THE METABOLIC SYNDROME FROM THE VIEW POINT OF PUBLIC HEALTH: WITH SPECIAL REFERENCE TO NONALCOHOLIC FATTY LIVER DISEASE

Tetsu WATANABE*, Chisato MURATA, and Yoshihisa WATANABE

Changes in human behavior and lifestyle over the last century have resulted in a dramatic increase in the incidence of obesity, type 2 diabetes, and the metabolic syndrome. Differences in the reported overall prevalence of the metabolic syndrome, which is generally in the range of 10–30% depend on the diagnostic criteria and subjects of the study. Recently, Japanese criteria for diagnosis of the metabolic syndrome were defined. With these criteria, presence of visceral obesity is essential for the diagnosis and is simply determined by measurement of waist circumference. Reflecting a dramatic increase in the incidence of obesity and type 2 diabetes, the incidence of the metabolic syndrome is increasing in Japan as well as in Western countries, regardless of the criteria applied.

Recently, the number of workers with elevated liver enzymes, in whom virus hepatitis, alcoholic liver disease, drug induced hepatitis, autoimmune hepatitis, and iron overload were ruled out as causal agents, has also be found to be increasing at workplace health checkups. Most of such workers have components of the metabolic syndrome and the presence of steatosis in the liver, this pathologic condition now being termed nonalcoholic fatty liver disease (NAFLD).

In this review, we describe the relationship between NAFLD and the metabolic syndrome.

Key words: metabolic syndrome, nonalcoholic fatty liver disease, visceral obesity, insulin resistance, aldehyde dehydrogenase 2 genotype

I. Introduction

The growing epidemic of non-communicable diseases can be seen not only in developed but also in less-developed countries with rapid demographic and lifestyle changes, including increased alcohol drinking, high calorie intake, low physical activity and extreme stress[1~3]. These changes in lifestyle lead to overweight, hyperlipidemia, hyperglycemia, hypertension and other metabolic disorders[2~5].

Many epidemiological studies have revealed that persons demonstrating several risk factors such as central obesity, dyslipidemia, hypertension, and glucose intolerance (type II diabetes, impaired glucose tolerance, or impaired fasting glycemia) are at higher risk of developing cardiovascular disease compared to persons who have none of these risk factors. Since the late-eighties, researchers have noticed that the risk factors co-occur in individuals more often than might be expected by chance and this condition was called "Syndrome X" by Reaven[6,7], the "Deadly Quartet" by Kaplan[8]. Subsequently, the "Insulin Resistance Syndrome" was proposed by DeFronzo[9], the "Visceral Obesity Syndrome" by Matsuzawa[10], the "Metabolic Syndrome X" by Matsuzawa[11], and the "Multiple Metabolic Syndrome" by Liese[12] based on the supposed etiology of the syndrome. Recently, a WHO working group named these conditions the metabolic syndrome and provided definition and diagnostic criteria for the disease[13]. Reaven found that insulin resistance is a basic condition for this systemic metabolic disorder[6]. Since then a number of researchers have attempted to clarify the relationship between insulin resistance and the metabolic syndrome[14]. The WHO definition is based on glucose intolerance and/or insulin resistance, together with two or more of the following risk factors; (1) hypertension: blood pressure $\geq$ 160/90 mmHg, (2) dyslipidemia: triglyceride (TG) $\geq$ 1.7 mmol/l and/or high density lipoprotein cholesterol (HDL-C) $<$ 0.9 mmol/l in men or $<$ 1.0 mmol/l in women, (3) obesity: west/hip ratio $>$ 0.90 in men or $>$ 0.85 in women and/or

* Department of Community Health, Tokai University School of Medicine
Department of Community Health, Tokai University School of Medicine, Bohseidai, Isehara City, Kanagawa 259-1193, Japan
E-mail: tewatana@is.icc.u-tokai.ac.jp

body mass index (BMI) > 30 kg/m^2, (4) microalbuminuria: urinary albumin excretion rate ≥ 20 μg/ml or albumin/creatinine ratio ≥ 20 mg/g[13]. WHO criteria include the measurement of insulin resistance, but such measurements can not be routinely performed in clinical practice. The report of the Third National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III) proposed similar standards for the diagnosis of metabolic syndrome[15]. According to the ATP III, metabolic syndrome is defined when a person has more than 3 of the following 5 risk items: (1) abdominal obesity (waist circumference) > 102 cm in men and > 88 cm in women, (2) TG ≥ 150 mg/dl, (3) HDL-C < 40 mg/dl in men and < 50 mg/dl in women, (4) blood pressure ≥ 130/85 mmHg, and (5) fasting blood glucose ≥ 110 mg/dl.

