Hypobaric Hypoxia Causes Body Weight Reduction in Obese Subjects

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The reason for weight loss at high altitudes is largely unknown. To date, studies have been unable to differentiate between weight loss due to hypobaric hypoxia and that related to increased physical exercise. The aim of our study was to examine the effect of hypobaric hypoxia on body weight at high altitude in obese subjects. We investigated 20 male obese subjects (age 55.7 ± 4.1 years, BMI 33.7 ± 1.0 kg/m^2). Body weight, waist circumference, basal metabolic rate (BMR), nutrition protocols, and objective activity parameters as well as metabolic and cardiovascular parameters, blood gas analysis, leptin, and ghrelin were determined at low altitude (LA) (Munich 530 m, D1), at the beginning and at the end of a 1-week stay at high altitude (2,650 m, D7 and D14) and 4 weeks after returning to LA (D42). Although daily pace counting remained stable at high altitude, at D14 and D42, participants weighed significantly less and had higher BMRs than at D1. Food intake was decreased at D7. Basal leptin levels increased significantly at high altitude despite the reduction in body weight. Diastolic blood pressure was significantly lower at D7, D14, and D42 compared to D1. This study shows that obese subjects lose weight at high altitudes. This may be due to a higher metabolic rate and reduced food intake. Interestingly, leptin levels rise in high altitude despite reduced body weight. Hypobaric hypoxia seems to play a major role, although the physiological mechanisms remain unclear. Weight loss at high altitudes was associated with clinically relevant improvements in diastolic blood pressure.

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INTRODUCTION

Obesity and associated disorders are a growing problem in many Western societies, and effective treatments remain elusive. It is known that spending time at high altitudes results in weight loss; however, the reason for this is unclear. The clarification of mechanisms leading to weight loss at high altitudes might provide new tools for treating obesity in the future.

It is thought that high-altitude weight loss is related to changes in basal metabolic rate (BMR) (1); however, published BMR data are inconsistent, and both increases (2) and decreases (3) in BMR have been reported. Much of the available data was gathered from hikers (4–6), and is therefore subject to confounding factors, such as cold and exertion. It is impossible to tease out the role of high altitude itself on body weight from these data sets.

One possible cause of high altitude–induced weight loss is the loss of appetite and associated decreased caloric intake that often occurs as a result of acute mountain sickness (AMS). Other symptoms of AMS include headache, nausea, and vomiting (7). After proper acclimatization, food intake returns to normal at altitudes below 4,500 m (1).

Leptin is a white adipose tissue secretagogue found at elevated levels in the plasma of obese subjects (8–10). It may be involved in the reduced food intake observed at high altitudes, making it an interesting factor in the present study. At high altitudes, low barometric pressure results in a reduction in available oxygen. There seems to be a correlation between leptin and hypobaric hypoxia. Increased leptin levels are thought to trigger appetite reduction at high altitudes, but the literature on plasma leptin levels in relation to high altitude is inconsistent, with various studies reporting increased (4,11), decreased (12–15), and unchanged (5,16,17) levels of plasma leptin. To further complicate matters, studies examining the relevance of leptin vary in exercise programs and diets, BMI of participants, means of ascent to high altitude, and length of high altitude stay.

Most published studies focus almost exclusively on athletes and normal-weight subjects. Data obtained from these studies cannot necessarily be applied to obese subjects. Moreover, these studies are performed in locations higher than 3,300 m. Obese subjects, however, are mostly untrained, which means exposing them to altitudes above 3,000 m could result in severe hypoxemia.

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The aim of our study was to examine the effect of hypobaric hypoxia on body weight at moderately high altitude in obese subjects. Levels of physical activity were kept constant, but no diet restrictions were imposed on participants. Because plasma leptin levels are high in obese subjects, special attention was paid to the influence of hypobaric hypoxia on plasma leptin levels. The lasting influence of the high-altitude stay 4 weeks after returning to low altitude (LA) was also analyzed.

METHODS AND PROCEDURES

Patients and methods

Study population. Twenty obese male patients (Ob) with metabolic syndrome (MS) participated in our study (mean age 55.7 ± 4.1 years, BMI 33.7 ± 1.0 kg/m^2). All the subjects normally lived at LA (571 ± 29 m).

