Health Education and Care

Research Article ISSN: 2398-8517

Effects of weight reduction in overweight and obese children and adolescents

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Introduction

In the last decades, in many countries worldwide childhood and adolescent levels of overweight and obesity have reached epidemic status. According to "WHO European Childhood Obesity Surveillance Initiative" [1] the prevalence of overweight (including obesity) ranged from 18% to 57% among boys and from 18% to 50% among girls aged 6 to 9 years. The highest overweight prevalence was found in Southern European countries [1]. In Greece for example, the prevalence of abdominal obesity in 7-year-old children was about 25% in 2010 [2]. A lower, but still very high prevalence was found in Germany: Here, in the period from 2014 up to 2017, the prevalence of overweight/obesity was 15.4%/5.9% in children and adolescents aged 3 to 17 years [3], yet no increase in the period from 2003 to 2006 was found. Similar figures were reported by Ogden, *et al.* [4]: In their cohort the prevalence of overweight and obesity among U.S. children/adolescents was 16.9%, but there was no further increase from 2003/2004 to 2011/2012 [4]. Interestingly, in most of the countries analyzed overweight and obesity were more prevalent in lower social classes [5-7].

These relatively high prevalences of overweight and obesity have also led to significant numbers of overweight- and obesity-related comorbidities at early ages. These comorbidities include metabolic disorders such as dyslipidaemia, type 2 diabetes mellitus, arterial hypertension, liver alterations and increased inflammatory activity as well as a reduced quality of life and well-being [8-21]. In a cohort of Japanese school children there was a clear association between obesity, higher levels of lipids (triglycerides LDL-cholesterol, HDL-cholesterol) and hs-CRP as marker of inflammatory disorders [22]. In a paper published in 2018, Yu, *et al.* found among a cohort of 408 adolescents (mean age of 13.2 years) with a body-mass index percentile of 98.0, a prevalence of non-alcoholic fatty liver disease (NAFLD) of 26.0% [23]. Yue S, *et al.* also revealed that "obese children with NAFLD are more susceptible to osteoporosis than children with only obesity" [24]. In a recently published review Coakley [20], using post-mortem studies of obese children, reported on coronary atheroma and other signs of premature cardiovascular diseases ("fatty streaks were found in the coronary arteries of 50% of 2-15-year-old children, while actual coronary atheroma were found in 8% of this age group. In the 16-20-year-old group, coronary atheroma was present in 33%", [20]). Additionally insulin resistance and a pre-diabetic state seem to be strongly associated to premature type 2 diabetes mellitus and its increasing incidence [21,25-26]. Van der Aa, *et al.* [27] found, in a meta-analysis of children and adolescents, prevalence rates of insulin resistance between 3.1 and 44%. Although there were significant differences between the studies all results demonstrated a notably elevated prevalence rate in overweight and obese children [27].

These consequential data highlight the importance and challenge of developing improved intervention and evaluation methods for effective and long-term weight reduction programs. The risk factors must also be assessed and analyzed at a very early age. Thus it was the aim of the present trial to analyze the effectiveness of an in-house 6-week weight reduction program for overweight and obese children and adolescents in a specialized hospital. In addition to weight reduction and changes in body composition, risk factors for obesity associated co-morbidities such as blood pressure, lipids, insulin resistance and parameters of liver function were studied.

Patients and methods

Totally 124 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 [Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter [AGA], 2012 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 (Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter [15,28]. The STTP was evaluated and demonstrated a good long-term effect (weight reduction and stabilization) over a period of 12 months [29,30].

