IMPACT OF DIET, PHYSICAL ACTIVITY, LIPID STATUS AND GLYCOREGULATION IN ESTIMATION OF SCORE (SYSTEMATIC CORONARY RISK EVALUATION) FOR TEN YEARS IN POSTMENOPAUSAL WOMEN

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Abstract

The incidence of cardiovascular diseases (CVD) in women, although lower than in men, increases dramatically after the menopause. Diabetes mellitus is a more powerful predictor of CHD risk and prognosis in women than in men. The aim of this study was to promote diet and physical activity (PA) regimen in order to decrease coronary risk in next years in postmenopausal women with impaired glucose tolerance. Methodological approach of this research is to compare data gathered trough prospective and retrospective analysis of anamnestic data, clinical research, diagnostic tests and biochemical parameters of 100 examinees, regarding the glycoregulation, lipid status, body mass indexes, incidence of hypertension, uric acid and fibrinogen level. The SCORE (Systematic Coronary Risk Evaluation) assessment system is derived from a large dataset of prospective European studies and predicts any kind of fatal CVD events over a ten-year period. It was documented that the then year risk of fatal CVD exerted a shift toward the lower percent value in postmenopausal women after proposed diet/PA regimen. In pre-menopausal women the estimated ten year risk of fatal CVD by SCORE was shifted toward the level bellow 1%. The risk of 15% and above was not documented after diet/physical activity regimen. The prevalence of the atherogenic lipid markers at the beginning and the end of the assay decreased for all investigated lipid parameters in the group of pre-menopausal women what was more than in postmenopausal ones. Presented data indicate that dietary regimen and physical activity are crucial factors in CVD prevention throughout menopause and beyond. Behavioral changes aimed at decreasing food intake and increasing energy expenditure, should be implemented in pre-menopausal period of life.

KEY WORDS: diet, physical activity, lipid status, glycoregulation , SCORE (Systematic Coronary Risk), postmenopausal women

Introduction

Significant advances in knowledge in interventions aimed to prevent female-specific cardiovascular disease (CVD) were pointed out after the first recommendations for preventive cardiology in 1999 (1). Despite research-based gains in the treatment of CVD, it remains the leading risk factor of women in the United States and developed parts of the world. In the United States alone, more than one half million women die of CVD each year, or approximately 1 death every minute, exceeding the number of deaths in men. Coronary heart disease (CHD) accounts for the majority of CVD deaths in women, disproportionately afflicting racial and ethnic minorities, and is a prime target for prevention (1,2). Because CHD is often fatal, nearly two thirds of women who die suddenly have no previously recognized symptoms, it is essential to make a specific approach in preventing CHD(2,3). The incidence of myocardial infarction (MI) in women, increases dramatically after the menopause. Risk factors such as smoking and dyslipidemia may be particularly important (4). Lifestyle intervention reduces the risk of progression from impaired glucose tolerance (IGT) to type 2 diabetes. It is widely assumed that current advice regarding physical activity and dietary modification is sufficient to reduce the risk of type 2 diabetes. It is presumably mediated via an improvement in insulin sensitivity. It appears that once abnormal glucose levels have developed, significant metabolic dysfunction has already occurred, and there is less chance of improving insulin sensitivity (5,6). According to the guidelines of the National Cholesterol Education Program (NCEP)(7) and a scientific statement from the American Heart Association (AHA) and American College of Cardiology (ACC)(8), the primary cardiovascular risk factors in women are: personal history of CHD; Age over 55; dyslipidemia: high LDL and/or low HDL; family history of premature CHD and diabetes mellitus; smoking; hypertension and peripheral vascular disease. Their assessment should be an important component of periodic health examinations. Elevated triglycerides, obesity and a sedentary lifestyle, while not considered primary risk factors in the NCEP guidelines, are also highly associated with coronary risk and assessment is recommended by the AHA/ACC guidelines (8, 9). Diabetes mellitus carries greater prognostic information in women than any of the other traditional cardiac risk factors and is confirmed to be the most important predictor for CHD in women (10). Menopause is defined, for statistical and epidemiologic purposes, as the absence of menses for 1 year. Menopause is adult-onset ovarian failure, with the loss of estrogens, progesterone, and ovarian androgens. The loss of estrogens can lead to vasomotor symptoms, sleep disturbances, mood alteration, depression, urinary tract and vaginal atrophy, and increased health risks for several chronic disorders, including osteoporosis, cardiovascular disease, and loss of cognitive function. Although the pathophysiological changes associated with estrogen deficiency in postmenopausal women are relatively well understood, the effects of the absence of progesterone and decrease of androgens are not fully appreciated (11). In the current study we tried to determine the impact of lipid status, glycoregulation body weight and hypertension as a risk of fatal CVD among postmenopausal women. The possible influence of lifestyle changes, such as six months physical activity and diet regimen, on coronary risk changes were assessed. The SCORE (Systematic Coronary Risk Evaluation) risk assessment system is derived from a large dataset of prospective European studies and predicts any kind of fatal atherosclerotic end-point i.e. fatal CVD events over a ten-year period. Using SCORE it is now possible to produce risk charts tailored for individual countries which may provide reliable national mortality informations.

