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Original Article

The role of adipokines in the improvement of diabetic and cardiovascular risk factors within a 52-week weight-loss programme for obesity

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ABSTRACT

Background: Obesity is an independent risk factor for cardiovascular disease and diabetes weight reduction not only reduces the risk for these diseases but leads to an alteration of the circulating adipokine levels. The aim of our study was to evaluate the effect of weight loss and lifestyle changes implemented in the form of the interdisciplinary weight management programme Optifast52® on cardiovascular and diabetic risk factors and on key adipokines.
Methods: 72 morbidly obese patients were included in the programme, which consisted of a very low-calorie diet followed by incremental food introduction and dietary stabilisation, accompanied by medical surveillance, physical activity, dietary counselling and psychological support. At baseline, and after 14, 26 and 49 weeks, risk factor profiles and adipokine levels were evaluated.
Results: 43 patients completed the programme with an average weight reduction of about 20%. Significant improvement was observed in the lipid and diabetic laboratory panels of all patients. In addition, adiponectin levels increased significantly (7.79 vs. 12.38 μg/ml, $p < 0.001$), while leptin levels decreased (7.29 vs 3.09 ng/ml, $p < 0.001$) during the course of the programme.
Conclusion: In this study, Optifast52®, a multidisciplinary programme focusing on diet and lifestyle changes, was found not only to affect a decrease in parameters associated with diabetes and cardiovascular disease, but also to ameliorate in part the obesity-related imbalance of pro- and anti-inflammatory adipokines.

1. Background

Obesity represents a global problem and is associated with dyslipidaemia, hypertension, type 2 diabetes, atherosclerotic cardiovascular disease and cancer [1–3].

Several different guidelines [4–6] propose treatment algorithms where diet, exercise, medical surveillance and behavioural therapy are the cornerstones of weight management [7–9].

Although the beneficial effect of lifestyle modifications on cardiovascular and diabetic risk factors has been established [2,3,10], little is known about the underlying mechanism responsible for the reduction of risk factor profile associated with weight reduction. It has become apparent that adipose tissue not only is a fat storage, but an active endo- and paracrine organ which releases cytokines and bioactive mediators influencing not only body weight, but also inflammation, coagulation, fibrinolysis, insulin resistance, diabetes, atherosclerosis and even some forms of cancer [11–13]. The imbalance of pro- and anti-inflammatory adipokines appears to be an important contributor to the pathogenesis of metabolic dysfunction [14]. There is emerging evidence that, along with common risk factors like cholesterol, adipose tissue derived mediators may play a pivotal role in the pathogenesis of cardiovascular disease and diabetes [15].

Adiponectin is abundantly expressed in mature adipocytes and plasma levels are high in persons of normal weight (2–20 μg/ml) [16], but are markedly decreased in the obese [17]. Dyslipidaemia

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[18], type 2 diabetes and insulin resistance have been attributed to decreased adiponectin levels [19,20], suggesting that this adipokine plays an important role in the regulation of glucose and lipid metabolism.

Other important adipokines are Leptin, Ghrelin and Resistin. Leptin regulates food intake and energy expenditure [21–23]. While high leptin levels usually counteract weight gain by reducing food intake, leptin resistance can occur, promoting the accumulation of fat tissue. In obese subjects, plasma leptin levels are significantly elevated, proportional to the degree of adiposity [24], suggesting that these individuals are highly leptin resistant. Due to its proinflammatory properties, leptin is suspected to play a role in the pathogenesis of obesity-related complications [25]. Ghrelin, a hormone secreted mainly by the stomach and duodenum, has been shown to stimulate food intake in rodents and humans [26,27]. It appears to be a factor in the long-term regulation of body weight, and its plasma levels may therefore be influenced by profound weight loss. Lastly Resistin is positively correlated with adiposity and thought to be implicated in the development of insulin resistance, which is in turn strongly associated with cardiovascular risk factors such as endothelial dysfunction, activation of the coagulation cascade, increased blood pressure and deterioration of lipid metabolism [28,29].

Many studies have shown weight loss achieved by a low-calorie diet to have a beneficial effect on metabolic risk factors [10], but the role of the key adipokines remains less clear.

The purpose of this study was therefore to investigate the efficacy of the interdisciplinary, non-surgical weight loss programme Optifast52® not only in terms of body weight reduction, but also of improvements in diabetic and cardiovascular risk factor profile, with particular regard to the presumably causal influence of shifts in the adipokine pattern.

