# Short-Term Treatment With Metformin Decreases Serum Leptin Concentration Without Affecting Body Weight and Body Fat Content in Normal-Weight Healthy Men

Bernd Fruehwald-Schultes, Kerstin M. Oltmanns, Barbara Toschek, Stefan Sopke, Werner Kern, Jan Born, Horst L. Fehm, and Achim Peters

**A weight-reducing effect of metformin has been demonstrated in obese subjects with and without diabetes. The mechanisms of this action are unclear, which may be partly due to the fact that in obese and diabetic patients the substance's effects result from a complex interaction with the distinct endocrine and metabolic disturbances in these patients. To dissociate primary from secondary action of metformin, we examined effects of the substance in normal-weight healthy subjects. Fifteen normal-weight men were treated with metformin (850 mg twice daily) or placebo for a 15-day period in a double-blind, placebo-controlled, cross-over study. Anthropometric, psychologic, cardiovascular, endocrine, and metabolic parameters were assessed before and at the end of the treatment period. Metformin did not affect body weight ($P = .838$) and body fat mass ($P = .916$). Yet, serum leptin concentration was distinctly reduced after metformin ($P < .001$). Also, metformin reduced the concentration of plasma glucose ($P = .011$), serum insulin ($P = .044$), and serum insulin-like growth factor -1 (IGF-1) ($P = .013$), while it increased serum glucagon concentration ($P < .001$). There were no effects of metformin on feelings of hunger, blood pressure, heart rate, resting energy expenditure, the respiratory quotient, free fatty acids, $\beta$-hydroxybutyrate, glycerol, triglycerides, cholesterol, and uric acid (all $P > .1$). Data indicate that metformin decreases the serum leptin concentration even without affecting body weight and body composition in normal-weight men.**


METFORMIN IS A DRUG widely used to lower blood glucose concentration in type 2 diabetic patients.[1] In contrast to other drugs with this action, such as sulphonylurea, thiazolidinediones, and insulin, metformin improves glucose control without increasing body weight.[2,3] Several studies have even found metformin to reduce weight in type 2 diabetic patients.[4-7] Moreover, adding metformin to insulin therapy prevents the typical gain in body weight associated with insulin therapy.[8-10] The mechanisms of the counteracting influence of metformin alone or in combination therapy with insulin on body weight gain in the presence of improved blood glucose control remain unclear. In obese subjects without diabetes, metformin has been shown to decrease body weight in some,[11,12] but not all,[13] studies. In both obese patients with[6] and without[12] diabetes, weight loss during metformin treatment is largely accounted for by a loss of adipose tissue.

It has been proposed that metformin could decrease body fat mass by reducing food intake, increasing energy expenditure, or partitioning fuel. Endocrine factors involved in the regulation of body weight and body composition, such as leptin, insulin, insulin-like growth factor-1 (IGF-1), and cortisol probably play a pivotal role in the weight reducing effects of metformin. Notably, however, the effects of metformin on these endocrine mediators have rarely been assessed. Here, we examined effects of a 15-day period of treatment with metformin on anthropometric, psychologic, metabolic, cardiovascular, and especially on endocrine parameters in 15 normal-weight healthy men. Normal-weight healthy men were chosen because we wanted to know whether weight reduction after metformin would occur also under normal nonpathologic conditions. Moreover, it was expected that the primary actions of metformin on metabolic functions are easier to dissociate in normal-weight healthy subjects than under pathologic conditions as in obese or type 2 diabetic patients, in which the effects of metformin may result from an interaction with the distinct endocrine and metabolic disturbances in these patients.

