

Alcohol consumption, alcohol dehydrogenase gene polymorphism and the risk of type 2 diabetes mellitus



Magdalena Firlej, MD

Graduated from the School of Medicine of the Medical University of Silesia, currently is a teaching assistant at the Nephrology Clinic and Dialysis Centre of the State Hospital in Bielsko-Biala.

Abstract

Alcohol consumption and the polymorphism of genes encoding enzymes involved in alcohol metabolism are two of the many modifiable risk factors for type 2 diabetes mellitus. Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are two principal enzymes involved in the metabolism of ethanol. Thanks to these two enzymes the toxic ethanol and acetaldehyde are degraded to CO₂ and H₂O.

Numerous studies have proved that moderate alcohol consumption reduces the risk of type 2 diabetes. This relationship is evident with respect to both the type and quantity of alcohol consumed and to the frequency of alcohol consumption. A daily consumption of 15–29 g of

alcohol reduces the risk of type 2 diabetes by 36% and each additional day of alcohol consumption in a week leads to a further risk reduction of 7%.

ADH and ALDH gene polymorphisms are crucial to the development of alcoholism and type 2 diabetes. We demonstrated that carriers of the ADH1B*2/*2, ADH1C*1/*1 and ALDH2*2/*2 alleles were intolerant of alcohol, which was manifested by the development of adverse reactions and deliberate avoidance of alcohol consumption.

Diabet Dośw i Klin 2008, 8, 4, 143–149

key words: diabetes mellitus, alcohol, alcohol dehydrogenase, aldehyde dehydrogenase, ADH gene polymorphism

Introduction

Diabetes mellitus is a pandemic of the beginning of the 21st century claiming an increasing number of lives each year. It is estimated that approximately 2 million people in Poland are affected by the condition, half of whom are unaware of its presence. According to King et

al., the worldwide prevalence of diabetes, which amounted to 4% in 1995, is bound to rise to approximately 5.4% in 2025. The number of diabetics worldwide in 2025 will have risen to 300 million from 135 million reported in 1995. Similarly, the percentage of diabetics in developing countries will have increased to 72% in 2025 from 62% in 1995. Most of the patients suffering from diabetes in developing countries will be in the age range of 45 to 65 years, and the age range in developed countries will shift beyond 65 years [1].

The prevalence of diabetes in Poland ranges from 1.6% to 3.7% and is greatest in urban populations. The incidence of diabetes in Poland is 200 new cases per 100,000 of the population per year, and the mortality rate is 15 per 100,000 per year. Taking into account

Address for correspondence:
lek. med. Magdalena Firlej
ul. Wapienna 11, 43–300 Bielsko-Biala
Tel/fax (+48 33) 810 05 98
e-mail: mfirm@hospital.com.pl



Diabetologia Doświadczalna i Kliniczna 2008, 8, 4, 143–149
Copyright © 2008 Via Medica, ISSN 1643–3165

type 2 diabetes, which accounts for about 90% of all the cases of diabetes, the standardised prevalence rate for the entire population of Poland is 5.35% and shows a permanent upward trend [2, 3].

Factors significantly affecting the development and course of diabetes and its complications include the environment and the rapid civilisation development giving rise to the many modifiable risk factors which can be eliminated. The increasing number of patients with diabetes and the very course of the disease, its complications and the costs of treatment have resulted in a plethora of research studies investigating the prevention, course and treatment of diabetes. It is obvious that prevention studies play the most important role. Risk factors of diabetes include genetic predisposition, abnormalities of insulin synthesis, abnormalities of insulin secretion, abnormalities of the number and function of insulin receptors, lifestyle, obesity, lack of physical activity, age, sex, ethnic origin, fertility, certain viral infections, chronic stress, diabetogenic drugs, smoking and alcohol.

Alcohol consumption is one of the modifiable risk factors of type 2 diabetes. Numerous studies have shown that this risk depends on the quantity and type of alcohol consumed and the way alcohol is metabolised by the individual enzymes.

In order to better understand results of the most recent research studies it is necessary to possess some knowledge of the effects of ethanol, ethanol metabolism and the factors modifying ethanol metabolism.

Ethanol and its metabolism in the body

Ethanol is a lipophilic substance, which is why it undergoes a very rapid and complete absorption from the gastrointestinal tract. Ethanol may undergo absorption already from the oral cavity.

