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Research Article

Non-Alcoholic Fatty Liver Disease (NAFLD) in overweight and obese children and adolescents

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Summary

Over the last decades overweight, obesity and non-alcoholic fatty liver disease (NAFLD) in childhood and adolescence increased. NAFLD is strongly associated with insulin resistance, hypertension, dyslipidemia and other pro-atherogenic conditions. It was the aim of the trial to analyze the prevalence of NAFLD, risk factors and comorbidities in a cohort of overweight and obese children and adolescents.

Patients and methods: Totally 79 children and adolescents with overweight/obesity (age 13.3 ± 2.4 years, BMI 33.4 ± 6.5 kg/m², BMI-SDS 2.72 ± 0.52) participated in a structured treatment and teaching program [STTP] (36.1 ± 5.9 days) for weight reduction were included.

Results: NAFLD was diagnosed in 42/79 (53%) of patients. Patients with NAFLD were older (14.0±2.2 vs 12.5±2.5 years, p=0.005), had a higher BMI (36.8±6.4 vs 29.6±4.1 kg/m², p<0.001), BMI-SDS (2.96±0.48 vs 2.45±0.42, p<0.001) and higher fasting C-peptide (0.77±0.33 vs 0.61±0.28 nmol/l, p=0.018), fasting insulin concentrations (23.4±11.4 vs 15.4±12.1 µIU/ml, p=0.004) and HOMA-index (4.80±2.48 vs 3.22±3.46, p=0.022). Moreover patients with NAFLD had higher values in thickness of A. carotis intima. After an in-patient treatment lasting in the mean 5 weeks children/adolescents reached a mean weight reduction of 3.8±2.7 (range, -15.5-+0.8) kg (p<0.001) along with an improvement of risk parameters. The most important factors associated with NAFLD (R-square=0.444) revealed by the multivariate analysis were: body weight (ß=0.407, p<0.001), HOMA (ß=0.265, p=0.014) and HDL-cholesterol (ß=-0.229, p=0.018) at onset of the trial.

Discussion: Children/adolescents with NAFLD were more likely overweight or obese, had more frequently metabolic risk factors and a higher thickness of A. carotis intima media. The data also suggest an improvement in metabolic and cardiovascular risk factors after a significant weight reduction.

Introduction

Over the last two decades Non-Alcoholic Fatty Liver Disease (NAFLD) in childhood and adolescence gained more and more interest. Already in 2006 Patton, et al. concluded "Although population prevalence is very difficult to establish, nonalcoholic fatty liver disease (NAFLD) is probably the most common cause of liver disease in the preadolescent and adolescent age group " [1]. A recently published meta-analysis suggested a prevalence ratio for NAFLD in children/adolescents aged 5 to 18 years with obesity relative to those of a "healthy weight" of 26.1 (95% Confidence Interval [CI], 9.4-72.3) [2]. Anderson, et al. found a "pooled mean prevalence of NAFLD in children from general population studies" of 7.6% (95% CI: 5.5-10.3%) and of 34.2% (95% CI 27.8-41.2%) in studies based on child obesity clinics" [3].

Important reasons for the great variability in awareness and prevalence rates of NAFLD are uncertainties in respect of

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diagnosis and a lack of simple, non-invasive diagnostic tests [4]. According to Bellentani and Marino in NAFLD there is an accumulation of fat in the liver without excessive alcohol consumption or other known liver pathologies [5]. Mostly NAFLD is defined by the ultrasonographic appearance of the liver (mild to severe steatosis) [4,6,7]. But, also biomarkers can play an important role: In some studies alanine (ALT) and aspartate aminotransferase (AST) where used [3,8], although Anderson, et al. concluded that "currently" there is "no consensus on the thresholds of liver enzymes that should be used to indicate NAFLD" [3]. Up to date according to Shah, et al. [9], Shakir, et al. [10], Vos, et al. [11] and Chalasani, et al. [12] liver biopsy is the gold-standard approach to determine the presence and severity of NAFLD.