## SUBJECTS AND METHODS

Fifteen normal-weight, healthy men participated in the study (mean age, 26.7 years; range, 21 to 33 years; body mass index [BMI] mean ± SEM, 23.3 ± 0.5 kg/m$^2$; range, 20.3 to 27.0 kg/m$^2$). Exclusion criteria were chronic or acute illness, current medication of any kind, smoking, alcohol or drug abuse, obesity (BMI > 27 kg/m$^2$), or diabetes and hypertension in first-degree relatives. The subjects were told that the study aimed to assess metformin effects on subjective symptoms, cognitive function, and physiologic variables, such as blood pressure and resting energy expenditure. However, no hints were given that the study primarily focused on factors involved in the regulation of body weight and body composition. This was done to avoid behavioral changes by the subject, such as paying more attention to their body weight, which could have influenced eating habits, thereby confounding results. Also, the subjects were instructed not to change their 'lifestyle' throughout the study. Each subject gave written informed consent, and the study was approved by the local ethics committee.

The study was performed in a placebo-controlled double-blind cross-over design with the order of conditions balanced across subjects. On one condition, subjects received 850 mg metformin twice daily for a 15-day period, on the other, placebo was administered with a 4-week interval between the 2 treatment periods. Compliance with drug treatment was assessed by repeated telephone calls and in an interview at the end of the treatment period. On the day before starting a treatment period, as well as on the last day of the treatment period (day 15), subjects were tested between 8:00 and 9:00 AM after an overnight fast of at least 10 hours. The test period comprised, in the following order, a semiquantitative questionnaire of the subjective symptoms and mood, a short-term memory task (word recall), Stroop interference test,

*From the Departments of Internal Medicine I and Neuroendocrinology, University of Luebeck, Luebeck, Germany.*

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*Address reprint requests to Bernd Fruehwald-Schultes, MD, Medical University Luebeck, Department of Internal Medicine I, Ratzeburger Allee 160, D-23538 Luebeck, Germany.*



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weighting, bioelectrical impedance analysis, indirect calorimetry, measurement of blood pressure and heart rate, and the drawing of a blood sample. In addition, the subjects were instructed to collect their urine from 8:00 PM until 8:00 AM on the last day of the treatment period for determination of urinary cortisol and creatinine concentration.

The questionnaire required ratings from 0 (none) to 9 (severe) of the following symptoms: hunger, tingling, tremor, palpitations, dizziness, sweating, itching, blurred vision, dry mouth, headache, physical indisposition, weakness, activity, anxiety, ability to concentrate, tension, fatigue, restlessness, alertness, drowsiness, anger, headache, sadness, and joy.

Short-term memory testing was comprised of the consecutive oral presentation of 2 different word lists each containing 15 words. The words belonged to 3 semantic categories: neutral words, such as 'tree' and 'field', food-related words, such as 'ham' and 'eggs', and emotional words, such as 'mother' and 'friend'. Each list included 5 words from each semantic category in random order, and parallel lists were used for repeated testing. After each list, the subject was required to recall verbally all words he remembered within 1 minute.

The Stroop test included 3 subtests, which were the word reading test, the color naming test, and the interference test. On the first test, the subject was presented a panel with a random series of 100 color words (green, red, blue, yellow) printed in black ink (word reading subtest). On the second test, the subject was presented with a series of 100 triplets of 'XXX' printed in green, red, blue, or yellow ink (color naming subtest). On these tests, his task was, respectively, to read the color words and to name the colors of the triplets as quickly as possible. On the interference task, the subject was presented with a series of color names (green, red, blue, yellow) printed with inks of different colors. His task was to selectively attend to and to name as quickly as possible the color of the ink in which each word was printed.

Subjects were weighed while wearing only their underwear, and body weight was recorded to the nearest 0.1 kg. Body composition was determined by bioelectrical impedance analysis (Body Composition Analyser; Akren-RJL BIA 101/S, DATA INPUT, Frankfurt, Germany). Indirect calorimetry was performed while subjects were lying on a bed in a horizontal position. Respiratory gas exchanges ($\dot{V}O_2$ and $\dot{V}CO_2$) were measured by placing a ventilated hood (MBM-200 Deltatrac II; Datex, Helsinki, Finland) over the head of the subject for 10 minutes. Blood pressure and heart rate were measured automatically by a BC 40 (Bose-Prestige "Automatic"; Bosch und Sohn, Jungingen, Germany), simulating the Riva-Rocci procedure.

