Education of obese patient through structured day-hospital program

Fridian, Litan

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

Fridian Litan

Education of obese patient through structured day-hospital program

GRADUATE THESIS

Zagreb, 2019

This graduate thesis was made at Croatian Obesity Treatment Referral Center, a part of Internal Medicine Department , Division of Endocrinology, and University Hospital Center Zagreb. Mentored by Maja Baretić, MD, PhD, and was submitted for evaluation in 2018/2019 academic year.

I would like to thank my mentor, for her dedication, motivation and guidance through all the process without her this thesis wouldn’t be the same.

Contents

List of Abbreviations 4

SUMMARY 5

SAŽETAK 6

INRODUCTION 7

DEFINITION OF OBESITY 8

EPIDEMIOLOGY 9

PATHOPHYSIOLOGY 10

Regulation of Body Weight in Humans 10

Protein balance 11

Carbohydrate balance 11

Fat balance 12

Basic hunger/satiety regulation 13

DIAGNOSIS OF OBESITY 16

Body mass index and waist-hip ratio 16

Bioelectrical impedance analysis 18

Dual-energy X-ray absorptiometry 19

WORKFLOW WITH OBESE PATIENT 20

Patient history 20

Risk factors in history for development of obesity 20

Medications connected to weight gain 22

Family history 22

Emotional and psychological background of the patient 23

Physical examination 25
Laboratory tests 26
Identifying comorbidities 26
TREATMENT 27
Lifestyle modification and behavioral therapy 27
Pharmacotherapy 29
Bariatric surgery 33
Psychological therapy- psychotherapy and it's help 34
5-DAY STRUCTURAL EDUCATIONAL PROGRAM 35
How to determine if the patient is a candidate for the program 35
The structure of the program 35
First day 36
Day 2-5 37
Follow up 38
Results and positive outcomes of 5-day structural educational program 38
ACKNOWLEDGEMENTS 40
BIOGRAPHY 41
BIBLIOGRAPHY 42

List of Abbreviations:

BMD - Body Mineral density

BMI - Body Mass Index

DXA - Dual- Energy X-ray Absorptiometry

PA - Physical Activity

WHO - World Health Organization

FDA - Food and Drug Administration

GLP-1 - Glucagon-Like Peptide - 1

NPY - Neuropeptide Y

POMC - Proopiomelanocortin

MSH - Melanocyte Stimulating Hormone

TSH - Thyroid Stimulating Hormone

FFM - Fat Free Mass

PCOS - Polycystic Ovary Syndrome

SUMMARY

Obesity is an astronomical epidemic all over the world. Obesity-related diseases such as diabetes, hypertension, hyperlipidemia and cardiovascular diseases are the main cause of mortality and morbidity in the developed countries. They are the major factors for the continuous search to efficient treatment for obesity. Obesity is a chronic disease, and as such, it requires chronic therapy. Obese patients should always be treated through lifestyle interventions as first and primary line of care. Clinical interventions, in order to achieve and maintain weight loss reduction, including a behavioral-based interventions, pharmacotherapy and even surgery. Changes in lifestyle involve much more than a diet modification or increasing physical activity. The theme of the thesis is a structural 5-day educational program for obese patients through a day outpatient clinic. They are attending a structural weight loss program at the Croatian Obesity Treatment Referral Center, a part of the Department of Internal Medicine, Division of Endocrinology and University Hospital Center Zagreb. The 5-day program includes daily consultations with a multidisciplinary healthcare team. The team is conducted by an Endocrinologist – Diabetologist, nurse-educator, as well as nutritionist, physiotherapist, psychiatrist, and a psychologist, who provides psychological support and facilitate behavior modifications and more subspecialists. The aim of this paper is to see whether it is sustainable, how effective a short education course can be in order to empowering and strengthening the participants' confidence and gaining control over their lives, and thus over their eating habits and weight, in the long term.

SAŽETAK

Debljina je poprimila epidemiološke razmjere u cijelom svijetu. Stanja povezane s debljinom, kao što su dijabetes, hipertenzija, hiperlipidemija i srčanožilne bolesti, vodeći su uzrok smrtnosti i pobola u razvijenim zemljama. Sve navedeno su razlozi za trajnu potragu za učinkovito liječenja debljine. Debljina je kronična bolest te zahtijeva kroničnu terapiju. Intervencije kojima se pokušava postići smanjenje i održavanje manje tjelesne mase uključuju utjecaj na promjenu načina života, farmakoterapiju i operativno liječenje. Početak liječenja debljine je uvijek promjena stila života. Promjena stila života je mnogo više od modifikacije prehrane i povećanja tjelesne aktivnosti; zapravo se mijenja cijeli obrazac načina življenja. Tema ovog diplomskog rada je opis rada strukturirane 5-dnevne edukacije pretilih bolesnika ambulantnim liječenjem putem dnevne bolnice. Bolesnici pohađaju program strukturiranog gubitka težine pri Referalnom centru za liječenje debljine Republike Hrvatske koji je dio Interne klinike, Zavoda za endokrinologiju Sveučilišnog bolničkog centra Zagreb. Uspjeh liječenja ukazuje na to da edukacija može imati značajan utjecaj na zdravlje čak i nakon završetka programa. 5-dnevni program se sastoji do svakodnevnih susreta s multidisciplinarnim timom. Tim vodi endokrinolog-dijabetolog, medicinska sestra-edukator, a također uključuje nutricionist, fizioterapeuta, psihijatara/psihologa koji pružaju psihološku podršku i omogućuju modifikaciju ponašanja te po potrebi druge subspecialiste. Cilj ovog pregledno rada je opisati procjenu dobiti strukturiranog programa na stjecanje kontrole nad hranjenjem te dugoročnim postizanjem optimalne tjelesne težine. Poseban naglasak je vrednovanje uspjeha promjena životnog stila radi usvojenih znanja koje su stekli tijekom programa i postizanja zdravijih načina života s gubitkom težine.

INTRODUCTION

Over the past centuries, many health improvements have been achieved, however chronic non-infectious diseases are still an unresolved problem. They have not been defiantly solved. Although lifestyle has been adjusted to suit the individual person; unfortunately, it is not appropriate for the physical constitution of human beings. There's a growing population in the modern world that is gaining weight. Obesity has become more common than ever, and effects variety of demographics regions and age groups. Although it is still not yet widely accepted in the non-medical surrounding, obesity is a disease. It is recognized by a code in the International Classification of Diseases as E66. Obesity is a chronic endocrine-metabolic condition of multifactorial etiologies and a polygenetic basis. Complex pathophysiological mechanisms accompanying obesity are the cause of numerous comorbidities including hypertension, dyslipidemia, insulin resistance, diabetes and cardiovascular diseases (mainly heart disease and stroke), all of which are strongly linked to obesity. Obese patients should always be treated through lifestyle interventions as the main line of therapy. Change in lifestyle involves much more than diet modification and increasing physical activity; rather changing the pattern of life.

The theme of the thesis is a description of a structural, 5-day education of obese patient through daily outpatient clinics. It points out that the educational process is taking place in the daily clinic can have a substantial effect on the health of the participants, even after the program is completed. The aim of this paper is to see whether it is sustainable, how effective such a short education course can be in order to establish participants' confidence, and whether they can then gain control over their lives, and thus over their eating habits and weight.

DEFINITION OF OBESITY

Obesity is a complex, multifactorial, largely preventable and manageable disease. According to the World Health Organization (WHO), obesity is defined as follows: 'An abnormal or excessive fat accumulation that presents a risk to health'. Obesity is defined as a body mass index (BMI) greater than 30 kg/m^2 (or a situation where the amount of adipose tissue exceeds 20% of the normal quantity). In those conditions, fat causes harmful changes in the organs where it accumulates, and causes a number of adverse endocrine-inflammatory conditions.

EPIDEMIOLOGY

The secular rise in overweight and obesity can be explained by physiological and behavioral factors as well as changes in social and environmental circumstances.