2. Methods

This study was conducted as a single centre open clinical trial in adult patients according to the guidelines laid down in the Declaration of Helsinki. All procedures were approved by the Committee of the local ethics committee, the *Landesärztekammer Hessen*, Germany (FF 112/2015). All participants provided written informed consent form indicating awareness of the investigative nature of the study and possible risks.

2.1. Patient selection

The inclusion criteria comprised an age of 18–70 years, body mass index (BMI) >30 kg/m^2, no comorbidities prohibiting participation in the programme, such as cardiac or pulmonal insufficiency class III/IV according to the New York Heart Association Functional Classification, cardiac arrhythmia, recent myocardial infarction, malignant disease, pregnancy or lactation, hypothyroidism, severe eating disorders or severe depression and being bedridden. Patients whom developed severe cardiopulmonary disease, malignant disease or pregnancy during participation were also excluded. Other comorbidities such as arterial hypertension, hypercholesterolaemia, diabetes and other metabolic disorders were not excluded but noted either by assessment of the patients' history or medical records, or through abnormal laboratory findings and were treated in consultation with the patient and their general practitioner according to common guidelines. However, most patients were receiving no medication on a regular basis. Medical treatment, especially diabetic medication where required, was adapted during the programme by the programme physician in conjunction with the GP.

2.2. Patient recruitment and structure of the programme

Ultimately, 72 participants matched the inclusion criteria and were included in the study. The patients selected underwent a 52-week hypocaloric diet (Optifast52®, franchise holder Nestlé Inc., Vervey, CH), during which they met weekly in groups of 12–15 persons at the University Hospital in Frankfurt/Germany to follow the structured programme. Due to the pilot character of the programme at our clinic, only one group was scheduled to meet per year. The advisory team consisted of a physician, a dietician/nutritionist, a psychologist and a physical therapist.

The programme consisted of five phases:

(1) a 1-week introduction period to check inclusion and exclusion criteria as described above;
(2) a 12-week "fasting" period of low-calorie diet during which participants exclusively consumed formula diet (Optifast 800 formula, Nestlé Inc.). Five shakes (160 kcal each) were ingested per day dissolved in 300 ml water, providing a total daily intake of 3200 kJ (800 kcal), 87 g protein, 12 g fat and 75 g carbohydrate, plus the recommended daily intake of vitamins, minerals and trace elements. Patients were advised to drink at least 2.5 litres additionally each day, preferably water, tea or low-calorie soft drinks. This phase was accompanied by 12 medical examinations, 12 exercise units, two behavioural therapy lessons and two nutrition counselling sessions;
(3) a 6-week refeeding phase, during which solid food was reintroduced and formula diet progressively replaced by normal diet without changing total energy intake, accompanied by six medical examinations, six exercise units, two behavioural therapy lessons and six nutrition counselling sessions;
(4) a 7-week stabilisation phase in which energy intake was raised incrementally to an individual level allowing weight stabilisation, accompanied by three medical examinations, four exercise units, four behavioural therapy lessons and three nutrition counselling sessions;
(5) a 26-week maintenance phase in which nutritional education and behaviour modification was intensified to learn coping strategies and to achieve long-term weight control, accompanied by six medical examinations, 13 exercise units, 22 behavioural therapy lessons and five nutrition counselling sessions.

2.3. Data analysis and laboratory tests

Clinical parameters (including age, sex, weight, height, waist circumference (WC), blood pressure) and laboratory parameters in serum for the lipid and diabetic panel (including fasting glucose including plasma glucose, plasma insulin, proinsulin, glycated haemoglobin A1c, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), ALT, gamma-glutamyl transpeptidase, sodium potassium, creatinine and uric acid) were assessed at the beginning and end of the programme (week 0 and week 49), as well as after the fasting period (week 14) and after 6 months (week 26), and analysed in the hospital laboratory according to common standards.

Each week, participants were weighed, blood pressure was measured and medication documented and adjusted by the physician. BMI was calculated, as well as relative weight loss in percent ($100 \times \Delta$weight loss in kg/initial body weight in kg) and excess weight loss in percent ($100 \times \Delta$weight loss in kg/initial body weight in kg – normal body weight in kg). Normal body weight was defined as the body weight corresponding to a BMI of 25 kg/m^2. Waist-to-hip ratio (WHR) was calculated according to the formula WHR = WC/body height.

Table 1
Baseline characteristics of the participants.

