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Association between leptin and transaminases: 1-year follow-up study in 180 overweight children

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Abstract

Leptin and insulin resistance are being discussed to be involved in the pathogenesis of nonalcoholic fatty liver disease, which is frequently characterized by moderately elevated transaminases. However, longitudinal studies proving an association between leptin, insulin resistance, and transaminases are scarce. We examined weight status, aspartate aminotransferase (AST), alanine aminotransferase (ALT), leptin, glucose, and insulin in 180 overweight children at baseline and 1 year later. Relationships between these parameters at baseline and their changes in the course of 1 year were determined by multiple regression analysis adjusted for age, sex, pubertal stage, and body mass index (BMI). Leptin but not homeostasis model assessment of insulin resistance index correlated significantly to transaminases in both cross-sectional and longitudinal analyses. The same findings were observed in 30 children with suspected nonalcoholic fatty liver disease by ultrasound. The 130 children who participated in a 1-year lifestyle intervention reduced their overweight (standard deviation score [SDS]–BMI, −0.37 ± 0.11). In the course of 1 year, their changes of transaminases depended on change of weight status (SDS-BMI decrease >0.5: ALT 12 [10-15] → 9 [8-13] U/L, AST 11 [9-12] → 9 [8-12] U/L; SDS-BMI decrease >0 but ≤0.5: ALT 14 [11-18] → 16 [12-26] U/L, AST 10 [8-14] → 10 [8-24] U/L; no SDS-BMI decrease: ALT 13 [11-20] → 20[13-33] U/L, AST 11 [9-21] → 15 [9-24] U/L; data as median and interquartile range). The 50 children without intervention increased their SDS-BMI (+0.02 ± 0.18) and transaminases (ALT 14 [11-18] → 19 [15-25] U/L, AST 10 [8-15] → 16 [10-25] U/L). These findings suggest that leptin may be involved in the pathogenesis of liver diseases. However, to test this hypothesis, careful histologic assessments in correlation to leptin levels are needed.

1. Introduction

Concurrent with the rise of childhood obesity [1], nonalcoholic fatty liver disease (NAFLD) is recognized as the most common cause of liver disease in obese youth [2-4]. Nonalcoholic fatty liver disease in children was first reported in the early 1980s [5]. Since then, a number of case series have been described with the following clinical characteristics: male predominance, elevated transaminases with a higher increase of serum alanine aminotransferase (ALT) than aspartate aminotransferase (AST), and a correlation to obesity [6-10]. Although the prognosis of NAFLD seems to be benign in most children, development of chronic liver dysfunction and liver cirrhosis as well as hepatocellular carcinoma has been reported [5,11,12]. The prevalence of NAFLD in children has been reported to be 2.6% in normal-weight children, whereas in overweight children and adolescents, it varied widely from 20% up to 77% [10,13-19].

The complete metabolic phenotype and the pathogenesis of NAFLD remain to be established [2]. The commonly favored 2-hit hypothesis is composed of an accumulation of fat ("first hit") within the liver, which predisposes to the "second hit," namely, hepatocyte injury, inflammation, and fibrosis, the so-called nonalcoholic steatohepatitis (NASH) [2,20]. The 2 main pathways of hepatocellular injury are considered to be lipid peroxidation induced by oxidative stress and inflammatory cytokine-mediated injury. Furthermore, a role of leptin in the pathogenesis of NAFLD has been discussed [21-23]: Studies in leptin-deficient *ob*/*ob* mice have dramatic hepatic steatosis, suggesting that leptin may have a role in promoting hepatic fibrogenesis, directly by an autocrine effect on hepatic stellate cells and indirectly by up-regulating the production of transforming growth factor–β from sinusoidal endothelial cells and Kupffer cells. Furthermore, high leptin concentrations favor the entry of free fatty acids (FFA) into mitochondria and their ligand

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action for the peroxisomal proliferation–activator receptor–α (PPARα). Peroxisomal proliferation–activator receptor–α is involved in lipid metabolism in the liver by regulating the transcription of some genes encoding enzymes involved in mitochondrial and peroxisomal β-oxidation. Moreover, fatty liver might also become a feature of the "metabolic syndrome" in which insulin resistance plays a key role [24]. In concordance, correlation between transaminases, homeostasis model assessment (HOMA) of insulin resistance index, and leptin has been described in cross-sectional analysis [16,24-26].

