

# Treatment of White Coat Hypertension With Metformin

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## SUMMARY

White coat hypertension (WCH) is most likely a disorder associated with metabolic syndrome.

The study was performed at the Internal Medicine Polyclinic of Dumlupinar University on routine check-up patients. WCH cases who were overweight or obese and desiring weight loss were divided into two subgroups according to whether they preferred to achieve weight loss by medication or diet therapy.

The study included 324 cases (204 females) with WCH, 45 of whom were in normal weight range. Therefore, 86.1% (279) of cases with WCH were either overweight or obese, and 41.3% (134) of all WCH cases had dyslipidemia. Twenty-five cases (14.7%) stopped metformin therapy due to excessive anorexia. At the end of a 6-month period, there were highly significant differences between the two groups with respect to the prevalences of resolved WCH, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, overweight and obesity, and decreased fasting plasma glucose below 110 mg/dL ( $P < 0.001$  for all).

Due to gradually increased prevalences of impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, excess body weight, and obesity-like disorders from sustained normotension towards WCH and hypertension (HT) cases, and very high prevalences of excess weight and dyslipidemia in the WCH group, WCH may be an associated disorder of metabolic syndrome rather than just being a predisposing factor of atherosclerosis or HT alone. Thus, the management of WCH should not focus solely on the regulation of blood pressure with antihypertensive medications, but rather on the prevention of future excess weight and various associated disorders, and metformin alone is an effective therapeutic option, most likely due to its powerful inhibitory effect on appetite. (Int Heart J 2008; 49: 671-679)

**Key words:** White coat hypertension, Metformin, Dyslipidemia, Excess weight

WHITE coat hypertension (WCH) is a frequent entity with an unknown etiologic and sequential nature clinically. A previous study reported that WCH is a risk factor for the development of home hypertension (HT).<sup>1)</sup> Sixty subjects (46.9%) with WCH and 144 (22.2%) with sustained normotension (NT) pro-

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gressed to home HT in another 8-year follow-up study,<sup>2)</sup> and the results demonstrated that WCH is a transitional condition eventually terminating with home HT. In addition, the intima-media thickness and cross-sectional area of carotid arteries were found to be similar in patients with WCH and HT, which were significantly higher than those in sustained NT cases, so the authors concluded that there is target organ damage in WCH, and thus it should not be considered as an innocent trait.<sup>3)</sup> Similarly, plasma homocysteine levels were significantly higher and left ventricle mass index was significantly greater in the WCH group compared to NT cases, but both were significantly lower in the WCH group than in the HT cases in another study.<sup>4)</sup> In a previous study, we determined that almost all of the disorders, including obesity, impaired glucose tolerance (IGT), type 2 diabetes mellitus (DM), hyperbetalipoproteinemia, hypertriglyceridemia, and dyslipidemia showed stepwise but significant progression in frequencies from sustained NT towards WCH and HT cases.<sup>5)</sup> On the other hand, metformin is an antihyperglycemic agent used worldwide for the treatment of type 2 DM. It is used orally and is not associated with hypoglycemia.<sup>6)</sup> Some additional benefits of metformin on blood pressure (BP) regulation have been reported in the literature.<sup>7)</sup> The aim of the present study was to determine whether or not metformin has some beneficial effects on WCH and various other associated disorders.

## METHODS

The study was performed at the Internal Medicine Polyclinic of Dumlupinar University on routine check-up patients between August 2005 and March 2007. Consecutive patients aged between 15 and 70 years were accepted into the study to avoid debility-induced weight loss in elderly patients. Their medical histories, including the presence of DM and dyslipidemia, and current medications were obtained, and a routine check-up procedure including fasting plasma glucose (FPG), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) was performed. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight and metformin-induced lactic acidosis. The body mass index (BMI) of each patient was calculated by the same physician via measurements in the clinic, instead of verbal expressions of the patients. Weight in kilograms was divided by height in meters squared. Underweight was defined as a BMI of lower than 18.5, normal weight as 18.5-24.9, overweight as 25-29.9, and obesity as a BMI of 30.0 kg/m<sup>2</sup> or greater.<sup>8)</sup> Cases with an overnight FPG level > 126 mg/dL on two occasions or already using antidiabetic medications were defined as diabetics. An oral glucose tolerance test with 75-gram glu-

