THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

MEDICINE
Review article

THE RELATIONSHIP BETWEEN NONALCOHOLIC FATTY LIVER DISEASE AND THE METABOLIC SYNDROME

ELENA CACEAUNE [1]

[1] National Institute of Diabetes, Nutrition and Metabolic Diseases "N.C. Paulescu", Bucharest
Corresponding author: Elena CACEAUNE, E-mail: elena_caceaune@yahoo.com

Received June 19, 2012

Nonalcoholic liver disease is considered the principal cause of chronic elevated liver enzymes with an increasing prevalence due to the association with overweight, dyslipidemia and diabetes. Many authors demonstred in epidemiological and demographics studies that NAFLD is a component of metabolic syndrome and is correlated with central obesity, glycemic disorders, hypertriglyceridemia, hypertension and low levels of HDL cholesterol. Liver fat is usually increased at the patients with type 2 diabetes but NAFLD has also been described at the nondiabetic subjects when the presence of hepatic steatosis is correlated with lipid disturbances, insulin disorders and can be considered markers for prediction of diabetes.

Key words: nonalcoholic fatty liver disease, obesity, metabolic syndrome, type 2 diabetes, dyslipidemia, insulin resistance.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver damage, characterized by fat accumulation in the liver in association with metabolic disorders. Other conditions correlated with fatty liver are: alcohol consumption, drugs toxicity, hepatitis C infection and nutritional causes: parenteral nutrition, rapid weight loss, bariatric surgery. Is the most common cause of abnormal liver tests with a increasingly importance due to the association with overweight and type 2 diabetes. The liver damage range from simple steatosis to non-alcoholic steatohepatitis (NASH) with different stages of fibrosis and cirrhosis[1,2]. In the future we expect to see an increasing incidence of NAFLD and many people will be at risk of development progressive liver disease because of the high prevalence of obesity and diabetes.

The **etiology** of NAFLD is multifactorial the principal factor being obesity, in particular central obesity but also glycemic disorders: impaired fasting glucose, impaired glucose tolerance, diabetes mellitus and lipid profile disturbances. The association of fatty liver with metabolic syndrome elements can be considered as secondary to central obesity and to the decrease in insulin sensitivity.

The study of fatty liver disease prevalence was based on screening population studies using for diagnosis ultrasound and liver tests. Actually we observed an increase from previous data: 10–24% to 17–33% for NAFLD and 5.7 to 16.5% for NASH and increases to 74% at the obese persons[1,3,4]. NAFLD is a increasing cause of chronic liver disease in children with a prevalence from 2.6% to 52.8% in obese children and 48% in type 2 diabetes children[5-8]. The **prevalence** of obesity in the patients with nonalcoholic fatty liver disease range from 30 to 100%[9]. Type 2 diabetes associated with NAFLD from 10 to 75% [1].

The patients with cryptogenetic cirrhosis have a history of diabetes mellitus or obesity, considering NAFLD as a primary cause for this end stage of liver disease[10,11].

In the patients with asymptomatic abnormal levels of liver tests, after exclusion of other causes of liver disease NAFLD can be attributed at these patient in approximately 90%[12,13].

One population – based study which used ultrasound scans and liver tests to diagnose NAFLD show a prevalence of 24.5% in the patients with BMI $\leq$ 25 kg/m^2, 67% for patients with BMI between 25 kg/m^2 and 30 kg/m^2 and 91% in the patients with BMI > 30 kg/m^2 [14,15]. About 50% of diabetic people and 100% of diabetic and obese persons have NAFLD [(16)]. The prevalence of hepatic steatosis in Dallas Heart Study which involved 2349 participants was estimated at 33.6% [17]. In this study, 345 patients who had no identifiable risk factors for hepatic steatosis (nonobese, nondiabetic subjects, normal liver tests), had a hepatic triglyceride content about 5.56% corresponds of 55.6 mg/g [17].

Steatohepatitis (NASH) affects 3% of the lean population, 19% of the obese population and 50% of morbidly obese people[18,19], also 50% of people with diabetes and obesity[16].

Classifying NAFLD

NAFLD represent a common liver disease caused by accumulation of fat in liver over 5–10% of its weight, or as the percentage of fat-laden hepatocytes observed at light microscopy with different stages of histological damage similar to those observed in alcoholic liver disease but not associated with alcohol consumption (< 20–30 g/day).

NAFLD comprises: hepatic steatosis, steatohepatitis (NASH) and cirrhosis. NASH is defined as steatohepatitis not caused by: alcohol, drugs, toxins, Wilson disease, parenteral nutrition, rapid weight loss and infectious agents. NASH play an important role in patient with cryptogenetic cirrhosis, most of them have history of diabetes and obesity[20,21].

