Insulin resistance and metabolic syndrome in patients with NAFLD but without diabetes : effect of a 6 month regime intervention

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Abstract

Background and study aims : **Non-alcoholic fatty liver disease (NAFLD) and the metabolic syndrome are two intertwined diseases sharing the same factor in their pathogenesis ; insulin resistance. The aim of the study was to establish a link between glucose tolerance and NAFLD.**

Patients and methods : **Fifty-two non-diabetic NAFLD patients were included in the study. Inclusion criteria were elevated alanine aminotransferase (ALT), hyperechogenic liver detected at ultrasonography, and exclusion of other causes of liver disease. Hepatobiliary ultrasonography and laboratory tests including biochemical and metabolic profiles were performed ; HOMA insulin resistance was calculated.**

Results : **The mean age was 43 years, and 61% were male. More than a two fold increase in alanine aminotransferase levels was seen in 37% of the patients. Serum levels of aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase (ALP) were elevated in 36%, 46%, and 30% of patients respectively. Low HDL-C levels were found in 46% and high LDL-C levels in 25%. Other results of note were elevated lipoprotein-a levels in 40%, impaired fasting glucose in 23%, impaired glucose tolerance in 26%, elevated fasting c-peptide levels in 61%, and elevated fasting serum insulin levels in 11% of patients. In 30% of patients, body mass index was over 30 kg/m^2 and 78% had a waist-hip ratio more than 0.9. HOMA insulin resistance was significantly related with elevated ALP levels and hepatomegaly. Following a 6 months treatment with a standard diet, liver enzymes and metabolic parameters both improved. Only 7 patients had persistently high liver enzymes.**

Conclusions : **Basal insulin levels and the oral glucose tolerance test should be an integral part of the evaluation of patients with NAFLD. The association between NAFLD and metabolic syndrome as well as the benefits of dieting on preventing progression of NAFLD should be stressed.** (Acta gastroenterol. belg., **2007**, 70, **253-259**).

Key words : nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, metabolic syndrome.

Introduction

Nonalcoholic fatty liver disease (NAFLD) which is a frequent cause of elevated liver enzymes is characterized by excess fat in hepatocytes in patients without significant alcohol use. It can progress from steatosis to steatohepatitis or cirrhosis. It was first described in obese, diabetic females who denied alcohol use but in whom the hepatic histology was consistent with alcoholic hepatitis (1). This typical patient profile has been expanded into a broad spectrum to include both genders without overt abnormalities in carbohydrate metabolism. It was believed to be a benign clinical entity at first, but nonalcoholic steatohepatitis (NASH) is now recognized as a cause of progressive fibrotic liver disease with clinical sequellae. It is important to emphasize that NASH is part of a larger spectrum of nonalcoholic fatty liver disease that is a consequence of insulin resistance, and ranges from fat alone to fat plus inflammation, fat plus ballooning degeneration, and nonalcoholic steatohepatitis which is the most serious form (2). As with any disease, the clinical importance of NASH is related to its prevalence and natural history. The prevalence of NAFLD and NASH are higher in certain subpopulations such as those with obesity and type 2 diabetes mellitus. Risk factors for the adverse clinical outcomes include patients older than 45 years, the presence of diabetes or obesity, an aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ratio > 1 and histology of hepatitis (3). However, a number of important unexplained intricate associations must be unravelled before the true natural history of this disease can be fully understood. NAFLD with elevated liver enzymes has also been implicated as a member of the disorders in the syndrome X family. As a link between NAFLD and insulin resistance has been established, restriction of calorie and fat on diet and obtaining weight loss can be a treatment choice for these patients (4).

The aim of this study was to offer better understanding of the pathogenesis and clinical associations of NAFLD by evaluating the patients' metabolic profile. The other aim of the study was to evaluate the effect of a standard diet on the course of the disease and the metabolic profile of the patients.

Patients and methods

Subjects

This study was conducted in a prospective manner. Patients presented to the gastroenterology, cardiology and internal medicine outpatient clinics at Hacettepe University Hospital with elevated liver enzymes, namely

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ALT were enrolled for initial evaluation. Patients were included on the basis of 3 criteria : 1) elevated ALT, 2) hyperechogenic liver on ultrasonography, 3) exclusion of other causes of liver disease.