Because insulin resistance, leptin levels, and the development of NAFLD depend on genetic factors and fat mass [2,27,28], it is difficult to distinguish the effect of insulin resistance, leptin, and obesity on transaminases. Most studies concerning this question were performed as multiple linear regression analysis or exploratory factor analysis in cross-sectional studies. Multiple regression equations become unreliable when there is a high degree of correlations between the dependent variables insulin resistance, leptin, and degree of overweight. Most importantly, cross-sectional analyses cannot prove causality and represent only a snapshot of a complicated physiologic system at a single point in time susceptible to confounder effects.

Therefore, longitudinal studies are necessary to analyze the relationships between obesity, insulin resistance, and transaminases. However, these studies are still lacking. The advantage of examining the liver enzymes in children is that there is no potential confusion with alcohol consumption and drugs. Therefore, we performed the following longitudinal study in a large cohort of overweight children to analyze the relationship between liver enzymes, leptin, and insulin resistance.

2. Methods

We examined weight, height, pubertal stage, and fasting serum AST, ALT, leptin, insulin, FFA, and glucose in 180 overweight children (mean age, 10.7 ± 2.5 years; 48% male; mean body mass index [BMI], 27.0 ± 4.5 kg/m^2; mean standard deviation score [SDS]–BMI, 2.29 ± 0.51; 47% prepubertal) with a 1-year follow-up at the outpatient Obesity Department of the Vestische Children's Hospital, University of Witten/Herdecke, Germany. In addition, an abdominal ultrasound was performed to screen for NAFLD. None of the children had endocrine disorders, premature adrenarche, or syndromal obesity. The participants were not on any regular medication. Overweight was defined according to the International Obesity Task Force using population-specific data [29,30].

Height was measured to the nearest centimeter using a rigid stadiometer. Weight was measured unclothed to the nearest 0.1 kg using a calibrated balance scale. The SDS-BMI was calculated according to German percentiles [30]. We used the last mean square (LMS) method to calculate BMI-SDS as a measure for the degree of overweight because of the skewness of BMI distribution [31].

Pubertal stage was determined according to Marshall and Tanner. Pubertal developmental stage was categorized into 2 groups (prepubertal: boys with gonadal stage I and girls with breast stage I; pubertal: boys with gonadal stage ≥II and girls with breast stage ≥II).

Blood sampling was performed in the fasting status at 8:00 AM. Serum fasting AST, ALT, FFA, and glucose concentrations were measured using commercially available test kits (ALTL, ASTPL Cobas Integra 400, Roche Diagnostics, Mannheim, Germany; Vitros analyzer, Ortho Clinical Diagnostics, Neckargemuend, Germany; MEIA, Abbott, Wiesbaden, Germany; WAKO Freie Fettsäure; Vitros analyzer, Ortho Clinical Diagnostics, Neuss, Germany). Insulin concentration was measured by microparticle enhanced immunometric assay (MEIA, Abbott). Intra- and interassay variations for the concentrations (coefficients of variation [CVs]) of these variables were less than 5%. Elevated transaminases were defined by ALT concentrations and/or AST concentrations greater than 20 U/L. Homeostasis model assessment was used to detect the degree of insulin resistance [32]: resistance (HOMA) = (insulin [milliunits per liter] × glucose [millimoles per liter])/22.5. Leptin was determined by radioimmunoassay (Human Leptin RIA, Mediagnost, Reutlingen, Germany; intraassay CV, <5%; interassay CV, <8%; sensitivity, 0.1 ng/mL). Leptin was transformed into SDS (SDS-leptin) according to sex, pubertal stage, and degree of overweight [33].

The suspicion diagnosis of NAFLD was derived from standardized liver ultrasound criteria measurements as well as absence of alcohol abuse according to the American Gastroenterological Association medical position statement [34]. The liver ultrasound procedures were read by a single blinded radiologist, and quantification of fatty liver was performed according to the criteria of Saverymuttu et al [35]. Differential diagnoses were excluded in all children with suspected NAFLD by measuring serum creatine kinase, antinuclear antibodies, liver autoantibodies (smooth muscle antibodies, liver kidney microsomal antibodies, soluble liver antigen antibodies), copper, ceruloplasmin, 24-hour urinary copper, and α1-antitrypsin and by Epstein-Barr virus, hepatitis A virus, hepatitis B virus, and hepatitis C virus serologies according to international recommendations [2].