Diagnosis

Even if the correct diagnosis of NAFLD is based on histological findings[20], in general practice we used clinical, biochemical and imagistic criteria. Usually, the patients addressed to gastroenterologic clinics for abnormal biochemical liver tests without clinical signs or non-specific symptoms: fatigue, sensation of fullness or discomfort on the right side of the upper abdomen and hepatomegaly[1]. If we analyze the personal medical history we can find diabetes, dyslipidemia, rapid weight gain or weight loss or cardiovascular diseases related to insulinresistance: arterial hypertension, or metabolic disorders in family medical history. Because histopathologists cannot make differential diagnosis between alcoholic hepatitis and steatohepatitis only based on morphological findings, the correlation of historical, clinical and histological data is essential[22].

Liver tests: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are moderately elevated, 1.5 to 3 fold, especially ALT with AST/ALT ratio < 1, but in some cases liver tests are normal. The elevated aminotransferase levels reflect nonalcoholic steatohepatitis (NASH), which occurs due to hepatic dysfunction secondary to progressive hepatic fat accumulation in patients with non- alcoholic fatty liver disease (NAFLD). The levels of AST and ALT are not always correlated with stage of hepatic steatosis. Some patients with ultrasonographically steatosis even they have normal aminotransferase values can have advanced liver disease[23,24]. A rise in AST and ALT levels reflects hepatic injury but some studies shows that alanine aminotransfearse could be used better as a marker for prediction of type 2 diabetes. ALT can predict the development of type 2 diabetes independent of other metabolic factors. The increasing of the liver fat is correlated with ALT value and is part of the pathogenic mechanism of diabetes, independent of the whole body adiposity[25]. Aminotransferase levels can show the histological evolution of NAFLD. A study made on 60 obese patients with hepatic steatosis which were analyzed biologic and histologic by biopsy before and after a significant weight reduction show that AST and better GGT lowering predict an improvement in inflammation and fibrosis. This is important for considering the value of GGT in evaluate the prognostic of NAFLD[26].

Imagistic techniques used for diagnose hepatic steatosis are: ultrasonography (US), computer tomography (CT), magnetic resonance (MRI). For US and CT is necessary a minimum of fat infiltration about 33% of hepatocytes. In clinical practice we used the evidence of “bright liver” with the reduction of posterior attenuation estimated with US. Ultrasonography has a sensitivity of 89% and a specificity of 93% in detection of steatosis and a sensitivity and specificity of 77%, respectively 89% for detection of fibrosis[1]. CT can be used to measure the fat content of the liver scanning low density hepatic parenchyma produced by fat infiltration and can

detect focal lesions. Magnetic resonance technique is the best quantitative method for diagnosis of steatosis because can detect fat tissue less than 33% and can distinguish better than US and CT the focal steatosis from space-occupying lesions[27]. Magnetic resonance spectroscopy (MRS) is also used as a quantitative assessment of fatty infiltration of the liver. Localized proton magnetic resonance spectroscopy (MRS) accurately measures hepatic triglycerides content even in early stages of steatosis but is used only in research studies[17]. An important evaluation for patients with NAFLD is to determined body composition: the total body fat and visceral adipose tissue with magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DEXA).

At present are no laboratory tests or imagistic techniques to be specific only for NASH[2].

Liver biopsy is considered gold standard technique to evaluate the stage of NAFLD and diagnosis of NASH. Histological findings are in principal fat accumulation and different degree of: inflammation, ballooning degeneration, Mallory hyaline and fibrosis. Because of limitations of liver biopsy related to accessibility and possible complications, the indication must be done if lifestyle interventions fail and after a evaluation of the presence of risk factors: age over 45 years, presence of obesity, T2D, a ratio: AST/ALT≥1. For severely obese patients we can use: body mass index>35, index of insulinresistance > 5, high blood pressure and high ALT level[1]. The assessment of liver histology cannot be substituted by liver tests and hepatic imaging in the advanced fibrosis stages.

Fibroscan is a new noninvasive method to evaluate the different stages of liver fibrosis. A mechanical pulse is generated at the skin surface and is propagated toward the liver. The velocity of the produced wave is measured by ultrasound and is correlated with the stiffness of the liver which reflects the degree of fibrosis. Non invasive methods for diagnosis NAFLD and NASH can be used in conjunction with biochemical markers[28].