Liver diseases including Wilson's disease, autoimmune liver diseases, hemochromatosis, hepatitis C virus (HCV) infection, and alcoholic liver disease were excluded before a reliable diagnosis of NAFLD. In order to describe the exact relation and to minimize the diabetes effect on fatty liver disease progression, diabetic patients were not included in the study. Patients with known diabetes, patients on antidiabetic medication, and patients with fasting plasma glucose ≥ 126 mg/dl on the first visit were excluded. Patients on hepatotoxic drugs (mostly phenytoin, amiodorone, L-thyroxin, tamoxifen, statins, and lithium), patients with a history of alcohol consumption greater than 30 g daily and patients who had positive Hepatitis B and C serology were also excluded.

After excluding these patients, NAFLD diagnosis of the patients with elevated transaminase levels was made by performing radiologic evaluations including ultrasonography and computerized tomography. Fifty two patients with NAFLD were eventually included in the study. This study received approval from the local ethics comittee, was consistent with the Declaration of Helsinki, and all patients gave informed consent.

Radiologic Evaluations

All of the 52 patients enrolled in the study had fatty liver determined by means of both ultrasonography and computerized tomography performed and examined by the same radiologist. Hepatobiliary ultrasonography was performed by using Siemens Sanoline Elegra 3.5 mttz konvex probe. Diffuse hepatosteatosis was defined as homogenous, focal hepatosteatosis together with hypoechoic spared areas of the liver defined as non-homogenous echopattern. Liver size exceeding the caudal border of the kidney was defined as hepatomegaly.

Metabolic and Laboratory Evaluations

Blood samples were obtained by venipuncture of antecubital vein after 12 hour fast. A detailed lipid profile (total cholesterol, LDL-C, HDL-C, apolipoprotein-A, Apo-B, and lipoprotein-a), ferritin, iron, transferrin, immunoglobulins, fasting glucose-C-peptid-insulin, second hour plasma glucose levels of oral glucose tolerance test (OGTT) and anti-insulin antibody were analysed. Hypercholesterolemia was defined as serum cholesterol levels greater than 200 mg/dl. Fasting plasma glucose greater than 110 mg/dl and below 126 mg/dl was defined as impaired fasting glucose (IFG). Plasma glucose between 140-200 mg/dl on the second hour of the OGTT which was performed by ingesting 75 g glucose after overnight fast was defined as impaired glucose tolerance (IGT).

HOMA insulin resistance was calculated for each patient using the following formula : (fasting serum insulin (μU/ml) X fasting plasma glucose (mmol/L))/22.5.

Anthropometric measurements including body mass index (BMI) and waist-hip circumference were evaluated by the same physician with the same tape measure and scale. Waist circumference greater than 88 cm in female and greater than 102 cm in male were grouped as elevated.

Metabolic syndrome diagnosis was made according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III). These criteria were as follows (5) :

1. Waist circumference > 102 cm for male, > 88 cm for female
2. Diagnosed hypertension or receiving antihypertensive or 2 measurement of blood pressure exceeding 130/85 mmHg
3. Diagnosed diabetes mellitus or receiving antidiabetic treatment or fasting plasma glucose > 110 mg/dl
4. HDL-cholesterol < 40 mg/dl for male, < 50 mg/dl for female
5. Triglyceride > 150 mg/dl

Follow-up Evaluation After Strict Diet

All the patients were taken into a follow up program for body mass index, liver function tests, lipid profile and fasting glucose for a period of 6 months, in which they were put on a strict diet low in lipids, cholesterols and calories, arranged by the same dietician for every patient. The patients were controlled on the 1st, 3rd and the 6th months for their consistency to the diet. Laboratory tests and anthropometric measurements were both analysed before and after a 6 month follow-up period with the standard diet.

Statistical analysis

Statistical package for social sciences (SPSS) version 10.0 for Windows was used for the statistical analysis. Categorical variables are demonstrated as frequencies, continuous variables with normal distribution were expressed as mean ± SD and skewly distributed continuous variables were shown as median (minimum-maximum). Relationship between categorical variables was tested by chi-square and Fisher's exact test. Correlations were tested by Pearson correlation test. Relationship between HOMA insulin resistance and laboratory parameters including ALT, AST, ALP, GGT and radiological findings was tested by one way analysis of variance ANOVA. Besides, a linear regression model was also performed for testing these relationships. To compare the data of biochemical and metabolic parameters before and after the standard diet therapy, analysis of variance designs with repeated measures was performed. For this purpose, paired samples t test for absolute values, and McNemar test for categorical variables were used.

