Clinical Studies

Non-alcoholic fatty liver disease – a common and benign finding in octogenarian patients


Abstract: Background: Non-alcoholic fatty liver disease (NAFLD), a common entity in the general population, has been shown to be linked with insulin resistance and metabolic syndrome. Several of the components of the metabolic syndrome are more common in the aged population. The aims of the current study were to determine in the aged, the prevalence and the clinical presentation of NAFLD, as well as the relation to the underlying metabolic abnormalities. Method: In this prospective study, we evaluated 91 octogenarians with a mean age of 85.56 ± 3.76 years, who were admitted to the rehabilitation departments of a geriatric hospital. Clinical evaluation included: abdominal ultrasound (US), fasting glucose and lipid levels, serum liver enzymes, ferritin, iron and transferrin saturation. Elderly patients with NAFLD were compared with 46 young patients with NAFLD. Results: NAFLD diagnosed by US was a common finding in this aged population, is present in 42/91 patients (46.2%). No significant differences were observed between the patients with or without NAFLD in the following: age, gender, chronic illnesses, anthropometric parameters, lipid profile, fasting glucose levels, metabolic syndrome prevalence, serum levels of transaminases, ferritin and iron. Young patients with NAFLD had significantly higher serum levels of triglycerides and a significantly higher prevalence of glucose intolerance, obesity and the metabolic syndrome compared with the elderly patients with NAFLD. Conclusions: NAFLD was a common finding in our group of elderly patients and the prevalence was higher than reported in the general population. In contrast to the well-described association between the metabolic syndrome and NAFLD in the general population, we did not find this association in the aged group. In addition, none of the patients had stigmata of advanced liver disease. These data suggest that NAFLD is a common and benign finding in the elderly population, but is not associated with the metabolic syndrome.

Key words: fatty liver – metabolic syndrome – octogenarians
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Non-alcoholic fatty liver disease (NAFLD) is a liver disease characterized by diffuse fatty infiltration and inflammation. The spectrum of disease is wide, ranging from mild fatty infiltration (steatosis), through steatohepatitis to fibrosis, cirrhosis, end-stage liver disease, and hepatocellular carcinoma (1, 2). The exact prevalence of the disease is unclear but it is more common than previously thought and is now considered to be a major cause of cryptogenic cirrhosis.

NAFLD may be diagnosed by imaging techniques such as ultrasound (US) or computed tomography (CT), although the sensitivity of these techniques is limited and cannot differentiate between steatosis, steatohepatitis and fibrosis (3, 4). It has been estimated that at least 35% fat content in the liver must be present before US can detect fatty changes (5). Diagnosis of NAFLD by non-invasive techniques such as US or CT scan has suggested prevalence, in the general population, of 16–23%. Post-mortem studies on subjects killed in automobile or plane crashes reported a prevalence of 15–39% (6).

The metabolic syndrome with insulin resistance, hypertension, obesity and hyperlipidemia is thought to play a central role in the pathogenesis...
of NAFLD (1, 2, 7). However in the elderly, some components of the metabolic syndrome such as obesity and hyperlipidemia are less prevalent, while others, including hypertension and diabetes, are more prevalent (8). Previous studies on NAFLD did not evaluate elderly subjects and, therefore, the prevalence, associated risk factors and the clinical significance of NAFLD in this age-group are unknown.

Methods

Study design and patients

A prospective study conducted at Kaplan–Harzfeld Medical Center, an 880-bed community hospital affiliated to the Hebrew University and Hadassah School of Medicine. The center serves an area of 450 000 people in the southern part of Israel. Since 1997, all patients’ charts and laboratory data in the hospital have been computerized.

Patients

The study population included patients, hospitalized between August 1, 2001 and February 28, 2002 at three rehabilitation departments at Harzfeld Medical Center – the geriatric division of the Kaplan Medical Center. A single well-trained research geriatrician conducted an evaluation, which included an interview with the patient and/or his caregiver and physical examination. The medical and laboratory charts were reviewed.