Patients and Methods

Patients and clinical examination: Methodological approach was examined trough prospective and retrospective analysis of anamnestic data, clinical research, diagnostic tests and biochemical parameters. Research was conducted at the Clinic for endocrinology Faculty of medicine Niš and Institute for prevention, treatment and rehabilitation of rheumatic and cardiovascular diseases Niška Banja Faculty of Medicine Niš and at the Center for medical biochemistry University Clinical Center Niš. The research study involved 100 examinees. All examinees were followed at least 6 moths. Examined groups were formed based on next criteria: presence of hyperlipidemia, menopause, as absents of regular menstrual bleeding in one whole year, values of glucose and other risk factors. Individuals were divided into 2 groups: I: postmenopausal women with hyperlipoproteinemia and glycoregulation disorder (N=50); II premenopausal women with hyperlipoproteinemia and glycoregulation disorders (N=50); Clinical evaluation at the beginning of research included precise anamnestic data based on a questionnaire designed by Institute for prevention, treatment and rehabilitation of rheumatic and cardiovascular diseases Niška Banja, anthropometric

measurements for calculating Body Mass Index (BMI) and type of obesity, registered blood-pressure (BP), clinical manifestation of dyslipidemias and atherosclerosis, determined diet and other components of life style (11). *Biochemical analyses*: Standard methods for determining lipids and lipoproteins, fibrinogen, uric acid and glucose in blood were used. On the basis of clinical examination and biochemical analyses, the atherogenic ratio, calculation of atherogenic phenotype, lipid levels of risk, glycoregulation, risk factor of non lipid origin and absolute ten year risk for nonfatal cardiovascular event were determined (12). After clinical examination, the examinees received recommendation for physical activities and diet. Control was done after third and sixth month. Total cholesterol (TC) was determined by enzyme color test (PAP method)(13). Triglycerides (TG) were determined by enzyme color test, modified PAP reaction- PAP (GPO) (14). Very low density lipoprotein cholesterol (VLDL-C) was calculated indirectly trough its formula VLDL-C= TG/2,2 (15). High-density lipoprotein cholesterol (HDL-C) was determined by enzyme color test (PAP method), (16). Low-density lipoprotein cholesterol (LDL-C) was calculated indirectly trough its formula LDL-C = TC - TG / 2,2 - HDL-C (15). Non high-density lipoprotein cholesterol (nonHDL-C) was calculated indirectly non HDL-C=TC – HDL-C.

Nutrient	Recommended intake
Saturated fat	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25-35% of total calories
Carbohydrate	50-60% of total calories
Fiber	20-30 g/day
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total calories (energy)	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

TABLE 1. Nutrient composition (7)

HDL ratio was calculated as HDL-C/(TC-HDL-C) (17). All reagents were purchased from the Randox Company, estimated on the Synchron CX, Beckman analyzer. Glucose was determined by GOD-PAP method on Synchron CX, Beckman analyzer (18). Uric acid was determined by enzyme color test, with modified Trinder, PAP method, measured on the Synchron CX, Beckman analyzer (19). Fibrinogen was determined by turbidimetric method (20). Oral glucose tolerance test oGTT was preformed in the morning after 10 hours abstinent from food intake. The patients were taking 75 grams of glucose dissolved in 200 ml of water with le mon. Blood for determining glucose was taken before and 30, 60, 90 and 120 minute after orally taken glucose (21). *Diet*: Food and energy intake were adjusted for achiev-

