OBESITY DISEASE

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Abstract

Obesity consists a major nutritional health problem in developed and developing countries, which has reached epidemic proportions. Obesity is defined as the condition of excessive fat accumulation to such an extent that affects the individual's health.

Objective: The purpose of the present review was to explore the obesity-related diseases and the medication for treatment of obesity.

Method and material : The method of this study included bibliography research from both the review and the research literature which carried out mainly internationally over the last five years and referred to obesity.

Results: The rapidly increased incidence of obesity is due to environmental factors that influence a genetically pathological predisposition. The body mass index (BMI) is an internationally accepted index to estimate body weight, which allows a comparison of prevalence rates worldwide.

Obesity has been recognized as an important contributing factor in the development of chronic and serious diseases, such as cardiovascular disease, diabetes mellitus type 2, hypertension, stroke, heart failure, dyslipidaemia, uric acid, sleep apnea which is the cause of sudden death in sleep and other diseases.

The majority of research studies indicate that weight loss is the main goal of treatment of obesity. Taking medication as an option for the treatment of obesity should be the ultimate therapeutic tool because it is associated with many side effects.

Conclusions: The results of the present review illustrate that obesity is a public health issue which is rapidly increasing and thus needs to be addressed seriously. Specific diet combined with physical activity can achieve the desired loss of body fat and are the most effective and long-lasting ways to treat obesity.

Keywords: obesity-related diseases to obesity- medication-complications

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Introduction

Obesity is a chronic disease which has spread all over the world and threatens public global health. The phenomenon of obesity has drawn the attention of the scientific community, organizations and governments worldwide because it affects people's lives negatively and imposes excessive financial implications

in every health system. In addition, obesity has been the major interest in health sciences and many research studies have focused not only on the prevalence and the risk factors of obesity but also on the significant consequences on the quality of patients' life. Furthermore, is associated with increased incidence of type 2 diabetes mellitus, hypertension, coronary heart disease, arthritis, sleep apnea, and certain forms of cancer. [1-7]

According to the World Health Organization (WHO), obesity is classified as chronic and severe disease in developed and developing countries, affecting both adults and children. Recent research data suggest that the global incidence of obesity has increased more than 75% since 1980, while the last twenty years has tripled in developing countries and particularly, in low-income countries. [-7] More than 1.1 billion adults are overweight, of which 312 million are obese. According to estimates of the International Obesity Task Force, 1,7 billion people are exposed to health risks related to body weight, while the increase in Body Mass Index (BMI) is responsible for more than 2.5 million deaths annually, which is expected to double by 2030. [8,9,10]

The incidence of obesity varies significantly among the different geographical regions of the planet. In Europe, higher incidence of obesity occurs in Central, Eastern and Southern regions compared to those of Western and Northern, while England is the country facing an explosion in rates of obesity. [11]

Regarding Greece, the studies that have been carried out report different incidence rates of obesity, although all converge at the same endpoint: that our country faces serious obesity problem. Greece ranks in the first positions among the developed European countries in rates of obesity and this finding underpins the spread of the problem in the Greek population, particularly after the formal abolition of the typical Mediterranean diet. [13-14]

Although obesity is a threat for public health, its' underlying etiology has not been fully understood. According to the literature, obesity is a result of the interaction of genetic factors, which determine the body weight by 25-40% and environmental factors. [13-14]

Assessment of obesity

Obesity is defined as the accumulation of fat in the human body beyond the amount required for the normal body function. This continuous accumulation has as a result weight gain. [14-15]

There are two types of body fat, the essential and the storage fat. The essential fat is necessary for the normal functions of the body and is mainly stored in the bone marrow, the heart, the lung, the liver, the spleen and the muscle. The essential fat also includes the female fat, which is stored in the breasts and hips. Storage fat is the fat stored mainly in the subcutaneous tissue as a result of the additional energy received through food. In healthy young adults the total body fat represents the 15-20% of total body weight for men and 20-25% of total body weight for women. [14-15]

The fat distribution differs in Central (Android type) and Regional (or female type). Central obesity is characterized by location of the fat in the upper torso and mainly in the abdomen and is common among the male population. Regional obesity is characterized by deposition of fat in the thighs and hips and it characterizes women. [14-16]