All overweight children were encouraged to participate in the 1-year outpatient intervention program "Obeldicks," which has been described in detail elsewhere [36,37]. Briefly, this outpatient intervention program for overweight children was based on physical exercise, nutrition education, and behavior therapy including individual psychologic care of the child and his or her family. Using the LMS calculation method described above, substantial weight loss in the lifestyle intervention in the course of 1 year was defined as a reduction of SDS-BMI of at least 0.5 because, with a reduction of less than 0.5 SDS-BMI, no improvement of insulin resistance and cardiovascular risk factors can be measured in obese children [38].

Statistical analysis was performed using the Winstat software package (R. Fitch Software, Bad Krozinger, Germany). Normal distribution of variables was tested by Kolmogorov-Smirnov test. Student *t* tests for paired and unpaired observations, Mann-Whitney *U* test, and Wilcoxon test were used as appropriate. Direct multivariate regression analyses with the dependent variables liver enzymes were performed including the independent variables age, sex, pubertal stage, weight status (BMI), leptin, and HOMA. Sex and pubertal stage were considered as classified variables in these models. Spearman correlations were calculated between changes of liver enzymes and changes of weight status (SDS-BMI), leptin, and insulin resistance index HOMA. Furthermore, direct multivariate regression analyses with the dependent variable change of liver enzymes in the 1-year observation period were performed including the independent variables age, sex, pubertal stage, change of weight status (SDS-BMI), change of leptin, change of HOMA, and participation in lifestyle intervention. Sex, pubertal stage, and participation in lifestyle intervention were considered as classified variables in these models. The children with suspected NAFLD by ultrasound were compared with the other children with respect to age, sex, pubertal stage, degree of overweight, FFA, transaminases, glucose, leptin, insulin, and HOMA of insulin resistance index. A *P* value less than .05 was considered as significant. Data were presented as mean and standard deviation for normally distributed variables or median and interquartile range for not normally distributed variables.

Written informed consent was obtained from all children and their parents. The study was approved by the local ethics committee of the University of Witten/Herdecke.

3. Results

3.1. Cross-sectional analyses

Alanine aminotransferase was significantly related to leptin (*b* coefficient: 0.08; 95% confidence interval [CI] ±0.06; $P = .005$) and HOMA (*b* coefficient: 0.49; 95% CI ±0.48; $P = .044$) in a direct multiple regression analysis adjusted to BMI, age, sex, and pubertal stage (explained variance of the model: $r^2 = 0.12$). The liver enzyme AST was significantly related to leptin (*b* coefficient: 0.05; 95% CI ±0.03; $P = .005$) but not to HOMA (*b* coefficient: 0.07; 95% CI ±0.17; $P = .370$) in direct multiple regression analysis adjusted to BMI, age, sex, and pubertal stage (explained variance of the model: $r^2 = 0.11$).

In 30 (17%) children, NAFLD was suspected by ultrasound (Table 1). These children were predominantly male. We found that the HOMA of insulin resistance index, FFA, and leptin concentrations were significantly higher in the children with suspected NAFLD as compared with the overweight children without NAFLD (Table 1). The SDS-leptin adjusted to BMI, age, and sex was also significantly higher in the children with NAFLD. Triglycerides tended to be higher in children with suspected NAFLD. The ALT levels were significantly ($P < .001$) higher than the AST levels in the children with suspected NAFLD.

Table 1
Age, sex, pubertal stage, weight status, transaminases, triglycerides, FFA, leptin, glucose, insulin, and insulin resistance index HOMA in children with and without suspected NAFLD by liver ultrasound

