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NONALCOHOLIC FATTY LIVER DISEASE AS A FEATURE OF THE METABOLIC SYNDROME

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The main criteria of the metabolic syndrome are obesity, insulin resistance and disturbed lipid metabolism. The same disturbances are regarded to be involved into the pathomechanism of nonalcoholic fatty liver disease which is shown by epidemiological studies and animal models. Thus NAFLD can be regarded a specific feature of the metabolic syndrome and it should be looked for in high risk populations.

Key words: insulin resistance, nonalcoholic fatty liver disease, obesity, lipid metabolism, atherogenesis

Słowa kluczowe: insulinooporność, niealkoholowe zapalenie wątroby ze stłuszczeniem, otyłość, metabolizm tłuszczy, miażdżyca

THE METABOLIC SYNDROME

The metabolic syndrome is one of the major public health issues of our time. It is described as a risk factor of diabetes and cardiovascular diseases. Several components of the metabolic syndrome are considered: obesity, hypertension, glucose intolerance, increased triglyceride concentration, decreased HDL cholesterol concentration. There is no epidemiological data available on the incidence of metabolic syndrome in Poland, still the American data point to relatively high incidence of this syndrome in young adults (6,7%) [17]. *Ferranti* et al.[16] based their epidemiological studies on more restrictive criteria established by Adult Treat-

ment Panel III (ATP III) which showed the incidence in teenagers to be as high as 9,2%. European studies estimate the incidence to be a little lower. Metabolic syndrome was observed in 0,4% lean children in Hungary and almost 9% obese children [12]. All epidemiological data point to the significant role of the metabolic syndrome in the population of teenagers and young adults.

The definition of the metabolic syndrome is based on the estimated risk of diabetes and cardiovascular disease, still the definitions given by different expert groups and medical societies differ. The International Diabetes Federation (IDF) formulated one of the latest definitions in 2005 (*1st International Congress on „Prediabetes" and Metabolic Syndrome*) [20] which considers metabolic syndrome in patients with central obesity defined as waist circumfenence ≥ 94 cm in men and ≥ 80 cm in women (for Europe), with ethnicity specific values for other groups which coexists with any two of the following four factors: (1) raised trigliceryde level: ≥ 1,7 mmol/L (150 mg/dL), or specific treatment for this lipid abnormality; (2) reduced HDL cholesterol: ≤ 1,0 mmol/l (40 mg/dL) in males and ≤ 1,3 mmol/L (50 mg/dL) in females, or specific treatment for this lipid abnormality; (3) raised blood pressure- systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg, or treatment of previously diagnosed hypertension; (4) raised fasting plasma glucose (FPG) ≥ 5,6 mmol/L (100 mg/dL), or previously diagnosed type 2 diabetes.

Definitions in children and adolescents are not unified and they generate substantial problems as all parametres are age-dependent. Still the main factors of metabolic syndrome seem to be the central obesity and insulin resistance [8, 9].

Cardiovascular disease seems to be mainly mediated by inflammatory processes within the vasculature and several cytokines and inflammatory markers have been described to be increased in atherosclerosis. Metabolic syndrome may be also characterized by increased inflammation which was proven in many studies in adults but recently it has been also reported in children and adolescents with metabolic syndrome. *Lambert* et al. [24] showed a strong relationship of CRP with body mass index and fasting insulin values in a large school-based survey. Several other abnormalities may be observed in conjunction with the metabolic syndrome, like osteoporosis, non-alcoholic fatty liver disease, clotting disturbances, hiperuricemia, night apnoe, ovarian policystic disease etc. These symptoms seem to be strictly related to metabolic disturbances.

NONALCOHOLIC FATTY LIVER DISEASE – EPIDEMIOLOGY AND CLINICAL CHARACTERISTIC

Nonalcoholic fatty liver disease (NAFLD) is a common finding in adults and its pathogenesis as well as epidemiology can be explained in relation to the metabolic syndrome. NAFLD is recognised by histopathological features in liver biopsy, which shows predominantly macrovesicular and to a lesser extend microvesicular hepatic steatosis that occur in individuals who do not consume alcohol in amounts considered harmful to the liver. Diagnosis of NAFLD is also based on exclusion of other etiologies like viral infections, *Wilson* disease, autoimmune liver disease, abetalipoproteinemia. Epidemiology of NAFLD points to associations with diabetes or obesity as it is predominantly observed in obese patients who present with insulin resistance or diabetes. The likelihood of having NAFLD is regarded to be

directly proportional to body weight. In studies from Italy and Japan the prevalence of simple fatty liver (FL) ranged from 3-58%. The most important risk factor for FL are consumption of alcohol, obesity and insulin resistance.