Approximately 20–25% of alcohol undergoes absorption in the stomach and 75–80% from the small intestine. Alcohol reaches its peak blood concentration within 0.5 to 2 hours following oral ingestion. The liver is the most important organ metabolising alcohol. Metabolism is the principal route of alcohol elimination. Approximately 2% of alcohol is eliminated with urine, 2% with the exhaled air and 1% as perspiration insensibilis.

Alcohol has a stimulatory effect at low blood concentrations and causes central nervous system depression at high concentrations. In the human body, alcohol:

- interferes with the energy balance resulting in obesity and liver cirrhosis in individuals with normal nutritional status or resulting in malnutrition and deficiencies of essential elements in malnourished individuals;

- interferes with the absorption and metabolism of fat-soluble vitamins;
- interferes with the enterohepatic circulation of folate;
- causes degradation of pyridoxal phosphate to glucose leading to hypoglycaemia;
- increases fatty acid synthesis;
- causes oxidative stress.

In addition to the above abnormalities, alcohol is considered a co-carcinogen, which does not initiate malignant processes alone, but does so in combination with other carcinogens [4–6].

Alcohol is metabolised to the toxic acetaldehyde and further to the safe acetic acid. Acetic acid, as acetyl-CoA, enters the citric acid cycle whose end products are CO₂ and H₂O. There are three pathways of alcohol metabolism — each involving a different enzyme.

The three enzymes involved in the metabolism of alcohol are:

- alcohol dehydrogenase (ALD) found in the cytosol of hepatocytes;
- the microsomal ethanol oxidation system (MEOS) found in the endoplasmic reticulum;
- peroxisomal catalase [5, 7, 8].

The ADH-mediated alcohol oxidation is characterised by a low Michaelis curve, which is why it may occur at low alcohol concentrations. The nicotinamide adenine dinucleotide NAD⁺ is involved in this process, which yields the reduced form of nicotinamide adenine dinucleotide, NADH, as a result of H⁺ transfer. The continuity of alcohol oxidation requires continued reoxidation of NADH, which takes place in hepatocytes [5, 7].

MEOS-mediated oxidation of alcohol requires not only NAD⁺, but also NADPH, O₂, NADPH reductase, cytochrome C, isocitrate and isocitrate dehydrogenase. In this pathway, the most key link is the cytochrome P450 isoenzyme CYP2E1. The pathway yields not only acetic acid, but also free radicals [5, 7, 9].

Ethanol oxidation by catalase is of little significance. The end product of the pathway is acetaldehyde, which is then converted to acetic acid by ALDH [5, 7]. Six isoforms of ADH and two of ALDH are currently known.

ALDH polymorphism considerably affects the development of alcoholism with little impact of ADH polymorphism. Alcohol hypersensitivity is thought to be manifested by a deficit in the activity of ALDH-2. Because the ALDH2/2 allele is responsible for the formation of inactive subunits, its presence in the homozygous or heterozygous form results in absent or markedly reduced ALDH activity, leading to increased serum concentration of acetaldehyde, which is responsible for the aversive response to alcohol. As individuals with these manifestations deliberately avoid alcohol consumption, it may be concluded that an atypical ADH2/2 allele is the genetic factor that protects from the development of alcoholism.

The allele largely prevails in the oriental populations. The protection may, however, be overcome by consuming large quantities of alcohol despite the symptoms of intolerance, leading to a considerably increased risk of many diseases. As mentioned above, ADH polymorphism plays a lesser role in the development of alcoholism. The presence of two atypical ADH2/2 alleles results in increased aldehyde concentrations leading to the emergence of alcohol intolerance manifestations. Alcoholics and patients with alcoholic liver disease show a significantly higher concentration of the homozygous ADH genotype, ADH1/2, than healthy individuals.

The processes associated with ethanol metabolism are affected by both modifiable and non-modifiable factors. The modifiable factors include:

- the quantity of consumed alcohol;
- the type of alcohol;
- the frequency of alcohol consumption;
- while the non-modifiable ones include:
 - the alcohol oxidation rate;
 - the quantity and quality of enzymes involved in alcohol metabolism;
 - the type of genes encoding the individual enzymes.

Alcohol dehydrogenase and its isoforms

Alcohol dehydrogenase (ADH) is a dimer composed of two subunits, each 373-amino-acid long. The enzyme also contains the zinc ion which acts as a cofactor. The enzyme is encoded by genes located on the long arm of chromosome 4.