Characteristics	
N (♀)	43 (31)
Age (mean ± sd)	45.5 ± 14.4
BMI (kg/m^2, mean ± sd)	41.62 ± 6.69
Weight (kg, mean ± sd)	121.23 ± 22.85
Height (cm, mean ± sd)	173.5 ± 10.10
Comorbidities (n, (%))	
Hypertension	19 (44.2)
Hyperlipidaemia	8 (18.6)
Type 2 Diabetes mellitus	34 (79.1)
Medication (n, (%))	
Antihypertensive agents	23 (53.5)
Oral antidiabetics	34 (79.1)
Insulin	3 (7.0)
Antihyperlipidemic agents	11 (25.6)
Smoking (n, (%))	4 (9.3)

BMI: Body Mass Index.

In addition, changes in body composition were determined using bioimpedance analysis (data input, Germany) according to the manufacturer's instructions.

Metabolic variables were assessed at baseline, and at 14, 26 and 49 weeks, through a series of biochemical and haematologic tests. The analyses were performed in an approved laboratory with internal and external quality control using standard laboratory assays. In samples from the serum bank, adipokine levels were determined by ELISA (adiponectin: ALPCO Diagnostics; proinsulin, insulin and C-peptide: DRG Diagnostics; leptin, ghrelin and resistin: LINCO Corp.). All assays were performed in accordance with the manufacturer's protocol.

HOMA (homoeostasis model assessment index) was calculated as follows: insulin (fasting, μU/ml) × blood glucose (fasting, mg/dl)/405.

2.4. Statistical analysis

Values are expressed as means ± SD if not indicated otherwise. Pairwise comparisons of serum concentrations of insulin, glucose, CRP, adiponectin, ghrelin, leptin and resistin were performed between different patient groups with the non-parametric student-t test. The one-way ANOVA was used to compare three or more groups. Associations between the concentrations of selected adipokines and cytokines within pairs were tested using Pearson correlation coefficients. The statistical software used for analysis was Sigma Stat v 3.1 (Systat Software, Inc. Chicago, IL, USA).

3. Results

In the end, 72 participants were included in the Optifast52® programme while 43 of them completed the programme, corresponding to a dropout rate of 40.3%. The main reasons for discontinuation of participation in the programme were job-related (27%), personal/familial (20%), financial (13%), medical (13%), mental/psychological (10%), weight gain (3%) and product dissatisfaction (3%). The rest of those who discontinued were excluded from the programme because of irregular participation or non-attendance (8%). More than half of the drop-outs (58%) occurred in the second half of the programme. Participants who completed the programme (31 female, 12 male) aged 18–65 years, with a mean age (±SD) of 45.5 ± 14.3 years, the baseline characteristics are summarised in Table 1.

3.1. Body weight and BMI

Average body weight and BMI decreased significantly in all participants whom completed the whole course. (Fig. 1, Table 2). The initial average body weight of 121.23 kg (SD 22.85) fell to 96.88 kg (SD 22.72, $p < 0.001$) in the course of the programme. This corresponds to a reduction in body weight of about 20% within one year. Average weight reduction was at its maximum at the end of the low-calorie phase (after 26 weeks), reaching approximately 22.8% (93.54 kg, SD 17.29). In most patients, weight loss achieved after 6 months of treatment was almost fully maintained until the end of the programme, with only minor weight gain (approximately 3 kg mean) observed during the second half of the year.

The initial average BMI of 41.62 kg/m^2 (SD 6.69) was reduced to 33.37 kg/m^2 (SD 7.21, $p < 0.001$) at the end of the programme, with 4 participants reaching a normal BMI level, while 15 had a BMI < 30 kg/m^2 and could be classified as overweight. As documented by bioimpedance analysis, weight loss was mainly due to reduction in body fat mass (53.81 kg, SD 12.57–36.43 kg, SD 14.08 ≅ 31.5%, $p < 0.001$) with only a slight reduction in lean body mass (66.60 kg, SD 15.54–60.62 kg, SD12.86 ≅ 8.3%) (Fig. 2).

3.2. Lipid profile

Serum triglycerides dropped significantly from 147.50 mg/dl (SD 71.56) to 102.84 mg/dl (SD 47.89, $p < 0.001$) during the programme. While cholesterol and LDL cholesterol decreased during fasting and finally remained slightly below the baseline value (cholesterol 208.94 mg/dl, SD 40.21 to 194.33 mg/dl, SD 37.82, $p < 0.001$; LDL cholesterol 121.99 mg/dl, SD 35.73 to 108.55 mg/dl, SD 32.71, $p < 0.001$), HDL cholesterol increased significantly throughout the programme (54.31 mg/dl, SD 14.83 to 63.54 mg/dl, SD 12.45, $p < 0.001$). HDL / LDL ratio increased progressively along with weight reduction and regular physical activity from 0.5 (SD 0.24) to 0.62 (SD 0.21, $p < 0.001$) (Table 2).