Very recently, new diagnostic criteria were announced for the metabolic syndrome in Japanese on behalf of eight Japanese Academic Societies[16]: A waist circumference ≥ 85 cm in men and ≥ 90 cm in women is an essential condition for the diagnosis, and the two of the following 3 conditions should be fulfilled; (1) TG ≥ 150 mg/dl, and/or HDL-C < 40 mg/dl, (2) blood pressure ≥ 130/85 mmHg, (3) fasting blood glucose ≥ 110 mg/dl. This criteria is almost same as that of ATP III except for the waist circumference. The WHO criteria for metabolic syndrome place a high priority on the presence of type II diabetes or insulin resistance whereas the ATP III and Japanese criteria emphasize the presence of visceral obesity and include measurement of waist circumference instead of BMI.

Elevated liver enzymes are often observed at workplace health checkup and in the majority of the individuals involved, virus hepatitis, alcoholic liver disease, drug induced hepatitis, autoimmune hepatitis, and iron overload can be ruled out as a cause. In the past two decades or so, we have noted that many workers with elevated liver enzymes at workplace health checkups have accompanying obesity, hypertension, dyslipidemia, and glucose intolerance with a high incidence and that some of them finally develop the metabolic syndrome. The presence of hepatic steatosis in the absence of other chronic liver diseases has been called nonalcoholic fatty liver disease (NAFLD)[17]. Recent evidence indicates that obesity and insulin resistance are major predisposing conditions for NAFLD[5,17~23].

This review discuses the epidemiology of the metabolic syndrome in Japan, the importance of insulin resistance pathogenesis as a public health problem, the relation of the metabolic syndrome to NAFLD, environmental and genetic factors for the development of NAFLD, and finally prevention of the metabolic syndrome.

II. Epidemiology of the Metabolic Syndrome in the World

According to the ATP III definition, the age-adjusted prevalence of metabolic syndrome was 23.7% for 8,814 men and women aged 20 years or older of the US population[24]. The prevalence increased from 6.7% among participants aged 20 through 29 years to 43.5% for participants aged 60 through 69 years. The Framingham Offspring Study (FOS) and the San Antonio Heart Study (SAHS) revealed that the metabolic syndrome typically affects 20–30% of middle-aged adults in the U.S. with both WHO and ATP III criteria[25]. Among FOS white subjects, the age- and sex-adjusted prevalence of the metabolic syndrome was 24% with both ATP III and WHO criteria. Among SAHS, 23 and 21% of non-Hispanic white subjects, and 31 and 30% of Mexican-American subjects were diagnosed as having metabolic syndrome with the ATP III and WHO criteria, respectively.

Prevalence of the metabolic syndrome as defined by ATP III criteria in 2,100 Italian subjects aged 19 years or more was 18% in women and 15% in men[26]. The prevalence increased from 3% among subjects aged 20–29 years to 25% in subjects aged 70 years or older. In the Botnia Study, which included a total of 4,483 Finnish and Swedish subjects aged 35–70 years, the metabolic syndrome was seen in 10 (women) and 15% (men) of subjects with normal glucose tolerance, 42 (women) and 64% (men) of those with impaired glucose tolerance, and 78 (women) and 84% (men) of those with type 2 diabetes by WHO criteria[27]. The Kuopio Ischaemic Heart Disease Risk Factor Study, a population-based, prospective cohort study of 1209 Finnish men aged 42 to 60 years at baseline (1984–1989) continued to the end of 1998, revealed that the prevalence of the metabolic syndrome ranged from 8.8–14.2% of the subjects, depending on the definition[28]. A study of Hong Kong Chinese of working age (1,513 subjects) revealed that the prevalence of metabolic syndrome was 9.6% (modified ATP III) and 13.4% (WHO) depending on the diagnostic criteria[29]. The definition of obesity modified using a waist circumference > 90 cm in men and > 80 cm in men, a waist/hip ratio > 0.9 in men and > 0.85 in women, and a BMI > 25 kg/m^2. According to modified ATP III, the prevalence of hypertension, low HDL-C, hypertriglyceridemia, and dysglycemia were 29.5%, 22.9%, 16.7%, and 5.7%, respectively.

