Effect of ethanol on metabolic syndrome

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Abstract: Metabolic syndrome is characterized by a group of risk factors for cardiovascular diseases, such as abdominal obesity, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides, elevated arterial blood pressure, insulin resistance or impaired glucose tolerance. A number of studies focused on the relationship between alcohol consumption and prevalence of metabolic syndrome and its individual components. Ethanol can either aggravate the syndrome or prevent it – this depends primarily on the amounts and types of alcohol beverages consumed. It is commonly believed that moderate alcohol consumption is associated with a decreased incidence of metabolic syndrome and beneficial effects on plasma lipid levels, waist circumference and fasting plasma glucose. Of all the components of metabolic syndrome, the most beneficial effect of ethanol arises from an increase in plasma HDL cholesterol levels. The relationship between alcohol consumption and incidence of metabolic syndrome is more pronounced among red wine drinkers because polyphenoles contained in red wine increase the activity of endothelial nitric oxide synthase (eNOS), which plays a key role in the pathogenesis of metabolic syndrome. Decreased activity of this enzyme contributes to the development of insulin resistance, arterial hypertension and dyslipidemia. Stimulation of eNOS activity, which participates in the transport of HDL molecules, may provide an explanation for the mechanism of the increase in plasma levels of this particular lipid fraction in response to ethanol. Endothelial nitric oxide synthase requires the presence of antioxidants, which prevent both inactivation of nitric oxide in the reaction with peroxide anions and the accumulation of peroxynitrates.

Key words: ethanol, metabolic syndrome

The term "metabolic syndrome" means the occurrence of several risk factors for cardiovascular system diseases and diabetes at the same time. The components of this syndrome are: abdominal obesity, hyperinsulinaemia, insulin resistance, impaired fasting and postprandial glucose tolerance, type 2 diabetes, arterial hypertension, hyperlipidaemia and dyslipidemia, elevated free fatty acids blood level, microalbuminuria, hiperuricaemia, elevated leptin and diminished adiponectin blood level, plasminogen activator inhibitor type-1 level elevation [1]. All mentioned factors, often occurring in one person, represent a serious population health threat as they accelerate the atherosclerosis formation and development, which is mentioned on top of the 21st century civilization diseases list [2]. There are no uniform definitions or diagnostic criteria for the metabolic syndrome, which would be accepted all over the world without reservation, as yet. The National Cholesterol Education Adult Treatment Panel III in the United States attempted to define diagnostic criteria in 2001 [3]. They include:

1) abdominal obesity (waist circumference): males >102 cm, females >88 cm
2) triglycerides (TG) level ≥150 mg/dl (1.7 mmol/l);
3) high-density lipoproteins (HDL) cholesterol level: males <40 mg/dl (1.3 mmol/l), females <50 mg/dl (1.04 mmol/l)
4) fasting glucose ≥100 mg/dl (6.1 mmol/l) or diagnosed diabetes
5) arterial blood pressure ≥130/85 mmHg or treated hypertension.

In order to diagnose the metabolic syndrome, 3 of 5 of the above mentioned criteria are sufficient. The mentioned definition does not include symptoms directly related to insulin resistance, which is measured with the use of such tests as fasting insulinaemia or by obtaining the homeostasis model assessment method ratio. Another metabolic syndrome definition differentiates:

1) main criteria: insulin resistance, abdominal obesity, dislipidaemia, arterial hypertension, impaired glucose tolerance or type 2 diabetes, hiperuricaemia
2) additional criteria: hypercoagulation, polycystic ovaries syndrome, endothelial function impairment, microalbuminuria, ischemic heart disease [4].

Another metabolic syndrome definition was formulated in 2005. It is based on the so called Berlin criteria of the International Diabetes Federation, which state that central obesity (≥80 cm waist circumference in European females and ≥94 cm

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waist circumference in European males) is associated with 2 of 4 of the following factors:

1) triglycerides level >150 mg/dl (1.7 mmol/l), or treatment of this disorder
2) HDL-cholesterol level: males <40 mg/dl (1. 3 mmol/l), females <50 mg/dl (1.04 mmol/l), or treatment of this disorder;
3) arterial blood pressure>135/80 mm Hg, or treatment of arterial hypertension;
4) fasting glucose >100 mg/dl (6.1 mmol/l), or earlier diagnosed type 2 diabetes 2 [5].