3.3. Insulin resistance

The decrease in fasting blood glucose levels (102.35, SD 97.00 to 87.62 mg/dl, SD 86.00) was accompanied by a significant drop in insulin levels from 24.72 μU/ml (SD 20.43) to 13.19 μU/ml (SD 6.30, $p < 0.001$). Proinsulin also decreased, from 6.74 pmol/l to 3.84 pmol/l, but this reduction was not significant. While a reduction in C-peptide was evident in the fasting phase, it reached almost baseline levels at the end of the programme (data not shown). HbA1c, a marker of average blood glucose values over the course of several months, decreased significantly throughout the programme from 6.27 %Hb (SD 1.62) to 5.38 %Hb (SD 0.57, $p < 0.001$). Furthermore, HOMA, used to evaluate insulin sensitivity, also dropped significantly from 6.64 (SD 7.42) to 3.02 (SD 1.95, $p < 0.005$), pointing to an improvement of the diabetic metabolic state (Table 2).

3.4. Adipokines

The effects of weight reduction on adiponectin, leptin and resistin levels are shown in Table 2. Adiponectin levels increased significantly from 7.79 μg/ml (SD 4.30) to 12.38 μg/ml, (SD 8.31, $p < 0.001$) in accordance with weight loss. Together with the reduction of body fat mass, leptin levels showed a marked decrease from 7.29 ng/ml (SD 2.95) to 3.09 ng/ml (SD 1.98, $p < 0.001$). Ghrelin values increased within the fasting period from 110.94 μmol/ml (SD 70.40) to 118.11 μmol/ml (SD 103.54) in week 14, falling to baseline levels at the beginning of the stabilisation phase (110.86 μmol/dl,

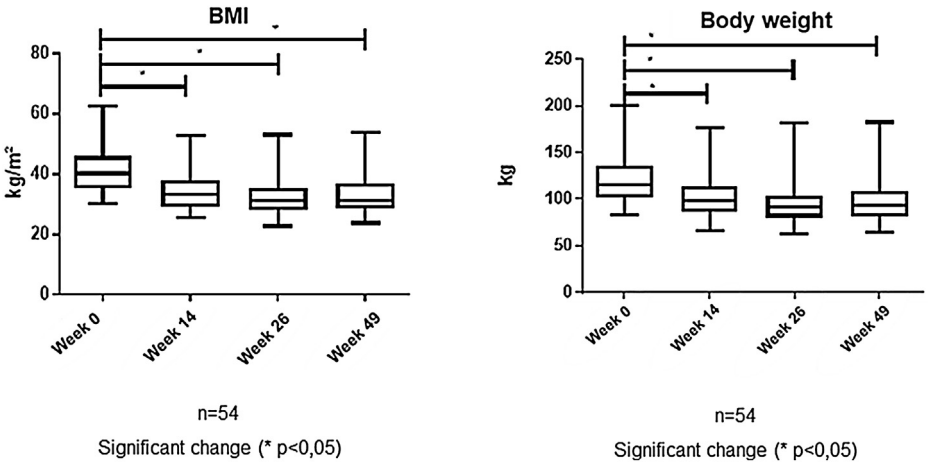

Fig. 1. Body weight of the participants during the programme.

Table 2
Change of the main parameters in the course of the programme.

