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Predictors of weight regain after the end of 10-week dietary weight-loss programme (NUGENOB study)

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Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma thesis to be used for study purposes.

In Prague on October 26th, 2008 Imre Kukel

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1. Introduction

1.1 Obesity

After the evolution human race has gone through, human organism has its optimal weight for functioning. This optimum is determined by the equilibrium between the need to store energy for the necessary biological processes within the body versus the burden the storage weight puts on the human body. This burden is determined by the fat that makes up most of the overweight. Fat tissue has various negative physical effects (as for the skeletal structure and the joints which have to carry more weight), chemical effects (acidic properties of FFA, their osmotic activity when needed to be transported within the body) and biological effects (hyperlipidemia and the resulting metabolic syndrome in obesity, hormonal activity of fat tissue). Body Mass Index (BMI, body weight in kg divided by the height in meters squared), is an indirect method of measuring body fat mass, thus having its limitations, but for its easy use it has prevailed as the most widespread method for clinical purposes. According to the contemporary norms humans are classified as normal weight with BMI 18,5-24,9, as overweight with BMI 25,0-29,9 and as obese with BMI >= 30,0.

Obesity poses a serious health problem, since it is an increased risk factor for metabolic syndrome, II type diabetes mellitus, hypertension, cardiovascular complications – mainly ischemic heart disease, oncologic disease, cholecytolithiasis and other less typical diseases (varix disease, trombophlebitis, arthrosis and spondylarthrosis). What make obesity an important risk factor to parry are its high prevalence, and its incidence which is increasing year by year. According to WHO projections there were approximately 1.8 billion adults overweight in the world from which 400million are obese. Another projection expects the numbers to rise to 2.3 billion overweight people with 700million obese by the year 2015. To focus on Europe, a WHO report on obesity in the European region from 2005 (based on data from 2002) states that Europe has one of the highest BMI amongst all WHO regions, equalling nearly 26.5. Overweight

affects 25-75% of the adult population in the European region, while the prevalence of obesity ranges from 5% to 20% in men and up to 30% in women. Czech Republic itself has (based on data from 2006) 51.73% of the population overweight (47.33% amongst women and 56.65% amongst men) and 15.05% of the population are obese (16.28% for females and 13.66% for males). It is alarming to see that the numbers were 51.60% overweight people in 1999 but only 11.33% of the population obese in 1999[1]. With these numbers Czech Republic comes as 34th most obese nation in the world, but 14th in the European region.

1.2 Endocrinology of the fat tissue

The data above illustrate how obesity is an important health issue from the epidemiologic point of view. In spite of its severity as an epidemic, the precise mechanisms causing obesity are not yet clear. Still, research is in progress, and is focused mostly on the fat tissue, the most prominent element of obesity. Let us look at the current understanding of this clearly unique organ on the molecular base.

For long fat tissue was considered to be an inert mass of storage energy. Not until the recent discovery of the important of signalling molecules was it understood, how fat cells are in fact an organic component of the regulatory pathways within the body. In fact, fat cells can interact with their surrounding in all possible ways of autocrine, paracrine and endocrine stimulation. Their main role is to regulate the energy balance and the differentiation of cells in the body. The main regulatory molecules excreted by fat cells are classified into the adipokine and the cytokine family (the latter playing an important role in the regulation of homeostasis, inflammatory and vasoregulatory pathways and in the steroid metabolism). Most of these proteins are produced in larger amounts with increasing fat tissue mass. Then, the elevated levels of TNFα and IL6α resistin play an important role in the insulin resistant of obesity. On the other hand, adiponectine and leptin have insulin sensitising effect by modulating fatty acid oxidation in striated muscles.

The current understanding of the pathophysiology of the metabolism in obesity is explained in the following. Insulin sensitivity is largely attributed to the so called lipotoxicity, caused by increased fat deposition in hepatocytes, striated muscle cells and cells of Islets of Langerhans causing local insulin insensitivity. Excessive fat tissue also causes local overproduction of glukocorticoids in the visceral fat tissue, leading to the so called omental Cushing's disease. Increases activity of 11β-hydroxisteroid dehydrogenase leads to higher cortisol levels in the fat tissue, which in turn leads to increase in of visceral fat, leading to increased release of adipokines with local and systemic effect. Amongst them are Leptin, TNF and IL6α, which in the hypothalamus modify the activity of the sympathetic nervous system, thermogenesis, food intake, reproductive functions as well as other HHA axis functions.

An important step in the lifecycle of adipocytes is their differentiation, which is controlled by PPAR (Peroxisome proliferator-activated receptor). In case of energy abundance differentiation of adipocytes and lipid accumulation is blocked by a feedback inhibition of adipocytes products like TNFα, angiotensinogen and resistin. On the contrary, in case of lack of energy adipokine and leptin secretion by fat cell decreases while trophic proteins like Acylation Stimulating Protein (ASP) and angiotensin II are secreted more leading to the formation of new adipocytes and accumulation of triacylglycerols. Insulin resistance accompanying excess body fat is only further aggravated when chronic dietary exposure of fat tissue by fatty acids and glucose leads to the release of inflammatory processes, hypertension and endothelial dysfunction, essentially causing a hypercoagulative state.

After repeated scientific evidence it was accepted that regional distribution of fat tissue makes a significant difference in its metabolic effect. Thus the so called central or android type of obesity – which is concentrated on the chest, abdomen and the belly – is considered worse as the gynoid type which is around the hips and the thigh and on the buttocks. A further division of the abdominal type of fat is possible to subcutaneous and visceral. The latter is considered more

metabolically active, whilst the former is regarded as metabolically harmless, but at the same time also less readily accessible source of energy. It is speculated that visceral fat tissue is the one responsible for insulin resistance, but for now little scientific evidence is at hand and there is still some controversy to be solved.

1.2.1. Hormones of the fat tissue

After considering the overall effect of fat tissue, a summary of its most important hormones and their actions should be looked at[2].

1.2.1.1. Adipokines that alter insulin sensitivity

Adiponectine is a 30kD peptide, with endogenous anti-inflammatory and antiatherogenic factor. It is also preventive against insulin resistance and macroangiopathy. It is the only hormone which has lower blood concentrations amongst obese people (while with weight loss its concentration decreases). Its concentration positively correlates with insulin sensitivity, and negatively with blood glucose levels. Even though it is not a typical insulin sensitiser, its administration strengthens the effect of insulin. The insulin sensitising effect of adiponectine is though to be due to 4 different mechanisms: stimulation of fatty acid oxidation (mainly by the striated muscle), direct effect on insulin signal transmission, inhibition of gluconeogenesis, and inhibition of TNFα signalling in the fat tissue.

Adiponectine concentrations are inversely related to BMI, % fat mass, waist-hip ratio, insulin concentration and plasma triglyceride levels, while positively correlate with plasma HDL cholesterol levels. Since differentiation of adipocytes is connected with significant adiponectine changes, it is assumed that the insulin sensitising effect of thiazolidindiones is through altering adipokine levels. Treatment of diabetics by thiazolidindione significantly increases blood adiponectine levels without a weight change.

Adiponectine also has significant antiatherogenic effect, mainly through altering macrophage activity, lowering TNFα production by macrophages, and blocking their transformation to foamy cells.

Leptin is an important factor for controlling fat reserves in the organism. It is a protein of 167 amino acids, and exist both in free form and bonded with a soluble receptor in the circulation. Its concentration is positively correlated with the amount of fat tissue – thus it is high in obese people – but significantly decreases with fasting and stays low 4-6 hours after food. It also has a circadian rhythm with peaks at 24.00 and between 10.00-12.00.

Leptin exerts its effect through coordinated regulation of food intake, metabolism, autonomic nervous system and energy balance of the organism. It is mostly produced by the fat tissue, and after entering the blood it is actively transported into the CNS, where it binds to leptin receptors of the hypothalamic nuclei. Through the hypothalamic nuclei it regulates neuropeptide secretion (such as neuropeptide Y, CRH, galanin, cholecystokinin, enterostatin, MSH, POMC, cocaine-amphetamine related transcript – CART) thus modifying food intake, thermogenesis and energy output.

Initial hopes (based on animal models) of using leptin for weight reduction have failed. It was shown then, that obese people in fact have high leptin levels coupled with leptin insensitivity. People with lipodystrophies are an exception, giving them leptin increases insulin sensitivity. It is thought that this insulin sensitising effect of leptin is through inhibiting malonyl CoA, thus increasing the fatty acid supply to mitochondria and their consequent oxidation.

Leptin production is regulated both constitutionally and hormonally. The important regulator by a negative feedback inhibition trough the sympathetic nervous system is the energetic state of the organism. Although not yet clear, the amount and localisation of fat tissue also plays a regulatory role. In detail that bigger fat cells contain more leptin than smaller cells and subcutaneous fat produces more leptin than visceral fat. Glucose and insulin are also important regulators: giving glucose to fasting individuals prevents fast decrease in leptin levels, while insulin stimulates leptin synthesis. Glukocorticoids also stimulate

leptin synthesis, and in obese people this stimulating effect is larger than amongst lean individuals.

As initial hopes for leptin to decrease food intake and feeling of hunger and to increase the rate of the metabolism have failed it was speculated that obese people have a leptin resistant state either on the level of leptin transport through the hematoencephalic barrier or on the postreceptor level. Furthermore, leptin from the phylogenetic point of might not serve for restricting food intake, but for adaptation on long lasting hunger. In conclusion, leptin administration to obese patients is only indicated in case of mutated leptin genes with completely unfunctional protein or in patients with hypoleptinemia coupled with lipoatrophic diabetes.

