

Obesity is a disease: A Consensus Report by the Alliance to Fight Obesity in Greece

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ABSTRACT

Obesity is defined as a chronic disease characterized by abnormal or excessive fat accumulation in the body. Obesity has taken on epidemic proportions, as the prevalence of overweight individuals globally is almost 30%. The causality of obesity is multifactorial; positive energy balance, genetic factors, endocrine diseases, medications, and food intake disorders are involved in the pathogenesis. Hippocrates wrote that "obesity is a disease itself and the harbinger of others", recognizing that obesity is a disease that leads to many other diseases. Many scientific societies and the World Health Organization recognized obesity as a chronic disease. Obesity adversely affects many tissues and organs of the human body and is considered a multisystem disease. Obesity is closely related to increased mortality, development of type 2 diabetes mellitus, hypertension, atherosclerotic and thrombotic events, malignancies, respiratory, renal, neurological, musculoskeletal, and gastrointestinal disorders, and it affects immune system and fertility. Obesity is related to high health costs

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DEFINITION

Obesity is defined as a chronic disease characterized by abnormal or excessive fat accumulation in the body.¹ This should be differentiated from increased body weight,

Submission: 19.09.2023, Acceptance: 07.10.2023

and affects quality of life. Primary prevention is of major importance and may lead to significant savings on resources. Upon establishment, it should be treated as a severe disease, the management of which reduce mortality and may prevent the development of severe and life-threatening complications. As a disease, it should stop being so underestimated and take the important part that it should be occupying in the public health and, once its importance has been recognised, it should be given the opportunity of being correctly treated in a scientifically way for the benefit of the people with obesity and the healthcare system.

KEY WORDS: *Obesity, body mass index, co-morbidities, survival, health costs*

because people with normal or even reduced body fat, yet increased muscle mass may be misclassified as overweight or obese when only the Body Mass Index (BMI) is used as diagnostic criterion for excess body weight.

Diagnosis of obesity, as well as to stage it, BMI, an equation that includes an individual's weight in kilograms (kg) and their height in meters (m) squared, is used (BMI: kg/m^2). Therefore, based on BMI, adults are classified into one of the following categories (Table 1):²

In addition to BMI, waist circumference, which is considered an indicator for assessing fat distribution, as well as the ratio of waist circumference to hip circumference (Waist-to-Hip Ratio, WHR), are also used for assessing obesity.^{1,2} Waist circumference is measured at the midpoint between the costal arch and the anterior superior iliac crest in the expiratory phase. Hip circumference is measured at the height of the greater trochanters. Waist circumference values >102 cm or WHR values >1.00 for men and waist circumference values >88 cm or WHR values >0.85 for women indicate a central type of fat distribution, as well as an increased amount of visceral fat, and are associated with increased risk for cardiometabolic diseases in comparison with people who do not have a central type of fat distribution.

EPIDEMIOLOGY

Obesity has taken on epidemic proportions, as the prevalence of overweight individuals globally has doubled since 1980, while 1/3 of the world population is considered overweight or obese.^{3,4} As regards Europe, it has been estimated that 30-70% of adults in the countries of the European Union are overweight and 10-30% are obese, while it is anticipated that these percentages may reach 89% and 50%, respectively, by 2030.⁵ According to recent epidemiological data collected on a representative sample of the adult population of Greece, 37.6% of Greeks are overweight (men: 45%, women: 30.6%) and 32.1% of Greeks are obese (men: 30.5%, women: 33.6%).⁶ Indeed, it appeared that residents of rural and semi-rural areas have a higher obesity rate (38.9% and

TABLE 1. Body weight categories based on BMI.

Individual classification	BMI (kg/m^2)
Underweight	< 18.5
Normal-weight	18.5 - 24.9
Overweight	25 - 29.9
Obese	≥ 30
Stage I obesity (Mild obesity)	30 - 34.9
Stage II obesity (Moderate obesity)	35 - 39.9
Stage III obesity (Severe obesity)	≥ 40

35.7%, respectively) in comparison with residents of urban areas (29.1%). The same study demonstrated that obesity frequency increases considerably after the age of 50 for both sexes.⁶

PATHOGENESIS

Energy balance

The causality of obesity is multifactorial. Obesity is mainly due to the creation of a positive energy balance, i.e. due to the combination of increased calorie intake and decreased energy expenditure, which is maintained for a long time.^{1,4} In recent years, the dietary patterns of societies have changed significantly. More explicitly, the promotion of 'fast food' and the frequent consumption of foods that are high in fat and refined carbohydrates in combination with decreased physical activity constitute the typical 'Western' dietary pattern (Western diet). It has been indicated that the consumption of the above foods, in addition to the increased calorie intake that it entails, stimulates the brain's reward centers, in a manner similar to that of addictive substances.^{1,4} Decreased physical activity is the second factor that has substantially contributed to the rise in prevalence of obesity. There are many factors that have led to the decrease in physical activity, such as the change in the nature of work and the shift from manual to sedentary labor, living in large urban centers,

the widespread use of cars, the use of remote controls, as well as the long-hour daily use of computers and televisions even from childhood.^{1,4,7}

Genetic factors

Genetic factors are also involved in the pathogenesis of obesity. These factors may be associated to single-gene mutations that result in the disruption of the normal function of the hunger and satiety regulatory systems. Therefore, there are single-gene mutations that cause either reduced leptin secretion or reduced leptin receptor activity or dysfunction of melanocortin receptors in the hypothalamus. However, single-gene mutations account for 5% of obesity cases among children. Additionally, there are some forms of obesity that are due to gene or chromosome disorders, such as Prader-Willi and Bardet-Biedl syndromes.^{1,7} In contrast, the most common form is polygenic obesity, which is caused by the accumulation of various genes that may be related to increased food intake, decreased satiety, a tendency to store fat and a sedentary lifestyle. One of these genes is the FTO gene (fat and mass obesity associated gene), which encodes a DNA demethylase that is expressed in the nuclei of the hypothalamus, in systems related to the regulation of energy balance, and contributes to the repair of genetic material.^{1,4,7}