Parameter	Baseline	Week 14	Week 26	Week 49
Body weight (kg)	121.23 (±22.85)	100.10 (±19.04) $p_1 < 0.001$	93.54 (±17.29) $p_2 < 0.001$	96.88 (±22.72) $p_3 < 0.001$
BMI (kg/m^2)	41.62 (±6.69)	34.77 (±6.18) $p_1 < 0.001$	32.79 (±6:42) $p_2 < 0.001$	33.37 (±7.21) $p_3 < 0.001$
Fat mass by BIA (kg)	53.81 (±12.57)	38.91 (±12.05) $p_1 < 0.001$	32.43 (±10.51) $p_2 < 0.001$	36.43 (±14.08) $p_3 < 0.001$
Triglycerides (mg/dl)	147.50 (±71.56)	105.87 (±49.41) $p_1 < 0.001$	104.55 (±48.50) $p_2 < 0.001$	102.84 (±47.89) $p_3 < 0.001$
Cholesterol (mg/dl)	208.94 (±40.21)	172.03 (±42.43) $p_1 < 0.001$	189.23 (±37.18) $p_2 < 0.001$	194.33 (±37.82) $p_3 < 0.001$
HDL (mg/dl)	54.31 (±14.83)	48.56 (±9.63) $p_1 < 0.001$	56.75 (±12.35) $p_2 < 0.001$	63.54 (±12.45) $p_3 < 0.001$
LDL (mg/dl)	121.99 (±35.73)	102.43 (±34.75) $p_1 < 0.001$	110.61 (±31.81) $p_2 = 0.063$	108.55 (±32.71) $p_3 < 0.001$
HDL/LDL Ratio	0.50 (±0.24)	0.53 (±0.18) $p_1 = 0.169$	0.56 (±0.23) $p_2 < 0.001$	0.62 (±0.21) $p_3 < 0.001$
Leptin (ng/ml)	7.29 (±2.95)	3.04 (±2.55) $p_1 < 0.001$	2.57 (±2.18) $p_2 < 0.001$	3.09 (±1.98) $p_3 < 0.001$
Adiponectin (µg/ml)	7.79 (±4.30)	9.38 (±5.15) $p_1 < 0.05$	11.22 (±6.41) $p_2 < 0.001$	12.38 (±8.31) $p_3 < 0.001$
Leptin/adiponectin ratio	1,33 (±1.01)	0,42 (±0.62) $p < 0.005$	0,29 (±0.27) $p_2 < 0.001$	0,36 (±0.35) $p_3 < 0.001$
Ghrelin (µmol/ml)	110,94 (±70,40)	118,11 (±103,54) $p_1 = 0.37$	110,86 (±88,40) $p_2 = 0.88$	102,02 (±70,74) $p_3 = 0.90$.
Resistin (ng/ml)	19.32 (±9.54)	19.32 (±9.32) $p_1 = 0.87$	16.41 (±6.39) $p_2 = 0.068$	13.71 (±5.94) $p_3 < 0.05$
HOMA:IR	6.64 (±7.42)	3.77 (±4.57) $p_1 < 0.05$	3.06 (±1.95) $p_2 < 0.005$	3.02 (±1.95) $p_3 < 0.005$
Insulin (µU/ml)	24.72 (±20.43)	16.07 (±14.67) $p_1 < 0.01$	13.38 (±7.30) $p_2 < 0.001$	13.19 (±6.30) $p_3 < 0.001$
Glucose (mg/dl)	102.35 (±97.00)	88.26 (±84.50) $p_1 < 0.001$	93.55 (±89.00) $p_2 < 0.01$	87.62 (±86.00) $p_3 < 0.001$
HbA1c (%Hb)	6.27 (±1.62)	5.59 (± 0.66) $p_1 < 0.005$	5.48 (±0.70) $p_2 < 0.001$	5.38 (±0.57) $p_3 < 0.001$
Uric Acid (mg/dl)	6.10 (±1.47)	5.12 (±1.30) $p_1 < 0.001$	5.47 (±1.38) $p_2 < 0.001$	5.20 (±1.44) $p_3 < 0.001$

p_1: Difference between baseline and week 14, p_2: Difference between baseline and week 26, p_3: Difference between baseline and week 49.
BMI: Body Mass Index, BIA: Bioelectrical Impedance Analysis, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, HOMA: Homeostatic Model Assessment measuring Insulin Resistance.

SD 88.40 in week 26), but data were not significant. Resistin showed a progressive decrease throughout the duration of the programme (19.32 ng/ml, SD 9.54–13.71 ng/ml, SD 5.94), but again data were not significant.

Correlating adiponectin with other parameters led to the conclusion that there is a strong negative correlation between adiponectin and BMI ($r = -0.52$, $p = 0.01$, Fig. 3) and a positive correlation of adiponectin with HDL-cholesterol ($r = 0.41$, $p = 0.01$, Fig. 4) and HOMA ($r = 0.23$, $p = 0.33$, Fig. 5).

3.5. Other parameters

In parallel with the nutritional regimen and weight change, uric acid serum levels dropped dramatically during fasting from 6.10 mg/dl (SD 1.47) at the beginning, to 5.12 mg/dl (SD 1.30, $p < 0.001$) at the end of the fasting period (week 14), and slightly increased towards the end of the programme, but stayed significantly below baseline values (5.20 mg/dl, SD 1.44, $p < 0.001$, week 49) (Table 2).