The scientific data confirm that central obesity is associated with greater health risks compared to the total obesity. In particular, it is associated with increased incidence of hypertension, cardiovascular disease, diabetes mellitus type II, as well as higher rates of sudden death. [14-16]

The severity of obesity is estimated from the total amount of fat and the fat distribution in the human body. The accurate measurement of the amount of fat requires methods and equipment that exist only in medical and research laboratories. [2] In clinical practice, more simple methods are used, such as the weight - height tables, the Body Mass Index (BMI) assessment and the skin fold measurement. [14-16] The weight - height tables, which are published in many different versions, indicate an acceptable weight range for a particular height, different between men and women, beyond which, a person is defined as either

underweight or overweight. The main disadvantage in using them, is the fact that it is not possible to distinguish between fat and muscle percentage. Consequently, a very muscular person is possible to be described by such a table as obese. [14-16]

The Body Mass Index (BMI) is a very common, easy and reliable way to classify patients into groups and compare them. Although there is a high correlation between BMI and fat percentage, it does not provide information about the weight of the muscle tissue and bones. BMI is a mathematical formula that is defined by dividing the body weight to the second power of the height: BMI = body weight (Kg) / height cm.^{2} The normal range is 20-25 kg/cm^2. When the BMI of a person is > 40 kg/cm^2, then this person is characterized as severely obese. [14-16]

Skin- fold measurements technique is the simplest method for measuring body fat percentage and the results are obtained according to specific tables. [14-16] Waist Circumference (WC) provides important information about the accumulation and distribution of the body fat. More specifically, it is considered an adequate tool for assessing central obesity. Also, the ratio of Waist to Hip (WHR) is another easy method for assessing central obesity. WHR is defined as the ratio between the lower part of the crest of the iliac ala and the perimeter of the hips, measured at the level of trochanters. [14-17]

Diseases associated with obesity

Obesity affects all aspects of human life in a negative way and is associated with many diseases. Scientific data argue that the higher the BMI, the higher the risk of morbidity, while 10 kg of weight loss can decrease this risk significantly. [14-17]

According to the literature, about 75-80% of diabetic patients are obese, showing that obesity is a strong risk factor for developing type 2 diabetes mellitus (DM). The risk for developing type 2 DM increases with higher BMI, whereas, in case a person has already developed the disease, weight loss reduces this risk as well as mortality rates. Nine kg of weight loss reduce type 2 DM associated mortality rates by 30-40% and 10-20% of weight loss can significantly improve the

metabolic control and possibly life expectancy. [15,18,19]

In 1998 the American Society of Cardiology classified obesity as an important independent factor of coronary heart disease. It is widely accepted that obesity exposes the individual to many cardiovascular risk factors and as it is shown by the Framingham Heart Study, body weight is classified as the third risk factor for developing cardiovascular disease in men, after age and dyslipidaemia. [15]

According to recent data, the negative effect of obesity on the cardiovascular system is mainly due to the associated clinical and biochemical disorders of the disease, such as hypertension, hyperglaecemia and dyslipidaemia. During the last two decades two important aspects have been developed about the detrimental effects of obesity. The first concerns the importance of visceral fat and the second the endocrine function of adipose tissue, which produces a large number of molecules that modify the vascular, metabolic, immune and other functions of the cardiovascular system. Fat accumulation is accompanied by a commensurate increase in the volume of cardiac cavities and the heart wall, while the reduction of body fat is accompanied by a reduction in the adverse effects of cardiac function. In addition, the increase of body fat results in a corresponding increase in heart work, which in a long-term basis causes cardiac hypertrophy, as a result of myocardial adaptation to the increased requirements. This increased work of the heart gradually leads to fatigue and heart failure. [15]

Another risk factor for developing cardiovascular disease is the age where obesity starts. According to the literature, the increase in body weight after the age of 18-20 years is associated with statistically significant incidence of cardiovascular disease. Also, the distribution of the fat and especially the accumulation of fat in the abdomen rather than the obesity itself are highly associated with the development of coronary heart disease. [20, 21]

Apart from diabetes and cardiovascular disease, obesity is strongly associated with hypertension and atherosclerosis.