Six isoenzymes have so far been identified, which differ in terms of the amino acid sequence, kinetic properties and localisation [10–12]. Due to the structural similarities the isoenzymes have been divided into six classes.

Class I. These isoenzymes are encoded by 3 gene loci: ADH1 = ADH1A, ADH2 = ADH1B and ADH3 = ADH1C located on the long arm of chromosome 4. The ADH2 and ADH3 genes are polymorphic, which means that they encode various forms of the β and γ alleles. The products of these genes (ADH1, ADH2*1, ADH2*2, ADH2*3, ADH3*1, ADH3*2) are the α , β 1, β 2, β 3, γ 1, γ 2 subunits which bind together to form homo- or heterodimers [12]. Most of the enzymes in this class show high affinity to ethanol. They mostly occur in the liver but can also be found in the gastric and intestinal mucosa and in the kidney. The principal class I isoenzyme in the gastric mucosa is $\gamma\gamma$ -ADH. The γ 1 subunit is more active than γ 2. The frequency of individual alleles varies depending on the population and they are found at a 1:1 ratio in the Caucasians and at a 9:1 ratio in the inhabi-

tants of Middle East, Brazilians and Afro-Americans. Alcoholics with liver disease and alcoholics with liver cirrhosis show a higher prevalence of the ADH3*1 allele than do healthy individuals and individuals drinking moderate to large quantities of alcohol without liver disease.

The $\beta\beta$ -ADH isoenzyme found in the gastrointestinal mucosa occurs in the form of three alleles: ADH2*1, ADH2*2 and ADH2*3, whose sequence differs only with respect to one amino acid, which still confers considerable differences in enzymatic properties. The β 2 subunit has the highest activity [13].

The ADH2*2 and ADH3*1 alleles, which are the predominant alleles in healthy Asians, encode the most active subunits: β 2 and γ 1, respectively. This allows ethanol to be rapidly oxidised to acetaldehyde, which stays in the serum for a long time because over a half of Asians carry the mutated ALDH2*2 gene which encodes an inactive ALDH subunit. The cumulation of acetaldehyde in the serum results in the unpleasant symptoms of intoxication: flushing, tachycardia, nausea, anxiety and dyspnoea. Carriers of the ADH2*2, ADH3*1 and ALDH2*2 avoid drinking alcohol, which may lead to a conclusion that the above alleles prevent excessive consumption of alcohol.

In the population of Chinese with liver cirrhosis and alcohol dependence, the ADH2*1 and ADH3*2 alleles are more prevalent, while the Caucasians have shown no significant differences in terms of the frequently of the individual ADH alleles.

As class I enzymes demonstrate high affinity to many substrates, they are involved in the metabolism of exo- and endogenous alcohols and in the oxidation of retinol to retinal.

Class II. These isoenzymes are encoded by the ADH4 gene. The π subunits are its products. This class of isoenzymes is found in the liver only and is characterised by a low Michaelis curve relative to ethanol and by a low sensitivity to the inhibitory action of 4-methylpyrazole. Class II isoenzymes are involved in the metabolism of alcohol, but only when it is present at high concentrations [14].

Class III. This class is made up of the isoenzyme composed of the χ subunits encoded by the ADH5 gene. This class is not inhibited by pyrazole or 4-methylpyrazole, although it is inhibited by o-phenanthroline. It is structurally similar to glutathione-dependent formaldehyde dehydrogenase. Due to the low affinity to short-chain alcohols it does not play any role in the metabolism of ethanol. It is, however, involved in the elimination of endogenous formaldehyde. Formaldehyde is formed in the metabolic processes or in the setting of methanol intoxication. It should be borne in mind that methanol and formaldehyde are highly toxic compounds and that

their content in alcoholic beverages may reach up to 0.15 g/L (up to 0.26 g/L in American whiskey) [15–17].

Class IV. This class is also referred to as human gastric alcohol dehydrogenase: it forms an isoenzyme composed of the δ subunits (also referred to as the μ subunits) encoded by the ADH7 gene. It is involved in the oxidation of ethanol and short-chain alcohols, but demonstrates a higher specificity for medium- and long-chain alcohols. Its involvement in the metabolism of ethanol is only evident at high concentrations of the latter. It is inhibited by pyrazole and 4-methylpyrazole. Its sequence is 72% similar to that of class I ADH. It is found in the upper gastrointestinal tract, mainly in the stomach, and is absent from the liver and the lower gastrointestinal tract [17].