	No NAFLD	NAFLD	*P* value
n	150	30	
Age (y)	10.7 ± 2.5	10.9 ± 2.4	.330
Male (%)	44	63	.040
Pubertal stage	47% Prepubertal	47% Prepubertal	.999
BMI (kg/m^2)	26.9 ± 4.5	27.6 ± 4.1	.581
SDS-BMI	2.28 ± 0.51	2.34 ± 0.27	.660
Glucose (mg/dL)	91 ± 7	91 ± 8	.722
Insulin (mU/L)[a]	15 (10-21)	17 (11-26)	.106
HOMA[a]	3.2 (2.0-4.3)	3.7 (2.6-6.3)	.046
Triglycerides (mg/dL)[a]	105 (75-150)	114 (77-169)	.101
FFA (mmol/L)	0.49 ± 0.19	0.64 ± 0.40	.021
Leptin (μg/L)[a]	21 (14-34)	38 (23-47)	<.001
SDS-leptin[b]	0.42 ± 0.17	1.22 ± 0.35	.048
AST (U/L)[a]	9 (8-10)	19 (13-26)	<.001
ALT (U/L)[a]	13 (10-15)	29 (24-43)	<.001

Data as mean and standard deviation.
[a] Not normally distributed variable; data as median and 25th/75th percentile.
[b] Adjusted to BMI, sex, and pubertal stage.

Analyzing only the 30 children with suspected NAFLD at baseline demonstrated that ALT was significantly related to leptin (*b* coefficient: 0.43; 95% CI ±0.39; $P = .035$) but not to HOMA (*b* coefficient: −0.16; 95% CI ±2.00; $P = .868$) in a direct multiple regression analysis adjusted to BMI, age, sex, and pubertal stage (explained variance of the model: $r^2 = 0.27$). The liver enzyme AST was significantly related to leptin (*b* coefficient: 0.23; 95% CI ±0.18; $P = .015$) but not to HOMA (*b* coefficient: −0.20; 95% CI ±0.93; $P = .662$) in these children in direct multiple regression analysis adjusted to BMI, age, sex, and pubertal stage (explained variance of the model: $r^2 = 0.36$).

3.2. Longitudinal analyses

A total of 130 (72%) children completed the 1-year lifestyle intervention. These children reduced their overweight (mean decrease of SDS-BMI, 0.37 ± 0.11) in contrast to the 50 children without lifestyle intervention. An SDS-BMI reduction of greater than 0.5 was associated with an improvement of FFA, insulin, HOMA of insulin resistance, and transaminases and a decrease in leptin concentrations (Table 2). Furthermore, prevalence of suspected NAFLD decreased in these children. In the children without lifestyle intervention and in the children without weight loss in the lifestyle intervention, transaminases and leptin levels increased (Table 2).

In univariate analyses, the changes of SDS-BMI significantly correlated to changes of ALT ($r = 0.13$) and AST ($r = 0.16$). Changes of leptin but not changes of HOMA

Table 2
Clinical characteristics, transaminases, triglycerides, FFA, glucose, insulin, insulin resistance index HOMA, leptin, and prevalence of suspected NAFLD at baseline and 1 year later in obese children with intervention and substantial weight loss (decrease of SDS-BMI >0.5), minimal weight loss (decrease of SDS-BMI <0.5), without weight loss (no decrease of SDS-BMI), and obese children without intervention

	Intervention and substantial weight loss		Intervention and minimal weight loss		Intervention and no weight loss		No intervention	
n	40		69		21		50	
Age (y)	9.7 ± 0.4		10.8 ± 0.3		11.1 ± 0.5		11.1 ± 0.3	
Sex	50% Male		54% Male		48% Male		38% Male	
BMI at baseline (kg/m^2)	26.3 ± 0.6		28.1 ± 0.5		28.2 ± 1.2		25.6 ± 0.6	
SDS-BMI at baseline	2.39 ± 0.08		2.43 ± 0.05		2.28 ± 0.11		2.01 ± 0.08	
Change of SDS-BMI	−0.74 ± 0.04		−0.29 ± 0.02		+0.06 ± 0.03		+0.02 ± 0.18	
	Baseline	1 y later	Baseline	1 y later	Baseline	1 y later	Baseline	1 y later
Triglycerides (mg/dL)	131 ± 8	99 ± 8	137 ± 11	130 ± 8	131 ± 20	133 ± 21	130 ± 13	133 ± 13
FFA (mmol/L)	0.62 ± 0.05	0.48 ± 0.03*	0.52 ± 0.03	0.44 ± 0.03	0.44 ± 0.05	0.49 ± 0.07	0.42 ± 0.03	0.43 ± 0.03
Glucose (mg/dL)	91 ± 1	89 ± 1	91 ± 1	91 ± 1	89 ± 1	91 ± 2	90 ± 1	90 ± 1
Insulin (mU/L)[a]	12 (8-18)	9 (6-15)*	16 (12-25)	18 (12-24)	17 (13-21)	20 (13-29)	14 (8-21)	17 (12-24)
HOMA[a]	2.8 (1.9-4.0)	2.0 (1.3-3.3)*	3.6 (2.6-5.1)	3.8 (2.6-5.4)	3.5 (2.6-4.5)	4.5 (2.7-7.2)	3.3 (2.0-4.6)	3.9 (2.5-5.0)
Leptin (μg/L)[a]	19 (14-35)	17 (9-30)*	21 (13-35)	27 (15-41)	23 (16-37)	32 (24-56)	31 (15-46)	44 (33-61)*
AST (U/L)[a]	11 (9-12)	9 (8-12)*	10 (8-14)	10 (8-24)	11 (9-21)	15 (9-24)*	10 (8-15)	16 (10-25)*
ALT (U/L)[a]	12 (10-15)	9 (8-13)*	14 (11-18)	16 (12-26)	13 (11-20)	20 (13-33)*	14 (11-18)	19 (15-25)*
NAFLD (%)	23	5*	16	19	19	29	12	16