The highest rates of obesity are reported in the Pacific Islands, Europe and North American. The lowest rates are in Asia (Dang M., 2010). The rates in Africa and Middle Eastern countries can be varying. In the USA today, overweight and obese, conjoined, eclipse the numbers of those who are normal weight by two fold (Ogden CL C. M., 2014). If secular trends continue, an estimated 38% of the world's adult population will be overweight and another 20% will be obese by 2030 (Kelly T, 2008). Obesity is estimated to affect, along with overweight, over a third of the world's population today (Ng M, 2013) (Stevens GA, 2012). USA National estimation of overweight or obesity in children based on the NHANES data show that in 2003–2006, 31.9% of children 2–19 years old had a BMI at or above the 85th percentile according to BMI for-age growth charts, and 16.3% were at or above the 95th percentile according to BMI for age (Ogden CL C. M., 2008). Looking at the Organization for Economic Co-operation and Development countries, women tend to be more obese than men but still in most of those countries (for which data is available), male obesity has been growing more rapidly. A systematic review of national and regional surveys conducted between 1990 and 2008 in European countries, points to obesity rates as low as 4.0 and 6.2% in French men and women, respectively, and as high as 30.0 and 32.0% in Czech men and women, respectively (Berghöfer A, 2008). Education and socio-economic background affect obesity. Evidence shows that less-educated women are two to three times more likely to be overweight.

PATHOPHYSIOLOGY

Regulation of Body Weight in Humans

The balance between energy intake (calories consumed) and energy expenditure (calories burned) determines body energy stores. The majority of the energy is stored in the body as fat, therefore, the balance between energy intake and energy expenditure, determines whether body fat, and hence body weight, is gained or lost. Carbohydrate, protein intake and oxidation rates are tightly regulated on a daily basis, and any inherent differences between energy intake and energy expenditure predominantly impact body fat stores. During overfeeding, the oxidation of carbohydrate and protein is favorized, leading to fat accumulation. The increase in oxidation is not equally coupled with intake. Thus, if sustained fat deposit is stored they expand and body weight is gained.

Agricultural and technological revolutions have coincided to allow significant changes to occur in both energy intake and energy expenditure (Aronne, 2007). The current Western environment supports sedentary behavior by allowing for profound reductions in the amount of physical activity necessary to exist and function successfully. One of the most remarkable occurrences of the past 50 years is that humans have developed methods for producing mass quantities of low-cost, energy dense foods with very minimal input of physical labor needed to produce them. The excess food availability and physical inactivity combined have created an ‘obesogenic’ environment that promotes energy imbalance and weight gain in everyone.

Protein balance

Protein intake is usually about 15% of daily calorie intake, and the protein stores in the body represent about one-third of the total stored calories in a 70 kg man. The daily protein intake amounts to a little over 1% of the total protein stores (Bray, 1991) (Snyder WS., 1975). The protein stores increase in size in response to growth stimuli such as growth hormone, androgens, physical training, and weight gain, but do not simply increase from increased intake of dietary protein. Therefore, protein imbalance is not implicated as a direct cause of obesity (Flatt J. e., 1985).

Carbohydrate balance

Carbohydrate is usually the main source of dietary calories, yet body stores of glycogen are very limited: 500-1000 grams on average (Acheson, 1988). Daily intake of carbohydrate corresponds to about 50-70% of the carbohydrate stores compared to about 1% for protein and fat (Schutz, 1989), so that over a period of hours and days, the carbohydrate stores fluctuate markedly compared with those of protein and fat. However, as with protein, carbohydrate stores are tightly regulated (Rising, 1992). Dietary carbohydrate stimulates both glycogen storage and glucose oxidation and suppresses fat oxidation (Flatt J. e., 1985). Once glucose is inside the liver, glucose is phosphorylated into glucose-6-phosphate, that is further metabolized into triglycerides, fatty acids, glycogen or energy. Excess of glucose is stored in a form of glycogen. The body's glycogen stores fill up quickly. When they are full, excess glucose converts into fat, a long-term source of energy. In such cases carbohydrates are catabolized to acetyl-CoA, which is an initiation of fatty acid synthesis pathway.

Fat balance

In marked contrast to the other nutrients, body fat stores are large and fat intake has no influence on fat oxidation (Flatt J. M., 1996) (Tobias, 2015). Daily fat intake represents less than 1% of the total energy stored as fat, but the fat stores contain about three times the energy of the protein stores (Smith, 2000). A deficit of 200 kcal of energy over 24 hours means 200 kcal comes from the fat stores, and the same holds true for an excess of 200 kcal of energy which ends up in the fat stores (Frayn, 1995). The amount of total body fat exerts a small, but significant, effect on fat oxidation and its activation. High body fat levels may represent a mechanism for attenuating the rate of weight gain (Zurlo, 1990). Energy balance is the driving force for fat oxidation (Frayn, 1995, Aronne, 2007): when it is negative (i.e., energy expenditure exceeding intake), fat oxidation increases (Smith, 2000).

The concept of imbalance between energy intake and energy expenditure, which is buffered by changes in fat stores, was introduced by Flatt (Flatt J. M., 1996). As a consequence of the fact that amino acids, glucose, and alcohol oxidation rates adjust themselves to the amount consumed, fat oxidation ends up being determined primarily by the 'gap' between total energy expenditure and energy ingested in the form of carbohydrates, protein and alcohol rather than just the amount of fat consumed on a given day. Therefore under physiological conditions, fat is the only nutrient capable of maintaining a chronic imbalance between intake and oxidation, and thus directly contributes to the flux in adipose tissue mass (Frayn, 1995). Dietary guidelines recommend a reduction in total dietary fat content to less than 30% of the energy intake to help reduce the prevalence of obesity. The most common adjustment to macronutrients for weight loss has been a reduction in fat intake

since in comparison to both carbohydrate and protein, fat contains more than twice the energy per gram. Dietary macronutrient composition has been studied extensively in regards to weight loss efficacy. The results of these studies were combined in a recent meta-analysis (Tobias, 2015), where a total of 53 randomized controlled trials that imposed a low-fat diet or an alternative dietary intervention for one year. Collectively, these studies showed that dietary interventions targeting reduced fat intake do not lead to a significantly greater weight loss than dietary interventions targeting reduced carbohydrate intake, which produced an average long-term weight loss of 1.15 kg. Better compliance, irrespective of the type of dietary intervention, is best predictor of weight loss. Offering individuals a choice of treatments is promising for improving dietary compliance.

Basic hunger/satiety regulation

The development of hunger as a physiological mechanism in response to extended periods of food deprivation is a primal motivated behavior, and comprises one of the most fundamental responses in all animals. Homeostatic regulation of energy balance requires the brain to maintain the appropriate energy levels by modulating metabolites, fuel stores or hormone secretion. The way the brain regulates and modulates behavior and action is by means of nerve impulses. Impulses conducted by electrical currents move up along the neurons to the edges, and chemical neurotransmitters are released in the synapse, in between the two neurons. Those molecules modulate brain activity, by inhibition of one or activation of the other. This requires first the ability to sense metabolic and hormonal changes in the periphery, by afferent signals projecting to the brain. A current classification of signals involved in the regulation of energy balance differentiates three basic signals:

1. Adiposity signals (i.e. leptin and insulin) are secreted in proportion to body fat stores;

2. Satiety signals (i.e. cholecystokinin, glucagon-like peptide 1 -GLP-1) which are gastrointestinal peptides, that are secreted in association with meals indicating caloric quantity and quality to the brain, and,

3. Nutrient-related signals (i.e. glucose, free fatty acids and amino acids) generated through the ingestion of a meal. Nutrient-related signals directly inform centrally located sensors about the current state of carbohydrate and lipid metabolism (Mobbs CV., 2001). Two major brain areas that play a key role in the homeostatic regulation of energy balance are the hypothalamus (including the arcuate nucleus- ARC) and the brainstem (including the nucleus tractus solitarius). The brainstem, integrates short-term signals, mainly originating from the gastrointestinal tract during eating or digestion, contributing to meal termination (e.g. cholecystokinin, and neuronal input from vagal afferents) (Broberger, 2005) (Berthoud HR., 2006). Factors secreted by other peripheral organs and tissues (e.g. adipose tissue, pancreas) serve to signal long-term changes in metabolic state or energy stores.

