Effects of alternate fasting or very low calorie diet and low calorie diet on metabolic syndrome in severely obese patients


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Abstract

Background and Aim: Weight loss improves the metabolic syndrome (MetS) features and related clinical abnormalities in obese subjects. The aim of this study was to assess the effects of a non-surgical therapeutic program on the MetS in severely obese patients.

Patients and Methods: Sixty-four extremely obese patients were involved in the therapeutic program, which consisted of two alternating phases: the three-week therapeutic fasting or semi-fasting in hospital conditions and the low calorie diet with dosed physical activity in outpatient conditions. At the baseline we measured: anthropometric parameters, blood pressure and lipid profile. Subjects underwent an oral glucose tolerance test and insulin resistance/sensitivity was evaluated by the homeostasis model assessment and the oral glucose insulin sensitivity. After weight reduction by at least 10%, all mentioned assessments were repeated.

Results: None of the patients had significant adverse effects. Forty-one patients aged 43.0±11.5 years completed the study. The mean weight loss was 27 kg or 18% of the initial weight (p<0.01), which was followed by a significant decrease of the insulin resistance, the overall prevalence of MetS (32%) and all MetS parameters, without the significant change in high-density lipoprotein. This weight loss program substantially improves the MetS in extremely obese patients.

Conclusion: The tailored alternating either fasting or semi-fasting should be considered as an optional approach to manage extreme obesity and related metabolic abnormality. Hippokratia 2012, 16, 4: 335-341

Key words: severe obesity, metabolic syndrome, diet, weight loss

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Introduction

Obesity is the oldest and still the most common metabolic disorder in humans. It is most likely associated with changes in the environment of subsequent generations that influence genetic and epigenetic propensity for the weight gain and with the current habitual lifestyle that promotes sedentary behavior and provides an oversupply of energy dense food in an “obesogenic” environment. Despite a multibillion-dollar industry geared toward the weight loss, the severity of obesity and related medical conditions continues to rise–by 2030 about 2.16 billions overweighted and 1.12 billion obese individuals are foreseen.

The abdominal obesity is the inevitable feature of the metabolic syndrome (MetS) definition. MetS is a clustering of risk factors for cardiovascular disease (CVD) and diabetes, which occur together more often than by chance alone. According to IDF and AHA/NHLBI representatives, the abdominal obesity [population- and country-specific definitions of elevated waist circumference (WC)] should not be the prerequisite for the MetS diagnosis, but the presence of any three of the following five criteria: WC equal or greater than 94cm for men and 80cm for women, serum triglyceride level (Tg) of 1.7mmol/l or greater, high-density lipoprotein (HDL) less than 1.0mmol/l in men and 1.3mmol/l in women, fasting glucose of 5.6mmol/l or more, and blood pressure of 130/85mmHg or greater. The prevalence of the MetS increases with obesity grade. A small percent of the obese patients are without metabolic alterations and have obesity as the sole criterion of the MetS. They fit the current definition of “metabolically healthy but obese” phenotype. The underlying abnormality in the pathophysiology of MetS is insulin resistance.

The corner stone of MetS management is effective weight reduction which improves all metabolic features
even in the case of a modest weight loss of less than 10\%\textsuperscript{7}. Starting from 18\textsuperscript{th} century a large number of diets has been created from partial to complete fasting. Systematic investigations of fasting during long periods of time performed on a heterogeneous population of patients revealed the numerous adverse effects. This led to conclusion that the fasting may be performed only in hospital conditions and only when rigorous criteria are applied in selecting obese patients\textsuperscript{8,9}.

A clinical approach to the treatment of obesity should adhere to the following principles: a reduced energy intake and enhanced energy expenditure through increased physical activity\textsuperscript{7}.

Based on these therapeutic principles at the Clinic for Endocrinology (Clinical Centre of Serbia, Belgrade), a program for the treatment of severe obesity has been developed, which resulted in significant improvement of MetS risk factors. The program consisted of two alternating phases: (i) the three-week therapeutic fasting or semi-fasting under the strict medical supervision and (ii) the prescribed low calorie diet (LCD) and gradual increase of physical activity in outpatient conditions. This paper presents main results on the weight reduction achieved by such a therapeutic strategy on the metabolic syndrome in extremely obese patients.