According to the National Cholesterol Education Program Adult Treatment Panel III, MS is defined as the presence of three or more of the following five criteria: increased waist circumference (≥102 cm), hypertriglyceridemia (≥150 mg/dl), low (≤40 mg/dl) high-density lipoprotein, hypertension (≥130/85 mm Hg), and high fasting glucose (≥110 mg/dl). All patients fulfilled at least three of these five criteria. Exclusion criteria were coronary heart disease, cardiac insufficiency, pulmonary disease, uncontrolled hypertension, poorly controlled diabetes mellitus, or malignancy. The study was approved by the local ethics committee of the University of Munich and performed according to the principles of the Declaration of Helsinki. All patients gave written informed consent.

Study design. Baseline (day 1, D1) and follow-up investigations (day 42, D42) were performed in Munich (altitude 530 m; Department of Internal Medicine, University Hospital of the Ludwig-Maximilians-University, Munich, Germany). High-altitude measurements (day 7, D7 and day 14, D14) were performed at the air-conditioned Environmental Research Station Schneefernerhaus (UFS, Zugspitze, Germany) at an altitude of 2,650 m (**Figure 1**), located 300 m below the top of Germany's highest mountain, Zugspitze. The station was effortlessly reached by cogwheel train and cable car during the afternoon of day 6. During the week, patients ate and drank without restriction, as they would have at home at LA. Activity was restricted to slow walks throughout the station: more vigorous activity was not permitted. Nutritional choices and physical activity were monitored by food protocols and by step counters, respectively. Laboratory testing and examinations were performed on the first full day (D7) and last day (D14) of the mountain stay. Follow-up examinations 4 weeks following the altitude stay (D42) were performed in Munich.

In order to examine the effects of hypoxia in patients with MS, we analyzed laboratory and performance parameters on D1, D7, D14, and D42 (**Table 1**), including fasting blood analysis (standard blood parameters, lipometabolism parameters, glucose metabolism, inflammation parameters, and the peptides insulin, ghrelin, and leptin). Furthermore, we measured cardiovascular parameters (systolic and diastolic blood pressure, and standard cardiopulmonary exercise testing—Oxycon Alpha; Cardinal Health, Höchberg, Germany), resting blood gas analysis (oxygen and carbon dioxide partial pressure and oxygen saturation—ABL 710; Radiometer, Copenhagen, Denmark), waist size, weight, muscle mass, fat mass, and body liquid (bioimpedance machine BG 22; Beurer, Ulm, Germany). The number of steps taken each day was determined by pace counter (Pedometer Plus; Silva, Oberursel, Germany). Symptoms were recorded in accordance with the Lake Louise Scoring System daily from day 7 to day 14 (7). Energy intake was documented in daily nutrition journals, which are also used routinely in our outpatient clinic. The selection and amount of foods was similar at the different locations. Food was freely available, and we made great efforts to accommodate individual food preferences. Resting energy expenditure (BMR) was determined during the 5-min reference phase at the beginning of the standardized cardiopulmonary exercise testing program. Indirect calorimetry was performed seated in an upright position. The subjects wore the same clothing for each of the calorimetric measurements. Testing was performed at the same time of day for each patient after a minimum of 8-h fasting. Due to the time consuming procedure, cardiopulmonary exercise testing was only performed during the last day at altitude. The patients' medications remained unchanged during the study period.

Blood sample processing. After at least 8 h of fasting, morning fasting blood samples were collected using serum tubes for standard blood analysis and peptide analysis, and NaF-containing tubes for the determination of glucose. For subsequent hormone analysis, samples were kept on crushed ice until centrifugation at 4,000 rpm for 15 min (4 °C) and aliquots were stored at −20 °C.

Leptin, ghrelin, and insulin enzyme-linked immunosorbent assay and radioimmunoassay. Human leptin enzyme-linked immunosorbent assay kits were purchased from IBL (Hamburg, Germany). Based on a sandwich principle, the microtiter wells of the kit are coated with a monoclonal antibody against an antigenic site unique to the leptin molecule. Fifteen microliters of undiluted unextracted patient plasma containing endogenous leptin were incubated in the coated well with a specific rabbit antileptin antibody. During incubation, a sandwich complex was formed. Unbound material was washed off and an anti-rabbit peroxidase conjugate was added for detection of the bound leptin. After adding substrate solution, the intensity of color developed was proportional to the concentration of leptin in patient sample.

