Fatty liver is an integral feature of familial combined hyperlipidaemia: relationship with fat distribution and plasma lipids

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ABSTRACT

Overproduction of VLDL (very-low-density lipoprotein) particles is an important cause of FCHL (familial combined hyperlipidaemia). It has been shown recently that VLDL production is driven by the amount of hepatic fat. The present study was conducted to determine the prevalence of fatty liver in relation to the different fat compartments and lipid parameters in FCHL. A total of 68 FCHL patients, 110 normolipidaemic relatives and 66 spouses underwent ultrasound of the abdominal region to estimate the amount of subcutaneous, visceral and hepatic fat. Skinfold callipers were used to measure subcutaneous fat of the biceps, triceps, subscapular and supra-iliacal regions. Fatty liver was observed in 18% of the spouses, 25% of the normolipidaemic relatives and 49% of the FCHL patients. After adjustment for age, gender and body mass index, the prevalence of fatty liver was significantly higher in FCHL patients compared with spouses [OR (odds ratio), 3.1; P = 0.03], and also in the normolipidaemic relatives compared with spouses (OR, 4.0; P = 0.02), whereas no differences were observed between FCHL patients and normolipidaemic relatives (OR, 0.8; P = 0.58). In the normolipidaemic relatives and FCHL patients combined, both visceral fat mass and subcutaneous abdominal fat were independent predictors of fatty liver (P < 0.001 for both fat compartments; FCHL status corrected). Of interest, fatty liver stages were correlated with both VLDL-apoB (apolipoprotein B) and VLDL-triacylglycerols (triglycerides) in a representative subset (n = 69) of patients and relatives (r² = 0.12, P = 0.006; and r² = 0.18, P = 0.001 respectively). These results show that fatty liver is a central aspect of FCHL, i.e. patients and normolipidaemic relatives. Both visceral and subcutaneous adiposity contribute to its 3–4-fold higher risk in FCHL.

Key words: familial combined hyperlipidaemia (FCHL), hypertriglyceridaemia, insulin resistance, steatosis, subcutaneous adiposity, very-low-density lipoprotein (VLDL), visceral adiposity.

Abbreviations: apoB, apolipoprotein B; BMI, body mass index; CI, confidence interval; FCHL, familial combined hyperlipidaemia; NL, normolipidaemic; OR, odds ratio; SAT-US, subcutaneous adipose tissue ultrasound; SKF, skinfold; VAT-US, visceral adipose tissue ultrasound; VLDL, very-low-density lipoprotein; WHR, waist to hip ratio.

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INTRODUCTION

More than 30 years ago, FCHL (familial combined hyperlipidaemia) was delineated as a genetic hyperlipidaemia, characterized by the presence of different hyperlipidaemic phenotypes, i.e. isolated hypercholesterolaemia, isolated hypertriglyceridaemia or the combination of both, within one family [1]. It was estimated that FCHL is highly prevalent (1/100) in the general population and even more abundant (1/10) among survivors of a premature myocardial infarction [1].

More recently it was shown that the presence of small-dense LDL (low-density lipoprotein) particles and elevated apoB (apolipoprotein B) levels are consistent features of FCHL [2,3]. Furthermore, most FCHL subjects exhibit many features of the metabolic syndrome, such as insulin resistance [4] and abdominal obesity [5,6]. Several studies have demonstrated that, although the expression of FCHL very much depends on the amount of (abdominal) fat [7], FCHL patients are still more hyperlipidaemic when corrected or matched for the degree of obesity [7,8]. These observations underline the complex pathogenesis of FCHL: both environmental and genetic factors are responsible for the FCHL phenotype.

The characteristic hyperlipidaemia of FCHL is the consequence of both a hepatic overproduction of VLDLs (very-low-density lipoproteins) and an impaired clearance of remnant particles [9–11]. Adiels et al. [12] very recently reported that the overproduction of VLDL particles is driven by the amount of fat that is accumulated in the liver in normal subjects and patients with Type 2 diabetes mellitus. Of interest, we recently demonstrated [13] that the prevalence of an increased amount of hepatic fat, i.e. fatty liver, was drastically increased in a small group of outpatient FCHL patients in comparison with community controls. Given these recent findings, it is anticipated that the fatty liver trait will play a very important role in the expression of the FCHL phenotype.

