Ultrasonographic and Biochemical Evaluation of Visceral Obesity in Obese Women with Non-alcoholic Fatty Liver Disease

S. Fenkci[1], S. Rota[2], N. Sabir[3], B. Akdag[4]

[1]Department of Internal Medicine, Division of Endocrinology and Metabolism, Pamukkale University, School of Medicine, Denizli,
[2]Department of Biochemistry, Pamukkale University, School of Medicine, Denizli,
[3]Department of Radiology, Pamukkale University, School of Medicine, Denizli,
[4]Department of Biostatistics, Pamukkale University, School of Medicine, Denizli, Turkey

Abstract

Objective: Identification of specific origin of lipid accumulation in the liver of patients with non-alcoholic fatty liver disease (NAFLD) is the most important step in preventing this condition. Because liver steatosis, in the obese patients without any systemic disease, can be graded easily by ultrasonography (US), we aimed to demonstrate the degree of liver steatosis and abdominal fat distribution by US, furthermore evaluate biochemical, anthropometrical measurements, and define the possible relationship between these parameters in obese women with different grades of liver steatosis.

Methods: In this controlled clinical study, according to US evaluation of liver steatosis, the patients were divided into four groups: control (no steatosis), mild, moderate and severe steatosis groups. Demographic, biochemical and anthropometric measurements were done. Insulin resistance was determined by using homeostasis model assessment (HOMA-IR). Liver steatosis and abdominal fat distributions were evaluated by US.

Results: The subcutaneous and preperitoneal fat layer measurements did not show any significant difference between the groups. The visceral fat layer thickness was significantly higher in severe liver steatosis group compared to the control and steatosis groups. The highest serum fasting insulin, uric acid levels and HOMA-IR index were observed in the severe liver steatosis group. Visceral fat thickness was positively correlated with serum UA levels and HOMA-IR

Conclusions: This study suggests that visceral adipose tissue, HOMA-IR and serum uric acid levels are the main determinants of NAFLD in obese patients.

Key words: Ultrasonography, NAFLD, abdominal fat distribution, uric acid

Introduction

Non-alcoholic fatty liver disease (NAFLD) affects 16-23% of general population. Clinical manifestations of NAFLD may range from simple steatosis and/or non-alcoholic steatohepatitis (NASH) to cirrhosis without history of alcohol abuse [1]. NAFLD is strongly associated with the metabolic syndrome or its components: obesity, insulin resistance, diabetes mellitus (DM), and hypertriglyceridemia [2]. Obesity might be seen in approximately 71 % of patients with NAFLD [3]. Obesity and insulin resistance are crucial for the pathogenesis of NAFLD [4].

Hepatic steatosis is regarded as a common feature of insulin resistance syndrome [5]. It has recently been demonstrated that the risk of hepatic steatosis increases exponentially by the addition of each component of metabolic syndrome: type 2 DM, hyperlipidemia, visceral obesity and hypertension (HT) [6]. Though the specific origin of lipid accumulation in the liver of patients with NAFLD remains unclear, the diffuse or focal changes in fat content of liver depend on the degree of fat infiltration [7]. Histological findings in the livers of subjects with NAFLD extend from fat accumulation alone to alcoholic hepatitis-like lesions including sinusoidal fibrosis and polymorphonuclear infiltrations with or without Mallory hyaline [8, 9]. In terms of free fatty acid (FFA) discharge and steatotic liver formation, visceral and central adipose tissues have more effective role in comparison with peripheral adipose tissue [10]. Abdominal fat layers comprise subcutaneous, preperitoneal and visceral fat compartments. The distribution of abdominal fat may be more important than total body fat. The specific origin of lipid accumulation in the livers of patients with NAFLD needs to be identified.

In this study evaluation of abdominal fat distribution and liver steatosis in obese patients were performed by US, which was considered a reasonable and easily applicable method. We also aimed to determine biochemical, anthropometrical measurements, and define whether there are any relationships between these parameters in obese women with different grades of liver steatosis.