cose was performed in cases with a FPG level between 100 and 126 mg/dL, and cases with a 2-hour plasma glucose level of 200 mg/dL or higher were diagnosed with DM and 140-199 mg/dL with IGT.<sup>8)</sup> Patients with dyslipidemia were identified using the National Cholesterol Education Program Expert Panel recommendations for defining dyslipidemic subgroups.<sup>8)</sup> A diagnosis of dyslipidemia was made when LDL-C was 160 or higher and/or TG was 200 or higher and/or HDL-C was lower than 40 mg/dL. 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 preceding 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 about proper BP measurement techniques.<sup>9)</sup> The education included a recommendation to use upper arm devices while discouraging wrist and finger devices, 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, and resting for at least 5 minutes in the seated position before a measurement. An additional 24-hour ambulatory blood pressure monitoring (ABP) was obtained only in cases with a higher OBP and/or HBP measurement. It was performed with oscillometrical equipment (SpaceLabs 90207, Redmond, WA, USA) set to take a reading every 10-minutes during the 24-hour period. Normal daily activities were allowed, and the subjects were instructed to keep the arm relaxed during measurements. WCH is defined as an OBP of 140/90 mmHg or greater, but a mean daytime ABP of < 135/85 mmHg (between 10 AM to 8 PM).<sup>9)</sup> Eventually, all cases of WCH associated with overweight or obesity and desiring weight loss were divided into two subgroups according to the wishes of the patient about whether they preferred to use medication or only a low-calorie diet. The diet was planned as a 1500 calorie containing diet which was low in animal source foods but rich in vegetables and fruits divided into 4-6 small meals and snacks everyday. To simplify the diet, only one kind of animal source diet with a low amount was permitted daily and fruits, in any amount, were recommended before meals to provide satiety. Additionally, foods that are high in sugars such as pastries, candy bars, pies, and candy were restricted. Metformin (850 mg tablets, Biokem, Turkey) at a total daily dose of 2550 mg/day in 3 divided dosages was administered to the medication group alone orally, but the maximal dose was achieved at the end of a two-week period by increasing the dose by 850 mg weekly, just to decrease some side effects of the drug. Patients were warned about possible side effects of the drug including nausea, vomiting, anorexia, flatulence, sensation of a metallic taste in the mouth, diarrhea, and abdominal discomfort. Patients were followed-up for a period of 6 months at 4 week intervals. At the end of this

period, patients completing the follow-up were evaluated again, and the prevalences of resolved WCH, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, excess body weight, and obesity and decreased FPG below 110 mg/dL were determined and compared among the groups. Comparison of proportions and one-way ANOVA tests were used as methods of statistical analysis. *P* values lower than 0.05 were accepted as statistically significant.

## RESULTS

The study included a total of 324 WCH cases (204 females and 120 males) (Table I), 45 of whom had normal weight and none were underweight. Therefore, 86.1% (279) of cases with WCH were either overweight or obese. Initially, 109 cases with WCH indicated a preference for diet therapy alone, while 170 preferred drug therapy. The drug therapy was stopped due to excessive anorexia in 25 cases and due to flatulence in 3 cases. No one left the study in the diet group. At the end of the 6-month period, there were highly significant differences between the two groups with respect to the prevalences of normalized WCH, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, excess body weight, and obesity according to the limits described above, and decreased FPG below 110 mg/dL ( $P < 0.001$  for all) (Table II). The mean weight loss was  $8.7 \pm 3.5$  kg (range, 3 to 15 kg) in the metformin group, whereas it was  $2.1 \pm 1.3$  kg (range, 0 to 6 kg) in the diet group ( $P < 0.001$ ). Although some cases went from being obese to overweight and from overweight to normal weight, none went from obesity to normal weight in this period of time. On the other hand, 279 cases

**Table I.** Characteristics of the Study Cases

| Variable                               | Cases with WCH ( <i>n</i> = 324) |
|----------------------------------------|----------------------------------|
| Mean age (years)                       | $47.03 \pm 13.05$ (15-70)        |
| Female ratio                           | 62.9% (204)                      |
| Prevalence of normal weight            | 13.8% (45)                       |
| Prevalence of excess weight            | 41.9% (136)                      |
| Prevalence of obesity                  | 44.1% (143)                      |
| Prevalence of IGT                      | 7.7% (25)                        |
| Prevalence of DM                       | 15.7% (51)                       |
| Prevalence of hyperbetalipoproteinemia | 20.9% (68)                       |
| Prevalence of hypertriglyceridemia     | 23.7% (77)                       |
| Prevalence of dyslipidemia             | 41.3% (134)                      |

WCH indicates white coat hypertension; IGT, impaired glucose tolerance; and DM, diabetes mellitus.