The common feature of NAFLD are increased transaminases. On physical examination hepatomegaly may be present (up to 75%) [9]. NAFLD may be associated with diabetes mellitus, dyslipidemia, insulin resistance. Hypertension is much less frequent. Splenomegaly was reported in 25% of the patients at the time of diagnosis [3]. Abnormal serum lipid profiles and elevated serum glucose are often found and they are related to the pathophysiology of fatty infiltrations [1]. Increases of alanine and aspartate aminotransferase are the most common laboratory findings in NAFLD, but can be within normal limits. In fact, GGT has been suggested to be a sensitive marker of insulin resistance [11]. Serum bilirubin and albumin are usually within normal limits unless the disease progresses to cirrhosis [15]. Non-invasive techniques have been used to diagnose steatosis- like ultarsound. Additionally computerized tomography (CT) and magnetic resonance imaging (MRI) are used to establish the diagnosis. Liver biopsy is a golden standard to diagnose fatty liver disease but it is not the first diagnostic procedure in the clinical evaluation as non-invasive methods seem to be relatively sensitive at the first steps of differential diagnosis and treatment planning.

Clinical observations and epidemiological studies tried to analyze associations of NAFLD with other diseases or metabolic disturbances. Most of the studies point to the associations between metabolic syndrome and NAFLD. Kim et al. [22] showed that NAFLD is a significant predictor of other metabolic disorders, including hypertriglyceridemia and hyperuricemia. Their study conducted in non-obese subjects presented associations between fatty liver disease and waist circumference and insulin resistance [25]. Obesity, insulin resistance and the metabolic syndrome are strong predictors of increased transaminase activity [21]. Moreover, insulin resistance and systemic hypertension, features of the metabolic syndrome, are independently associated with NASH [14]. Insulin resistance seems to be a common finding in NASH and it was described in 85% of the patients tested by *Willner* et al. [33] and *Cassader* et al. [8] studied the influence of fat load in NASH patients and found increase in postprandial triglyceride levels with production of large VLDL that suggests atherogenic behavior of lipid metabolism [8]. Other numerous studies in children support metabolic observations in adult patients. Schwimmer et al. identified significant predictors of liver pathology in children with NAFLD which are insulin resistance and BMI [30]. *Hamaguchi* et al. in a prospective observational study showed that participants with the metabolic syndrome defined by the modified ATP III criteria have a 4 to11 times higher risk for future nonalcoholic fatty liver disease and when metabolic syndrome coexist disease regression is less likely [19].

PATHOGENESIS OF NAFLD AND NASH

As already discussed the major risk factors of NAFLD are obesity, insulin resistance, disturbances of lipid metabolism and free radical injury. The 'two-hit' theory tries to explain the progression of the disease to non-alcoholic steatohepatitis and cirrhosis [13]. The first hit is steatosis, and this is postulated to sensitize the liver to fatty acids that are delivered to the liver from peripheral adipose tissue or from local synthesis in the liver as a result of either protein or carbohydrate excess. Mitochondrial ß-oxidation to ATP and ketone bodies, and secretion into the