Accumulation and swelling in the artery walls, which is made by immune cells and consists of lipids (mainly) and connective tissue, leads to development of atheromatous plaques. Hypertension is a common disease among people whose weight increases with age, while almost half of obese people suffer from hypertension. According to the literature, increase of body weight by 10%, increases systolic blood pressure (SBP) by 6 mmHg and diastolic blood pressure (DBP) by 4 mmHg. The risk is even higher among people with genetic predisposition. As a general rule, for every 1% reduction in body weight SBP reduces by 1 mmHg and DBP by 2 mmHg.[15,22]

Obesity is characterized by a pathologic situation with increased total cholesterol and triglycerides, elevated levels of LDL cholesterol and reduced levels of HDL cholesterol. This metabolic profile is common among obese people and especially among people with central obesity. Many studies have shown that there is a strong association between obesity and the metabolic syndrome. Insulin resistance, increased levels of plasma free fatty acids, reduced activity in muscle lipoprotein lipase and reduced effectiveness of the LDL receptor are some of the mechanisms of development of the metabolic syndrome.[5,23-25]

There are also data showing a strong correlation between obesity and endocrine disorders such as ovarian dysfunction, hormone-related cancers etc., which are directly related to fat distribution. Menstruation is affected by obesity regardless of fat distribution and studies have shown that menarche occurs at an earlier age in obese girls. Weight loss has beneficial effects on ovarian function and may result in the normalization of the menstrual cycle in obese women with amenorrhea. In men, central obesity is associated with reduced levels of testosterone. In addition, glucocorticoid levels change with increased levels of plasma cortisol.[25]

Obesity in combination with other predisposing factors increase the incidence of certain types of cancer. Mortality rates by prostate and colon cancer are increased among obese men. In consistence to that, mortality rates by endometrium, uterine, cervical, ovarian, breast and gall bladder cancer are also increased among obese women. The two factors that might explain the link between obesity and cancer are diet and endocrine disorders. Diet is related to gastrointestinal cancer and endocrine disorders are related to hormone-related cancer.[26-30]

Furthermore, respiratory complications play an important role on the morbidity and mortality in obese patients, although they are usually underestimated. The syndrome obesity-hypoventilation is a heterogeneous disease with different clinical manifestations, such as breathing dysfunction and failure of lung function, which leads to both hypoxemia and hypoventilation of the lung cells and the night-apnea syndrome. The sleepiness that is sometimes observed in obese people is a result of the night-apnea syndrome. Sometime after they are asleep, the upper respiratory tract gets blocked and hypoxemia and hypercapnia occur. This has as a result the patient to wake up suddenly, in order to be able to breath normally again. This can happen multiple times during the night, especially during the REM phase of sleep, which can lead to chronic insomnia and sleepiness during the day. Although the night-apnea syndrome is observed among people with normal body weight, the effect of obesity on breathing function increases the frequency of such incidents and can result in severe hypoxia, cardiac arrhythmia and heart failure.The reduction in body weight reverses these abnormalities, if heart problems have not been permanent yet.[31-34]

Body weight determines the degree of load exerted to bones and joints and explains the association between obesity and arthritis, especially in the hip and the knee. Weight loss has as a result pain relief from the back and the legs but also causes decrease in bone mass, which increases with obesity.[15]

The majority of the data relating obesity and overall mortality risk, indicate that the higher the BMI (> 30) the higher the risk of mortality. In contrast, more than 9 kg weight loss in obese women is associated with 25%

reduction in risk of mortality from all causes, such as type 2 diabetes mellitus, cardiovascular disease and cancer. Also, in case the patient has already developed an obesity-related disease, intentional weight loss still reduces mortality risk by 20%, especially related to cancers (40-50% reduction) and type 2 diabetes mellitus (30-40% reduction). It is important to distinguish between intentional weight loss and weight loss that accompanies some diseases. [15]

Pharmaceutical treatment of obesity

Proper diet and physical exercise is the ideal method for creating a negative energy balance and consequently losing weight. Medication, as a method of treating obesity, should be chosen only when the nutritional treatment has been shown to fail. Although medication helps in weight loss and prevents relapse, it has many side effects and the patient still needs to follow a certain diet and exercise. [15]

Long-term treatment of obesity using medication must meet the following criteria:
1) BMI should be $\geq 30 kg/m^2$

2) BMI should be $\geq 27 kg/m^2$, and other diseases related to obesity such as diabetes mellitus, hypertension, cardiovascular disease, night-apnea syndrome, degenerative arthritis, etc. should have been developed already.