A variety of analyses have shown, that additional to overweight and obesity NAFLD is strongly associated with insulin resistance, hypertension, dyslipidemia and other pro-atherogenic conditions (like inflammatory disorders or endothelial dysfunction) [3,4,13,14]. Pacificio, et al. [13] wrote in 2011: "Pathological studies have shown that atherosclerosis is an early process beginning in childhood [...]. There is a positive correlation between the extent of early atherosclerotic lesions in the [...] carotid arteries and cardiovascular risk factors [...]". The "Guide for General Practitioners" [10] concluded: "Successful management of pediatric NAFLD requires that clinicians identify children with the highest risk through early screening, understand the comorbidities, and offer a multi-disciplinary treatment approach that emphasizes diet and physical activity modification [...]." On this background it was the aim of the present trial to analyze the prevalence of NAFLD, risk factors and comorbidities in a cohort of overweight and obese children and adolescents admitted to a specialized hospital.

Patients and methods

Totally 79 children and adolescents with overweight and obesity successively admitted to our hospital were included in the trial (inclusion criteria: BMI [body mass index]/BMI-SDS [body mass index standard deviation score] > 97. Percentile [15] and/or diagnosis for admittance: code according to ICD-10-GM-2019 "E66.0", http://www.icd-code.de/icd/code/ICD-10-GM.html). The patients participated in a structured treatment and teaching program [STTP] for weight reduction [15,16]. The STTP was evaluated and demonstrated a good long-term effect (weight reduction and stabilization) over a period of 12 months [17,18]. Further details of the study protocol used in the present trial were published in 2019 [19].

Schedule of the trial

At the beginning of the trial and at the end of the inpatient treatment period (36.1±5.9 [22-57] days) the following examinations were performed:

1. In all patients physical examinations were performed.

2. Measurements of height and weight were assessed with patients wearing light clothing and without shoes. BMI and BMI-SDS were calculated according to the formulae "BMI=kg/m²" and "BMI-SDS=([BMI/$M_{(t)}$]$L_{(t)}$-1)/($L_{(t)}$*$S_{(t)}$" ($M_{(t)}$, $L_{(t)}$ and $S_{(t)}$ are pre-defined parameters depending on $age_{(t)}$ and sex [15].

3. Body composition analyses were done using a Body composition analyzer (BC418MA, TANITA Europe GmbH, Sindelfingen, Germany).

4. Blood pressure in the sitting position was measured after the patients had rested for 10 min by using a standard sphygmomanometer according to the World Health Organization (WHO) recommendations [20]. In all patients a 24-hour-monitoring was performed (Premo Trend, Zimmer Elektromedizin, Neu-Ulm, Germany).

5. Ultrasound examination (Siemens Acuson X300PE, München, Germany): On ultrasound images the diagnosis steatosis hepatis (fatty liver) was given, if the liver looks brighter than normal (but not lumpy or shrunken like cirrhotic livers). NAFLD was diagnosed according to ultrasonographic appearance of fatty liver [4] without anamnesis of alcohol consumption or other known liver pathologies [5].

6. Measurements of carotid intima-media thickness (IMT) were done by one physician performing 5 measurements on each side and calculating the mean. Definition of normal values was according to the German standard [21].

7. Blood-glucose (glucose-oxidase-method, Speedy, Müller Gerätebau GmbH, Saalfeld, Germany) and HbA1c-measurements (DCA2000®-method, Bayer Diagnostics, Leverkusen, Germany, following DCCT-standard [HbA1c/mean normal] x mean according to the DCCT-standard [22]) were done directly in the laboratory of the Medigreif Inselklinik Heringsdorf GmbH using blood samples derived from finger pricking. Additionally venous blood samples taken in the morning of the first day after hospital admission (at onset/beginning of the trial) and at the last day of patients' in-hospital stay (at the end of the trial) following an overnight fasting period were analyzed (Laborgemeinschaft IMD, Prof. Dr. med. G. Menzel, Pappelallee 1, 17489 Greifswald, Germany) from all patients. The following parameters were analyzed: total cholesterol (TC), low density lipoprotein (LDL)–cholesterol, high density lipoprotein (HDL)–cholesterol, triglycerides (TG) (enzymatic color test), uric acid (enzymatic color test); C-reactive protein (turbidimetry); creatinine (enzymatically); estimated glomerular filtration rate (GFR) (186 x [creatinine (mgdl)]$^{-1.154}$x[age(years)]$^{-0.203}$,MDRD-formula according the recommendations of the Deutsche Diabetes-Gesellschaft [DDG] [23]); asparte-aminotransferase (ASAT), alanine-aminotransferase (ALAT); gamma-glutamyl-transferase (gGT) (kinetic color test); insuline (chemiluminescence assay); thyroidea stimulating hormone (TSH), free triiodothyronine (fT3); free