Associated factors

The most frequently associated factors with NAFLD are: overweight, obesity, central fat accumulation, glycemic disorders (from impaired fasting glucose to diabetes), hypertriglyceridemia and the decrease of HDL-cholesterol. These conditions are risk factors for “primary NAFLD” and are considered to be related with insulin resistance. Many studies established a link between NAFLD and insulin sensitivity, but the relation with obesity and diabetes is a continue subject of debate because not all the people with obesity and diabetes have nonalcoholic fatty liver disease and not all patients with NAFLD are overweight or develop glycemic disorders. Predictors for the evolution to nonalcoholic steatohepatitis are increasing age, obesity, and diabetes[20].

1. Obesity. Obesity is the most common entity associated with NAFLD and a significant risk factor for the development of fatty liver and is also predictive for the presence of fibrosis[2]. Many epidemiological studies demonstrated a strong correlation between body mass index and the presence of fatty liver diagnosed by ultrasonography. 30 to 100% of patients diagnosed with NAFLD are obese[1], in obese persons 76% have NAFLD compare with 16% in normal weight persons[29]. BMI is an important predictor for hepatic steatosis but also for evolution to steatohepatitis. In overweight and obese patients with abnormal liver tests, liver biopsy showed 30% septal fibrosis and 10% cirrhosis. To evaluate the risk of fibrosis was calculated a score combining: BMI, age, alanine aminotransferase and triglyceride value[30]. A predictive value for progression to fibrosis was assigned to a quantitative index of insulin resistance (homeostasis model assessment –HOMA) in severely obese patients[31].

The studies which used liver histology to define the presence of NAFLD showed that some of patients with NAFLD have normal weight and normal waist circumference. 431 patients with NAFLD diagnosed by liver biopsy were analyzed depending the waist circumference as a surrogate marker of visceral adiposity. The increasing of visceral obesity are correlated with older age, higher prevalence of female gender, lower HDL, higher triglycerides, altered glucose metabolism, arterial hypertension and metabolic syndrome. The evolution to NASH and the presence of fibrosis were not associated with visceral adiposity. NASH was associated with higher levels of ALT, HOMA –IR >4 independent of the presence of visceral adiposity. The patients with NAFLD can develop NASH even they have normal waist circumference[5]. NASH can progress to cirrhosis/end-stage liver disease. Angulo et al studied one hundred and forty-four patients which underwent liver biopsy and identified that body mass index was the only independent predictor of the degree of fat infiltration and older age, obesity, presence of

diabetes mellitus and aspartate transaminase/ alanine transaminase (AST/ALT) ratio greater than 1 were significant predictors of severe liver fibrosis[32].

Because adipose tissue is recognized an active endocrine organ which produce different hormones and cytokines the increase of total body fat mass is a source of inflammatory cytokines which can promote pathogenetic mechanisms of steatohepatitis.

2. **Glycemic disorders**. Because both T2D and NAFLD are dependent on genetic and environmental factors, the study of the relation between them demonstrated a link of these pathogenetics mechanisms. Due to large extension of ultrasound as method used to diagnosed fatty liver many news cases of T2D patients are discovered after an oral glucose tolerance test in the patients with nonalcoholic fatty liver diseases. Higher level of liver triglycerides production is caused by an excess in glucose and free fatty acids (FFA) in patients with high plasma insulin levels[33].

NAFLD can precedes type 2 DM, obesity and metabolic syndrome but also among diabetic patients we can find a high prevalence of fatty liver. In NAFLD patients the presence of diabetes is a predictor for the evolution of liver disease to fibrosis and other liver related complications[18,34]. The prevalence of NAFLD is high in the patients T2D, 71.1% in men and 68% in women[35]. Glycemic disorders has been reported in 20–75% of patients with NAFLD[36]. A recent study demonstrated a high prevalence of prediabetes and type 2 diabetes: 86% vs. 30% in patient with fatty liver overweight and obese versus normal group without NAFLD which underwent a 75 g OGTT [37].

The patients with diabetes and fatty liver are more insulin resistant then those with diabetes but without fatty liver[38]. The results of a study[39] on 70 diabetic patients and 70 non-diabetic subjects show that type 2 diabetic patients had 80% more liver fat and 16% more intra-abdominal fat than the nondiabetic subjects at any value of BMI and waist circumference. Fasting plasma glucose, HbA1c, fasting plasma insulin, triglycerides, HDL-cholesterol were correlated with fatty liver. For the patients with higher values of ALT, the patients with type 2 diabetes had 70–200% more liver fat. This difference was not found in the patients with normal liver enzyme[39].

3. **Lipid disturbances**. About 20–92% of patients with fatty liver have dyslipidemia especially hypertriglyceridemia[1]. Triglycerides are stored in the liver, secreted as very –low-density lipoprotein (VLDL) or can be oxidated but hepatic insulin resistance can alterate these proceses in the liver. The first disorders is the increase rate of hepatic tryglicerides synthesis and VLDL production. The accumulation of fat in the liver can be explained by: "excess dietary fat, increased delivery of free fatty acids (FFA) to the liver, inadequate fatty acid oxidation, and increased de novo lipogenesis"[6].