All blood samples were immediately centrifuged, and the supernatants were stored at −24°C until assay. Serum insulin, C-peptide, glucagon, and leptin concentrations, as well as urinary cortisol concentration, was measured by standard assays as previously described.[14-17] Insulin resistance was estimated by using the homeostasis model assessment (HOMA).[18] Serum IGF-1 concentration was measured by enzyme-linked immunosorbent assay (ELISA) (Active IGF-I; Diagnostic Systems Laboratories, Sinsheim, Germany) with an intra-assay coefficient of variance (CV) of 6.5% and an interassay CV of 4.8%. Serum IGF binding protein-3 (IGFBP-3) concentration was measured by ELISA (Active IGFBP-3; Diagnostic Systems Laboratories) with an intra-assay CV of 7.3% and an interassay CV of 8.2%. Serum levels of free fatty acids (FFA), β-hydroxybutyrate, glycerol, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides (TG), and uric acid were measured only at the end of the treatment period. Commercially available kits were used to determine serum concentration of FFA, β-hydroxybutyrate, and glycerol (Freie Fettsäuren Halbmikro-Test; Roche Diagnostics, Mannheim, Germany; Triglyceride GPO-Trinder; Sigma Diagnostics, St Louis, MO; β-Hydroxybutyrate; Sigma Diagnostics, respectively). Plasma glucose concentration and serum concentration of total cholesterol, LDL-cholesterol, HDL-cholesterol, TG, and uric acid, as well as urinary creatinine concentration, were determined by routine clinical methods.

All values are presented as mean ± SEM. A sample size of 15 provided a statistical power of 0.89 to detect changes in body weight that were smaller than 0.8 kg during the treatment period given a standard deviation of 1 kg. Statistical analysis on variables assessed before and after the treatment period was based on analysis of variance (ANOVA) including the repeated measures factors 'time' (before *v* after treatment) and 'drug' (metformin *v* placebo). The interaction term between both factors indicated effects of metformin. For statistical comparisons of variables assessed only at the end of the 2 treatment periods, paired Student's *t* tests were used. Correlation coefficients were determined to detect associations between variables before and after the treatment period separately for the metformin and placebo condition (Pearson's correlation). Also, correlations between percent changes in serum leptin (value after minus value before treatment divided by value before treatment) and changes in other variables during the treatment period (value after minus value before treatment) were determined. A $P$ value less than .05 was considered significant.

## RESULTS

### *Adverse Effects, Symptoms, and Cognitive Function*

Metformin treatment was well tolerated. None of the subjects stopped taking the drugs because of adverse side effects. Two subjects reported mild diarrhea, and another subject reported nausea and abdominal discomfort while taking metformin.

Metformin had no effect on rating of hunger (placebo *v* metformin: 3.2 ± 0.5 *v* 3.1 ± 0.6; $P = .898$). Compared with placebo, subjects felt less weakness (1.07 ± 0.4 *v* 0.67 ± 0.3; $P = .028$) and fatigue (3.73 ± 0.5 *v* 2.33 ± 0.4; $P < .001$) during metformin treatment, while ratings on the other symptoms did not differ between the treatments ($P > .1$ for all variables).

Short-term memory, assessed by the number of correctly recalled words, was not affected by metformin (placebo before: 10.3 ± 0.6 words; after: 10.0 ± 0.6 words; metformin before: 10.1 ± 0.6 words; after: 10.5 ± 0.8 words; $P = .328$). Also, the percentage of correctly recalled food-related words did not significantly differ between metformin (before: 34.3% ± 2.0%; after: 30.5% ± 1.3%) and placebo (before: 34.0% ± 2.2%; after: 34.2% ± 2.4%) treatment ($P = .264$). Analysis of the Stroop interference test also showed no effect of metformin on measures of selective attention ($P = .616$).