Structure of the STTP

In respect of weight reduction and long-term goal achievement multicomponent interventions have been highlighted as essential for lifestyle modification (Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter [15,28]. The STTP should empower patients to make behavioral changes. Strategies should include and combine aspects of diet, physical activity and weight maintenance techniques (Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter [15,28]. The STTP (Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter [15,28] used in the present trial consisted of 28 therapeutic sessions

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Received: October 15, 2019; **Accepted:** October 29, 2019; **Published:** October 31, 2019

with a duration of 45 minutes each. The main topics and techniques of the therapeutic sessions were the following:

1. Self-esteem

- 2 therapeutic sessions
- Brief discussion on self-esteem
- Feelings, individual goals

2. Eating behavior

- 10 therapeutic sessions
- Patients educated on healthy eating, portion size
- Patients taught to read and interpret food labels
- Patients trained in preparing their meals

3. Physical activity

- 8 therapeutic sessions
- Patients educated in healthy physical activity
- Patients trained in physical activity during daily life
- Self-monitoring
- 2 therapeutic sessions
- Food, physical activity and mood diary
- Identification of triggers influencing eating behavior, physical activity and mood

4. Goal setting

- 1 therapeutic session
- Encouraging patients to make short- and long-term goals, brainstorming and to define individual steps with regard to diet and physical activity

5. Cognitive re-structuring

- 2 therapeutic sessions
- Discussion of positive and negative thoughts and beliefs, interactions with behavioral changes, goals and strategies for maintaining weight reduction

6. Maintenance

- 3 therapeutic sessions
- Discussion and development of general and individual strategies for long-term weight reduction and avoiding relapse

As support of the STTP teaching materials were developed [15]. During the therapeutic sessions the children and adolescents used these materials. They used them also in homework for repetition. The details of the program and its evaluation were published by Schiel, *et al.* in 2008 [30].

Schedule of the trial

At the beginning of the trial and at the end of in-house rehabilitation during inpatient treatment 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 (Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter [28].
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 [31]. 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).

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 [32].

6. 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 [33]) 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 parameters analyzed and the methods of measurement are shown in (Table 1).

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-tests or Fisher's exact test in case of frequencies less than 5. Paired Student's t-test and Wilcoxon-tests were used to compare the mean values. Correlations were calculated according to Pearson and for multivariate analyses

Table 1. Laboratory parameter and method of measurement

Parameter	Method
Total cholesterol (TC)	Enzymatic color test
Low density lipoprotein (LDL) – cholesterol	Enzymatic color test
High density lipoprotein (HDL) – cholestrerol	Enzymatic color test
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])$^{-0.203}$ **
Cystatine C	Immunoturbidimetry
Asparte-aminotransferase (ASAT)	UV-test
Alanine-aminotransferase (ALAT)	UV-test
Gamma-glutamyl-transferase (gGT)	Kinetic color test
Insuline	Chemiluminescence assay
Thyroidea stimulating hormone (TSH)*	Chemiluminescence assay
Free triiodothyronine (fT3)*	Chemiluminescence assay
Free thyroxine (fT4)*	Chemiluminescence assay
C-peptide	chemiluminescence assay
*laboratory parameter was solely measured at onset of the trial. **MDRD-formula according the recommendations of the Deutsche Diabetes-Gesellschaft (DDG) (Rüster et al., 2015)	

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 2). (Table 3) shows the educational levels of the 124 children and adolescents.

Changes of body weight, BMI and body composition

After an in-patient treatment lasting in the mean 5 weeks, children and adolescents reached a mean weight reduction of 4.2 ± 3.1 (range, -15.9-+0.9) kg ($p<0.001$) accompanied by a reduction of body fat mass (Table 4). At baseline the mean weight percentile of the patients was 98.9 ± 1.86 (range, 83.0-99.5). 8/124 (7%) of the children and adolescents were below the 97th percentile, 39/124 (31%) of the patients ≥ 97th ≤ 99th percentile, and 77/124 (62%) >99th percentile.