The increase of FFA is correlated with insulin resistance, inhibits apo B degradation and increased VLDL formation[40]. At the excess stored of the triglycerides in the liver can contribute the visceral fat which is at a high level at the patients with metabolic syndrome and type 2 diabetes patients. Hepatic steatosis is frequently associated with an atherogenic lipid profile: high level of triglycerides, low level of HDL-cholesterol, and increasing of small and dense LDL and apolipoprotein B100 (apoB) concentration in type 2 diabetes patients. Severals studies had analyzed if hepatic insulin resistance is the cause or the consequence of liver steatosis[24,41,42]. The problem is even under debate. Insulin suppression of lipolysis is affected and can explain the increased release of free fatty acids from adipose tissue and high flux of FFA in to the portal vein in the liver. In this process visceral adipose tissue (VAT) is important because of it's metabolic activity[26,43]. Liver fat is positive correlated with total adiposity of the body, with percent of adipose tissue but a strong correlation was observed with visceral adiposity estimated regularely by waist circumference[39,44].

The correlation between hepatic steatosis and atherogenic lipid profile characteristic to type 2 diabetes (elevated triglycerides, low high-density lipoprotein cholesterol, small dense low-density lipoprotein and high levels of postprandial lipemia), can be explained through insulin resistance but it is not clear which process is primary, the increased liver fat content or lipid disturbances. It is wellknown that in adults with T2D and hepatic steatosis the distribution and size of lipoprotein subclasses are modified but this isuue was less studied in children. To asses if hepatic steatosis can predict a proatherogenic lipid profile, Anna M. G. Cali *et al.* demonstrated that in a group of obese adolescents normal glucose tolerant intrahepatic lipid content measured with magnetic resonance imaging was associated with an increase in VLDL particle size and number, increase of small dense LDL and decrease of large HDL particles. This can suggest that liver steatosis is related with early pathogenesis mechanism which preced the onset of type 2 diabetes[45].

4. **Hypertension**. Bedgoni *et al.* in a study on a representative sample of the general population demonstrated that NAFLD was associated with systolic hypertension[15]. A study made on healthy volunteers compared plasma biomarkers of inflammation and endothelial dysfunction in patients with versus without nonalcoholic fatty liver disease. The patients with NAFLD diagnosed by ultrasound and computed tomography had significantly higher values for: waist circumference, BMI, CT-measured visceral fat, diastolic blood pressure, plasma triglycerides and lower for HDL-cholesterol. Only diastolic blood pressure and not systolic blood pressure in these patients was significantly higher. HOMA index and the markers of inflammation and endothelial dysfunction were also higher in patients with hepatic steatosis[46].

As features of metabolic syndrome, "insulin resistance and systemic hypertension are independently associated with advanced forms of NAFLD" and can be considered predictors for NASH[47].

5. **Insulinresistance**. In the pathogenetic mechanisms of **insulinresistance**, liver and muscle may have a key roles, being related to fatty overload from obesity. The impaired suppression of the glucose production in the liver and of the glucose uptake by muscle tissue and increased lipolysis in adipose tissue leads to a high storage of fatty acids in the liver. Insulinresistance is associated not only with a high lipid influx into the liver but also with de novo hepatic lipogenesis. The lipid utilization disorders causing by mitochondrial oxidation contribute to triglycerides fat accumulation, lipotoxicity and hepatic injury. Insulinresistance presented in the obese patients can be found in non-obese and non-diabetic patients with fatty liver accumulation. This suggests insulin resistance as a significant factor responsible for NAFLD. Insulin resistance and hyperinsulinemia as a principal disorders of these metabolic disorders can be considered the link between NAFLD and metabolic syndrome[48,49]. To demonstrate this patho-physiological state we can use homeostasis model assessment of insulin resistance (HOMA-IR) and compare to a normal/control group. In some cases can be performed a 75 g glucose tolerance test with simultaneous determined of plasma glucose and insulin levels. Fasting C- peptid level can be also used as an indicator of insulin secretion is important in evaluation of patients with NAFLD and metabolic disorders.

Is well known that hepatic steatosis is associated with overweight and diabetes but some patients have normal weight and normal glucose tolerance. The patients with NAFLD have fasting hyperinsulinemia and insulin resistance independent of weight and fasting plasma glucose[50]. Animal studies shows that NAFLD is primary and precedes the insulin resistance state. Fat accumulation and hepatic insulin resistance can contribute to the development of peripheral insulin resistance. This model can be explained in patients with hepatic cirrhosis. Diabetes as a complication of liver cirrhosis is characterized by a reduction in insulin action and a β – cell secretor defect is not able to compensate for insulin resistance. The peripheral insulin resistance is associated with impaired glucose transport and glycogen synthesis. After liver transplantation the normal insulin sensitivity is restore at the liver, skeletal muscle and adipose tissue and the glucose tolerance is estabileshed[44,51].