### *Anthropometric Variables, Indirect Calorimetry, and Cardiovascular Parameters*

Body weight, body fat mass, and percentage of body fat mass remained remarkably stable over time and were closely comparable on both metformin and placebo conditions (Table 1). Also, there was no effect of metformin on resting energy expenditure (REE), respiratory quotient (RQ), blood pressure, and heart rate (Table 1).

### *Endocrine and Metabolic Parameters*

Data on the measurement of endocrine parameters are summarized in Table 2. Despite stable body weight and body fat mass, metformin distinctly reduced serum leptin concentration by 24% in comparison to baseline ($P = .016$) and by 30% in comparison to placebo ($P = .019$). Also, plasma glucose and serum levels of insulin and IGF-1 significantly decreased dur-

**Table 1. Mean ± SEM Values of Body Weight, Body Fat Mass, Percentage Body Fat, REE, RQ, Blood Pressure, and Heart Rate Before and After Metformin and Placebo Treatment**

| | Placebo | | Metformin | | |
|---|---|---|---|---|---|
| | Before | After | Before | After | *P* Value |
| Body weight (kg) | 80.0 ± 2.0 | 80.2 ± 2.0 | 80.4 ± 2.1 | 80.5 ± 2.0 | .838 |
| Body fat mass (kg) | 13.1 ± 1.2 | 13.3 ± 1.1 | 13.6 ± 1.0 | 13.9 ± 1.1 | .916 |
| Percent body fat (%) | 16.3 ± 1.3 | 16.5 ± 1.2 | 16.9 ± 1.1 | 17.2 ± 1.2 | .960 |
| REE (kcal/d) | 1,749 ± 54 | 1,740 ± 44 | 1,819 ± 70 | 1,730 ± 30 | .260 |
| RQ | 0.86 ± 0.02 | 0.82 ± 0.02 | 0.87 ± 0.02 | 0.80 ± 0.01 | .983 |
| Systolic BP (mm Hg) | 123.6 ± 2.5 | 122.6 ± 2.3 | 121.0 ± 2.9 | 122.1 ± 2.7 | .610 |
| Diastolic BP (mm Hg) | 73.1 ± 2.2 | 72.1 ± 1.7 | 74.3 ± 2.0 | 71.8 ± 1.7 | .487 |
| Heart rate (beats/min) | 62.9 ± 2.1 | 64.1 ± 3.2 | 63.8 ± 2.3 | 66.1 ± 2.7 | .680 |

NOTE. Data analysis was based on ANOVA for repeated measures. *P* values are given for the interaction 'time by drug' indicating an effect of metformin.

Abbreviation: BP, blood pressure.

ing metformin treatment, while serum glucagon levels increased (Table 2). In addition, metformin significantly decreased insulin resistance, as estimated by HOMA. There were no significant effects of metformin on serum IGFBP-3 levels and urinary cortisol excretion. As shown in Table 3, there was also no difference in serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, TG, FFA, glycerol, $\beta$-hydroxybutyrate, and uric acid between the 2 conditions at the end of the treatment period.

### *Correlation Analysis*

Results of the correlation analysis are summarized in Table 4. Before starting the treatment period, serum leptin concentration was significantly correlated with body weight, body fat mass, percentage body fat, and serum insulin in both treatment conditions, while the correlation with C-peptide and glucagon reached significance only in the metformin condition. At the end of the treatment period, serum leptin concentration was correlated with body weight, body fat mass, percentage body fat, C-peptide, and glucagon in both treatment conditions. Interestingly, serum leptin concentration was also inversely correlated with self-reported feelings of hunger at the end of placebo, but not metformin, treatment. Percent changes in serum leptin concentrations during both treatment conditions were inversely correlated with changes in body fat mass. In the metformin condition, percent changes in serum leptin were additionally correlated with changes in serum insulin and C-peptide concentrations.