1.2.1.2. Adipokines that alter insulin resistance

Resistin a protein based hormone produced only by white fat cells. Knowledge about resistin is controversial up to date. This is reflected by the fact that depending on the experimental model used insulin is found both stimulating and inhibiting on resisting secretion. Physiologically resisting levels decrease while fasting and after meal it goes back to initial levels. Amongst obese people the gene for resistin is expressed more than in control individuals. The current understanding of resistin is that it is unlikely to be the link between human obesity and insulin resistance, but rather it is a regulator of adipocyte proliferation and differentiation.

Tumor necrosis factor α (TNFα) is a cytokine produced mostly by activated macrophages in reaction to invasive stimuli, but it is also produced by other cells like connective and muscle tissue. TNFα is a peptide hormone with two membrane bound receptors TNFR-I and TNFR-II. In obese people TNFα, but also TNFR-I and TNFR-II is increasingly expressed and synthesised. The autocrine effects of TNFα are considered to be responsible for its insulin resistance creating potential.

TNFα has different pathways of creating its effect. Most important are the inhibition of adipocyte differentiation, the reduction of the expression of GLUT-4, glycogen synthase, fatty acid synthase (thus inhibiting the conversion of glucose to glycogen or fatty acids) and decreasing the expression of genes responsible for taking up free fatty acids for triacylglycerol synthesis (such as lipoprotein lipase, acyl-CoA synthetase, diacylglycerol acyl-transferase). Consequently insulin dependent glucose uptake decreases, as well as changes in the lipid metabolism leading to fat accumulation and insulin resistance in the liver and muscles. These effects, however, could also be through the direct toxic effect of TNFα on intracellular insulin signalling pathways. In spite of successful models on animals finding correlation between TNFα and insulin resistance, in people no direct correlation was found. Also administering monoclonal antibodies against TNFα doesn't improve insulin resistance in people. It is speculated that if TNFα plays a role in insulin resistance, then it would be only locally.

Interleukin-6 (IL6) is a multifunctional cytokine produced by many different types of cells and only 10% of all IL6 is produced by fat cells; the rest is produced in the stromovascular fraction of the fat tissue. IL6 levels are elevated in obese people and more is produced in visceral fat tissue. Patients suffering from type II diabetes mellitus also have higher IL6 levels and a correlation between IL6 and obesity or insulin resistance was found in many studies. On the other hand patients with polymorphism of IL6 gene have better insulin sensitivity and lower glucose levels after glucose load.

IL6 on one hand improves the glucose take up in adipocytes and utilisation of glucose in the whole organism. In the other hand it increases glucose and triacylglyceride productions by the liver while decreasing lipoprotein lipase activity leading to lower clearance of triacylglycerides. Insulin resistance might be due to the increasing triacylglyceride production of the liver, the increased glucose production by the liver but also the fact that IL6 is a primary stimulus of acute phase reactants (like C-reactive protein, fibrinogen, haptoglobin). This latter effect is responsible for a procoagulative, prothrombotic potential as well as it leads to the expression of adhesive molecules by the endothelium.

In spite of the insulin resistance potentiating effect of IL6 it also has insulin sensitising effect by increasing glucose take up by adipocytes and inhibition of TNFα production. Also, physical exercise improves insulin sensitivity presumably through stimulating IL6 secretion. May be the controversial role of IL6 on the metabolism can be explained through its chronic versus acute or local versus central effect.

1.2.1. Fat proteins and factors affecting lipid metabolism

Adipsin is a protease produced by fat tissue necessary for acylation stimulating protein (ASP) synthesis. As opposed to animal models, in people adipsin levels are high amongst obese individuals and low in lean individuals but increase after food intake.

Acylation stimulating protein is a cleavage product of C3 factor of complement and is formed by interaction between C3 with factor B and adipsin (components of the alternative complement pathway). ASP stimulates the uptake of fatty acids and their esterification to triacylglycerides. Almost 1/4 of patients with ischemic heart disease have elevated ASP levels, but also hyper-apoβ-lipoproteinemia, familiar dyslipidemia can be the result is impaired ASP effect in the fat tissue.

ASP probably exerts is effect through its receptor in the adipocytes. Possible mechanisms of action are through activating the diacylglycerol/protein kinase-C pathway transferring glucose transporters to the surface membrane; increasing fatty acid esterification by increasing the activity of diacylglycerol acyl-transferase; and decreasing lipolysis by inhibition of hormone-sensitive lipase (independently from insulin).

Even though plasma ASP levels are significantly increased amongst obese people and 2.type diabetics they also negatively correlate with glucose levels during euglycemic hyperinsulin lock of people.

Fat aquaporin (AQPap) is a glycerol canal of fat tissue only produced by white fat cells. Insulin has a negative effect on the promotor of the AQPap gene through the insulin response element. Even so the transcription of the gene is also regulated through nutritional stimuli and increases in insulin resistant situations. Thus it is one of the reasons of increased glycerol levels and increased glucose production by the liver in obese and insulin resistant individuals.

Plasminogen activator inhibitor-1 (PAI1) is part of the plasma serine protease family. It has a dual role: in the plasma contributes to aggregate formation while in tissues it supports the accumulation of extracellular matrix, regulates vascular reconstruction, heart fibrosis and glomerulosclerosis. All these effects are present in 2.type diabetes, and can be the cause of vascular complications. Serum PAI1 levels increase with the amount of fat tissue and omental fat tissue expresses more PAI1 than subcutaneous one. Increased PAI1 levels are a contributor to the prothrombotic, proatherosclerotic situation in obese individuals.

The rennin-angiotensin system (RAS) regulates the fat mass and energy reserves through paracrine and autocrine effects on adipocyte differentiation and lipid storage. Plasma angiotensinogen levels and rennin activity positively correlate with body weight while angiotensinogen expression in fat tissue correlates with waist-hip ratio. More precise role of the RAS in adipocytes and in the pathogenesis of obesity and hypertension is not yet clear.

Aromatase is mostly active in mesenchymal nondifferentiated preadipocytes. Fat estrogen production increases with the amount of fat tissue but also with the age of the individual. Estrogens produced by fat tissue redirect fat storage into the subcutaneous and breast region as opposed to androgens that support visceral accumulation of fat. Also aromatase is more expressed in fat tissue on the but and thighs then of that on the belly and chest.

11β-hydroxysteroid dehydrogenase (11βHSD) is the enzyme transforming cortison to the active cortisol and has an increased activity in the fat tissue of obese people. In animal experimental models with increased 11βHSD level lead to increased visceral accumulation of fat and a metabolic state similar to that of human metabolic syndrome. On the other hand administration of thiazolidindione lowers 11βHSD mRNA expression and selectively reduces visceral fat in people.

1.2 Clinical aspects of obesity

Even if the causality of obesity is not yet precisely defined, from the practical point of view it is useful to differentiate between primary and secondary obesity. The former describes a state in which obesity is not a symptom of another disease and is the most important type of obesity in developed countries. Secondary obesity is rare, and it can be part of Babinsky-Fröhlich syndrome, Cusching's syndrome, syndrome of polycystic ovaries and insulinoma. It is also part of some genetic syndromes and exists in organic lesions of the hypothalamus. The precise diagnosis of primary versus secondary obesity is important for therapy and also prognosis differs significantly.

1.2.1. Ethiopathogenesis of primary obesity

The direct cause of primary obesity is a positive energy balance. However, the main reason for positive energy balance is not known. It is only clear that obesity is bound on the surrounding with enough food and only develops in some of the exposed individuals. As such, obesity could be understood as maladaptation on abundance of food. The reason for this maladaptation is thought to be in genetic predisposition for positive energy balance. The genes participating in this, sometimes called thrifty genes, are thought to cause insulin resistance in the liver and muscles but not in fat tissue. Therefore energy from food intake is largely directed towards storage in fat tissue.

Since no single gene was identified to be responsible a polygenic predisposition for obesity is thought to exist (even if there are some rare cases of monogenic obesity amongst people). Products of these genes are thought to exert their effect through the lateral and ventromedial areas of the hypothalamus. Hypothalamus is responsible for processing afferent signals and producing efferent response through increased production of mediators, changes in food intake, basal metabolism and thermogenesis.

An alternative understanding of primary obesity postpones a possible causality between obesity and adenoviral infection in humans.

Not without relevance are social and personality factors leading to obesity, which are more dominant amongst women, but their relative importance in the development of obesity is unclear.

1.2.2. Behavioural aspects of obesity

Classical models thinking of obesity as a result of a single gene determined disease or as a pathophysiologic interaction of endogenous and exogenous factors are not completely satisfactory to solve all the problems connected with the ongoing epidemic. Hence some argue that more to the point would be looking at the behavioural aspects that lie behind the development and the spreading of obesity worldwide.

The traditional understanding of obesity as a result of abundance of food and lack of self restraint is likely to be oversimplified. We see rising numbers of obese people in developing countries traditionally affected by famines, like Bangladesh, when at the same time the rest – or large share – of their population is starving. The other controversy that challenges the concept of lack of self control and education on the topic is that many who are well accustomed about problems of obesity – or is their field of work even might have severe problems of weight control. Not to mention that this latter point – today's lack of information

and self control – would imply that they were both on higher level 30years ago[3]. On the other hand Cohen A.D. points out 10 possible subconscious stimuli that increase food energy intake and lead to the development of obesity. Some of these are irrelevant to our study, but the rest are important to note.

