

Metformin and Parameters of Physical Health

Mehmet Rami Helvacı¹, Hasan Kaya¹, Ali Borazan¹, Cahit Ozer¹,
Mahmut Seyhanlı² and Atilla Yalcin²

Abstract

Background The prevalence of excess weight, including overweight and obesity, is increasing with a high cost on health in society.

Methods Consecutive cases with excess weight, aged between 50 and 70 years and desiring weight loss, were divided into two subgroups according to wishes of patients about whether they prefer medication or just a diet. Metformin at a daily dose of 2,550 mg was given to the medication group.

Results As for the very high prevalences, 84.8% (313/369) of cases at or above the age of 50 years were overweight or obese, 67.2% (248/369) of them had white coat hypertension (WCH) or hypertension (HT), 52.5% (194/369) of them had impaired glucose tolerance (IGT) or diabetes mellitus (DM), and 68.8% (254/369) of them had dyslipidemia. Initially 143 cases with excess weight preferred the diet and 162 of them preferred the metformin therapy. But 42 cases (25.9%) stopped the drug because of excessive anorexia. At the end of the six-month period, there were highly significant differences between the two groups according to prevalences of resolved WCH, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, overweight, and obesity and a decreased fasting plasma glucose below 110 mg/dL ($p < 0.001$ for all).

Conclusion Due to the very high prevalences of excess weight and probably many associated disorders with the excess weight, including IGT or DM, WCH or HT, and dyslipidemia, above the age of 50 years, and the detected significant benefits of metformin on all of the above parameters, metformin treatment should be initiated in patients with excess weight in their fifties.

Key words: metformin, excess weight, fifty years of age

(Inter Med 47: 697-703, 2008)

(DOI: 10.2169/internalmedicine.47.0787)

Introduction

The prevalence of excess weight is increasing all over the world; it is a major health problem, as it is well recognized that excess weight causes a high cost on health even in early decades. Excess weight is a disorder characterized by increased mass of adipose tissue. The foremost physical consequences of excess weight are impaired glucose tolerance (IGT) or type 2 diabetes mellitus (DM), white coat hypertension (WCH) or hypertension (HT), dyslipidemia, and coronary heart disease (CHD) (1, 2). For example, atherogenic dyslipidemia is commonly seen in cases with excess weight, and it is characterized by an increased level of triglycerides or low density lipoprotein cholesterol (LDL-C), or a decreased level of high density lipoprotein cholesterol

(HDL-C) in serum (1). Persons with excess weight have a higher prevalence of elevated blood pressure (BP) than lean persons, and some of the well-known complications of HT are left ventricular hypertrophy, CHD, heart failure, chronic renal failure, and stroke (3). On the other hand, excess weight is accompanied by several types of coagulation and fibrinolytic abnormalities, suggesting that it induces a prothrombotic and proinflammatory state terminating with atherosclerotic events all over the body (4). The chronic inflammation inducing endothelial dysfunction probably is the reason that excess weight causes increased atherogenicity (5, 6). As a supporting evidence of the role of inflammation in atherosclerosis, elevations of serum C-reactive protein (CRP) carry predictive power for the development of major cardiovascular events (7). In particular, excess weight is considered a strong factor in controlling the concentration of circu-

¹Medical Faculty of the Mustafa Kemal University, Antakya, Turkey and ²Medical Faculty of the Mersin University, Mersin, Turkey

Received for publication November 30, 2007; Accepted for publication January 23, 2008