## DISCUSSION

To our knowledge, the present study is the first to evaluate the effects of short-term treatment with metformin on body weight and body fat content in normal-weight, healthy subjects. Unlike in obese subjects,[11,12] metformin did not reduce body weight and body fat content in normal-weight subjects. Notably, leaving body weight unaffected, metformin distinctly reduced the serum leptin concentration. Also, insulin and IGF-1 serum concentrations were reduced, and serum glucagon concentration was increased after metformin treatment.

In contrast to the present findings in normal-weight subjects, in obese subjects, Paolisso et al[12] found a 2.8-kg reduction in body weight and a 1.4-kg reduction in body fat mass during a 15-day treatment with 500 mg metformin twice daily. Because this study was performed in a between-subjects design with 2 groups each containing 15 subjects, the statistical power of that study was lower than in the present study. Therefore, it appears unlikely that the absence of a significant effect of metformin on body weight here is due to a type 2 error. Also, the metformin

**Table 2. Mean ± SEM Values for Endocrine Parameters and Insulin Resistance (as estimated by HOMA) Before and After Metformin and Placebo Treatment**

| | Placebo | | Metformin | | |
|---|---|---|---|---|---|
| | Before | After | Before | After | *P* Value |
| Glucose (mmol/L) | 5.1 ± 0.1 | 5.2 ± 0.1 | 5.2 ± 0.1 | 4.9 ± 0.1 | .011 |
| Insulin (pmol/L) | 43.6 ± 4.6 | 41.3 ± 4.6 | 47.6 ± 4.9 | 32.4 ± 3.1 | .044 |
| C-peptide (nmol/L) | 0.53 ± 0.06 | 0.52 ± 0.07 | 0.53 ± 0.05 | 0.39 ± 0.04 | .117 |
| Glucagon (ng/L) | 140.4 ± 17.6 | 136.5 ± 19.6 | 143.6 ± 18.7 | 201.5 ± 23.0 | <.001 |
| Leptin ($\mu$g/L) | 3.09 ± 0.55 | 3.36 ± 0.56 | 3.08 ± 0.43 | 2.35 ± 0.26 | <.001 |
| IGF-1 ($\mu$g/L) | 287 ± 20 | 263 ± 14 | 287 ± 15 | 237 ± 14 | .013 |
| IGFBP-3 ($\mu$g/L) | 4,038 ± 163 | 3,680 ± 164 | 4,004 ± 180 | 3,484 ± 183 | .330 |
| Urinary cortisol (nmol/L)/creatinine ($\mu$mol/L) | NM | 154 ± 14 | NM | 146 ± 6 | .637 |
| Insulin resistance (pmol/L · mmol/L) | 7.02 ± 0.20 | 7.29 ± 0.23 | 7.19 ± 0.47 | 6.46 ± 0.23 | .011 |

NOTE. Data analysis was based on ANOVA for repeated measures. *P* values are given for the interaction time by drug indicating the effects of metformin on parameters. Cortisol excretion was compared between the 2 conditions by Student's paired *t* test.

Abbreviation: NM, not measured.

**Table 3. Mean ± SEM Values of Metabolic Parameters at the End of the 15-Day Treatment With Metformin and Placebo**

| | Placebo | Metformin | *P* Value |
|---|---|---|---|
| Total cholesterol (mmol/L) | 4.06 ± 0.19 | 3.79 ± 0.21 | .139 |
| LDL-cholesterol (mmol/L) | 2.87 ± 0.22 | 2.63 ± 0.22 | .116 |
| HDL-cholesterol (mmol/L) | 1.19 ± 0.05 | 1.18 ± 0.06 | .897 |
| TG (mmol/L) | 0.66 ± 0.08 | 0.61 ± 0.06 | .523 |
| Free fatty acid (mmol/L) | 1.45 ± 0.16 | 1.33 ± 0.12 | .266 |
| Glycerol (mmol/L) | 0.37 ± 0.05 | 0.32 ± 0.03 | .140 |
| $\beta$-hydroxybutyrate ($\mu$mol/L) | 113.5 ± 17.3 | 104.9 ± 16.4 | .677 |
| Uric acid ($\mu$mol/L) | 338 ± 24 | 347 ± 12 | .585 |

