

The Effect of Gemfibrozil, Niacin and Cholestyramine Combination Therapy on Metabolic Syndrome in the Armed Forces Regression Study

Richard A. Krasuski, MD, Ganesh P. Devendra, BA, George Cater, BS, MS
and Edwin J. Whitney, MD

Abstract: *Introduction:* Metabolic syndrome is a powerful predictor of cardiovascular events independent of overt diabetes. Dietary restriction and weight loss modify metabolic syndrome components. This study addresses whether combination pharmacologic therapy focused on dyslipidemia provides additional benefit. *Methods:* This study examines the effect of 1 year of gemfibrozil, niacin and cholestyramine therapy on a baseline of aggressive dietary and lifestyle intervention in 143 clinically stable, nondiabetic patients with coronary disease, randomized into a double-blind, placebo-controlled trial. *Results:* Cohort characteristics included age 63 ± 7 years, 92% men, 43% with previous myocardial infarction, systolic blood pressure 139 ± 17 mm Hg, triglycerides 168 ± 81 mg/dL and high-density lipoprotein cholesterol 34 ± 6 mg/dL. The mean number of metabolic syndrome components decreased from 2.2 ± 0.9 to 1.5 ± 1.1 , $P < 0.001$, and metabolic syndrome prevalence decreased from 38% to 18% ($P < 0.001$) for the entire cohort. In the lifestyle intervention and placebo group, the mean number of metabolic syndrome components decreased from 2.2 ± 0.9 to 1.9 ± 1.1 ($P = 0.01$), and prevalence of metabolic syndrome decreased from 44% to 30% ($P = 0.15$). A far more marked change was observed with lifestyle intervention and pharmacologic therapy: abnormal metabolic components decreased from 2.2 ± 0.9 to 1.0 ± 1.0 ($P < 0.001$), and prevalence of metabolic syndrome decreased from 32% to 6% ($P < 0.001$). *Conclusions:* The combination of gemfibrozil, niacin and cholestyramine has profound, beneficial effects on the components of metabolic syndrome. These benefits are additive to those seen with aggressive diet and lifestyle modification.

Key Indexing Terms: Metabolic syndrome; Diabetes; HDL; Exercise. [Am J Med Sci 2011;341(5):378–382.]

Because of high calorie intake and a progressive reduction in physical activity, Americans have suffered from a 100% increase in the prevalence of obesity over the past 2 decades.¹ More than 40% of Americans now perform no significant leisure-time physical activity, and more than 60% of our population is either obese or overweight.² Gains in body weight are associated with greater degrees of insulin resistance³ and result in the development of dyslipidemia, hypertension and diabetes mellitus.^{4,5} The constellation of these findings has been coined the metabolic syndrome. The presence of metabolic syndrome is associated with increased cardiovascular morbidity and mortality and results in up to a 3-fold increase in

coronary artery disease and stroke.⁶ Although the presence of diabetes has been previously identified as a coronary disease equivalent,⁷ there is growing evidence that insulin resistance may itself be the culprit in accelerating atherosclerosis.⁸

Treatment for patients with metabolic syndrome has slowly been evolving. At the heart of risk modification is the recommendation for a healthy diet with a reduction in caloric intake appropriate for sustained weight loss.^{9,10} Patients should also be encouraged to participate in regular physical activity.¹¹ Unfortunately, despite the proven efficacy of both diet and exercise intervention in treating metabolic syndrome,^{12,13} compliance with lifestyle changes remains a significant obstacle.¹⁴ Certainly, the presence of these hurdles would suggest a more expansive role for pharmaceutical intervention in metabolic syndrome.

The Armed Forces Regression Study was a randomized, double-blind, placebo-controlled trial of gemfibrozil, niacin and cholestyramine combination therapy on a baseline of aggressive dietary and lifestyle intervention.¹⁵ This substudy was designed to examine the effect of 1 year of combination drug therapy on the prevalence of metabolic syndrome in a population of nondiabetic patients with angiographic evidence of coronary artery disease. The beneficial effect of 30 months of combination therapy, including regression of angiographic stenosis and reduction in clinical events, has previously been reported for the entire cohort.¹⁵

METHODS

Men and women younger than 76 years with suspected stable coronary artery disease and a fasting lipid panel demonstrating low-density lipoprotein cholesterol (LDL-c) levels ≤ 160 mg/dL and high-density lipoprotein cholesterol (HDL-c) levels < 40 mg/dL were recruited after documented adherence to the American Heart Association (AHA) Step II diet for at least 6 months. The exclusions have previously been published¹⁵ and included a major vascular event (myocardial infarction, cerebrovascular accident, coronary artery bypass grafting or other coronary catheter-based intervention) within 6 months, a history of congestive heart failure (other than in the setting of a myocardial infarction) or a left ventricular ejection fraction $< 40\%$ by ventriculography.