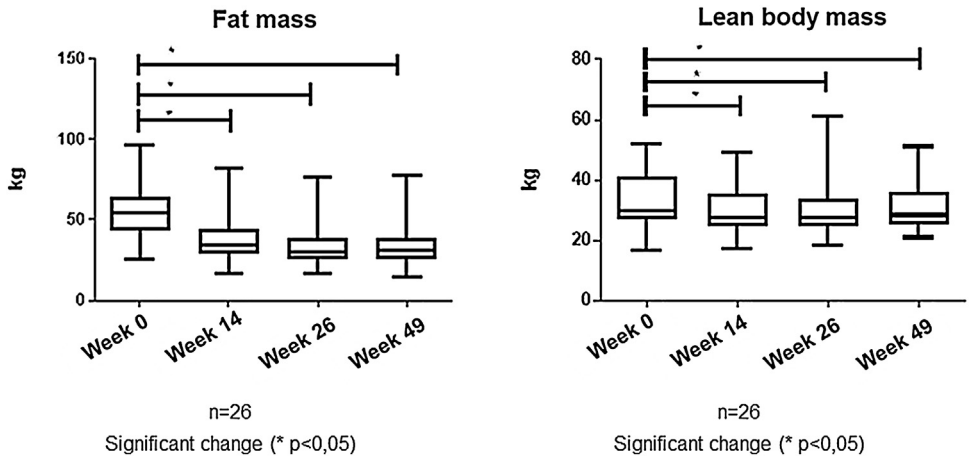

Fig. 2. Development of body fat mass and lean body mass of the participants during the programme.

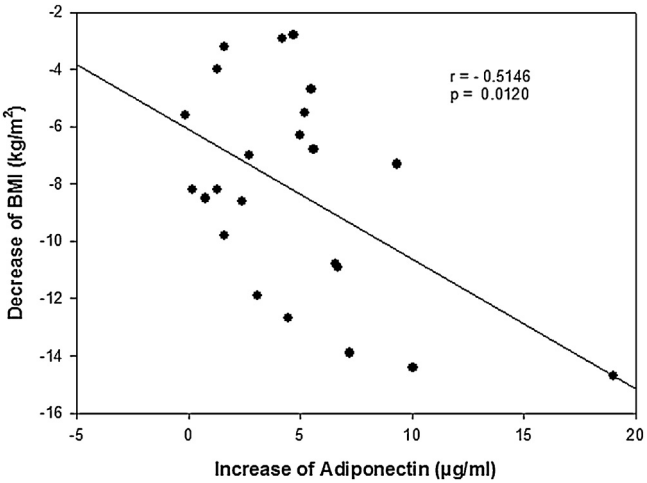

Fig. 3. Correlation of adiponectin and BMI.

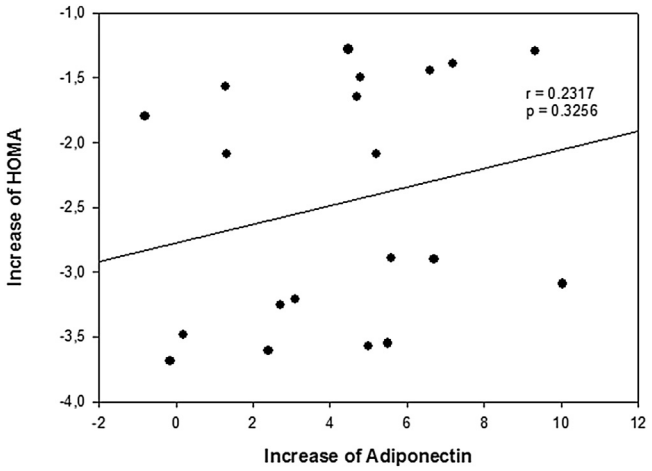

Fig. 5. Correlation of adiponectin and HOMA.

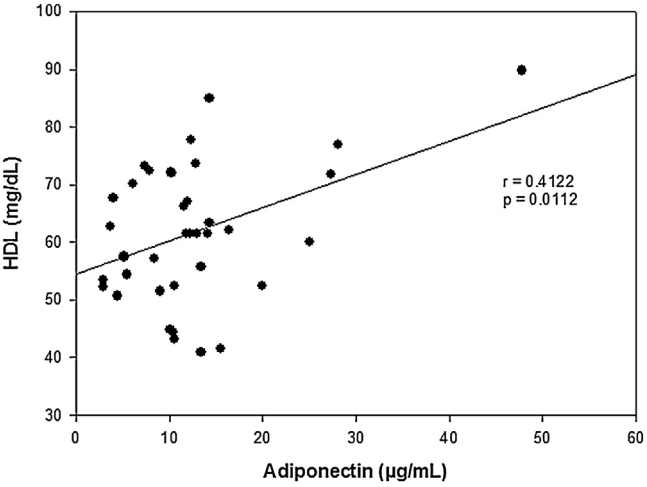

Fig. 4. Correlation of adiponectin and HDL cholesterol.