The importance of insulin resistance was studied in NAFLD but also in genotype 3 chronic hepatitis C. A study of 132 patients with "viral" steatosis and 132 patients with "metabolic" steatosis caused by nonalcoholic fatty liver disease NAFLD analyzed the relation between clinical, metabolic characteristics, insulin resistance – HOMA –R and histological features. In the patients with NAFLD the parameters correlated with: the severity of fibrosis, high aminotransferases, HOMA-R, ferritine and low HDL- cholesterol; for CHC-3 the correlation was found with: HOMA-R and a low plateled count[52].

Insulin resistance was analyzed in patients with NAFLD as hepatic insulin sensitivity (HIRi = fasting EGP [hepatic glucose production] – FPI concentration), a validated index in the fasting state and as adipose tissue insulin resistance Adipo-IRi (Adipo-IRi = fasting plasma FFA – FPI concentration). The patients with NAFLD only with prediabetes and type 2 DM had significantly impaired hepatic insulin resistance compared with the patients without NAFLD. Adipo-IRi was higher in patients with NAFLD normal glucose tolerant, prediabetes and type2DM. Adipose tissue insulin resistance in patients with T2DM was correlated with hepatic insulin resistance and intrahepatic lipid content assesed by magnetic resonance spectroscopy. The worsening of adipose tissue IR was associated with the presence of fatty liver and with the progression of glycemic disorders[37].

Metabolic syndrome is present in 60% of female and 30% of male with NAFLD. The presence of metabolic syndrome elements in the patients with NAFLD is associated with a higher risk to progress to NASH independent of sex, age and body mass[2,53].

The risk of hepatic steatosis increase exponenttially with the addition of each component of the metabolic syndrome. A study on 271 nondiabetic subjects demonstrated that liver fat was 4-fold higher in subjects with than without the metabolic syndrome. Among the components of metabolic syndrome the best correlation of liver fat was with waist circumference both in women and in men[54]. Overweight and diabetes increase fatty infiltration as well as clinical and biochemical disorders[2]. In NAFLD and metabolic syndrome the high level of circulating and intracellular fatty acids concentration can explain the inflammatory state and insulin resistance in adipose tissue and in the liver.

The dysregulation of proinflammatory cytokines: leptin, TNF-α, IL-6 and low level of adiponectine can explain the link between T2DM, metabolic syndrome and fatty liver and the progression of NAFLD to NASH. TNF- α and IL-6 are implicated in the pathogenesis of insulin resistance. Adiponectin as an insulin-sensitizing adipocytokine is reduced in diabetes and obesity and many studies showed a low level of adiponectine in the patients with hepatic steatosis. Adipocyte fatty acid-binding protein may also influence insulin resistance. Leptine deficiency or leptine receptor inhibition can be associated with liver fat accumulation.

The link between NAFLD and metabolic syndrome is sustained in the studies which analyzed the clinical and histological changes in the obese patients with hepatic steatosis before and after an weight reduction obtained by laparoscopic adjustable gastric band placement. The patients with metabolic syndrome, after surgery weight loss had major clinical and histological improvement and resolution of obesity and metabolic syndrome - associated[43].

In overweight and obese adolescents intra-abdominal fat and hepatic triglyceride content were studied to define the independent role of each as predictor for insulin sensitivity disorders and progression to T2DM. For a similar visceral fat mass and percent body fat, the patients with liver steatosis versus without steatosis had higher values for body mass index and waist circumference, insulin sensitivity 55% lower and the presence of metabolic syndrome two fold higher.

Hepatic steatosis was associated with the presence of metabolic syndrome, insulin sensitivity and dyslipidemia independent of visceral fat mass[55].

Cardiovascular risk

Obesity and visceral adiposity are considered risk factors for type 2 diabetes and cardiovascular diseases. In correlation with visceral adiposity, NAFLD is an independent predictor for diseases.

A study of 132 nondiabetic subjects show that the liver fat measured with proton spectroscopy is associated with hepatic insulinresistance and inversely correlated with serum adiponectin, independent of body mass index. Liver fat content is associated with intra-abdominal fat but not with subcutaneous fat (measured with magnetic resonance imaging)[56]. Insulin resistance is associated with chronic inflammation. Fibrinolysis, endothelial dysfunction presented in these patients can explain the increase of cardiovascular risk which is also increased by the aggregation of metabolic features presented at the patients with fatty liver disease.