Feeling of hunger is one of the factors that Cohen A.D. identifies as important. Even though it is put in the context of being altered by advertising techniques, it is clearly felt by every individual. Thus it's measuring is not without relevance. Self control is mentioned next mostly focusing on that it is lost through the different manipulation of food industry. Still its role in food intake is undoubted. Foraging behaviour has to do with food intake as well, contributing to the list of possible behavioural causes of obesity. The author claims that a natural tendency (behaviour) to conserve energy also exists in humans. Mimicking the behaviour of others is one of the main ways of human learning, thus when eating together, the group has a tendency to push the individual towards consuming more. The whole process is thought to happen on the subconscious level of the psyche or the so called mirror neurons in the brain. Conditioned responses should play a role when branding is achieved by companies in the food industry, which for other reasons (cost effectiveness) tend to produce high sugar and fat products, thus preparing the terrain for unbalanced high energy intake.

In a clinical review Greenwood L.J.J. and Stanford B.J. identify more of specific eating behaviours that lead to overweight[4]. Restaurant/Fast Food consumption have increased from 9.6% to 23.5% between 1977 and 1996 in the USA, while restaurant food is thought to have more calories than home prepared food and people who consume restaurant food have higher odds of being overweight. Consumption of beverages with sugar added is also contributing to the increased energy intake of nowadays. Conversely, consumption of low energy dense food, ie, fruits and vegetables which can help to maintain or lose weight even is on the decline. Additional behaviours associated with overweight and obesity in adults include nighttime eating, snacking, and alcohol consumption.

1.2.3. Diagnosis of obesity

1.2.3.1 Measuring the amount of fat tissue

Even if excessive fat amount is usually obvious at inspection, some "camouflaged type obesities and for precise quantification different methods exist. Upper physiologic level of fat tissue is thought to be 25% for men and 30% for women. Complicated methods such as hydrostatic weighting, K isotope administration, Dual Energy X-ray Absorptiometry are of little clinical use.

Calliper skinfold measurement is based on the fact that subcutaneous fat tissue is a relatively stable part of total fat. It is measured in 4 places: in the middle of the left arm above m.biceps, above m.triceps, below the left scapule and on the left side above the iliac crest of the hip bone. The results are added and the corresponding %of fat mass is found in tables.

In bioelectrical impedance (BIA) high frequency low amplitude current is lead through the body to find out the amount of fat tissue. Results are accurate only with normal hydration of the organism.

The use of height-weight tables is out of practice by now.

At the time most used method is the body mass index (BMI) which is also the method of used in this study, and is explained in detail in methods.

1.2.3.2. Clinical picture of obesity

The clinical picture of obesity is useful for the diagnosis of obesity as well, but is over the range of this thesis and will not be elaborated here.

1.2.4. Therapy of obesity

Since predisposition to obesity is lifetime long, its therapy has to be as well. As such, therapy is divided into two stages, when the first is based on reducing weight, while the second is about keeping the weight loss. Since causality of obesity is not yet understood, therapy can also be only symptomatic. As such the main goal of the therapy is to permanently change the eating habits and the physical activity of obese individuals. Results in the long run aren't very encouraging; some studies show that only 5% of individuals are successful at sustaining weight loss after 3 years.

For weight reduction low calorie diet is the main possibility. For maintaining the weight loss, there are more than one approaches. Behavioural intervention is targeted at changing the eating habits of obese individuals. It also helps to understand the energy intake in different alimentary products, thus being able to regulate the energy intake. Increased physical activity is another way of trying to achieve sustained weight loss. In particular it changes the relative amount of fat tissue versus active body mass and lowers insulin resistance.

Pharmacotherapy of obesity is also only symptomatic, even if it can help reduce weight. The first anorectics (drugs decreasing the feeling of hunger) stopped being used because of their psychoexcitatory effect. At the time there are only two substances used in the pharmacotherapy of obesity. Sibutramin is a central serotonin-dopamine-noradrenalin reuptake inhibitor which suppresses feeling of hunger and by central activation of sympathetic system it increases thermogenesis. Orlistat is an inhibitor of both pancreatic and intestinal lipase. It decreases the resorption of ingested fat by 30%. Effects of these two drugs are limited and usage longer than 3 months is contraindicated.

Surgical intervention is now indicated rarely, in case of obesity with severe complications. The only method used is not bandage of the stomach leading to the formation of a small remaining portion now able to store much food. The operation has many side effects.

1.3 The NUGENOB project

Once understood that obesity is a significant problem in Europe, the European Commission has declared nutrition, physical activity and obesity to be key priorities in the public health policy and are taken up by the Public health action programme (2008-2013)[5]. Prevention is, however, a better approach to treat disease both for human benefit and economic costs. Realizing this, a project was launched to study obesity in Europe back in 2001, called the NUGENOB (nutrient-gene interactions in human obesity) project[6].

The objective of the NUGENOB project was to improve understanding of the role of interaction between nutrition, especially fat intake, and genetic variations in obesity, which may be the basis for revision of dietary guidelines. The main aims were to:

1) identify and characterise novel nutrient-sensitive candidate genes for obesity,

2) assess differential gene expression in adipose tissue in relation to the acute intake of a high fat meal as well as long term intake of a hypocaloric diet with either a high or a low fat content,

3) assess effects of functional variants of the candidate genes on physiological responses in obese subjects to a high-fat test meal: appetite, energy expenditure, partitioning, and circulating obesity related hormones and metabolites, and

4) identify on this basis predictors of changes in body weight and composition during dietary intervention, including changes in fat intake.

In eight European cities – amongst which was the Sport Medicine Department of the 3rd faculty of medicine of the Charles University in Prague – source populations were defined from which the study population of a total of 750 obese and 115 normal weight reference subjects were selected.

1.3 The dietary questionnaires used in the study

1.3.1 The three-factor eating questionnaire (TFEQ)

The three-factor eating questionnaire (TFEQ) to measure dietary restraint, disinhibition and hunger was published by Albert J. Stunkard and Samuel Messick in 1984. It was constructed to measure cognitive dietary restraint, the tendency to disinhibition, and susceptibility to hunger. TFEQ was constructed because at the time problems with the Restraint Scale [7] and the appearance of the Latent Obesity Questionnaire[8] called for a new instrument to measure restrained eating and related issues. The TFEQ items were derived initially from three sources: Herman and Polivy's Revised Restraint Scale (10 items)[9], Pudel's Latent Obesity Questionnaire (40 items)[10] and seventeen newly written items based on clinical experience. After repeated statistical analyses, revision of the questions (both reformulating and taking out questions that proved to be confounding) and interpreting the found factors a new questionnaire was composed. The three factors were found to reflect "conscious mechanisms for restrained food intake" (Factor I), "a variety of disinhibitors" (Factor II), "feelings of hunger and its behavioural consequences" (Factor III). According to the interpretation given in the initial study the scores obtained on different factors could be useful in determining the kind of treatment the patient would benefit the most from. High scores on scale I (restraint of eating) might be especially responsive to information – about caloric balance, about nutrition, and particularly about traditional behavioural strategies for stimulus control. High scores on scale II, on the other hand, like alcoholics, may benefit from the kind of behavioural management devised by Marlatt for the "abstinence violation effect"[11]. They may also respond to the interpersonal supports of group approaches, especially in dealing with emotional disinhibitors such as anxiety, depression or loneliness. High scores on scale III might benefit from attributional techniques for coping with hunger or, alternatively, from long-term use of appetite-suppressant medication[12].

1.3.2 The BITE questionnaire

A self-rating scale for Bulimia, the "BITE" was designed by M. Henderson and C.P.L. Freeman in 1987 for the detection and description of binge-eating. At the time the authors felt that there was a need for a more sensitive questionnaire to identify people suffering from binge-eating disorder. This questionnaire was to be more specific than the ones that had been in use for individual studies only and had not been tested on a wider set of population. Other than identifying binge-eaters, the new questionnaire should have provided clinical information on cognitive and behavioural aspects of the disorder and should have had properties similar to those of the Eating Attitudes Test (EAT – a screening tool to identify both clinical and subclinical cases of anorexia nervosa)[13]. In addition they wanted to make a useful tool in a treatment setting, allowing severity to be quantified as well as a questionnaire that could be a measure of response to treatment.

The BITE questionnaire was constructed on the basis of all symptoms and behaviour associated with binge-eating collected from the contemporary literature. It was then tested on clinically defined groups of binge-eaters and normal controls. Scoring was designed to be carried out by computer, using SPSS system. In the later stages of validating the questionnaire, after the necessary amendments, it proved to be sufficiently sensitive in identifying binge eaters. Further testing proved that the BITE was sensitive to change during therapy of binge eating disorder.