Materials and Methods

Subjects

One hundred-five obese women who were admitted to our Obesity Clinic between April 2003 and December 2004 were consecutively enrolled into this prospective study. Before the study, all subjects were evaluated by an extensive physical examination. A standardized interview was conducted by trained personnel and de-

tailed information for each subject was collected on medical history. Exclusion criteria included alcohol consumption, histories of liver disease, coronary artery and chronic kidney diseases, DM, cerebrovascular and peripheral vascular disease, hypertension, hypothyroidism, chronic and acute inflammatory diseases, asthma, chronic bronchial diseases, smoking and use of all medications known to alter lipid metabolism, liver function and insulin secretion or action. Hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody (antiHCV) were negative in all patients as well. In terms of presence and severity of liver steatosis, all patients were evaluated by US examination. These evaluations were done for each subject by the same radiologist. Informed consent was obtained from each subject.

SAMPLES AND ANALYTICAL METHODS

Venous blood samples were drawn from the participants after a fasting of 12 hours. Samples were collected in serum separator tubes, allowed to clot for 30 min, centrifuged for 15 min at 2000 x g at room temperature. All biochemical measurements were performed on the same day. Biochemical measurements were done by using commercial kits. The serum uric acid (UA), glucose, triglyceride (TG), total cholesterol (TC), aspartat amino transferase (AST), alanine amino transferase (ALT) and gamma glutamyl transferase (GGT) measurements were performed by enzymatic methods and high-density lipoprotein-cholesterol (HDL-C) without precipitation by using liquid selective detergent homogeneous technique (Synchrone LX-20) (Beckman Coulter, Fullerton, CA, USA). Low-density lipoprotein-cholesterol (LDL-C) levels were calculated by using Friedewald's formula. Insulin measurements were done by solid phase chemiluminescence's immunoassay "IMMULITE ONE" (DPC Biosystems, CA, USA). Insulin resistance was calculated by using homeostasis model assessment score that employs the formula: fasting insulin concentration (mU/l) x glucose (mmol/l) /22.5 as described by Matthews et al [11]. Individuals with HOMA-IR > 2.7 were accepted as insulin resistant.

ANTHROPOMETRIC MEASUREMENTS

All anthropometric measurements were done by the same physician on the day blood specimen taken. Height, weight, and waist and hip circumferences of the subjects were obtained in light clothing without shoes. Height was measured as the distance from the top of the head to the bottom of the feet (no shoes) using a fixed stadiometer. Waist circumference (cm) was taken with a tape measure as the point midway between the costal margin and iliac crest in the mid-axillary line with the subject standing and breathing normally. Hip circumference (cm) was measured at the widest point around greater trochanter. The waist-to-hip ratio (WHR) was calculated as the waist measurement divided by hip measurement. Body mass index (BMI) was calculated as the weight (kg) divided by square of the height (m). The total fat mass (FM) was evaluated by bioimpedance analysis with an electronic

scale (Tanitascale, WA). Systolic (SBP) and diastolic blood pressure (DBP) were determined after 15 min resting in sitting position and the mean value of the two measurements were recorded.

ULTRASONOGRAPHIC MEASUREMENTS

Ultrasonography was carried out by using GE logic α 200-ultrasound machine. The linear array probe (7.5 MHz) was used to measure the subcutaneous (SC) and preperitoneal (PP) abdominal fat layers. The subcutaneous minimum (SC_{min}) and preperitoneal maximum (PP_{max}) measurements were taken from the region just below the xyphoid process, whereas the subcutaneous maximum (SC_{max}) and preperitoneal minimum (PP_{min}) fat layers were measured from the region just above the umbilicus [8]. The convex-array probe (3.5 MHz) was used for measuring visceral abdominal fat and anterior wall of the aorta [9]. The patients were asked to suspend respiration during examination and special care was taken to keep the probe just touching the skin to prevent compression of fat layers. A convex-array probe (3.5 MHz) was used to demonstrate liver fatty infiltration. This was defined as increased echogenicity of the liver parenchyma without obvious mass effect and slightly impaired or poor visualization of the intrahepatic vessels and diaphragm. The patients were evaluated by the same radiologist in four groups according to the presence and severity of liver steatosis determined by ultrasonography. The changes of the echogenicity due to the fatty infiltration of liver parenchyma were evaluated according to the adjacent renal parenchyma. Liver fatty infiltration varied depending on the amount of fat and considered accordingly as control (no steatosis), mild (group 1), moderate (group 2) and severe (group 3) hepatosteatosis. Mild hepatosteatosis was revealed as minimal diffuse increase in the hepatic echogenicity with slightly impaired visualization of the intrahepatic vessels and diaphragm. Moderate hepatosteatosis was shown as moderate increase in echogenicity with slightly impaired visualization of intrahepatic vessels and diaphragm. Severe hepatosteatosis was displayed as marked increase in the echogenicity with poor penetration of the posterior segment of the right lobe of the liver and poor or non-visualization of the hepatic vessels and diaphragm [12].