Table 1. — **Baseline characteristics of patients**

Characteristic	*Patient*	
	n	%
Sex		
Male	32	61.5
Female	20	38.5
Age (yr)		
< 45	30	57.7
≥ 45	22	22.3
Family history of diabetes mellitus	19	36.5
History of hypertension	12	23.1
Smoking > 10 packet-year	19	36.5
Basal AST level (U/L)		
< 40	33	63.5
40-80	12	23.0
> 80	7	13.5
Basal ALT level (U/L)		
50-80	33	63.5
> 80	19	36.5
Basal GGT level (U/L)		
< 40	28	53.8
≥ 40	24	46.2
Basal ALP level (U/L)		
< 280	36	69.2
≥ 280	16	30.8
Basal Albumin level (mg/dl)		
< 3.5	5	9.6
≥ 3.5	47	90.4
Basal HDL level (mg/dl)		
< 45	24	46.2
≥ 45	28	53.8
Basal LDL level (mg/dl)		
< 100	11	21.2
100-160	28	53.8
> 160	13	25.0
Basal TG level (mg/dl)		
< 200	35	67.3
≥ 200	17	32.7
Basal Cholesterol level (mg/dl)		
< 200	39	75.0
≥ 200	13	25.0

Table 2. — **Lipid levels and anthropometric parameters of patients**

Parameters	*Patient*	
	n	**%**
Basal level of Apolipoprotein-A (mg/dl)		
< 100	6	11.5
≥ 100	46	88.5
Basal level of Apo-B (mg/dl)		
< 110	22	42.3
≥ 110	30	57.7
Basal level of lipoprotein-a (mg/dl)		
< 30	31	59.6
≥ 30	21	40.4
Diastolic blood pressure (mmHg)		
< 85	28	53.8
≥ 85	24	46.2
Systolic blood pressure (mmHg)		
< 135	31	59.6
≥ 135	21	40.4
Fasting blood glucose (mg/dl)		
< 110	40	76.9
≥ 110-126	12	23.1
2. hr postprandial blood glucose (mg/dl)*		
≤ 140	38	73.1
140-199	14	26.9
Fasting c-peptide levels (ng/ml)		
< 2.8	20	38.5
≥ 2.8	32	61.5
Fasting insulin levels (mIU/ml)		
< 22	46	88.5
≥ 22	6	11.5
Anti-insulin antibody (%)		
< 7	46	88.5
≥ 7	6	11.5
Waist circumference (cm)		
≥ 102 in males	15	46.9
≥ 88 in females	17	85.0
Body mass index (kg/m^2)		
< 30	29	55.8
≥ 30	23	44.2

*Second hour post-prandial (PP) blood glucose after oral glucose tolerance test.

Results

General characteristics and demographics

Within the 52 NAFLD patients evaluated, 32 were male (61.5%), and the mean age of the study group was 43.2 ± 10.5 years. Baseline characteristics of the patients are depicted in Table 1.

Biochemical profile

The percentages of the patients with elevated AST, ALP, and GTT levels are given in Table 1. The mean levels of AST, ALT, GGT, and ALP before and after diet are demonstrated in Table 3. Albumin and bilirubin levels, international normalized ratio, and renal function tests were normal in all patients. Eight patients had elevated transferrin saturation. None of these patients' transferrin levels exceeded normal limits, which excluded hemocromatosis. Twenty-three patients (44.2%) had elevated levels of ferritin. Serum iron and serum iron binding capacity were all within normal limits. High levels of ALT was related with hip circumference and systolic hypertension ($p = 0.04$ and 0.03 respectively).

The biochemical profiles of the patients are given in Table 1.

Radiologic results

Ultrasonographic examination revealed that 44 patients (84.6%) had homogeneous echopattern and 12 (23.1%) had hepatomegaly. No relationship between hepatomegaly and homogeneous echopattern was determined.

Metabolic profile

Results of the metabolic profile of the patients including lipid levels, anthropometric measurements and parameters regarding glucose tolerance are demonstrated in Table 1, Table 2 and Table 3.