The final questionnaire is subdivided into 2 subscales. It contains 33 questions, from which 30 make up the symptom scale (measures the degree of symptoms present) and 3 the severity scale (which provides and index of the severity of bingeing and purging behaviour as defined by their frequency). Subjects can be subdivided on the bases of their score in the symptom scale into 3 groups: high scores with a score of 20 or more, medium scorers with a score of 10-19 and low scorers with a score below 10. High scorers are likely to have a

highly disordered eating pattern and are probably binge-eaters. Medium scorers probably have an unusual eating pattern, but not to the extent that they would meet diagnostic criteria of bulimia. These subjects should be followed up by an interview. Subclinical binge-eaters and people either in the initial stages of the disorder or recovered bulimics could also be found in this range. Low scorers are likely to be individuals free of compulsive or binge-eating. A score of 5 or more on the severity scale is clinically significant, which should be followed up by an interview, while a score of 10 or more indicates a high degree of severity and may alone identify the presence of psychogenic vomiting or laxative abuse, in the absence of binge-eating. It is important to note, however, that there are some disorders which would score high on one but not the other scale, therefore diagnosis of binge-eating should only be made when the subject score 25 or more in the sum of both scales.

1.4 Hypothesis

Our hypothesis is that the successful long-term weight loss is, to some extent, dependent on the psychological factors and attitude to food. As these variables can be measured using the standardised test, we asked whether higher scores achieved on the subscales of the TFEQ and the BITE questionnaires increase the risk of weight regain after 1 year following the end of 10-week dietary programme and whether the achieved scores can explain the weight evolution in the subsequent year following the end of dietary intervention programme

2. Methods

2.1 Participants

In the Prague centre of the Sport Medicine Department of the 3rd Faculty of Medicine 124 Caucasian Europeans were recruited. Their body mass index (BMI) was greater than or equal to 30kg/m2, their age was 20-50 years and they had no weight change more than 3 kg within the 3 months prior to the study. Participants reporting clinically diagnosed hypertension, diabetes or hyperlipidemia treated by drugs, untreated thyroid disease, surgically or drug-treated obesity, pregnancy, or alcohol or drug abuse were excluded. Participants were recruited through local advertisement campaign. The ethical committee of the participating centre approved the study. Volunteers were informed about the nature of the study, and written consent was obtained prior to study participation.

2.2 Interventions

All subjects were invited to a one-day clinical investigation programme, during which anthropometric measurements were made. Height was measured with a calibrated stadiometer and weight (in light indoor clothes and without shoes) with a calibrated set of scales. Waist-hip ratio, body composition measurement (measuring free fat mass with bioimpedance measurements), and biopsies from the subcutaneous adipose tissue were also measured. The measurements were repeated following the 10 week intervention program in obese subjects.

The 10 week intervention program started after the clinical investigation. The subjects were randomised to a 10-week low calorie dietary intervention (LCD) programme consisting of a hypocaloric diet (~ 600 Kcal energy deficit per day), either with a low fat content (20-25% fat) or with a high fat content (40-45% fat). The individually estimated energy requirement was based on pre-treatment resting metabolic rate multiplied by a physical activity level of 1.3, assuming a

sedentary life style. The dietary programme is described in detail on the Web site http://www.nugenob.org. Participants were requested to abstain from alcohol consumption. The dietary instructions were reinforced and monitored and participants were weighed weekly. Participants were advised to follow their habitual activity patterns throughout the dietary intervention period. After the 10 weeks LCD intervention subjects were advised to keep their newly acquired dietary habits, but no regular weight checks were kept other than the follow-up performed after 1 and 5 year.

For the purpose of this study the patients' dietary habits were examined by asking the subject individuals to fill out a three-factor eating questionnaire (TFEQ)[14] and a Bulimic Investigatory Test, Edinburgh (BITE)[15] questionnaire. Only subjects who participated in the one-year follow up and filled in the questionnaires were included in the present analysis.

2.3 Statistical Methods

The data were analysed with the use of SPSS 13.0 for Windows.

2.3.1. Analysis of psychological predictors of weight regain

The group was split into halves based on the median of weight regain one year after the 10-week LCD intervention after (median = 2.70 kg). Subjects who achieved less that 2.70 kg of weight regain after one year were considered as "successful" in weight maintenance while subjects gaining more than 2.70 kg were considered as "unsuccessful". The stepwise binary logistic regression analysis was performed to identify possible predictors of successful weight maintenance with weight regain as a dependent variable and scores in restraint, disinhibition and hunger scale in the TFEQ, and scores in the symptom scale, severity scale and sum score scale in the BITE questionnaire as independent variables.

An identical analyses was carried out using the median of relative (%) weight regain one year after the 10-week LCD intervention, where the group was split based on median of relative weight regain (median of % weight regain = 2.97 %),

2.3.2. Odds ratio analysis of weight regain

In this analysis subjects who gained no weight or continued to loose weight one year after the 10-week LCD intervention were assigned as "successful" in weight maintenance, while those who gained any amount of weight after one year were considered as "unsuccessful". Analysis was performed to analyze, whether high versus low score in parameters of TFEQ and BITE questionnaires increase the risk of unsuccessful weight management.

High scores on TFEQ and BITE questionnaires were defined either as scores above the median value. In addition the cut-off value given for clinical use in the original publications of the BITE questionnaire were also used to define high scores versus low scores for odds ration analyses. These cut-off points were at 10 and 20 points on the symptom scale, 10 and 5 points on the severity scale and 25 points on the sum scale.

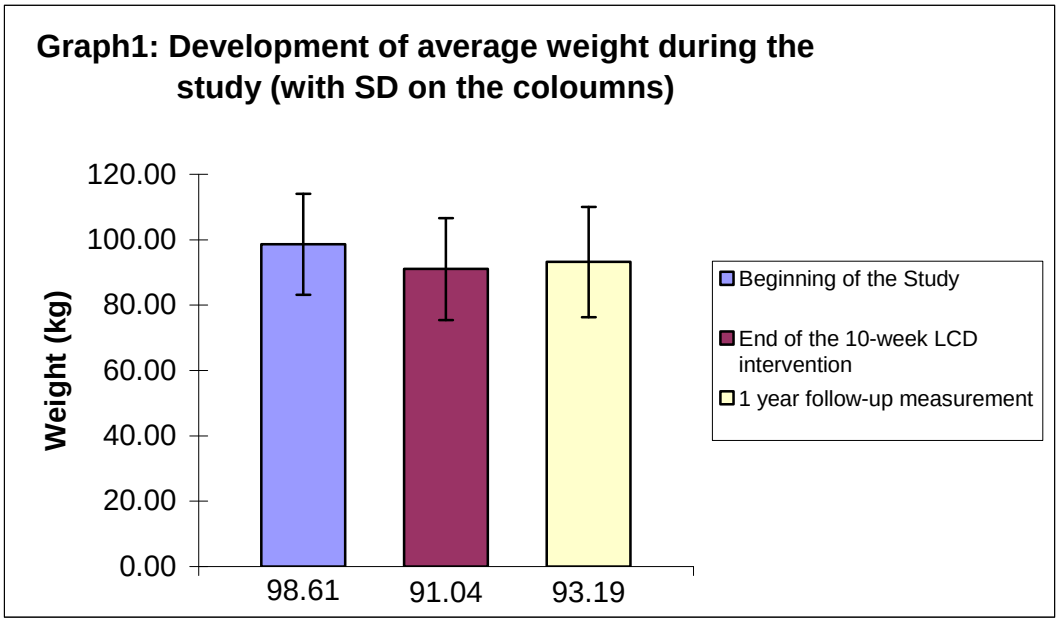
Data are presented as mean ± SD. A p value of 0.05 was considered statistically significant in all the tests.

3. Results

3.1 Patient flow and Numbers Analysed

From the initially recruited 124 subjects 9 didn't finish the 10-week LCD intervention, 19 didn't come to the 1 year follow-up and another 33 could not be included as they didn't fill the questionnaires (the ones who filled only 1 questionnaire fell into the previous categories). All these individuals were excluded from the analysis, and the data of the resting 63 individuals is presented in this study.

The anthropometric data and their changes are represented in the following graphs.

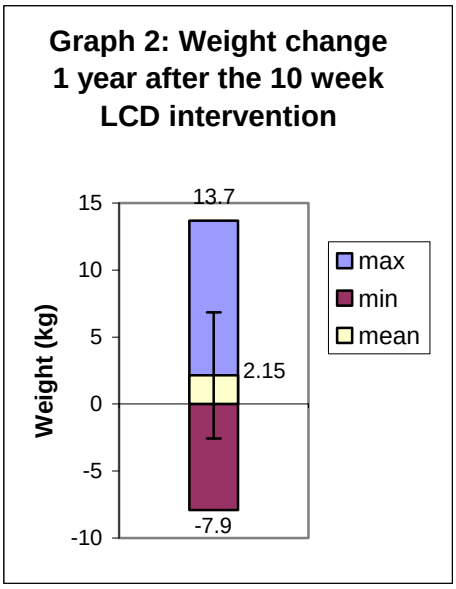


Subjects' weight was 98.61kg ± 15.45kg ranging from 66.8kg to 160.5kg with BMI 34.7 ± 4.1 ranging from 30.0 to 47.9. At the end of the 10-week LCD intervention subjects' weight was 91.04kg ± 15.13kg ranging from 63.1kg to 147.1kg. After 1 year after the end of 10-week LCD intervention subjects' weight was 93.19 kg ± 15.60kg ranging from 67.4kg to 145.6kg.