STATISTICAL ANALYSIS

Since many variables had a non-gaussian distribution with positive skewness, statistical analysis was performed with non-parametric tests: Kruskal-Wallis and Mann-Whitney U tests. The data were expressed as means ± SD (Standard Deviation). Correlations between variables were calculated with Spearman's correlation coefficient. Statistical significance was set at p <0.05. Data were analyzed with the SPSS (Statistical Package for the Social Science, version 11.0).

RESULTS

According to the ultrasonographic evaluation of liver steatosis, the patients were divided into four groups:

Table 1. Clinical features, anthropometric and ultrasonographic measurements of the groups.

	Control (n = 10)	Group1 (n = 43)	Group2 (n = 33)	Group3 (n = 19)
Age (years)	38.7 ± 13.4	43.8 ± 12.1	44.2 ± 11.1	48.3 ± 10.1
BMI (kg/m^2)	31.3 ± 2.2	34.7 ± 4.7[a]	35.8 ± 3.6[a]	42.9 ± 8.3[a,b,c]
Waist/hip ratio	0.82 ± 0.1	0.85 ± 0.1	0.92 ± 0.1[a,b]	1.0 ± 0.2[a,b]
Waist-cr (cm)	86.9 ± 4.1	94.2 ± 8.8[a]	98.4 ± 9.1[a]	113.7 ± 9.0[a,b,c]
FM (%)	40.5 ± 5.9	42.6 ± 5.1	42.7 ± 4.3	46.4 ± 5.6[a]
SBP mmHg	113.9 ± 13.6	121.2 ± 23.1	127.5 ± 13.5	137.0 ± 17.7[a]
DBP mmHg	78.3 ± 6.1	82.7 ± 6.0	84.6 ± 8.4	89.0 ± 8.8[a]
VS (mm)	61.0 ± 16.2	63.4 ± 18.7	68.6 ± 16.5	98.8 ± 24.0[a,b,c]
SC max (mm)	36.5 ± 8.8	34.5 ± 10.2	35.8 ± 9.5	39.5 ± 11.2
PP max (mm)	16.2 ± 6.3	17.5 ± 5.3	18.3 ± 5.2	22.0 ± 7.0

[a]p<0.05 versus control group, [b]p<0.05 versus group 1, [c]p<0.05 versus group 2

Table 2. Biochemical characteristics of the groups.

	Control (n = 10)	Group1 (n = 43)	Group2 (n = 33)	Group3 (n = 19)
Glucose (mg/dl)	103.5 ± 9.9	107.4 ± 18.4	119.4 ± 32.2	113.6 ± 40.4
TC (mg/dl)	204.2 ± 53.5	197.6 ± 38.9	199.7 ± 38.3	213.6 ± 35.4
LDL-C (mg/dl)	130.2 ± 40.7	131.6 ± 34.1	126.3 ± 33.4	128.0 ± 41.6
TG (mg/dl)	116.4 ± 62.1	110.2 ± 60.9	131.6 ± 70.0	164.9 ± 97.7
HDL-C (mg/dl)	50.8 ± 14.5	44.2 ± 9.7	48.6 ± 14.0	47.7 ± 12.6
Insulin (mmol/l)	10.2 ± 4.1	11.7 ± 7.6	12.1 ± 5.6	18.7 ± 7.6[a,b,c]
HOMA-R	2.6 ± 1.1	3.1 ± 2.1	3.5 ± 1.7	4.9 ± 2.5[a]
UA (mg/dl)	4.7 ± 1.1	5.0 ± 0.9	5.3 ± 1.2	6.1 ± 1.3[a,b]
ALT (IU/L)	21.5 ± 5.5	24.3 ± 6.6	40.5 ± 3.3	30.5 ± 11.1
AST (IU/L)	22.1 ± 4.6	22.7 ± 5.0	32.1 ± 19.3	27.6 ± 8.9
GGT (IU/L)	12.9 ± 6.5	17.9 ± 12.0	21.8 ± 15.0	24.2 ± 19.4

[a]p<0.05 versus control group, [b]p<0.05 versus group 1, [c]p<0.05 versus group 2

control group (n = 10) consisted of obese patients with no sign of liver steatosis, group 1 with mild liver steatosis (n = 43), group 2 with moderate liver steatosis (n = 33), group 3 with severe liver steatosis (n = 19).