Plasma ghrelin concentrations were determined with a commercial radioimmunoassay (Phoenix Pharmaceuticals, Belmont, CA). The assay uses ^{125}I-labeled bioactive ghrelin as a tracer molecule and a polyclonal antibody raised in rabbits against full-length octanoylated human ghrelin, which detects both active and inactive ghrelin. The interassay coefficient of variation was 10% and the intra-assay coefficient of variation was 4%.

Insulin concentrations were determined using insulin kit EZHI-14K (Linco, St Charles, MO). Glucose concentrations were measured by the hexokinase method (Roche Diagnostics, Mannheim, Germany) (mg/dl × 0.055 = mmol/l).

All samples from one subject were tested in duplicate in the same assay.

Statistics. Data were analyzed using SPSS software (release 15.0; SPSS, Chicago, IL). We used the nonparametric test for multiple related samples (Friedmann procedure with exact significance) as this test is especially appropriate for small samples with similar data distribution. When the Friedmann procedure indicated a significant difference (rank) in the results from D1, D7, D14, or D42, Wilcoxon signed-rank method tests for two related samples were performed to detect significant differences between the two test results. A P value of ≤0.05 was regarded statistically significant. Values are expressed as mean (s.e.m.) or median (range) as appropriate.

RESULTS

Energy intake, BMR

Study participants reduced their energy intake slightly during high-altitude stay (D7, D14) and significantly thereafter (D42) compared to D1.

The BMR was significantly increased at high altitude. It returned to baseline values on day 42 (**Table 1**, **Figure 2**).

Body weight, BMI, waist

Body weight changed from 105.2 ± 3.0 kg at D1 to 105.1 ± 3.0 kg (D7), 103.6 ± 3.0 kg (D14; $P < 0.001$ vs. D1), and 104.1 ± 2.9 kg

Table 1 Demographic data of the study population and parameters of the glucose and fat metabolism

	D1	D7	D14	D42
Obesity				
Body weight (kg)	105.2 ± 3.0	105.1 ± 3.0	103.6 ± 3.0*	104.1 ± 2.9*
BMI (kg/m^2)	33.7 ± 1.0	33.7 ± 1.0	33.2 ± 1.0*	33.4 ± 1.0*
Waist circumference (cm)	117.3 ± 2.1	117.8 ± 2.3	116.7 ± 2.3	116.1 ± 2.2
Energy intake (calories/day)	2,989 ± 332	2,262 ± 194*	2,256 ± 224	2,195 ± 163*
Basal metabolic rate (EE/kg/day)	23.7 ± 1.3	ND	27.3 ± 1.3*	24.2 ± 1.4
Muscle mass (%)	35.9 ± 0.3	35.8 ± 0.3	35.9 ± 0.3	35.8 ± 0.3
Fat mass (%)	33.9 ± 0.8	34.0 ± 0.9	33.7 ± 0.9	33.8 ± 0.8
Body liquid (%)	48.7 ± 1.0	48.5 ± 1.2	48.8 ± 1.2	48.5 ± 1.1
Exertion				
Pace counting (paces/day)	5,550 ± 704	ND	5,406 ± 424	6,796 ± 732
6-min walking test (m)	585.2 ± 17.5	ND	596.6 ± 19.3	625.5 ± 19.5*
Cardiovascular parameters				
Systolic blood pressure (mm Hg)	143.6 ± 4.0	152.1 ± 5.7	140.9 ± 3.8	143.5 ± 4.9
Diastolic blood pressure (mm Hg)	93.7 ± 2.9	83.7 ± 2.7*	80.4 ± 2.8*	80.4 ± 2.8*
Heart rate (beats/min)	133.4 ± 4.4	ND	127.6 ± 3.5	131.6 ± 4.0
Glucose metabolism				
Fasting blood glucose (mg/dl)	125.2 ± 10.9	123.0 ± 6.5	123.3 ± 7.6	117.5 ± 7.4
Insulin (μU/ml)	14.9 ± 2.3	15.0 ± 2.2	18.4 ± 3.9	15.6 ± 3.0
HbA_{1c} (%)	6.6 ± 0.3	6.5 ± 0.4	6.5 ± 0.3*	6.3 ± 0.3*
HOMA	5.0 ± 1.0	4.9 ± 0.8	6.3 ± 1.9	5.2 ± 1.3
Fat metabolism				
Cholesterol (mg/dl)	200.9 ± 8.6	204.8 ± 9.9	199.2 ± 9.6	196.5 ± 9.8
HDL (mg/dl)	42.4 ± 2.2	40.6 ± 2.0	38.1 ± 1.7*	42.7 ± 2.0
LDL (mg/dl)	119.4 ± 7.5	125.0 ± 8.3	126.4 ± 9.4*	111.1 ± 8.6
Triglyceride (mg/dl)	202.4 ± 25.1	196.4 ± 22.1	174.7 ± 21.2	221.5 ± 30.9
Blood gas analysis (mm Hg)				
Oxygen dioxide partial pressure	77.4 ± 1.7	52.4 ± 1.5*	58.8 ± 1.0*	77.1 ± 1.5
Carbon dioxide partial pressure	37.0 ± 0.9	32.6 ± 0.8*	29.1 ± 0.8*	36.8 ± 0.9
Oxygen saturation (%)	95.2 ± 0.3	85.9 ± 2.5*	88.5 ± 1.8*	95.3 ± 0.3

