Influence of Plasma Cortisol and Other Laboratory Parameters on Nonalcoholic Fatty Liver Disease

Abstract

The objective of the present study was to analyse the association between the plasma cortisol concentration and nonalcoholic fatty liver disease (NAFLD). A total of 1326 subjects (age 18–65 years) were examined in the context of an epidemiological study of a population-based random sample. Medical history and anthropometric data of 662 women and 664 men were documented. In addition, laboratory examinations were performed and the fat concentration of the liver was estimated by ultrasound examination. Mean cortisol concentration in plasma was 260.4 ± 156.8 nmol/l for women and 295.8 ± 161.2 nmol/l for men. NAFLD was identified in 17.7% in women and 35.1% in men. Plasma cortisol concentration showed no association with the existence of NAFLD. NAFLD correlated positive with age, body-mass index (BMI), waist-to-hip-ratio (WHR), alanine aminotransferase (ALT), and triglycerides. The present study failed to establish any association of plasma cortisol concentrations and NAFLD.

Abbreviations

ALT  Alanine aminotransferase
AP  Alkaline phosphatase
AST  Aspartat aminotransferase
BMI  Body-mass-index
EMIL  Echinococcus multilocularis in Leutkirch
GGT  γ-glutamyl-transferase
HD  High-density lipoprotein
MRS  Magnetic resonance spectroscopy
NAFL  Nonalcoholic fatty liver
NAFLD  Nonalcoholic fatty liver disease
NASH  Nonalcoholic Steatohepatitis
WHR  Waist-to-hip-ratio
11β-HSD1  11β-Hydroxysteroid dehydrogenase type 1

Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterised by a liver triglyceride content > 5% by weight (liver fat content of the liver > 95th percentile for normal-weight, healthy subjects) or the presence of fat droplets the cytoplasm of > 5% of hepatocytes [1]. With a prevalence of up to 30% of adults in the general population, NAFLD represents the major chronic liver disease in Western industrial nations [2]. The prevalence may reach 70% and even exceed 90% in patients with diabetes and extreme obesity [3]. The degree of hepatic steatosis can be detected by imaging techniques. For example, magnetic resonance spectroscopy (MRS) allows for exact identification of the fat content in the liver [4]. Ultrasonography diagnoses NAFLD with a sensitivity of 85–94% and a specificity of 84–93% [5, 6]. NAFLD includes both benign, nonalcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), which is accompanied by histological evidence of inflammatory markers. Ultrasound cannot differentiate between NAFL and NASH. The latter may be associated with progressive fibrosis and may ultimately lead to cirrhosis of the liver and hepatocellular carcinoma [7]. Histological examination of the organ is required for identifying the exact state of the liver disease [8]. Possible causes for NAFLD include an increased supply of fat with the diet [9], an increased supply of free fatty acids from the adipose tissue that reaches the liver and increased de novo lipogenesis in the liver [1, 10]. In addition, an increased supply of carbohydrates may promote development of NAFLD by increasing the de novo synthesis of fat in the liver [1, 11–13]. In particular, an
increased intake of fructose increases the fat content of the liver by stimulating hepatic de novo lipogenesis [14]. Whether this is due to insulin resistance, which is closely associated with an increased fat content of the liver [15], or as a result of a NAFLD remains unclear [1].

Genetic factors are also known to play a role in the pathogenesis of NAFLD. For example, a high percentage of children with NAFLD have siblings and parents who share this disorder [16]. The genetical basis, however, remains largely unknown [17]. Glucocorticoids and the regulation of glucocorticoid metabolism may also play an important role in the pathogenesis of NAFLD. Hepatic changes in glucocorticoid metabolism attributable to an increased cortisol production have been demonstrated in patients with NAFLD [18].

Objective of the present study, which was performed in the context of an epidemiological study of an urban population in Leutkirch (Southwestern Germany), was to analyse the association of plasma cortisol concentrations and NAFLD.

Participants and Methods

Participants

The EMIL study (Echinococcus multilocularis in Leutkirch), a cross-sectional study of the prevalence of Echinococcus multilocularis infection in a urban population-based sample in Southwestern Germany, was conducted over a 4-week period in November and December, 2002. A secondary objective was to estimate the prevalence of NAFLD in the general population. Four-thousand inhabitants randomly selected out of an urban population of 22 093 inhabitants were contacted with the request to take part in the study. Of these, a total of 3 893 persons aged 10–65 years were successfully contacted. The study was conducted in accordance with the principles of the Helsinki Declaration and the guidelines of Good Clinical Practice (GCP).

