ISSN: 2304-2354
Number 3, Volume 44, 2013

# NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)/NON-ALCOHOLIC STEATOHEPATITIS (NASH) AND TYPE 2 DIABETES MELLITUS (T2 DM)

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**Abstract**

**Background/Aim.** NAFLD/NASH, the common liver disease, represents a worldwide health problem. It has gained considerable attention for the fascinating relation between insulin resistance and slow-evolving course towards the end stage liver disease. We aimed to know the prevalence of NAFLD/NASH in patients with type 2 DM and to assess the correlation between the severity of fatty liver changes and anthropometric and biochemical parameters of the subjects.

**Methods.** A total of 127 patients with type 2 DM, 60 (47.2%) male and 67 (52.8%) female, with median age 59.3±9.3 years old, attending a specialized policlinic center care in Tirana during the period between January 2011 and July 2012 were included in current study. Subject giving a history of alcohol abuse (> 0 gr/daily) and who were found to have evidence of hepatitis B or C, autoimmune hepatitis, drug toxicity, tuberculosis or concomitant steroid therapy were excluded. Blood samples were drowning for measurements of alanin aminotransferaze (ALT), aspartat aminotransferase (AST), fasting blood glucose, insulin, cholesterol and triglycerides. It was assumed insulin resistance (IR) when HOMA-IR > 3.9 and BMI > 28 kg/m2. Fatty liver was diagnosed by ultrasonography and NASH was based on the most accepted criteria. The scoring system was used in order to graduate the severity of the liver. Univariate and multivariate analysis were used to compare the study parameters between the subjects with and without NAFLD (group 1 vs group 2) and to assess the correlation between the severities of fatty liver infiltration and study parameters.

**Results.** NAFLD was present in 94/127 (74%) of the patients with type 2 DM. Mild, moderate and severe degree of fatty liver changes were found in 39/94 (41.5%), 45/94 (47.9%) and 10/94 (1o.6%), respectively. NASH was seen in 29/127 (23%) of the subjects. Univariate analysis revealed that BMI (p=0.001), abdominal perimeter (0.01), ALT level (p=0.034), cholesterol P=0.008) triglycerides (p=0.004) and HOMA-IR (p=0.001) were significantly associated with the presence of NAFLD. Although there were no statistical difference, the mean ± SD of age, AST level, fasting blood glucose, insulin, HbA1c were higher in diabetic patients with NAFLD than those without liver steatosis. Multivariate analysis revealed a positive association between severity of fatty liver infiltration and age (p=0.036), BMI (p=0.001), abdominal perimeter (p=0.001), HbA1c (p=0.031) and HOMA-IR (p=0.001).

**Conclusions.** NAFLD/NASS are frequent among patients with type 2 DM. Age, BMI and insulin resistance are the strongest independent predictors for developing NAFLD/NASH in these subjects.

**Keywords:** Non-alcoholic fatty liver, Non-alcoholic steatohepatitis, Type 2 Diabetes mellitus, insulin resistance, metabolic syndrome

## Introduction

NAFLD/NASH represent a worldwide health problem, concerning approximately 20%-30% of the adult population in both development and developing countries (1,2,3). The rising prevalence of obesity and diabetes influence evidently in an increasing prevalence of NAFLD regardless of alcohol and viruses (4,5). This trend is of particular concern in the pediatric population where the reported increase in obesity will undoubtedly result in a higher incidence and prevalence of pediatric and adult NAFLD in the future (6).

Cases of fatty liver disease with inflammation that resembles alcoholic liver pathology but occurring in nondrinkers were described 30 years ago (7,8), but

ISSN: 2304-2354
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in the last twenty-years there has been an explosion of interest in this. The initial assessment of NAFLD/NASH as a benign is not supported by current evidence. Convincing studies have made clear that a subset of patients with NAFLD/NASH are at increasing risk of progression live diseases and may experience all the complications of cirrhosis, such as end-stage liver disease and hepatocelullar carcinoma (9,10,11,12). Indeed, it can be argued that most cases of cryptogenic cirrhosis, which ranks as the third leading indication for liver transplantation after alcohol and hepatitis C, are due to burned out NASH (13).