Class V. The presence of the ADH6 gene, which could be the origin of this ADH class, has been found in the stomach and liver. The sequence of this class shows 62% similarity with that of class VI ADH [18].

Class VI. This ADH class is found in the rat, mainly in the liver but in small quantities also in the kidneys.

In the oesophagus, where the concentration of alcohol is highest, class IV ADH is present. Its activity is much higher than that of oesophageal ALDH, leading to a reduction in the concentration of alcohol and an increase in the concentration of acetaldehyde which damages the cells of the oesophageal mucosa.

In the stomach, class I, III and IV alcohol dehydrogenases are present. The activity of ADH in the stomach is much lower than that in the oesophagus, but due to the higher area and longer exposure to alcohol this class is involved in the first-pass effect. The concentration of ethanol following ingestion of the same quantity of alcohol is higher in women than it is in men, which proves that the activity of class IV ADH is lower in women. A considerably lower activity of class IV ADH has been demonstrated in persons chronically consuming alcohol versus non-drinkers.

The liver expresses class I, II and III alcohol dehydrogenases. In patients with liver cirrhosis, ADH activity is significantly lower than that in non-cirrhotic individuals who drink small amounts of alcohol or who abuse alcohol.

Aldehyde dehydrogenase

Aldehyde dehydrogenase (ALDH) is the enzyme involved in the oxidation of acetaldehyde. ALDH is a metalloflavoprotein homotetramer associated with flavin adenine dinucleotide (FAD). The molecule contains molybdenum and non-haem iron. The enzyme is involved in the oxidation of aldehydes, amines, drugs and xenobiotics. Twelve types have so far been identified, which differ in terms of kinetic properties, organ location and

cellular location [11]. The mitochondrial type is the type involved in the metabolism of acetaldehyde. Some of the ALDH types are controlled by female sex hormones. Type 1 and 2 ALDH are involved in the metabolism of acetaldehyde. Type 1 is encoded by the ALDH1 gene, whose product, ALDH1, is found in the cytoplasm of liver and stomach cells, while type 2, encoded by the ALDH2 gene, is found in the mitochondria of these cells. ALDH2 shows a much greater affinity to acetaldehyde than does type 1. All the ALDH types are inhibited by disulfiram, which has been used in the treatment of alcohol dependence because the compound precipitates alcohol intolerance [19].

As with ADH polymorphism, ALDH variability affects alcoholism and its influence on the body. The ALDH2 gene may take the typical (active) form or the untypical (inactive) form. This is associated with the presence of two alleles, ALDH2*1 and ALDH2*2, which encode active and inactive subunits, respectively. The lack of ALDH2 activity is associated with the presence of the homozygous ALDH2*2/*2 genotype, while partial deficiency of the activity results from the presence of the heterozygous ALDH2*2/*1 genotype. As with ADH, the frequency of individual ALDH alleles varies depending on ethnic origin: in Americans and Blacks the frequency of the 1/1 allele is 100%, in the Chinese, the frequency of the 1/1, 1/2 and 2/2 alleles is 50%, 41% and 9%, respectively, and in Caucasians, the frequency of the 1/1 allele is < 90% with the 1/2 allele present in the rest (the 2/2 allele does not occur in Caucasians) [20].

Ethanol consumption and diabetes mellitus

The high prevalence of diabetes and the consequences it causes have prompted many research centres to conduct studies investigating the effects of alcohol consumption on the risk of type 2 diabetes mellitus. The Atherosclerosis Risk in Communities Study [21, 22] conducted in 1990–1998 enrolled over 12 thousand volunteers of both sexes 45 to 64 years of age. The quantity of alcohol consumed was determined using a questionnaire. The study demonstrated that the risk of diabetes increased by 50% in men consuming more than 21 drinks a week compared to men consuming less than 1 drink a week (OR 1.5, 95%CI 1.02–2.20). While this relationship was confirmed in men consuming ethanol, it was not confirmed for beer or wine.