The study was approved by the ethics committee the Landeszirktekammer Baden-Württemberg. All subjects were informed about the study and its procedure in detail. After adequate time for consideration and before the beginning of the study, all participants provided written consent to participate in the study. In order to compare the study results with those of others, only the results of the adults were considered in this study. Participants with self-reported daily alcohol consumption exceeding 60 g/day in men and 20 g/day in women were not included in the study. Subjects with acute or chronic liver diseases and disorders with potential liver involvement, autoimmune or metabolic) diseases of the heart, lung, gastrointestinal tract and kidney, as well as those with hormonal disorders and those treated with glucocorticoids were excluded from the study. However, women receiving estrogen therapy (n = 845) were not excluded. Subjects with a fasting time less than 1 h were also not considered because of the food-dependent influence on the cortisol level. Also, subjects whose records were incomplete due to missing data were not included in the statistical analysis.

The results of the remaining 1 326 subjects [662 (49.9 %) women and 664 (50.0 %) men, age 18–65 years] were included in the statistical analysis (Fig. 1).
Results

The study collective consisted of 1326 subjects [662 (49.9 %) women and 664 (50.0 %) men; age 18–65 years, mean 41.5 ± 12.7 years]. Broken down by gender, there were statistically significant differences in terms of the anthropometric variables BMI and WHR, in the prevalence of NAFLD, and in the laboratory parameters ALT, AST, GGT, AP, and triglycerides. By contrast, no significant differences were found between men and women in terms of age and total cholesterol (Table 1). Sonographic evidence of NAFLD was returned in 353 subjects (26.4 %): here, men showed a higher prevalence than women (35.1 % vs. 17.1 %; p < 0.0001).

Total cortisol concentrations were further studied in subjects with and without hepatic steatosis. Cortisol values for subjects with and without hepatic steatosis were grouped in tertiles and analysed. There was a statistically significant difference for the parameters gender, age, ALT and total cholesterol among subjects without hepatic steatosis. In the group of subjects with evidence of hepatic steatosis there was no significant difference (Table 2).

The association between NAFLD and possible risk factors are listed in Table 3. Increasing age was positively associated with NAFLD (p < 0.0001). The risk of NAFLD increased with increasing BMI (p < 0.0001) and with increasing WHR (p < 0.0001). Elevated

**Table 1** Characteristics of the subjects.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Female n = 662</th>
<th>Male n = 664</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>(49.9 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>(50.0 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.8 ± 12.6</td>
<td>41.2 ± 12.7</td>
<td>0.3925</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 5.1</td>
<td>26.2 ± 4.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>WHR</td>
<td>0.8 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>12.4 ± 4.6</td>
<td>18.3 ± 9.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>8.6 ± 2.4</td>
<td>10.6 ± 4.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>GGT (U/l)</td>
<td>9.8 ± 11.0</td>
<td>17.1 ± 16.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>AP (U/l)</td>
<td>78.8 ± 25.7</td>
<td>85.1 ± 19.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.5 ± 1.0</td>
<td>5.5 ± 1.1</td>
<td>0.3089</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.3 ± 0.8</td>
<td>1.9 ± 1.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total cortisol (mmol/l)</td>
<td>260.4 ± 156.8</td>
<td>295.8 ± 161.2</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

**Table 2** Demographics and other characteristics of subjects with and without hepatic steatosis according to cortisol tertiles.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Subjects without hepatic steatosis</th>
<th>Subjects with hepatic steatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%)</td>
<td>Tertile 1 (n = 327)</td>
<td>Tertile 2 (n = 323)</td>
</tr>
<tr>
<td>Female</td>
<td>208 (63.6)</td>
<td>186 (57.6)</td>
</tr>
<tr>
<td>Male</td>
<td>119 (36.4)</td>
<td>137 (42.4)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.9 (11.2)</td>
<td>40.3 (12.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 (3.8)</td>
<td>24.5 (4.2)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.8 (0.1)</td>
<td>0.8 (0.1)</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>12.9 (4.9)</td>
<td>13.3 (5.0)</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>8.8 (2.3)</td>
<td>9.0 (2.1)</td>
</tr>
<tr>
<td>GGT (U/l)</td>
<td>10.9 (12.9)</td>
<td>10.9 (8.5)</td>
</tr>
<tr>
<td>AP (U/l)</td>
<td>78.9 (22.1)</td>
<td>79.9 (22.7)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.3 (0.8)</td>
<td>1.4 (1.0)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.3 (1.0)</td>
<td>5.5 (1.1)</td>
</tr>
</tbody>
</table>