**Table II.** Comparison of the Study Cases

| Variable                                                  | WCH cases treated with diet alone (n = 109) | WCH cases treated with metformin alone (n = 142) | P       |
|-----------------------------------------------------------|---------------------------------------------|--------------------------------------------------|---------|
| Mean age and range(years)                                 | 46.1 ± 13.2 (25-70)                         | 47.7 ± 9.3 (31-70)                               | > 0.05  |
| Female ratio                                              | 62.3% (68)                                  | 64.7% (92)                                       | > 0.05  |
| Prevalence of resolved WCH                                | 25.6% (28/109)                              | 69.0% (98/142)                                   | < 0.001 |
| Prevalence of resolved hyperbetalipoproteinemia           | 22.7% (5/22)                                | 52.6% (20/38)                                    | < 0.001 |
| Prevalence of resolved hypertriglyceridemia               | 16.6% (5/30)                                | 51.1% (22/43)                                    | < 0.001 |
| Prevalence of resolved dyslipidemia                       | 16.6% (8/48)                                | 48.6% (36/74)                                    | < 0.001 |
| Prevalence of decreased FPG below 110 mg/dL               | 9.0% (2/22)                                 | 44.1% (19/43)                                    | < 0.001 |
| Prevalence of resolved excess weight                      | 3.7% (2/54)                                 | 18.5% (13/70)                                    | < 0.001 |
| Prevalence of resolved obesity by declining to overweight | 5.4% (3/55)                                 | 23.6% (17/72)                                    | < 0.001 |

WCH indicates white coat hypertension and FPG, fasting plasma glucose.

**Table III.** Mean Blood Pressure Values of the Study Cases

| Variable                     | Overweight or obese WCH cases before diet or metformin (n = 279) | Unresolved WCH cases with metformin or diet (n = 125) | Resolved WCH cases with diet or metformin (n = 126) |
|------------------------------|------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------|
| Mean OBP                     | 157.5 ± 13.7/101.3 ± 11.1                                        | 153.7 ± 11.3/99.9 ± 17.3                              | 123.5 ± 7.7/75.5 ± 7.3                              |
| Mean HBP                     | 121.1 ± 11.3/73.3 ± 6.9                                          | 119.3 ± 9.7/79.2 ± 4.7                                | 116.3 ± 8.7/73.7 ± 7.7                              |
| Mean ABP                     | 119.7 ± 13.7/77.3 ± 6.3                                          | 116.5 ± 12.5/76.1 ± 5.7                               | Not performed                                       |
| Mean heart rate(beat/minute) | 75.2 ± 11.3 (63-155)                                             | 73.5 ± 13.7 (60-143)                                  | 68.3 ± 9.3 (59-137)                                 |

WCH indicates white coat hypertension; OBP, office blood pressure; HBP, home blood pressure; and ABP, 24-hour ambulatory blood pressure monitoring.

with WCH were diagnosed both via HBP and ABP, and no difference was observed between the two methods according to the total number of cases diagnosed. The mean systolic/diastolic OBP, HBP, and ABP values and mean heart rates of the groups are summarized in Table III. ABP analysis revealed that the white coat effect was initiated when the patient left home to go to the hospital.

## DISCUSSION

White coat hypertension is a well-described clinical entity defined as a persistently elevated BP in a physician's office that is otherwise normal. In a previous study,<sup>10)</sup> we observed very high prevalences of WCH in Turkish society; 33.3% in the second decade of life, 46.6% in the third, and 50.0% in the fourth, and the prevalence of HT initially exceeded 40% in the sixth decade and reached 75% in the eighth decade. On the other hand, in the same study, the prevalence of HT was only 3% in the third, 8% in the fourth, and 21% in the fifth decades of life. The high prevalences of WCH in society were also reported in other stud-