Depending on the metabolic status signal integration in hypothalamic nuclei mainly contributes to meal initiation. The most important neurotransmitters regulating neuronal activity in the hypothalamus are glutamate and gamma-aminobutyric acid (GABA) (Kampe J M. T., 2010). GABA represents the main inhibitory neurotransmitter in the central nervous system and glutamate represents the main excitatory neurotransmitter in the hypothalamic neuroendocrine regulation (Meister, 2007).

Neuropeptides and brain derived factors

Orexigenic Neuropeptide Y (NPY) is one of the most abundant and widely distributed neuropeptides within the nervous system, and is one of the most potent stimulators of feeding. NPY that is administered repeatedly into the hypothalamus induces obesity accompanied by hyperphagia, hyperinsulinemia, hypercorticosteronemia, decreased thermogenesis in brown adipose tissue, reduced plasma testosterone levels and increased insulin resistance in skeletal tissues. The levels of NPY mRNA in the arcuate nucleus are increased during fasting (Kalra, 1991). Proopiomelanocortin (POMC) is a large precursor peptide that is cleaved within neurons to several specific peptides. These include melanocyte stimulating hormone (MSH), ß-Endorphin and adrenocorticotropin with opposing effects on energy balance. Within the hypothalamus, POMC neurons, localized in ARC, innervate areas of the hypothalamus. ß-Endorphin increased food intake.

Anorexigenic MSH is cleaved from the POMC precursor molecule. It acts as an endogenous agonist of the melanocortin receptors that are important in the regulation of food intake. The melanocortin system is one of the most significant pathways involved in the regulation of food intake, with mutations within the system found in approximately 2% of the cases of genetic obesity in humans (Kampe J M. T., 2010). Leptin is predominantly produced by fat cells and is expressed according to the size of fat stores (Friedman, 2002). Its administration induces a negative energy balance mediated by neuronal structures in the hypothalamus and the brainstem. The role of leptin in signaling the brain about chronic changes in energy status is completed by the pancreas derived hormone insulin, which conveys additional information about long-term changes of peripheral metabolism to the brain.

DIAGNOSIS OF OBESITY

Since an excess of body fat is the defining variable of obesity, a proper diagnosis of obesity would require the assessment of body fat. Today, there are many ways to estimate body fat; both anthropometric and body composition measurments.

Body mass index and waist-hip ratio

Body fat mass can be measured in several ways. The most common and practical way is by BMI, which is defined as weight/height^2 (kg/m^2), giving a rough estimation on how the body weight to the height comparing to a standard scale relative to the population. There are four major categories for BMI: underweight (18.5 ≥), desirable weight/ healthy (18.5-24.9), overweight (30 kg/m2), obese (≥ 30). According to the World Health Organization (WHO), obesity is classified as class I for a BMI between 30 and 34.9 kg/m2, class II for a BMI between 35 and 39.9 kg/m2, and class III for a BMI ≥ 40 kg/m2 (WHO, 2000)-Table 1. The BMI lacks sensitivity to gender and ethnicity, which consist of normal relative differences in body fatness. In fact, for the same BMI, women are, on average, fatter than men, and Asians are, on average, fatter than Caucasians. As a result, in Japan, obesity is diagnosed at a BMI ≥ 25 kg/m2 (Inoue S. Kanazawa M, 2002), in China at a BMI ≥ 28 kg/m2 (Z., 2020), while for Caucasians, a BMI in the interval 30kg/m2 is diagnosed as overweight, not yet obese. It was suggested that not only total body mass is an indicator for mortality/morbidity, but the fat distribution will also have a large impact. Even between same weights, the distribution can be different and thus the risk is substantially changed. Abdominal or visceral fat, as opposed to lower body fat, has shown to be the most significant determinant for cardiovascular disease (CVD). For this reason, abdominal fat was precluded to be measured as ‘waist to hip’ ratio

and sometimes waist circumference alone. Due to the relative ease of obtaining waist circumference, the method is more common than the waist–hip ratio. WHO expert consultation report published in 2008 (Consultation, 2008) compare the specificity and sensitivity of each method in regard to risk for CVD. Waist to hip and waist circumference alone showed better correlation to CVD risk than the BMI. However, WHO expert conclude that for this method there are some issues concerning the accuracy of the measurements in gender, ethnic groups and age, which should all be taken in to consideration. The standard now is to combine both the BMI and waist circumference measures.

Table 1 shows a classification of obesity according to BMI

BMI < 18.5	**Underweight**
BMI 18.5 – 24.9	**Normal weight**
BMI 25.0 – 29.9	**Overweight**
BMI 30.0 – 34.9	**Obesity 1. Class**
BMI 35.0 – 39.9	**Obesity 2. Class**
BMI > 40.0	**Obesity 3. Class**

Bioelectrical impedance analysis

Bioelectrical impedance analysis is a non-invasive, low cost and a commonly used approach for body composition measurements and assessment of clinical condition. From an electrical point of view, impedance is an obstruction of the flow of an alternating current. The biological aspect is affected by the water content of a tissue. The higher the water content, the better is the flow, meaning the lower resistance. Fat, different to muscle, has relative low water content and thus higher resistance (low flow). In bio-impedance measurements, the human body is divided into five inhomogeneous segments, two for upper limbs, two for lower limbs and one for the trunk. Each of these five compartment modules contains fat mass considered a non-conductor of electric charge, and fat free mass (FFM) considered as the conducting volume that helps the passing of electric current, which consists of bone minerals and body cell mass. That includes protein and total body water, consistence of extracellular fluid and intracellular fluid. Measurement of bio-impedance is obtained from the whole body and body segments separately, using single frequency, multiple frequencies and bio-impedance spectroscopy analysis. Measurement of total body bio-impedance is the most commonly used method for estimating whole body compartments. Many of the whole body bio-impedance instruments apply three approaches for impedance measurement: hand to foot method (the most commonly used), foot to foot, method and hand to hand method. (Ibrahim F., 2014).

Dual-energy X-ray absorptiometry

Fat tissue 'dual-energy X-ray absorptiometry' (DXA) quantifies total and regional body fat by assessing the differential attenuation of two x-ray beams with different intensities (energy levels) as they travel through the body of an individual (De Groot LJ, 2018). This technique is used to measure bone mineral density, measure bone mineral content, FFM, and provides estimates of percent body fat. It relies on transmission measurements made at two photon energies to allow calcium, and thereby bone mineral, to be assessed. The preferred regions for bone mineral density measurement are lumbar spine, proximal femur and whole body. Typically the energy source produces photons at two different energy levels, 40 and 70 keV, which pass through tissues and attenuate at rates related to its elemental composition. Bone is rich in highly attenuating minerals, calcium and phosphorous, and is readily distinguished from soft tissues. The unique elemental profiles of bone, fat, and no bone lean tissue allow for visualization and separate analysis of each tissue type. Two limitations of DXA scanners are the weight limitation of the scanning bed (typically 136 kg) and the width of the scanning area (usually ~60 cm). This limitation has lead to the development of a technique to estimate total-body composition from a half-body scan. However, this methodology requires a special machine which involves minimal exposure to x-rays. In everyday practice, the measurement of body weight has been adopted as a valid proxy for body fat and it is used to calculate the BMI (Rothney, 2009). Today, DXA is mostly used in clinical trials.

WORKFLOW WITH OBESE PATIENT

Screening for obesity begins with review of medical history involving previous diseased, medications, eating habits, lifestyle, exercise, and a physical examination. Blood tests may indicate secondary causes or consequences of obesity.