The aim of the present study was to extend and refine current knowledge of fatty liver in FCHL. For this, we estimated the prevalence of fatty liver not only in a larger sample of FCHL patients, but also in their NL (normolipidaemic) relatives, derived from our 21 well-defined FCHL families. These prevalence numbers were subsequently compared with their spouses, who are exposed to a similar environment. Furthermore, analogous to the reported contribution of abdominal obesity to the expression of FCHL [7], we investigated whether abdominal obesity, more specifically visceral and abdominal subcutaneous obesity, contribute to the expression of fatty liver in FCHL. Finally, we correlated plasma insulin, apoB and triacylglycerol (triglyceride) levels, three hallmarks of FCHL [2,3,14], with the different stages of fatty liver development.

MATERIALS AND METHODS

Study population

FCHL family members (i.e. FCHL patients and their NL relatives) and spouses of ages ranging between 20–70 years were invited to participate in this study. Diagnosis of FCHL was established as described previously [15]. The FCHL-affected state was defined as plasma levels of total cholesterol > 6.5 mmol/l and/or triacylglycerols > 2.3 mmol/l (classical criteria [1]). More recently, it was proposed to redefine FCHL according to plasma triacylglycerols > 1.5 mmol/l and apoB levels > 1.2 g/l [14]. Some of our analyses were repeated with these newly proposed criteria to exclude the possibility that our observations depend on one particular definition of the affected and non-affected state.

Subjects visited the clinical research centre after an overnight fast and abstinence from alcohol for the previous 3 days. Lipid-lowering medication was stopped 2 weeks prior to the visit. Furthermore, subjects had a stable weight, did not take any medication associated with the development of fatty liver [16] and consumed no more than 20 g of alcohol daily. One subject was found to be seropositive for hepatitis C and was therefore excluded from the present study.

The study protocol was approved by the Human Investigations Review Committee at Maastricht University/Academic Hospital Maastricht. All subjects gave written informed consent.

Anthropometric measurements

Subjects were weighed in their underwear, height was determined by a stadiometer and BMI (body mass index) was calculated with weight (kg) divided by height (m) squared. Hip circumference was determined in a standing position at the level of the trochanter major. SKF (skinfold) thickness was measured with plastic calipers at the left biceps, triceps, subscapular and supra-iliac sites. Waist circumference and sagittal diameter were measured in the supine position at the level midway between the iliacal crest and lowest rib at the end of a normal expiration. Sagittal diameter was measured with a sliding beam calliper. WHR (waist to hip ratio) was calculated as the ratio between waist and hip circumference.

Ultrasound

All ultrasound measurements were performed with an ATL 9 HDI ultrasound system. Both VAT-US (visceral adipose tissue ultrasound) and SAT-US (subcutaneous adipose tissue ultrasound) were determined at the same level as waist circumference and sagittal diameter. SAT-US was measured at the midline as the distance between skin and linea alba, using a L5-10 transducer. VAT-US was determined as the distance between the anterior of the vertebrate body and the peritoneum,
Table 1  General descriptive and anthropometric data for the study population

Values are means ± S.D. or medians (interquartile range). *P < 0.05 compared with spouses and FCHL patients; †P < 0.05 compared with spouses when age- and gender-adjusted; ‡P < 0.05 compared with NL relatives when age- and gender-adjusted. All analyses are Hochberg-corrected.