Analyses of risk parameters for metabolic and cardiovascular complications

In total about 70% of the children and adolescents (87/124) showed non-normal laboratory parameters as well as higher blood pressure values and/or an increased thickness of A. carotis intima media or steatosis hepatis. Three 3 patients were treated with antihypertensive drugs (ACE-inhibitors). Mean thickness of carotid intima-media was 0.43 ± 0.08 (range, 0.30 – 0.60) mm (n=68); n=46/68 (67%) of the patients showed a normal range (<0.45mm), 6/68 (8%) slightly elevated (≥ 0.45-≤ 0.50mm) and 17/68 (25%) an elevated (>0.50mm) thickness (Table 5).

Laboratory parameters

Lipids

During the in-house rehabilitation there was a significant reduction in all lipid sub-groups. Moreover, the percentage of children and adolescents with concentrations of total cholesterol, LDL-cholesterol and triglycerides above the recommended level [21] decreased significantly. However, in contrast to international recommendations [21], following participation in the structured treatment and teaching program (Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter [15,28] for patients with overweight and obesity, there was no increase, but a decrease of HDL-cholesterol in the present cohort (Table 6).

Glucose metabolism

At initiation of the trial 4 patients (3%) presented with diabetes mellitus type 2 (code according to ICD-10-GM-2019 "E11.9", http://www.icd-code.de/icd/code/ICD-10-GM.html) in addition to overweight/obesity. Two of these patients had an HbA1c higher than 6.5% and all were treated with antidiabetic drugs (female, 10 years old, BMI-SDS 2.1, HbA1c 6.2% [44.3 mmol/mol], Metformin; male, 15 years old, BMI-SDS 3.5, HbA1c 6.1% [43.2 mmol/mol], Metformin; female, 13 years old, BMI-SDS 2.8, HbA1c 10.4% [90.2 mmol/mol], Metformin, insulin; male, 16 years old, BMI-SDS 3.1, HbA1c 8.3% [67.2 mmol/mol], Metformin). In all patients fasting blood glucose levels were analyzed at the beginning of the trial. In the patients without the diagnosis of diabetes mellitus an oGTT [34] was also performed. Following the oGTT [34] there was no additional diagnosis of diabetes mellitus. However, following the oGTT [34] in 1 (1%) patient there was a diagnosis of impaired glucose tolerance [34]. On the other hand, in 23% of the patients the values for HOMA were elevated, indicating clinically relevant insulin resistance with risk for type 2 diabetes mellitus. After rehabilitation and weight loss the percentage decreased by up to 14% ($p=0.015$) (Table 6). The other parameters analyzed are shown in (Table 6).

Parameters of liver function

The parameters of liver function are shown in (Table 7).

Correlation analyses

In the total cohort of 124 children and adolescents with overweight and obesity there were significant correlations between BMI-SDS and body fat mass ($r=0.74$, $p<0.001$), percentage of body fat ($r=0.70$, $p<0.001$), concentration of uric acid ($r=0.19$, $p=0.035$), triglycerides ($r=0.21$, $p=0.023$), LDL/HDL quotient ($r=0.19$, $p=0.044$), eGFR ($r=-0.19$, $p=0.037$), Cystatin C ($r=0.23$, $p=0.015$), ASAT ($r=0.24$, $p=0.008$), ALAT ($r=0.23$, $p=0.013$), gGT ($r=0.26$, $p=0.005$), C-peptide ($r=0.24$, $p=0.008$), insulin concentration ($r=0.23$, $p=0.013$), ß-cell function ($r=0.24$, $p=0.011$), insulin sensitivity ($r=-0.25$, $p=0.008$), insulin

Table 2. Baseline characteristics of 124 patients with overweight and obesity studied

Paramter	MW ± SD	Min.	Max.
Number (n)	124	/	/
Age (years)	13.4 ± 2.8	6.1	20.1
Females (n [%])	66 (53.2)	/	/
Duration of in-house rehabilitation (days)	35.9 ± 6.7	22	57
Height (m)	1.61 ± 13,7	126	190
Body weight (kg)	88.5 ± 27.1	39,1	182,1
BMI (kg/m²)	33.3 ± 6.4	21,6	50,4
BMI-SDS	2.71 ± 0.51	1,5	4,2