Table 1: Weight characteristics of the study group during the experiment

	Beginning of the Study	End of the 10-week LCD intervention	1 year follow-up measurement
Mean weight (kg)	98.61	91.04	93.19
Max weight (kg)	160.50	147.10	145.60
Min weight (kg)	66.80	63.10	67.40
Median weight (kg)	97.90	90.40	92.40
SD	15.45	15.13	15.60

The weight regain after 1 year after the end of 10-week LCD intervention was 2.15kg ± 4.71 ranging from 13.70 gain to 7.90 loss, while in percentages the weight regain was 2.48% ± 5.43% ranging from 16.08% gain to 8.40% loss.



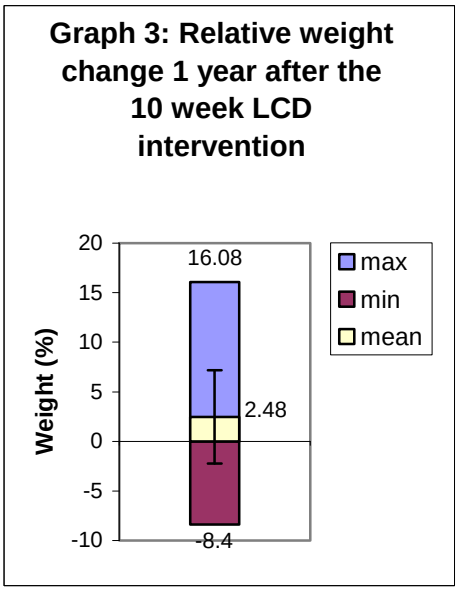


Table 2: Subjects' scores in the questionnaires

	Factor I - TFEQ	Factor II - TFEQ	Factor III - TFEQ	Symptom s. -BITE	Severity s. - BITE	Sum s. - BITE
Median	14	9	4	12	3	14
Max score	20	15	11	20	10	30
Min score	4	2	0	5	0	5

Subjects scored a median of 14 points (4 to 20) in Factor I, 9 points (2 to 15) on Factor II and 4 points (0 to 11) on Factor III of the TFEQ. In the BITE questionnaire the median scores were 12 (5 to 20) on the symptom scale, 3 (0 to 10) on the severity scale and 14 (5 to 30) on the sum scale.

3.2 Predictors of successful weight maintenance

3.2.1. Stepwise binary logistic regression analyses

Hunger score of the TFEQ was found to be the only significant predictor of unsuccessful weight maintenance in absolute numbers (kg) after 1 year following the 10-week LCD intervention (p = 0.030, the coefficient = 0.219).

When the outcome was expressed as the relative value (weight regain as the percentage of weight after the 10-week LCD intervention), Severity Scale of the BITE questionnaire was the only predictor in the forward stepwise logistic regression analysis. (p= 0.038, the coefficient = 0.276).

Table 3: Predictors of successful weight maintenance

	Predictor	Coefficient of the equation	P
Absolute weight maintenance	Factor III (Hunger)	0.219	0.030
Relative weight maintenance	Severity Scale	0.276	0.038

3.2.2. Risk of weight regain

Among the analysed psychological and food attitude factors, high score of disinhibition (Factor II in TFEQ) represented a strong risk for subsequent weight regain during the 1-year follow-up period with Odds ratio = 3.348 (95% CI 1.120 – 10.007) compared to subjects with low disinhibition score.

High Hunger score of the TFEQ represented a risk of subsequent weight regain during the 1-year follow-up period with Odds ratio = 2.786 (CI 0.958 – 8.099) with the borderline statistical significance (p = 0.051).

Table 4: Risks of weight regain 1 year after the LCD intervention

	Odds ratio (95% CI)	P
Disinhibition (Factor II of TFEQ)	3.348 (1.120, 10.007)	0.026
Hunger (Factor III of TFEQ)	2.786 (0.958, 8.099)	0.051

4. Discussion

4.1. This study in context of other studies

This study was the first one to assess the Czech version of the TFEQ and the BITE questionnaires for their predictive value of long run weight regain after LCD intervention. A similar study on weight maintenance after weight loss in relation to biological, psychological and genetic determinants was conducted by Vogels N et al[16]. The weight regain was evaluated at the 1 year follow up in both studies but Vogels N et all used a larger number of subjects (n=120 compared to n = 63) while from the questionnaires only used TFEQ to measure attitude toward eating. Their criteria for successful weight maintenance (< 10% weight regain) was milder (in this study < 0% weight regain), but the dietary intervention also only lasted 6 weeks as opposed to the 10 weeks LCD intervention in this study. Also the dropout rate was lower (13 from 133 as opposed to 61). The results of their logistic regression analysis with successful weight maintenance as the categorical outcome variable showed a statistically significant value for Factor III (Hunger) (Odds ratio 0.792, 95% CI 0.671-0.934, P = 0.006) and a statistically non significant results for Factor II (Disinhibition) (Odds ratio 1.234, 95% CI 0.943-1.616, P = 0.126). In our study disinhibition was the statistically significant one with P = 0.026 and a higher Odds Ratio (3.348) but a very wide 95% Confidence interval (1.120-10.007). Hunger was just above the significant P level (P = 0.051), but had it been significant it would have contradicted the results of the study by Vogels N et al since the Odds ratio was above 1 as opposed to under 1 (2.786, 95% CI 0.958 – 8.099). Still the hypothesis was formulated different: Vogels N et al looked at successful weight maintenance, while this study was looking for weight regain. Hence, both studies would have pointed (in case this study had a statistically significant P value for Factor III) that successful weight maintenance is coupled with lower scores on the Hunger scale. On the other hand, the statistical evidence from this study shows that subjects with successful weight maintenance have lower scores in Disinhibition while the data from the study of Vogel N et. al show the opposite: higher scores for successful weight maintenance

on the disinhibition scale. On the other hand they state in discussion that increase in dietary restraint is coupled with successful weight maintenance, while dietary restraint is inversely related to disinhibition – this latter they claim to be supported by their results. Hence a lower disinhibition is expected to be significant for successful weight maintenance, and this is exactly the result of our analysis.

Both the BITE questionnaire and the TFEQ was used by Pekkarinen T. et al to investigate correlation between the questionnaires and the weight maintenance[17]. The length of the study was 2 years, but included a 1 year follow up as in our study. The dietary intervention took 17 weeks (as opposed to 10 weeks in this study) and had behavioural modification included. The subject size of 62 was very close to the 63 in this study. They report that the mean binge eating, disinhibition and hunger scores decreased in all patients by the end of the therapy and that at the end of the two years these improvements in the scores were maintained in patients with a good result (weigh loss > 10% of initial weight at the beginning of the therapy) but the scores returned to the pretreatment levels in the patients with partial or poor result (weight loss 0-10% and < 0% of initial weight respectively).

Foster GD et al[18] only included women in the study, but the sample size of 223 was three times of this study. They found that before treatment, higher restraint scores were associated with lower body weights ($P = 0.02$), while higher disinhibition scores were associated with greater binge eating severity ($P<0.0001$). Weight loss treatment was associated with significant increases in restraint and decreases in disinhibition and hunger (all $Ps<0.0001$). Greater increases in restraint during treatment were associated with larger weight losses ($P<0.0001$). Decrease in disinhibition and hunger during weight loss treatment seems to correspond with the findings of this study, i.e. that successful candidates for weight maintenance have lower disinhibition and hunger scores.

A smaller sample of 36 individuals was studied by Borg P et al during and 2 years after dietary counselling in weight reduced obese men[19]. The dietary

counselling was included in 2 months weight reduction with very-low-energy-diet and in 6 months weight maintenance programme, which also included physical activity counselling, clearly a more controlled approach than the 10 week LCD intervention of this study. The 23 months unsupervised follow-up used the TFEQ to assess eating behaviour. The results showed that an increased consumption of low-fat cheese, low-fat margarine, vegetables and high-fibre bread, and decreased consumption of sugar, sausage, high-fat cheese, high-fat margarine, fat products and sweets were observed during dietary counselling. However, most of these changes returned later to pre-study consumption level and the relapse in dietary changes was partly associated with scoring low in restraint and high in disinhibition and hunger. This is in accordance with our finding that high scores in disinhibition and hunger are associated with unsuccessfulness in weight maintenance.

One of the first studies on assessing the long term predictory value of the TFEQ was done by Adami GF et al[20] in a sample of obese patients after biliopancreatic diversion operation (BDP). They found these obese subjects to score higher on the disinhibition and the hunger score than normal weight control subjects. When the subjects filled out the TFEQ on follow-ups after the operation, they also found a negative association between the time elapsed and the scores on the disinhibition and the hunger scale. Even though the subjects did not have to respect any dietary advice after the BDP, successful weight maintenance occurred in spite of absolutely free food consumption. These subjects – successful at weight maintenance – also had their disinhibition and hunger score "normalised" (similar to those of the control subjects). As we can see the findings are in accordance with our study results. Even if the follow up was 2 years (when in our study it was 1 year), the same 2 scale – disinhibition and hunger – were identified as statistically significant when successful weight maintenance was concerned. Our study, however, did not check for changes in the scores of the TFEQ at the 1 year follow up, but we can assume that higher scores on disinhibition and hunger in the study of Adami et al support our findings about the negative correlation between these scores and successful weight maintenance.