Metabolic syndrome was detected in 19 (36.5%) patients with NAFLD, according to ATPIII criteria. HOMA insulin resistance was significantly higher in patients with metabolic syndrome (4.8 ± 1.9, vs. 2.8 ± 1.4, respectively ; $p < 0.001$). When relationship between liver function tests (ALT, AST, ALP, and GGT) and metabolic syndrome was evaluated, only ALP was

Table 3. — **Summary of NAFLD and parameters related with metabolic profile of the patients**

Parameters	*Mean*	*Minimum*	*Maximum*	*SD*
Glucose levels (mg/dl)				
Fasting	95.2	52	135	17.8
PP 2. hour*	127.4	76	198	34.9
Insulin levels (µIU/ml)				
Fasting	15.2	4.7	45.3	5.4
PP 2. hour*	15.5	1.9	134	27.4
C-peptide levels (ng/ml)				
Fasting	4.4	1.1	40	8.1
PP 2. hour *	35.2	4.1	126	29.1
Anti-insulin antibody (%)	5.6	3.4	8.6	1.03
Waist circumference (cm)	103.8	78	134	12.2
Hip circumference (cm)	108.2	85	132	11.3
Basal weight (kg)	80.2	49	117	12.6
Basal body mass index (kg/m^2)	29.7	22	38	3.4
Basal waist-hip ratio	0.95	0.75	1.14	0.08
HOMA	3.54	0.17	9.51	1.83

*Second hour post-prandial (PP) blood glucose, insulin and c-peptide levels after oral glucose tolerance test.

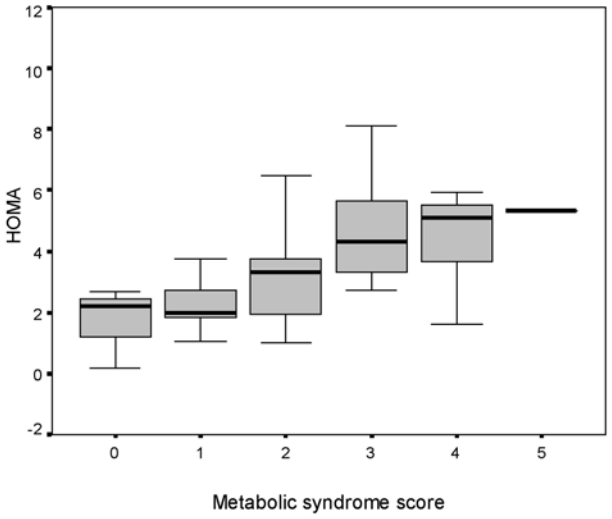

Fig. 1. — Correlation between HOMA score and the number of criteria of the metabolic syndrome according to ATP III.

found to be significantly related (269.2 ± 81.4, vs 221.3 ± 69.7, respectively ; p = 0.029). HOMA scores of the patients according to the number of criteria of metabolic syndrome fulfilled were found as follows : patients with 0 criteria had 1.7 ± 1.3, 1 criterion had 2.3 ± 0.9, 2 criteria had 3.2 ± 1.4, 3 criteria had 4.9 ± 2.2, 4 criteria had 4.4 ± 1.6, and 5 criteria had 5.3 (Fig. 1). Components of metabolic syndrome were analysed seperately and the results are given below.

Impaired fasting glucose was present in 23.1% and impaired glucose tolerance was present in 26.9% of the patients. Patients with a homogenous echopattern on liver ultrasonography had significantly higher fasting glucose levels when compared with those with a non-homogenous liver echopattern (p = 0.03, ANOVA). Fasting glucose levels and ALP seemed to have a statistically significant correlation (p = 0.002, Pearson correlation test). The relationship between basal fasting glucose levels and lipoprotein-a was also statistically significant (p = 0.03, Pearson correlation test). There were no apparent association between fasting glucose levels and GGT, AST, cholesterol, triglyceride, immunglobulin, ferritin, and transferrin levels, or the anthropometric parameters such as body mass index and umbilical circumference. Also of note, 75% of patients with IFG had concurrent IGT. ALT levels were not significantly different between patients with IGT, IFG and normal glucose homeostasis.