NAFLD/NASH are now regarded as a hepatic manifestation of the metabolic syndrome and the link between them and obesity, T2 DM, HTA and cardiovascular disease is likely to reflect shared pathological factors (14, 15, 16, 17). In fact, NAFLD/NASH is frequently seen in conjunction with other component of the metabolic syndrome, especially diabetes mellitus (18, 19). Insulin resistance is the underlying link between these various disorders and numerous studies have shown virtually all patients with NAFLD/NASH have insulin resistance (20, 21, 22). The pathogenesis of NAFLD is not jet completely understand. Recent advances demonstrate that fatty liver disease and its progressive development in NASH is a complex phenomenon which originates by multiple hits (23,24,25). The first hit is the development of steatosis caused by insulin resistance in muscle, adipose tissue and liver. Alterations in several cytokines (including elevated levels of tumor necrosis factor-TNF and interleukin-6 and decreased adiponectin levels) have proposed as mediators of insulin resistance, although the precise mechanisms remains incompletely defined. The major subsequent processes include the formation of free radicals (induced by fatty acids in the liver), lipid peroxidation and proinflammatory cytokines. The final effect of these alternations is the necrosis, formation of Mallory hyaline, inflammation and fibrosis, the characteristic feature of NASH (26). On the basis of this concept, a number of pilot studies have tested the hypotheses that therapy directed at improving insulin resistance with metformine or thiazolidinechinones may be beneficial in patients with NASH (27, 28, 29, 30, 31, 32, 33, 34).

Liver biopsy is regarded as the gold standard for assessment of fatty liver damage. However, currently clear guidance for biopsy in NAFLD does not exist. On the other hand, its invasiveness and clinical risk even in experienced hands limits its use, especially in outpatients and in large epidemiological study. Moreover, the potential for false negative, as tissue changes tend to be unevenly distributed throughout the liver, variation in interpretation of histological section and the real cost, reduced the number of patients requiring liver biopsy. On the other side, ultrasound, the cheapest option, has been reported to have a sensibility of 89% and specificity of 93% for the identification of fatty liver (35,36). However, in the morbidity obese, the performance of ultrasound is considered weaker; a sensitivity of only 49% with a specificity of 75% (37).

The present study aimed to know the prevalence of NAFLD/NASH in patients with T2 DM and to assess the correlation between the severity of fatty liver changes and anthropometric and biochemical parameters of the subjects.

## Methods

A total of 127 patients with T2 DM, 60(47,2%) male and 67 (52.8%) female with median age 59.3±9.3 years old, attending a specializes policlinic center care in Tirana during the period between January 2011 and July 2012 were included in the current study. Subjects giving a history of alcohol abuse (> 20 gr/daily) and who were found to have evidence of hepatitis B or C infection, autoimmune hepatitis, drug toxicity, metabolic liver diseases, tuberculosis or concomitant steroid therapy were excluded. Informed consensus was obtained for each patient. The study was approved by the Albanian Ethic Committee.

All subjects underwent a through medical history and physical examination, which included measurements of weight and height. Body Mass Index (BMI) was calculated as the weight (kg) divided by the square of height (m). Weight status was determined using the Diseases Control Central and Prevention 2000 growth curves that define as: underweight (BMI $<5^{th}$ percentile), normal weight ($5^{th}$<BMI<$84^{th}$ percentile), overweight ( $85^{th}$ <BMI<$95^{th}$ percentile) and obese (BMI>$95^{th}$ percentile).

Blood samples were drown from the forearm by vein-punction in the fasting condition for measurements of ALT, AST, glucose, insulin, HbA1c, cholesterol and triglycerides. Insulin resistance (IR) was calculated by means of the Homeostasis Model Assessment using the formula for the HOMA-IR = fasting plasma insulin in microunity/ml X fasting plasma glucose in mg/dL: 405. It was assumed IR when the HOMA-IR > 3.9 and BMI> 28kg/m2. Study parameters of the subjects with NAFLD (group 1, n=134) were compare with those of the subjects without NAFLD (group 2, n=60).