Current medical sciences development brings new information thanks to which the metabolic syndrome definition and diagnostic criteria can be evolved. There are suggestions for including other factors in the syndrome's criteria, like, for example, adiponectin, interleukin 6 (IL-6) and C – reactive protein [6].

Lack of precise criteria for the metabolic syndrome definition is the reason why clinical data concerning its incidence are equivocal. The tendency for the incidence to rise with age (from 5% at 20–30 years to >40% over 60 years) is observed [2].

One of the components of the metabolic syndrome is obesity, which is diagnosed at the body mass index value >30 kg/m^2. Based on the waist-to-hip ratio, that is the ratio of waist circumference to hip circumference at the superior iliac spin, obesity may be either gynoidal or androidal (visceral and abdominal). Visceral obesity constitutes 96% cases of themetabolic syndrome. The pathogenesis is related to numerous, various factors, the most important ones being genetic and environmental. Genetic defects concern mainly appetite and satiety regulation and thermogenesis. Another reason is fetal and infantile malnutrition. Among the environmental obesity development factors, lack of physical exercise and inappropriate nutrition, play a dominant role [7].

The most serious obesity consequences are: diabetes, ischemic heart disease, arterial hypertension and atherosclerosis. Adipose tissue is not only an energy store, but also plays an important role in the metabolic processes as an active endocrine and paracrine gland. Compounds secreted by the adipose tissue regulate the lipid metabolism and influence hemostasis. These substances include leptin, responsible for the energetic balance, and resistin, the adipokine which inhibits the differentiation of adipocytes, regulates the adipose tissue mass and influences the development of insulin resistance. Angiotensinogen, the linking factor for obesity and arterial hypertension development, is also produced in adipocytes. The substances secreted by the adipose tissue are cytokines, like the tumor necrosis factor α, IL-6, transforming growth factor β, adipsin. An important adipocytokine is adiponectin which regulates the metabolism of free fatty acids and glucose in the liver and in skeletal muscles, in which the insulin sensitivity rises. This cytokine plays the endogenic anticoagulating factor role, and its insufficiency is the reason for thromboembolic complications [8]. It has the ability of inhibiting the proliferation and migration of smooth muscle cells and limits the development of foam cells, as well as augments the endothelium nitric oxide synthesis [9].

Apart from that a diminished adiponectin level is seen as an independent type 2 diabetes and metabolic syndrome development risk factor. Okamoto et al. [10] showed a negative correlation between adiponectin levels and the extent of insulin resistance.

Insulin resistance depends on an impaired function and an improper organism response to endogenic and exogenic insulin in processes concerning the carbohydrates, lipids and proteins metabolism. This condition leads to endothelium damage, vascular wall fibroblast proliferation, chronic inflammation, atheromatic plaque formation, and hypercoagulation [11]. The abdominal adipose tissue plays a key role in the development of insulin resistance. An increased lipolysis results in an augmented liver glucose production and a diminished muscle uptake of glucose.

However, a diminished nitric oxide production and augmented endotheline 1 synthesis occur in the vascular endothelium. Insulin resistance is the main drive of metabolic disorders, leading to the development of diabetes. An elevated glucose level is the reason for its autooxidation, being the base for oxidative stress. Free oxygen radicals have an impact on hemostasis and fibrinolysis and damage the endothelium through protein, lipids and nucleic acids oxidation. Endothelium dysfunction is aggravated by glycation of numerous proteins, including the endothelium function regulating protein [12,13]. Proteins of the basement membrane, as well as collagen and extracellular matrix also undergo glycation which causes the membrane thickening. Oxidative stress, protein glycation and lipoprotein oxidation lead to a chronic inflammatory condition. Released chemotaxin induces the adherence of macrophages to the endothelium, and monocytes transformation to tissue macrophages that absorb lipid deposits. Foam cells and atheromatic plaque which damages the vascular wall, are being formed. Apart from that the oxidative stress through the decrease of nitric oxide (NO) vascular synthesis inhibitor activity, increases the vascular contractility. These factors lead to arterial hypertension development, which is another metabolic syndrome element. [14].