When correlations with waist circumference were evaluated, Pearson correlation test did not show any correlation between waist circumference and ferritin levels, basal insulin, c-peptide, fasting glucose, second-hour glucose levels on OGTT, total cholesterol, LDL, HDL, TG, ALT, AST, GGT and ALP levels neither in male nor in female.

Patients were assigned to two groups based on basal c-peptide levels. IFG was present in 34% of the high and 15% of the normal c-peptide group. All of the patients with elevated fasting insulin levels had high c-peptide levels (p = 0.01, chi-square). Furthermore, 30% of patients in the high c-peptide group had hepatomegaly, which was apparent in only 10% in the normal group. ALT and GGT levels did not show significant difference between groups.

To evaluate the insulin resistance and its relationship with the biochemical and radiological findings in NAFLD, HOMA insulin resistance was calculated for each patient. The mean value for HOMA was 3.54 ± 1.83. Thirty six patients (69.2%) scored greater than 2.5 in HOMA, regarding insulin resistance. HOMA was found to be higher in patients with high ALT, AST, ALP or AST levels, indicating insulin resistance. Within these findings only relationship of ALP was statistically significant (p = 0.05, ANOVA). When relationship between HOMA and ultrasonographic findings were evaluated, although HOMA was higher in patients with homogenous echopattern and hepatomegaly, these relationships were not statistically significant. Multivariate linear regression analysis was performed for the all above

Table 4. — **Relationship between HOMA and laboratory parameters**

	HOMA	*P value*
ALT(U/L)		0.60
< 50	3.4 ± 2.1	
≥ 50	3.7 ± 1.1	
AST(U/L)		0.49
< 40	3.4 ± 2.1	
≥ 40	3.8 ± 1.3	
GGT(U/L)		0.33
< 40	3.3 ± 1.9	
≥ 40	3.8 ± 1.7	
ALP(U/L)		0.05*
< 280	3.2 ± 1.8	
≥ 280	4.3 ± 1.7	
ECHOPATTERN		0.92
Homogenous	3.5 ± 1.8	
Non-homogenous	3.6 ± 2.3	
HEPATOMEGALY		0.15*
Present	3.3 ± 1.7	
Absent	4.2 ± 2.2	

P values were obtained by usibg one way analysis of variance ANOVA. *Multiple lineer regression analysis demonstrated that high ALP levels and hepatomegaly were independent correlates of HOMA (p = 0.036 and 0.013 respectively).

mentioned parameters and it was shown that hepatomegaly and high ALP levels were independent correlates of HOMA (t = 2.16, p = 0.036 and t = 2.58, p = 0.013 respectively). These findings are depicted in Table 4.

The associations with radiologic findings were examined. Although fasting plasma glucose of the patients with non-homogenous echopattern were all normal, impaired fasting glucose was detected in 27% of the patients with homogenous echopattern (p = 0.03, chi-square). Plasma glucose on second hour of OGTT was also significantly higher in patients with homogenous echopattern (131.9 ± 35.9, 103.0 ± 13.6 respectively ; p = 0.03, ANOVA). Impaired glucose tolerance was detected in 31% of the patients with homogenous echopattern (p = 0.01, chi-square). Possible associates of homogenous echopattern including anti-insulin antibodies, waist circumference, hip circumference BMI, levels of ALT, AST, GGT, ALP, HDL, LDL, TG, total cholesterol, lipoprotein-a, ferritine and transferrin saturation were not significantly related. Logistic regression analysis showed that none of these parameters were significantly associated with homogenous echopattern.