<table>
<thead>
<tr>
<th></th>
<th>Spouses</th>
<th>NL relatives</th>
<th>FCHL patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (n)</td>
<td>34/32</td>
<td>50/60</td>
<td>31/37</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.0 (43.0–56.3)</td>
<td>37.5 (28.8–52.0)*</td>
<td>54.0 (46.5–60.0)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.3 ± 1.0</td>
<td>5.0 ± 0.8</td>
<td>7.2 ± 2.0†‡</td>
</tr>
<tr>
<td>Triacylglycerols (mmol/l)</td>
<td>1.1 (0.8–1.7)</td>
<td>1.1 (0.9–1.5)</td>
<td>2.6 (1.6–3.5)†‡</td>
</tr>
<tr>
<td>ApoB (g/l)</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.3</td>
<td>1.3 ± 0.3†‡</td>
</tr>
<tr>
<td>Insulin (units/l)</td>
<td>4.6 (2.0–8.7)</td>
<td>5.4 (2.0–8.9)</td>
<td>9.5 (6.9–13.7)†‡</td>
</tr>
<tr>
<td>Lipid medication (%)</td>
<td>6</td>
<td>10</td>
<td>50†‡</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4 ± 4.2</td>
<td>25.2 ± 4.3</td>
<td>28.2 ± 3.9†‡</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>89.2 ± 12.4</td>
<td>88.2 ± 12.1</td>
<td>97.5 ± 9.9†‡</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>100.6 ± 8.2</td>
<td>100.4 ± 8.0</td>
<td>104.1 ± 8.0</td>
</tr>
<tr>
<td>WHR</td>
<td>0.88 ± 0.08</td>
<td>0.88 ± 0.08†</td>
<td>0.94 ± 0.06†‡</td>
</tr>
<tr>
<td>Sagittal diameter (cm)</td>
<td>19.6 (17.9–23.1)</td>
<td>19.5 (17.8–21.8)</td>
<td>22.8 (21.0–25.1)†‡</td>
</tr>
<tr>
<td>SAT-US (cm)</td>
<td>2.5 ± 1.1</td>
<td>2.5 ± 1.2</td>
<td>2.9 ± 1.1†‡</td>
</tr>
<tr>
<td>VAT-US (cm)</td>
<td>6.7 (5.6–9.0)</td>
<td>6.9 (5.5–8.6)†</td>
<td>8.4 (7.3–10.5)†‡</td>
</tr>
<tr>
<td>SKF thickness (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps</td>
<td>8 (6–11)</td>
<td>9 (6–14)</td>
<td>11 (7–17)†‡</td>
</tr>
<tr>
<td>Triceps</td>
<td>15 (10–20)</td>
<td>16 (11–23)</td>
<td>16 (10–24)</td>
</tr>
<tr>
<td>Subscapular</td>
<td>18 (13–22)</td>
<td>20 (14–25)</td>
<td>24 (18–30)†‡</td>
</tr>
<tr>
<td>Supra-iliac</td>
<td>22 (16–32)</td>
<td>25 (16–32)</td>
<td>26 (22–31)</td>
</tr>
<tr>
<td>Fatty liver (%) (mild, moderate, severe)</td>
<td>18 (5, 7, 6)</td>
<td>25 (15, 7, 3)</td>
<td>49 (24, 12, 13)†‡</td>
</tr>
</tbody>
</table>

Fatty liver was detected by ultrasound as well, using a C7-4 and C4-2 transducer. Standardized images of the liver and right kidney were recorded on videotape and examined by an independent radiologist unaware of the subject’s clinical characteristics. The severity of fatty liver was graded into mild, moderate and severe fatty liver by using the criteria of posterior beam attenuation, increased echogenicity (‘bright liver’) and decreased visualization of intrahepatic vessels, as described previously [18,19]. The intra-observer agreement expressed as κ, determined in 30 random scans, was substantial for both the presence of fatty liver (present/absent) (κ = 0.74) and the different fatty liver stages (normal, mild, moderate and severe) (κ = 0.68). This is in agreement with a previous study [18].

Laboratory measurements

Plasma total cholesterol, triacylglycerol, apoB and insulin concentrations were measured as described previously [20]. VLDL isolation was done as described by Redgrave et al. [21]. ApoB concentration in this fraction was quantified by gel electrophoresis as described by Karpe et al. [22].

Statistical analyses

Differences in continuous and binary variables between spouses, NL relatives and FCHL patients, included as dummy variables, were tested with multivariate linear and logistic regression respectively.