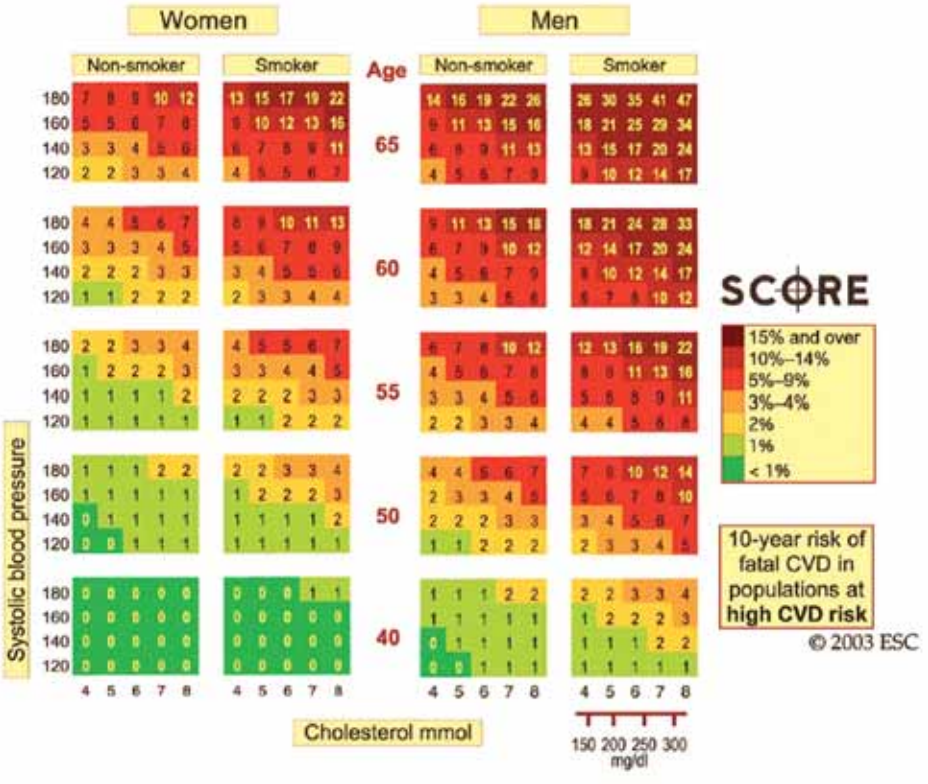

FIGURE 1. Figure 1. Ten year risk of fatal CVD in high risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status (22)

Non-lipid risk factors	Postmenopausal women with hyperlipoproteinemia and glycoregulation disorder			
	Baseline value	6-Month value	Residuum (%)	p
BMI (kg/m²)	30,41 ± 4,31	27,82 ± 3,69	- 8,5	0,05
Systolic blood pressure (mmHg)	149 ± 15,36	132 ± 9,52	- 11,5	0,0001
Diastolic blood pressure (mmHg)	94,5 ± 6,86	84,5 ± 5,11	- 10,6	0,0001
Fibrinogen (g/L)	4,42 ± 1,18	4,13 ± 0,95	- 6,6	NS
Uric acid (µmol/l)	313,71 ± 105,1	279 ± 88,9	- 11,1	0,05
Waist circumference (cm)	94,2 ± 11,7	84,2 ± 10,6	- 10,7	0,001
Fasting plasma glucose (mmol/l)	7,47 ± 0,79	5,44 ± 0,83	- 27,2	0,00001
2-h postload glucose (mmol/l)	10,66 ± 0,87	8,33 ± 0,95	- 21,9	0,00001

TABLE 2. Examined non-lipid risk factors at the beginning and the end of assay for postmenopausal women

ing an ideal weight. Next types of food should be recommended: fruit and vegetables, products with less fat and fish meat. For fat intake the advice was not to precede more than 30% of total energy intake, for saturated fat to be 1/3 of total fat intake. Cholesterol intake should be less than 200 mg per day (Table 1.) (7).