The inclusion criteria were hospitalized patients aged 80 years or older. Exclusion criteria were: moderate-to-severe renal failure (creatinine > 3.5 mg/dl), severe congestive heart failure (New York Heart Association classification (NYHA), class > 3), any type of other known liver disease, malignancy, acute intercurrent illness, severe chronic obstructive pulmonary disease, history of jejunooileal bypass or extensive small bowel resection. Patients who had received previous or current treatment with amiodarone, tamoxifen, methotrexate, estrogen, cytostatic agents, total parenteral nutrition and any anti-tuberculosis treatment were excluded. Alcohol consumption was measured by the semiquantitative questionnaire delivered to the patient or caregiver and alcohol intake of more than 5 g/day was an additional exclusion criterion (alcohol consumption is relatively low in the Israeli population, and we excluded patients even with minimal alcohol consumption). All remaining consecutive patients underwent blood tests for hepatitis B and C serology, auto-antibodies (anti-nuclear antibody (ANA), anti-smooth muscle antibody and anti-mitochondrial antibody). Patients with positive results except levels of ANA antibodies equal or less than 1:60 were also excluded from the study.

We evaluated an additional group of 46 younger patients with NAFLD (aged < 70 years), who were followed in the gastroenterological unit for investigation of elevated liver enzymes and who were diagnosed with NAFLD based on US criteria (similar to those used in the elderly group) with a negative thorough workup for other etiologies of chronic liver disease.

Clinical and laboratory evaluation

Patient’s complaints were assessed by the predeigned questionnaire and included fatigue, weakness, right upper quadrant (RUQ) pain and pruritus.

Blood tests were performed at the central clinical chemistry laboratory of the Kaplan–Harzfeld Medical Center. They included serum liver tests: aspartate–aminotransferase, alanine–aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, total bilirubin levels and international normalized ratio. Serum levels of fasting glucose and lipids, albumin, iron, ferritin and transferrin (with calculation of transferrin saturation) were measured.

Metabolic evaluation

All patients underwent an anthropometric evaluation that included weight, height (with body mass index (BMI) calculation) and waist circumference. Lipid determinations were performed on fasting blood samples in a Boehringer–Hitachi analyzer using Boehringer–Mannheim kits (Hitachi system, Roche Diagnostic System, USA). High-density lipoprotein cholesterol (HDL-C) was determined after precipitation of low-density lipoproteins (LDLs) and very-low-density lipoproteins (VLDLs) with phosphotungstate. Cholesterol concentration was determined in the supernatant. Lipoprotein abnormalities were defined according to the Lipid Research Clinic data. Metabolic syndrome was diagnosed according to the new National Cholesterol Education Programme (NCEP) criteria (9). Patients having three or more of the following criteria were defined as having the metabolic syndrome: abdominal obesity – waist circumference > 102 cm for men and > 88 cm for women; hypertriglyceridemia – triglycerides (TG) = 150 mg/dl; low HDL-C – HDL-C < 40 mg/dl in men and < 50 mg/dl in women; high blood pressure: blood pressure = 130/85 mmHg; glucose intolerance – high fasting glucose = 110 mg/dl.
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Roentgenological evaluation

All patients underwent an US scan of the liver, using an ATL 5000 machine (Bothwell, WA, USA). Each examination was performed by a single experienced observer (Z. F.) and reviewed independently by an experienced second observer (D. K.). Both observers were blinded to the details of the patients. The presence of four signs suggestive of fatty liver was examined for: increased contrast of the hepatic compared with the renal or splenic parenchyma, vessel blurring, focal sparing and narrowing of the lumen of the hepatic veins (3, 4, 10). The diagnosis of fatty liver required the presence of at least two of these signs agreed and confirmed by both examining physicians.

As a control group, we chose patients less than 70 years of age, who were referred to the liver clinic of Kaplan Medical Center for investigation of elevated liver enzymes and who were diagnosed with NAFLD after appropriate laboratory and imaging investigations.

Statistical analysis

Univariate comparison of groups was performed by two-sample \( t \)-test for continuous parameters, and by the \( \chi^2 \) test or the Fisher exact test for categorical parameters. Multivariate forward stepwise logistic regression was used to examine the simultaneous effect of various risk factors. \( P < 0.05 \) was considered significant.

The correlation between different US results was measured by the \( \phi \) coefficient. All statistical analyses was performed using the SAS 8.2 software program.