Univariate correlations of anthropometric variables and plasma insulin, triacylglycerols and apoB levels with the different stages of fatty liver development were calculated with ordinal regression in all FCHL family members. Several multivariate ordinal regression models were constructed to study the independent effects of different anthropometric variables on the prediction of fatty liver. FCHL patients and NL relatives were included in these models as dummy variables. The overall goodness of fit of the model was expressed as Nagelkerke’s pseudo r², a parameter that serves the same function as r² in linear regression models.

SPSS 13.0 for Windows was used for all statistical analyses.

RESULTS

General and anthropometric characteristics of FCHL patients, NL relatives and spouses

In total, 178 FCHL family members (68 FCHL patients and 110 NL relatives) and 66 spouses from 21 families participated in this study. Table 1 shows their general
and anthropometric characteristics. As the NL relatives were significantly younger than the spouses and FCHL patients, all analyses were adjusted for age and gender. By definition, FCHL patients had higher total cholesterol and serum triacylglycerol values compared with NL relatives and spouses. Furthermore, FCHL patients were more obese. This was explained, at least in part, by an increased visceral fat depot reflected by increased waist circumference, WHR, sagittal diameter and, more directly assessed, by increased VAT-US. Furthermore, the subcutaneous fat compartment also appeared to be increased, as expressed by increased SAT-US, and biceps and subscapular SKF thicknesses. The latter two were only significantly different from the spouses. However, other markers of subcutaneous adipose tissue, i.e. hip circumference, and triceps and supra-iliacal SKF thicknesses, were not statistically different between the three groups. Of interest, both WHR and VAT-US were significantly higher in NL relatives in comparison with spouses (Table 1).

Prevalence of fatty liver in FCHL patients, NL relatives and their spouses

The prevalence of fatty liver measured with ultrasound was 49% in FCHL patients, which was significantly higher in comparison with 18% in spouses [OR (odds ratio), 2.9 (95% CI (confidence interval), 1.5–5.5); \( P = 0.003 \)], but not with the 25% as observed in NL relatives [OR, 1.6 (95% CI, 0.8–3.3); \( P = 0.18 \)] after correction for age and gender (Table 1). Of interest, when these analyses were repeated with further adjustment for obesity, measured as BMI, the prevalence of fatty liver remained elevated in FCHL patients in comparison with spouses [OR, 3.1 (95% CI, 1.1–8.7); \( P = 0.03 \)]. Moreover, a significant difference in prevalence was also observed for NL relatives compared with spouses [OR, 4.0 (95% CI, 1.3–12.3); \( P = 0.02 \)], whereas the difference between FCHL patients and NL relatives was completely abolished after correction for BMI [OR, 0.8 (95% CI, 0.3–1.9); \( P = 0.6 \)].

Of note, very similar results were obtained when FCHL patients were defined according to more recently proposed criteria of plasma triacylglycerols >1.5 mmol/l and apoB levels >1.2 g/l [14] [OR, 4.2 (\( P = 0.02 \)) for FCHL patients compared with spouses; OR, 4.7 (\( P = 0.006 \)) for relatives compared with spouses]. In addition, similar trends were observed when only one FCHL patient or one NL relative from each family was taken for analysis (results not shown).

Independent contribution of different fat compartments to fatty liver in FCHL patients and NL relatives

In all FCHL family members, i.e. FCHL patients and NL relatives combined, all anthropometric variables were significantly correlated with the different stages of fatty liver in univariate analysis (Table 2; results for BMI, waist circumference, VAT-US and subcapular SKF thickness are shown in Figure 1). Subsequently, age- and gender-corrected multivariate models were constructed to study the independent contribution of the different fat compartments to the fatty liver stages. As shown in Table 3, the prediction models that included either overall obesity, represented by BMI (model 1), or abdominal obesity (model 2) resulted in very similar correlation coefficients (0.46 and 0.44 respectively). A model with only visceral obesity, i.e. VAT-US measured at the same level as waist circumference, yielded a substantially lower coefficient (model 3). Of interest, when SAT-US was added to VAT-US (model 4a), the correlation coefficient very much approached the \( r^2 \) of the model that included waist circumference (model 2). Replacing SAT-US by subcapular SKF thickness resulted in a similar model (model 4b), whereas biceps SKF thickness only marginally added to the contribution of VAT-US (model 4c compared with model 3). Combining VAT-US, and subcapular and biceps SKF thicknesses into one model (model 5) showed that both visceral and subcutaneous obesity of the trunk, but not of the upper limb, independently contributed to the prediction of the different stages of fatty liver. Of note, correction for the hyperlipidaemic state, i.e. being a FCHL patient or NL relative (classical [1] or newly proposed [14] criteria), did not influence these results.