Real time ultrasonography of the liver was performed in fasting condition by the same

ISSN: 2304-2354
Number 3, Volume 44, 2013

experienced radiologist (to avoid interobserver variation). Fatty liver was diagnosed by ultrasonography detection of the most characteristic features of fatty infiltration in the liver, regarding to its echo texture, echo penetration, liver-diaphragm differentiation of the echo amplitude and clarity of the liver blood vessel structure. The scoring system was used in order to graduate the severity of the liver pathology, similar to that described by Tominga and Chan (38,39). The patients was considered to have mild, moderate and severe fatty liver change if the overall score was 1-3, 4-6 and 7-9, respectively. Diagnosis of NASH was based on the most accepted criteria, such as: 1) ultrasound evidence of fatty liver, 2) ethanol intake equal or lower than 20 gr/daily, 3) increase of ALT level, 4) presence of IR, 5) age over 50 years, BMI > 28 Kg/m2 and 7) hipertriglyceridemia ( 40,41 ). Means, standard deviation and percentage were reported for various anthropometric and biochemical parameters. Univariate analysis was used for comparing the data between the subjects with and without NAFLD/NASH. Multivariate linear regression analysis was than used to assess the correlation between severities of fatty liver changes and anthropometric and biochemical parameters. The level of significance was defined as $p<005$.

## Results

The study participants comprised 127 patients with T2 DM, including 60 (47.2%) male and 67 (52.8%) female, with a mean (SD) age of 59.3±9.3 years old. NAFLD was present in 94/127 (74%) of the subjects. Mild, moderate and severe degree of fatty liver infiltration were found in 39/94 (30.7), 45/94 (35,4%) and 10/94 (7.9%) respectively. NASH diagnosed by defined criteria was seen in 29/127 (23%) of the patients.

Study parameters of the patients with NAFLD, group 1, n=94 were compared with those of the patients without NAFLD, group 2, n=33 (Table nr. 1).

**Table nr.1. Comparison of study parameters between the subjects with and without NAFLD**

| Variables | Group 1 (with NAFLD, n=94) | Group 2 ( without NAFLD, n=33) | p value |
|---|---|---|---|
| Age ( years ) | 59.84±8.4 | 57.93±9.8 | NS |
| Duratin of diabetes (years) | 9.02±5.9 | 7.24±6.1 | NS |
| BMI ( kg/m2) | 33.44±3.7 | 26.50±3.6 | 0.001 |
| Abdominal perimeter (cm) | 113.41±8.1 | 98.66±10.4 | 0.001 |
| ALT ( UI/l ) | 34.30±13.2 | 26.87±14.7 | 0.032 |
| AST ( UI/l ) | 22.79±5.9 | 19.27±6.1 | NS |
| Glucose ( mmol/L ) | 169.6±40.3 | 168.1±42.3 | NS |
| Insulin level ( μmol UI/ml) | 16.9±9.3 | 15.8±8.2 | NS |
| HbA1c (%) | 10.26±2.8 | 9.83±2.4 | NS |
| Cholesterol ( mg/dL ) | 219.23±47.1 | 193.27±41.7 | 0.008 |
| Triglycerides ( mg/dL ) | 225.68±96.8 | 141.74±68.5 | 0.004 |
| HOMA-IR | 8.6±2.2 | 5.7±2.4 | 0.001 |

As shown in table 1, univariate analysis revealed that anthropometric parameters, such as, BMI and abdominal perimeter were significantly associated with the presence of NAFLD (p= 0.001 for both). It was found as well a significant difference between patients with and without NAFLD in ALT level (0.032), cholesterol (p=0.008), triglycerides (p=0.004) and HOMA-IR (p=0.001). ALT elevation > 40 UI/l was present only in patients with NASH (30/127 - 23.6%). The frequency of NAFLD within different age and duration of diabetes between the two groups was not significant (p=0.54 and p=0.12 respectively). Although there were no statistical differences, the M+/-SD of AST level, fasting blood glucose, insulin and HbA1c were higher in diabetic patients with NAFLD than those without liver steatosis.

The data relative to the correlation between the degree of fatty infiltration of the liver and study parameters are presented in the Table nr. 2.