The mechanism of hypertension development in this syndrome may be as follows:

1) insulin resistance and hyperinsulinaemia increase the sympathetic system activity which results in augmentation of cardiac output and peripheral resistance
2) adrenergic activation causes the constriction of renal vessels and sodium reuptake increase
3) hyperinsulinaemia stimulates vascular wall myocyte proliferation and increases its rigidity
4) insulin has direct inotropic effect.

The analysis of initial arterial blood pressure values and the body mass index relation, revealed there being a positive correlation, which, however, was statistically non-significant [15].

In arterial hypertensive patients endothelium dysfunction results in disorders which are metabolic syndrome components

[16]. The studies have shown that in arterial hypertensive patients, insulin resistance, hyperinsulinaemia and dislipidaemia occur. A whole variety of lipid disorders can be seen in the metabolic syndrome. Hypertriglycerydemia and a diminished HDL fraction level are found in the lipid profile of patients with this syndrome. In low-density lipoproteins fraction (LDL) dominate so called small dense LDL, revealing a much greater than normal LDL molecules atherogenic effect. It is a consequence of physiological hepatocyte LDL receptors lower affinity [17]. Insulin resistance, which increases lipolysis and leads to FFA levels elevation is the initial point in the metabolic syndrome dislipidaemia pathogenesis. These in turn, impair the insulin effect in the liver, thus increasing gluconeogenesis and glycogenolysis and a very low density lipoprotein (VLDL) production. As a result of a non sufficient cholesterol ester transfer protein (CETP) inhibition by insulin, a large quantities of TG are being absorbed by the HDL and LDL molecules. This way the small and dense LDL and dense HDL3, which are unstable and easily decomposed in the liver, are being formed. A diminution of HDL level, followed by an increased risk for ischemic heart disease, can therefore be seen in the metabolic syndrome [18].

Ethanol and the metabolic syndrome

The mechanism of metabolic syndrome development is not fully revealed yet. It is possibly the result of the interaction of several genetic and environmental factors, like: physical activity, diet, cigarette smoking, and alcohol intake. Numerous studies concerning the ethanol influence on metabolic syndrome indicate that it can either enhance or inhibit the disease development. [19,20]. It is related to a variety and multiplicity of metabolic syndrome components and depends on the amount and type of ethanol consumed. A positive influence of ethanol on one of the factors, provided it does not cause unwanted alterations concerning another component, may be linked to the metabolic syndrome risk reduction. It is believed that a moderate alcohol intake leads to a diminution of the metabolic syndrome occurrence risk. The alcoholic drinks intake of ≤20 per month reduces the risk by 35%, while the intake of >20 doses per month by as much as 66% [21].

The suggested ethanol protective mechanism takes into consideration its influence on lipoprotein synthesis, mainly through the increase of the HDL level and a rise in the hepatic apolipoproteins class A production, in molecules containing this protein. According to Rimma et al. [22], a daily dose of 30 g ethanol results in an average HDL level rise of 3.99 mg/dl, and an apolipoproteins A I level rise of 8.82 mg/dl. Ethanol also causes an increase of triglyceride lipase activity and a decrease of the HDL removal from the circulation [23]. It has also been found that alcohol influences the CETP activity rise and the reduction in cholesterol ester transformation from the HDL to more atheromatic molecules [24]. The blood HDL level rise is observed regardless of the amount of alcohol consumed. Unfortunately, ethanol in doses >30 g/d in females and males can augment the TG level. It has been found that the ethanol intake of 60 g/d increases the TG level by about 0.19 mg/dl per 1 gram of alcohol consumed. However, the TG level augmentation results in the intensification of extra hepatic lipoprotein lipase production. The lipolysis of the TG rich molecules increases the transformation of cholesterol to the HDL molecules from the circulating VLDL remnants, and increases the total HDL level [25]. Therefore the final risk balance speaks in favor of mechanisms inhibiting the metabolic syndrome development, the more so because in individuals drinking up to 15 g/d, a diminution of the TG level and a rise in the HDL level can be observed [20].