**Patients and Methods**

1. **Study protocol**

This was a prospective clinical study, approved by the local ethics committee. The homogenous sample including 20-60 year old patients with a severe obesity had been chosen according to the corresponding medical history. The study included severely obese persons who previously unsuccessfully tried to lose weight in outpatient conditions.

The following exclusion criteria were applied: secondary obesity, previous or current malignancies, neuromuscular, kidney or liver disease, psychiatric disorders, binge-eating disorders, cardiopulmonary disease, pregnancy, smoking, abuse of alcohol or of any kind of psychiatric drug. ECG had to be normal.

Sixty-four severely obese patients (BMI $\geq$40 kg/m\textsuperscript{2}), aged 40.45$\pm$11.52 years, started the treatment. Twenty-three of these patients abandoned further participation in the study due to poor compliance, personal reasons or lack of time.

2. **Assessments**

The body weight was measured in light clothing in the morning. The height was measured by a stadiometer without shoes. The data were used to evaluate the body mass index (BMI). WC was measured between the lower rib and the iliac crest. The blood pressure was measured using a standard sphygmomanometer in the sitting position: three values are obtained at a 2 minute distance and the average is recorded.

We performed baseline biochemical evaluation after a 1-week eucaloric diet. Initial blood samples were collected after 12-14 hours of overnight fast to measure concentrations of Tg, total cholesterol and glucose. The oral glucose tolerance test (OGTT) was performed measuring the glucose and insulin every half an hour for 2 hours. The OGTT was done for all patients for whom a diagnosis of diabetes type 2 was not available. Impaired glucose tolerance (IGT) was diagnosed when the 2-hour plasma glucose was $\geq$ 7.8 mmol/L; diabetes was diagnosed when the 2-hour plasma glucose was $\geq$11.1 mmol/L. Diabetic state improvement was assessed through the measurement of fasting plasma glucose levels obtained monthly and HbA1C at 3-month intervals\textsuperscript{11}. Biochemical tests were performed by enzymatic methods using the analyzer Olympus Au 400. Insulin was determined by radioimmunoassay (INEP, Belgrade, Serbia). The low-density lipoprotein (LDL) in mmol/L was estimated by the Friedewald formula\textsuperscript{12}: $\text{LDL} = \text{total cholesterol} - \text{Tg}/2.18 - \text{HDL}$.

Persons were characterized as having the metabolic syndrome if they fulfilled at least 3 of the aforementioned criteria\textsuperscript{7}. The individuals who reported current use of antihypertensive medication, antidiabetic medication or drugs for elevated Tg and reduced HDL were counted as meeting the high blood pressure, the glucose or the lipids criterion, respectively.

The homeostasis model assessment (HOMA) was used to determine the insulin resistance as\textsuperscript{13}: $\text{HOMA} = (\text{basal glucose (mmol/L)} \times \text{basal insulin (\muU/mL)})/22.5$. The insulin sensitivity in response to the OGTT was evaluated by the oral glucose insulin sensitivity (OGIS), using a web-derived formula\textsuperscript{14}. HOMA and OGIS have been applied to identify hepatic and peripheral insulin sensitivity/resistance, respectively.

3. **Diet in hospital conditions**

Patients younger than 40 years of age with severe obesity without hypertension or diabetes were on a three-week therapeutic fasting mode. From the first day these patients were allowed to use only mineral water in the amount of 3l a day.

All other patients were on a very low calorie diet (VLCD) with real “home-made” food prepared by a team of nutritionists. Patients younger than 40 years of age with antihypertensive therapy and patients between 40 and 50 years old were on the VLCD of 400 kcal/day. Participants older than 50 and patients with diabetes were on the VLCD of 800 kcal/day. From the fourth day of the diet, patients used the multivitamin preparation. Allopurinol tablets were introduced for patients with high values of uric acid.

4. **Diet and physical activity in outpatient conditions**

In outpatient conditions a balanced food restriction and LCD (1000-1200 kcal/day for women and 1200-1600 kcal/day for men) had been recommended. Patients were advised of the gradual introduction of salt. The 30-90 minutes brisk walking every day with a gradual increase in the duration was suggested. After 2-4 months recovery period at home, patients were again hospitalized. A weight reduction of at least 8 kg in outpatient conditions was a prerequisite for the re-hospitalization. Follow-up
weight loss results after hospital discharge were obtained from office visits or phone interviews monthly. This pattern of the treatment has been repeated until the body weight loss reached 10%. In that case, we performed all before mentioned assessments after a 1-week recovery period at home with a eucaloric diet. Most patients were hospitalized twice and only a small number of them had to be hospitalized three times to achieve this reduction of body weight.