Results

During the 6-month period of this study, 134 patients older than 80 years were admitted to the hospital. Twenty-seven of them were excluded from the study because of the following reasons: (7) acute illnesses, (3) renal failure, (4) congestive heart failure, (2) other liver diseases, (4) different usage of drugs that can influence liver function tests, (2) alcohol consumption and (5) malignancy. The remaining 107 patients met the initial inclusion criteria. On further serologic evaluation, an additional 10 patients were excluded from the study: 6 patients because of a positive reaction for hepatitis C antibodies and 4 patients because of a significantly positive reaction for ANA antibodies. From the 97 patients remaining in the study, an additional 6 patients were removed from the study because of the disagreement between the interpretations of the US findings between the two independent observers. Finally, 91 patients who met all inclusion and exclusion criteria were included in this study.

Table 1 shows the basic clinical and laboratory data of the patients. The mean age of the patients was 85.6 ± 3.7 years. There was a preponderance of females – 79% of patients were women. The mean BMI was 25 ± 5.57 kg/m\(^2\): 56% of the patients were within normal–low BMI (<25 kg/m\(^2\)), 38% were overweight (25–29.9 kg/m\(^2\)) and 6% were obese (at least 30 kg/m\(^2\)). Most of the laboratory parameters including total, HDL and LDL cholesterol, TGs, liver enzymes and transferrin saturation were in the normal range. The only exception was GGT that was almost two times higher than the normal level (58.4 ± 67.9 U/dl; normal range, 5–45 U/dl). Thirty-seven percent of the patients had ischemic heart disease (IHD) (data are not shown), 19% had suffered a cerebro-vascular accident and 24% suffered from diabetes mellitus. Patients received on average 4.5 ± 1.6 chronic medications. Twenty-seven percent of the patients complained of right-upper quadrant pain.

US findings

Fatty liver detected by US (see criteria in the methods) was found in 42 (46.2%) patients. It is interesting to note that increased contrast of the liver, compared with the renal or splenic parenchyma, was the most common sign of NAFLD (Fig. 1): it was found alone in 67% of patients and was seen in every patient who had an additional positive sign. Vessel blurring, found in 42% of the patients, had the strongest correlation
US findings in NAFLD positive patients

Fig. 1. US findings in NAFLD-positive patients. Abbreviations: US, ultrasound; NAFLD, non-alcoholic fatty liver disease. US signs: 1, increased contrast of the hepatic compared with the renal or splenic parenchyma; 2, vessel blurring; 3, focal sparing and 4, narrowing of the lumen of the hepatic veins.

Table 2. Clinical and laboratory characteristics in patients with and without NAFLD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with NAFLD (n = 42)</th>
<th>Patients without NAFLD (n = 49)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>85 ± 3</td>
<td>86 ± 4</td>
<td>0.7</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>17/83</td>
<td>24/76</td>
<td>0.4</td>
</tr>
<tr>
<td>Increased waist circumference BMI (%)</td>
<td>69.1%</td>
<td>59.2%</td>
<td>0.32</td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>47.6</td>
<td>63.3</td>
<td>0.3</td>
</tr>
<tr>
<td>25–30 kg/m²</td>
<td>38.1</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>&gt;30 kg/m²</td>
<td>14.3</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>31%</td>
<td>18.4%</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>28.6%</td>
<td>28.6%</td>
<td>1</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>71.4%</td>
<td>77.1%</td>
<td>0.54</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>57.1%</td>
<td>53.1%</td>
<td>0.7</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>45.2%</td>
<td>42.9%</td>
<td>0.82</td>
</tr>
<tr>
<td>AST (IU/ml)</td>
<td>25.2 ± 10.7</td>
<td>29.2 ± 16.7</td>
<td>0.172</td>
</tr>
<tr>
<td>ALT (IU/ml)</td>
<td>23.6 ± 15.5</td>
<td>24.2 ± 16.3</td>
<td>0.860</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD, or % NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; WC, waist circumference; AST, serum aspartate-aminotransferase; ALT, serum alanine-aminotransferase; TGs, triglycerides; HDL-C, high-density lipoprotein cholesterol. Increased waist circumference = waist circumference > 102 cm for men and > 88 cm for women; hypertriglyceridemia = TG = 150 mg/dl; low HDL-C = HDL-C < 40 mg/dl in men and < 50 mg/dl in women; high blood pressure = 130/85 mmHg; glucose intolerance = high fasting glucose = 110 mg/dl. Metabolic syndrome was defined according to the National Cholesterol Education Programme criteria (9).