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thyroxine (fT4)* (chemiluminescence assay); C-peptide (chemiluminescence assay). The HOMA calculation is an iterative structural model to estimate the ß-cell function together with insulin sensitivity. HOMA was calculated according to the formula: HOMA = (fasting plasma insulin x fasting plasma glucose)/22.5 (http://www.dtu.ox.ac.uk/homacalculator/index.php, 27.06.2019).

Ethics vote

The trial was approved by the local ethics committee (Auswirkungen einer sechswöchigen spezifischen Rehabilitationsmaßnahme bei Kindern und Jugendlichen mit Übergewicht und Adipositas auf Gewichtsverlauf, Veränderungen von Risikoparametern und Mikrobiom, Reg.-No. BB 119/17, 28.07.2017, Universitätsmedizin Greifswald, Ethikkommission, Greifswald).

Statistical analysis

Statistical analysis was performed using SPSS®22.0 (Statistical Package for Social Science, SPSS, Chicago, IL, USA). Values showing normal distribution were registered as Mean (MW) ± Standard Deviation (SD), non-normal distributed values were given as median and range. Comparisons were evaluated with chi-square-test or Fisher's exact test in case of frequencies less than 5. Paired Student's t-test and Wilcoxon-test were used to compare the mean values. Correlations were calculated according to Pearson and for multivariate analyses ANOVA models were used. Significance was set at $p<0.05$. Two-tailed significance tests were used throughout.

Results

Baseline characteristics

The baseline characteristics of the patients in respect of age, sex, height, weight, BMI, BMI-SDS and duration of in-house rehabilitation are given in Table 1.

Additionally to overweight/obesity 15 patients have diagnoses like diabetes mellitus or arterial hypertension (Table 2).

Patients with vs without NAFLD, additional diagnoses and changes of body weight, BMI and body composition.

In the present cohort NAFLD was diagnosed in 42/79 (53%) of patients. In respect of additional diagnoses there was a tendency ($p<0.05$) towards more diagnoses in patients with vs without NAFLD (E 03.9: n=1 vs n=1, E 10.9: n=1 vs n=0; E 11.9: n=4 vs n=1; I 10.9: n=3 vs n=1; J 45.9: n=4 vs n=1, L 20.9: n=1 vs n=0), there were no differences regarding sex (females: with NAFLD vs without NAFLD: 45% vs 51% [p=0.59]).

Patients with NAFLD were older (14.0±2.2 vs 12.5±2.5 years, p=0.005) and higher (1.64±13.6 vs 1.57±12.2 m, p=0.022) than patients without NAFLD. Patients with NAFLD had a higher body weight, BMI, BMI-SDS, body fat mass and percentage of body fat, but also a higher fat-free mass. Moreover, patients with NAFLD had higher fasting C-peptide (0.77±0.33 vs 0.61±0.28 nmol/l, p=0.018), fasting insulin concentrations (23.4±11.4 vs 15.4±12.1 µIU/ml, p=0.004) and HOMA-index (4.80±2.48 vs 3.22±3.46, p=0.022).

Table 1: Baseline characteristics of 79 patients with overweight and obesity studied.

Paramter	MW±SD	Min.	Max.
Number (n)	79	/	/
Age (years)	13.3 ± 2.4	7.4	18.0
Females (n[%])	38 (48.1)	/	/
Duration of in-house treatment period (days)	36.1 ± 5.9	22	57
Height (m)	1.61 ± 13.3	128	190
Body weight (kg)	88.6 ± 27.4	39.1	182.1
BMI (kg/m²)	33.4 ± 6.5	21.6	50.4
BMI-SDS	2.72 ± 0.52	1.5	3.8

Table 2: Additional diagnoses in 79 patients with overweight or obesity studied.