Data are expressed as mean ± s.e.m. D1 and D42: low altitude; D7 and D14: high altitude, $n = 20$.
EE, energy expenditure; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; ND, not determined.
*$P \leq 0.05$ vs. D1.

(D42; $P = 0.018$ vs. D1) (Figure 2). Waist size and bioimpedance results did not change significantly during the study period (Table 1).

Biochemical measurements

Basal leptin levels showed an increase at D7 and D14 when compared to D1 or D42, and a further decrease at D42 compared to baseline levels. Plasma ghrelin levels did not change significantly during the study period (Table 2).

Glucose metabolism

Neither blood sugar levels nor insulin levels changed significantly during the study period. HbA_{1c} decreased significantly during the study period. HOMA score increased during the high-altitude stay; however, these changes were not statistically significant (Table 1).

Fat metabolism

HDL dropped significantly from 42.4 ± 2.2 mg/dl (D1) to 38.1 ± 1.7 mg/dl (D14; $P = 0.01$), whereas LDL rose significantly between D1 (119.4 ± 7.5 mg/dl) and D14 (126.4 ± 9.4 mg/dl; $P = 0.025$). There were no differences of HDL and LDL plasma levels between D1 and D42, respectively. Total cholesterol did not change significantly from D1 to D14. Triglycerides showed a decreasing trend in high altitude that did not reach statistical significance (Table 1).

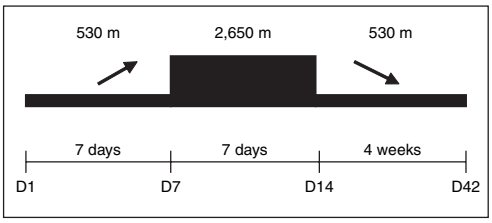

Figure 1 Chronological study protocol.

Table 2 Basal plasma ghrelin and leptin levels in 20 obese subjects at D1, D7, D14, and D42

	D1	D7	D14	D42
Leptin (ng/ml)	17.1 ± 4.1	18.7 ± 4.0*	19.8 ± 4.0*	15.0 ± 2.6
Ghrelin (pg/ml)	174.1 ± 18.3	185.3 ± 19.5	171.2 ± 16.4	181.1 ± 14.6

Data are expressed as mean ± s.e.m. D1 and D42: low altitude; D7 and D14: high altitude, $n = 20$.
*$P < 0.05$.

Blood gas analysis, respiratory exchange ratio

Oxygen partial pressure decreased significantly from D1 to D7 and increased slightly by D14 due to ventilatory acclimatization. There was no significant correlation between plasma leptin levels and oxygen saturation, oxygen and carbon dioxide partial pressure, respectively (Table 1).

The mean measured respiratory exchange ratio at rest was 0.89 ± 0.089 at D1, 0.84 ± 0.053 at D14, and 0.89 ± 0.112 at D42.

Hemoglobin and hematocrit

Hemoglobin values were 15.3 ± 0.22 g/dl at D1, 15.4 ± 0.25 g/dl at D7, 15.6 ± 0.24 g/dl at D14, and 15.2 ± 0.27 g/dl at D42. Hematocrit changed from 44.0 ± 0.52% (D1) to 47.6 ± 1.0% (D7), 48.2 ± 0.8% (D14), and 44.0 ± 0.7% at D42.