There were no significant differences in the mean age and the % fat mass (FM) between the groups. The moderate and severe steatosis groups had higher waist/hip ratio (WHR) than the mild steatosis and the control groups. The highest waist measurements were found in severe liver steatosis group. The mean BMI of each steatosis group was significantly higher than that of control group. The subcutaneous (SC$_{max}$, SC$_{min}$) and preperitoneal (PP$_{max}$, PP$_{min}$) fat layer measurements did not show any significant difference between the groups (data were not shown for SC$_{min}$ and PP$_{min}$), but the visceral (VS) fat layer thickness was significantly higher in group 3 with severe liver steatosis compared to the mild, moderate liver steatosis and control groups. The mean SBP and DBP were significantly higher in the severe steatosis group compared to the control group (Table 1).

There were no significant differences in serum glucose, lipid fractions, and GGT, ALT and AST levels between the groups. The subjects in the severe liver steatosis group had significantly higher fasting insulin, uric acid levels and HOMA-IR index than the others. (Table 2). Visceral fat thickness was positively correlated with serum UA levels (r = 0.246; p<0.05), HOMA-IR (r = 0.233; p<0.05), TG (r = 0.518; p<0.0001), waist-cr (r = 0.753; p<0.0001). There were not any significant relationships between other parameters.

DISCUSSION

NAFLD describes a spectrum of various conditions. This spectrum is mainly characterized by histological findings of macrovesicular hepatic steatosis in individuals consuming little or no alcohol [13]. NAFLD possesses many components of the metabolic syndrome

such as obesity, DM, hypertriglyceridemia but may also occur in patients with insulin resistance without obesity. Moreover, fatty liver has been considered to be hepatic component of metabolic syndrome. NAFLD consists of two stages: in the first stage, the liver becomes steatotic mainly by the transport of free fatty acids from adipose tissue, in the second stage, oxidative stress and consequently released cytokines lead to fibrosis and dysfunction of hepatocellular organelle [14, 15]. The incidence of advanced fibrosis and cirrhosis are approximately 3-28 % in obese subjects and in patients with NASH [16-18]. Simple steatosis remains stable in some patients; however, it progresses to advanced fibrosis and cirrhosis in others. The reason of this circumstance is still unclear. Identification of specific origin of lipid accumulation in the livers of patients with NAFLD is the most important step to prevent and improve this condition [5, 19].

Although any imaging method is not available to distinguish simple steatosis from NASH and also to detect the stage of fibrosis [20], recently, ultrasonographic examination has been proposed as an alternative non-invasive, cheap and reliable technique to evaluate intra-abdominal fat thickness and liver steatosis [21-23]. The changes in fat content of liver can be assessed by ultrasonographic examination. Increased echogenic regions within normal liver parenchyma owing to focal hepatic fat infiltration can be observed and compared with the echogenicity of spleen or renal cortex by ultrasound [24].

In this ultrasonographic study, we demonstrated the relationships between biochemical, anthropometric measurements, abdominal fat distribution and liver steatosis in obese patients. In our study, even though increased BMI was observed progressively with the degree of steatosis, total fat mass (%) was significantly increased in severe steatosis compared to the control group. In our study, waist circumference, which is a good predictor of the visceral obesity [25], also increased according to the severity of liver steatosis. We did not find any significant differences in subcutaneous and preperitoneal fat layer measurements between the groups, but the visceral (VS) fat layer thickness was significantly higher in group 3 with severe liver steatosis compared with the mild, moderate liver steatosis and control groups.