4. Discussion

In this study, we sought to determine the impact of controlled weight loss and lifestyle modification within the Optifast52® programme on blood lipids, blood glucose parameters and the most prominent adipokines in obese people over a period of one year. The study is based on the observation that obesity leads to the elevation of many risk factors for cardiovascular disease and diabetes [1,11,30,31], and that adipokines seem to be involved in these processes, probably serving as the cellular link between insulin resistance, endothelial dysfunction and obesity [12,32].

In the Optifast52® programme, participants succeeded in reducing their body weight by an average of 20% within one year of treatment. Of those 43 participants who completed the programme, only 7 participants lost under 10% of their initial body weight, thus failing to achieve substantial weight loss during that time. Although the reasons for failure were not further analysed, irregular participation in group meetings or resistance to the weight stabilisation training may have been causal factors.

As expected, most metabolic risk factors decreased substantially in response to weight loss during the programme, which is in accordance with other studies [31,33]. Cardiovascular and diabetic laboratory parameters improved markedly, indicating the potential health benefit of the Optifast52® programme. It is very likely that at least some of the beneficial effects on metabolic parameters can be related to a reduction in body fat mass and subsequent modification of adipocyte-derived hormones, especially adiponectin, as a significant correlation was found between fat cell derived adiponectin and HDL cholesterol (Fig. 4) as well as adiponectin and HOMA (Fig. 5).

Adiponectin and its receptors (AdipoR1 and AdipoR2) are reduced in obese subjects, implying a reduced action of the adiponectin system in obesity [20,34]. We not only observed a

negative correlation of adiponectin and BMI (Fig. 3), but also demonstrated that adiponectin levels can be increased by means of weight reduction.

However, changes in total plasma adiponectin concentration seem to depend on the amount of weight lost: While moderate weight loss leaves adiponectin levels unchanged [35–37], major weight reduction has been found to lead to a significant increase in plasma adiponectin [38–41]. Esposito et al. successfully demonstrated a significant increase of adiponectin levels when BMI was reduced by 14% as a result of intensive lifestyle changes [35]. Similarly, we observed a significant increase of adiponectin (approximately 59%) in subjects who had achieved an average weight loss of 20%.

Concerning the diabetic parameters, several studies have shown a correlation between plasma adiponectin levels and insulin sensitivity [42–45]. Some groups have demonstrated that administration of adiponectin can improve insulin resistance by increasing fat oxidation and suppressing hepatic glucose production [20,42]. Thus, adiponectin has been identified as a key factor linking obesity with insulin resistance [46] and a potential target for therapeutic intervention. In our study, the increase in adiponectin was associated with decreases in fasting blood glucose, insulin, proinsulin, HbA1c and HOMA, pointing to improved insulin sensitivity. In addition, we found a significant correlation of adiponectin and HOMA (Fig. 5), suggesting that the increase in adiponectin levels might be associated with an improvement of the diabetic laboratory parameters (i.e. fasting glucose including plasma glucose, plasma insulin, proinsulin, glycated haemoglobin A1c). However, it should be noted that insulin and glucose concentrations are relatively sensitive to weight loss, thus a direct, adiponectin-independent effect cannot be ruled out. As C-peptide could not be correlated to any of the other parameters in our study, its role remains unclear.

Emerging data support the proposal that obesity, and notably abdominal obesity, not only leads to changes in fat tissue development and growth and the induction of insulin resistance, but also to endothelial dysfunction via proinflammatory and prothrombotic effects of adipokines [12,47]. Pischon et al. showed that subjects with a higher adiponectin level had a significantly decreased risk of myocardial infarction, even after adjustment for LDL and HDL levels, BMI, history of diabetes and hypertension at baseline [48].

Plasma adiponectin levels have been shown to be positively correlated with HDL in patients with type 2 diabetes and negatively correlated with triglycerides, CRP and PAI-1 [49,50]. In accordance with these data, we found that the increase in adiponectin levels was positively associated with HDL and HDL/LDL ratio, and negatively correlated with triglycerides and homocysteine levels.

Leptin, an adipokine with proinflammatory properties, has been shown to decline along with body weight [51,52], and is highly responsive to the degree of weight loss [53]. In our study, weight loss led to a decrease in leptin to 42.4% of baseline values. Furthermore, this decline in leptin levels correlated with the loss of body fat mass. Since higher leptin concentrations are an independent risk factor for coronary artery disease [54,55], the decrease of leptin brought about by reduction of weight, and in particular of body fat mass, may further contribute to improvement of the cardiovascular risk factor profile.