Code according to ICD-10-GM-2019*	Disease	Number (n/ %)	Medication in n patients
E 03.9	Hypothyreosis	2 (2%)	Thyroxine n=2
E 10.9	Diabetes mellitus type 1	1 (1%)	Insulin n=1
E 11.9	Diabetes mellitus type 2	5 (6%)	Metformin n=4
I 10.9	Arterial hypertension	4 (5%)	ACE-inhibitor n=2
J 45.9	Asthma bronchiale	5 (6%)	ß-Sympatho-mimetic n=5
L 20.9	Atopic dermatitis	1 (1%)	No medication

*(http://www.icd-code.de/icd/code/ICD-10-GM.html), 22.08.2019

After an in-patient treatment lasting in the mean 5 weeks, in the total group children and adolescents reached a mean weight reduction of 3.8±2.7 (range, -15.5-+0.8) kg ($p<0.001$) accompanied by a reduction of body fat mass. At baseline the mean weight percentile of all patients studied was 98.7±1.83 (range, 83.0-99.5). Both groups, patients with and without NAFLD, reached a significant reduction of body weight, BMI and body fat during the in-patient rehabilitation procedure. In all groups these changes were accompanied by an improvement of HOMA-index (Table 3).

Patients with NAFLD had more frequently laboratory abnormalities (i.e. higher concentrations of uric acid, higher triglycerides, lower HDL-cholesterol levels, higher CRP concentrations, higher ALAT, higher ASAT, higher HbA1c, higher C-peptide, higher insulin concentrations, lower beta-cell function, lower insulin sensitivity with a higher level of insulin resistance). Moreover patients with NAFLD had higher values in thickness of A. carotis intima too, but there were no differences in respect of blood pressure values. After participation in an in-patient treatment program in both groups most parameters improved (Table 4).

Multivariate analyses

The most important factors associated with NAFLD (R-square=0.444) revealed by the multivariate analysis were: body weight (ß=0.407, $p<0.001$), HOMA (ß=0.265, p=0.014) and HDL-cholesterol (ß=-0.229, p=0.018) at onset of the trial.

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Table 3: Patients with vs without NAFLD and changes of body weight, BMI and body composition.

	Patients with NAFLD (n=42)			Patients wihout NAFLD (n=37)				
	Onset of the trial	End of the Trial	Onset vs end	Onset of the Trail	End of the trail	On set vs end	Onset, with vs without NAFLD	End, With Vs without NAFGLD
Parameter	MW± SD	MW± SD	P-value			P-value	P-value	P-value
Weight (kg)	100.9±276	96.3±25.7	<0.001	74.7±19.6	71.7±18.7	<0.001	<0.001	<0.001
BMI(kg/m2)	36.8±6.4	35.1±5.8	<0.001	29.6±4.1	28.4±3.9	<0.001	<0.001	<0.001
BMI SDS	2.96±0.48	2.82±0.52	<0.001	2.45±0.42	2.30±0.44	<0.001	<0.001	<0.001
Weight reduction (kg)	/	-4.48±3.01	/	-3.07±2.15	/	/	/	0.021
Body composition								
Percentage of body fat (%)	44.6±7	41.2±6.2	<0.001	37.2±6.4	34.4±6.1	<0.001	<0.001	<0.001
Fat mass (kg)	45.6±16.1	40.1±13.5	<0.001	28.9±11.6	26.1±9.9	<0.001	<0.001	<0.001
Fat free mass (kg)	56.2±15.1	56.2±14.9	<0.001	46.2±9.7	46.0±10.8	<0.001	<0.001	<0.001

Table 4: Laboratory values at onset vs end of the trial, thickness of A. carotis intima media and blood pressure of patients with and without NAFLD.