The epidemiological surveys results concerning the relation between the alcohol intake and obesity are not compatible. If drinking is associated with food consumption there is a risk of an increase in body mass. However, if there are digestive tract problems, a loss of body mass and even cahexia may be expected, as the use of hepatic glycogen, one of the energetic substrates of the organism, is not being compensated [26]. Sakurai et al. [27] found that drinking alcohol shows a positive correlation with the waist circumference versus hip circumference at the level of superior iliac spine, but does not show an important correlation with the body mass index. At the same time, according to Liu et al. [28] alcohol does not influence any of these ratios and does not result in an obesity risk increase. Other studies, in which the odds ratio (OR) of abdominal obesity occurrence increases with the rise of alcohol intake, do not confirm it however. In males drinking >30 g/d and >80 g/d the OR is 1.08 and 2.02, respectively, and in females drinking >30 g/d the OR is 1.72 [20]. On the other hand it should be noted that some studies showed that a waist circumference diminution can be found in individuals drinking a moderate amount of alcohol , especially wine [29].

The disturbances of carbohydrate metabolism are very frequent in people abusing alcohol. Ethanol induces disturbances of hepatic gluconeogenesis preventing lactate oxidation to pyruvate. What is more, the excess of NADH leads to the diminution of pyruvate and oxaloacetate amount, which are being reduced respectively to lactate and malate. Thus, acute alcohol poisoning may induce hypoglycemia, especially in individuals with initially low glycogen storages or in people with earlier disturbances of carbohydrate metabolism. The exhaustion of the glycogen reserve leads to serious hypoglycemia. Immediately after alcohol consumption the glucose level increases and then, decreases [30]. It must be remembered however, that with the stimulation of the sympathetic system and adrenal medulla epinephrine secretion, and in individuals with primary anomalous insulin secretion, after the intake of alcohol an acceleration rather than inhibition of gluconeogenesis as well as glucose release from liver glycogen reservoirs are found, which leads to a rise in blood glucose level. Chronic pancreatitis is a result of long term alcohol abuse. It has been observed that it most often occurs in the 40–50-year-old males after 10 years of drinking and causes exocrine and endocrine disturbances of the pancreas function [31]. Alcohol may therefore

induce the occurrence of secondary diabetes resulting from the pancreatic B cell islets destruction, but may also be a risk factor of type 2 diabetes. This is probably related to the fact that alcohol abuse induces the rise of 2 blood diols: 2.3-butenodiol and 1.2-propanediol, levels. These compounds reduce the glucose utilizing ability of the organism (by about 30%), decrease the glycogen synthesis in muscles and the heart, and are responsible for the insulin resistance rise [32]. Alcohol may also influence the therapy of diagnosed diabetes. One drink a day may have a positive effect on the diabetic patient, as it increases insulin sensitivity and the HDL level, and decreases platelet aggregation; however habitual drinking increases the risk of lactic acidosis and ketoacidosis. Alcohol abuse is a contraindication to the biguanides use, which also creates the risk of lactic acodisis [33].

The results of studies of the alcohol intake influence on the glucose level are often equivocal. It is observed that the OR is <1 for males (regardless of the amount alcohol consumed) and for females (<30 g/d), however it rises with the rise of the amount of ethanol consumed. Some studies suggest that a moderate alcohol intake reduces diabetes risk, and others that it either increases it or has no effect on the development of this disease [34,35]. It may result from differences in used methods, measurements and in the amounts and types of alcoholic beverages studied. In individuals drinking 6–48 g/d the risk for diabetes occurrence is described as lower by about 30% than in abstainers, and in individuals drinking >48 g/d the OR ratio to abstainers was 1.04 [36].