ies.<sup>11,12)</sup> Therefore, as a hypothesis, we came to the conclusion that all HT cases, 75% in the eighth decade, may arise from previous WCH cases, but that this process takes a very long period of time to develop, reaching up to the normal life span of a human being, but there would be some other clinical impacts of WCH for human health. Thus, in another study, we evaluated WCH not as a cause of HT or atherosclerosis alone, but as a coexisting condition and thus an alarming sign of a deterioration in health.<sup>5)</sup> When we compared the sustained NT, WCH, and HT cases, the prevalences of nearly all health problems, including obesity, IGT, type 2 DM, hyperbetalipoproteinemia, hypertriglyceridemia, and dyslipidemia showed significant progression from the sustained NT towards the WCH and HT groups, and the WCH group was found to be a significant intermediary progression step between NT and HT. Similarly, 86.1% of cases with WCH had excess weight, and 41.3% of all WCH cases had dyslipidemia, indicating a very close relationship between WCH and excess weight and dyslipidemia in the present study. Thus, the high prevalence of dyslipidemia in the WCH group may indicate some adverse effects on health, since dyslipidemia is associated with obesity, HT, type 2 DM, coronary heart disease (CHD), and stroke-like health problems in the future. In other words, WCH may show a tendency of excess weight. In this way, higher prevalences of WCH were detected even in the second (33.3%) and third decades (46.6%),<sup>10)</sup> although the lower prevalences of excess weight in these age groups may represent a trend towards weight gain, and dyslipidemia may be another precursor sign of excess weight in these cases. Similarly, we previously reported that WCH and HT have significantly lower prevalences in underweight than normal weight and overweight cases, as another indicator of the effects of body weight on BP.<sup>13)</sup> Similarly, the relationship between the excess weight and HT is also described under the heading of metabolic syndrome, and clinical manifestations of the syndrome include abdominal obesity, dyslipidemia, HT, insulin resistance, and proinflammatory as well as prothrombotic states. It is already known that excess weight leads to both structural and functional abnormalities of many systems of the body, so the risk of death from all causes including cardiovascular diseases and cancers increases throughout the range of moderate and severe excess weight for both sexes in all age groups.<sup>14)</sup>

A recent review article stated that patients with WCH are characterised by an absence of a lowering of BP by antihypertensive treatments.<sup>15)</sup> On the other hand, metformin, which is a biguanide, is currently being used in more than 90 countries worldwide. It is not metabolized in the body, and 90% of the absorbed drug is eliminated unchanged in urine. The drug is dialyzable because plasma protein binding is negligible. According to the literature, the antihyperglycemic effect of metformin is largely caused by inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal, and inhibition of fatty acid oxida-

tion.<sup>16-18)</sup> The reduction of intestinal glucose absorption has been postulated as another possible mechanism of action, although the data have been inconsistent.<sup>19)</sup> The precise mechanism of intracellular action of metformin remains uncertain. Interestingly, 14.7% (25 cases) of treated cases stopped the metformin due to an excessive loss of appetite in our study. Additionally, 21.1% (30 cases) of cases who were overweight and obese in the metformin group improved to either the normal weight or overweight by weight loss even in the absence of any given diet, whereas this ratio was only 4.5% (5 cases) in the diet group. Thus, we believe the major effect of metformin may be the inhibition of appetite given the already known role of excess weight in HT, type 2 DM, dyslipidemia, and CHD-like disorders. Similar results indicating the beneficial effects of metformin on BMI, BP, and dyslipidemia have also been reported by other researchers.<sup>20,21)</sup> Therefore, as also shown in the present study, the prevention of excess weight by metformin will probably prevent not only WCH but also most of the other deleterious consequences excess weight has on health.

The literature has reported numerous side effects of metformin, including nausea, vomiting, anorexia, diarrhea, sensation of a metallic taste in the mouth, and lactic acidosis.<sup>22)</sup> Lactic acidosis is a very rare side effect with an estimated incidence of 0.03 per 1000 patient-years, and it was almost always observed in critically ill, particularly septic patients or in suicide attempt cases.<sup>22)</sup> Metformin causes lactic acidosis through two mechanisms, namely, a shift in the intracellular redox potential away from aerobic towards anerobic metabolism, and suppression of hepatic gluconeogenesis from lactate. Similarly, it was observed in another study that there was an increase in the plasma lactate concentration in the absence of any substantial change in the arterial pH in patients receiving metformin.<sup>23)</sup> The clinical significance of this accumulation of lactate without acidosis is unclear. It has been previously shown in septic patients that the increased lactate concentrations resulted from an acceleration in glycolysis in excess of glucose oxidation.<sup>23)</sup> On the other hand, two reports by Lalau, *et al* indicated that neither the degree of hyperlactatemia nor the accumulation of metformin is of prognostic significance for mortality, and the mortality appears to be linked to concurrent diseases rather than drug accumulation in the body.<sup>24,25)</sup>