**Sonographic findings**

<table>
<thead>
<tr>
<th>Hepatic steatosis n (%)</th>
<th>No</th>
<th>Tertile 1 (n = 327)</th>
<th>Tertile 2 (n = 323)</th>
<th>Tertile 3 (n = 326)</th>
<th>Tertile 1 (n = 116)</th>
<th>Tertile 2 (n = 117)</th>
<th>Tertile 3 (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>–</td>
<td>327 (100)</td>
<td>323 (100)</td>
<td>326 (100)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Grade II/III</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>70 (60.3)</td>
<td>63 (53.8)</td>
<td>69 (59.0)</td>
</tr>
</tbody>
</table>

Values are mean ± SD

ALT: Alanine aminotransferase; AP: Alkaline phosphatase; AST: Aspartate aminotransferase; GGT: Gamma glutamyltransferase; HDL: High-density lipoprotein; LDL: low-density lipoprotein; WHR: Waist-to-hip ratio

*p < 0.001; **p < 0.05; ***p < 0.01
levels of ALT (p<0.0001) and triglycerides (p=0.0001) were associated positively with NAFLD. AST, GGT, AP, and cholesterol levels were not associated with NAFLD. Also, total cortisol concentrations showed no significant association with NAFLD (p=0.1518).

**Discussion**

In the present random population sample, the prevalence of NAFLD was 26.2%. This corresponds with the prevalences of 23% to 31% reported in the literature for developed countries [2, 20–22]. Differences in prevalence rates result from the characteristics of the studied population. In Asia, the reported prevalences of 11.5–20.8% are significantly lower [23, 24] than in European countries. Recently, however, the variable increases in obesity and diabetes in different Asian populations is reflected in the prevalence of NAFLD ranging from only 5% to as high as 32% [25], showing that not only obesity and diabetes, but also ethnicity have an influence on the prevalence of NAFLD. In the USA, the prevalence rates of 45%, 33%, and 24% for Hispanics, Caucasians, and African-Americans, respectively, would appear to bear this out [22].

Divergent prevalence data may also arise by reason of different diagnostic methods to identify NAFLD [26]. Compared to MRI, the sensitivity of sonography for determining the fat content of the liver, especially when there is a low fat content, is weak [27]. Thus, when the fat content of the liver is <20%, the prevalence of NAFLD could be underestimated [28]. Liver biopsy remains the gold standard for confirming the diagnosis of NAFLD and for measuring the fat content in this organ [9]; nevertheless, sonographic diagnosis of fatty liver is easy to perform and has an established role in hospitals and outpatient settings [29]. It has proven to be valuable in our study although NASH and fibrosis cannot be adequately recognised and distinguished from benign NAFLD [8].

In the present study, the NAFLD risk in the general population increased significantly with age. This result corresponds with reports in the literature [26]. The influence of age on the incidence of NAFLD is particularly evident in women [30, 31]. In our population with a 50.1% proportion of women, the prevalence of NAFLD was 17.3% for women and 35.1% men. The difference between the sexes is already well known. Compared to rates observed in women, NAFLD is found about twice as frequently in men in studies in the USA (42% in men and 24% in women [22]), Israel (38% in men and 21% in women [20]), and China (15.8% in men and 7.5% in women [30]), but not in Hispanics and African-Americans [22].