Correspondence to Dr. Mehmet Rami Helvacı, mramihelvaci@hotmail.com

lating CRP concentrations because adipose tissue is involved in the regulation of cytokines (8), and individuals with excess weight have elevated levels of CRP suggesting that excess weight is a proinflammatory state (9). In addition to the above, excess weight is accompanied by some other medical complications including fatty liver, cholesterol gallstones, sleep apnea, osteoarthritis, and polycystic ovary disease, and the majority of people with excess weight have a clustering of these risk factors. Furthermore, excess weight is highly correlated with dietary intake of increased calories and fat, both of which have been linked to several types of cancer including breast, colon, and prostate (10). So excess weight, including overweight and obesity, is associated with an increased risk of death (11). On the other hand, metformin as an antihyperglycemic agent may be the first therapeutic option in treatment of type 2 DM with overweight or obesity, since it may prevent some vascular complications and mortality (12). It is effective enterally and not associated with hypoglycemia (13), thus it may be advantageous by diminishing risk of iatrogenic hypoglycemia. There are reports about some additional benefits of metformin on excess weight and many associated disorders in the literature (14, 15). Here we tried to elucidate whether or not metformin has some beneficial effects on excess weight and some associated disorders other than IGT or DM.

Materials and Methods

The study was performed in Internal Medicine Polyclinic of Dumlupinar University on routine check up patients between August 2005 and October 2006. Consecutive patients aged between 50 and 70 years were taken into the study to avoid debility-induced weight loss and metformin-induced lactic acidosis in elders. Their medical histories including HT, DM, dyslipidemia, and already used medications were recorded, and a routine check-up procedure including fasting plasma glucose (FPG), triglyceride, HDL-C, and 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. Body mass index (BMI) of each case was calculated by measurements of the same physician instead of verbal expressions. Weight in kilograms was divided by height in meters squared, and 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 30.0 kg/m² (2) or greater (1). Cases with an overnight FPG level of 126 mg/dL or higher on two occasions or already using antidiabetic medications were defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level of 200 mg/dL or higher is DM and 140-199 mg/dL is IGT (1). Additionally patients with dyslipidemia were detected, and we used the National Cholesterol Education Program Expert Panel's recommendations

for defining dyslipidemic subgroups (1). Dyslipidemia was diagnosed when LDL-C was 160 mg/dL or higher and/or triglyceride was 200 mg/dL or higher and/or HDL-C was lower than 40 mg/dL. Office blood pressure (OBP) was checked after 5 minutes of rest in seated position with a 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 about proper BP measurement techniques (16). The education included recommendation of upper arm while discouraging wrist and finger devices by 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 taking a rest at least for a period of 5-minute in the seated position before measurement. An additional 24-hour ambulatory blood pressure monitoring (ABP) was obtained just 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-minute throughout the 24-hour. Normal daily activities were allowed, and subjects were told to keep the arm as relaxed during measurements. Eventually, HT was defined as a BP of 135/85 mmHg or greater on mean daytime (between 10 AM to 8 PM) ABP, WCH as an OBP of 140/90 mmHg or greater but mean daytime ABP of <135/85 mmHg, and masked HT as an OBP of <140/90 mmHg or HBP of <135/85 mmHg but mean daytime ABP of 135/85 mmHg or greater (16). Eventually, all cases with overweight or obesity at and above the age of 50 years and desiring weight loss were divided into two subgroups according to wishes of patients about whether they prefer medication or just with a low-calorie diet. The diet was planned as a 1,500 calorie containing diet which was poor in animal source foods but rich in vegetables and fruits divided in four to six 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 were advised before meals to provide saturation with a freedom in amount. Additionally, foods that are high in sugars such as pastries, candy bars, pies, and candy were restricted. Metformin (850 mg tablet, Biokem, Turkey) at a dose of 2,550 mg/day in three divided dosages was given to the medication group orally, but the total dose was reached at the end of two weeks by increasing the dose 850 mg each week just to decrease some side effects of the drug. Patients were warned for the possible side effects of the drug including nausea, vomiting, anorexia, flatulence, sensation of a metallic taste in mouth, diarrhea, and abdominal discomfort. Patients were followed up for a period of six months with four-week intervals. At the end of this period, patients completing the follow-up were evaluated again, and prevalences of resolved WCH, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, overweight and obesity and prevalence of cases with a decreased

Table 1. Characteristics of All Cases at and above the Age of 50 Years

Variables	Prevalence in all (n=369)
Overweight	42.2% (156)
Obesity	42.5% (157)
White coat hypertension	43.6% (161)
Hypertension	23.5% (87)
Impaired glucose tolerance	21.1% (78)
Diabetes mellitus	31.4% (116)
Hyper-LDL-C*	33.6% (124)
Hypertriglyceridemia	44.4% (164)
Dyslipidemia	68.8% (254)

*Low density lipoprotein cholesterol

FPG below 110 mg/dL were detected in each group and compared in between. Student t-test and paired samples t-test were used as methods of statistical analysis.