Table 3. Educational level of 124 patients with overweight and obesity studied

Educational level	Number (n)	Percentage (%)
Special school	11	9
Elementary school	33	27
Medium school	40	32
Higher school	16	13
Vocational training/other activities	24	19

Table 4. Changes of weight, BMI, BMI-SDS and body composition during the period of inpatient treatment (baseline vs at the end of inpatient treatment) in 124 children and adolescents

	Baseline			At the end of inpatient treatment			
Parameter	**MW ± SD**	**Min.**	**Max.**	**MW ± SD**	**Min.**	**Max.**	**p-value**
Weight (kg) (n=124)	88.5 ± 27.1	39.1	182.1	84.3 ± 25.1	37.8	173.5	<0.001
BMI (kg/m²) (n=124)	33.3 ± 6.4	21.6	50.4	31.7 ± 5.9	21.8	48.1	<0.001
BMI-SDS (n=124)	2.71 ± 0,51	1.5	4.2	2.55 ± 0.53	1.3	4.1	<0.001
Body composition							
Percentage of body fat (%) (n=122)	41.0 ± 7.6	23.3	62.8	37.9 ± 7.0	18.1	57.1	<0.001
Fat mass (kg) (n=122)	37.7 ± 15.9	12.4	80.8	33.2 ± 13.6	12.4	74.4	<0.001
Fat-free mass (kg) (n=122)	51.2 ± 13.6	26.7	104.5	51.5 ± 13.7	25.2	99.1	0.31

Table 5. Laboratory values and risk parameters of 124 patients with overweight and obesity studied

Paramter	**MW ± SD**	**Min.**	**Max.**
24-h-blood pressure systolic (mmHg)	130.5 ± 11.6 (n=116)	102	160
24-h-blood pressure systolic ≥ 135 mmHg (n/%)	41 (35%)	/	/
24-h-blood pressure diastolic (mmHg)	76.8 ± 8.5 (n=116)	58	110
24-h-blood pressure diastolic ≥ 85 mmHg (n/%)	19 (16%)	/	/
Systolic blood pressure during the day period (mmHg)	134.7 ± 12.6 (n=114)	102	167
Diastolic blood pressure during the day period (mmHg)	80.4 ± 9.7 (n=114)	60	117
Systolic blood pressure during the night period (mmHg)	118.1 ± 15.5 (n=113)	92	186
Diastolic blood pressure during the night period (mmHg)	67.1 ± 11.8 (n=113)	43	119
Carotis-Intima-Media Thickness (mm)	0.43 ± 0.08 (n=68)	0.30	0.60
Carotis-Intima-Media Thickness ≥ 0.45 mm (n/%)	23/68 (32%)	/	/
Steatosis hepatis (n/%)	42/79 (53%)	/	/

Table 6. Laboratory analyses and changes in lipid profiles, glucose metabolism, CRP, renal and thyreoidal parameters in 124 children and adolescents