Clinical and laboratory data of young and old patients with NAFLD

We compared the group of aged patients with NAFLD with the group of young patients with NAFLD (Table 3). Almost four times more young patients were obese (BMI > 30 kg/m²) compared with the old patients (47.8% vs 14.3%) and only a quarter of the young patients had a BMI less than 25 kg/m² compared with the elderly (10.9% vs 47.6%), P < 0.0001. In contrast, a high percentage of patients with central fat accumulation (manifested by increased waist circumference) was observed both in the young and in the old patients with NAFLD. In the young group with NAFLD glucose intolerance and hypertriglyceridemia were more common (P = 0.009 and P < 0.0001, respectively); however, both groups had similarly high prevalence of low HDL-C levels. Fifty-seven percent of the elderly patients had hypertension compared with the 37% of the younger group (P = 0.057). Young patients with NAFLD had significantly...
higher prevalence of the metabolic syndrome compared with the older group (67.4% vs 45.2%, respectively, \( P = 0.004 \)). In the old group, 19 patients had three of the five criteria of the metabolic syndrome (data are not shown), 13 patients had only 2 and 10 patients had only one criteria of the metabolic syndrome, whereas in the young group the corresponding numbers of patients were 31, 10 and 5, \( P = 0.03 \). All patients with NAFLD in the two groups had at least one component of the metabolic syndrome.

### Discussion

In a group of octogenarians, we found a high prevalence of NAFLD as determined by US criteria (46.1%). Previous population-screening studies in the general population, using US or CT, have reported a prevalence of 16–23% (11–15). These studies did not investigate the prevalence of NAFLD in an octogenarian population and our findings suggest that the prevalence increases with advancing age. Our data may still underestimate the true prevalence of NAFLD, because of our strict exclusion criteria. In addition, in order to increase the accuracy of our US diagnosis, we included only those cases that had at least two of the accepted criteria for NAFLD and in which there was an agreement between two physicians, both blinded to the patients’ data.

US has a limited sensitivity for detecting NAFLD. It has been estimated from a comparison of histological and ultrasonographic findings that US has a positive predictive value of 77% and a negative predictive value of 67% for detecting NAFLD (5). US has a sensitivity of 100% for detecting NAFLD when there is greater than 35% fat in the liver (3). It is reasonable to assume that if we had performed liver biopsy we may have detected an even higher prevalence of NAFLD (12, 13), but for ethical reasons, we did not feel we could perform the gold-standard test of liver biopsy in this cohort of elderly asymptomatic patients.

In the general population, there is a strong link between NAFLD, insulin resistance and the metabolic syndrome (7, 15–17). The prevalence of the metabolic syndrome in our study in elderly patients with NAFLD was 45.2%, which is similar to the prevalence found in the National Health and Nutrition Examination Survey (NHANES III) (16) in subjects older than 70 years and in the several other studies (18). The prevalence of the metabolic syndrome increases with age, although there are age-related changes in the various components of this syndrome. With age there is a decrease in weight with altered fat distribution (increase in waist circumference) and increase in the prevalence of hypertension (16–20). It is interesting to emphasize that in our study, despite the decrease in BMI in the old patients with NAFLD relative to the young patients with NAFLD, there was no difference in the prevalence of central obesity in the two groups. Moreover, despite the high prevalence of metabolic syndrome found in our elderly patients, there were no associations between the presence of NAFLD on US and the metabolic syndrome or any of its components, suggesting a weakened association between the metabolic impairments and NAFLD in octogenarians. Metabolic syndrome was significantly more common in young patients with NAFLD compared with the old ones. This finding highlights the fact that insulin resistance, at least as measured by components of the metabolic syndrome, is not a universal finding in all patients with NAFLD, especially in the older group.

The pathogenesis of NAFLD is unclear but has been suggested that NAFLD evolves via a two-hit hypothesis (21): first, a relatively benign accumulation of fat in the liver in the form of macrovesicular steatosis and second, subsequent necroinflammatory changes and fibrosis (22). Our findings of a high prevalence of NAFLD in our population of octogenarians, but lack of an association with the metabolic syndrome are intriguing. One possible explanation may be because of the changes of the pathogenesis of NAFLD...
Fatty liver in octogenarians