Results

The study included 369 cases between the ages of 50 and 70 years, but 56 of them were of normal weight and none of them was in the underweight range. Regarding the very high prevalences, 84.8% (313/369) of cases at and above the age of 50 years were overweight or obese, 67.2% (248/369) of them had WCH or HT, 52.5% (194/369) of them had IGT or DM, and 68.8% (254/369) of them had dyslipidemia (Table 1). Initially 143 cases with excess weight preferred the diet and 162 of them preferred the metformin therapy. But 42 cases (25.9%) stopped the drug therapy because of an excessive anorexia. No one left the study in the diet group. At the end of the six-month period, there were highly significant differences between the two groups according to the prevalences of resolved WCH, hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, overweight, and obesity and a decreased FPG below 110 mg/dL ($p < 0.001$ for all) (Table 2). The mean weight loss was 10.3 ± 5.3 kg (range 3 and 17) in the metformin group, whereas it was 3.2 ± 4.7 kg (range 0 and 9) in the diet group. Although some cases progressed from obesity to overweight and from overweight to normal weight, there was no case going from obesity to normal weight in this period of time. Mean values of BMI, LDL-C, triglyceride, and HDL-C both in the metformin and diet groups before and after the therapies are shown in Tables 3, 4. On the other hand, nine cases (10.3%) of HT were masked HT, and the nine cases and 161 cases 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. Mean systolic/diastolic OBP,

HBP, ABP values and mean heart rates of the groups are summarized in Table 5. It was observed on ABP that the white coat effect was initiated by leaving home to come to the hospital.

Discussion

Excess weight probably leads to structural and functional abnormalities of body systems. Recent studies have revealed that adipose tissue produces biologically active leptin, tumor necrosis factor- α , plasminogen activator inhibitor-1, and adiponectin, which are closely related to development of complications (17), so it is important in medical terms to specify the excess weight not only as one of the risk factors, but as 'an obesity disease'. For example, cardiovascular field has recently shown great interest in role of inflammation in the development of atherosclerosis. Numerous recent epidemiological studies have indicated that inflammation plays an important role in pathogenesis of atherosclerosis and thrombosis (5, 6), and adipose tissue is involved in the regulation of cytokines (8). On the other hand, individuals with excess weight have an increased circulating blood volume as well as an increased cardiac output, thought to be a result of increased oxygen demand of the excess adipose 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 those, the prevalences of high FPG, high serum total cholesterol, and low HDL-C, and their clustering were all raised with increases in BMI (18). The combination of these cardiovascular risk factors eventually leads to an increase in left ventricular stroke work with a higher risk of arrhythmias, cardiac failure, and even a sudden cardiac death. Thus, the above prospective cohort study and some others showed that the BMI is one of the independent risk factors for stroke

Table 2. Comparison of the Study Cases

Variables	Cases of excess weight treated with diet alone (n=143)	Cases of excess weight treated with metformin alone (n=120)	p-value
Mean age (year)	56.9 ± 5.8 (50-70)	57.8 ± 6.3 (50-70)	>0.05
Female ratio	63.6% (91)	63.3% (76)	>0.05
Prevalence of resolved WCH*	20.0% (15/75)	65.1% (43/66)	<0.001
<u>Prevalence of resolved hyper-LDL-C†</u>	23.9% (11/46)	52.3% (22/42)	<0.001
Prevalence of resolved hypertriglyceridemia	19.6% (13/66)	57.6% (30/52)	<0.001
Prevalence of resolved dyslipidemia	18.0% (17/94)	47.6% (41/86)	<0.001
Prevalence of decreased FPG‡ below 110 mg/dL	19.7% (15/76)	52.3% (33/63)	<0.001
Prevalence of resolved overweight	4.2% (3/70)	15.2% (9/59)	<0.001
Prevalence of resolved obesity	2.7% (2/73)	13.1% (8/61)	<0.001