ISSN: 2304-2354
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**Table nr.2 Correlation between the degree of liver steatosis and the study parameters**

| Variables | Without NAFLD ( n=33 ) | Fatty liver infiltration Mild n =39 Moderate n=45 Severe n=10 | | | p value |
|---|---|---|---|---|---|
| Age ( year) | 57.9±9.8 | 60.1±8.7 | 59.2±10.0 | 61.9±5.8 | 0.036 |
| Duration of diabetes(years ) | 7.2±6.1 | 10.6±6.7 | 7.9±5.9 | 7.7±5.5 | NS |
| BMI ( kg/m2) | 26.5±3.6 | 32.2±3.9 | 33.9±5.5 | 35.9±3.9 | 0.001 |
| Abdominal perimeter (cm) | 98.6±10.4 | 110.8±13.4 | 115.2±15.8 | 115.4±7.4 | 0.001 |
| AST ( UI/l ) | 19.2±6.1 | 20.2±5.6 | 24.2±10.9 | 26.2±8.4 | NS |
| ALT ( UI/l ) | 26.8±14.7 | 30.8±10.7 | 35.7±20.0 | 41.1±22.4 | NS |
| Glucose ( mmol/L ) | 168.2±48.3 | 167.6±59.1 | 169.4±53,6 | 171.4±52.1 | NS |
| Insulin ( mmUI/ml ) | 16.1±5.6 | 16.8±7.2 | 17.8±8.2 | 17.9±.7 | NS |
| HbA1c (%) | 9.8±2.4 | 9.7±1.8 | 10.5±4.8 | 9.4±2.0 | 0.031 |
| Cholesterol ( mg/dL ) | 193.9±41.4 | 225.6±49.6 | 222.1±56.5 | 181.4±45.0 | NS |
| Triglycerides ( mg/dL) | 141.7±88.5 | 230.5±151.4 | 227.9±56.2 | 196.6±81.67 | NS |
| HOMA-IR | 5,7±7.3 | 7.1±3.6 | 9.1±4.2 | 9.5±4.4 | 0.001 |

Multivariate analysis revealed a positive association between severity of the fatty liver and age (p=0.036), BMI (p=0.001), HbA1c (p=0.031) and HOMA-IR (p=0.001). On the other hand, there were no significant difference between M±SD value of AST, ALT, glucose, insulin level, cholesterol, triglycerides and severity of liver steatosis.

## Discussion

The dramatic worldwide increase in the prevalence of T2 DM is posing a massive health problem in both developed and developing countries (42). Prevalence increased progressively with age, so that more than 20% of the population aged over 60 have T2 DM (43). The magnitude of the healthcare problem of T2 DM results not just from the disease itself but also from its association with obesity and cardiovascular risk factors, potentially dyslipidemia and hypertension. In fact, T2 DM has now been recognized as manifestation of the metabolic syndrome and associated with a range of pathologies, including NAFLD/NASH. Indeed, increasing evidence suggests that patients with T2 DM, characterized by the simultaneous occurrence of both insulin-resistance and relative insulin-deficiently are particularly at risk for developing the progressive form of NAFLD, i.e. NASH (19, 21, 44, 45, 46, 47, 48).

In this study, the incidence of NAFLD in patients with T2 DM was 74%, similar to that obtained by other authors (4, 49, 50). Nevertheless, liver steatosis is lacking in 33/127 (26%) of subjects. The most convincing factor for the explanation of this statement could be the lack of obesity. In fact, 96/127 (76%) of our patients and 104/127 (82%) of those with NAFLD were obese, which has been shown to be an independent predictors of advanced fibrosis (51). Moreover, central obesity (visceral obesity) may have implication for the development of NAFLD independent of overall obesity, historically defined by BMI (52). In addition, visceral adipocites have been shown to be more resistant to insulin and associated with elevated of inflammatory mediators compared with subcutaneous adipocytes (53). Concretely, compared the two groups of the patients (with and without NAFLD), we observed a positive correlation between the presence of NAFLD and the anthropometric measurements, such as BMI and abdominal perimeter (p=0.001 for both parameters). As well, in conformity with other study (54), although with not statistically different, we observed the higher mean age in group with NAFLD as the other group without NAFLD (59.84± 8.4 vs 57.93±9.8 years). Likeness, the mean duration of diabetes, although higher in patients with NAFLD (9.02+/-5.9 vs 7.24±6.1), did not show any significant difference, possibly on account of the successfully or unsuccessfully control of diabetes. In our study we could see, as well, no statistically difference in fasting blood glucose, insulinaemia and Hb1Ac level between the two groups. It is hard to find any credible explanation for the lack of this correlation. Anyhow, it is well known that fasting glucose is results of hepatic insulin resistance, but most importantly of beta-cell dysfunction. Differently to the glycemic control, univariate analysis confirms that insulin resistance (HOMA-IR) were significantly associated with the presence of NAFLD (p=0.001). For the moment it is broadly accepted that the underlying link factor between obesity, NAFLD/NASH and other components of metabolic syndrome is insulin resistance (47,48).