	Patients with NAFLD (n=42)			Patients wihout NAFLD (n=37)				
	Onset of the trial	End of the Trial	Onset vs end	Onset of the Trail	End of the trail	On set vs end	Onset, with vs without NAFLD	End, With Vs without NAFGLD
Parameter	Mean± SD	Mean± SD	P-value	Mean± SD	Mean± SD	P-value		P-value
Uric acid (Umol/sl)	383.1+77.5	35.8+85.9	<0.01	35.4+87.2	317.8+69.4	<0.01	0.131	0.029
Triglycerides(mmol/l	1.42+0.58	1.09+0.33	<0.01	1.13+0.46	1.01+0.42	<0.01	0.018	0.349
Total cholesterol (mmol/l	4.36+0.82	3.63+0.69	<0.01	4.29+0.47	3.65+0.61	<0.01	0.632	0.908
HDL-cholesterol(mmol/l)	1.14+0.26	1.06+0.18	<0.01	1.28+0.24	1.16+0.23	<0.01	0.023	0.043
LDl-cholesterol(mmol/l)	3.00+0.71	2.37+0.60	<0.01	2.87+0.52	2.29+0.47	0.003	0.396	0.569
LDL/HDL- quoyient	2.72+0.78	2.27+0.59	<0.01	2.36+0.78	2.03+0.53	<0.01	0.047	0.083
Fasting blood glucose(mmoll/l)	4.64+0.46	4.44+0.59	0.028	4.45+0.61	4.30+0.46	0.001	0.131	0.253
Blood glocose 2h following oGTT(mmol/l)	6.03+1.19	/		5.85+0.79	/	/	0.085	/
HBA1c (%)	5.69+0.93	5.55+0.74	0.06	5.35+0.32	5.26+0.35	0.004	0.042	0.035
HbA1c (mmol/l)	38.7+10.19	37.12+8.10	0.05	35.04+3.45	33.76+3.08	0.015	0.043	0.022
c-peptide (nmol/l)	0.77+0.33	0.71+0.25	0.238	0.61+0.28	0.57+0.17	0.001	0.018	0.013
Insulin concentration (ulU/ml)	23.4+11.4	19.33+9.75	0.071	15.4+12.1	12.25+5.25	0.02	0.004	0.001
B-cell function (%)	242.98+67.24	22.9+78.5	0.0835	181.5+68.9	176.97+55.4	<0.01	<0.005	0.002
Insulin sensitivity (%)	40.7+20.6	52.35+29.10	0.085	77.5+46.0	80.22+41.94	0.003	<0.005	0.002
HOMA	4.80+2.48	2.42+1.11	0.049	3.22+3.46	1.52+0.64	<0.01	0.022	<0.01
TSH (ul U/ml)	2.93+1.08	/	/	3.02+1.55	/	/	0.73	/
fT3 (pg/ml)	3.89+0.66	/	/	3.92+0.61	/	/	0.798	/
fT4 (ng/dl)	1.06+0.11	/	/	1.04+0.13	/	/	0.429	/
GFR	85.7+17.9	91.03+18.10	0.01	83.5+10.9	87.97+12.28	0.001	0.539	0.424
Creatinine (µm ol/l)	54.2+10.2	52.67+9.28	0.022	52.1+9.8	49.97+8.36	0.002	0.359	0.211
Cystatinc (mg/l)	1.04+0.18	0.98+0.17	0.01	1.03+0.14	0.98+0.14	0.001	0.989	0.989
ASAT (µm ol/sl)	0.52+0.31	0.44+0.20	0.04	0.43+0.12	0.38+0.11	0.027	0.119	0.141
ALAT (µm ol/sl)	0.44+0.20	0.65+0.47	0.066	0.38+0.11	0.47+0.33	0.631	0.013	0.076
gHT (µm ol/sl)	0.44+0.22	0.34+0.23	<0.01	0.39+0.39	0.29+0.34	0.001	0.448	0.498
Thickness of A.carotisintima media (mm)	0.45+0.0-08			0.40+0.07			0.014	
Mean systolic blood pressure during 24h (mmhg)	1.32+11.0	/	/	129.4+12.5	/	/	0.255	/
Mean diastolic blood pressure during 24h (mmhg)	77.1+7.7	/	/	76.1+9.6	/	/	0.606	/

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All other parameters analyzed in the model (sex, age, height, BMI, BMI-SDS, fat mass, percentage of body fat, fasting blood glucose, blood glucose after oGTT [performed not in patients with known diagnosis of diabetes mellitus], C-peptide, insulin concentration, ß-cell function, insulin sensitivity, insulin resistancy, HOMA, triglycerides, total cholesterol, LDL-cholesterol, LDL/HDL-cholesterol-quotient, ASAT, ALAT, gGT, uric acid, CRP, TSH, fT3, fT4, thickness of A. carotis intima-media, systolic and diastolic blood pressure during a 24 hours-period) showed no associations.