Exercise capacity

Daily pace counting did not increase until the end of the high-altitude stay. However, pace counting was higher on day 42 compared to baseline examination (6796 ± 732 paces vs. 5550 ± 704 paces), which is effectively 785 m more daily presuming a pace length of 63 cm. Accordingly, the results of the 6-min walking test increased significantly at D42 (D1: 582.2 ± 17.5 m, D42: 625.5 ± 19.5 m; $P = 0.02$, Table 1).

Cardiovascular parameters

Diastolic blood pressure was significantly lower at D7, D14, and D42 compared to D1. Systolic blood pressure remained unchanged except for an increasing trend at D7 compared to D1. Heart rate was elevated at D14 compared to D1 and returned to baseline levels thereafter (Table 1).

AMS score (Lake Louise Scoring System)

All subjects tolerated the altitude exposure without major symptoms. The AMS showed a decline from 2.5 (range 0–7) on day 1 at high altitude to 0 (range 0–2) on day 6.

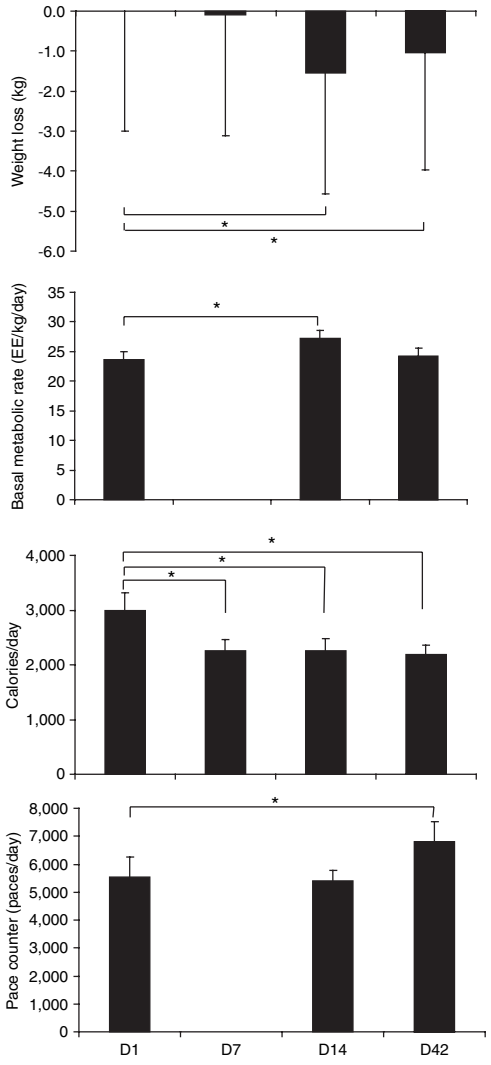

Figure 2 Body weight reduction (kg), basal metabolic rate (EE/kg/day), energy intake (kcal/day), and pace counter (paces/day) in 20 obese subjects at D1, D7, D14, and D42 (mean ± s.e.m). *$P \leq 0.05$. EE, energy expenditure.

DISCUSSION

In subjects with normal BMI, loss of body weight during high-altitude mountain expeditions has been described in several studies (4–6). Probable causes for the weight loss are higher metabolic rate, different energy output, reduced perception of hunger feeling together with decreased food intake and several endocrine factors.

Body weight reduction is undesired in athletes but desired in obese individuals. Yet only one single study investigated obese subjects (17) in high altitude. In contrast to our study, these investigators included an exercise intervention in which subjects participated in walking tours 4–5 times a week. The aim of our study was to clarify the independent effect of hypobaric hypoxia on body weight without additional exercise. Thus, exertion at high altitude was maintained at the same level as on D1, which we documented by using pace counters. Exertion did not change from D1 to D14. There was even a

trend toward less physical activity at high altitude, probably due to the limited walking space in the high-altitude research station. To our knowledge, this is the first study demonstrating significant weight loss in obese subjects with MS under hypobaric hypoxic conditions.

The majority of early weight loss at high altitudes is usually due to loss of body water. The bioimpedance analysis, however, could not detect significant differences in body water in the course of the study, nor could we find any significant changes in fat or muscle mass.

In concordance with previous studies, the present study showed a raised BMR at high altitude, although the mechanism is not fully understood (3,18,19). BMR is generally elevated during the first days of a high-altitude stay and decreases thereafter, plateauing at or slightly above basal levels (2,3,18,19). Because our study only assessed BMR once at high altitude, we were not able to demonstrate this trend.