In conclusion, due to the gradually increased prevalences of IGT, type 2 DM, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, and excess weight and obesity-like disorders from the sustained NT towards the WCH and HT groups, and the very high prevalences of excess weight and dyslipidemia in the WCH cases, and again the very high prevalences of WCH even in early decades, WCH may be a disorder associated with metabolic syndrome and many disorders associated with it, rather than just being a predisposing factor of atherosclerosis or HT alone. Therefore, the management of WCH should not focus just

on the regulation of BP with antihypertensive medications, but rather on the prevention of future excess weight gain and many associated disorders, and metformin alone is a very effective therapeutic option, most likely due to its powerful inhibitory effect on appetite.

## REFERENCES

1. Ohkubo T, Asayama K, Kikuya M, *et al.* How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study. *J Hypertens* 2004; 22: 1099-1104.
2. Ugajin T, Hozawa A, Ohkubo T, *et al.* White-coat hypertension as a risk factor for the development of home hypertension: the Ohasama study. *Arch Intern Med* 2005; 165: 1541-6.
3. Nakashima T, Yamano S, Sasaki R, *et al.* White-coat hypertension contributes to the presence of carotid arteriosclerosis. *Hypertens Res* 2004; 27: 739-45.
4. Curgunlu A, Karter Y, Uzun H, *et al.* Hyperhomocysteinemia: an additional risk factor in white coat hypertension. *Int Heart J* 2005; 46: 245-54.
5. Helvacı MR, Kaya H, Seyhanlı M, Cosar E. White coat hypertension is associated with a greater all-cause mortality. *J Health Sci* 2007; 53: 156-60.
6. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med* 1995; 333: 541-9.
7. Schmidt R, Horn E, Richards J, Stamatakis M. Survival after metformin-associated lactic acidosis in peritoneal dialysis--dependent renal failure. *Am J Med* 1997; 102: 486-8.
8. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adult (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106: 3143-421.
9. O'Brien E, Asmar R, Beilin L, *et al.* European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; 21: 821-48. (Review)
10. Helvacı MR, Seyhanlı M. What a high prevalence of white coat hypertension in society! *Intern Med* 2006; 45: 671-4.
11. Hozawa A, Ohkubo T, Kikuya M, *et al.* Blood pressure control assessed by home, ambulatory and conventional blood pressure measurements in the Japanese general population: the Ohasama study. *Hypertens Res* 2002; 25: 57-63.
12. Celis H, Fagard RH. White-coat hypertension: a clinical review. *Eur J Intern Med* 2004; 15: 348-57.
13. Helvacı MR, Kaya H, Yalcin A, Kuvandik G. Prevalence of white coat hypertension in underweight and overweight subjects. *Int Heart J* 2007; 48: 605-13.
14. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999; 341: 1097-105.
15. Verdecchia P, Staessen JA, White WB, Imai Y, O'Brien ET. Properly defining white coat hypertension. *Eur Heart J* 2002; 23: 106-9. (Review)
16. Nagi DK, Yudkin JS. Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects. A study of two ethnic groups. *Diabetes Care* 1993; 16: 621-9.
17. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; 333: 550-4.
18. Riccio A, Del Prato S, Vigili de Kreutzenberg S, Tiengo A. Glucose and lipid metabolism in non-insulin-dependent diabetes. Effect of metformin. *Diabete Metab* 1991; 17: 180-4.
19. Jackson RA, Hawa MI, Jaspan JB, *et al.* Mechanism of metformin action in non-insulin-dependent diabetes. *Diabetes* 1987; 36: 632-40.

20. Campbell IW, Howlett HC. Worldwide experience of metformin as an effective glucose-lowering agent: a meta-analysis. *Diabetes Metab Rev* 1995; 11: S57-62.
21. Wu MS, Johnston P, Sheu WH, *et al.* Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. *Diabetes Care* 1990; 13: 1-8.
22. Chang CT, Chen YC, Fang JT, Huang CC. Metformin-associated lactic acidosis: case reports and literature review. *J Nephrol* 2002; 15: 398-402. (Review)
23. Gore DC, Jahoor F, Hibbert JM, DeMaria EJ. Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. *Ann Surg* 1996; 224: 97-102.
24. Lalau JD, Lacroix C, Compagnon P, *et al.* Role of metformin accumulation in metformin-associated lactic acidosis. *Diabetes Care* 1995; 18: 779-84.
25. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf* 1999; 20: 377-84.