Patient history

Risk factors in history for development of obesity

Risk factors can be sub-classified into ‘factors we can control’ and ‘factors that we can’t control’. In the first group, the major risk factor to developing obesity is the sedentary lifestyle. Today, everything can be reached from home; purchasing goods is easier than ever, you can conduct interactions for almost everything with your smartphone. When one chooses to leave their home, food is a major obstacle to curing obesity that the modern world has created. Restaurant chains offer ‘drive through’ options, with well organized machinery of fast and efficient take away food which is obtainable without leaving the car. Research conducted in the 1950s by Jeremiah Morris et al, which followed a large cohort of London transport workers found that sedentary bus drivers had higher rates of CVD, and higher mortality than their active counterparts, the conductors. They postulated that physically active work has a cardio-protective effect (Morris JN, 1966). Morris et al. reported a significant relationship between occupational physical activity (PA) and CVD. CVD and other risk factors, such as hypertension and lipids panel, were reduced in physically active conductors compared with the sedentary drivers. PA and exercise denote different concepts, although

they are commonly interchanged wrongly. According to the US Department of Health and Human Services, and the Centers for Disease Control and Prevention, PA refers to any bodily movement produced by skeletal muscles that results in an expenditure of energy, which includes a broad range of occupational, leisure and daily activities; 'exercise' refers to planned or structured PA (Rosenow F, 2012). Nevertheless, it's proven that any PA appears to impact CVD risk through beneficial effects on several factors, including adiposity, insulin sensitivity, glycemic control, type 2 diabetes incidence, blood pressure, blood lipids, endothelial function, hemostasis, and inflammatory defense systems (Bassuk SS, 2005). In dealing with the sedentary lifestyle, guidelines were made, based on evidence in research study and observation in the population. They elaborate how to perform PA which will reduce the morbidity in the population. They state the length, and intensity, and the frequency in which PA need to be done per week for each age group. For example, the guide from American Heart Association Recommendations for Physical Activity in Adults recommends at least 30 min of moderate-intensity aerobic activity at least 5 days/week for a total of 150 min/week; or at least 25 min of vigorous aerobic activity at least 3 days/wk for a total of 75 min/week; or a combination of moderate- and vigorous-intensity aerobic activity, and moderate- to high-intensity muscle-strengthening activity at least 2 days/week for additional health benefits. They recommend further adding an average 40 min of moderate- to vigorous-intensity aerobic activity 3 or 4 times/week to lower blood cholesterol level.

The second risk factor is 'fast food' consumption, which is motivated because a fatty fast food meal is often cheaper than a healthy meal. Food is one of the most common 'social events'. In any age group food become an event, as a place to go for a business meeting, or after school as a 'hot meal'. Food is everywhere, turning on the TV in prime time and in almost every channel, cooking shows, reality shows, teaching show and traveling shows. All

the media is ‘feeding-streaming’ our brain nonstop with food. There’s even a ‘food channel’. A quick search on the web demonstrates the aggravation of global disease with this fast food consumption. Some find in warmth and comfort in food, and eating can be a coping mechanism with emotional distress on a daily basis. ‘Emotional eating’ is the urge to eat without the internal signal of hunger and feeding signals. This urge can come from both negative and positive impulses (Bongers, 2016). Today, life is full of stressors; obese people are, unfortunately, considered unpopular, unattractive, and repelling. This can put many people in a vicious cycle of eating when they feel transparent and ignored by society because they are obese.

Medications connected to weight gain

Finally, an important part of medical history is drug-induced weight gain. A serious side effect of many commonly used drugs is weight gain. Improved glycemic control achieved by insulin, insulin secretagogues or thiazolidinedione therapy is generally accompanied by weight gain. Weight gain is also common in psychotropic therapy; antiepileptic drugs that promote weight gain include valproate, carbamazepine and gabapentin. The risk of persistent obesity is also a result of chronic corticosteroid therapy.

Family history

The aspect of family history can be presided in a few ways, like genetic predisposition as risk factor, and familial habits (perhaps the stronger one). Some families enjoy family time by eating together, and they choose a fast food option because of its ease. Others go hiking

every weekend, and some like watching TV. The heredity, culture and environment form the family dynamic, the way they grew up, and their surroundings, what kind of food they mostly eat. It's important to access the family as a unit and not as an individual, nuclear family. By accessing the family as a unit, it is easier to address the family and their issues, the ways of treatment and the family planes, which will be suitable for them, and custom made. In addition looking at the family as a unit will facilitate to uproot the issue and treating the entire family, by primary/secondary prevention. Family background and history will help the physician to get better prognosis and outcome for the patient. The best way to approach the family status is by asking the patient if he lives by himself, if he has obese/overweight family members. Inquiring, the death cases in the family and their causes, included the ages of each deceased, as we want to establish, the family connection (blood wise). As mentioned earlier, we classify differently 'early age' for CVD death both for male and females. Therefore, we want to establish medical data that will include all the relevant influence there is.

Emotional and psychological background of the patient

There is a strong connection between eating and emotions, called 'emotional eating'. We can look at this as a bidirectional path; one way is from deep sadness/depression, which some people can't handle, so they may choose comfort in food, eating emotionally desirable food. The comfort food is usually high in sugar and calories, so the satisfaction is immediate. Each time that sadness and depression reappear, the need to get rid of it is stronger, so more carbohydrates are consumed. On the other hand, there are obese and overweigh people, who lost the hope of losing weight and having healthier life. They would

maintain all the horrible feelings, so they would continue their bad eating manner. It's a vicious cycle. Both of the pathways will cross each other and in some cases will be the continuation of one another. The emotional and mental health of the patient is a crucial component in treatment and reaching successful results. These vicious cycles need to be stopped. The doctor's aim is to support the patient medically and emotionally. Whether it by referring the patient to psychologist, dietician or to a support group. Asking the patient about his/her eating habit, how many meals they consume per day, whether they cook at home or eat outside, with whom they eat, and advising them to write a diary regarding their food and emotions each day are good practices.

Physical examination

Examination of organ systems should include the following:

Cutaneous – to search for intertriginous rashes from skin-on-skin friction; also search for hirsutism in women, acanthosis nigricans, and skin tags, which are common with insulin resistance secondary to obesity.

Cardiac and respiratory systems- to exclude cardiovascular and respiratory insufficiency. In some obese patient, sleep is irregular due to ‘sleep apnea’. To assess the body fat distribution to identify risk for CVD, blood pressure should be measured in all adipose patients. Blood pressure measurements should be made with a cuff matching the upper arm of an obese person.

Abdomen - to exclude hepatomegaly, which may suggest hepatic fatty infiltration or non-alcoholic steatohepatitis , and distinguish the striate distensae from the pink and broad striate that suggest cortisol excess. Cushing’s syndrome/disease is also associated with truncal or visceral obesity, which can be difficult to differentiate from simple obesity.

Extremities- to search for joint deformities (i.e., coxa vara), evidence of osteoarthritis, and any pressure ulcerations.

Laboratory tests

There are tests aiming to exclude secondary causes of obesity; thyroid stimulating hormone (TSH) to exclude hypothyroidism (which is mandatory). If the clinical status and anamnesis data point to other causes, make additional screening for hormonal imbalance. A Low-dose dexamethasone suppression test is aided in the differentiation of Cushing's syndrome/disease from obesity. A wide hormonal panel to exclude polycystic ovary syndrome and hypogonadism (follicle-stimulating hormone, luteinizing hormone, testosterone and estrogen), and in rare cases pituitary and hypothalamic hormone deficiency can be evaluated. The other lab test panel is to evaluate the consequences of obesity (fasting blood parameters, total blood count, standard biochemistry tests, urine chemistry, oral glucose tolerance test, 24-hour urine protein excretion and glomerular filtration assessment, lipid profile).