*White coat hypertension †Low density lipoprotein cholesterol ‡Fasting plasma glucose

Table 3. Comparison of Metformin Group before and after Therapy

Mean values	Before metformin therapy	After metformin therapy	p-value
Body mass index	32.4 ± 4.3 (25.2-40.5)	28.6 ± 3.7 (23.4-39.3)	<0.001
LDL-C*	146.5 ± 22.3 (99-242)	131.4 ± 18.7 (87-189)	<0.001
Triglyceride	182.4 ± 52.6 (77-382)	169.4 ± 49.2 (66-266)	<0.001
HDL-C†	42.2 ± 4.9 (27-69)	44.5 ± 4.9 (30-68)	<0.001

*Low density lipoprotein cholesterol †High density lipoprotein cholesterol

and CHD (18, 19). Eventually, risk of death from all causes, including cancers, increases throughout the range of moderate and severe excess weight both for men and women in all age groups (20).

In a previous study (21), we observed very high prevalences of WCH in society, 33.3% even in the second, 46.6% in the third, and 50.0% in the fourth decades of life, and prevalence of HT initially started to be higher than 40% in

Table 4. Comparison of Diet Group before and after Therapy

Mean values	Before diet therapy	After diet therapy	p-value
Body mass index	34.1 ± 4.2 (25.0-42.3)	33.9 ± 4.0 (23.6-41.0)	<0.001
LDL-C*	148.9 ± 20.3 (100-221)	146.0 ± 26.6 (70-221)	<0.001
Triglyceride	179.1 ± 32.1 (79-400)	178.9 ± 29.3 (110-350)	>0.05
HDL-C†	40.6 ± 5.3 (25-50)	41.5 ± 4.6 (19-60)	<0.01

*Low density lipoprotein cholesterol †High density lipoprotein cholesterol

Table 5. Mean Blood Pressure Values of the Study Cases

Variables	WCH* cases with excess weight before diet or metformin (n=150)	Unresolved WCH cases with diet or metformin (n=83)	Resolved WCH cases with diet or metformin (n=58)
Mean OBP†	155.3 ± 11.7/99.3 ± 13.1	157.3 ± 12.3/100.7 ± 15.3	121.5 ± 6.6/74.3 ± 5.3
Mean HBP‡	120.3 ± 12.3/74.3 ± 7.9	117.2 ± 8.9/78.3 ± 5.6	117.2 ± 6.9/75.5 ± 8.1
Mean ABP§	121.7 ± 11.7/75.3 ± 7.3	118.3 ± 11.5/77.1 ± 6.7	Not performed
Mean heart rate (beat/minute)	77.2 ± 13.3 (58-157)	74.3 ± 14.8 (59-153)	66.5 ± 11.3 (56-141)

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

the sixth and it reached up to 75% in the eighth decades of life. On the other hand, the prevalence of HT was detected only as 3% in the third, 8% in the fourth, and 21% in the fifth decades of life in the same study. The high prevalences of WCH in society have also been shown in some other studies (22, 23). So as a hypothesis, we came to propose that all HT cases, 75% in the eighth decade, may arise from the previously WCH cases, but this process takes a very long period of time reaching up to the normal life span of human being. So there would be some other significances of WCH for human health, thus in another study we evaluated the WCH not as a cause of HT or atherosclerosis alone but as a coexisting factor thus an alarming sign of something going bad for health (24). When we compared the sustained NT, WCH, and HT cases, prevalences of nearly all of the