5. Statistical analysis

Within-group comparisons between the baseline and follow-up were performed using a two-sided, paired t-test and Wilcoxon Signed Rank for continuous variables and McNemar test for categorical variables. Due to the skewness of total cholesterol and Tg, logarithmic transformation was applied. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 15 (SPSS, Chicago, IL, USA). The P values less than 0.05 were considered as statistically significant, while the P values less than 0.01 were accepted as highly statistically significant.

Results

None of the patients included in the study during the three weeks reduction diet had significant adverse effects. The patients mainly complained of sporadic fatigue, dizziness, sickness, hunger and constipation. In outpatient conditions the patients were without symptoms. ECG changes were not registered for any of the patients. None is excluded due to side effects. Eventually, 41 severe obese patients (24 men and 17 women), 43.0±11.5 years of age, weighting 148.52±28.51 kg and with BMI=49.52±7.51 kg/m² accomplished the dieting programme.

Anthropometric and metabolic data before and after the dieting are presented in Table 1. After the alternating diet phases for the average duration of 6 months (3-11 months) the mean weight loss was 27 kg which represents ~18% of the initial weight. Although this BMI reduction is significant, the subjects who were severe obese at the beginning of the program remained severe obese. The mean change in the weight circumference during the follow-up was 20 cm. After the weight reduction the minimum WC was greater than 94 cm in men and greater than 80 cm in women.

The values of systolic and diastolic blood pressure were significantly reduced by 17/10 mmHg. Total cholesterol and triglyceride significantly decreased by 9% and 32%, respectively. The 5% decrease in LDL and the 2% increase in HDL cholesterol did not reach significance. The significant reduction in fasting glucose (16%), insulin (41%) and HOMA (49%) was accompanied by the significant increase of OGIS (22%).

Values of glucose and insulin during OGGT are shown in Figure 1 and Figure 2. As indicated by P values, the glucose decreased significantly for each OGGT point, (20%; 28%; 25%; 20%), while the significantly decreased insulin values are observed at zero (39%), sixty (46%) and one hundred twenty minutes (51%).

Diabetes was found in 7 patients. Five of them were on oral hypoglycemic agents and the other two patients were without medication. All of them had HbA1C>7%. During follow-up hypoglicemic agents were discontinued in two patient according to the fasting plasma glucose levels and HbA1C. At the end of the study, 4 of 7 diabetic patients returned to the “normal” measures of glucose metabolism (HbA1C<6%, fasting glucose <5.6 mmol/l, normal response in OGTT) in the absence of active pharmacologic therapy or insulin. Three out of 7 patients who remained diabetic had good glycemic control (HbA1C<7%) on oral hypoglycemic medications. The weight reduction reduced both the number of patients with diabetes (from 17% to 7%) and the number of patients with IGT (from 27% to 7%). This means that 57% of diabetic patients and 78% of subjects with IGT who participated in this study had the normal glucose tolerance after the weight loss.

The fraction of patients with total number of identified MetS parameters before and after the weight loss is presented in Figure 3. Before the diet all patients were positive for at least two and 15% of them had all five MetS parameters. After the weight loss no one had all five MetS parameters. The percentage increase of patients with two and three MetS factors is the result of reducing the number of patients originally having positive four or five MetS parameters.

All patients remained with abdominal obesity after the weight loss (Figure 4).

Except for a slight improvement of HDL values (by 2%), all other MetS parameters improved after the treatment: hypertension by 32%, glucose by 36% and triglycerides by 34%. The overall prevalence of MetS decreased by 32%.

Discussion

Our results clearly show that significant weight loss after dietary treatment consisting of the three-week therapeutic fasting and semi-fasting diet induced a significant reduction of body weight which was accompanied by a significant improvement of most metabolic parameters in the severely obese patients. The weight loss during the three weeks of fasting is significant, which is a great motivation and a confidence gainer for the next step in further reducing body weight, especially for patients who have previously dieted unsuccessfully.