Relationship of plasma triacylglycerol, apoB and insulin levels with fatty liver stages in FCHL patients and NL relatives

In univariate ordinal regression analysis, insulin levels were positively correlated with the different stages of fatty liver.
fatty liver ($r^2 = 0.32$, $P < 0.001$; Figure 2), independent of the affected state.

Of the two newly proposed parameters to diagnose FCHL [14], only plasma triacylglycerols were significantly related with the fatty liver stages ($r^2 = 0.22$, $P < 0.001$), whereas plasma apoB levels were not ($r^2 = 0.002$, $P = 0.6$).

Since plasma triacylglycerols are mainly secreted by the liver as VLDL particles, we subsequently measured VLDL-triacylglycerol and VLDL-apoB concentrations in a representative subset of relatives and patients ($n = 69$) and to relate these parameters with fatty liver. VLDL-triacylglycerols were similarly correlated with fatty liver stages ($r^2 = 0.18$, $P = 0.001$; Figure 3A) as for total plasma triacylglycerols. Of interest, VLDL-apoB did show a correlation with fatty liver ($r^2 = 0.12$, $P = 0.006$, Figure 3B) in contrast with total plasma apoB.

**DISCUSSION**

We [7] and others [8] have previously demonstrated that FCHL develops against a background of abdominal obesity. The present study was conducted to relate these findings to fatty liver, a condition that is known to drive the production of VLDL particles [12], which is an important feature of FCHL [9,10].

The results of the present study demonstrate that both NL relatives and FCHL patients exhibited a 3–4-fold increased risk (as expressed by the OR) of having fatty liver in comparison with spouses. The prevalence of fatty liver was considerably higher in FCHL patients in comparison with spouses (49% compared with 18% respectively). This value seems to be somewhat lower than the prevalence of 76% in an outpatient FCHL population reported previously [13]. This discrepancy is
Table 3  Prediction models of fatty liver stages with different fat compartments in all FCHL family members
Analysed with ordinal regression with inclusion of age and gender as covariates. Including the FCHL status, i.e. being a FCHL patient or NL relative, as a covariate did not influence the results.

<table>
<thead>
<tr>
<th>Fat compartment</th>
<th>Model number</th>
<th>Model $r^2$</th>
<th>Variables entered</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall obesity</td>
<td>1</td>
<td>0.46</td>
<td>BMI</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>2</td>
<td>0.44</td>
<td>Waist circumference</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Visceral obesity</td>
<td>3</td>
<td>0.35</td>
<td>VAT-US</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Visceral + subcutaneous obesity</td>
<td>4a</td>
<td>0.43</td>
<td>VAT-US, SAT-US</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>0.40</td>
<td>VAT-US, Subcapular SKF thickness</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>4c</td>
<td>0.36</td>
<td>VAT-US, Biceps SKF thickness</td>
<td>0.01</td>
</tr>
<tr>
<td>Visceral + subcutaneous (limb + trunk) obesity</td>
<td>5</td>
<td>0.41</td>
<td>VAT-US, Subcapular SKF thickness</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

likely to be explained by the higher co-morbidity that is often seen in outpatient populations in comparison with a non-outpatient population, as was predominantly the case in the present study. Furthermore, the previous study [13] was conducted in a relatively small sample, thus yielding prevalence numbers with large confidence intervals. The prevalence estimate from the present larger population is therefore expected to be more reliable.