Identifying comorbidities

Seeing obesity as 'chronic' and 'progressive', allows for a better approach and understanding of the risk factors preceding it. This approach gives the tools for prevention. Damage to macro-vasculature is the hallmark of CVD in obesity. Screening for comorbidities includes screening for diabetes and lipid abnormalities, cardiovascular disease, and also for the psychological issues, infertility, musculoskeletal damage and many others.

TREATMENT

The complexity of several pathophysiological mechanisms accompanying obesity is the cause of numerous co-morbidities. Treatment must be addressed in two levels of care, in order to investigate comorbidity variety and the find best way to handle it. The therapy of obesity consists of three major strategies, each one set once the previous level has failed. One reason for failure could be due to bad adherence to therapy, while another can relate to the obesity and its consequences when they are too difficult and need a complex, multi-disciplinary approach. The first step is usually non-invasive and non-medicament, but rather a lifestyle modification.

Lifestyle modification and behavioral therapy

Lifestyle modification includes both dieting, emphasizing on what to eat and when, and introducing new and healthy eating habits. Individuals can lose body weight and improve health status on a wide range of energy (calorie)-restricted dietary interventions. The most commonly utilized diets are low-fat, low-carbohydrate, and Mediterranean approaches, in addition to commercial slimming programs, meal replacements, and newly popularized intermittent fasting diets. None of these diets seem to have any advantages than others regarding weight loss. Optimizing adherence is the most important factor for weight loss success, and this is enhanced by regular professional contact and supportive behavioral change programs. The Mediterranean diet is characterized by the regular intake of legumes, nuts and fish, as well as a moderate intake of wine, generally consumed with meals. The Mediterranean diet is distinguishable from other dietary patterns by a high intake of monounsaturated fatty acids, mostly from olive oil. The health benefits of the Mediterranean

diet were recognized some years ago. Such diet provides same weight loss but with cardiovascular protection.

In addition to diet, PA must be tailored to the physical capabilities of the patient and his health status. If the goal is to achieve a regular routine, behavioral changes must be implemented to modify and follow carefully, especially in the beginning, when it's not yet the patient's norm. There are various strategies for how to increase everyday physical activities: The U.S. Public Health Service and the American College of Sports Medicine recommends approximately 30 minutes daily of moderate-intensity physical activity (i.e. brisk walking) for the improvement of cardiovascular and metabolic function, and the consequent reduced prevalence of important conditions such as dyslipidemia, hypertension and insulin resistance (Pate RR, 1995). There is now evidence that the exercise dose related to successful prevention of excess weight gain (Blair SN D. P., 2004, L., 1999) is far less than that needed to reverse obesity (Janssen I, 2001, Freeman JA, 2000) or to sustain weight loss following obesity. It appears that about 45-60 minutes per day-1 of moderate activity is necessary to prevent the transition from normal weight to obesity, at least for a large part of the population (Blair SN D. P., 2003). Note that this level of activity is significantly higher than the recommendations aimed at improving obesity-related comorbidities. Caloric restriction without exercise may result in a loss of lean mass along with adipose tissue, thereby resulting in a drop in the metabolic rate and setting the stage for relapse. Both aerobic and resistance exercise can preserve lean tissue during weight loss, however, this is primarily a function of the amount of exercise performed over the weight loss period (Jakicic JM, 1999). Combining resistance training with aerobic exercise has been shown to enhance lean body mass preservation and improve overall health results during a caloric-restriction weight loss regimen (Chaabene M, 2016, Abid M, 2009). Resistance

training is especially important in aging because of improved functionality. In older obese adults, during caloric restriction, total body weight loss was similar during exercise across three different exercise groups: aerobic exercise alone, resistance training alone and a combined program aerobic exercise with resistance training. However, other measures of physical function were all improved to the greatest extent by the combined aerobic exercise with resistance training protocol in the 65+ group (Armamento-Villareal R, 2017). Given the high degree of negative energy balance required for weight loss, high levels of lifestyle activity combined with caloric restriction are now prescribed for both initial and long-term weight loss in obese and overweight individuals. One of the ways to increase the daily activity is to focus on the area where we live in. Attempts to improve lifestyle have been focused on urban areas; it should be modified in a way that promotes movement (e.g., parking further away from the building, taking the stairs instead of using the elevator, etc.).

With only lifestyle intervention, the weight loss is often short-term and scanty, as mentioned; therefore the best method to reach, and most importantly maintain weight loss, is to combine all the recommendation at once. To restrict calorie intake while performing both aerobic and resistance training with a small lifestyle modification, such as parking the car a bit further away from home or taking the stairs instead the elevator , would lead to substantial and effective weight loss, which is also maintainable.

Pharmacotherapy

Pharmacotherapy is the second step in the treatment of obesity, approved only when weight loss targets were not reached through lifestyle intervention. During the history of anti-obesity drugs, many of them were withdrawn because of their side effects. To mention a few,

fenfluramine (Connolly HM, 1997) was withdrawn following reports of heart valve disease and pulmonary hypertension; amphetamine causes addiction and is now a DEA (Drug Enforcement Administration) Schedule II drug; rimonabant was withdrawn due to severe depression and frequent suicidal thoughts. On the other hand the effects of the anti-obesity drugs on weight loss are generally modest, rarely exceeding more than 10% of initial body weight. So far, there has been no drug on the market with prolonged activity. One of the needed criteria to prescribe drugs is the BMI, which helps the clinician to classify obesity and its severity. According to NICE clinical guideline, patients with normal BMI in the range from 18.5 to 24.9 kg/m^2 should not be treated with drugs for obesity. If the patient is overweight with a BMI from 25 to 29.9 kg/ m^2 and co-morbidities are present (diabetes, hypertension, dyslipidemia, etc.), drugs could be prescribed. The same rule applies for first grade obesity (BMI from 30 to 34.9 kg/m^2). Patients with second grade obesity (or BMI from 35 to 39.9 kg/ m^2) and third grade obesity (with BMI higher than 40 kg/m^2) could receive drug therapy regardless of comorbidities. Those guidelines generally do not recommend anti-obesity drugs for children younger than 12 years. Other more strict guidelines in drug management, like the National Institutes of Health Guidelines, are slightly different. They recommend drug therapy for overweight patients only if they have comorbidities and their BMI is higher than 27 kg/m^2, as with the other guidelines, they suggest patients with first grade obesity to receive the drugs regardless of comorbidities. Other guidelines place a condition on the use of the drugs only as part of a program that includes diet, physical activity and behavior therapy, and anti-obesity drugs are considered only if a patient has lost at least 5% of their initial body weight since starting drug treatment. (Steinberg GR, 2002) When addressing the type and mode of action of the drugs they divided in to 'central' acting and ' gastrointestinal tract' acting.

Central acting drugs; lorcaserin, a selective serotonin receptor agonist, was approved by the Food And Drug Administration (FDA) in 2012 as a long-term treatment for obesity for adults with a BMI $\geq$ 30 kg/m^2 or with a BMI $\geq$ 27 kg/m^{2}with at least one weight-related comorbidity. It reduces appetite by binding to the 5-HT$_{2C}$ receptors on POMC neurons in the hypothalamus. In the phase 3 of the trial, BLOSSOM, patients were treated with placebo, lorcaserin 10 mg once daily, or lorcaserin 10 mg twice daily. After one year, the group assigned to lorcaserin 10 mg twice daily showed an average placebo-subtracted weight loss of 3.1%. The most common adverse reactions reported in those taking lorcaserin include headache, dizziness, fatigue, nausea, dry mouth, and constipation. A potentially life-threatening side effect from lorcaserin is serotonin syndrome (Anderson CM, 2012). Single-tablet combination phentermine plus topiramate was approved by the FDA in 2012 as a long-term treatment for obesity for adults with a BMI $\geq$ 30 kg/m^2 or with a BMI $\geq$27 kg/m^2, and one weight related comorbidity at least. Phentermine is thought to promote weight loss by increasing norepinephrine (more than dopamine) release and decreasing its uptake in hypothalamic nuclei, leading to a decrease in food intake. It also acts as an adrenergic agonist that activates the sympathetic nervous system and increases resting energy expenditure. Topiramate is an FDA-approved medicine for epilepsy and migraine prophylaxis that has been shown to reduce body weight by promoting taste aversion and decreasing caloric intake, Multiple Phase 1, 2, and 3 studies including more than 5000 subjects have evaluated the efficacy and safety of phentermine/topiramate combination therapy. The one-year EQUIP trial, a phase three 56-week randomized controlled trial enrolled 1267 patients with obesity (mean BMI of 42.0 kg/m^2) and showed 3.5% in the starting dose group (3.75 mg P /23 mg) and 9.3% placebo-subtracted weight loss in the top treatment dose (15 mg/92 mg) group (Connolly HM, 1997). Phentermine-topiramate is not recommended for patients with