In this study, there were significant correlations between visceral fat thickness and waist circumference, TG, fat mass, HOMA-IR levels. The potential source of lipid accumulation in the livers of patients with NAFLD is the fat stored in adipose tissue. Approximately 80 % of fatty acid content of plasma NEFA pool is contributed by adipose tissue [26]. Thus, the most likely explanation for excess TG accumulation in patients with NAFLD may be the overproduction of fatty acids in the adipose tissue and their flow to the liver via the NEFA pool [26]. In a previously published histopathological study, it was determined that abdominal fat distribution was a predictor of hepatic steatosis [27]. Although subcutaneous fat layer is more sensitive to the inhibitory effect of insulin, visceral fat comportment is relatively resistant to insulin and is metabolically active with high rate of FFA turnover in individuals with abdominal obesity [28, 29]. Therefore,

visceral fat layer provides FFA to the liver and other tissues. The data of the study support the significance of visceral fat on liver steatosis. In accordance with our result Thomas et al. demonstrated the significant relationship with hepatic steatosis and central adiposity with proton magnetic resonance spectroscopy in 11 hepatic steatosis patients [30].

Free fatty acids are produced within the liver by de novo lipogenesis and dietary fatty acids [31, 32]. The stored fat flows to liver via plasma non-esterified fatty acid (NEFA) pool and insulin regulates re-esterification of FFA. Hyperinsulinemia is consequence of insulin resistance and leads to an increase in serum FFA levels. In the current study, in accordance with visceral fat thickness the highest fasting insulin, HOMA-IR were observed in the severe liver steatosis group, while there were no significant differences in serum glucose and lipid fraction levels between the groups. Also, visceral fat thickness was positively correlated with HOMA-IR, waist circumference and serum TG. Increased FFA is taken up by the liver to be driven for production of TG. Visceral adipose tissue may be the starting current of this pathological process. This process may give rise to hepatic steatosis [33]. The steatotic liver becomes resistant to insulin [34]. Chronic hyperinsulinemia promotes de novo hepatic lipogenesis through up-regulation of lipogenic transcription factors [35], and may activate some cytokines inducing the progression of liver damage [36].

Elevated ALT levels are frequently observed in obese patients, but this elevation is not associated with fatty liver [37]. Liver enzyme levels do not consistently correlate with liver histology. Therefore, the full range of disease can be seen in patients with NAFLD, even if these patients have normal serum transaminase levels [37]. In fact, elevated ALT levels are related with insulin resistance, because the subjects with NAFLD have features of the metabolic syndrome [38]. We did not demonstrate any significant differences according to serum ALT levels between the study groups. But there were significant correlations between liver steatosis degree and serum ALT, AST, GGT, TG and visceral fat thickness.

Elevated serum UA concentration is positively correlated with insulin resistance, dyslipidemia, obesity and visceral fat thickness [39-41]. Therefore, hyperuricemia may be considered as a component of metabolic syndrome [42]. Increased serum UC levels might be caused by reduced UA clearance in obese subjects, because UA clearance is inversely related with body weight [43]. In this current study there were positive correlations between serum UA and liver steatosis degree, waist circumference, visceral fat thickness, serum ALT, AST and GGT levels. Serum UA concentration were significantly higher in the severe steatosis group than mild steatosis and control groups. In our opinion these outcomes were not correspondence of a cause-result effect thereby consistent with that UA as a parameter of the insulin resistance.

In conclusion, this study suggests that visceral adipose tissue, HOMA-IR and serum uric acid levels are main determinants of NAFLD in obese patients and reducing visceral fat tissue and serum uric acid levels might be important for the management of liver

steatosis. For evaluating liver steatosis, ultrasonographic examination can easily be used in most obese patients with suspected liver steatosis without the need to liver biopsy, which is an invasive method firmly reluctant by most of patients.