In some cases, fatty liver is associated with elevated serum ALT concentration, and this commonly

ISSN: 2304-2354
Number 3, Volume 44, 2013

biochemical analysis, closely related to insulin resistance, is now considered a surrogate marker of liver fatty accumulation. In fact, insulin resistance increased proinflammatory cytokine production, oxidative stress and mitochondrial dysfunction leading to hepatocytes damage or destruction (26). However, ALT level is not sufficiently sensitive for the diagnosis of NAFLD (55). Whereas the sole determination of ALT does not prove the existence of NAFLD, a previous study has shown a strong association with obesity, hyperdyslidemia and insulin resistance (21, 52). Entirely similar to other studies (56, 57), elevated ALT level > 40 UI/l was found in 30/127 (23.6%) of our patients with NAFLD, with statistically significant between the subjects with and without NAFLD. Moreover, the subject that are attributable fractions of elevated ALT activity were all among those with moderate and severe degree of fatty infiltration of the liver. On contrary with ALT, the AST level was found to be in normal value. In fact, AST higher than ALT level is meaning of alcoholic hepatitis, as potentially bad prognostic sign and indicate in general liver fibrosis or cirrhosis (58). As for lipid parameters, we found a significant differences of lipid parameters, in particular hypertriglyceridemia (p=0.004), between subject with and without NAFLD. Different studies have shown that 20.92% of patients diagnosed with NAFLD have hyperlipidemia (4), including hypertriglyceridemia, hypercholesterolemia or both (18).

In parallel with fatty liver infiltration, inflammation and fibrosis can also be found in the liver of patients with T2 DM. Contrary of remarkable benign clinical course of NAFLD, NASH is a potentially serious condition associated with significant increase in overall and liver related morbidity and mortality (59,60). Unfortunately, to date, in the absence of liver biopsy, none of the available biochemical markers are able to distinguish accurately NAFLD from NASH (57). Anyhow, the prevalence of presumed of NASH in our patients with T2 DM, defined by the valuation of accepted criteria, such as, ultrasonographic evidence of fatty liver, ethanol intake equal or lower than 20 gr/daily, age over 50 years, increase of ALT level, presence of insulin resistance (HOMA-IR > 3.9) and BMI>28kg/m2, was found in 29/127 (23%). Multivariate analysis, in order to assess the correlation between the severity of fatty liver changes and anthropometric and biochemical parameters revealed a positive association between the severity of the fatty infiltration of the liver and age (p=0.036), BMI (p=0.001), HbA1c (p=0.031) and HOMA-IR (p=0.001).

Apart from the lack of histological data, another limitation of this study is the measurements of liver chemistry at single point of time, having in regard underestimate the real prevalence of NASH because of that serum ALT level may fluctuate over time.

In conclusion, T2 DM is a manifestation of metabolic syndrome, strongly associated with NAFLD. The main findings of this observational study are the high prevalence of NAFLD/NASH in patients with T2 DM. On the other hand, age over 50 years, BMI>28kg/m2, HbA1c and insulin resistance (HOMA-IR > 3.9) are strong independent predictors for the development of NASH in subjects with T2 DM. Diabetic patients with NAFLD should be target of future investigations and should be treated for NASH.

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