significant cardiac history such as coronary disease and uncontrolled hypertension. Phentermine/topiramate carries an increased risk of cleft lip/palate in infants exposed to the combination drug during the first trimester of pregnancy. The combination tablet of bupropion and naltrexone was FDA approved for weight loss in September 2014. Bupropion's primary mechanism of action is as a reuptake inhibitor of dopamine and norepinephrine that promotes activation of the central melanocortin pathways. The second component is naltrexone, a pure opioid receptor antagonist that diminishes the auto-inhibitory feedback loop on neurons activated by bupropion, thereby allowing for sustained weight loss. The most common side effects of bupropion/naltrexone include nausea/vomiting, constipation, headache, dizziness, insomnia, and dry mouth.

Gastrointestinal tract acting drugs; the gut is the place where degradation and absorption happens. It's an important and crucial place of action for the drugs targeting obesity. The gut is also the place where many intestinal peptides, are secreted that interact with bowel motility and hypothalamic centers, thus mimicking the effect to the centrally acting drugs without the severe side effects. One of the most common and widely use 'anti-obesity' gut is orlistat. Orlistat's mechanism of action is by deactivation of intestinal lipase and it inhibits intestinal fat lipolysis and absorption. It enables only one-third of fat absorption from the intestine. Unabsorbed fat is excreted through the feces and a significant amount of eaten energy thus does not get stored in the body. It has a modest weight loss effect by producing approximately 100 kcal a day deficit and is effective in weight maintenance (Heck A, 2000). In the large study, XENDOS, which observed 3,305 obese patients over four years, participants were randomized with regard to lifestyle changes plus orlistat three times daily or a placebo. Orlistat therapy reduced weight and the incidence of diabetes beyond the results achieved through lifestyle changes alone. The outcome of orlistat minus placebo over four years was

only −2.8 kg. (Boldrin MN, 2004). Side effects rarely result in discontinuation of orlistat treatment. Side effects include oily stools, fecal urgency and oily spotting. Side effects are usually mild and improve with continued use. Orlistat is contraindicated in patients with malabsorption, major intestinal problems and disorders of bile flow, pregnant women and nursing mothers. Incretins are substances secreted in the gut after a meal. GLP-1 is released from intestinal enteroendocrine L cells in response to a carbohydrate meal. GLP-1 has many levels of action, but currently it is primarily known for its effect on beta cells (the peptide lowers blood sugar by stimulating insulin secretion, which augments pancreas response within a safe glycemic range without inducing hypoglycemia). GLP-1 reduces gastric emptying, lowers appetite by promoting satiety via hypothalamic receptors and reduces food intake. As a consequence, GLP-1 action promotes weight loss. GLP-1 receptor agonists are injectable hypoglycemic, they regulate glucose level and promote weight loss. One of these agents, liraglutide, is currently indicated at a higher dosage for the treatment of obesity.

Bariatric surgery

Bariatric surgery includes variety of procedures; gastric bypass, sleeve gastrectomy, gastric banding and biliopancreatic bypass. They produce substantial and durable weight loss, but they are not widely available for obese people. The principal mechanisms vary between these procedures and include control of hunger, change of appetite, restriction of intake, diversion of food from the proximal small intestine, malabsorption of macronutrients, food aversion and possibly changes to the gut microflora. Weight loss outcomes are typically 50-60% of excess weight loss at 10 years for gastric bypass, 45-55% for gastric banding, and 70% for biliopancreatic bypass. In association with the weight loss there are significant and sustained improvements in the life expectancy, in the quality of life and in many of the

comorbidities of obesity. In particular, all procedures have been shown by randomized controlled trials to induce remission of diabetes better than non-surgical therapies in the short-term. Medium and long term data are not yet available. The mortality risk reflects the type of surgery and varies between 0.1% for gastric banding to 1-2% for other procedures. The criteria for consideration of bariatric surgery include the presence of obesity (BMI > 30Kg/m2), a history of multiple attempts at weight reduction by non-surgical means, an awareness of the potential risks and a commitment to attend the follow up program. The decision on which procedure should be used is based on patient or surgeon preference, availability of appropriate aftercare and the patient's tolerance of risk and permanent anatomical change.

Psychological therapy- psychotherapy and its ability to help

In a meta-analysis (Bouvy PF, 2010) a reciprocal link between depression and obesity was confirmed. Obesity was found to increase the risk of depression, most pronounced among Americans. In addition, depression was found to be predictive of developing obesity. Being obese significantly influences the well-being and state of mind of a person. While treating the apparent obesity, special care should be given to the state of mind of the patient. In weight management, the state of mind has a lot to do with the physical diseases, starting with why the patient gained weight; whether it was emotional eating or whether he was struggling with severe depression, and was unmotivated. Cognitive behavioral therapy was shown to assists in maintaining the weight and to achieve the goal in several trials (Keränen AM1, 2011).

5-DAY STRUCTURAL EDUCATIONAL PROGRAM

How to determine if the patient is a candidate for the program

All individuals with a BMI over 30 kg/m^2, those with a BMI 25-29.9 kg/m^2 and with a high waist circumference are potential candidates for the 5-day program. Patients, who have a BMI between, 25-29.9, but who do not have any risk factors or comorbidities should be individually counseled to avoid further weight gain. The goal of weight control is both reduction of weight and maintenance of healthy body weight for the long term. Weight loss should be achieved through high-intensity lifestyle interventions. If the patient is not open to weight loss, at least prevention of further weight gain should be attempted. Those with BMI over 35 kg/m^2 are unlikely to be able to achieve sufficient fat loss on a usual low calorie diet of 1,200 to 1,500 calories without regimes that must continue for many months. That is why they should be referred for care by such multidisciplinary team specializing in obesity. Patients are referred to 5-day program only by endocrinologists-diabetologists.

The structure of the program

The 5-day program included daily consultations with a multidisciplinary healthcare team. The team, which was led by endocrinologist-diabetologist and nurse-educator, also includes a nutritionist, physiotherapist, psychiatrist, and a psychologist who provided psychological support and facilitated behavior modifications and other subspecialists. Sometimes groups formed based on the comorbidities (i.e group of the obese infertile women with polycystic ovary syndrome -PCOS).

First day

People are in small groups ranging between 5-7 patients and a nurse educator is always present in the group. On the first day, they come to the clinic at 8 o'clock, and leave at 4 o'clock. On that day patients have a lecture about obesity itself, the importance of normal weight and the implication on the human body once obesity take place. They also have exercise, consultation with a psychologist and with a registered nutritionist. The baseline anthropometric values (height, weight, BMI) as well as body composition are measured by bioelectrical impedance analysis (fat mass, muscle mass). Family history is taken and extended laboratory panel done aiming to exclude secondary causes of obesity as well to identify consequences of obesity. All types of treatment and complications are possible (i.e. if the patient has cardiovascular disease; treatment option range from invasive vascular procedures on beds for very obese patients, to cardiac transplantation). The hospital is paper-free, with all data kept in Hospital Information Systems (including information about a patient's health history, laboratory and all the medical exams). The system controls who can access the data and under what circumstances. It is also used as a database. Sometimes groups are formed according to their co-morbidities as stated earlier. In such cases, a gynecologist is involved in the education team, when the group is PCOS based. If there are patients with high cardiovascular risk a cardiologist is present.