Physical activity: Patients received recommendation for physical activity lasting 30-60 min, 4-6 times a week or 30 min every day, the load not to exceed 60-75% average of maximal heart rate. Physical activities should start with warm up and then successively cooling. Exercise comprised of various activities such as: driving a bicycle, swimming, fast walking, and housework.

Statistical tests: Student's independent t-test (normal distribution); $\chi 2$-test; The Pearson product – moment coefficient of correlation (r) was used to assess associations between variables.

Estimation of SCORE: Ten year risk of fatal CVD in high risk regions of Europe was estimated according to the guidelines recommending a new model for total risk estimation based on the SCORE (Systematic Coronary Risk Evaluation) system. It predicts any kind of fatal atherosclerotic end-point i.e. fatal CVD events over a ten-year period. In SCORE the following risk factors are integrated: gender, age, smoking, systolic blood pressure and either total cholesterol or the cholesterol/HDL ratio. Since this chart predicts fatal events the threshold for being at high risk is defined as ≥5%, instead of the previous ≥20% in charts using a composite coronary endpoint (22).

Results

Postmenopausal women with hyperlipoproteinemia and glycoregulation disordes: Assay had 50 individuals age behalf with 58,11 ± 5,88 who had positive family history of cardiovascular disease (CVD) risk (70%). Among them, 55% were smokers. Non lipid risk factors have noted significant reduction after 6 month carried out diet and physical activity in the BMI, systolic and diastolic blood pressure and waist circumference. In this group a trend of a significant decrease of fasting plasma glucose and 2h-post load glucose after six months therapy was documented (Table 2). Only fibrinogen was not significantly changed. After six months of diet/physical activity regimen, the atherogenic lipid profile (TC, LDL-C, TG) was significantly decreased, while HDL cholesterol tended to be higher (Table 3).

Pre-menopausal women with hyperlipoproteinemia and glycoregulation disorders: Assay had 50 individuals age 41,55 ± 4,55 year, 60% had positive family history of CVD. Among them, 45% were smokers. Non lipid risk factors have noted significant reduction after 6 month carried out diet and physical activity in the BMI, systolic and diastolic blood pressure and waist circumference. Only fibrinogen and uric acid level remained unchanged (Table 4).

In this group a highly significant decrease of fasting plasma glucose and 2h-post load glucose after six months therapy was documented as well (Table 2). A six

Lipid risk factors	Postmenopausal women with hyperlipoproteinemia and glycoregulation disorder			
	Baseline value	6-Month value	Residuum (%)	p
Total cholesterol (TC)	7,42 ± 1,18	6,74 ± 1,16	- 9,2	0,05
Triglyceride (TG)	3,19 ± 1,24	2,74 ± 0,99	- 14,2	0,01
VLDL-C	1,45 ± 0,56	1,24 ± 0,45	- 14,5	0,01
LDL-C	4,97 ± 0,69	4,37 ± 0,64	- 12,1	0,005
nonHDL-C	6,39 ± 1,22	5,64 ± 1,19	- 11,8	0,01
HDL-C	1,02 ± 0,21	1,11 ± 0,17	+ 8,8	NS
LDL-C/HDL-C	5,07 ± 1,27	4,04 ± 0,87	- 21,4	0,001
TC/HDL-C	7,58 ± 2,12	6,26 ± 1,64	- 17,5	0,01
TC/LDL-C	1,51 ± 0,26	1,56 ± 0,29	+ 3,3	NS
HDL-ratio	0,17 ± 0,05	0,21 ± 0,05	+ 23,5	0,001

TABLE 3. Lipid parameters and ratio at the beginning and the end of assay for postmenopausal women