Fatty liver has an important role in predicting coronary artery disease. A prospective study made on 612 patients which underwent coronary angiogram show that 356 (58.2%) had fatty liver assessed by ultrasonography. Coronary artery disease occurred in 84.6% of patients with fatty liver and 64.1% of those without fatty liver. Fatty liver was associated with coronary artery disease in this study independently of age, sex and metabolic factors[57].

A recent study demonstrated that serum adipocyte fatty acid-binding protein (A-FABP) levels in type 2 diabetic patients are associated with NAFLD independent of body mass index, waist circumference, HOMA-IR, HbA1c, triglycerides, HDL-cholesterol and CRP-level. Serum A-FABP may be considered an independent marker of NAFLD in type 2 diabetic patients. The correlation with hyperglycemia, lipid disorders, insulinresistance and inflammation sustain an important role in development of metabolic syndrome, type 2 diabetes and a possible causative role in NAFLD[58].

Nonalcoholic steatohepatitis is defined by elevated liver enzymes and liver biopsy disorders similar to those met in alcoholic hepatitis: fatty degeneration, inflammation and fibrosis. The evolution of fatty liver to non-alcoholic steatohepatitis is related to the presence of diabetes, metabolic syndrome, environmental factors, bowel bacterial overgrowth which increase the hepatic level of TNF-α, but also with a genetic component. New data clarification regardless the pathogenesis of steatohepatitis can increased our possibility to avoid the progression to fibrosis and to development new effective therapies.

The importance of epidemic increasing of diabetes and obesity is reflected in a greater prevalence of fatty liver disease in last years in a population which have a mortality rates caused by liver disease exceeded that from cardiovascular disease.

Treatment

The weight reduction is the main and primary attitude applied in the patients with NAFLD, lifestyle behaviors, diet composition and sedentary activity being the first disorders which appear in the patients with NAFLD and NASH. The alcohol consumption is excluded and also other hepatotoxic substances. Because metabolic syndrome are closely associated with hepatic steatosis we have to treat and prevent all the metabolic syndrome elements: weight excess, dyslipidemia, glucose disorders, hypertension. The action of insulin sensitivity agents (glitazones and metformin) and of hepatoprotective drugs were evaluated in many studies but in present we haven't a final conclusion of the effect of the pharmaceutical agents, keeping in mind the side effects recorded after utilization of glitazones. New chemical agents which inhibit serum A-FABP may have beneficial effects in NAFLD[58].