It remains unequivocal that moderate consumption of alcohol does not increase the risk of diabetes in middle-aged men or women. The British Regional Heart Study [23] demonstrated a 40% reduction in the risk of type 2 diabetes when 16–24 drinks a week were consumed.

Table 1. Characteristics features of the NHS and HPFS studies (adapted from [23])

	Studies to evaluate the effect of ADH1C on the development of diabetes mellitus	
	NHS	HPFS
Start year	1976	1986
Participants	121,700 women	51,529 men
Age (years)	30–55	40–75
Assessment method of the quantity of alcohol consumed	Questionnaire	Questionnaire
Detected cases of diabetes	678 in the year 2000	431 in the year 2002
Method of diabetes detection	Contemporary guidelines	Contemporary guidelines
Number of individuals in the control group	1000	382
Individuals who provided blood for testing	18,225	32,826

In the Osaka Health Survey [24], which enrolled over 6 thousand Japanese 35 to 61 years of age without a diagnosis of diabetes, glucose intolerance, hypertension or liver cirrhosis, 456 cases of type 2 diabetes were identified. An relationship between the quantity of ethanol consumed and the development of type 2 diabetes depending on body mass index (BMI) values was discovered. In men with BMI < 22 kg/m² who consumed large quantities of alcohol, an increased risk of diabetes compared to non-drinkers was observed. In men with BMI > 22 kg/m² who consumed moderate quantities of alcohol, a reduced risk of diabetes compared to non-drinkers was reported.

The Cooper Clinic Study [25], which enrolled over 8 thousand men 30–79 years of age, demonstrated:

- an increase in the risk of type 2 diabetes in non-drinkers and individuals consuming large quantities of alcohol;
- a tendency towards a reduced risk of diabetes with reduced consumption of alcohol. In the study, the lowest risk of type 2 diabetes was observed at 61.9–122.7 g of alcohol per week.

Polymorphism of the genes encoding alcohol dehydrogenase and the risk of type 2 diabetes mellitus

As the knowledge on the metabolism of alcohol and on the enzymes involved in the process accumulated, researchers began to ponder over the effects of the polymorphism of the genes encoding these enzymes on the risk of type 2 diabetes.

The studies which evaluated the effect of ADH genes on the risk of diabetes in addition to the effects of alcohol included the Health Professionals Follow-up

Study (HPFS) and the Nurses' Health Study (NHS) [26–28].

The NHS study was launched in 1976, involved 121,700 women 30–55 years of age and assessed, using a questionnaire, the quantity of alcohol consumed. In 2000, based on the contemporary guidelines, 678 cases of diabetes were diagnosed in this group. The HPFS study was initiated in 1986 and involved 51,529 men 40–75 years of age. Four hundred and thirty-one cases of diabetes were diagnosed in the study population. In the NHS study, the study group and the control group consisted of 640 and 1000 individuals, respectively. In the HPFS study, the study and control groups comprised 383 and 382 individuals, respectively. So the pooled number of individuals was 1023 in the study groups and 1382 individuals in the control groups (Table 1).

The studies evaluated the frequency of individual alleles in the study groups and the control groups. The homozygous ADH1C*1/*1 allele was present in 36.8% of patients in the study groups and 34.7% of patients in the control groups. The homozygous ADH1C*2/*2 allele was present in over 17% in the study groups and the control groups alike. The most frequent allele was the heterozygous ADH1C*1/*2 allele, which was present in 45.8% and 48.1% of patients, respectively.

The quantity of consumed alcohol was determined with the use of a questionnaire. The largest group of women were abstainers and the largest group of men were those who consumed 0–9.9 g of alcohol per 24 hours. The studies analysed the relationship between the quantity of alcohol consumed and the ADH genotype.

The distribution of the mean consumption of alcohol in women was as follows.

In the group consuming low quantities of alcohol:

- 2.2 g/24 h for ADH1C*1/*1;
- 2.1 g/24 h for ADH1C*1/*2;
- 2.2 g/24 h for ADH1C*2/*2.

In the group consuming moderate quantities of alcohol:
 — 16.2 g/24 h for ADH1C*1/*1;
 — 14.1 g/24 h for ADH1C*1/*2;
 — 14.4 g/24 h for ADH1C*2/*2.

The distribution of the mean consumption of alcohol in men was as follows.

In the group consuming low quantities of alcohol:
 — 4.5 g/24 h for ADH1C*1/*1;
 — 4.5 g/24 h for ADH1C*1/*2;
 — 4.0 g/24 h for ADH1C*2/*2.