In Japan, a case-control study of 122,051 workers demonstrated that having 3 to 4 risk factors

Table 1. Prevalence of metabolic syndrome among the residents of Ebina City[1)]

Sex	Age-group	Total number	Number of risk factors*		
			4	3	2
Male	40～49	89	0	8	21
	50～59	187	10	21	67
	60～69	793	41	124	266
	70～79	527	25	84	166
	≥80	79	2	7	18
Total		1,675	78	244	538
Female	40～49	340	3	17	46
	50～59	1,088	34	110	291
	60～69	1,585	67	247	457
	70～79	697	46	109	222
	≥80	140	8	21	39
Total		3,850	158	504	1,055

1) Okazaki I, Watanabe T and Watanabe Y. unpublished data. Data were collected in 2002.

* Risk factors: obesity, BMI≥25 kg/m^2; hypertension, blood pressure≥140/90 mmHg; dyslipidemia, TG≥150 mg/d*l* and/or HDL-C＜40 mg/d*l*; fasting blood glucose≥110 mg/d*l*.

(obesity, hypertension, hyperglycemia, and hypercholesterolemia) increased the odds ratio for developing ischemic heart disease to 31.34 (95% confidence interval: 5.81–168.93), indicating the gravity of the accumulation of risk factors for the individual, although the diagnostic criteria used were different from those of WHO or ATP III[30)].

As mentioned above, diagnostic criteria for the metabolic syndrome for Japanese have been just determined, and a few epidemiological studies were conducted using modified ATP III criteria, because to employ ATP III definitions directly for Japanese is not appropriate, because Asian populations have a high percentage of body fat at a low BMI[3)]. In the Tanno and Sobetsu Study, 25.3% of 808 male subjects were diagnosed as having the metabolic syndrome and cardiac disease occurred in 11.7% of this subgroup as compared to 6.7% of the subjects in the non-metabolic syndrome group[31)]. The relative risk of cardiac disease in the metabolic syndrome group was 2.2. The survey depended on modified ATP III criteria, in which the cut-off value of 85 cm for waist circumference were used. Another cross-sectional study of 5,033 workers aged between 35 and 65 years gave a prevalence of the metabolic syndrome of 15.6% (men, 20.3%; women, 6.6%) with modified ATP III criteria[32)]. They used a BMI＞25 kg/m^2 as a surrogate of waist circumference.

We have investigated the prevalence of the metabolic syndrome among the residents of Ebina City in Kanagawa Prefecture using records obtained in 2002. The ethics committee of the Tokai University School of Medicine as well as the City of Ebina approved the study protocol, and informed consent was obtained from each resident before participation in the study. The prevalence increased with age in both sexes, and at least 20% of residents overall were estimated to be suffering from the metabolic syndrome (Table 1). Nakai town in Kanagawa Prefecture also exhibited the same tendency. In these studies, we defined the metabolic syndrome as having 4 risk factors, obesity (BMI≥25 kg/m^2), hypertension (blood pressure≥140/90 mmHg), dyslipidemia (TG≥150 mg/dl and/or HDL-C＜40 mg/dl), and fasting blood glucose≥110 mg/dl. In future we have to include the waist circumference, however, in the items for the periodical health checkup conducted at both workplace and community by law in Japan.

III. Insulin Resistance as a Public Health Problem

The purpose of establishing diagnostic criteria for the metabolic syndrome is to establish efficient preventive measures against the development of atherosclerotic cardiovascular disease and actual parameters applied must fit this purpose. Therefore, newly defined Japanese criteria for the diagnosis of the metabolic syndrome focused on the presence of visceral obesity[16)].