REFERENCES

1. Angulo P. Non-alcoholic fatty liver disease. N Engl J Med. 2002 Apr 18; 346(16): 1221-31.
2. Guidorizzi de Siqueira AC, Cotrim HP, Rocha R, Carvalho FM, de Freitas LA, Barreto D, Gouveia L, Landeiro L. Non-alcoholic fatty liver disease and insulin resistance: importance of risk factors and histological spectrum. Eur J Gastroenterol Hepatol. 2005 Aug; 17(8): 837-41.
3. Wanless IR, Lentz J. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. Hepatology. 1990 Nov; 12(5): 1106-10.
4. Marceau P, Biron S, Hould FS, Marceau S, Simard S, Thung SN, Kral JG. Liver pathology and the metabolic syndrome X in severe obesity. J Clin Endocrinol Metab. 1999 May; 84(5): 1513-7.
5. 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 syndrome: further evidence for an etiologic association. Hepatology. 2002 Feb; 35(2):367-72.
6. Garcia-Monzon C, Martin-Perez E, Iacono OL, Fernandez-Bermejo M, Majano PL, Apolinario A, Larranaga E, Moreno-Otero R. Characterization of pathogenic and prognostic factors of nonalcoholic steatohepatitis associated with obesity. J Hepatol. 2000 Nov; 33(5): 716-24. Erratum in: J Hepatol 2001 Jan; 34(1):180.
7. Wilson SR, Rosen IE, Chin-Sang HB, Arenson AM. Fatty infiltration of the liver--an imaging challenge. J Can Assoc Radiol. 1982 Dec; 33(4): 227-32.
8. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Non-alcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999 Jun; 116(6): 1413-9.
9. Lee RG. Nonalcoholic steatohepatitis: tightening the morphological screws on a hepatic rambler. Hepatology. 1995 Jun; 21(6): 1742-3.
10. Medina J, Fernandez-Salazar LI, Garcia-Buey L, Moreno-Otero R. Approach to the pathogenesis and treatment of nonalcoholic steatohepatitis. Diabetes Care. 2004 Aug; 27(8): 2057-66.
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and b-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985 Jul; 28(7): 412-9.
12. Rumack CM, Wilson SR, Charboneau JW. In Diagnostic Ultrasound 2nd Edition (ed. C.M. Rumack, S.R. Wilson & J.W. Charboneau) pp. 110-111. Mosby, St. Louis, 1998.
13. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980 Jul; 55(7): 434-8.
14. Day CP. Non-alcoholic steatohepatitis (NASH): where are we now and where are we going? Gut. 2002 May; 50(5): 585-8.
15. Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology. 1998 Apr; 114(4): 842-5.
16. Willner IR, Waters B, Patil SR, Reuben A, Morelli J, Riely CA. Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. Am J Gastroenterol. 2001 Oct; 96(10): 2957-61.
17. Sheth SG, Gordon FD, Chopra S. Non-alcoholic steatohepatitis. Ann Intern Med. 1997 Jan 15; 126(2): 137-45. Erratum in: Ann Intern Med 1997 Oct 15; 127(8 Pt 1): 658

18. Klain J, Fraser D, Goldstein J, Peiser J, Avinoah E, Ovnat A, Charuzi I. Liver histology abnormalities in the morbidly obese. Hepatology. 1989 Nov; 10(5): 873-6.
19. Marchesini G, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, McCullough AJ, Forlani G, Melchionda N. Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med. 1999 Nov; 107(5): 450-5.
20. Joy D, Thava VR, Scott BB. Diagnosis of fatty liver disease: is biopsy necessary? Eur J Gastroenterol Hepatol. 2003 May; 15(5): 539-43.
21. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology. 2002 Sep; 123(3): 745-50.
22. Mottin CC, Moretto M, Padoin AV, Swarowsky AM, Toneto MG, Glock L, Repetto G. The role of ultrasound in the diagnosis of hepatic steatosis in morbidly obese patients. Obes Surg. 2004 May; 14(5): 635-7.
23. Sabir N, Sermez Y, Kazil S, Zencir M. Correlation of abdominal fat accumulation and liver steatosis: importance of ultrasonographic and anthropometric measurements Eur J Ultrasound. 2001 Dec; 14(2-3): 121-8.
24. White EM, Simeone JF, Mueller PR, Grant EG, Choyke PL, Zeman RK. Focal periportal sparing in hepatic fatty infiltration: a cause of hepatic pseudomass on US. Radiology. 1987 Jan; 162(1 Pt 1): 57-9.
25. Jia WP, Lu JX, Xiang KS, Bao YQ, Lu HJ, Chen L. Prediction of abdominal visceral obesity from body mass index, waist circumference and waist-hip ratio in Chinese adults: receiver operating characteristic curves analysis. Biomed Environ Sci. 2003 Sep; 16(3): 206-11.
26. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest. 2005 May; 115(5): 1343-51.
27. Kral JG, Schaffner F, Pierson RN Jr, Wang J. Body fat topography as an independent predictor of fatty liver. Metabolism. 1993 May; 42(5): 548-51.
28. Imbeault P, Lemieux S, Prud'homme D, Tremblay A, Nadeau A, Despres JP, Mauriege P. Relationship of visceral adipose tissue to metabolic risk factors for coronary heart disease: is there a contribution of subcutaneous fat cell hypertrophy? Metabolism. 1999 Mar; 48(3): 355-62.
29. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. Endocr Rev. 2002 Apr; 23(2): 201-29.
30. Thomas EL, Hamilton G, Patel N, O'Dwyer R, Dore CJ, Goldin RD, Bell JD,Taylor-Robinson SD. Hepatic triglyceride content and its relation to body adiposity: a magnetic resonance imaging and proton magnetic resonance spectroscopy study. Gut. 2005 Jan; 54(1): 122-7.
31. Miles JM, Park YS, Walewicz D, Russell-Lopez C, Windsor S, Isley WL, Coppack SW, Harris WS. Systemic and forearm triglyceride metabolism: fate of lipoprotein lipase-generated glycerol and free fatty acids. Diabetes. 2004 Mar; 53(3): 521-7.
32. Havel RJ, Hamilton RL. Hepatic catabolism of remnant lipoproteins: where the action is. Arterioscler Thromb Vasc Biol. 2004 Feb; 24(2) :213-5.
33. Fromenty B, Robin MA, Igoudjil A, Mansouri A, Pessayre D. The ins and outs of mitochondrial dysfunction in NASH. Diabetes Metab. 2004 Apr; 30(2): 121-38.
34. Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, Conti M, Huet S, Ba N, Buffet C, Bedossa P. High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. Hepatology. 2001 Oct; 34(4 Pt 1): 738-44.