Participants were informed of the complete details of the study, and they enrolled voluntarily. Each patient signed an "Informed Consent Statement" that was reviewed and approved by the institutional review board at Wilford Hall Air Force Medical Center in San Antonio, Texas. Patient selection has been previously described in detail.¹⁵

After inclusion and exclusion criteria were met, a 6- to 8-month run-in period was performed to ensure that patients were capable of adhering to the prescribed diet. During this phase, all patients received dietary counseling from a study dietitian and exercise guidance from an exercise physiologist.

From the Division of Clinical Cardiology (RAK, GPD, GC), Department of CV Medicine, The Cleveland Clinic, Cleveland, Ohio; and Heart and Vascular Institute of San Antonio (EJW), San Antonio, Texas.

Submitted May 20, 2010; accepted in revised form August 13, 2010.

This study was supported by an unrestricted grant from Pfizer Pharmaceuticals.

Correspondence: Richard A. Krasuski, MD, Department of Cardiovascular Medicine, Desk F15, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195 (E-mail: krasusr@ccf.org).

They were enrolled in a smoking cessation program if necessary. All study participants also committed to attend a bi-monthly food show for training in the AHA Step II diet with reinforcing presentations from the dietitian, exercise specialist and cardiologist discussing cardiac risk factor modification.

Each participant was then block randomized to 1 of 2 treatment groups: pharmacologic therapy with gemfibrozil, niacin and cholestyramine and conventional therapy (which at the time of study enrollment did not include statins). The study was double blinded and placebo controlled. All medications and placebos were prepared by the pharmaceutical company and were dispensed at 30-day intervals. The pharmacologic therapy group began gemfibrozil at a dose of 600 mg twice a day, and short-acting niacin was added in the third month at a dose of 250 mg per day and titrated up to 3000 mg per day as tolerated. Cholestyramine was added in the sixth month, and the dose was titrated up to 16 g per day as tolerated. The conventional therapy group was maintained on the AHA Step II diet and applicable matching placebos for the duration of the investigation. Provisions were made to administer cholestyramine in an open-label fashion if LDL-c exceeded 160 mg/dL during the trial.

Participants visited a single clinic on a monthly basis for the duration of the study. At each monthly visit, vital signs and weight were measured, unused study drugs were returned and counted, changes in medications or medical status were reviewed, new supplies of study drugs were provided and fasting blood was sampled. Full lipid profiles (including measured LDL-c), liver enzymes and fasting blood glucose were obtained monthly for the first 6 months and then bimonthly for the remainder of the study. Metabolic syndrome parameters were defined as a body mass index (BMI) ≥ 30 , triglycerides ≥ 150 mg/dL, a HDL-C < 50 mg/dL for women and < 40 mg/dL for men, a systolic blood pressure ≥ 130 mm Hg, and a fasting blood sugar ≥ 110 mg/dL.

Data were compiled and analyzed using a statistical software package (JMP 8.0, © SAS Institute, Cary, NC). Comparison of continuous variables was performed using a 2-sample *t* test on mean percent changes from baseline to 50 weeks of follow-up. Comparisons of dichotomous outcomes were performed using Fisher exact test or χ^2 test where appropriate. Data are presented as mean \pm standard deviation for continuous variables and as a number (percentage) for dichotomous variables. A *P* value less than or equal to 0.05 was considered statistically significant.

RESULTS

The baseline demographic information of the 143 patients randomized into the Armed Forces Regression Study is listed in Table 1. Seventy-one patients received the combination of gemfibrozil, niacin and/or cholestyramine and 72 received corresponding placebos. All but 2 patients in each group tolerated the goal dose of 600 mg of gemfibrozil (or matching placebo) daily. The mean dose of niacin achieved in the treatment arm was 2.5 ± 1.0 g daily, whereas the mean dose of cholestyramine was 8.4 ± 6.2 g daily. Seventeen patients in the placebo arm and only 2 in the treatment arm received open-label cholestyramine ($P < 0.001$). Patient characteristics were well balanced between the drug and placebo arms.