Recent advances in basic research on obesity have provided a great deal of information on the molecular mechanisms underlying development of the metabolic syndrome. Once adipocytes deposit substantial amounts of fat, they are destined to express the phenotype of producing tumor necrotizing factor-α (TNF-α), plasminogen activator inhibitor-1 (PAI-1) and other cytokines, with reduced production of adiponectin[11,33,34)]. Changes in the level of these cytokines as well as increased free fatty acids (FFA) released from expanded adipose tissue reduce the action of insulin by inhibiting insulin-mediated uptake of glucose in skeletal muscles. This phenomenon is termed "Insulin Resistance." Compensatory hyperinsulinemia that accompanies insulin resistance generates either a normal or a stronger-than-normal initial signal at the level of the insulin receptor. If the person has insulin resistance, the blood glucose level remains high regardless of the diet. Hyperinsulinemia may enhance sodium reabsorption and increase sympathetic nervous system and cause hypertension (Figure 1). In adipocytes, insulin resistance increases hormone-sensitive lipase

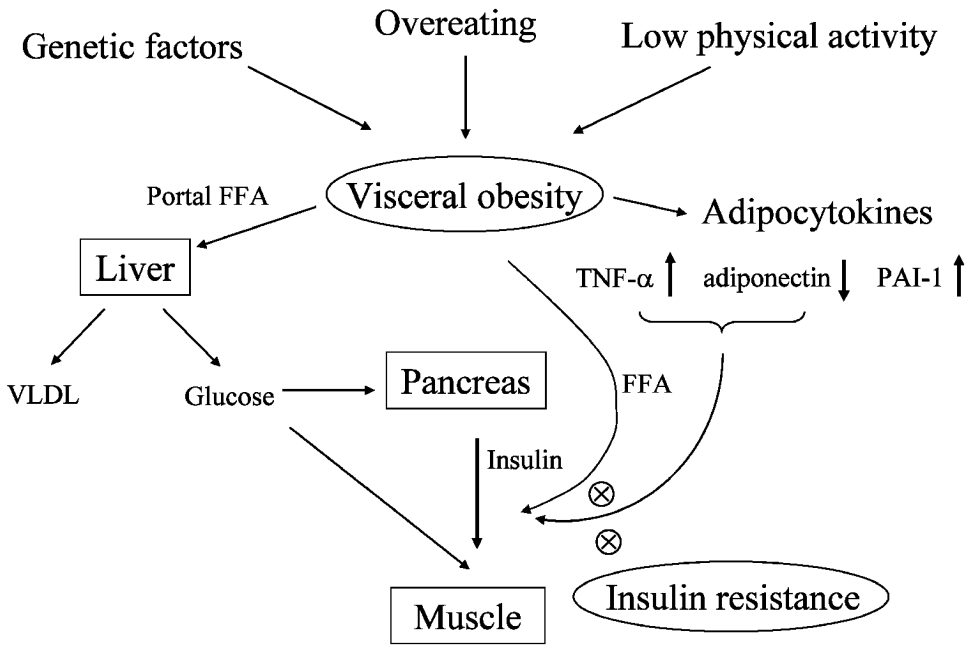

Figure 1. Proposed Mechanisms underlying the Metabolic Syndrome (Watanabe T et al). FFA, free fatty acids; TNF-α tumor necrosis factor-α PAI-1, plasminogen activator inhibitor-1; VLDL, very low-density lipoprotein; ⊗, increased FFA, TNF-α, and decreased adiponectin inhibit the action of insulin.

activity, resulting in elevated rates of triglyceride lipolysis and enhanced FFA flux to the liver. Accumulation of FFA in the liver produces an increased production of glucose, triglycerides and secretion of very low-density lipoprotein. Enhanced secretion of TNF-α and interleukin-6 by adipocytes exacerbates insulin resistance. Overproduction of PAI-1 by adipose tissue also results in a pro-thrombotic state. Understanding the pathophysiology of the metabolic syndrome is important for the management of underlying risk factors, which should lead to prevention of cardiovascular disease.

The Hisayama study revealed that the risk factors for cardiovascular diseases observed in recent inhabitants (the third group, 1990 to 2000) were quite different from those identified in the first (1950–1970) and second (1970–1990) groups[35]. The third group showed that the major risk factor of this group for the development of cardiovascular and cerebrovascular disease was type II diabetes and that even after controlling blood pressure the incidence of these diseases does not decrease without controlling type II diabetes, that is, the metabolic syndrome. Type II diabetes is not only a risk factor for cardiovascular diseases but also for development of malignancies[36]. Obesity thus may increase the incidence of lung, colon, breast, and prostate cancers[37]. Recent understanding of signal transduction downstream of the insulin receptor may provide an explanation for the close linkage between insulin resistance and cancer development[38].

As the metabolic syndrome causes not only cardiovascular disease, but also liver disease (described below in detail), hyperuricemia[39,40] and gallbladder stones[41], it is the most important emerging medical problem for modern humankind.