Tseng MC et al studied 189 obese subjects (form which 115 completed the study) for short-lime weight maintenance in a clinical setting after a weight reduction program[21]. They used a 12 week weight reduction program as opposed to the 10 weeks in this study, and there was no follow up in their study. Thus we can compare only with limitations. The BITE was used to monitor the change in binge-eating characteristics of the patients through the program. It was found that subjects who completed the program had a significantly decreased BITE scores at the end of the program, but this was not measured by our study. On the other when they looked for significant predictors of successful short-term weight loss two biologic factors (initial weight loss, initial body weight) and one behavioural factor (attendance rate) were identified. BITE wasn't identified as a significant predictor of successful weight maintenance. In our study – even though using approximately half the sample size – we found the Severity Scale of BITE to predict successful relative weight maintenance (coefficient 0.276, P = 0.030). It is noteworthy that previous studies did not quantify the relationship between weight regain and the Severity Scale. The Symptom Scale and the Sum Scale weren't of statistic predictory value, which is in accordance with other studies using this questionnaire ([22],[23]).

Weight maintenance was studied by Sarlio-Lähteenkorva S et al in a retrospective study of 9 women who successfully maintained their weight loss for 7 years (from 1986 to 1993) and 42 control obese women[22]. Hence the sample size was much smaller than in this study, but the follow up was also longer, as well as it was a retrospective rather than a prospective study. Still, they used a wide range of questionnaires amongst which both TFEQ and BITE. They found the restraint scale to significantly differ between successful and unsuccessful candidates for weight maintenance (14.6 vs. 8.4, p = 0.002), but the scores of BITE were within normal range in both groups.

Generally speaking, when TFEQ was used, a predictory value for successful weight maintenance was always found in at least on of the subscales, in two cases (Foster GD et al. and Borg P et al.) all three factors were found to be

predictory to the weight maintenance. On the other hand, the BITE questionnaire when used as a predictory measurement for weight maintenance had some predictory value in the study by Pekkarinen T et al but Tseng MC et al showed that even though BITE scores decreased among patients who successfully reduced weight, their initial scores had no predictory value for weight reduction.

The result of our study not yet mentioned, is the significant predictory value (coefficient 0.219, P = 0.030) for successful absolute weight maintenance of Factor III (Hunger) in a binary logistic regression model (forward stepwise). This is, however, not a very precise formulating since initial weight of the subject individuals varied significantly. Thus we should rather look at the relative weight maintenance, in which the Severity Scale of the BITE questionnaire was found to be a statistically significant (coefficient 0.276, P = 0.038) 1 point more on the Severity Scale predicted 27.6% more weight regain after 1 year after the 10-week LCD intervention.

At this point we could mention that other studies not directly looking for predictors of successful weight maintenance but using TFEQ have usually singled out Factor II (disinhibition) as a significant one when looking for predictors of body size, (Whitehall II study[24]) fat mass (Hood MY et al[25]) or susceptibility to palatability of food (Yeamans MR end co.[26]). This further supports findings about the statistical significance of disinhibition in our study but also that its use can go beyond predicting successful weight maintenance.

4.2 Limitations of this study

When comparing with other studies, this study used an average sample size (63 as opposed to 120, 62, 223, 36, 115 and 51) but had a high dropout rate (61 from 124 which is only comparable the study by Tseng MC with 74 dropouts from 189). This might have compromised the statistical significance of Factor III (Hunger) in TFEQ, which would have probably been within the P = 0.05 limits with lower dropouts or a larger sample size. When considering the dropouts there

is a possibility that individuals who failed to come for the 1 year follow up form a distinct group of weight retainers, thus their absence may be giving a bias to the data. Therefore this low response rate should be improved.

Increasing the sample size in itself could have helped to improve statistical significance, thus narrowing the wide 95% CI (1.120 – 10.007) for Factor II (Disinhibition), or making Factor III fall within statistically significant P values. This could have been achieved by a longer follow up rate as the 1 year follow in this study was shorter than in other studies which used 2 and even 7 years follow ups.

Another limitation of this study was that the subjects' selection did not include randomisation, since the narrow range of obese individuals willing to undergo weight reduction therapy did not allow the luxury to search for randomly chosen individuals. Still, if a bigger study was to be conducted, randomisation could be considered to improve the validity of the results.

It should be noted that this study was based on data obtained at the Prague centre of Sport Medicine Department in the 3rd faculty of Medicine. Therefore the results should only be extrapolated with care to other populations outside the Czech Republic. Even so since the response rate to the questionnaires might contain a bias, they might not even represent the studied population at the Prague centre.

4.3 Preventive measures

Weight reduction programs for obese people are based on the preventive effect of eliminating the risk factors associated with obesity. On the other hand abrupt weight change is unlikely to last. Hence the aim of weight reduction programmes is to lower body weight to a level that can be kept or even lowered further by the individuals in the long run. Achieving this, however, needs a differentiated approach for different patients. Stunkard et al described the possible

significance of scores on the subscales in the publication of TFEQ. The group of patients in this study had a significant predictory value of their Hunger scores, which according to Stunkard et al. means that they could benefit from attributional techniques for coping with hunger or, alternatively, from long-term use of appetite-suppressant medication. Disinhibition score also had predictory value, which again in the interpretation of Stunkard et al. mean that patients could benefit from behavioural management and group therapies (especially when dealing with emotional disinhibitors such as anxiety, depression, loneliness).

The construction of this study, when patients were required to control their caloric intake during the 10 week dietary intervention would rather suggest a predictory value for scores on the restraint scale, which, however, was not found statistically significant. At this point it is interesting to consider the results of Neale BM and co[27] who examined the genetic, common environment and specific environmental effects on each in a sample of female-female twin pairs. The heritabilities of scores on the subscales of the TFEQ were estimated at 45% (CI 32-57%) for Disinhibition, 8% (CI 0-38%) for Hunger, and 0% (CI 0-30%) for Restraint, while common environmental influences were estimated at 0% (CI of 0-23%) for Disinhibition, 16% (CI of 0-34%) for Hunger, and 31% (4-42%) for Restraint. As we see, Disinhibition is most affected by heritability, while Hunger is still, but already less affected by heritability. It would be interesting to know, which – Hunger or Disinhibition – is more important, as that would give a clue on whether we are facing an environmentally changeable situation or more a genetically determined one.

The 10 week LCD intervention that is clearly attempting to change the environmental setting of the subjects and this might reflect on the Hunger scale. Thus, in accordance with the study results, we could assume that patients scoring on the Hunger scale of the TFEQ are potential benefactors of a LCD intervention when long-term weight maintenance is considered. On the other hand, people high on the Disinhibition scale were not addressed by group therapy or behavioural approaches in this study, but their scores still predicted the weight regain after the

study. Hence it would be an error trying to solve weight problems of individuals scoring high on the Disinhibition scale of the TFEQ with LCD intervention only. These people could be candidates for behavioural therapies before undergoing an LCD intervention (low on Hunger scales).

The results for the predictive value of the Severity Scale of the BITE questionnaire suggest that it is relevant to actively search for severe binge eating behaviour in obese people, before letting them to undergo LCD intervention, because without solving the problem of their binge eating tendency long time weight regain is likely to happen.

4.4 Future perspectives

Asking for more data from the other centres who have participated in the NUGENOB project would be the best possible way to improve the statistical validity of the study. It is a question, though, how much different language versions of the used dietary questionnaires are compatible with each other. Even so, TFEQ and the BITE questionnaire have been successfully used in clinical practice over a time now, thus they should be comparable even if different language variants are given to the subject individuals.

The five year follow up in the study, which is yet to come, could be interesting for data collection. Not only it could show the natural development of the subjects examined in this study, but it might also give statistically significant predictory values that were not yet visible in the 1 year follow up.

An analysis using the data of the biochemical markers measured and putting them into correlation with the two questionnaires would be a further way of expanding the study. It is a question though, what the practical implications of such a comparison would be.

5. Summary

This study investigates the predictory value of eating habit questionnaires – the Three Factor Eating Questionnaire and the Bulimic Investigatory Test, Edinburgh – on successful weight maintenance of obese individuals in the Prague sample of the multicentre interventional study NEGENOB 1 year after a 10 week low calorie dietary intervention. Subjects were divided into successful and unsuccessful group of weight maintenance and the predictory value of scores on the subscales of the questionnaires were analysed using the SPSS 13.0 for windows program. The odds ratio of Disinhibition for successful weight maintenance was statistically significant (3.348, CI = 1.120-10.007, P = 0.026) while that of Hunger subscale was on the edge of statistical significance (2.786, CI = 0.958-8.099). Successful relative weight maintenance was predicted by Severity Scale of BITE a binary logistic regression model (coefficient = 0.276, P = 0.038). Other subscales were not found to be statistically significant of successful weight maintenance. These findings are in accordance with other studies showing that Disinhibition and Hunger scales of the TFEQ are good predictors of successful long term weight maintenance, while the role of BITE is marginal in these predictions.