The lipid profiles, fasting blood sugars and blood pressures at the time of randomization are also listed in Table 1. Adherence to the AHA Step II diet was assessed by 3-day diet histories at study initiation, after 50 weeks of drug or placebo therapy and at the completion of the study. These demonstrate

TABLE 1. Baseline demographic data of patients randomized in the AFREGS trial

Demographics	All patients (n = 143)
Age (yr; mean \pm SD)	63.2 \pm 7.1
Female (%)	7.7
History of hypertension (%)	71.3
History of angina (%)	65.0
History of myocardial infarction (%)	43.4
Previous smoker (%)	84.6
Active smoker (%)	8.4
Weight (lbs; mean \pm SD)	182.9 \pm 28.1
Body mass index (kg/m ² ; mean \pm SD)	26.5 \pm 3.7
Systolic blood pressure	138.9 \pm 17.3
Diastolic blood pressure	75.8 \pm 9.6
Fasting blood glucose	81.8 \pm 13.6
Total cholesterol	196.2 \pm 30.6
LDL cholesterol	128.3 \pm 26.5
HDL cholesterol	34.1 \pm 5.7
Triglycerides	168.2 \pm 81

AFREGS, Armed Forces Regression Study; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

remarkable compliance with the imposed dietary and caloric restrictions. The comparison of dietary parameters at study initiation and after 50 weeks of therapy is presented in Table 2.

Table 3 compares the change in bloodwork in the 2 groups observed after 50 weeks of therapy. Substantial reductions were seen in total cholesterol, LDL-C and triglycerides and an increase in HDL-C in the treatment arm compared with the placebo arm at 50 weeks. Both groups experienced a loss of weight and a decrease in BMI, although the magnitude was greater in the treatment arm. There was an increase in the fasting blood glucose in the treatment arm, although this did not translate to more diagnoses of diabetes using the widely accepted fasting glucose threshold of 126 mg/dL. Reported adverse reactions to the medication regimen have been previously described¹⁵ and included skin rash, flushing and abdominal pain.

Figure 1 compares the distribution of abnormal metabolic parameters for the entire patient population at baseline and after 1 year. The prevalence of metabolic syndrome decreased from 37.9% to 18.0% during the course of the year

TABLE 2. Measures of compliance with American Heart Association Step II diet during the AFREGS trial

Measure	Time	All patients ^a
Calories	Baseline	1545.4 \pm 430
	50 weeks	1555.9 \pm 453
Cholesterol (mg)	Baseline	144.2 \pm 82.1
	50 weeks	155.5 \pm 81.4
Fat (%)	Baseline	22 \pm 8.1
	50 weeks	21 \pm 6.8
Saturated fat (%)	Baseline	4.3 \pm 2.2
	50 weeks	4 \pm 1.9

^a Mean \pm standard deviation.

AFREGS, Armed Forces Regression Study.

TABLE 3. Percent changes in laboratory parameters in patients randomized in the AFREGS trial

Percent change ^a	Drug therapy	Placebo	P
BMI	-4.8	-0.8	<0.001
Systolic blood pressure	-9.8	-6.6	0.14
Fasting glucose ^b	17.6	8.1	0.006
Total cholesterol	-16.7	2.8	<0.001
LDL cholesterol	-21.8	4.6	<0.001
HDL cholesterol	37.9	2.0	<0.001
Triglycerides	-45.6	4.2	<0.001

^a 100 × (value at 50 weeks – value at baseline)/(value at baseline).

^b Zero patients had fasting glucose ≥126 mg/dL at baseline or at 1 year.

AFREGS, Armed Forces Regression Study; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

(*P* < 0.001). Figure 2 compares the distribution of abnormal metabolic parameters for both the treated and placebo groups at baseline and at 1 year, respectively. The prevalence of metabolic syndrome decreased from 43.5% to 30.4% in the placebo group (*P* = 0.15), whereas the prevalence of metabolic syndrome decreased from 32.4% to 5.7% in the treated group (*P* < 0.001). There was not a significant difference in the prevalence of metabolic syndrome between the placebo and treatment groups at baseline (*P* = 0.22), but a significant difference was apparent (*P* < 0.01) at 1 year.