Numerous epidemiological and clinical studies point to about a 30% risk of arterial hypertension occurrence due to the ethanol intake [20,37]. There is a significant rise in the systolic and diastolic blood pressure. The hypertensive response of the circulatory and vascular systems to ethanol has not been fully revealed yet. The concept of the repeated withdrawal syndrome during which time the activity of the sympathetic and the rennin-angiotensin-aldosterone systems rises, seems most probable. Another suggested mechanism consists in the rise of systemic resistance as a result of the direct influence of ethanol. It has been found that the risk for hypertension rises with the amount of alcohol consumed. It white males due to alcohol consumption of about 15–30 g/d the OR was 1.29, and with the consumption of >80 g/d it rose to 1.88. There are reports about the hipotensive effect of ethanol, which recommend a daily intake of alcohol of about 15 g/d [20]. It should also be stressed that after the withdrawal from alcohol the blood pressure values may come back to normal.

Apart from the HDL level, which advantageously rises, even with large amounts of alcohol consumed, the other components of the metabolic syndrome show less favorable alterations.

The value of OR for high TG levels, obesity, fasting glucose and hypertension rises with the rise of alcohol consumption. However, the OR of metabolic syndrome occurrence in people abusing alcohol does not show a statistically significant rise. It is probably due to the masking effect of HDL, which plays a key role in the metabolic syndrome [20].

The dependence of metabolic syndrome occurrence frequency on the alcohol intake is more pronounced in whites than in blacks. This concerns the mentioned syndrome incidence diminution with a moderate, occasional ethanol intake (so called: social drinking), as well as the increase of the number of the metabolic syndrome cases due to alcohol abuse. It has also been found that of all alcoholic beverages, red wine, for which the OR at a consumption of 20–30 drinks per month is 0.28, has a positive impact [21]. It is related to the presence of polyphenols in red wine, which have strong antioxidant properties. Apart from that these natural flavonoids (especially quercetin) may lower the blood pressure through their influence on the vascular endothelium and the inhibition of the endotelin1 secretion, which has a vasoconstrictive effect [38]. Ethanol also induces the nitric oxide endothelium production, the vascular relaxation main mediator. Endothelial nitric oxide synthase (eNOS) plays an important role in this process [39,40]. The produced nitric oxide is however very sensitive to the presence of free radicals, which react with it and form peroxinitrates which damage the vascular walls. The endothelial nitric oxide synthase defect plays an important role in the pathogenesis of the metabolic syndrome. The consequence of the diminished activity of this enzyme is insulin resistance, arterial hypertension and dyslipidemia. The stimulation of the eNOS, which takes part in the HDL transportation, may explain the mechanism of the rise of this fraction due to alcohol influence. The endothelial nitric oxide synthase requires the presence of the antioxidants, protecting from the NO inactivation due to reaction with superoxide anions and from peroxinitrates accumulation. Also tetrahydrobiopterin, being the cofactor for the eNOS, must be protected from oxidation by antioxidants [41]. This protective role may be played by polyphenols contained in red wine. Apart from that polyphenols have a positive effect on the gamma receptors activated by peroxisome proliferators which stimulate the NO release from endothelial cells, and their defects lead to the development of metabolic syndrome [42]. An additional confirmation of the hypothesis that red wine takes part in the metabolic syndrome control is the fact that oxidative stress plays an important role in the pathogenesis of this syndrome. The oxidative stress reduction causes not only the diminution of biological structures damage, but also a change in metabolic pathways responsible for the syndromes development. The high eNOS activity, which requires an antioxidative protection of, for example, polyphenols, limits superoxides production and decreases the oxidative stress [43].