The cause of increases in BMR at high altitude remains the source of specific discussion. Nair and colleagues hypothesized that upregulation of thyroid function due to cold is the cause, whereas Mawson *et al.* suggested that increased sympathetic drive plays a role (3,18). Whatever the cause, it seems clear that increases in BMR lead to weight loss.

Participants in our study consumed an average of 734 kcal/day less at high altitude, which corresponds to 5,138 kcal/week, even though food intake was not restricted. There are several potential explanations for this decrease in food intake. Loss of appetite is a common symptom of AMS. It is known that below 4,500 m, appetite and food intake return to normal after acclimatization (20). In our participants, AMS scores returned to 0 on day 11, meaning that the effects of AMS on appetite would have resolved by D14. Nevertheless, food intake at D14 was significantly reduced. The reason is not yet clear. Reductions in the perception of hunger in hypobaric hypoxia have been previously reported (4,21). Furthermore, there is an earlier feeling of satiety under these conditions (22). Additional factors may include group dynamics and underreporting of food intake (23–25). Interestingly, we could show that subjects maintained their decreased food intake during the follow-up period. This might be important for antiobesity therapy strategies.

In hypobaric chamber studies by Westerterp and Rose (26,27), young healthy males were examined during progressive hypobaric decompression during 31 and 40 days with minimal physical activity. As in our study, the authors observed a reduction of body weight associated with reduced food intake. The amount of weight reduction was higher than they would have expected based on calculations comparing energy intake with energy expenditures. However, the atmospheric pressure experienced by subjects in those studies was much lower than in our study. The mean atmospheric pressure in our study was 547 mm Hg (= 730 hPa), whereas participants in the studies by Westerterp and Rose spent all but the first 2 days at much lower atmospheric pressures. For this reason, a direct comparison between those studies and our results is not possible. Nevertheless, our results showed a similar trend, with a discrepancy between the amount of weight loss expected based on calculations (1 kg) and the actual measured decrease in weight (1.54 kg, (calculation of expected weight loss: mean reduction of caloric intake at altitude was 734 kcal/day, or 5,138 kcal/week. Together with an increase in metabolic rate (268 kcal/day or 1,876 kcal/week), we found a total difference of 7,013 kcal/week. Assuming that 7,000 kcal equals 1 kg of body fat, our subjects should have lost only 1 kg during 1 week.)). This may have been due to increased resting energy expenditure, perhaps due to increased sympathetic drive, during the first days at altitude. In our study, resting energy expenditure was assessed at the end of the high-altitude stay (D14), and so transitory increases early in the week could not be detected. Obesity and impaired glucose tolerance might be the reasons for higher overall resting energy expenditure values in our study as previously shown by Nakaya and co-workers (28).

Another potential explanation for the loss of weight in our subjects may be loss of body water. Although no significant differences in bioimpedance were measured between low and high altitude, our bioimpedance measurements may not have been sensitive enough to detect very small changes in body composition.

A major hormonal candidate for reduced food intake in high altitude is the adipocyte secretory product leptin. The majority of studies investigating normal-weight subjects showed a decrease in plasma leptin levels, with (12,14) and without (13,15) significant weight reduction at high altitude. The results from other studies contradicted these findings, reporting unchanged leptin with weight loss (5) and with stable weight (16). Two further studies with healthy untrained males reported an increase of plasma leptin levels at altitudes above 4,000 m (4,11). In agreement with those two previous studies, obese participants in our study also showed elevated plasma leptin levels under comparable severe hypoxia (pO_2 52.4 mm Hg). Plasma leptin levels seem to be stimulated by hypobaric hypoxia in high altitude. This effect seems to be independent of body weight. One possible mechanism is suggested by Grosfeld and co-workers (29). They showed that hypoxia induces leptin gene expression in a human cell line via hypoxia-inducible factor I. Of course, this deserves further evaluation in clinical studies. To our knowledge, there is one study investigating obese subjects at high altitude by Schobersberger and colleagues. Plasma leptin levels did not change in their study (17); however, their participants had an average BMI of 3 kg/m^2 lower than in our population. Moreover, the study group was only exposed to moderate altitude (1,700 m), which, although it was not explicitly described in their paper, probably resulted in a lesser degree of hypoxia.