Table 4 shows the change in mean number of abnormal metabolic parameters during the observation period. In the placebo group, the mean number of metabolic syndrome components decreased from 2.2 ± 0.9 to 1.9 ± 1.1 (*P* = 0.01). A far more marked change was observed in the treatment group with abnormal metabolic components decreasing from 2.2 ±

0.9 to 1.0 ± 1.0 (*P* < 0.001) There was no significant difference in the number of abnormal metabolic parameters among patients assigned to placebo and treatment groups at baseline (*P* = 0.73), but a significant difference was noted (*P* < 0.001) at 1 year.

DISCUSSION

In a population of patients already undergoing aggressive diet and exercise modifications to reduce cardiovascular risk factors, the addition of combination pharmacologic therapy significantly decreased the prevalence of metabolic syndrome after only a year of therapy. Although previous studies have indicated that weight reduction and regular exercise are the most important therapeutic interventions for the treatment of metabolic syndrome,¹⁶ to our knowledge, this study is the first to imply that drug therapy in combination with lifestyle modifications has profound, additional benefit on metabolic syndrome components.

In the analysis of this extremely compliant patient population, there was an overall reduction in the mean number of metabolic syndrome components from 2.2 ± 0.8 to 1.5 ± 1.1 (*P* < 0.001), with a corresponding decrease in metabolic syndrome prevalence from 37.9% to 18.0% (*P* < 0.01) after 1 year of intervention. Those who received placebo on top of diet and exercise modification had a modest improvement in metabolic syndrome prevalence (43.5% to 30.4%, *P* = 0.15) and mean number of abnormal metabolic parameters (2.2 ± 0.9 to 1.9 ± 1.1, *P* = 0.01). These results are consistent with previous reports that demonstrated the benefit of cardiac rehabilitation and exercise training on metabolic syndrome.¹⁷ Interestingly, those who received pharmacologic therapy on top of diet and exercise modification demonstrated a more robust improvement in prevalence of metabolic syndrome (32.4% to 5.7%, *P* < 0.001) and mean number of abnormal metabolic parameters (2.2 ± 0.9 to 1.0 ± 1.0, *P* < 0.001).

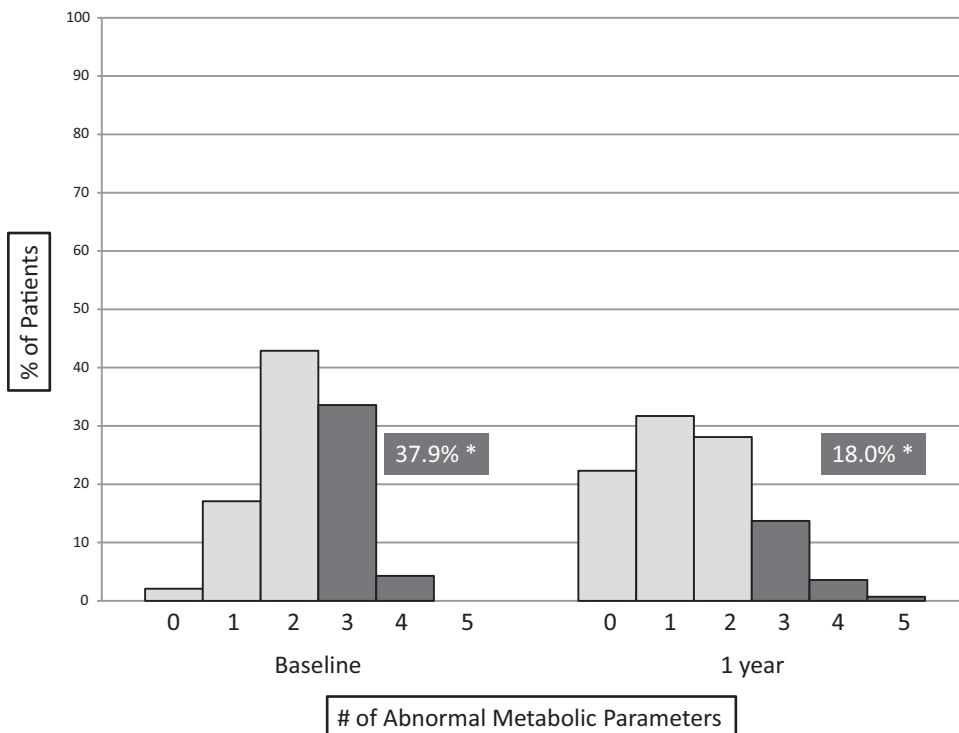
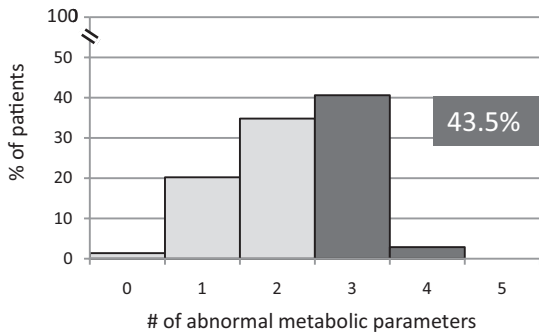
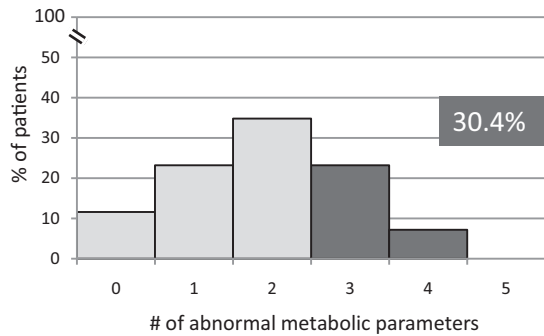