Data as mean and standard error of the mean or percentage.
[a] Not normally distributed variable; data as median and 25th/75th percentile.
* P less than .05, baseline compared with 1 year later.

significantly correlated to changes of ALT (r = 0.39) and AST (r = 0.45) (Fig. 1). In direct multiple regression analysis adjusted to BMI, age, sex, pubertal stage, and lifestyle intervention (explained variance of the model: r^2 = 0.13), changes of ALT significantly related to leptin (b coefficient: 0.05; 95% CI ±0.03; P = .004) but not to HOMA (b coefficient: −0.01; 95% CI ±0.58; P = .763). Changes of AST were significantly related to leptin (b coefficient: 0.05; 95% CI ±0.03; P = .017) but not to HOMA (b coefficient: 0.09; 95% CI ±0.59; P = .949) in direct multiple regression analysis adjusted to BMI, age, sex, pubertal stage, and lifestyle intervention (explained variance of the model: r^2 = 0.08).

Analyzing the relationships between transaminases, weight status, leptin, and HOMA index, only the 30 children with suspected NAFLD demonstrated in univariate analyses that the changes of SDS-BMI significantly correlated to changes of ALT (r = 0.54) and AST (r = 0.38). Changes of leptin but not changes of HOMA significantly correlated to changes of ALT (r = 0.63) and AST (r = 0.69). In direct multiple regression analysis adjusted to BMI, age, sex, pubertal stage, and lifestyle intervention (explained variance of the model: r^2 = 0.49), changes of ALT significantly related to leptin (b coefficient: 0.27; 95% CI ±0.22; P = .017) but not to HOMA (b coefficient: 0.65; 95% CI ±3.35; P = .688). In these children, changes of AST were significantly related to leptin (b coefficient: 0.21; 95% CI ±0.12; P = .002) but not to HOMA (b coefficient: 0.62; 95% CI ±1.85; P = .494) in direct multiple regression analysis adjusted to BMI, age, sex, pubertal stage, and lifestyle intervention (explained variance of the model: r^2 = 0.48).

At baseline, the children with and without lifestyle intervention did not differ significantly with respect to their transaminases (Table 2). Furthermore, there was no significant difference concerning transaminases at baseline between the children separated by degree of overweight reduction. At baseline, 35 (27%) children of the intervention group had elevated transaminases; and 12 (24%) children without intervention showed elevated transaminases. One year later, 21 (16%) children of the intervention group had elevated transaminases; and 15 (30%) children without intervention demonstrated elevated transaminases.

4. Discussion

This is the first large longitudinal study in overweight children demonstrating a relationship between leptin and transaminases in both cross-sectional and longitudinal analyses in concordance with previous cross-sectional studies [16,24-26]. These relationships were also found in children with suspected NAFLD by ultrasound measurements, supporting the theory that leptin may be involved in the pathogenesis of liver diseases [2,28].