6. References

[1] *Global Database on Body Mass Index* available from http://www.who.int/bmi/index.jsp

[2] KREZE, Alexander et al. *Všeobecná a klinická endokrinológia* Bratislava : Academic Electronic Press, 2004. p.515-528. ISBN 80-88880-58-0

[3] COHEN, DA. Neurophysiological Pathways to Obesity: Below Awareness and Beyond Individual Control. *Diabetes,* July 1 2008, 57, 1768-1773

[4] GREENWOOD, L.,J.,L., STANFORD, B., J. Preventing or Improving Obesity by Addressing Specific Eating Patterns. *J Am Board Fam Med,* 2008, 21, 135–140

[5] *Europa - Public Health - Health Determinants - Lifestyle - Nutrition* available from http://ec.europa.eu/health/ph_determinants/life_style/nutrition/nutrition_en.htm

[6] Nutrient - gene interactions in human obesity: Implications for Dieatary Guidelines Available from www.nugenob.org

[7] HERMAN, CP., MACK, D. Restrained and unrestrained eating. *J Personality*, 1975, 43, 647-660

[8] PUDEL, VE. Psychological observations on experimental feeding in the obese. In *Recent Advances in Obesity Research: I* (Edited by Howard A). London: Newman, 1975

[9] HERMAN, CP., POLIVY, J. Restrained eating. In *Obesity* (Edited by Stunkard AJ). Philadelphia: Saunders, 1980

[10] PUDEL, VE., METZDORFF, M., OETTING, MX. Zur Persoehnlichkeit Adipoeser Tests unter Berueecksichtigung latent Fettsuechtiger. *Psychosom Med Psychoanalyse*, 1975, 21, 345-350

[11] MARLATT, GA. Craving for alcohol, loss of control and relapse: a cognitive-behavioral analysis. In *Alcoholism: New Directions in Behavioral Research and Treatment* (Edited by Nathan PE, Marlatt GA, Loberg T). New York: Plenum, 1978

[12] STUNKARD, AJ. Appetite suppressants lower a body weight set point. *Life Sci* 1982, 30, 2043-2055.

[13] GARNER, DM., GARFINKEL, PE. The Eating Attitudes Test: an index of the symptoms of anorexia nervosa. *Psychol Med.* 1979 May, 9(2), 273-9.

[14] STUNKARD, AJ., MESSICK, S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res*. 1985, 29(1), 71-83.

[15] HENDERSON, M., FREEMAN, CP. A self-rating scale for bulimia. The 'BITE'. *Br J Psychiatry*. 1987 Jan, 150, 18-24.

[16] Vogels N, Mariman EC, Bouwman FG, Kester AD, Diepvens K, Westerterp-Plantenga MS. Relation of weight maintenance and dietary restraint to peroxisome proliferator activated receptor gamma2, glucocorticoid receptor, and ciliary neurotrophic factor polymorphisms. Am J Clin Nutr. 2005 Oct;82(4):740-6.

[17] PEKKARINEN, T, TAKALA, I., MUSTAJOKI, P. Two year maintenance of weight loss after a VLCD and behavioural therapy for obesity: correlation to the scores of questionnaires measuring eating behaviour. *Int J Obes Relat Metab Disord*, 1996 Apr, 20(4), 332-7.

[18] FOSTER, GD., WADDEN, TA., SWAIN, RM., STUNKARD, AJ., PLATTE, P., VOGT, RA. The Eating Inventory in obese women: clinical correlates and relationship to weight loss. *Int J Obes Relat Metab Disord,* 1998 Aug, 22(8), 778-85. Erratum in: *Int J Obes Relat Metab Disord,* 1999 Jan, 23(1), 106.

[19] BORG, P., FOGELHOLM, M., KUKKONEN-HARJULA, K. Food selection and eating behaviour during weight maintenance intervention and 2-y follow-up in obese men. *Int J Obes Relat Metab Disord,* 2004 Dec, 28(12), 1548-54.

[20] ADAMI, GF., GANDOLFO, P., DAPUETO, R., JURICH, D., SCOPINARO, N. Eating behavior following biliopancreatic diversion for obesity: study with a three-factor eating questionnaire. *Int J Eat Disord,* 1993 Jul, 14(1), 81-6.

[21] TSENG, MC., LEE, YJ., CHEN, SY., LEE, MB., LIN, KH., CHEN, PR., LAI, JS. Psychobehavioral response and weight loss prediction in a hospital-based weight reduction program. *J Formos Med Assoc*. 2002 Oct, 101(10), 705-11.

[22] FOGELHOLM, M., KUKKONEN-HARJULA, K., OJA, P. Eating control and physical activity as determinants of short-term weight maintenance after a very-low-calorie diet among obese women. *Int J Obes Relat Metab Disord*, 1999 Feb, 23(2), 203-1

[23] SARLIO-LÄHTEENKORVA, S., RISSANEN, A. Weight loss maintenance: determinants of long-term success. *Eat Weight Disord*, 1998 Sep, 3(3), 131-5.

[24] DYKES, J., BRUNNER, EJ., MARTIKAINEN, PT., WARDLE, J. Socioeconomic gradient in body size and obesity among women: the role of dietary restraint, disinhibition and hunger in the Whitehall II study. *Int J Obes Relat Metab Disord*, 2004 Feb, 28(2), 262-8.

[25] HOOD, MY., MOORE, LL., SUNDARAJAN-RAMAMURTI, A., SINGER, M., CUPPLES, LA., ELLISON, RC. Parental eating attitudes and the development of obesity in children. The Framingham Children's Study. *Int J Obes Relat Metab Disord*, 2000 Oct, 24(10), 1319-25.

[26] YEOMANS, MR., TOVEY, HM., TINLEY, EM., HAYNES, CJ. Effects of manipulated palatability on appetite depend on restraint and disinhibition scores from the Three-Factor Eating Questionnaire. *Int J Obes Relat Metab Disord*, 2004 Jan, 28(1), 144-51.

[27] NEALE, BM., MAZZEO, SE., BULIK, CM. A twin study of dietary restraint, disinhibition and hunger: an examination of the eating inventory (three factor eating questionnaire). *Twin Res,* 2003 Dec, 6(6), 471-8.

7. Attachments

7.1. The Three-factor Eating Questionnaire – TFEQ

One point is given for each item in Part I and for each item (numbered question) in Part II. The correct answer for the true/false items is underlined and beside it is the number of the factor that it measures. The direction of the question in Part II is determined by splitting the responses at the middle. If the item is labelled '+', those responses above the middle are given a zero. Vice versa for those with a '-'. For example, anyone scoring 3 or 4 on the first item in Part II (item No. 37) would receive one point. Anyone scoring 1 or 2 would receive a zero.

Part I

				Factor Number
1.	When I smell a sizzling steak or see a juicy piece of meat, I find it very difficult to keep from eating, even if I have just finished a meal.	T	F	2
2.	I usually eat too much at social occasions, like parties and picnics.	T	F	2
3.	I am usually so hungry that I eat more than three times a day.	T	F	3
4.	When I have eaten my quota of calories. I am usually good about not taking any more.	T	F	1
5.	Dieting is so hard for me because I just get too hungry.	T	F	3
6.	I deliberately take small helpings as a means of controlling my weight.	T	F	1
7.	Sometimes things just taste so good that I keep on eating even when I am no longer hungry.	T	F	2
8.	Since I am often hungry, I sometimes wish that while I am eating, an expert would tell me that I have had enough or that I can have something more to eat.	T	F	3
9.	When I feel anxious, I find myself eating.	T	F	2
10.	Life is too short to worry about dieting.	T	F	1
11.	Since my weight goes up and down, I have gone on reducing diets more than once.	T	F	2
12.	I often feel so hungry that I just have to eat something.	T	F	3
13.	When I am with someone who is overeating, I usually overeat too.	T	F	2
14.	I have a pretty good idea of the number of calories in common food.	T	F	1
15.	Sometimes when I start eating, I just can't seem to stop.	T	F	2
16.	It is not difficult for me to leave something on my plate.	T	F	2
17.	At certain times of she day, I get hungry because I have gotten used to eating then.	T	F	3
18.	While on a diet, if I eat food that is not allowed, I consciously eat less for a period of time to make up for it.	T	F	1
19.	Being with someone who is eating often makes me hungry enough to eat also.	T	F	3
20.	When I feel blue, I often overeat.	T	F	2
21.	I enjoy eating too much to spoil it by counting calories or watching my weight.	T	F	1
22.	When I see a real delicacy,I often get so hungry that I have to eat it right away.	T	F	3
23.	I often stop eating when I am not really full as a conscious means of limiting the amount that teat.	T	F	1
24.	I get so hungry that my stomach often seems like a bottomless pit.	T	F	3
25.	My weight has hardly changed at all in the last seven years.	T	F	2
26.	I am always hungry so it is hard for me to stop eating before I finish the food on my plate.	T	F	3
27.	When I feel lonely, I console myself by eating.	T	F	2
28.	I consciously hold back at meals in order not to gain weight.	T	F	1
29.	I sometimes get very hungry late in the evening or at night.	T	F	3
30.	I eat anything I want anytime I want.	T	F	1
31.	Without even thinking about it, I take a long time to eat.	T	F	2
32.	I count calories as a conscious way of controlling my weight.	T	F	1
33.	I do not eat some foods because they make me fat.	T	F	1
34.	I am always hungry enough to wat at any time.	T	F	3
35.	I pay a great deal of attention to changes in my figure.	T	F	1
36.	While on a diet, if I eat a food that is not allowed, I often then splurge and eat other high calorie foods.	T	F	2

Part II

Directions: Please answer the following questions by circling the number above the response that is appropriate to yon.