FIGURE 1. Distribution of abnormal metabolic parameters at baseline and at 1 year for all patients. Number of metabolic syndrome components decreased from 2.2 ± 0.9 to 1.5 ± 1.1, *P* < 0.001. *Prevalence of metabolic syndrome decreased from 37.9% to 18.0%, *P* < 0.001.

A Baseline Placebo

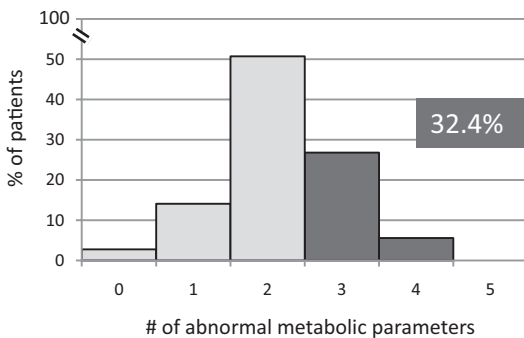


B 1 year Placebo



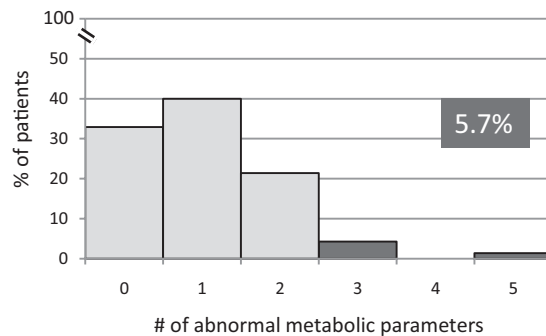
P=0.15

C Baseline Treated



P=0.22

D 1 year Treated



P<0.001

P<0.001

FIGURE 2. Distribution of abnormal metabolic parameters in treated and untreated patients at baseline and after 1 year.

These results confirm the benefits of dietary modifications and regular exercise on factors such as BMI, glucose tolerance, hypertension and hyperlipidemia. Interestingly, however, significant differences were noted in many of these factors between the control and combination drug therapy groups. It would be expected that significant improvements in the lipid profile would be seen with pharmacologic therapy, because the therapeutic targets of gemfibrozil, niacin and cholestyramine lead to reductions in LDL-C and triglycerides and increases in HDL-C. The significant decrease in BMI in patients receiving drug therapy, however, also suggests other, less well-defined targets of these agents, which may lead to reductions in body weight and ultimately impact the other components of metabolic syndrome. It is important to note that these improvements occurred in the context of a significant increase in fasting blood glucose, undoubtedly the result of niacin. It has previously been suggested that niacin should be avoided in patients with insulin

resistance for this reason, and insulin resistance seems to be the backbone of metabolic syndrome. Despite these adverse effects on glycemic control, no patients developed overt diabetes, and the other components of the metabolic syndrome were improved to the extent that metabolic syndrome prevalence was actually reduced. These results reflect those of other previous studies, including the Arterial Disease Multiple Intervention Trial,¹⁸ and suggest safety of niacin-based regimens in such patients.