blood as triglycerides in very low-density lipoprotein (VLDL) are major pathways of fatty acid disposal. Disturbed lipid metabolism results in accumulation of triglycerides in the liver. Insulin resistance also plays a central role in liver accumulation of triglycerides and initation of the inflammatory cascade. Liver accumulation of fat in patients with the insulin resistance syndrome is mainly related to increased lipolysis of adipose tissue, with increased free fatty acids delivered to the liver that exceeds the liver's capacity to export VLDL. Hypertriglyceridaemia is often accompanied by low high-density lipoprotein cholesterol (HDL-C) concentration in patients with NAFLD. A role for microsomal triglyceride transfer protein (MTP) in the development of steatosis and even fibrosis has recently been suggested, MTP is crucial for the assembly and secretion of hepatic triglyceride as VLDL, and MTP promoter polymorphisms was related to both steatosis and the degree of fibrosis. Steatosis can also occur in other conditions such as protein-energy malnutrition. The second hit may be oxidative stress or increased abnormal cytokine production. Mitochondria are the source of the reactive oxygen species (ROS) leading to lipid peroxidation. The increased hepatic free fatty acid levels that result from the reduced ability of insulin to suppress lipolysis, are suspected to increase mitochondrial ß oxidation, producing ROS and the oxidative stress cascade. Cytokines, mainly tumor necrosis factor-α (TNF-α) are important in the pathogenesis of NAFLD. The concept of metabolic syndrome includes hypertrigluceridemia, obesity, glucose intolerance, insulin resistance, hypertension and low high density lipoprotein cholesterol (HDL-C) level [5]. Hypothesis of the role of insulin resistance refers to lipolysis in adipose tissue that leads to increased free fatty acid levels, which can stimulate overweight or obesity. There is also evidence that other cytokines such as leptin may be associated with development of the fibrosis associated with steatosis. Abnormal cytokine production in NAFLD patients may also be due to abnormal macrophage function, oxidative stress resulting in nuclear translocation of the transcription factor κB. This association may be of special importance linking the characteristic metabolic changes occurring in patients to their liver disease, as recent data have shown increased activity of the TNF-α system in obesity and insulin resistance. Adiponectin is an anti-inflammatory cytokine, which is produced by adipocytes. The release of adiponectin, from adipose tissue, appears to enhance insulin sensitivity and improve lipid metabolism [32].

THERAPY

Because obesity is the most common condition related to NAFD, weight loss is regarded to be the most important treatment of this condition [18]. Intentional weight loss improves many of the existing medical complications associated with obesity and it can prevent the development of new obesity-related diseases. Many of these beneficial effects are directly related to the amount of weight that is lost and become noticeable after only modest weight losses of 5% to 10% of initial body weight [23]. Data from the Framingham Offspring Study found that modest weight loss can affect a cluster of risk factors simultaneously. A weight loss of $\geq$ 2.25 kg over 16 years was associated with a 40% to 50% reduction in the sum of risk factors: systolic blood pressure, serum triglyceride, serum total cholesterol, fasting blood glucose, and lowest quintile of HDL- cholesterol in men and women [34]. Colles et al. observed the effect of rapid weight loss by a very-low-energy diet (VLED) in severely obese patients on liver volume (LV) and visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT).

This therapy was implicated as a preoperative treatment. Mean LV, VAT/SAT and body weight decreased significantly. The degree of LV reduction was directly related to the reduction in relative body weight and initial liver volume. Eighty percent of the reduction in liver volume occurred between 0 and 2 weeks, but reduction of body weight and VAT were uniform over 12 week period. Acceptability was adequate, but waned over time [10]. According to *Vajro* at al. clearly weight reduction is able to reduce transaminase levels as it was shown in obese children [35], but some researchers noticed that rapid weight loss may worsen NAFLD [31].

Physical activity seems to be the major option of therapy. Baba at al. study shows that regular aerobic exercise duration per day, and training to achieve a heart rate of 60-70% of his/her maximal heart rate at least 5 days a week helps in normalizing ALT levels in patients with NASH, independent of weight reduction. No influence of diet reduction was reported in this study. This effect seems to be related to waist circumference reduction and WHR decrease that reflects decreased insulin resistance [4].

Caloric restricted diet and its macronutrient composition is an important tool in therapy of metabolic syndrome and NASH. Conventional diets usually fall into two main categories: low-fat and low-carbohydrates diets. Low carbohydrate diets have been popular periodically over the last several decades. These diets limit the composition and/or amount (<100g) of carbohydrates, with an increase in dietary protein and fat. A diet high in carbohydrates results in an increase in blood glucose, insulin and triglicerides, all of which are the risk factors for the development of NALD. Carbohydrate restriction leads to ketosis resulting not only in weight loss, but also a decrease in blood glucose, insulin and triglyceride levels. Early weight loss is the result of diuresis associated with ketone and urea nitrogen excrection, however, over time, weight loss is a result of body fat loss. Results of a long-term low carbohydrate diet feeding are unknown and this diet can not be recommended at the moment [18]. *Valtuena* at al. investigated relation of insulin resistance and liver steatosis (LS) to total carbohydrate, total dietary fiber, the glycemic index (GI) and glycemic load of the diet in patients who were unselected for alcoholic intake. Data shows that high-GI dietary habits are associated with HG-LS, particulary in unsulin-resistant subjects. No relation was observed with total carbohydrates, total dietary fiber or glycemic load. So, it seems that quality of carbohydrates sources may be a complementary tool for preventing or treating LS of metabolic origin [37].