NOTE. Comparisons between the 2 conditions were based on Student's paired *t* test.

dose used by Paolisso et al[12] was distinctly lower than in the present study. Hence, the failure of metformin to reduce body weight in normal-weight subjects suggests that normal-weight subjects are more resistant to the weight-reducing effects of metformin than obese subjects. However, it should be pointed out that in the absence of a direct comparison of the effect of metformin on body weight between normal-weight and obese subjects, this view remains speculative.

The most remarkable finding in this study is that metformin decreased the serum leptin concentration without simultaneously decreasing body weight and body fat content. Serum leptin concentrations are known to be closely related to body fat content.[19-24] A decrease in the serum leptin concentration during metformin treatment has previously been found in obese subjects,[12,25,26] but this decrease was accompanied by a reduction of body weight and body fat. Here, in addition to reduced leptin concentrations in the absence of changes in body fat, correlation analysis indicated a negative correlation between the changes in leptin concentration and body fat content. This finding is surprising, because a decrease in body fat (as the source of leptin) is expected to be associated with a decrease in leptin concentration. Keeping in mind that correlation analysis cannot clarify the cause-effect relationship, a possible explanation for this pattern could be that the serum leptin concentration exerts a feedback influence on body fat content, possibly via stimulating hunger, which was also inversely related to leptin concentration at the end of placebo treatment. A similar relationship between hunger and leptin has been reported in 2 previous studies.[27,28]

Short-term fasting and hypocaloric food intake decreases circulating leptin concentration even before influencing body weight.[29-31] On this basis, one may argue that subjects in the present study decreased food intake during metformin treatment to an extent that decreased leptin concentration without detectable changes in body weight and body fat content. However, such a hypocaloric food intake would also have induced distinct metabolic changes, which are characterized by increased lipolysis.[29] In the present study, multiple parameters were used to asses potential changes in lipid oxidation (FFA, glycerol, $\beta$-hyroxyburyrate, RQ). Yet, none of these parameters indicated any increase of lipid oxidation during metformin treatment. Therefore, it is unlikely that the decrease in leptin concentration after metformin was a consequence of hypocaloric food intake.

Insulin, as well as glucose, can acutely increase leptin secretion.[15,30] Consistent with previous findings,[21-24] the serum leptin concentration was found to be correlated with the serum insulin concentration. Because metformin, as expected, decreased the serum insulin and plasma glucose concentrations, it could be that the associated decrease in leptin concentration was a consequence of the decreased stimulation by insulin or glucose. This view is supported by the correlation found between changes in serum leptin and serum insulin, as well as the C-peptide concentration, during metformin treatment. However, another explanation may derive from 2 recent in vitro studies[32,33] showing a direct inhibitory influence of metformin on leptin secretion from adipocytes. In light of these data, one may speculate that metformin may also directly inhibit leptin secretion.

Besides the effects on leptin concentration, metformin induced profound changes in other endocrine parameters, ie, a decrease in serum insulin and IGF-1 concentration and an increase in serum glucagon concentration. While decreases in insulin concentration have been found by many others,[6,11-13,25]

**Table 4. Correlation Coefficients Between Serum Leptin Concentration and Body Weight, Body Fat, Insulin, C-Peptide, Glucagon, and Self-Rated Feeling of Hunger Before and After Treatment Period, as Well as Between Percent Changes in Serum Leptin Concentration (Δ leptin %) and Changes in Other Variables During Treatment Period, Respectively**

