BRIEF COMMUNICATION

Metformin superior to low-fat diet for the treatment of patients with nonalcoholic fatty liver disease and/or steatohepatitis

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Introduction Nonalcoholic fatty liver disease (NAFLD) constitutes a worldwide health challenge. Cases of fatty liver diseases with inflammation that resemble alcoholic steatohepatitis but occur in nondrinkers were first described 30 years ago.[1,2] In the last decade, the disorder has aroused a real interest. NAFLD is believed to account for up to 90% of the cases of elevated liver function tests in patients without an identifiable cause of liver disease.[3] Recent studies have made it clear that a subset of patients who develop nonalcoholic steatohepatitis (NASH), mostly those with alanine transaminase (ALT) levels higher than twice the upper limit of normal, are at increased risk of progression to liver disease and may experience all complications of cirrhosis, such as end-stage liver disease and hepatocellular carcinoma.[4-8] 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.[9]

The rising prevalence of obesity, diabetes, and metabolic syndrome evidently results in an increasing prevalence of NAFLD. This trend is of particular concern in the pediatric population, in which the reported increase in obesity will undoubtedly result in a higher evidence and prevalence of pediatric and adult NAFLD in the future.[10,11] In Albania, excess weight and obesity is becoming the major public health problem, primarily in middle-aged women.[12] NAFLD and NASH are frequently observed in conjunction with other components of the metabolic syndrome, such as arterial hypertension, diabetes, obesity, and elevated lipids, which are considered the hepatic manifestations of the syndrome.[13-16] Why insulin resistance leads to fatty liver injury is not completely clear. The most widely accepted patophysiological model of NAFLD is a two-hit process: 1) the development of steatosis caused by insulin resistance in the muscle, adipose tissue, and liver and 2) cytokine-mediated inflammation, lipid peroxidation, and apoptosis.[17-19]

Assessing liver injury in insulin resistant states has become a major concern and no less of a challenge given the current diagnostic tools. Liver biopsy is regarded as the gold standard for the assessment of fatty liver disease; however, its invasiveness limits its use, especially in outpatients and research. On the other hand, sonography has shown significantly high specificity and relatively high sensitivity for the diagnostic occurrence of hepatic steatosis.[20,21]

The search for the therapy of NASH is ongoing. Based on the concept of insulin resistance, a number of pilot studies have shown that reduction of body weight and improvement of insulin sensitivity by metformin or thiazolidinediones provide positive biochemical and histological results.[22-29] Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is an antihyperglycemic drug of the biguanide class, which decreases hepatic glucose production, decreases intestinal glucose absorption, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Despite that, it is known that metformin therapy can lead to body weight loss.[24,25,30]

The objective of this study was to evaluate the efficacy of metformin compared with low-fat diet (LFD) in patients with NAFLD and/or NASH.

Patients and methods **Study population** The study was a 24-week prospective controlled trial comparing metformin plus LFD with LFD alone in 61 outpatients with NAFLD and/or NASH, 46 men (75%) and 15 women (25%), who presented at our university department of gastroenterology and

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hepatology during 2008–2009. All patients fulfilled the following criteria: 1) insulin resistance (Homeostasis Model Assessment Insulin Resistance – HOMA-IR) value above 3.6; 2) elevation in the levels of ALT and aspartate transaminase (AST); and 3) ultrasound evidence of fatty liver. The exclusion criteria were as follows: 1) presence of hepatitis B and C virus infection markers (HBsAg and anti-HCV); 2) evidence of alcoholic liver disease (less than 20 g ethanol per day); 3) evidence of autoimmune liver disease; 4) use of insulin-sensitizing and hepatotoxic drugs in the previous 6 months; 5) presence of diabetes or a severe systemic disease; 6) evidence of metabolic liver disease (α-1-antitrypsin deficiency, Wilson disease, or hemochromatosis); 7) active substance abuse; and 8) pregnancy.

The study was approved by the National Ethics Committee. Informed consent was obtained from all patients.

Procedures Patients were divided into 2 groups. Group A included 35 patients (26 men and 9 women; mean age, 41.8 ±8.1 years) receiving metformin 850 mg/daily plus low-fat dietary regime that aimed to reduce fat to 30% or lower as generally recommended for 24 weeks. Group B included 26 patients (20 men and 6 women; mean age, 42.6 ±7.3 years) receiving the same dietary counseling for the same period of time. No vitamins or other nutritional supplements were prescribed. Blood samples were obtained before and after the treatment (0 and 24 weeks) to determine serum levels of bilirubin, ALT and AST, fasting and postprandial blood glucose, fasting insulin, total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol.

HOMA-IR was calculated using the formula: HOMA-IR = fasting plasma insulin (microU/ml) × FPG (mg/dl)/405. We assumed IR when HOMA was more than 3.6 and body mass index more than 27.5 kg/m2. Pre- and post-treatment body mass, biochemical data, and insulin resistance were compared. The efficacy endpoints at 24 weeks of the treatment were the normalization of ALT and decreased insulin resistance.

Statistical analysis Continuous variables are presented as mean ± standard deviation. Group comparisons were conducted using the *t* test. Differences were considered significant at the *P* level above 0.005.