	Baseline			At the end of inpatient treatment			
Parameter	**MW ± SD**	**Min.**	**Max.**	**MW ± SD**	**Min.**	**Max.**	**p-value**
Lipids*							
Total cholesterol (mmol/l) (n=104)	4.42 ± 0.71	2.7	6.1	3.66 ± 0.61	2.3	5.1	<0.001
Total cholesterol ≥ 5.2 mmol/l (n/%)	17/104 (16%)	/	/	0	/	/	
HDL-cholesterol (mmol/l) (n=104)	1.22 ± 0.24	0.46	1.94	1.11 ± 0.21	0.64	1.70	<0.001
HDL-cholesterol <1.0 mmol/l (n/%)	21/104 (20%)	/	/	34/104 (33%)	/	/	
LDL-cholesterol (mmol/l) (n=104)	3.02 ± 0.69	1.2	4.7	2.30 ± 0.54	1.0	3.7	<0.001
LDL-cholesterol ≥ 2.6 mmol/l (%)	73/104 (70%)	/	/	29/104 (28%)	/	/	
LDL/HDL-quotient (n=104)	2.58 ± 0.80	1.09	5.43	2.14 ± 0.63	0.84	4.06	<0.001
LDL/HDL-quotient ≥ 2.5 mmol/l (n/%)	55/104 (53%)	/	/	27/104 (26%)	/	/	
Triglycerides (mmol/l) (n=104)	1.27 ± 0.50	0.51	3.41	1.07 ± 0.37	0.50	2.35	<0.001
Triglycerides ≥ 1.70 mmol/l (n/%)	22/104 (21%)	/	/	5/104 (5%)	/	/	
Glucose metabolism							
Fasting blood-glucose (mmol/l) (n=105)	4.6 ± 0.5	3.8	6.8	4.4 ± 0.6	3.6	7.5	0.07
oGTT: blood-glucose 2 h after glucose-loading (mmol/l) (n=113)	6.0 ± 1.0	3.3	9.1	/	/	/	/
HOMA (n=102)	3.91 ± 2.74	0.06	21.06	3.26 ± 1.87	0.11	11.81	0.016
No insulin resistancy (HOMA <2.0)	17/102 (17%)	/	/	27/102 (26%)	/	/	0.015
Insulin resistancy possibly (HOMA ≥ 2.0<2.5)	12/102 (12%)	/	/	14/102 (14%)	/	/	0.57
Insulin resistancy very likely (HOMA ≥ 2.5<5.0)	49/102 (48%)	/	/	47/102 (46%)	/	/	0.048
Insulin resistancy (HOMA ≥ 5.0)	24/102 (23%)	/	/	14/102 (14%)	/	/	0.026
HbA1c (%) (n=113)	5.47 ± 0.63	4.60	10.40	5.39 ± 0.58	4.70	9.00	0.016
HbA1c >6.5%	2/113 (2%)	/	/	/	/	/	/
HbA1c (mmol/mol) (n=113)	36.4 ± 6.9	26.80	90.20	35.3 ± 6.2	27.90	74.90	0.007
C-peptide (nmol/l) (n=103)	0.66 ± 0.29	0.10	1.89	0.66 ± 0.24	0.10	1.50	0.887
Other parameters							
Creatinine (µmol/l) (n=103)	54.5 ± 11.0	33	86	52.8 ± 9.8	36	81	<0.001
Estimated glomerular filtration rate (eGFR) (ml/min/1,73m²)	85.2 ± 15.5	56	138	90.8 ± 16.2	55	142	<0.001
Uric acid (µmol/l) (n=106)	369.7±84.6	52	628	333.3 ± 85.9	43	605	<0.001
Hyperuricaemia (≥ 440 µmol/l) (%)	22/106 (21%)	/	/	11/106 (10%)	/	/	0.018
CRP (mg/dl)* (n=118)	3.28	0.12	66.1	0.98	0.12	21.9	<0.001
CRP > 0.5 mg/dl (%)	101/118 (86%)	/	/	67/118 (57%)	/	/	0.007
TSH (µIU/ml) (n=115)**	3.00 ± 1.49	0.16	9.30	/	/	/	/
Hypothyreosis (TSH>4.00 µIU/ml) (%)	20/115 (17%)	/	/	/	/	/	/
fT3 (pg/ml) (n=115)	3.83 ± 0.64	1.22	6.21	/	/	/	/
fT3 <2.25 ng/dl (n/%)	1/115 (1%)	/	/	/	/	/	/
fT4 (ng/dl) (n=115)	1.08 ± 0.23	0.73	3.21	/	/	/	/
fT4 <0.84 pg/ml	3/115 (3%)	/	/	/	/	/	/