Lieber at al. study with animal model shows that rats fed the high-fat diet (71% of energy from fat, 11% from carbohydrates, 18% from protein) ad libitum for 3 weeks developed panlobular steatosis. The high-fat diet caused abnormal mitochondria and mononuclear inflammation which were accompaniated by increased hepatic tumor necrosos factor α (TNF- α), TNF- α messenger RNA (mRNA), collagen type 1, and α 1, procallagen mRNA. In addition, these rats had increased cytochrome P4502E1 mRNA, which was accompanied by CYP2E1 induction and oxidative stress with reflected insulin resistance, a NASH pathogenic factor. Rats fed the restricted high-fat diet as two-thirds of the amount consumed developed only mild steatosis with attenuated biochemical changes.

Rats fed standard diet (35% of energy from fat, 47% from carbohydrates, 18% from protein) ad libitum had few fat droplets whereas those given a restricted standard diet had normal livers. This study shows that a high-fat diet with 71% of energy derived from fat is more deleterious to the liver than is a normal diet (with 31% of fat), but also illustrated that even when restricted, the high-fat diet produces some undesirable liver changes that are not present with equivalent amounts of the standard diet [26].

A pilot study by *Capanni* at al. indicates, that n-3 polyunsaturated fatty acids supplementation may play an important role in treatment of NAFD. In this study fifty six patients with NALD were observed. 42 consumed 1g of n-3 PUFA daily for 12 months, 14 pts. refused the treatment and they were analysed as controls. N-3 PUFA supplementation significantly decreased serum aspartate transaminase, alanine transaminase, γ-glutamyl transpeptidase, triglicerides, fasting glucose and circulating arachidonate and n-6/n-3 ratio was reduced in comparison with controls. Moreover, ultrasound demonstrated improvement of liver echotexture after n-3 PUFA and increase of Doppler perfusion index, whereas no significant changes occurred in controls [7].

Recently there is growing interest in drug treatment, still there are only small or pilot studies available. Thiazolidinediones and metformin directed at insulin resistance seem to ameliorate fatty liver disease symptoms [6, 28]. Antioxidants have been also used and there are two studies performed in children which suggest good effects of this treatment [25, 35]. Several other treatment options are also considered like UDCA therapy.

CONCLUSIONS

NAFLD is usually associated with obesity or insulin resistance and thus can be regarded a sign of the metabolic syndrome. It should be looked for in patients with obesity, diabetes or lipid disturbances. Ultrasound examination and transaminase activity can be regarded to be a screening test for fatty liver disease. Moderate weigh reduction seems to be the major approach to the patient with NAFLD. At the moment dietary composition where fat delivers 30% of energy is the safest option of therapy. Preliminary data point to a significant role of glicemic index in diet planning, and some dietary supplements like fish oil can be also considered.

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Summary

The main features of the metabolic syndrome are obesity, insulin resistance and disturbed lipid metabolism. The same disturbances are regarded to be involved into the pathomechanism of nonalcoholic fatty liver disease which is shown by epidemiological studies and animal models. Thus NAFLD can be regarded a specific feature of the metabolic syndrome and it should be looked for in high risk populations.

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Streszczenie

Głównymi kryteriami zespołu metabolicznego są otyłość, insulinooporność i zaburzenia gospodarki lipidowej. Te same mechanizmy wydają się odgrywać główną rolę w rozwoju niealkoholowej choroby stłuszczeniowej wątroby (nonalcoholic fatty liver disease- NAFLD), co wykazano w badaniagh epidemiologicznych i na modelach zwierzęcych. Dlatego NAFLD można uważać za specyficzną prezentację zespołu metabolicznego i powinno się prowadzić diagnostykę w kierunku stłuszczenia wątroby w grupach zwiększonego ryzyka.

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