Day 2-5

Patients come to the clinic at 11 o'clock, leave by 4 o'clock. They have an interactive talk, exercise, lunch, and consultation with an endocrinologist and a nutritionist, physical exercise, and during the last part of the day, a psychiatric group therapy session. Joining a group of strangers can be intimidating for anyone, and especially for an obese patient, but group therapy provides benefits that individual therapy may not. Groups can act as a support network where other members of the group often help to come up with specific ideas for improving a difficult situation or life challenge. It is a safe place where each can share the struggle they are facing, and they are all united. Regularly talking and listening to others also helps to put their own problems in perspective. Many people experience mental health difficulties related to obesity, but only few speak openly about that, especially near people that they don't know well each other. It can be a relief to hear others discuss what they're going through, and realize that they are not alone. Diversity is another important benefit of group therapy. People have different personalities and backgrounds, and they look at situations in different ways. By seeing how other people tackle problems and make positive changes, one can discover a whole range of strategies for facing their own concerns. There are also positive links between eating meals together, learning how to eat and interact. Frequent and sustainable contact is the future of obesity treatment and lies in the implementation of evidence-based interventions that must be sustainable and accessible.

Follow up

Monthly gathering of all obese patients, where a recapitulation of previously implemented knowledge is available, during follow up, they are using number of brochures, pamphlets and information from hospital website etc. After 3 months anthropometric values as well as body composition are measured by bioelectrical impedance analysis.

Results and positive outcomes of 5-day structural educational program

Data from 58 obese patients (13 men, 45 women), mean age 45 years (20-68), who attended 5-day structural weight loss programs were analyzed and presented at a previous meetings (M. Matovinović et al. 2016) At the baseline and after 3 months, measurements of anthropometric values (height, weight, BMI) as well as body composition taken by bioelectrical impedance analysis (fat mass, muscle mass) were compared. Baseline mean body mass was 125 kg, BMI was 44.2 kg/m2, FFM 59.4 kg, muscle mass 61.4 kg. After 3 months, mean body mass was 119 kg, BMI 42.1 kg/m2, FFM 53.6 kg muscle mass 62.3 kg. Statistical analyses showed significant decrease in body weight, BMI and body fat mass after 3 months, but no significant difference in muscle mass. Patients were divided into two groups; those who did not lose any weight (≤1 kg) were considered non- responders, others were considered responders. Thirteen patients (22%) were non-responders and 45 patients (78%) were responders. Mean weight loss of responders was 6.2% (1-38). According to FDA Guidance for developing products for weight management, the product is effective if there is a statistically significant decrease in body weight of ≥5% beyond the placebo effect or at least 35% of patients lose ≥5% of their body weight at 3 months. The overall weight loss corresponds to fat mass, with preserved muscle mass. As slight as 5% weight loss, still, the results show an improvement in blood pressure, levels of triglyceride in the blood, and blood

glucose levels, which are all risk factors for heart disease, as stated in the paper. This study is a reminder of the benefits of gradually getting to a healthier state. Setting realistic goals such as 5% weight loss is a good way to maintain healthy weight loss.

There are many positive outcomes of weight loss: even small reductions in body weight can have a profound impact on the health of obese people and their risk of future disease. The changes are a lower risk of diabetes and heart disease, which along with cancer, rank among the most serious complications that people with obesity faces. There are also positive changes in self-esteem, depressive symptoms, body image and health related quality of life. Overall response to this structured program is effective during the 3 months follow-up period. It is fulfilling criteria for weight management products, even without pharmacotherapy.

ACKNOWLEDGEMENTS

While, I was writing my graduation paper, I was invited by Dr. Maja Baretić to meet the patients, at one of the meeting. That was a significant day for me. Participants' from all genders and ages, with only one purpose in mind, they all wish to get help and to become healthier and happier, thus getting control over their lives. It was interesting to know, whether the 5 day custom made program of meeting and guiding, can give them the tools to derive the changes for the long term. I was surprised to hear that the program has already a positive impact on the participants. I was happy to hear regarding some healthier choices that they already implanted to their lives, such as having a regular daily eating routine with a variety of healthy food to choose from, it is a progress, but already in motion. They truly inspired me.

BIOGRAPHY

Litan Fridian was born in December 1991, in Tel Aviv, Israel. Throughout her life, she dreamt to be a physician. In September 2013, she enrolled to University of Zagreb, School of Medicine, in Croatia. Her goal is to influence other in the most prefund and crucial way. She was biology and chemistry major in Zafit, Kfar-Menachem high-school, graduated in 2010. In July 2010, she enlisted to the army and served for two years. In July 2019, she will graduate. Her next dream is to become a Neurologist, as well as, to participate in research in one of the most unknown field in medicine.

Her motto is ‘I don’t stop when I’m tired. I only stop when I’m done ...’ credit to Marilyn Monroe.

BIBLIOGRAPHY

Anderson CM, Fidler MC, O'Neil PM, Smith SR, Raether B, Sanchez M, et al. (2012). Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: . BLOOM-DM study NAASO.

Armamento-Villareal R, Aguirre L, Colombo E, Gurney AB, Sinacore DR, Villareal DT et al. (2017). Aerobic or Resistance Exercise, or Both, in Dieting Obese Older Adults. Ne. Eng. J. Med, 376:1943-1955.

Aronne, L., Thornton-Jones, Z. (2007). New Targets for Obesity Pharmacotherapy. Clinical Pharmacology & Therapeutics., 81(5),748-52,.

American Heart Association Recommendations for Physical Activity in Adults last review . Retrieved 10 2018, from http://www.heart.org/HEARTORG/HealthyLiving/PhysicalActivity/FitnessBasics/American-Heart-Association-Recommendations-for-Physical-A

Bassuk SS, Manson JE. (2005). Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. J Appl Physiol , 99:1193-1204.

Berghöfer A, Pischon T, Reinhold T, Apovian CM, Sharma AM, Willich SN. (2008). Obesity prevalence from a European perspective: a systematic review. BMC Public Health, 8(1):200.

Berthoud HR., Sutton GM., Townsend RL., Patterson LM., Zheng H. (2006). Brainstem mechanisms integrating gut-derived satiety signals and descending forebrain information in the control of meal size. Physiol Behav 89, 517-524 .

Blair SN, Davies PSW, Di Pietro L, Eaton SB, Fogelholm M, et al. (2003). How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st Stock .

Blair SN, Di Pietro L, Dziura J. (2004). Estimated change in physical activity level (PAL) and prediction of 5-year weight change in men: the Aerobic Center Longitudinal Study. Int J Obes Relat Metab Disord. , 28(12):1541-7.

Boldrin MN, Hauptman J, Sjöström L, Torgerson JS, (2004). XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diab car 27, 155-161.

Bongers, P., Jansen, A. (2016). Emotional Eating Is Not What You Think It Is and Emotional Eating Scales Do Not Measure What You Think They Measure. Frontiers in Psychology, 7, 1932.

Bouvy PF, Cuijpers P, de Wit LM, Luppino FS1, et al. (2010). Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psyc , 67 (3): 220-229 .

Bray, G. (1991). Treatment for obesity: a nutrient balance/nutrient partition approach. Nutr Rev, (249): p. 33-45.

Broberger, C. (2005). Brain regulation of food intake and appetite: molecules and networks. J Intern Med 258, 301-327.

Chaabene M, Elleuch MH, Elleuch W, Ghroubi S, Kossemtini W, Mahersi S, (2016). Contribution of isokinetic muscle strengthening in the rehabilitation of obese subjects. . Annals of Physical and Rehabilitation Medicine, 59:87-93.

Connolly HM, Crary JL, Edwards BS, Edwards WD, Hensrud DD, McGoon MD, et al. (1997). Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med, 337:581-588 .