*no patient was treated with lipid-lowering drugs, **in 4/124 patients (3%) a thyreoidal disease was known (code according to ICD-10-GM-2019 [http://www.icd-code.de/icd/code/ICD-10-GM.html]: 3 patients with E03.- [hyothyreosis], 1 patient with E06.3 [autoimmune thyreoiditis]), all the patients were treated with L-thyroxine

Table 7. Parameters of liver function in 124 children and adolescents

	Baseline			At the end of inpatient treatment			
Parameter	**MW ± SD**	**Min.**	**Max.**	**MW ± SD**	**Min.**	**Max.**	**p-value**
ASAT (µmol/sl) (n=104)	0.45 ± 0.21	0.20	1.87	0.40 ± 0.15	0.17	1.06	<0.001
ALAT (µmol/sl) (n=104)	0.61 ± 0.51	0.17	4.00	0.54 ± 0.38	0.16	2.14	0.097
ɣGT (µmol/sl) (n=104)	0.39 ± 0.28	0.11	2.50	0.30 ± 0.25	0.13	2.08	<0.001

resistancy (r=0.28, p=0.003), HOMA (r=0.22, p=0.017), carotis intima media thickness (r=0.46, p<0.001), steatosis hepatis (r=0.48, p<0.001), mean systolic blood pressure during 24 hours (r=0.42, p<0.001) and mean diastolic blood pressure during 24 hours (r=0.23, p=0.013).

Multivariate analyses

Thickness of A. carotis intima media

The most important factors associated with thickness of A. carotis intima media (R-square=0.375) revealed by the multivariate analysis were: body weight at onset of the trial (ß=0.510, p<0.001), HbA1c (ß=0.440, p=0.001) and fasting blood glucose (ß=0.360, p=0.004). All other investigated parameters in the model (sex, age, height, BMI, BMI-SDS, fat mass, percentage of body fat, blood glucose after oGTT, C-peptide, insulin concentration, ß-cell function, insulin sensitivity, insulin resistancy, HOMA, triglycerides, total cholesrerol, LDL- and HDL-cholesterol, LDL/HDL-cholesterol-quotient, ASAT, ALAT, gGT, uric acid, CRP, TSH, fT3, fT4, systolic and diastolic blood pressure during a 24 hours-period) showed no associations.

HOMA

Multivariate analysis demonstrated that the only factor associated with HOMA was body weight (R-square=0.156, ß=0.405, p<0.001). All other parameters included in the model (sex, age, height, BMI, BMI-SDS, fat mass, percentage of body fat, triglycerides, total cholesrerol, LDL- and HDL-cholesterol, LDL/HDL-cholesterol-quotient, ASAT, ALAT, gGT, uric acid, CRP, TSH, fT3, fT4, systolic and diastolic blood pressure during a 24 hours-period) revealed no associations.

Systolic and diastolic blood pressure

In multivariate analyses systolic blood pressure measured during a 24-hour period was associated with BMI (R-square=0.181, ß=0.435, p<0.001), diastolic blood pressure was associated with BMI-SDS (R-square=0.036, ß=0.213, p=0.025). The other parameters included in the models showed no associations (sex, age, height, body weight, fat mass, percentage of body fat, blood glucose after oGTT, C-peptide, insulin concentration, ß-cell function, insulin sensitivity, insulin resistancy, HOMA, triglycerides, total cholesterol, LDL- and HDL-cholesterol, LDL/HDL-cholesterol-quotient, ASAT, ALAT, gGT, uric acid, CRP, TSH, fT3, fT4, thickness of A. carotis intima).