| | Before Treatment | | After Treatment | | Δ Leptin % | |
|---|---|---|---|---|---|---|
| | Placebo | Metformin | Placebo | Metformin | Placebo | Metformin |
| Body weight | 0.61* | 0.55* | 0.51 | 0.52* | 0.28 | 0.12 |
| Body fat mass | 0.89† | 0.77† | 0.63* | 0.79† | −0.59* | −0.58* |
| Percent body fat | 0.80† | 0.59* | 0.53* | 0.68‡ | −0.56* | −0.39 |
| Insulin | 0.69§ | 0.77† | 0.37 | 0.41 | 0.18 | 0.52* |
| C-peptide | 0.45 | 0.72§ | 0.58* | 0.56* | 0.11 | 0.54* |
| Glucagon | 0.49 | 0.61* | 0.59* | 0.53* | 0.26 | 0.28 |
| Hunger score | | | −0.56* | −0.33 | | |

NOTE. Correlations between serum leptin concentration and changes in serum leptin during the treatment period with other variables did not reach significance.

*$P < .05$.

†$P < .001$.

‡$P < .01$.

§$P < .005$.

the effects on IGF-1 and glucagon concentration represent novel findings. The changes could be explained by a direct influence of metformin on IGF-1 and glucagon secretion and degradation. However, to our knowledge, such effects of metformin have not been described. Alternatively, changes in IGF-1 and glucagon concentration could be related to the decreased plasma glucose concentration or result from an interaction of the different hormonal changes during metformin treatment. For instance, the increase in glucagon concentration during metformin treatment could have derived from the decrease in circulating insulin and IGF-1 levels, because both of these hormones are known to suppress pancreatic glucagon secretion.[34-36] While cause and effect cannot be dissociated among the concurrent changes in endocrine parameters on the basis of the present data, it remains to be pointed out that this pattern of changes induced by metformin is remarkably comparable with patterns observed during starvation and states of negative energy balance.[36,37]

That metformin did not affect body weight and body fat content in our normal-weight subjects sheds new light on the mechanisms underlying the weight-reducing effects of metformin in obese and diabetic subjects. Modification of fuel partitioning,[38] characterized by improved lipid oxidation rates, has been proposed to be one of the mechanisms through which metformin exerts its blunting effect on body fat storage.[39] However, only a few studies showed an increasing effect of metformin on lipid oxidation,[39] while the majority of studies found unchanged[3,6,40-42] or even decreased[3,7,43-46] lipid oxidation during metformin treatment. Here, parameters of lipid oxidation also did not indicate any effect of metformin, and REE was unaffected by metformin, which agrees with previous results.[6,12,42] In this setting, changes in fuel partitioning and REE probably do not represent mechanisms essential for the weight-reducing effects of metformin.

Another mechanism could be a reduction in food intake during metformin treatment, which has been found in animals[47,48] and in obese humans.[4,10,42] Furthermore, metformin has been shown to decrease feelings of hunger in obese subjects.[4] In the present study, food intake was not assessed to prevent subjects from paying attention to their eating habits. However, ratings of hunger and also recall of food-related words, which can be considered an implicit measure of hunger motivation,[49] did not indicate any significant effect of metformin on hunger. This finding contrasts with the observations in obese subjects,[4] suggesting that the effects of metformin on hunger may differ between normal-weight and obese subjects. One possible explanation for the absence of a metformin effect on hunger in normal-weight subjects could derive from the decrease in serum leptin levels during metformin treatment. Consistent with results of previous studies,[27,28] leptin levels were inversely correlated with feelings of hunger, suggesting an influence of leptin on hunger. According to the hypothesis of leptin being a satiety signal, the decrease in leptin would be expected to promote hunger. Metformin, on the hand, is thought to exert an anorectic effect via an unknown mechanism.[10,42] Taken together, one may speculate that in normal-weight subjects, the putative anorectic effect of metformin was compensated by a hunger-stimulating effect of decreased leptin concentration, resulting in unchanged feelings of hunger as the net effect of metformin. Because obesity is thought to be associated with leptin resistance,[50,51] the decrease in leptin levels may not compensate the anorectic effects of metformin in obese subjects. Thus, differences in leptin sensitivity may explain the different effect of metformin on hunger and body weight in normal-weight and obese subjects.

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