cardiac end-organ changes in white coat hypertension. Hypertension 1993;21:835–844.
5. Palatini P, Mormino P, Santonastaso M, Mos L, Follo MD, Zanata G, Pessina AC: Target-organ damage in stage I hypertensive subjects with white coat and sustained hypertension. Results from the HARVEST study. Hypertension 1998;31:57–63.
6. Gosse P, Promax H, Durandet P, Clementy J: "White coat" hypertension, no harm for the heart. Hypertension 1993;22:766–770.
7. Kuwajima I, Suzuki Y, Fujisawa A, Kuramoto K: Is white coat hypertension innocent? Structure and function of the heart in the elderly. Hypertension 1993;22:826–831.
8. Glen SK, Elliott HL, Curzio JL, Lees KR, Reid JL: White coat hypertension as a cause of cardiovascular dysfunction. Lancet 1996; 348:654–657.
9. Zakopoulos N, Papamichael C, Papaconstantinou H, Dubbins PA, Burrell CJ, Lekakis J, Stamatelopoulos S, Moulopoulos S: Isolated clinic hypertension is not an innocent phenomenon: effect on the carotid artery structure. Am J Hypertens 1999;12:245–250.
10. Julius S, Mejia A, Jones K, Krause L, Schork N, van de Ven C, Johnson E, Petrin J, Sekkarie MA, Kjeldsen SE: "White coat" versus "sustained" borderline hypertension in Tecumseh, Michigan. Hypertension 1990;16:617–623.
11. Kario K, Pickering T: White-coat hypertension or white-coat hypertension syndrome: Which is accompanied by target organ damage? Arch Intern Med 2000;160:3497–3498.
12. Bjorklund K, Lind L, Andren B, Lithell H: White-coat hypertension is related to insulin resistance, but not increased left ventricular mass in elderly men. Am J Hypertens 2001;14:O–13.
13. McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned N, Temple LA, Duncan AW: Diagnosing insulin resistance in the general population. Diabetes Care 2001;24:460–464.
14. Mathews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and $\beta$-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419.
15. Chalmers J, MacMahon S, Mancia G, Whitworth J, Beilin L, Hansson L, Neal B, Rodgers A, Ni Mhurchu C, Clark T: WHO–ISH Hypertension Guidelines Committee. 1999 World Health Organisation–International Society of Hypertension Guidelines for the management of hypertension. J Hypertens 1999;17:151–185.
16. O'Brien E, Coats A, Owens P, Petrie J, Padfield PL, Littler WA, de Swiet M, Mee F: Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. BMJ 2000;320:1128–1134.
17. Palatini P, Penzo M, Racioppa A, Zugno E, Guzzardi G, Anaclerio M, Pessina AC: Clinical relevance of nighttime blood pressure and of daytime blood pressure variability. Arch Intern Med 1992;152: 1855–1860.
18. Owens P, Atkins N, O'Brien E: Diagnosis of white coat hypertension by ambulatory blood pressure monitoring. Hypertension 1999; 34:267–272.
19. Muscholl MW, Hense HW, Bröckel U, Döring A, Riegger GA, Schunkert H: Changes in left ventricular structure and function in patients with white coat hypertension: cross sectional survey. Br Med J 1998;317:565–570.
20. Sahn DJ, Demaria A, Kisslo J, Weyman A: Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58: 1072–1083.
21. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986; 57:450–458.
22. Keith NM, Wagener HP, Barker MW: Some different types of essential hypertension: their course and prognosis. Am J Med Sci 1939;197:332–343.
23. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW: Body mass index and mortality in a prospective cohort of US adults. N Engl J Med 1999;341:1097–1105.
24. Abbasi F, Brown BW, Lamendola C, McLaughlin T, Reaven GM: Relationship between obesity, insulin resistance, and coronary heart disease risk. J Am Coll Cardiol 2002;40:937–943.


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25. Muldoon MF, Nazzaro P, Tyrrell KM, Manuck SB: White-coat hypertension and carotid artery atherosclerosis. Arch Intern Med 2000;160:1507–1512.
26. Pickering TG, Kario K: Comments on the study of Zakopoulos et al. Am J Hypertens 1999;12:1158–1160.
27. Owens PE, Lyons SP, Rodriguez SA, O'Brien ET: Is elevation of clinic blood pressure in patients with white coat hypertension who have normal ambulatory blood pressure associated with target organ changes? J Hum Hypertens 1998;12:743–748.
28. Palatini P, Penzo M, Canali C, Dorigatti F, Pessina AC: Interactive action of the white-coat effect and the blood pressure levels on cardiovascular complications in hypertension. Am J Med 1997;103: 208–216.
29. DeFronzo RA: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerosis. Neth J Med 1997;50:191–197.
30. DeFronzo RA, Ferrannini E: Insulin resistance, a multifactorial syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173–194.
31. Toyozaki T, Hiroe M, Hasumi M, Horie T, Hosoda S, Tsushima T, Sekiguchi M: Insulin-like growth factor I receptors in human cardiac myocytes and their relation to myocardial hypertrophy. Jpn Circ J 1993;57:1120–1127.
32. Long CS, Kariya KI, Karms L, Simpson PC: Sympathetic activity modulator of myocardial hypertrophy. J Cardiovasc Pharmacol 1991;17(Suppl 2):20–24.
33. Koren MJ, Ulin RJ, Koren AT, Laragh JH, Devereux RB: Left ventricular mass change during treatment and outcome in patients with essential hypertension. Am J Hypertens 2002;15: 1021–1028.
34. Lind L, Andersson P-E, Andren B, Hanni A, Lithell HO: Left ventricular hypertrophy in hypertension in association with the insulin resistance metabolic syndrome. J Hypertens 1995;13:433–438.
35. Paslisso G, Galderisi M, Tagliomonte MR, de Dinitis M, Galzerano D, Petrocelli A, Gualdiero P, de Dinitis O, Vernichio M: Myocardial wall thickness and left ventricular geometry in hypertensives: relationship with insulin. Am J Hypertens 1997;10: 1250–1256.

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