In the group consuming moderate quantities of alcohol:
 — 25.9 g/24 h for ADH1C*1/*1;
 — 26.3 g/24 h for ADH1C*1/*2;
 — 25.7 g/24 h for ADH1C*2/*2;

According to these studies, compared to abstinence, consumption of 15–29 g of alcohol per 24 hours reduces the risk of type 2 diabetes by 36% (RR 0.64, 95%CI 0.53–0.72). Consumption of more than 50 g of alcohol per 24 hours reduces the risk of diabetes by 40% (RR 0.6, 95%CI 0.43–0.84). This relationship is applicable to women only, being not so unequivocal in men.

The risk of type 2 diabetes is reduced by 36% in men with BMI > 25 kg/m² (RR 0.64, 95%CI 0.52–0.79) and by 37% in leaner men (RR 0.63, 95%CI 0.39–1.00) with consumption of 15–29 g per 24 hours. As far as age is concerned, in men below 65 years of age there was a 36% reduction in the risk of diabetes (RR 0.64, 95%CI 0.51–0.82) at a consumption of alcohol amounting to 15–29 g per 24 hours, while the risk reduction in men over the age of 65 was 35% (RR 0.65, 95%CI 0.48–0.89).

It has also been shown that men who consume alcohol less frequently than twice a week are not at a higher risk of diabetes than abstainers. The risk begins to decrease at alcohol consumption 3–4 times a week. The lowest risk of diabetes is present in men who consume alcohol five or more days a week. It has also been calculated that each additional day of alcohol consumption per week reduces the risk of diabetes by 7% (RR 0.93, 95%CI 0.90–0.97).

Almost every type of alcohol reduces the risk of type 2 diabetes with red wine being one notable exception. When beer consumption rose by 15 g per day, the risk decreased by 30% (RR 0.7, 95%CI 0.6–0.81). Increasing the consumption of white wine by 5 g daily reduces the risk by 26% (RR 0.74, 95%CI 0.62–0.88) and increasing the consumption of liqueur by 15 g daily reduces the risk by 25% (RR 0.75, 95%CI 0.66–0.84).

In addition to the above relationships, it has also been shown that the ADH1C genotype changes the relationship between alcohol consumption and the risk of diabetes. The level of reduction in the risk of type 2 diabetes was 56% in ADH1C*1/*1 homozygotes, 35% in heterozygotes and 22% in ADH1C*2/*2 homozygotes compared to the homozygous ADH1C*1/*1 abstainers.

Summary

The studies discussed above demonstrate that moderate consumption of alcohol reduces the risk of type 2 diabetes mellitus, although the quantity of alcohol responsible for this reduction varies in individual studies. In addition to the quantity of alcohol consumed, the studies have shown relationships of the type of alcohol and the frequency of alcohol consumption with the risk of diabetes. The above relationships are important due to the fact that they may be individually adjusted. The studies have also shown that the ADH1B*2/*2w, ADH1C*1/*1w and ALDH2*2/*2 alleles, while triggering alcohol intolerance, prevent excessive consumption of alcohol and all the related consequences.