Non-lipid risk factors	Pre-menopausal women with hyperlipoproteinemia and glycoregulation disorder			
	Baseline value	6-Month value	Residuum (%)	p
BMI (kg/m²)	27,31 ± 2,32	24,96 ± 1,72	- 8,7	0,005
Systolic blood pressure (mmHg)	136,75 ± 13,69	124,25 ± 4,38	- 9,2	0,001
Diastolic blood pressure (mmHg)	88,25 ± 7,99	83,25 ± 4,06	- 5,7	0,05
Fibrinogen (g/l)	3,85 ± 1,02	3,67 ± 0,84	- 4,7	NS
Uric acid (µmol/l)	260,75 ± 65,34	249,93 ± 56,68	- 4,2	NS
Waist circumference (cm)	88,4 ± 11,4	82,5 ± 10,7	- 6,7	0,05
Fasting plasma glucose (mmol/l)	6,58 ± 0,68	5,21 ± 0,52	- 20,9	0,00001
2-h postload glucose (mmol/l)	10,43 ± 0,85	7,95 ± 0,67	- 23,8	0,00001

TABLE 4. Examined non-lipid risk factors at the beginning and the end of assay for postmenopausal women

Lipid risk factors	Pre-menopausal women with hyperlipoproteinemia and glycoregulation disorder			
	Baseline value	6-Month value	Residuum (%)	p
Total cholesterol (TC)	7,17 ± 1,05	6,51 ± 0,95	- 9,3	0,05
Triglyceride (TG)	2,81 ± 0,79	2,54 ± 0,71	- 9,7	0,01
VLDL-C	1,27 ± 0,36	1,16 ± 0,32	- 8,7	NS
LDL-C	5,03 ± 0,74	4,55 ± 0,66	- 9,6	0,01
nonHDL-C	5,81 ± 1,15	5,06 ± 1,08	- 12,9	0,01
HDL-C	1,37 ± 0,33	1,45 ± 0,33	+ 5,8	NS
LDL-C/HDL-C	3,92 ± 1,31	3,34 ± 1,07	- 14,8	0,01
TC/HDL-C	5,54 ± 1,74	4,74 ± 1,45	- 14,5	0,01
TC/LDL-C	1,45 ± 0,27	1,46 ± 0,27	+ 0,7	NS
HDL-ratio	0,25 ± 0,09	0,31 ± 0,11	+ 24	0,001

TABLE 5. Lipid parameters and ratio at the beginning and the end of assay for pre-menopausal women

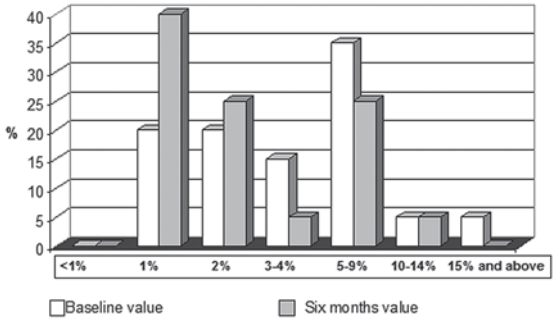

FIGURE 2. Ten-year risk assessment of fatal CVD in postmenopausal women

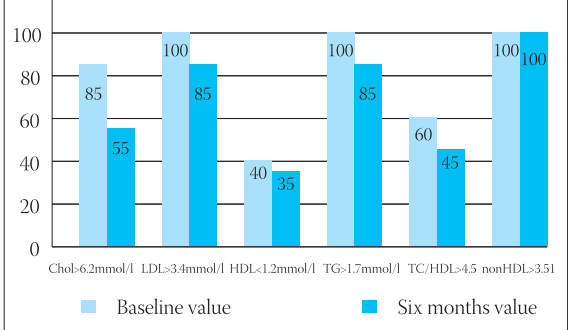

FIGURE 3. Percent of the prevalence of atherogenic markers at the beginning and after six months in postmenopausal women

months of diet/physical activity regimen exerted benefit on the atherogenic lipid profile (TC, LDL-C, TG), did not change significantly VLDL cholesterol, while HDL cholesterol tended to be higher (Table 5).