Recent animal studies demonstrated that the hormone leptin, encoded by the obese (*ob*) gene and expressed predominantly by adipocytes, influences the accumulation of lipids and their further oxidation in the liver [28]. In addition, leptin is discussed to promote hepatic fibrogenesis, directly by an autocrine effect on hepatic stellate cells and indirectly by up-regulating the production of transforming growth factor–β from sinusoidal endothelial cells and Kupffer cells

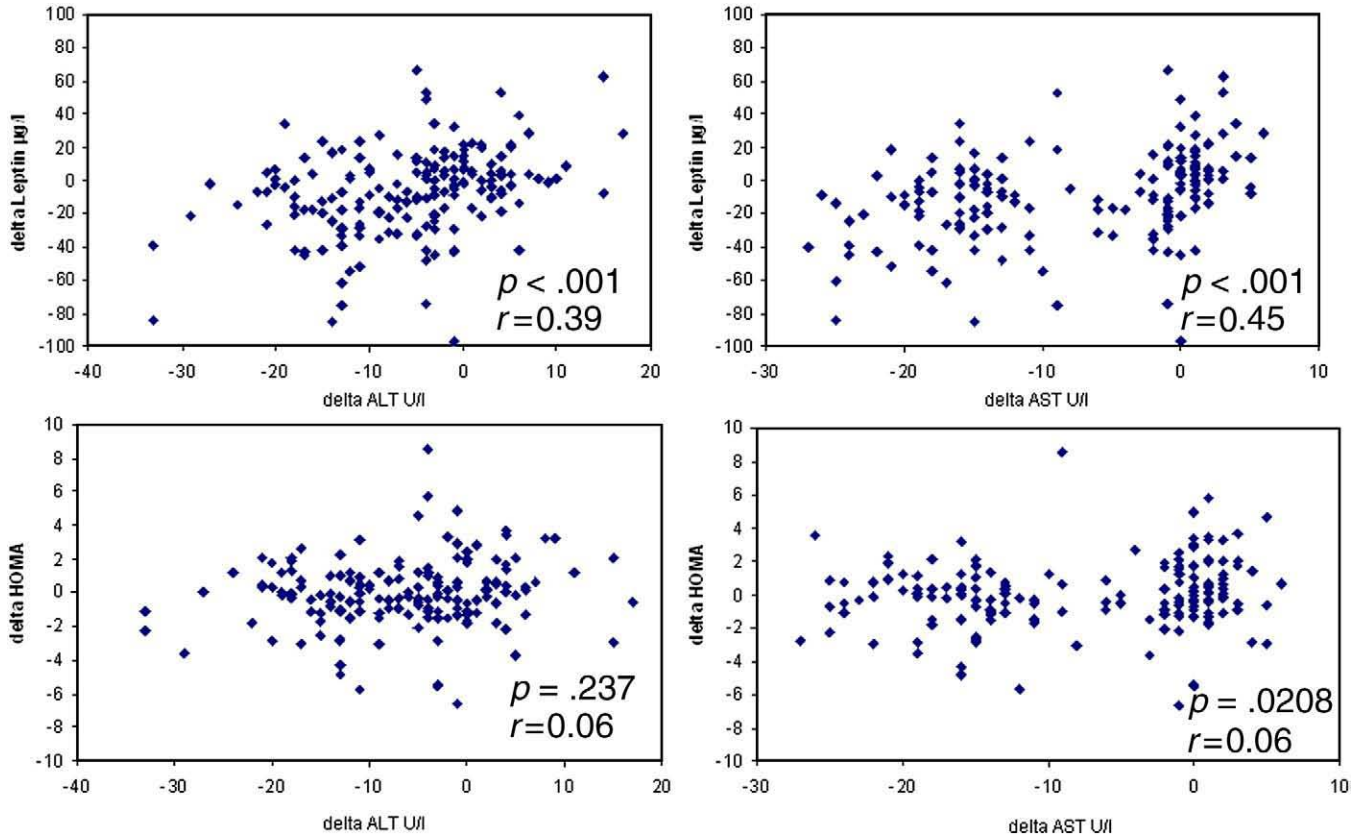

Fig. 1. Associations between changes (Δ) of AST, ALT, leptin, and HOMA of insulin resistance index in the course of 1 year (Δ variable: variable at baseline − variable 1 year later) in 180 overweight children.

[39]. Conversely, leptin-deficient *ob*/*ob* mice have dramatic hepatic steatosis demonstrating hepatic injury in obesity without the influence of leptin [36].