Treatment results

By the end of the 6 months of diet therapy, only 7 patients (13%) persistently had high levels of liver enzymes. Normal and elevated level categories of liver enzymes were analysed before and after diet therapy by analysis of variance with repeated measures, and the results revealed that the decrease in liver enzymes, especially ALT, GGT and ALP were significant (p = 0.001, 0.001, and 0.001 respectively ; McNemar test). ALT levels significantly decreased after the standard diet therapy (before diet : 78.1 ± 21.1, after diet : 41.0 ± 13.3 ; p = 0.001 ; paired samples t test). Lipid levels including HDL, LDL, TG, and total cholesterol were also significantly improved after diet therapy (p = 0.001, 0.001, 0.001, and 0.001 respectively ; McNemar test). The results of the comparison of absolute values of liver enzymes and lipid profile are demonstrated on Table 5. Repeated anthropometric measurements after diet therapy also showed significant difference. Waist circumference, hip circumference, and BMI (p = 0.001, 0.002, 0.002, respectively ; McNemar test), were significantly reduced after the standard diet. Changes in these anthropometric measurements and changes in laboratory tests were not found to be correlated. After diet therapy only 5 patients did not lose weight. These were not the patients who persistently had high levels of ALT. The antropometric and metabolic profile of the patients with high and low levels of ALT were compared. Patients with high levels of ALT after 6 months had lost weight by 4.8 ± 2.3kg ; whereas the weight loss of the patients with lowered ALT levels was 4.4 ± 4.1kg (p = NS). Metabolic syndrome was present in 50% of the patients who had persistently elevated ALT levels. Neither weight loss, nor metabolic syndrome differed between patients who normalized ALT and those who did not.

Table 5. — **Biochemical and metabolic parameters before and after diet therapy**

Parameter	*Baseline*	*After diet*	*P value*
ALT	78.1 ± 21.1	41.0 ± 13.3	0.001
AST	50.2 ± 24.8	30.9 ± 9.6	NS
GGT	50.1 ± 38.5	36.4 ± 27.2	0.001
ALP	238.8 ± 76.9	215 ± 54.4	0.001
HDL	49.0 ± 11.6	50.0 ± 9.1	0.001
LDL	131.1 ± 45.2	107.8 ± 30.8	0.001
TG	199.0 ± 151.3	177.9 ± 101.8	0.001
Total cholesterol	217.5 ± 48.7	195.4 ± 40.4	0.001

Absolute values before and after diet therapy are tested by paired samples t test.

Discussion

In this present study we have demonstrated that NAFLD is associated with high levels of fasting glucose, basal c-peptid, lipoprotein-a, total cholesterol as well as greater body mass index and waist-hip ratio. We have also demonstrated that insulin resistance (calculated by HOMA) was associated with high levels of ALP and hepatomegaly. It was also shown that 6 months of diet improved liver enzymes as well as metabolic profile of the patients.

Altered liver function tests are still a complex diverse clinical problem with many etiological factors to be studied. One of the popular causes is NAFLD, a condition with a broad clinical spectrum which is still not easily diagnosed. The association of steatosis, inflammation and cirrhosis with obesity and diabetes was established as far back as 1958 (6). NASH has also been shown in several studies to be associated with insulin resistance.

Obesity is present in 40-100% of patients with NASH. However, Bacon *et al.* have shown that NASH also can occur in lean individuals without any other risk factors (6).

Our patients had elevated liver enzymes and fatty liver demonstrated by non-invasive methods (ultrasonography and computerized tomography) which may seem as a limitation of the study due to the absence of liver biopsy. However, for exactly this reason, some authors have proposed the use of the term "possible steatohepatitis" in NAFLD patients with elevated liver enzymes. The wide range in the prevalence of NAFLD is probably related to differences in study designs. Patients undergoing liver biopsy are usually carefully selected based on certain indications ; therefore such data does not reflect the exact prevalence of NAFLD and NASH in the general population.

The most common reported liver enzyme abnormality seen with NAFLD is a two- to five fold elevation in ALT and AST with occasional reports of 10- to 15-fold elevations. The AST/ALT ratio can be used to distinguish it from alcohol related injury. A ratio < 1 can be seen in 65-90% of NAFLD patients, although a ratio > 1 is associated with an advanced NAFLD. In our study population 96.2% of the patients' AST/ALT ratio was < 1. This result not only supports the diagnosis of NAFLD but also suggests that the disease is not advanced. This might have a role in the high frequency of the patients returning to normal levels of liver enzymes after diet therapy.