SUMMARY

Ethanol is one of the factors influencing the metabolic syndrome development. The action of ethanol may either encourage or limit the development of this syndrome, which depends mainly on the amount of alcohol consumed. In individuals drinking 15–20 g of alcohol daily a metabolic syndrome incidence of >60% less than in abstainers, is observed, and it

is even less in individuals consuming red wine. This is due to polyphenols contained in it, and their protective action towards the eNOS. From among elements constituting the metabolic syndrome the most positive seems to be the influence of ethanol on the increase of the HDL cholesterol fraction level.

REFERENCES

1. Reaven GM. The metabolic sydrome, requiescat in pace. Clin Chem. 2005; 51: 93-98.
2. Janeczko D. Zespół metaboliczny – epidemia XXI wieku. Przew Lek. 2005; 3: 14-27.
3. Executive Summary of the Third Report of the National Education Program (NCLP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001; 248-2497.
4. Kahn R, Buse J, Ferrannini E, et al. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2005; 28: 2289-2304.
5. Kociecki M. Zespół metaboliczny w roku 2006. Przegl Kard. 2006; 1: 55-60.
6. Ravanglia G, Forti P, Maioli F, et al. Metabolic Syndrome: prevalence and prediction of mortality in elderly individuals. Diabetes Care. 2006; 29: 2471-2476.
7. Despres JP. Is visceral obesity the cause of the metabolic syndrome? Ann Med. 2006; 38: 52-63.
8. Kato H, Kashiwagi H, Shiraga M, et al. Adiponectin acts as an endogenous antithrombotic factor. Arterioscler Thromb Vasc Biol. 2006; 26: 224-230.
9. Kopff B, Jegier A. Wysiłek fizyczny a wybrane adipokiny: adiponektyna, leptyna i rezystyna. Pol Arch Med Wewn. 2006; 116: 73-84.
10. Okamoto Y, Kihara S, Funahashi T, et al. Adiponectin: a key adipocytokin in metabolic syndrome. Clin Sci. 2006; 110: 267-278.
11. Reaven GM. Role of insulin resistance in human disease. Diabetes. 1998; 37: 1595-1607.
12. Tan K, Chow WS, Ai VH, et al. Advanced glycation end products and endothelial dysfunction in type 2 diabetes. Diabetes Care. 2002; 25: 1055-1059.
13. Meigs JB, Hu FB, Rifai N, et al. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA. 2003; 291: 1978-1986.
14. Ronnback M, Isomaa B, Fagerudd J, et al. Complex relationship between blood pressure and mortality in type 2 diabetic patients: a follow-up of the Botnia Study. Hypertension. 2006; 47: 168-173.
15. Kałka D, Sobieszczańska M, Marciniak W, et al. Zależność ciśnienia tętniczego od indeksu masy ciała u pacjentów z chorobą niedokrwienną serca poddanych rehabilitacji kardiologicznej. Pol Arch Med Wewn. 2006; 116: 741-748.
16. Steciwko A, Reksa D, Grotowska M. Śródbłonek i jego rola w patogenezie różnych jednostek chorobowych. Pol Arch Med Wewn. 2006; 116: 819-831.
17. Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. JAMA. 1996; 276: 875-881.
18. Gott AM, Brinton EA. Assessing low levels of high-density lipoprotein cholesterol as a risk factor in coronary heart disease: a working group report and update. J Am Cardiol. 2004; 43: 717-724.
19. Goude D, Fagerberg G, Hulthe J. Alcohol consumption, the metabolic syndrome and insulin resistance in 58-year-old clinically healthy men. Clin Sci. 2002; 102: 345-352.
20. Yoon YS, Oh SW, Baik H, et al. Alcohol consumption and the metabolic syndrome in Korean adults: the 1998 Korean National Health and Nutrition Examination Survey. Am J Clin Nutr. 2004; 80: 217-224.
21. Freiberg MS, Cabral HJ, Heeren TC, et al. Alcohol consumption and the prevalence of the Metabolic Syndrome in the US.: a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey. Diabetes Care. 2004; 27: 2954-2959.