By estimating SCORE it was documented that the then year risk of fatal CVD exerted a shift toward the lower percent value in postmenopausal women. It was mainly due to the increased number of examinees with SCORE being 1%. The risk of 15% and above was not documented after diet/physical activity regimen (Figure 2). By estimating the prevalence of atherogenic lipid markers it was documented that TC decrease was amongst the most important predictive factors for decreasing atherogenic risk in this population (Figure 3). In pre-menopausal women the estimated ten year risk of fatal CVD by SCORE was shifted toward the level bellow 1%. No one was noted to have a risk above 1% (Figure 4). The prevalence of the atherogenic lipid markers at the begin-

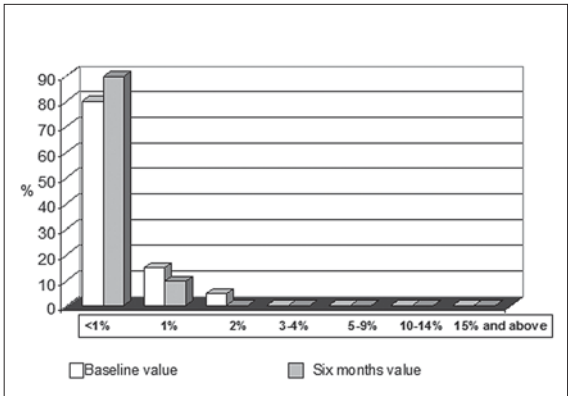

FIGURE 4. Ten year risk of fatal CVD in pre-menopausal women

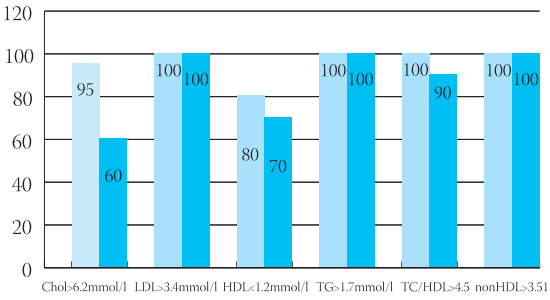

FIGURE 5. Percent of the prevalence of atherogenic markers at the beginning and after six months in pre-menopausal women

ning and the end of the assay was decreased for all investigated lipid parameters in this group of women (Figure 5).

Discussion

Menopause is often associated with weight gain. The early postmenopausal years are associated with accelerated weight gain. Evidence for this comes from a Swedish study that assessed BMI in a cross-sectional sample of adult population 16-84 years of age (23). Women exhibit a sharp increase in obesity between the ages 45 and 54. There is also evidence suggesting that menopause is associated with changes in body composition and fat distribution. The proportion of android (upper-body) fat to gynoid (lower-body) fat deposition is greater in postmenopausal than in pre-menopausal women. In the Iowa Women's Study, which followed over 30 000 postmenopausal women, the difference between the two sites of fat deposition became clear (24). The estrogen has an effect on the form of obesity, its deficiency leads women to attain the metabolic syndrome of overweight/obese men. Both overall and cardiovascular mortality correlated better with abdominal adiposity, as assessed by the waist hip ratio, than with BMI (a more general measure of adiposity). The hormone replacement therapy has been shown to decrease the shift from gynoid to android fat deposition after menopause (25). A comparison of middle-aged female twins found that among environmental factors influencing total and abdominal fat mass, physical activity (PA) had the strongest effect. The postmenopausal years have been associated with lower levels of PA, leading to a lower energy expenditure and greater abdominal adiposity in this time of life. Among women aged 50-64, only half reported doing any regular PA, while only about one quarter report high intensity exercise (26). Therefore, insufficient PA can be an important factor in postmenopausal weight gain. It was documented that the type 2 diabetes mellitus can be prevented or delayed through lifestyle interventions, because this disease has a prolonged pre-diabetic phase. Patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) have a risk for diabetes. Among other risk factors for diabetes are body mass index (BMI) greater than 25 kg per m2, sedentary lifestyle, hypertension, dyslipidemia, history of gestational diabetes or large-for-gestational-age infant, and polycystic ovary syndrome (5). Up to now, 279 potentially relevant studies were occupied with the relation between physical activity and glucose tolerance (27). A great number of patients with IGT have shown success for lifestyle interventions in delaying or preventing the development of diabetes. There is a strong evidence that a well structured program of diet and exercise may reduce the risk of progression to type 2 diabetes in patients with IGT. It was shown that the risk of diabetes was reduced by approximately 50% with changes in physical activity levels. The contribution of physical activity independent of dietary or weight loss changes to the prevention of type 2 diabetes in people with pre-diabetes is equivocal. Moderate exercise on a regular, long-term basis has several effects on muscle function that lead to more efficient use of energy. These changes include increases in the quantity of mitochondrial enzymes and the number of "slow-twitch" muscle fibers, and the development of new muscle capillaries. There is also increased translocation of insulin-responsive glucose transporters (GLUT4) from intracellular stores to the cell surface. GLUT4 promotes glucose uptake, which probably explains the overall increase in insulin sensitivity (28). The Finnish Twin Cohort study of almost 8000 same sex twin pairs found an odds ratio for death of 0,66 in occasional exercisers and 0,44 in conditioning exercisers compared with their sedentary twins (29). A benefit from light to moderate exercise has been also shown for Healthy ; the benefit is again related to the duration of exercise (30). Virtually identical findings were noted in a review of over 70,000 postmenopausal women in the Women's Health Initiative Observational Study in which prolonged sitting predicted an increase in cardiovascular risk (31). Exercise training programs increase activity of mitochondrial enzymes, leading to improved muscle energy expenditure, decreased insulin resistance, and a lower rate of progression to overt type 2 diabetes (5,6). A number of studies have shown a strong inverse relationship between leisure time activity and energy expenditure, habitual exercise, and fitness and the risk of coronary disease and death. Although most observa-