Non alcoholic fatty liver diseases may yet be a mere consequence of suboptimal biological response to insulin action, otherwise known as insulin resistance, the basic pathophysiological factor shared by the components of the insulin resistance syndrome. Obesity, diabetes, hyperlipidemia, male predominance, as seen in our study, hypertension, and more recently NAFLD are the accepted members of the syndrome-X family (7). In one study on patients with the metabolic syndrome with elevated liver enzymes, 86% were found to have steatosis, 24% fibrosis and 2% had cirrhosis (8). Our results also seem to support this correlation, by means of impaired fasting glucose-insulin-C-peptid levels and antiinsulin antibody seropositivity. Most subjects with NAFLD had at least one of the components of the insulin resistance syndrome. The association of peripheral insulin resistance, increased fatty acid oxidation and hepatic oxidative stress with fatty liver and NASH has been well documented (9) ; however, NASH is itself strongly associated with mitochondrial structural defects and consequent mitochondrial loss. Insulin resistance may be one of the etiologic factors of NASH that seems to be a part of a metabolic syndrome and further studies are needed to understand intertwined relations between NASH and syndrome X.

Our study results depict a correlation between elevated liver enzymes and several components of the metabolic syndrome like hyperlipidemia, hypertension, IFG, IGT and certain anthropometric measures. However, the small study population limits the value of the results. Besides, this study shows the importance of glucose tolerance and insulin resistance in fatty liver. ALP levels and hepatomegaly due to NAFLD was found related to insulin resistance calculated by HOMA. Insulin resistance seems to be the major factor in both fatty liver and metabolic syndrome ; and fatty liver may be a part of metabolic syndrome. A role for genetic factors in NASH has been suggested by two recent reports of family clustering (10,11).

Several studies have reported an association of increased hepatic iron concentration with increased severity of fibrosis. Bacon et al had documented elevated ferritin and/or transferrin saturation in 58% of their NASH patients (12). In an Italian study 40 patients with increased ferritin but normal transferrin saturation were evaluated and it was noted that 77% had histology compatible with NASH (13). A two hit hypothesis proposed by Day and James in 1998 attempts to explain the pathogenic mechanisms in NASH ; the first hit is the development of steatosis and the second a trigger of necroinflamation (14). On the second hit, increased hepatic iron stores (as a source of reactive oxygen species) are aggrevating factors. In patients with NASH, hyperferritinemia and hypertransferrinemia are frequent occurrences. It is speculated that insulin resistance could be the reason, since an association between insulin resistance and the hepatic iron overload syndrome has been newly described. Iron accelerates the progression of fatty liver, triggers steatohepatitis, initiates oxidative stress, increases lipid peroxidation, and increases fibrogenesis (15). The results of our study may reflect an association between elevated ferritin and transferrin saturation levels and the fore-mentioned pathologic process, however, since the hepatic iron index was not evaluated, it is not possible to come to a firm conclusion.

This present study showed that diet is effective in lowering liver enzymes, improving lipid and lipoprotein levels and gaining a loss in anthropometric measurements. As NAFLD is thought to be closely associated with some components of metabolic syndrome, especially insulin resistance, the first step of the treatment is life style modifications which focus on diet therapy in order to achieve weight loss (4,16). A low-fat low-calorie diet together with other lifestyle modifications including exercise and weight loss has been shown to have favorable effects body composition and insulin resistance (17). Besides from achieving weight loss, restriction in diet itself plays role in the treatment of NAFLD by affecting insulin resistance (18). However we have found that diet is effective in controlling liver functions in fatty liver disease, its effect on improvement in histological findings is not clearly defined. Randomised controlled clinical trials are lacking to support the hypothesis that restiction of fat and calorie in diet can improve NAFLD or its complications. Dieting may be the key point in breaking the insulin resistance, and further studies are needed to support our data.

Conclusion

This study shows the possible role of elevated fasting plasma glucose, c-peptide levels and insulin resistance in fatty liver disease patients with elevated liver enzymes. Further studies done with liver biopsies and measurement of all the metabolic syndrome components are necessary to understand the intricate relationship between the metabolic syndrome and fatty liver disease progression. While obesity and/or insulin resistance are directly involved in the pathogenesis of steatosis, some other environmental or genetic factors still play an important role in the progression to NASH (19). This study further supports the role of diet, remaining the most effective treatment option for this disease.

Abbreviations

ALP : Alkaline phosphatase
ALT : Alanine aminotransferase
AST : Aspartate aminotransferase
BMI : Body mass index
IFG : Impaired fasting glucose
IGT : Impaired glucose tolerance
NAFLD : Nonalcoholic fatty liver disease
NASH : Nonalcoholic steatohepatitis
OGTT : Oral glucose tolerance test
TG : Triglyceride

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