REFERENCES

1. Angulo P. Nonalcoholic Fatty Liver Disease. The New England Journal of Medicine, Vol. 346, No. 16: 1221-1231, 2002.
2. D. Festi, A. Colecchia, T. Sacco, M. Bondi, E. Roda and G. Marchesini: Hepatic steatosis in obese patients: clinical aspects and prognostic significance. Obesity reviews 5: 27-42, 2004.
3. Luyckx FH, Desaive C, Thiry A, *et al.*, Liver abnormalities in severely obese subjects: effect of drastic weight loss after gastroplasty. Int J Obes Relat Metab Disord 22:222-226, 1998.
4. Arthur J. McCullough. The epidemiology and risk factors of NASH. Fatty Liver Disease NASH and Related Disorders 3: 23-37, 2005.
5. Fracanzani AL, Valenti L, Bugianesi E, Vanni E, Grieco A, Miele L, Consonni D, Fatta E, Lombardi R, Marchesini G, Fargion S. Risk of nonalcoholic steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease and low visceral adiposity. J Hepatol, 54 (6): 1244-9, 2011.
6. Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G: Insulin resistance in nonalcoholic fatty liver disease. Curr Pharm Des, 16 (17): 1941-51, 2010.
7. Tominaga K, Kurata JH, Chen YK, Fujimoto E, Miyagawa S, Abe I, Kusano Y. Prevalence of fatty liver in Japanese children and relationship to obesity : an epidemiological ultrasonographic survey. Dig Dis Sci 40: 2002-2009, 1995.
8. Franzese A, Vajro P, Argenziano A, Puzzielo A, Iannuci MP, Saviano MC, Brunetti M, Rubino A. Liver involvement in obese children. Ultrasonography and enzyme levels at diagnosing and during follow-up in a italian population. Dig Dis Sci 42: 1438-1442, 1997.
9. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experience with a hitherto unnamed disease. Mayo Clinic Proc 55: 434-8, 1980.
10. Anna Kotronen, Leena Juurinen, Annti Hakkarainen, Jukka Westerbacka, Anja Corner *et al.*, Liver fat is Increased in Type 2 Diabetic Patients and Underestimated by Serum Alanine Aminotransferase Compared With Equally Obese Nondiabetic Subjects. Diabetes Care, vol.1, Number 2, 2008.
11. Caldwell SH *et al.*, Cryptogenetic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology 29: 664-669, 1999.
12. Daniel S, Ben-Menachem T, Vasudevan G, Ma CK, Blumenkehl M. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. Am J Gastroenterol 94:3010-3014, 1999.
13. Clark JM, Brancati FL, Diehl AME. Nonalcoholic fatty liver disease: the most common cause of abnormal liver enzymes in the U.S. population. Gastroenterology 120:Suppl:A-65, 2001.
14. Claus Thamer, Jurgen Machann, Michael Haap *et al.*, Intrahepatic Lipids Are Predicted by Visceral Adipose Tissue Mass in Healthy Subjects. Diabetes Care, volume 27, Number 11, November 2004.
15. Bedogni G *et al.*, Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology 42: 44-52, 2005.
16. Silverman JF, Pories WJ, Caro JE. Liver pathology in diabetes mellitus and morbid obesity: clinical, pathological and biochemical consideration. Pathol Annu 24: 275-302, 1989.
17. Szczepaniak LS, Nurenberg P, Leonard D, Browning JD, Reingold JS, Grundy S, Hobbs HH, Dobbins RL. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population.Am J Physiol Endocrinol Metab. 288(2):E462-8, 2005.
18. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity; an autopsy study with analysis of risk factors. Hepatology 12:1106-10, 1990.
19. Silverman JF, O'Brian KF, Long S *et al.*, Liver pathology in morbidly obese patients with and without diabetes. Am. J Gastroenterol 85: 1349-55, 1990.
20. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD single topic conference. Hepatology 37: 1202-1219, 2003.
21. Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology 29:664-9, 1999.
22. Pauline de la M. Hall, Richard Kirsch. Pathology of hepatic steatosis, NASH and related conditions. Fatty Liver Disease NASH and Related Disorders 3: 23-37, 2005.
23. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, Sterling RK, Shiffman ML, Stravitz RT, Sanyal AJ,. Clinical and histological spectrum of non-alcoholic fatty liver disease associated with normal ALT values. Hepatology 37: 1286-1292, 2003.
24. Marchesini G, Marzocchi R, Agostini F, Bugianesi E. Nonalcoholic fatty liver disease and the metabolic syndrome. Curr Opin Lipidol.16(4):421-7, Aug 2005.
25. Hanley AJG, Williams K., Festa A, Wgenkknecht LE, D'Agstino RB Jr, Kempf J, Ziman B, Haffner SM.