tions were made in men, a similar cardiovascular benefit from fitness has been found in women and across different ethnic groups (32). The Nurses' Health study of 72,488 women between 40 to 65 years of age found that brisk walking or vigorous exercise was inversely related to the risk of a coronary event; in a multivariate analysis, women in increasing quintile groups for energy expenditure had age-adjusted relative risks for coronary events of 0,88; 0,81; 0,74 and 0,66, indicating a graded benefit from exercise. Sedentary women who became active in mid life or later had a lower incidence of coronary events compared to those who remained inactive (32). Prolonged exercise programs cause a greater decrease in abdominal fat. This is important because subjects with abdominal obesity are at increased cardiovascular risk. Exercise reduces serum triglycerides and increases serum HDL-cholesterol, with variable effects on total cholesterol, LDL-cholesterol and VLDL-cholesterol (33). The risk of cardiovascular diseases increases continuously as blood pressure (BP) rises from levels that are considered to be within the normal range. The decision to start treatment, however, depends not only on the level of blood pressure, but also on an assessment of total cardiovascular risk and the presence or absence of target organ damage (34,35. The institution of a regular exercise regimen (such as jogging two miles or riding a bicycle for 45 minutes) can, within four weeks, lower the BP by as much as 5 to 15 mmHg in patients with essential hypertension (5).

Conclusion

Obtained results confirmed that diet/physical activity regimen has a great impact on delay of possible cardiovascular events in both, postmenopausal and pre-menopausal women. By using SCORE it is now possible to produce risk charts tailored for individual countries that may provide reliable national mortality information available. Practitioners should use total CVD risk estimation when decisions are taken to intensify preventive actions when dietary advice should be more specified, when the physical activity prescription should be more individualized, when drugs should be prescribed, dosages adapted or combinations started to control risk factors. These decisions should usually not be based on the level of any one risk factor alone. The data presented above strongly indicate that physical activity is a crucial factor in weight control and disease prevention throughout menopause and beyond. Another action against modern day illnesses is proper nutrition, comprising of fruit, vegetables and grains, with limited fat and salt. Behavioral changes aimed at decreasing food intake and increasing energy expenditure should be implemented in the life.

List of Abbrevations

ACC-	American College of Cardiology
AHA	American Heart Association
BMI	Body Mass Index
BP	Blood Pressure
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
GLUT-4	Insulin-Responsive Glucose Transporters
HDL-C	High Density Lipoprotein Cholesterol
IGT	Impaired Glucose Tolerance
LDL-C	Low Density Liporotein Cholesterol
NCEP	National Cholesterol Education Program
OGTT	Oral Glucose Tolerans Test
PA	Physical Activity
SCORE	Systematic Coronary Risk Evaluation
TC	Total Cholesterol
TG	Triglicerydes
VLDL	Very Low Density Lipoprotein

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