Furthermore, deranged leptin secretion has been suggested to contribute toward switching from insulin sensitivity to insulin resistance. Hepatic insulin resistance and high leptin concentrations are 2 factors that favor the entry of FFA into liver mitochondria [40]. Furthermore, FFA stimulate the hepatic triglyceride synthesis and lead to steatosis [2,17,41]. In addition, there is growing evidence implicating FFA in the production of oxidative stress within hepatocytes [2]. Increased fatty acid β-oxidation and peroxisomal fatty acid oxidation can both lead to increased generation of reactive oxygen species and subsequent lipid peroxidation leading to hepatocellular injury with an increase of transaminases. Leptin also modulates inflammatory states and is involved in the regulation of cytokines [42]. There is growing evidence from both experimental and human studies suggesting a central role of cytokines in the pathogenesis of NAFLD and NASH [43-45].

Besides genetic factors leading to NAFLD [46], insulin resistance is a further suggested factor to be involved in NAFLD and elevated transaminases in obesity [17,24-26,47]. Peripheral insulin resistance increases the supply of FFA to the liver, and hepatic insulin resistance favors the development of oxidative stress leading to hepatic injury. However, we did not find a significant correlation between changes of transaminases and changes of HOMA of insulin resistance, questioning a causal relationship between insulin resistance and elevated transaminases. This discrepancy to previous studies may be explained by the fact that insulin resistance index (HOMA) was used to calculate insulin resistance. Homeostasis model assessment reflects more the peripheral insulin resistance than the hepatic insulin resistance, which seems to be more important in the pathogenesis of NAFLD. Furthermore, clamp studies are the criterion standard to measure insulin resistance [47]. However, because the insulin resistance index HOMA correlated well to clamp studies and has low CVs [48,49], this measurement is a well-established method to study insulin resistance in longitudinal field studies. In addition, based on the second hit hypothesis, insulin resistance plays a key role in a later stage of liver diseases: Insulin is involved in switching from NAFLD to NASH [50], which likely has not occurred in most of our children.

Because in multiple regression analysis changes of leptin and insulin resistance index HOMA explained only a low variance of changes of transaminases, further influencing factors on the levels of transaminases are very likely. For example, family history and ethnic differences suggest a genetic predisposition for elevated transaminases in certain individuals [51,52].

In concordance with previous studies [13,53,54], we found a decrease of transaminases parallel to a decrease of overweight in children who participated in a lifestyle intervention, suggesting that lifestyle interventions are effective in treating elevated transaminases and probably NAFLD. However, we should keep in mind that the diagnosis of NAFLD was not confirmed by liver biopsy in our study. Furthermore, this study was not randomized for participating in the lifestyle intervention. Therefore, we cannot rule out different degrees of motivation between the children with and without lifestyle intervention. Interestingly, the transaminases decreased in children participating in the lifestyle intervention even if the liver enzymes were within the reference range, which was the case in most of these children.

The strengths of this study are its longitudinal design and the large study sample. However, this study has some potentially important limitations. First, BMI percentiles were used to classify overweight. Although BMI is a good measure for overweight, one needs to be aware of its limitations as an indirect measure of fat mass. Second, the liver enzymes were in the reference range in most of our children, questioning a real liver disease. However, NAFLD has frequently been described in children with normal transaminases. Furthermore, the children with suspected NAFLD demonstrated ALT levels higher than AST levels, male predominance, and a tendency for higher FFA and triglyceride levels, which are typical for NAFLD in childhood [2,3]. Most importantly, the diagnosis of liver disease was not confirmed by liver biopsy. Liver biopsies are difficult to perform in large longitudinal studies, also for ethical reasons, as no specific therapy follows histologic diagnosis of NAFLD apart from recommending reduction of overweight that is generally advised to all overweight children. Finally, the levels of transaminases are only an indirect and limited parameter of liver injury; and, for example, liver cirrhosis has been described in children with normal transaminases. However, other measurements such as liver ultrasound are not useful to describe the degree of liver damage.

In summary, reduction of overweight and lifestyle intervention were associated with a decrease of liver enzymes. Leptin but not insulin resistance index HOMA significantly correlated to transaminases in both cross-sectional as well as longitudinal analyses, and the same relationships were observed in obese children with suspected NAFLD. To test the hypothesis of a potential role of leptin in the pathogenesis of liver diseases based on these preliminary observations, further careful histologic studies are necessary.

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