health problems including obesity, IGT, type 2 DM, hyperbetalipoproteinemia, hypertriglyceridemia, and dyslipidemia showed significant progressions from the sustained NT towards the WCH and HT groups, and the WCH group was found as a significant progression step in between (24). Additionally, plasma homocysteine levels were significantly higher ($p<0.001$) and left ventricle mass index was significantly greater in the WCH group compared to the NT cases ($p<0.001$), but both were significantly lower in the WCH group than the HT cases ($p<0.001$ and $p=0.005$, respectively) in another study (25). Similarly, the very high prevalences of dyslipidemia (68.8%), excess weight (84.8%), and WCH (43.6%) may indicate a very close relationship between them in the present study, since the dyslipidemia will probably come with excess weight, HT, type 2 DM, CHD,

and stroke-like health problems in the future. In other words, WCH may show an accelerating trend of gaining weight. By this way, the detected higher prevalences of WCH even in the second (33.3%) and in the third decades of life (46.6%) (21), although the lower prevalences of excess weight in these age groups may show the trend of getting weight, and the dyslipidemia may be another pioneer sign of excess weight in these cases. Similarly, we previously detected that WCH and HT have significantly lower prevalences in underweight than in normal weight and overweight cases, probably as another indicator of the effects of weight on BP (2). Thus, in the present study, probably due to the significantly reduced prevalences of overweight and obesity in the metformin against the diet groups, the resolved WCH cases were significantly higher in the metformin group (20.0% vs 65.1%, $p < 0.001$). In other words, the ability of metformin to facilitate weight reduction or even stabilization, at least according to our opinion, is probably its main action to prevent WCH. On the other hand, the relationship between excess weight and elevated BP 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.

Biguanide was synthesized from two guanides which are the active components. Three widely used biguanides, metformin, buformin, and phenformin, were introduced in the late 1950s. Phenformin was withdrawn from clinical use in the late 1970s due to its close association with lactic acidosis (26). Metformin 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 as unchanged in urine. Plasma protein binding is negligible, so the drug is dialyzable. According to literature, antihyperglycemic effect of metformin is largely caused by inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal, and inhibition of fatty acid oxidation (27). Reduction of intestinal glucose absorption has been postulated as another possible mechanism of action, although data have been inconsistent (28). The precise mechanism of intracellular action of metformin remains uncertain. Interestingly, 25.9% (42 cases) of treated cases stopped the metformin therapy due to an excessive loss of appetite in the present study. Additionally, 14.1% (17 cases) of overweight or obese cases in the metformin group reached the normal weight or the overweight group, respectively, due to weight loss even in the absence of any given diet, whereas this ratio was only 3.4% (five cases) in the diet group. Thus, in our opinion, the major effect of metformin may be a powerful inhibition of ap-

petite under the light of already known role of excess weight on 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 previously reported by other researchers (14, 15). Although thiazolidine derivatives may also exhibit an improvement in glucose and lipid metabolism, we think that the major component of metabolic syndrome is excess weight, and by breaking it we are also able to prevent most of its consequences on health. Thus, we preferred the presence of excess weight to initiate the metformin therapy in the present study. So prevention of excess weight with metformin will probably prevent not only IGT or DM but also most of the other consequences of excess weight on health.

Numerous side effects of metformin have been reported in the literature including nausea, vomiting, anorexia, diarrhea, sensation of a metallic taste in mouth, and lactic acidosis (29). Lactic acidosis is a very rare side effect with an estimated incidence of 0.03 per 1,000 patient-years, and it is typically observed in critically ill patients particularly those with sepsis or suicide attempt (29). Metformin causes lactic acidosis through two mechanisms, namely a shift in the intracellular redox potential away from an aerobic towards an anaerobic metabolism, and suppression of hepatic gluconeogenesis from lactate. Similarly, it was observed in another study that there is an increase in the plasma lactate concentration in absence of any substantial change in arterial pH in patients receiving metformin (30). The clinical significance of this accumulation of lactate without acidosis is unclear. It was previously shown in septic patients that the increased lactate concentrations resulted from an acceleration in glycolysis in excess of glucose oxidation (30). 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 (31, 32). Due to the very low risk of life threatening side effects of metformin, even we have never seen in our clinic before, it can be initiated for the majority of cases with excess weight, but clinicians must be careful with patients above the age of 70 years due to risk of comorbid disorders such as chronic renal failure and a tendency to develop sepsis.