In all FCHL family members, obesity was an important contributor to the grade of fatty liver: 46% of the variation in fatty liver grade was accounted for by BMI.
Of interest, a very similar correlation was observed for the abdominal compartment, quantified as waist circumference, indicating that it is specifically this region that predicts fatty liver in FCHL. A more detailed study of this region revealed that both the visceral as well as the subcutaneous fat depot, both measured with ultrasound, were independent predictors of fatty liver grade. Furthermore, the combination of these two compartments very much approached the model that included only waist circumference. The association of visceral fat with fatty liver has been demonstrated in several other conditions associated with the metabolic syndrome [23–25], whereas the correlation of the subcutaneous adipose tissue with fatty liver is more controversial [23,24]. Nielsen et al. [26] have elegantly shown that both visceral adipose tissue and subcutaneous adipose tissue contribute to the flux of non-esterified fatty acids (free fatty acids) to the liver [27], which is thought to be the most important process that drives hepatic fat accumulation [28]. The results from the present study also suggest that the independent contribution of the subcutaneous fat depot in FCHL is confined to the truncal region. Of interest, Abate et al. [29] have demonstrated that subcutaneous truncal, but not peripheral, fat is associated with the hepatic glucose production, a process that is related to hepatic fat accumulation [23].

The importance of obesity in the relationship with fatty liver was also illustrated by the observation that BMI completely abolished the seemingly marked difference in prevalence of fatty liver between FCHL patients and NL relatives (49% compared with 25% respectively). This indicates that FCHL patients and their NL relatives are very similar with regard to the prevalence of fatty liver, with the only exception being that the patients are more obese and older. In contrast, the almost 3-fold higher prevalence of fatty liver in FCHL patients in comparison with spouses remained significant after correction for age, gender and BMI. Additionally, the apparently small prevalence difference between NL relatives and spouses became significant after correction for age, gender and BMI. These results imply an increased susceptibility of FCHL family members in general for the development of fatty liver, independent of the affected state (defined by both the classical [1] and the more recently proposed [14] criteria). Genetic factors could account for this lower threshold, since FCHL family members and spouses share the same environment.

The central role of fatty liver in FCHL was emphasized further by its association with both insulin levels and plasma triacylglycerols. ApoB levels, another hallmark of FCHL, were not related to the different fatty liver stages. These results are in concordance with Toledo et al. [30], who reported very similar outcomes in a diabetic population. Of interest, in that report [30], the relationship of fatty liver with plasma triacylglycerols was mainly explained by VLDL particle size [30], whereas our study suggested that VLDL particle number, as reflected by VLDL-apoB levels, was associated with the different stages of fatty liver. It should be noted that an increase in VLDL particle number could be due not only to increased VLDL production, but also to impaired clearance. The apparent discrepancy between our findings in FCHL and previous observations in Type 2 diabetes mellitus [30] may be explained by the study populations that were under investigation. Previous studies have suggested that VLDL particles are larger in patients with Type 2 diabetes mellitus, but of normal size in FCHL patients [31,32].

In the present study, we used liver ultrasound to detect hepatic fat accumulation. The gold standard, liver biopsy, was not ethically accepted in this relatively healthy population. Liver ultrasound was therefore used as an alternative validated method to detect hepatic fat accumulation [18,19]. Since ultrasound is less sensitive in detecting mild stages of fatty liver [18], it is anticipated that the prevalence of fatty liver in FCHL in the present study is somewhat underestimated. Of note, the prevalence of fatty liver in the spouses included in the present study was similar to the prevalence of fatty liver detected by histology in a general population [33,34].

In summary, we have shown that not only FCHL patients, but also their NL relatives, have a 3-fold higher risk of developing fatty liver compared with spouses. Within the FCHL population, BMI is an important contributor to the grade of fatty liver, and both the subcutaneous truncal and visceral fat depots contributed independently to this association. The relationship of fatty liver with plasma insulin, VLDL-triacylglycerols and VLDL-apoB levels underlines further the central role of fatty liver in the pathogenesis and expression of FCHL.

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