IV. Metabolic Syndrome and NAFLD/NASH

As mentioned above, nonalcoholic fatty liver disease (NAFLD) may be defined by the presence of elevated alanine aminotransferase (ALT) in the absence of other known liver diseases, such as viral hepatitis, alcoholic liver disease, metabolic iron overload, or autoimmune hepatitis[42]. We used the term "NAFLD" by this definition in this review.

In the last two decades, NAFLD has been increasingly recognized as the most common liver disease in Western countries[43]. A recent report from Italy described that the prevalence of NAFLD was 20% among 5,780 individuals in the general population[44], which was within the range (20–30%) earlier hypothesized for Western countries[45]. Another large population-based study in the US showed that the prevalence of NAFLD among 8,004

subjects was 3.4%[27] and that the presence of increased BMI, insulin resistance, or the metabolic syndrome was very strongly associated with increased serum ALT.

The prevalence of NAFLD is increased with type 2 diabetes, obesity[46], visceral obesity defined by waist circumference or waist/hip ratio[21,23], and hypertriglyceridemia[17]. Moreover, an association of insulin resistance with NAFLD even in the absence of obesity and diabetes suggests that it might be the liver component of metabolic syndrome[20,23].

About 15% of NAFLD cases demonstrate progression from steatosis to steatohepatitis, that is called nonalcoholic steatohepatitis (NASH), and 20% of those with NASH progress to liver cirrhosis, and 3% die from liver failure[17]. In the Rochester Epidemiology Project (REP), which was aimed to determine survival and liver-related morbidity among community-based NAFLD patients, mortality was higher than in the general population (standardized mortality ratio, 1.34; 95 % CI, 1.003–1.76)[47]. Moreover, it was associated with age, impaired fasting glucose, and cirrhosis.

We have reported that workers with elevated liver enzymes without other causes of chronic liver disease, found at work place health checkup, are likely to have metabolic syndrome[48]. The values for liver enzymes were thus associated with a number of components of the metabolic syndrome and obesity was observed in all the subjects (Table 2)[48].

We have the consider the metabolic syndrome as a possible cause of elevated ALT seen in workplace checkup if other particular causes of liver diseases can be excluded from the diagnosis. As metabolic complications were found to develop 4–5 years after the diagnosis of NAFLD in the population-based cohort study (REP), this condition may be an early manifestation of the metabolic syndrome[47].

V. The Environmental and Genetic Factors for the Development of NAFLD

Genetic factors participate in the development of NAFLD, since not all subjects who gain weight exhibit liver dysfunction. We focused on two genes that are assumed to be candidates for the development of NAFLD. Several reports have described a relationship between NAFLD and insulin resistance[20,49] and β3-adrenergic receptor (AR) gene polymorphisms are thought to be related to visceral obesity and insulin resistance[50~56]. Therefore, an involvement in the development of NAFLD can be speculated. We selected the aldehyde dehydrogenase 2 (ALDH2) gene as another candidate gene for NAFLD, because the ALDH2 genotype is related to the alcohol drinking habit[57~59] and glycemic control in patients with type II diabetes mellitus[60]. Our study showed a high prevalence of active ALDH2 among workers with NAFLD, similar to a study that revealed that habitual drinkers with active ALDH2 show liver dysfunction more often than the subjects with inactive ALDH2[61]. ALDH2 may participate in the metabolism of not only alcohol but also other chemicals with aldehyde radicals, resulting in the alteration of lipid metabolism.

It is interesting to note that the Trp64Arg polymorphism of the β3-AR gene and active ALDH2 were each independently associated with elevated ALT level (β3-AR: $P=0.0390$, ALDH2: $P=0.0286$, Scheffe's test) among the subjects with normal body weight in our previous study[48]. Moreover, all four individuals with NAFLD and normal BMI had an active ALDH2 genotype and the Arg geno-

Table 2. Accumulation of risk factors and levels of AST, ALT and γ-GTP[1]

Number of risk factors	0	1	2	3 or more	*P* value
Number of subjects	49	49	35	15	
AST (IU/L)	19.8±4.7	20.4±6.3	30.3±23.4*	28.8±11.0	.0003
ALT (IU/L)	18.3±8.3	22.5±14.5	41.5±28.8†	45.9±24.2††	<.0001
γ-GTP (IU/L)	17.8±9.3	28.4±20.0	47.5±32.8§	40.5±33.7§§	<.0001

1) Murata C, Watanabe T et al. Metabolism 2003

Values are means±SDs

Risk factors were obesity, hypertension, dyslipidemia and impaired glucose tolerance, as components of the metabolic syndrome.