Ghrelin is believed to have a role in long-term regulation of body weight [56,57]. In obesity, mildly decreased ghrelin levels have been observed [58], and these levels have been shown to increase in response to diet-induced weight loss – an effect that was confirmed in our study, even though data were not significant. During the second half of the programme, in which study participants returned to regular food intake and body weight slightly increased, ghrelin levels dropped to baseline values. It has been suggested that ghrelin, in increasing the desire to eat, may be partly responsible for the adaptive response which limits the degree of diet-induced weight loss [57]. This hypothesis may be true, but further studies elucidating the mechanism of ghrelin's action are needed.

To date there are very few data concerning the effect of diet-induced weight reduction on resistin values. Whereas some studies reported a decrease in resistin (7–14%) alongside weight loss (<5%) [59], others demonstrated no effect in spite of the same amount of weight loss [60]. In our study, we found a progressive, non-significant reduction of resistin (about 29%) together with a loss of body fat mass. While it is probable that the observed improvement of diabetic laboratory parameters during the programme, reflected in a lower HOMA, is the result of reduced resistin levels, the role of the latter still remains unclear.

A relevant limitation of our study is the missing data on the participant's physical activity, exercise and fitness regimen during the programme, as studies have shown that physical activity might play a more important role in overall prognosis of the patients than weight reduction [61–63]. Although there may only be a limited effect on weight loss, physical activity seems to be crucial in preventing in regaining weight and supports weight maintenance [64].

Our data show that weight loss of 20%, achieved by the interdisciplinary, life-style modifying Optifast52® programme, is highly effective in improving the serum lipid profile and diabetes-associated parameters in obese patients. This is very probably due to the dramatic reduction in body fat mass and associated changes in adipokine levels. The fact that lean body mass was only minimally reduced is accreditable to the adequate protein supply and regular physical activity. Although physical exercise plays an important role in weight management and may have beneficial effects on metabolic risk factors [65], training alone does not improve the adipokine profile [66]. It may be concluded that, since adiponectin, independent of its insulin-sensitising action, has marked anti-inflammatory and anti-atherosclerotic effects in humans [14,67,68], weight loss also results in diminishment of the cardiovascular risk. The reduction of proinflammatory leptin may contribute to the risk factor improvement.

In spite of the apparent health benefit, the long-term effect of this programme still has to be established. It is very likely that the clinically beneficial effects of increased plasma adiponectin and reduced leptin levels persist, provided weight gain can be avoided after termination of the programme. As this is, of course, a major problem in weight management [7–9], appropriate follow-up programmes need to be established and further studies carried out to evaluate the long-term efficacy of the Optifast52® programme.

5. Conclusions

It was demonstrated that the interdisciplinary, long-term weight management programme Optifast52® is not only effective in reducing body weight and improving blood lipids and diabetic parameters, but can also significantly shift the adipokine pattern in a positive way. As the improvement of the adipokine profile might be a potential target for the treatment of diabetes and dyslipidaemia; it can be hypothesised that the participants may also benefit from the programme in terms of diabetes and cardiovascular risk reduction.

Competing interests

All authors, except JH, are engaged in Optifast® centers (Nestlé HealthCare Nutrition GmbH, Munich, Germany). Apart from that all authors declare no competing interests. They are all independent from funders.

Author's contributions

The study was designed by AW and JS. AW, IB, MB, IB, JH, AA and JS carried out the study, SML and AA collected and analysed the data. AW drafted the manuscript. JH, AA, IB, SML and JS reviewed the manuscript. All authors read and approved the final manuscript.

Ethical statement

All procedures were approved by the Committee of the local ethics committee, the *Landesärztekammer Hessen*, Germany (FF 112/2015). All participants provided written informed consent form indicating awareness of the investigative nature of the study and possible risks.

CRediT authorship contribution statement

Johannes Hausmann: Investigation, Writing - review & editing. **Astrid Waechtershaeuser:** Conceptualization, Investigation, Writing - original draft. **Imke Behnken:** Investigation. **Aysegül Aksan:** Investigation, Validation, Data curation, Writing - review & editing. **Irina Blumenstein:** Investigation, Writing - review & editing. **Michael Brenner:** Investigation. **Stefan M. Loitsch:** Validation, Data curation, Writing - review & editing. **Juergen Stein:** Conceptualization, Investigation, Writing - review & editing, Supervision.

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