37. How often are you dieting in a conscious effort to controt your weight?

1	2	3	4	
rarely	sometimes	usually	always	+ 1

38. Would a weight fluctuation of 5 lbs affect the way you live your life?

1	2	3	4	
not at all	slightly	moderately	very much	+ 1

39. How often do you feel hungry?

1	2	3	4	
only at mealtimes	sometimes between meals	often between meals	almost always	+ 3

40. Do your feelings of guilt about overeating help you to control your food intake?

1	2	3	4	
never	rarely	often	always	+ 1

41. How difficult would it be for you to stop eating halfway through dinner and not eat for the next four hours?

1	2	3	4	
easy	slightly difficult	moderalely difficult	very difficult	+ 3

42. How conscious are you of what you ate eating?

1	2	3	4	
not at all	slightly	moderalely	extremely	+ 1

43. How frequently do you avoid ‘stocking up’ on tempting foods?

1	2	3	4	
almost never	seldom	usually	almost always	+ 1

44. How likely are you to shop for low calorie foods?

1	2	3	4	
unliktely	slightly unlikely	moderately likely	very likely	+ 1

45. Do you eat sensibly in front of others and splurge alone?

1	2	3	4	
never	rarely	often	always	+ 2

46. How likely are you to consciously eat slowly in order to cut down on how much you eat?

1	2	3	4	
unlikely	slightly likely	moderately likely	very likely	+ 1

47. How frequently do you skip dessert because you are no longer hungry?

1	2	3	4	
almost never	seldom	at least once a week	almost every day	- 3

48. How likely are you to consciously eat less than you want?

1	2	3	4	
unlikely	slightly likely	moderately likely	very likely	+ 1

49. Do you goon eating binge though you are not hungry?

1	2	3	4	
never	rarely	sometimes	at least once a week	+ 2

50. On a scale of 0 to 5, where 0 means no restraint in eating (eating whatever you want, whenever you want it) and 5 means total restraint (constantly limiting food intake and never ‘giving in’): what number would you give yourself?

0
eat whatever you want, whenever you want it + 1

1
usually eat whatever you want, whenever you want it

2
often eat whatever you want, whenever you want it

3
often limit food intake, but often ‘give in’

4
usually limit food intake, rarely ‘give in’

5
constantly limiting food intake, never ‘giving in’

51. To what extent does this statement describe your eating behavior? ‘1 start dieting in the morning. but because of any number of things that happen during the day, by evening I have given up and eat what I want, promising myself to start dieting again tomorrow.’

1	2	3	4	
not like me	little like me	pretty good description of me	describes me perfectly	+ 2

7.2. The Bulimic Investigatory Test, Edinburgh - BITE

Appendix 2

BITE Instruction. for administratino and scoring

Uses

The BITE is a 33-item self-report measure, designed to identify subjects with symptoms of bulimia or binge-eating. It can be used to identify binge-eaters in a given population or as a screening instrument for use in a clinical setting. In addition, it serves as a useful measure of severity and response to treatment. The BITE consists of two subscales, the Symptom Scale, which measures the degree of symptoms present, and the Severity Scale which provides an index of the severity of bingeing and purging behaviour as defined by their frequency. Scores on the Symptom Scale can be subdivided into three groups: high, medium and low scores. Those subjects achieving a high score have a high probability of meeting the DSM-III criteria for bulimia and Russell‘s (1979) criteria for bulimia nervosa. An additional front data sheet accompanies the BITE, which provides useful demographic data relevant to the study and treatment of binge-eating. Use of this data sheet is optional; it does not contribute to the subject’s final score.

Administration

When the BITE is used as a screening instrument or in survey work, the subjects should be asked to complete the questionnaire based on their feelings and behaviour over the past 3 months. Where the BITE is to be used as a measure of respons to treatment, only the past month should be considered.

Scoring

Symptom Scale

All the questions, with the exception of the three starred (6, 7 and 27), make up the Symptom Scale. The underlined questions (1, 13, 21, 23, and 31) score one point for a ‚No‘ response. The remaining 25 items score one point for a ‚Yes‘ response. The maximum possible score is 30.

Severity Scale

The threee starred items (6, 7 and 27) comprisee the Severity Scale. The total score is the sum of the numbers corresponding to the circled responses.

Interpretation of results

Symptom Scale

In general the scorers on this scale can be subdivided into three main groups; high scorers with a score of 20 or more, medium scorers with a score of 10—19 and low scorers with a score below 10.

A symptom score of 20 or more indicates a highly disordered eating pattern and the presence of binge-eating. There is a high probability that a subject who achieves such a score will fulfill the DSM III criteria for a diagnosis of bulimia.

A symptom score in the mediun range (10-19) suggests an unusual easing pattern, but not to the extent that a subject in this range would meet all the criteria for a diagnosis of bulimia. An example of this might be a compulsice]slve eater who eats

excessively but does not binge-eat. A score in the 15-19 range should certainly be followed up by an interview. Subjects in this category may well reflect a subclinical group of binge-eaters, either in the initial stages of the disorder or recovered betlimics.

A symptom score in the low range (0-10) falls within normal limits. Such a score indicates the absence of both compulsive eating and binge-eating.

Severity Scale

The severity scale measures the severity of bingeing and purging behaviour, as defined by its frequency. A score of 5 or more on this scale is considered clinically significant. A score of 10 or more indicates a high degree of severity. A significant score on this scale should ideally be followed up by interview, regardless of the symptom score.

A high score on this scale alone may identify the presence of psychogenic vomiting or laxative abuse, in the absence of binge-eating.

Any score on the severity scale should be checked against the relevant question in order to check for this type of behaviour.

Appendix 2

Builmic Investigatory Test, Edinburgh (BITE)

Optional front data sheet

1. What is your sex? Male 1 Female 2 (*please circle number*)

2. Are you:
Married 1 single 2 divorced 3 separated 4 widowed 5

3. What is your occupation?
_____

4. If married, what is your spouse's occupation?_____

5. What is your age? _____years

6. What is your height? _____feet _____inches, or _____cm

7. What is your wieght?
_____stone_____pounds, or _____kg

8. What is the most that you have ever weighed?
_____stone_____pounds, or _____kg

9. What is the least that you have weighed at your present height? _____stone_____pounds, or _____kg

10. What would your ideal weight be if you could choose it?_____stone_____pounds, or _____kg

11. Do you feet yourself to be very owerwegiht 5
owerweight 4 (*please*
average 3 *circle*
underweight2 *number*)
very underweight 1

12. Do you have regular periods? (if applicable) Yes 1
No 2

13. How often, on average, do you eat the following meals?

	Every-Day	5/7 Days	3/7 Days	1/7 Days	Never	
Breakfast	1	2	3	4	5	
Lunch	1	2	3	4	5	(*circle*
Dinner	1	2	3	4	5	*number)*
Between Meal Snacks	1	2	3	4	5	

14. Have you ever consulled someone in a professional capacity for advice on dieting/eating? Yes 1
No 2

15. Have you ever been a member of a slimming club?
Yes 1 No 2

16. Have you ever suffered from any type of eating disorder?
Yes 1 No 2

17. .....if yes, please five details over:

Bulimic lnvestigatory Test, Edinburgh

1. Do you have a regular daily eating pastern? Yes No

2. Are you a strict dieter? Yes No

3. Do you feel a failure if you break your diet once?
Yes No

4. Do you count the calories of everything you eat, even not on a diet? Yes No

5. Do you ever fast for a whole day? Yes No

*6....If yes, how often is this?
EVERY SECOND DAY 5 2-3 TIMES A WEEK 4
ONCE A WEEX 3 NOW AND THEN 2 HAVE ONCE 1

*7. Do you do any of the following to help you lose weight? (*circle number*)

	Never	Occasionally	Once a week	2-3 Times Week	Daily	2-3 Times a Day	5+ Times a Day
Take diet pills	0	2	3	4	5	6	7
Take diuretics	0	2	3	4	5	6	7
Take Laxatives	0	2	3	4	5	6	7
Make yourself Vomit	0	2	3	4	5	6	7

8. Does your pattern of eating severely disrupt your life?
Yes No

9. Would you say that food dominated your life?
Yes No

10. Do you ever eat and eat until you are stopped by physical discomfors?
Yes No

11. Are there times when all you can think about is food?
Yes No

12. Do you eat sensibly in front of others and make up in private?
Yes No

13. Can you always stop eating when you want to?
Yes No

14. Do you ever experience overpowering urges to eat and eat and eat?
Yes No

15. When you are feeling anxious do you tend to eat a lot?
Yes No

16. Does the thought of becoming fat t*errify* you?
Yes No

17. Do you ever eat large amounts of food rapidly (not a meal)?
Yes No

18. Are you ashamed of yost eating habits?
Yes No

19. Do you worry that you have no control over how much you eat?
Yes No

20. Do you turn to food for comfort?

Yes No

21. Are you able to leave food on the plate at the end of a meal?
Yes No

22. Do you deceive other people about how much you eat?
Yes No

23. Does how hungry you feel determine how much you eat?
Yes No

24. Do you ever binge on large amounts of food?
Yes No

25. . . . If yes, do such binges leave you feeling miserable?
Yes No

26. If you do binge, is this only when you are alone?
Yes No

*27. If you do binge, how often is this?

Hardly ever	1	Once a month	2
Once a week	3	2-3 times a week	4
Daily	5	2-3 times a day	6

28. Would you go to great lengihs so satisfy an urge to binge?
Yes No

29. If you overeat do you feel very guilty?
Yes No

30. Do you ever eat in secret?
Yes No

31. Are your eating habits what you would consider to be normal?
Yes No

32. Would you consider yourself to be a compulsive eater?
Yes No

33. Does your weight fluctuate by more than 5 pounds in a week?
Yes No