3) At least two risk factors such as age $\geq$ 45 in men and $\geq$ 55 in women, smoking, hypertension, high LDL cholesterol, low HDL cholesterol, high levels of fasting plasma glucose or family history of early coronary di sease should be present.

4) No beneficial results after following certain diet and physical exercise program for at least 6 months should have been obtained. [15]

The history of the pharmaceutical treatment of obesity starts back in 1893 using when thyroid hormone was used to increase thermogenesis. Since then, there have been many drugs, which aimed either to reduce the appetite or increase the energy costs. Many of them used only for a short period of time and almost all were withdrawn from the market due to the severe side effects. Today, the drugs for obesity are classified into 3 major categories; the ones that reduce desire for food, the ones that inhibit the absorption of food from the gastrointestinal tract and the ones that increase energy cost. [35-38]

The drugs that reduce desire for food or suppress the appetite lead to a reduced food intake and consequently to weight loss. According to their effect in the Central Nervous System, they are classified in three additional categories: the ones that work through adrenergic receptors (eg, amphetamines), those that work through the serotonergic receptors and those that work through both receptors, such as Simbutramin (Reductil). Simbutramin inhibits the binding of serotonin and nor-adrenaline with the neurons, through two specific metabolites. Weight loss is achieved by reducing the calorie intake as a result of saturation while the increase in energy cost due to an increase in thermogenesis. [35-38]

Simbutramin can be almost completely absorbed by the gastrointestinal tract and has a long half-life, which allows daily administration, starting with 10 mg (maximum dose 15 mg). The drug is metabolized in the liver and is excreted (together with the metabolites), mainly by the kidneys. The main side effects include dry mouth, headache, insomnia and constipation. The drug is not recommended for people with a history of cardiovascular disease and tachycardia, and in patients with non-regulated arterial hypertension. Studies have shown that simbutramin increases heart rate by 4-5 beats/min and blood pressure by 3 mmHg. The increase in blood pressure is rarely the cause for stopping the specific treatment. [39]

Another category of drugs is the ones that inhibit the absorption of food from the gastrointestinal tract and are divided into 2 further categories: a) the drugs that inhibit gastric emptying and b) the drugs that inhibit intestinal absorption, like orlistat (Xenical). Orlistat inhibits the action of gastric and pancreatic lipase, causes reduction of triglyceride hydrolysis and therefore inhibits the absorption by the intestine. The reduction of absorption of dietary fat can reach up to 30%. The maximum activity is achieved with a dose of 120 mg, 3 times daily or immediately after meals. It has been shown that the orlistat leads to a moderate

decrease in total cholesterol, 10% reduction of LDL-cholesterol, 10% reduction of fasting insulin and reduction of systolic blood pressure by 2 mmHg after one year of administration. Orlistat has also been tested as a drug of diabetes type II prevention, when administered to people with a predisposition for the disease. The gastrointestinal disorders are the main side effects of the drug and occur with oily stools, diarrhea and possibly tenesmus (because of steatorrhea). The symptoms, which occur in 15-30% of the patients who use the drug, are usually mild and subside with time.[39,40]

The thermogenetic-lipolytic drugs increase thermogenesis and thus, basic metabolism. This category includes thyroid hormones, caffeine, nicotine, drugs that act as the sympathetic NS such as ephedrine, the ones that act against the B-Adrenergic receptors, and hormones such as growth hormone and human gonadotropin that give positive results in the treatment of obesity.[39,40]

Today, the most appropriate and common used drugs for the treatment of obesity internationally are orlistat and Simbutramin. The choice of medication is based on family history, the accompanying diseases and the diet, and should not be administered for more than 3-6 months.

Conclusions

Obesity is a severe pathologic situation that causes both morphological and functional disorders in the human body and is associated with a high risk of morbidity and mortality.

Obesity affects every aspect of an individual's life and has deleterious effects, not only on health and self-esteem but also on the socio-economic status of the patient. At the same time, each government spends a huge amount of money for the treatment of the different diseases caused by obesity.

Seeking medical help is an essential step because it helps to reduce morbidity and mortality rates among obese individuals.

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