To our knowledge, no data have been published on equivalently designed program for the treatment of severe obesity. In addition, relatively few studies have used established MetS criteria and none of them applied it in evaluating outcomes after the weight loss in severely obese subjects. In this context a comparison of our results with other published results is limited to the qualitative domain.

Our results for weight loss (18% or 27 kg for 6 months) are similar to those of Anderson et al treated 1531 severe patients with VLCD and the low energy diet with intensive behavioral treatment. The weight loss
Figure 1: Significant changes (p<0.05) are represented by an asterisk (*).

Figure 2: Significant changes (p<0.05) are represented by an asterisk (*).

Figure 3: The fraction of the patients with total number of identified MetS parameter before and after the weight loss.

Figure 4: Change in each of the five components of the Metabolic Syndrome and in the prevalence of the Metabolic Syndrome as defined by the reference 15. Significant changes (p<0.05) are represented by an asterisk (*).
achieved in this way was 18.5 to 22.5% for 7.5 months. Sacks et al have randomly assigned 811 overweight adults to LCDs with different amounts of energy derived from protein, carbohydrate, and fat. The patterns of weight loss for all combinations of diet were similar with an average weight loss of 6 kg or 7% for 6 months.

We observed significant improvements in the overall prevalence of MetS which decreased from 83% to 51%. This indicates the lower fraction of patients with a high number of identified MetS parameters and the reduction of prevalence of MetS parameters, what is consistent with the results of other studies. All participants in this study had abdominal obesity before and after the weight loss, but with a significant WC decrease of 20 cm for about 18% of weight loss. This reduction in WC and visceral obesity with the weight loss is in agreement with numerous published studies. However, it is noted that for subjects with the most severe grades of obesity the waist circumference is not a reliable parameter of abdominal obesity. In these cases the evaluation of central fat size should be more properly based on imaging technique, computed tomography or magnetic resonance imaging. Unfortunately, these techniques were not available for investigations in our study.

According to the European Society of Hypertension, the reduction in body weight and an increase in physical activity of 30 min of moderate-intensity physical activity a day are the first-line therapy of high blood pressure in MetS. A meta-analysis with 4874 participants was performed to estimate the effect of weight reduction on blood pressure. Mean initial BMI was 30.7 kg/m². Mean net change in body weight of 5.8% by energy restriction, increased physical activity or both, reduced blood pressure by 4.44/3.57 mmHg, which means 0.77/0.62 mmHg per percent of weight loss and 1.05/0.92 mmHg per kilogram of weight loss. When the decrease of mean blood pressure values of 17/10 mmHg (for reduction of body weight of 18%) obtained in our study is expressed in these units, the following values are found: 0.94/0.56 mmHg per percent of weight loss and 0.63/0.56 mmHg per kilogram of weight loss. The less reduction in blood pressure per kg of body weight obtained by our patients is due to their significantly higher body weight and therefore the greater change of weight expressed in kilograms. However, the tendency of blood pressure reduction with the percent of weight loss after dieting is similar.