Eevato nmarkers o iver injury and risk of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. Diabetes 53 (10): 2623-32, 2004.
26. Adler M, Schaffner F. Fatty liver hepatitis and cirrhosis in obese patients. Am J Med 67:811-6, 1979.
27. Mitchell DG, Focal manifestations of diffuse liver disease at MR imaging. Radiology 185: 1-11, 1992.
28. Ernesto Roldan-Valadez *et al.*, Imaging techniques for assessing hepatic fat content in nonalcoholic fatty liver disease. Annals of Hepatology 7(3): 212-220, 2008.
29. Adams LA, Angulo P. Recent concepts in non-alcoholic fatty liver disease. Diabet Med 22(9): 1129-33, 2005.
30. Ratziu V, Giral P, Charlotte F, *et al.*, Liver fibrosis in overweight patients. Gastroenterology 118:1117-23, 2000.
31. Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 121:91-100, 2001.
32. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology 30:1356-62, 1999.
33. Ionescu Tîrgovişte C: Tratat de Diabet Paulescu, Ed. Academiei Romane, 321-335, 387, 2004.
34. Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. Clin Gastroenterol Hepatol. 4 Mar;2(3):262-5, 2004.
35. Targher G, Bertolini R, Padovani R, Rodelle S, Tessari R, Zenari L, Day C, Arcaro G. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes care 30: 1212-1218, 2007.
36. Reid AE Nonalcoholic steatohepatitis. Gastroenterology 121(3): 710-23, 2001.
37. Carolina Ortiz-Lopez, Romina Lomonaco, Beverly Orsak et al. Prevalence of prediabetes and diabetes and metabolic profile of patients with nonalcoholic fatty liver disease (NAFLD). Diabetes Care, Vol. 35, number 4:873-878, April 2012.
38. Kelley DE, McKolanis TM, Hegazi RA, Kuller LH, Kalhan SC: Fatty liver in type 2 diabetes mellitus: relation to regional adiposity, fatty acids, and insulinresistance. Am J Physiol 285: E906-E916, 2003.
39. Kotronen A, Juurinen L, Hakkarainen A, Westerbacka J, Cornér A, Bergholm R, Yki-Järvinen H: Liver fat is increased in type 2 diabetic patients and underestimated by serum alanine aminotransferase compared with equally obese nondiabetic subjects. Diabetes Care, 31(1): 165-9, Jan 2008.
40. Toledo FG, Sniderman AD, Kelley DE: Influence of hepatic steatosis (fatty liver) on severity and composition of dyslipidemia in type 2 diabetes. Diabetes Care. 29(8):1845-50, 2006.
41. Adiels M, Olofsson SO, Taskinen MR, Boren J. Diabetic dyslipidaemia, Curr Opin Lipidol, 17 (3: 238-46), Jun 2006.
42. Niina Matikainen, Sakari Mänttäri, Jukka Westerbacka, Satu Vehkavaara, Nina Lundbom, Hannele Yki-Järvinen, Marja-Riitta Taskinen Postprandial lipemia associates with liver fat content J Clin Endocrin Metab 92(8): 3052, Aug 2007.
43. Powell EE, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. Hepatology 11:74-80, 1990.
44. Perseghin G, Mazzaferro V, Sereni LP, Regalia E, Benedini S, Bazzigaluppi E, Pulvirenti A, Leão AA, Calori G, Romito R, Baratti D, Luzi L.:Contribution of reduced insulin sensitivity and secretion to the pathogenesis of hepatogenous diabetes: effect of liver transplantation.Hepatology 31(3):694-703, Mar 2000.
45. Anna M. G. Cali, Tosca L. Zern, Ana Mayra de Oliveira, Sylvie Dufour, James D. Otvos, Sonia Caprio. Intrahepatic fat accumulation and alterations in lipoprotein composition in obese adolescents. Diabetes Care, Vol. 30, number 12: 3093-3098, December 2007.
46. G. Targher, L. Bertolini, L. Scala, G. Zoppinit, L. Zenari and G. Falezza. Non-alcoholic hepatic steatosis and its relation to increased plasma biomarkers of inflammation and endothelial dysfunction in non-diabetic men. Role of visceral adipose tissue. Diabetic Medicine, 22: 1354-1358, 2005.
47. Dixon JB, Bhathal PS and O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 121: 91-100, 2001.
48. Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, Cassader M, David E, Cavallo-Perin, P, Rizzetto M. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrom further evidence for an etiologic association. Hepatology 35: 367-372, 2002.
49. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome, Diabetes 50: 1844- 50, 2001.
50. Marchesini G, Brizi M, Morselli-Labate AM, *et al.*, Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med 107: 450-5, 1999.
51. O Selberg, W Burchert, J vd Hoff, G J Meyer, H Hundeshagen, E Radoch, H J Balks and M J Müller: Insulin resistance in liver cirrhosis. Positron-emission tomography scan analysis of skeletal muscle glucose metabolism. J Clin Invest. 91(5):1897–1902. doi:10.1172/JCI116407, 1993.
52. Bugianesi E, Marchesini G, Gentilcore E, Cua IH, Vanni E, Rizzetto M, George J Fibrosis in genotype 3 chronic hepatitis C and nonalcoholic fatty liver disease: Role of insulin resistance and hepatic steatosis. Hepatology 44(6):1648-55, dec 2006.
53. Marchesini G, Bugianesi E, Forlani G *et al.*, Non alcoholic fatty liver, steatohepatitis and the metabolic syndrome. Hepatology 37: 917-23, 2003.
54. Kotronen A, Westerbacka J, Bergholm R, Pietilainen KH, Yki-Jarvinen H. Liver fat in the metabolic syndrom. J Clin Endocrinol Metab 92: 3490-3497, 2007.
55. Brandy A. Wicklow, Kristy D. M. Wittmeier, Andrea C. MacIntosh et al. Metabolic consequences of hepatic steatosis in overweight and obese adolescents. Diabetes Care, vol. 35, number 4: 905-910, April 2012.
56. Westerbacka J, Corner A, Tiikkainen M, *et al.*, Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: implications for sex differences in markers of cardiovascular risk. Diabetologia 47: 1360-1369, 2004.
57. Vincent Wai-Sun Wong, Grace Lai-Hung Wong, Gabriel Wai-Kwok Yip, *et al.*, Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease: Gut:10.1136/gut.2011.242016
58. Jang Hyun Koh, Young Goo Shin, Soo Min Nam, *et al.*, Serum adipocyte fatty acid-binding protein levels are associated with nonalcoholic fatty liver disease in type 2 diabetic patients. Diabetes Care, volume 32, number 1: 147-152, January 2009.