In our study of healthy subjects, risk factors for NAFLD such as increasing age, male sex, increased levels of BMI, WHR, ALT, and triglycerides were associated with NAFLD corresponding to reports in the literature [21, 25, 31]. No association was observed between the presence of NAFLD and serum cortisol concentrations. The lack of correlation between NAFLD and serum cortisol does not rule out that glucocorticoids nevertheless play a pathogenetic importance in the development of NAFLD. Supporting that hypothesis is the finding that development of severe fatty liver was observed under treatment with the synthetic glucocorticoid, dexamethasone [32]. In line with these clinical observations, animal studies demonstrate that dexamethasone increases hepatic triglyceride synthesis and intrahepatic storage of triglycerides [33]. To accompany this pathogenetic significance, it is also suggested that the presence of NAFLD is correlated with increased activity of the pituitary-adrenocortical axis (HPA) resulting in subclinical hypercortisolism [34, 35]. Compared to controls, patients with NAFLD show an increased cortisol turnover [19, 35]. The increased excretion of cortisol metabolites in urine could lead to compensatory increases of cortisol secretion and furthermore to a subclinical hypercortisolism. A corresponding increased cortisol secretion could not be detected in our study by simply determining the concentration of cortisol in serum. Recently it was proven that the activity of 11ß-hydroxysteroid dehydrogenase type 1 (11ß-HSD1) in visceral adipose tissue leads to portal hypercortisolism and is associated with NAFLD [36]. Visceral adipose tissue is of considerable importance in terms of cardiovascular risk. Visceral fat is positively associated with waist circumference, blood pressure, triglycerides and negatively with HDL-cholesterol [37], and it also is significant in terms of the glucocorticoid metabolism [38]. At the same subcutaneous fat mass, male adolescents with NAFLD have more visceral fat than female adolescents with NAFLD [39]. Furthermore, the visceral fat mass correlates closely with a fatty liver [40]. Compared to women, increased visceral fat in men and in persons with increased BMI and/or an increased WHR might explain the different prevalences of NAFLD in men and women and the high prevalence in individuals with abdominal obesity, both in our own and in other studies [20, 22, 30].

The present study has weaknesses and strengths. One strength of the study is the large number of healthy persons examined (n = 1348). For the diagnosis of fatty liver, sonography was selected as a noninvasive, fast, and low-cost method. Medical ultrasonography has proven to be sufficiently suitable in both in- and outpatient settings for establishing the diagnosis. Because of the lower sensitivity of sonography compared to the MRI, the high prevalence of NAFLD may have been underestimated with sonography. How-

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.578 (1.083–2.297)</td>
<td>0.0174</td>
</tr>
<tr>
<td>Male</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–30</td>
<td>Ref.</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>31–40</td>
<td>3.063 (1.528–6.138)</td>
<td></td>
</tr>
<tr>
<td>41–50</td>
<td>3.776 (1.823–7.819)</td>
<td></td>
</tr>
<tr>
<td>51–65</td>
<td>7.271 (3.548–14.901)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>Ref.</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>25–30</td>
<td>4.092 (2.662–6.290)</td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>Ref.</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>elevated</td>
<td>2.536 (1.760–3.653)</td>
<td></td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>1.092 (1.053–1.132)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>1.014 (0.938–1.097)</td>
<td>0.7241</td>
</tr>
<tr>
<td>GGT (U/l)</td>
<td>0.994 (0.981–1.006)</td>
<td>0.3081</td>
</tr>
<tr>
<td>AP (U/l)</td>
<td>0.993 (0.985–1.001)</td>
<td>0.9087</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>1.131 (0.956–1.339)</td>
<td>0.1920</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.360 (1.162–1.592)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total cortisol (mmol/l)</td>
<td>1.001 (1.000–1.002)</td>
<td>0.1518</td>
</tr>
</tbody>
</table>

ALT: Alanine aminotransferase; AP: Alkaline phosphatase; AST: Aspartate aminotransferase; GGT: γ-glutamyl-transferase; OR: Odds ratio; 95% CI: 95% confidence interval
ever, for screening under field conditions ultrasonography is the
only practical method for estimating the fat content of the liver.
A weakness of the study is that not all investigations took place
in the morning. Instead, examinations were performed between 1
PM and 9 PM and the serum cortisol reference range for the
second half of the day was used. Although the schedule of each
activity was known and every procedure has been previously
explained and performed under quiet conditions, it cannot be
excluded that individual stress influenced cortisol levels in some
cases. Another weakness of the study is that only the current
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Conclusion

The present population-based cross-sectional study found no
association between serum cortisol concentrations and the
presence of NAFLD. The determination of total cortisol in serum
would appear to be of no independent value in the diagnosis of
NAFLD in routine clinical practice. Nevertheless, glucocorticoid
metabolism is an important factor in the pathogenesis of NAFLD.
Ultrasonography of the liver is a practical, reproducible, and
cost-effective method for detecting NAFLD.

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P, Kirch A, Klass D, Koenig W, Kron M, Manfras B,
Meitinger K, Mertens T, Oehme R, Pafl G, Pechotowski I, Reuter
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Conflict of Interest

The authors declare that they have no conflict of interest.

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