Discussion

Children and adolescents with NAFLD had a tendency towards more diagnoses (diabetes mellitus, arterial hypertension, asthma bronchiale), they were older, higher, had a higher body weight, BMI, BMI-SDS, body fat mass and percentage of body fat. Moreover, patients with NAFLD had higher fasting C-peptide, fasting insulin concentrations and a mean HOMA-index. Additionally children and adolescents with NAFLD had more frequently other laboratory abnormalities too (i.e. higher concentrations of uric acid, higher triglycerides, lower HDL-cholesterol levels, higher CRP concentrations, higher ALAT, higher ASAT, higher HbA1c) and higher values in thickness of A. carotis intima. All these data suggest that NAFLD is a substantial problem in overweight and obese children and adolescents.

During the last decades the prevalence of NAFLD in children and adolescents increased [3]. According to Aggarwal, et al. [24] and Goyal, et al. [14] it is already one of the leading causes for chronic liver diseases in this age group. In 2008 in a case-control study of 150 overweight and obese children Schwimmer, et al. [25] found that NAFLD was strongly associated with metabolic syndrome. In a review published in 2011 Pacifico, et al. [13] demonstrated an elevated risk for NAFLD in children and adolescents with abdominal obesity, type 2 diabetes, dyslipidemia and insulin resistance. In a recently published study with 520 obese children, aged 3.4-17.1 years, Han, et al. [6] revealed in those with NAFLD higher fasting C-peptide and insulin concentrations along with a higher HOMA index. In stepwise multiple logistic regression models the authors showed that fasting C-peptide was an independent indicator for NAFLD. Moreover, in children with overweight and obesity the data of Schwimmer, et al. [25] also suggest an increased risk for cardiovascular abnormalities. Similar results were found by Mohamed, et al. [7]: In their cohort 62% of overweight and obese children with NAFLD had a metabolic syndrome. All the findings of Schwimmer, et al. [25], Pacificio, et al. [13], Han, et al. [6] and Mohamed, et al. [7] are in agreement with the results of our present study.

Following the literature there is still discussion about the diagnostic criteria for NAFLD [3,6,9,10,11,12,14]. After the exclusion of other causes of liver disease (such as viral hepatitis, autoimmune liver diseases, Wilson disease, hepatotoxic agents) liver biopsy remains the gold standard for the diagnosis of NAFLD [9,11,12]. However, liver biopsy is associated with some risks. Among these are bleedings, pains, leakages of bile or formation of arteriovenous fistulas [9,11,12]. On this background in multiple studies [3] NAFLD was diagnosed non-invasive. Like in the present study Han, et al. [6], Mohamed, et al. [7] and Kim, et al. [4] used ultrasound imaging for diagnoses of NAFLD. Hence, although ultrasound examination is not a gold standard for diagnosis [9,11,12] the method seems to be suitable in cross-sectional studies like the present one.

Interestingly, our data also suggest an improvement in metabolic and cardiovascular risk factors after a significant weight reduction. According to Pacificio, et al. [13] "In children, the cardiovascular system remains plastic and damage-reversible if early and appropriate interventions are established effectively." On this background the weight reduction following a rehabilitation procedure [19] along with the improvement in metabolic and cardiovascular risk profile maybe lead to an improvement in long-term outcome. This suggestion is in accordance with the "Overview of updated practice guidelines for pediatric nonalcoholic fatty liver disease" updated in July 2018 ("Although lifestyle modification (ie, diet and exercise) are recommended as first-line approaches in the management of pediatric NAFLD..." [9]). However, more and more rigorous studies over longer periods of time are required in order to understand these effects and clinical outcome of patients. Additionally Shah, et al. [9] "expected that promising therapeutic agents for NAFLD will transform the way clinicians care for children with this disease."

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