WHO Expert Consultation (2012) Waist Circumference and Waist-Hip Ratio, WHO. Retrieved 07 08, 2018, from Report of a WHO Expert Consultation: http://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf?

Dang M., Nguyen MD., El-Serag HB, MD(2010). MPH The Epidemiology of Obesity. Gastroenterology Clinics of North America, 1-7.

De Groot LJ, Chrousos G, Dungan K, et al.(2018). Definitions, Classification, and Epidemiology of Obesity. (P. JQ., Ed.) Retrieved 2018, from MDText.com: https://www.ncbi.nlm.n,

Flatt JP, Ravussin E , Acheson KJ, Jéquier E (1985). Effects of dietary fat on postprandial substrate oxidation and on carbohydrate and fat balances. J Clin Invest, , (376): p. 1019-24.

Flatt JM. (1996). Diet, lifestyle, and weight maintenance. Am j C N, . 62(4): p. 820-36.

Frayn, K. (1995). Physiological regulation of macronutrient balance. . Int J Obes Relat Metab Disord, 19 Suppl 5: p. S4-10.

Freeman JA, Janssen I, Ross R, (2000). Exercise alone is an effective strategy for reducing obesity and related comorbidities. Exerc Sport Sci Rev, 28:165-170.

Friedman, J. M. (2002). The function of leptin in nutrition, weight, and physiology. Nutr Rev 60, S1-14; discussion S68-84, 85-17.

Ghroubi S, Elleuch H, Chikh T, Kaffel N, Abid M, Elleuch MH. (2009). Physical training combined with dietary measures in the treatment of adult obesity. A comparison of two protocols. Ann Phys Rehabil Med, 52:394-413.

Heck A, Yanovski J, Calis J. (2000). Orlistat, a new lipase inhibitor for the management of obesity. Pharmacotherapy, 20:270-279.

Ibrahim F., Khalil SF., Mohktar MS., (2014). The Theory and Fundamentals of Bioimpedance Analysis in Clinical Status Monitoring and Diagnosis of Diseases. Sensors, 14, 1 0895-10928; .

Inoue S, Kanazawa M, Yoshiike N, Osaka T, Numba Y, Zimmet P. (2002). Criteria and classification of obesity in Japan and Asia-Oceania. Asia Pac J Clin Nutr, 11 Suppl 8:S732-S737.

Jakicic JM, Lang W, Winters C, Wing RR. (1999). Effects of intermittent exercise and use of home exercise equipment on adherence, weight loss, and fitness in overweight women: a randomized trial,. JAMA, 27;282(16):1554-60.

Janssen I, Ross R, (2001). Physical activity, total and regional obesity: dose-response considerations. Med Sci Sports Exerc, 33:S521-527; discussion S528-529.

Kalra SP., Dube MG., Pu S., Xu B., Horvath TL., (1991). Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. Endocr Rev 20 , 68-100.

Kampe J, Tschöp M, Horvath TL, Widmer P (2010). endotext. Retrieved 09 28, 2018, from Neuroendocrine Integration of Body Weight Regulation.

Kelly T, Yang W, Chen CS, Reynolds K, He J. (2008). Global burden of obesity in 2005 and projections to 2030. Int J Obes , 32(9):1431–7.

Keränen AM1, Laitinen JH, Strengell K, Savolainen MJ (2011). Effect of weight loss intervention on the association between eating behaviour measured by TFEQ-18 and dietary intake in adults Appetite. Epub, 56(1):156-62.

Di Pietro L. (1999). Physical activity in the prevention of obesity: current evidence and research issues. Med Sci Sports Exer., 31:S542-S546 .

Matovinović Osvatić M, Baretić M ,Rabađija N, Bival S, Pavić E, Uroić V et al. (2016). Structural 5-day weight loss program ; results of 3 months follow-up. Diabetologia croatica supplement 1 vol 45.

Meister, B. (2007). Neurotransmitters in key neurons of the hypothalamus that regulate feeding behavior and body weight. Physiol Behav 92, 263-271.

Mobbs CV., Kow LM., Yang XJ. (2001). Brain glucose-sensing mechanisms: ubiquitous silencing by aglycemia vs. hypothalamic neuroendocrine responses. Am J Physiol Endocrinol Metab 281, E649-654.

Morris JN, Kagan A, Pattison DC, Gardner MJ. (1966). Incidence and prediction of ischaemic heart-disease in London busmen. Lancet, 2:553-559.

Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. (2013). Global, regional, and national prevalence of overweight and obesity in children and adults during

1980–2013: a systematic analysis for the Global Burden of Disease Study. The Lancet, 30;384(9945):766-81.

Ogden CL, Carroll MD, Flegal KM. (2008). May High body mass index for age among US children and adolescents. JAMA, 28;299(20):2401–2405.

Ogden CL, Carroll MD, Kit BK, Flegal KM. (2014). Prevalence of Childhood and Adult Obesity in the United States 2011-2012. JAMA, 26;311(8):806.

O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, et al,. (1988). Glycogen storage capacity and de novo lipogenesis during massive carbohydrate overfeeding in man. Am J Clin Nutr, (248): p. 240-7.

Pate RR. (1995). Physical activity and health: dose-response issues,. Research Quarterly for Exercise and Sport :Volume 66, 66:313-317.

Rising R, Alger S, Boyce V, Seagle H, Ferraro R, Fontvieille AM, et al. (1992). Food intake measured by an automated food-selection system: relationship to energy expenditure. Am J Clin Nutr, , (255): p. 343-9.

Rosenow F, Schade-Brittinger C, Burchardi N, et al. (2012). The LaLiMo Trial: lamotrigine compared with levetiracetam in the initial 26 weeks of monotherapy for focal and generalised epilepsy--an open-label, prospective, randomised controlled multicenter stusy. Neur Neuro Psy, 83: 1093-1098.

Rothney, MP., Brychta, RJ., Schaefer, EV., Chen, KY., Skarulis, MC. (2009). Body Composition Measured by Dual-energy X-ray Absorptiometry Half-body Scans in Obese Adults. Obesity Silver Spring, Md., 17(6), 1281–1286.

Schutz Y, Flatt JP, Jequier E, (1989). Failure of dietary fat intake to promote fat oxidation: a factor favoring the development of obesity. Am J Clin Nutr, (250): p. 307-14.

Smith SR1, de Jonge L, Zachwieja JJ, Roy H, Nguyen T, Rood JC, et al. (2000). Fat and carbohydrate balances during adaptation to a high-fat. Am J Clin Nutr, (271): p. 450-7.

Snyder WS., Cook MJ, et al. (1975). Report of the task group on reference man. The International Commission on Radiological Protection no. 23 ed, 40-45.

Smith SR (2000). Fat and Carbohydrate balances during adaptation to high-fat diet. . Am J Clin Nutr, 450-457.

Steinberg GR, Parolin ML, Heigenhauser GJ, Dyck DJ. (2002). Leptin increases FA oxidation in lean but not obese human skeletal muscle: evidence of peripheral leptin resistance. Am J Physiol Endocrinol Metab, ;283:187-192.

Stevens GA, Singh GM, Lu Y, Danaei G, Lin JK, Finucane MM, et al. (2012). National, regional, and global trends in adult overweight and obesity prevalences. Popul Health Metr, 10(1):22.

Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB (2015). Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. The Lancet. Diabetes & endocrinology,, 3(12): p. 968-79.

WHO. (2000). Preventing and managing the global epidemic. . Geneva: World Health Organization.

Bei-Fan Z. (2002). Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Asia Pac J Clin Nut suppl 8, S685-S693.

Zurlo F, Lillioja S, Esposito-Del Puente A, Nyomba BL, Raz I, Saad MF, et al (1990). Low ratio of fat to carbohydrate oxidation as predictor of weight gain: study of 24-h RQ. . Am J Physiol, (5 Pt 1259):p. E650-7.