Furthermore, although the prevalence of metabolic syndrome in both groups of patients was similar at baseline, the pharmacologic therapy group had a significant reduction in metabolic syndrome than the group that received diet and exercise alone. This demonstrates that adjunctive pharmacologic therapy targeted at optimizing lipid levels provides enhanced outcomes in the population of patients who have metabolic syndrome and have yet to progress to diabetes. With modifications of the current therapeutic approach, it may be possible to further reduce the incidence of the metabolic syndrome and thus reduce the risk for cardiovascular events. Our analysis is limited by the fact that none of these patients were treated with a statin drug, which would now be standard of care for a majority of patients in this cohort. The administration of a statin would of course contraindicate the inclusion of gemfibrozil in the regimen.

In summary, these data support the current guidelines of lifestyle changes to combat metabolic syndrome and suggest

TABLE 4. Mean number of abnormal metabolic parameters at baseline and at 1 year

	Baseline	1 Year	P
Placebo	2.2 ± 0.9	1.9 ± 1.1	0.01
Treated	2.2 ± 0.9	1.0 ± 1.0	<0.001
P	0.73	<0.001	

that they can successfully accomplish this goal. However, the addition of a therapeutic regimen using gemfibrozil, niacin and cholestyramine can further reduce metabolic syndrome in these patients. The mechanism by which this occurs seems to be through the optimization of the lipid profile and reduction in BMI. Although glucose levels may increase, they do not seem to result in the development of diabetes. Our study size was small and the population was predominantly men, making the applicability to female patients less clear. Our analysis is strengthened, however, by a compliant patient population, allowing for the true evaluation of the interventions studied. The fact that the study was conducted in the pre-statin era allows insight into a nontraditional approach and should stimulate consideration of a head-to-head comparison with statin therapy in this high cardiovascular risk patient population.

REFERENCES

1. Khan LK, Sobush K, Keener D, et al. Recommended community strategies and measurements to prevent obesity in the United States. *MMWR Recomm Rep* 2009;58:1–26.
2. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006;295:1549–55.
3. Pereira MA, Kartashov AI, Ebbeling CB, et al. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. *Lancet* 2005;365:36–42.
4. Colditz GA, Willett WC, Rotnitzky A, et al. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995; 122:481–6.
5. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009;53:1925–32.
6. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; 24:683–9.
7. Juutilainen A, Lehto S, Ronnema T, et al. Type 2 diabetes as a “coronary heart disease equivalent”: an 18-year prospective population-based study in Finnish subjects. *Diabetes Care* 2005;28:2901–7.
8. Lempiainen P, Mykkanen L, Pyorala K, et al. Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. *Circulation* 1999;100:123–8.
9. Wagh A, Stone NJ. Treatment of metabolic syndrome. *Expert Rev Cardiovasc Ther* 2004;2:213–28.
10. Pasanisi F, Contaldo F, de Simone G, et al. Benefits of sustained moderate weight loss in obesity. *Nutr Metab Cardiovasc Dis* 2001;11: 401–6.
11. Pacholczyk M, Ferenc T, Kowalski J. [Metabolic syndrome. Part III: its prevention and therapeutic management]. *Postepy Hig Med Dosw (Online)* 2008;62:559–70.
12. Singh RB, Singh NK, Rastogi SS, et al. Effects of diet and lifestyle changes on atherosclerotic risk factors after 24 weeks on the Indian Diet Heart Study. *Am J Cardiol* 1993;71:1283–8.
13. Anderssen SA, Hjermann I, Urdal P, et al. Improved carbohydrate metabolism after physical training and dietary intervention in individuals with the “atherothrombotic syndrome.” Oslo Diet and Exercise Study (ODES). A randomized trial. *J Intern Med* 1996;240:203–9.
14. Fappa E, Yannakoulia M, Pitsavos C, et al. Lifestyle intervention in the management of metabolic syndrome: could we improve adherence issues? *Nutrition* 2008;24:286–91.
15. Whitney EJ, Krasuski RA, Personius BE, et al. A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events. *Ann Intern Med* 2005;142:95–104.
16. Jiamsripong P, Mookadam M, Alharthi MS, et al. The metabolic syndrome and cardiovascular disease: part 2. *Prev Cardiol* 2008;11: 223–9.
17. Milani RV, Lavie CJ. Prevalence and profile of metabolic syndrome in patients following acute coronary events and effects of therapeutic lifestyle change with cardiac rehabilitation. *Am J Cardiol* 2003;92: 50–4.
18. Chesney CM, Elam MB, Herd JA, et al. Effect of niacin, warfarin, and antioxidant therapy on coagulation parameters in patients with peripheral arterial disease in the Arterial Disease Multiple Intervention Trial (ADMIT). *Am Heart J* 2000;140:631–6.