35. Youssef WI, McCullough AJ. Steatohepatitis in obese individuals. Best Pract Res Clin Gastroenterol. 2002 Oct; 16(5): 733-47.

36. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, Sterling RK, Shiffman ML, Stravitz RT, Sanyal AJ. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology. 2003 Jun; 37(6): 1286-92.

37. Sakugawa H, Nakayoshi T, Kobashigawa K, Nakasone H, Kawakami Y, Yamashiro T, Maeshiro T, Tomimori K, Miyagi S, Kinjo F, Saito A. Alanine aminotransferase elevation not associated with fatty liver is frequently seen in obese Japanese Women. Eur J Clin Nutr. 2004 Sep; 58(9): 1248-52.

38. Marchesini G, Avagnina S, Barantani EG, Ciccarone AM, Corica F, Dall'Aglio E, Dalle Grave R, Morpurgo PS, Tomasi F, Vitacolonna E. Aminotransferase and gamma-glutamyltranspeptidase levels in obesity are associated with insulin resistance and metabolic syndrome. J Endocrinol Invest. 2005 Apr; 28(4): 333-9.

39. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, Lee MH, Park JR, Kim H, Rhee EJ, Lee WY, Kim SW, Ryu SH, Keum DG. Relationship Between Serum Uric Acid Concentration and Insulin Resistance and Metabolic Syndrome. Circ J. 2005 Aug; 69(8): 928-33.

40. Miyawaki T, Abe M, Yahata K, Kajiyama N, Katsuma H, Saito N. Contribution of visceral fat accumulation to the risk factors for Atherosclerosis in non-obese Japanese. Intern Med. 2004 Dec; 43(12): 1138-44.

41. Hayden MR, Tyagi SC. Uric acid: A new look at an old risk marker for cardiovascular disease, metabolic syndrome, and type 2 diabetes mellitus: The urate redox shuttle. Nutr Metab (Lond). 2004 Oct 19; 1(1): 10

42. Ishizaka N, Ishizaka Y, Toda E, Nagai R, Yamakado M. Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. Arterioscler Thromb Vasc Biol. 2005 May; 25(5): 1038-44. Epub 2005 Mar 3.

43. Yamashita S, Matsuzawa Y, Tokunaga K, Fujioka S, Tarui S. Studies on the impaired metabolism of uric acid in obese subjects: marked reduction of renal urate excretion and its improvement by a low-calorie diet. Int J Obes. 1986; 10(4): 255-64.

Address for correspondence:
Semin Fenkci, M.D.
Zeytin Koy Mah.
Dogalevler Sitesi 5097 Sokak
M blok kat: 2 Daire: 4
Bagbasi, Denizli
Turkey
Tel: +90-505-400 40 27
Fax: +90-258-261 92 34
E-mail: sfenkci@yahoo.com