Results Baseline body weight, biochemical data, and insulin resistance (HOMA-IR) of the patients are presented in TABLE 1. Both groups were similar in terms of age, sex, body weight, biochemical data, and insulin resistance.

Significantly more patients treated with metformin plus LFD (group A) achieved normal serum ALT and AST levels and improvement of insulin resistance compared with patients treated with LFD alone (group B; $P < 0.05$; TABLE 2).

There was no significant difference in body weight loss, fasting and postprandial blood glucose, total cholesterol, triglyceride and HDL cholesterol between the 2 groups ($P > 0.005$) (TABLE 2).

No serious adverse events of metformin were observed and treatment was not discontinued in any of the patients.

Discussion There is currently no proven and approved treatment for patients with NAFLD and/or NASH. Although body weight loss and life-style modifications have been shown to be effective,[31,32] only a minority of patients are able to adhere to sustained and intensive dietary intervention.[33-35] In the present study, we observed that body mass loss (4–6 kg) at the end of treatment with LFD alone was associated with normalization of ALT in 21 of 26 patients (82%) and attenuation of insulin resistance only in 20% of the patients (TABLE 2).

On the other hand, we found that a 24-week treatment with metformin at doses of 850 mg/daily plus LFD was associated with a significantly higher rate of the normalization of ALT levels and improvement of insulin resistance when compared with LFD alone. These data clearly indicate the beneficial effect of metformin on insulin action. In fact, the role of hyperinsulinemia and increased insulin resistance as major pathogenic factors in the development of NAFLD and/or NASH, and in this manner the therapeutic value of insulin-sensitizing agents including thiazolidinediones or biguanides, has been demonstrated in several trials.[28,36-39] Moreover, it has been shown that biochemical response to treatment with metformin continued during a 6- to 12-month follow-up period, suggesting the sustained effect of the drug.[40]

The metabolic effect of metformin is thought to be mediated through the activation of adenosine

TABLE 1 Baseline characteristics of body weight, biochemical data and insulin resistance

Characteristics	MET + LFD (n = 35)	LFD (n = 26)
age, y	41.8 ±8.1	42.6 ±7.3
male, n (%)	26 (74.3)	20 (76.9)
body weight, kg	72.8 ±12.6	71.7 ±12.2
ALT, IU/l	86.0 ±10.2	82.0 ±8.4
AST, IU/l	64.0 ±8.1	60.0 ±7.2
total bilirubin, mg/dl	0.7 ±0.2	0.8 ±0.2
fasting glucose, mg/dl	113 ±16	114 ±14
postprandial glucose, mg/dl	134 ±14	130 ±11
total cholesterol, mg/dl	180 ±18	174 ±16
triglycerides, mg/dl	155 ±13	152 ±16
HDL cholesterol, mg/dl	52 ±7	51 ±10
HOMA-IR	5.2 ±1.2	4.8 ±1.0

Data are presented as mean ± standard deviation.

Abbreviations: ALT – alanine transaminase, AST – aspartate transaminase, HDL – high-density lipoprotein, HOMA-IR – Homeostasis Model Assessment Insulin Resistance, LFD – low-fat diet, MET – metformin

TABLE 2 Body weight, biochemical data, and insulin resistance at 24 weeks

Outcome	MET + LFD (n = 35)	LFD (n = 26)	*P*
body weight loss (4–6 kg)	30 (86)	21 (82)	NS
ALT normalization	20 (57)	5 (19)	<0.05
AST normalization	9 (27)	5 (21)	NS
decrease in fasting glucose	16 (47)	14 (42)	NS
decrease in postprandial glucose	16 (46)	14 (41)	NS
reduction of total cholesterol	11 (31)	10 (29)	NS
reduction of triglycerides	24 (34)	10 (30)	NS
increase in HDL cholesterol	23 (32)	10 (29)	NS
decrease in HOMA-IR	21 (61)	8 (22)	<0.05

Data are presented as number (percentage).

Abbreviations: NS – nonsignificant, others – see **TABLE 1**

monophosphate (AMP)-activated protein kinase in hepatic and peripheral tissue either directly or indirectly through another serine-threonine kinase known as LKB1.[41] It has also been demonstrated that the activation of AMP kinase leads to transactivation of genes that inhibit gluconeogenesis and lipogenesis and promote fat acid and glucose uptake in the liver and muscles.[24]

It is also known that metformin therapy can lead to weight loss.[24,25,30] Body weight loss (4–6 kg) during 24-week treatment in group A was in fact a little higher compared with that in group B (**TABLE 2**). These results provide evidence that the beneficial effect of metformin therapy on NAFLD and/or NASH is mediated mainly by the improvement of insulin action and, at least in part, by body mass loss.

Finally, we would like to underline the limitations of the study: lack of histological data and re-evaluation of the positive results after the end of treatment, as well as short period of treatment (24 weeks). In fact, therapies for NAFLD and/or NASH are likely to require long-term treatment, including metformin treatment.

In conclusion, therapy directed at improving insulin resistance with metformin is beneficial in patients with NAFLD and/or NASH. Metformin is more effective than LFD in treatment of patients with NAFLD and/or NASH.

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