In conclusion, due to the very high prevalence of excess weight and probably many associated disorders including IGT or DM, WCH or HT, and dyslipidemia above the age of 50 years, and the detected significant benefits of metformin on all of the above disorders, metformin should be initiated in individuals with excess weight in their fifties.

References

1. 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* 17: **106**: 3143-3421, 2002.
2. Helvacı MR, Kaya H, Yalcin A, Kuvandik G. Prevalence of white coat hypertension in underweight and overweight subjects. *Int Heart J* **48**: 605-613, 2007.
3. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the

- Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* **42**: 1206-1252, 2003.
4. De Pergola G, Pannaciuoli N. Coagulation and fibrinolysis abnormalities in obesity. *J Endocrinol Invest* **25**: 899-904, 2002.
5. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol* **42**: 1149-1160, 2003.
6. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* **103**: 1813-1818, 2001.
7. Ridker PM. High-sensitivity C-reactive protein and cardiovascular risk: rationale for screening and primary prevention. *Am J Cardiol* **92**: 17-22, 2003.
8. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* **19**: 972-978, 1999.
9. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* **282**: 2131-2135, 1999.
10. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* **348**: 1625-1638, 2003.
11. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* **355**: 763-778, 2006.
12. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev* **3**: CD002966, 2005.
13. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med* **333**: 541-549, 1995.
14. Campbell IW, Howlett HC. Worldwide experience of metformin as an effective glucose-lowering agent: a meta-analysis. *Diabetes Metab Rev* **11**: 57-62, 1995.
15. Wu MS, Johnston P, Sheu WH, et al. Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. *Diabetes Care* **13**: 1-8, 1990.
16. O'Brien E, Asmar R, Beilin L, et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* **21**: 821-848, 2003.
17. Funahashi T, Nakamura T, Shimomura I, et al. Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. *Intern Med* **38**: 202-206, 1999.
18. Zhou B, Wu Y, Yang J, Li Y, Zhang H, Zhao L. Overweight is an independent risk factor for cardiovascular disease in Chinese populations. *Obes Rev* **3**: 147-156, 2002.
19. Zhou BF. Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases—report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. *Biomed Environ Sci* **15**: 245-252, 2002.
20. 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* **341**: 1097-1105, 1999.
21. Helvacı MR, Seyhanlı M. What a high prevalence of white coat hypertension in society! *Intern Med* **45**: 671-674, 2006.
22. 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* **25**: 57-63, 2002.
23. Celis H, Fagard RH. White-coat hypertension: a clinical review. *Eur J Intern Med* **15**: 348-357, 2004.
24. Helvacı MR, Kaya H, Seyhanlı M, Cosar E. White coat hypertension is associated with a greater all-cause mortality. *J Health Sci* **53**: 156-160, 2007.
25. Curgunlu A, Karter Y, Uzun H, et al. Hyperhomocysteinemia: an additional risk factor in white coat hypertension. *Int Heart J* **46**: 245-254, 2005.
26. Natrass M, Alberti KG. Biguanides. *Diabetologia* **14**: 71-74, 1978.
27. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med* **333**: 550-554, 1995.
28. Jackson RA, Hawa MI, Jaspán JB, et al. Mechanism of metformin action in non-insulin-dependent diabetes. *Diabetes* **36**: 632-640, 1987.
29. Chang CT, Chen YC, Fang JT, Huang CC. Metformin-associated lactic acidosis: case reports and literature review. *J Nephrol* **15**: 398-402, 2002.
30. 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* **224**: 97-102, 1996.
31. Lalau JD, Lacroix C, Compagnon P, et al. Role of metformin accumulation in metformin-associated lactic acidosis. *Diabetes Care* **18**: 779-784, 1995.
32. Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf* **20**: 377-384, 1999.