Discussion

The prevalence of overweight and obesity in childhood and adolescence is strikingly high, and has continued to increase over the last decades in most countries [1]. In addition to this epidemiological phenomenon is the significantly increased incidence of risk profiles in children and adolescents (dyslipidaemia, type 2 diabetes mellitus, arterial hypertension, liver alterations, high inflammatory activity, reduced quality of life and well-being) [8-21]. Following these findings the American Heart Association (AHA) updated their scientific statement "Cardiovascular Risk Reduction in High-Risk Pediatric Patients" in 2019. In this new statement the authors clearly state that "the evidence base has grown sufficiently to justify the need for an updated scientific statement to guide the provider, researcher, and policy maker concerned with youth at increased risk for premature CVD" [21]. Moreover the American Heart Association strongly suggested: "Early identification and treatment are important for all youth but particularly for the high-risk patients…" [21]. In view of these recommendations, it was the goal of the present trial to analyze and identify the risk profile of overweight and obese children admitted to an in-house rehabilitation.

The results of the study were impressive: More than two thirds of all the children and adolescents who were treated during the rehabilitation had at least one risk factor at beginning of the procedure. These were either non-normal laboratory parameters or higher blood pressure values and/or increased thickness of A. carotis intima media or steatosis hepatis. In particular, increased levels of insulin resistancy (in 48% of the patients), elevated LDL-cholesterol (in 70% of the patients), fatty liver (in 53% of the patients) and increased thickness of A. carotis intima media (in 32% of the patients) were striking. Multivariate analysis showed that the most important factors associated with thickness of A. carotis intima media were patients' body weight, HbA1c and fasting blood glucose. Similar results were found with regard to the HOMA index (as parameter indicating the risk for premature type 2 diabetes mellitus) and blood pressure. In both models body weight or BMI were identified as the most important factors associated. These results agree well with the literature: For at least 20 years obesity has been known to be a correlating factor with vascular fatty streaks and atherosclerotic lesions [21,35,36]. Also more recently published studies confirm this association [37-39]. Furthermore higher BMI is often accompanied by dyslipidemia, hyperglycemia and insulin resistance, inflammation and oxidative stress [21,40,41].

During the in-house rehabilitation grogram overweight and obese children and adolescents reached a mean weight reduction of about 4 kg, accompanied by a reduction in BMI, BMI-SDS and body fat mass. These changes were associated with an improvement in laboratory parameters (total cholesterol, LDL-cholesterol, glucose metabolism, liver enzymes). However, the follow-up period was too short to demonstrate improvements in sonographical density of the liver, in blood pressure or in carotid-intima media thickness. In children and adolescents with overweight and obesity rehabilitation has proven to be an effective therapeutic approach for weight reduction. The effectiveness of this therapy was evaluated by Schiel, *et al.* [15,30], but also in a German multicenter-trial by van Egmond-Fröhlich [29]. In general the weight and BMI-reduction in these studies were comparable to the effects of the present trial, but they lacked data on the improvement of risk parameters. In 2019 Ferranti, *et al.* conclude: "The magnitude of weight loss necessary to elicit meaningful improvement in CVD risk factors among youth with obesity has not been fully determined; a BMI reduction of 5% to 10% or 0.25 to 0.5 in BMI standard deviation score could be required". In view of this lack of evidence the American Heart Association cites the CHARON study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label) which was able to demonstrate in children that treatment with rosuvastatin let to regression of carotid intima-media thickness [21,42]. Similar results in regarding risk reduction for type 2 diabetes mellitus were found in the TODAY 2 study (Treatment Options for Type 2 Diabetes in Adolescents and Youth Phase II Study) [43] or for children and adolescents with elevated blood pressure values [21].

In conclusion, the present trial demonstrates that in-house rehabilitation leads to an effective weight reduction in children and adolescents with overweight and obesity. Moreover, overweight and obese children and adolescents already show a magnitude of metabolic

and cardiovascular risk factors. Along with weight reduction there is also an improvement regarding these risk factors. However, up today there remains a lack of data about long-term benefits. Further controlled trials are mandatory to elucidate the long-term effect in regarding body weight, BMI and BMI-SDS, but also with respect to risk factors and the development of metabolic and cardiovascular disorders.

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