HOMA as a surrogate of hepatic insulin sensitivity and OGIS as a surrogate of peripheral sensitivity to insulin are altered in the presence of morbid obesity, although the hepatic defect seems more closely associated with MetS and abdominal obesity. In our study, blood glucose, insulin, and HOMA index significantly decreased and OGIS index significantly increased after the diet and physical activity, which is in accordance with the results.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Before</th>
<th>After</th>
<th>P value</th>
</tr>
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<tr>
<td>Weight</td>
<td>kg</td>
<td>148.52 ± 28.51</td>
<td>121.71 ± 22.97</td>
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</tr>
<tr>
<td>BMI</td>
<td>kg/m²</td>
<td>49.52 ± 7.51</td>
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<tr>
<td>Waist circumference</td>
<td>cm</td>
<td>141.40 ± 17.12</td>
<td>121.31 ± 15.58</td>
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<tr>
<td>Systolic blood pressure</td>
<td>mmHg</td>
<td>139.39 ± 20.22</td>
<td>122.80 ± 12.20</td>
<td>0.000 **</td>
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<tr>
<td>Diastolic blood pressure</td>
<td>mmHg</td>
<td>89.340 ± 13.84</td>
<td>79.83 ± 7.88</td>
<td>0.000 **</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>mmol/l</td>
<td>5.65 ± 0.21</td>
<td>5.15 ± 0.20</td>
<td>0.000 **</td>
</tr>
<tr>
<td>HDL</td>
<td>mmol/l</td>
<td>1.02 ± 0.22</td>
<td>1.04 ± 0.43</td>
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<tr>
<td>LDL</td>
<td>mmol/l</td>
<td>3.57 ± 1.78</td>
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<tr>
<td>Triglyceride</td>
<td>mmol/l</td>
<td>2.27 ± 1.33</td>
<td>1.54 ± 0.60</td>
<td>0.000 **</td>
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<tr>
<td>Glucose</td>
<td>mmol/l</td>
<td>4.93 ± 0.86</td>
<td>4.14 ± 0.65</td>
<td>0.000 **</td>
</tr>
<tr>
<td>Insulin</td>
<td>(mU/l)</td>
<td>27.62 ± 24.94</td>
<td>16.41 ± 9.42</td>
<td>0.007 **</td>
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<tr>
<td>HOMA</td>
<td></td>
<td>6.08 ± 5.01</td>
<td>3.12 ± 1.82</td>
<td>0.001 **</td>
</tr>
<tr>
<td>OGIS</td>
<td></td>
<td>402.6 ± 94.4</td>
<td>491.5 ± 94.02</td>
<td>0.005 **</td>
</tr>
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</table>

High significant changes (P<0.01) are represented by two asterisks(**).
of numerous published studies\textsuperscript{27}. Diabetes (from 17\% to 7\%) and IGT (from 27\% to 7\%) disappeared in some patients.

Our results show that HDL cholesterol levels do not significantly change during the diet (by 2\%) in contrast to significantly lowering of Tg levels (by 34\%). These results are in agreements with those published by Fleckner-Mors et al\textsuperscript{28} and by Tuomilheto et al\textsuperscript{29}.

It is noted that according to various investigations the bariatric surgery also improves lipid profile, decreases Tg levels and increases, decreases or does not change HDL value\textsuperscript{23,30,31}.

As mentioned in the Introduction, the zero diet has been linked to a significant number of adverse effects such as gout, postural hypotension, muscle cramps, amenorrhea, ventricular fibrillation, lactic acidosis, vitamin and electrolyte deficiency and even sudden cardiac death\textsuperscript{8,9}. Fasting also results in substantial loss of lean (protein) tissue. The mass of lean tissue is the major factor that influences basal metabolic rate (BMR). The contribution of active physical activity to BMR is 5 to 10\%\textsuperscript{32,33}. Thereofore, the introduction of physical activity in order to increase BMR is mandatory in order to achieve further weight loss.

The total fasting is not the only therapy of obesity with a risk. Many medical experts argued the safety of popular diets with high protein and low carbohydrate content. Further, according to the Swedish Obese Subjects study the bariatric surgery carries a 0.25\% risk of death and 13\% risk of serious postoperative complications such as embolism, thrombosis or pulmonary complications. Nonetheless, these short-term risks are considered to be outweighed by the long-term (10 years) benefits in reduction of cardiovascular risk factors\textsuperscript{34}.

The costs of this combined weight loss program including hospital days are lower than bariatric surgery, at least in our country. The aforementioned medically supervised option offered exclusively in hospitals and medical centers should be carried out only when diet and exercise have been previously tried and failed. It is designed for severely obese people who want to lose a significant amount of weight in a short period of time. It should be applied for weight loss prior to a surgical procedure and to patients who wish to achieve serious weight loss in a non-surgical way or to those who are on the long waitlists for the bariatric surgery. Surgical options are more effective, but they are only accessible to a limited number of patients. For example, in Canada, the USA and the United Kingdom far less than 1\% of eligible patients currently receive a bariatric procedure. In Canada these patients are waitlisted 5 years on average\textsuperscript{35}.

This study shows that weight loss is the crucial determinant of the drastic improvement in blood pressure, lipid profile, glucose metabolism and MetS as a whole in extremely obese patients. The program consisting of the therapeutic fasting or semi-fasting under a strict medical supervision which alternates with the prescribed LCD and a gradual increase of physical activity in outpatient conditions should be considered as a therapeutic option in the treatment of severe obesity.

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The authors declare no conflicts of interest.

References


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