* $P=.0038$ vs. subjects without risk factors by Scheffe's test.

† $P<.0001$ vs. subjects without risk factors by Scheffe's test.

†† $P<.0001$ vs. subjects without risk factors by Scheffe's test.

§ $P<.0001$ vs. subjects without risk factors by Scheffe's test.

§§ $P=.0124$ vs. subjects without risk factors by Scheffe's test.

Table 3. Relationship between elevated ALT and the ALDH2 and β_3-AR genotypes[1)]

ALDH2 genotype	Active		Inactive	
β3-AR genotype	Arg64Arg Trp64Arg	Trp64Trp	Arg64Arg Trp64Arg	Trp64Trp
All subjects (n=148)				
ALT>40 IU/L (n=23)	6(26.1%)	9(39.1%)	3(13.0%)	5(21.7%)
ALT≤40 IU/L (n=125)	21(16.8%)	42(33.6%)	16(12.8%)	46(36.8%)
19.8≤BMI<24.2 (n=80)				
ALT>40 IU/L (n=4)	4(100.0%)	0(0.0%)	0(0.0%)	0(0.0%)
ALT≤40 IU/L (n=76)	12(15.8%)	27(35.5%)	11(14.5%)	26(34.2%)

1) Murata C, Watanabe T et al. Metabolism 2003

type of β3-AR (Arg genotype means Arg/Arg or Trp/Arg), as shown in Table 3[48)]. These results suggest that active ALDH2 and the Arg genotype of β3-AR are involved in elevation of the ALT level in men by a mechanism other than obesity.

Change of jobs which influence lifestyle, regarding work hours, sleeping time, drinking and smoking habits, or increase or decrease of on-the-job stress, for example, may cause disorder in some workers. A car manufacturing company ordered 43 male workers to work at the car-sales department for two years, before returning to the car-manufacturing department. Environmental change, mainly the changes of contents of work and life-style caused obesity, dyslipidemia, hypertension, impaired glucose tolerance and elevated liver enzymes in considerable numbers of these 43, and in some cases they recovered normal levels when back in car-manufacturing[62,63)].

VI. Prevention of the Metabolic Syndrome

As abdominal obesity is most closely associated with the metabolic syndrome, the fundamental approach to prevent the disease is weight reduction[64)]. This may best be achieved by changing the daily life to reduce energy intake and enhance caloric expenditure by physical activity[65)]. To date, using drugs are not practical for weight reduction therapy. The principles of daily diet to prevent metabolic syndrome are decreased intake of saturated fats, cholesterol, simple sugars, and increased consumption of fruits, vegetables and whole grains[15)]. Smoking and drinking habits also influence the prevalence of the metabolic syndrome. Chronic cigarette smoking is associated with insulin resistance and the metabolic syndrome[32,66)], which explain why smoking increases risk of coronary heart disease. On the other hand, moderate alcohol consumption is associated with lower prevalence of the metabolic syndrome[67,68)], especially among wine and beer drinkers[68)].

Education aimed at preventing metabolic syndrome for children, young parents, and young workers is necessary. Content of education should include optimal caloric intake, best exercise for burning fat, how to stop smoking, and to moderate use of alcohol.

Secondary prevention is to take a regular physical checkup for early detection of risk factors for the metabolic syndrome. Legally defined items of physical checkups in Japan are already almost satisfactory for this purposes, but measurement of waist circumference should be added for the diagnosis of visceral obesity. The homeostasis model assessment of insulin resistance (HOMA-IR)[69)] is an additional candidate to use as a health checkup item for early detection of insulin resistance in young persons, because abnormalities with this examination appear before the signs and symptoms of metabolic syndrome develop. At present, careful follow up of workers with NAFLD should be considered to prevent the development of cardiovascular disease. Diet and physical exercise are usually recommended to treat NAFLD, though there is little evidence that these therapies improve the outcome. A large, randomized, placebo-controlled trial of adequate treatment, with baseline stratification according to histological severity, is necessary. Furthermore, knowledge about one's ALDH2 and β3-AR genotype may motivate people to correct their lifestyle, including drinking habits.

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