Another further strength of our data is the documentation of sustained weight loss 4 weeks after returning from high altitudes. At this time point, plasma leptin levels had returned to the basal levels measured before the mountain stay. Thus, leptin alone is probably not the cause of the decrease in weight, nor is ghrelin, a hormone which correlates inversely with body weight (30). Obese subjects show lower basal ghrelin levels compared to normal-weight subjects. Literature on ghrelin in high altitude is sparse and inconsistent, with reports of both decreased

ghrelin levels and no change in ghrelin at high altitude (5,11). In our study, the average ghrelin level was 174 pg/ml, which is rather low compared to the literature (10,31). Nevertheless, an increase after weight loss could not be observed, probably because the absolute amount of weight loss was so small. This agrees with findings from Benso *et al*., who showed unchanged ghrelin levels despite a weight reduction of 5 kg (5). We could not find a significant correlation between oxygen saturation or oxygen partial pressure, and either ghrelin or leptin.

A very interesting discovery is that the weight decrease observed in high altitude was maintained in the follow-up period. As far as we know, this observation has not been previously described. This effect may be due to the maintained decreased food intake and increased physical activity. Participants showed a higher walking distance of about 790 m/day more than before the high-altitude stay. They also showed a significantly better 6-min walking test.

We suspect that physiological responses to high altitude improved our subjects' ability to exert themselves upon their return to LA. During their stay at the UFS, subjects in our study were confronted with a substantially lower PaO_2 than they experience in Munich. This relative hypoxia forced them to slowly increase their ventilatory response to physical activity while at high altitude. The increase in ventilatory acclimatization is shown by the reduction of $PaCO_2$ during the course of the week at high altitude. In addition, the relative hypoxia led to increases in the subjects' hemoglobin levels. We hypothesize that these factors combine to produce an "altitude training and memory effect," positively influencing levels of physical activity and fitness even after return to LA.

Due to the increase in hemoglobin levels, our subjects' blood oxygen content at LA was higher after their high-altitude stay, which may have allowed them to maintain higher activity levels during the subsequent weeks at LA.

In addition, the ventilatory acclimatization may have allowed the subjects to exert themselves at LA without feeling out of breath. These two factors might have led to an overall increase in activity and therefore helped to maintain the reduced body weight.

As both ventilatory acclimatization and increases in hemoglobin are inevitable due to the reduced atmospheric pressure at high altitudes, the stay at high altitude might be superior to other forms of activity enhancement, as it does not depend on the active participation and motivation of the subjects.

Our study seems to provide some evidence that this altitude training and memory effect may last 4 weeks. Whether longer exposure times could prolong this effect remains to be the subject for further studies. However, new data from Han Chinese exposed to long periods of time at high altitudes show that acclimatization can be preserved over a period of 5 months at LA (32).

The reduced body weight was associated with clinically relevant improvements in diastolic blood pressure, an effect which remained during the follow-up period. Additionally, there was a trend toward lower systolic blood pressure, although this trend was not significant. The study Schobersberger conducted with obese subjects at moderate altitude showed a significant decrease in systolic but not diastolic blood pressure (17). This discrepancy cannot be explained by the present data, but could be further investigated in future studies.

Metabolic parameters such as glucose, insulin, and insulin sensitivity did not change significantly during the study. Larger changes in body weight are probably required in order to positively influence these parameters. However, HbA_{1c} decreased significantly in the follow-up period. More significant effects on blood glucose and insulin levels might have been observed in diabetic patients, making this population an interesting group for future studies.

The effect of high altitude on plasma lipids is inconsistent in the literature, showing both positive (33–35) and negative effects (36,37), or no change in total cholesterol (17,38). However, only the minority of studies investigated subjects with increased BMI above 25 kg/m^2 (17,38). Consistent with these results, we found no change in total cholesterol. Although most studies found elevated HDL levels and decreased LDL levels (17,33,39,40), our data show the reverse, a discrepancy which remains to be explained.

In conclusion, we could show weight reduction at high altitude in obese subjects with MS combined with an improvement of blood pressure and metabolic parameters such as HbA_{1c}. Weight reduction seems to be mainly due to raised BMR and reduced food intake. We improved on previous studies by maintaining a constant level of exercise-induced energy expenditure. The weight reductions at high altitude were maintained in the follow-up period, an observation which should be further verified in future studies as it might have impact on antiobesity therapy. Leptin might be involved in the effect of hypobaric hypoxia on weight reduction, but seems to have no significance in the follow-up period.

DISCLOSURE

The authors declared no conflict of interest.

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