References

- King H, Aubert RE, Herman WH. Global Burden of Diabetes 1995–2025. Prevalence, numerical estimates and projections. *Diabetes Care* 1998; 21: 1417–1431.
- Szurkowska M, Szubiński Z, Nazim A, Szafranec K, Jedrychowski W. Zapadalność na cukrzycę typu 2 w populacji miasta Krakowa. *Pol Arch Med Wewn* 2001; 106: 771.
- Łopatyńska J, Mardarowicz G, Nicer T. et al. Badanie nad występowaniem cukrzycy typu 2 w populacji powyżej 35. roku życia na wsi i w mieście w regionie lubelskim. *Pol Arch Med Wewn* 2001; 106: 781.
- Bosron WF, Li TK. Catalytic properties of human liver alcohol dehydrogenase. *Enzyme* 1987; 37: 19–38.
- Fleming K, McGee J. Alcohol induced liver disease. *J Clin Pathol* 1984; 37: 721–733.
- Edenberg HJ. The genetic of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. *Alcohol Res Health* 2007; 30: 5–30.
- Bidziński A. Przemiany metaboliczne alkoholu etylowego. In: Kostowski W, Wald J. eds. *Działanie biologiczne alkoholu etylowego*. PWN, Warszawa 1991; 22–35.
- Agarwal DP, Goedde H. Ethanol oxidation: ethnic variations in metabolism and response. *Prog Clin Biol Res* 1986; 214: 99–112.
- Mi LJ, Mak KM, Lieber CS. Attenuation of alcohol-induced apoptosis of hepatocytes in rat livers by polyenylophosphatidylocholine (PPC). *Alcohol Clin Exp Res* 2000; 24: 207–212.
- Matsushima T. Alcohol dehydrogenase. *Nippon Risho* 2004; 64 (supl. 11): 438–441.
- Agarwal DP. Genetic polymorphism of alcohol metabolizing enzymes. *Pathol Biol* 2001; 49: 703–709.
- Crabb DW, Matsumoto M, Chang D, You M. Overview of the role of alcohol dehydrogenase and aldehyde dehydrogenase and their variants in the genetic of alcohol-related pathology. *Proc/Nutr Soc* 2004; 63: 49–63.
- Ang HL, Deltour L, Zgombic-Knigh MA, Duester G. Expression patterns of class I and class IV alcohol dehydrogenase genes in developing epithelia suggest a role for alcohol dehydrogenase in local retinoid acid synthesis. *Alcohol Clin Exp Res* 1996; 20: 1050–1064.
- Svensson S, Stromberg P, Sandalova T, Hoog J. Class II alcohol dehydrogenase — adding and structure. *Chem Biol Interact* 2001; 130–132: 339–350.
- Galter D, Carmine A, Buervenish S, Duester G, Olson L. Distribution of class I, III and IV alcohol dehydrogenase MRNAs in the adult rat, mouse and human brain. *Eur J Biochem* 2003; 270: 1316–1326.
- Kaiser R, Holmquist B, Vallee BL, Jornvall H. Human class III alcohol dehydrogenase/glutathione-dependent formaldehyde dehydrogenase. *J Protein Chem* 1991; 10: 69–72.

17. Jelski W, Chrostek L, Szmitkowski M, Laszkiewicz W. Activity of class I, III, IV alcohol dehydrogenase in human gastric mucosa. *Dig Dis Sci* 2002; 47: 1554–1557.
18. Stromberg P, Hoog JO. Human class V alcohol dehydrogenase: a complex transcription unit generates C-terminal multiplicity. *Biochem Res Commun* 2000; 278: 544–549.
19. Crabb DW, Edenberg HJ, Bosron WF, Li TK. Genotypes of aldehyde dehydrogenase deficiency and alcohol sensitivity: the inactive ALDH2 allele is dominant. *J Clin Invest* 1989; 83: 314–316.
20. Goedde HW, Agarval DP, Fritze G i wsp. Distribution of ADH2 and ALDH 2 genotypes in different populations. *Hum Genet* 1992; 88: 344–346.
21. Kao WHL, Puddey IB, Boland LL, Watson RL, Brancati FL. Alcohol consumption and the risk of type 2 diabetes mellitus: Atherosclerosis Risk of Communities Study. *Am J Epidemiol* 2001; 154: 748–757.
22. The Atherosclerosis Risk of Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol* 1989; 129: 687–702.
23. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG. Prospective study of risk factors for development of non-insulin diabetes in middle-aged British men. *BMJ* 1995; 310: 560–564.
24. Tsumara K, Hayashi T, Suematsu C, Endo G, Fujii S, Okada K. Daily alcohol consumption and the risk of type 2 diabetes in Japanese men: the Osaka Health Survey. *Diabetes Care* 1999; 22: 1432–1437.
25. Wei M, Gibbons LW, Mitchell TL, Kampert JB, Blair SN. Alcohol intake and incidence of type 2 diabetes in men. *Diabetes Care* 2000; 23: 18–22.
26. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use and the risk of diabetes in men. *BMJ* 1995; 310: 555–559.
27. Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, Stampfer MJ. A prospective study of alcohol consumption and the risk of coronary disease in men. *Lancet* 1991; 338: 464–468.
28. Beulens JWW, Rimm EB, Hendriks HFJ i wsp. Alcohol consumption and type 2 diabetes. Influence of genetic variation in alcohol dehydrogenase. *Diabetes* 2007; 56: 2388–2399.