22. Rimm EB, Williams P, Fosher K, et al. Moderate alcohol intake and lower coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. BMJ. 1999; 319: 1523-1528.
23. Savolainen MJ, Kesaniemi YA. Effects of alcohol lipoproteins in relation to coronary heart disease. Curr Opin Lipidol. 1995; 6: 243-250.
24. Hannuksela M, Marcel YL, Kesaniemi YA. Reduction in the concentration and activity of plasma cholesteryl ester transfer protein by alcohol. J Lipid Res. 1992; 33: 737-744.
25. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceryde level, low-density lipoprotein particle diameter, and risk of myocardial infarction. JAMA. 1996; 276: 882-888.
26. Sieradzki J. Zespól metaboliczny – wznowiona dyskusja. Terapia. 2006; 5: 29-32.
27. Sakurai Y, Umeda T, Shinchi K. et al. Relation of total and beverage-specific alcohol intake to body mass index and waist-to-hip ratio: a study of self-defense officials in Japan. Eur J Epidemiol. 1997; 13: 893-898.
28. Liu S, Serdula MK, Williamson D, et al. A prospective study of alcohol intake and change in body weight among US adults. Am J Epidemiol. 1994; 140: 912-920.
29. Duncan BB, Chambless LE, Schmidt MI, et al. Association of the waist-to-hip ratio is different with wine than with beer or hard liquor consumption. Atherosclerosis Risk in Communities Study Investigators. Am J Epidemiol. 1995; 142: 1034-1038.
30. Polskie Forum Profilaktyki. Alkohol a choroby układu sercowo-naczyniowego. 2006; 1: 1-8.
31. Greenhouse L, Lardinois CK. Alcohol-associated diabetes mellitus. A review of the impact of alcohol consumption on carbohydrate metabolism. Arch Fam Med.1996; 5: 229-233.
32. Xu D, Dhillon AS, Abelmann A, et al. Alcohol – related diols cause acute insulin resistance in vivo. Metabolism.1998; 47: 1180-1187.
33. Cox WM, Blount JP, Crowe PA, et al. Diabetic patients alcohol use and quality of life: relationships with prescribed treatment compliance among older males. Alcohol Clin Exp Res. 1996; 20: 327-331.
34. Holbrook T, Barrett-Connor E, Wingard D. A prospective population-based study of alcohol use and non-insulin-dependent diabetes mellitus. Am J Epidemiol. 1990; 132: 902-909.
35. Tsumura K, Hayashi T, Suematsu C, et al. Daily alcohol consumption and the risk of type 2 diabetes in Japanese men: the Osaka. Diabetes Care. 1999; 22: 1432-1437.
36. Carlsson S, Hammar N, Efendic S, et al. Alcohol consumption, Type 2 diabetes mellitus and impaired glucose tolerance in middle-aged Swedish men. Diabet Med. 2000; 17: 776-781.
37. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003; 289: 2560-2572.
38. Corder R, Douthwaite JA, Lees DM, et al. Endothelin-1 synthesis reduced by red wine. Nature 2001; 414: 863-864.
39. Leikert JF, Rathel TP, Wohlfart P, et al. Red wine polyphenols enhance endpthelial nitric oxide synthase expression and subsequent nitric oxide release from endothelial cells. Circulation. 2002; 106: 1614-1617.
40. Leighton F, Miranda-Rottmann S, Urquiaga I. A central role of eNOS in the protective effect of wine against metabolic syndrome. Cell Biochem Funct. 2006; 24: 291-298.
41. Landmesser U, Dikalov S, Price SR, et al. Oxidation of tetrahydrobiopterin leads to uncoupling of endothelial cell nitric oxide synthase in hypertension. J Clin Invest. 2003; 111: 1201-1209.
42. Gurnell M, Savage DB, Chatterjee VK, et al. The metabolic syndrome: peroxisome proliferator – activated receptor gamma and its therapeutic modulation. J Clin Endocrinol Metab. 2003; 88: 2412-2421.
43. Stoclet JC, Kleschyov A, Andraimbeloson E, et al. Endothelial NO release cased by red wine polyphenols. J Physiol Pharmacol. 1999; 50: 535-540.