Intestinal microbiome

The intestinal microbiome has been the subject of intensive research in the last years and it has been indicated that 'dysbiosis', i.e. the disturbance in the balance of microbiome populations, is associated with various diseases, such as obesity. One of the suggested mechanisms is the altered enzyme function and the production of short-chain fatty acids, which further affects the glucose and insulin homeostasis, and contributes to obesity development. Moreover, apart from genetic factors, epigenetic mechanisms also seem to be involved in the pathogenesis of obesity. The main epigenetic mechanisms are DNA methylation, histone modification and non-coding RNAs, and through the regulation of various genes they can promote lipogenesis and obesity.^{1,4}

Endocrine diseases

Endocrine diseases associated with an increase in body weight are hypothyroidism, polycystic ovary syndrome, Cushing's syndrome, menopause/andropause, the diseases of the hypothalamus and pituitary gland that cause insufficient secretion of hormones, growth hormone deficiency and pseudohypoparathyroidism.¹

Medicines

Medicines that may increase body weight are antipsychotics and especially olanzapine, almost all antidepressants, lithium, corticosteroids, some contraceptives and progestogens, beta-adrenergic blockers, from antidiabetics insulin, sulfonylureas and glitazones, from antiepileptics phenytoin and sodium valproate, antihistamines and pizotifen that is used to prevent migraines.¹

Food intake disorders

Bulimia nervosa and nocturnal hyperphagia syndrome are two food intake disorders that are directly associated both with obesity and depression. These disorders are common in patients who are followed up in obesity clinics and must be identified, because these individuals are in need of psychological and psychiatric care.¹

OBESITY IN CHILDREN AND ADOLESCENTS

Obesity during childhood and adolescence is one of the most serious public health problems of the 21st century. According to recent data from the World Health Organization, 41 million children of preschool age (<5 years old) are overweight or obese, 340 million children and adolescents aged 5-19 years are overweight or obese, and 124 million children and adolescents are obese.^{8,9,10} In Greece, overweight and obesity prevalence ranges from 21% in preschool age to 41% in school age and adolescence and is considerably higher compared to all European countries in total (15% and 25%, respectively).^{11,12}

For the diagnosis of overweight and obesity in children older than 2 years, the use of BMI is recommended. For children and adolescents, these limits are different to those of the adults and are defined based on sex and age.

At an individual level, it is recommended to use the curves of World Health Organization. A child or an adolescent is considered overweight if their BMI is above the 85th percentile, while they are considered obese if their BMI is above the 95th percentile.^{9,13} Additionally, severe forms of obesity are also defined.^{9,13} At population level and with a view to comparing epidemiology and prevalence studies between different countries, it is recommended to use the thresholds determined by the International Obesity Task Force (IOTF). As a threshold for overweight children and adolescents the BMI up to the age of 18 years corresponds to 25-30 kg/m² and as threshold for obese children and adolescents the BMI up to the age of 18 years corresponds to 30 kg/m² of adults.¹⁴

Obesity is characterized by systemic, chronic inflammation and increased production and release of pro-inflammatory, atherogenic cytokines and oxidative stress. There are many complications of obesity, including in-

sulin resistance, type 2 diabetes mellitus, hypertension, hyperlipidemia, endothelial dysfunction, early onset of atherosclerotic cardiovascular disease, hypogonadism, orthopedic problems, fatty liver disease, cholecystitis, social stigma and increased incidence of malignancies, and account for a significantly high percentage of public health costs.¹⁵⁻¹⁹

Children and adolescents with overweight or obesity are more likely to become adults with excess weight and they develop diseases at a younger age that lead to early mortality. This possibility ranges from 8% for children aged 1-2 years without obese parents to 79% for children/adolescents aged 10-14 years with at least one obese parent. After the age of 6, the possibility of developing obesity in their adult life exceeds 50%, compared to approximately 10% for children of normal weight. The parents' obesity more than doubles the risk of obesity in adulthood for all children aged under 10 years.²⁰

Important data that highlight the need for timely management of childhood obesity include the association of adolescence obesity with an increased risk in adulthood for the development of type 2 diabetes mellitus, cardiovascular diseases and malignant diseases such as leukemia, Non-Hodgkin's lymphoma, pancreatic cancer, gastroesophageal cancer and colorectal cancer.²¹ Furthermore, decreasing BMI, and, even more so, achieving a normal BMI in-between adolescence and adulthood is significantly associated with a reduced risk of developing type 2 diabetes mellitus, dyslipidaemia and arterial hypertension, placing emphasis on the need for effective intervention during childhood and adolescence.

Consequently, it is absolutely necessary to put emphasis on both prevention and treatment of obesity during childhood and adolescence, so as to effectively help improve the health of our country's citizens during adulthood and reduce the costs of their hospitalization that is due to the complications of obesity.²²⁻²⁴

The axes of the primary prevention of obesity must include the following:

- Care of the pregnant woman (normal BMI or BMI as close to normal as possible before pregnancy, appropriate weight gain during pregnancy, management of diabetes complicating pregnancy, monitoring of fetal growth).
- Reinforcing breastfeeding (information, legislative regulations).
- Importance of a proper diet and the ideal rate of weight gain during the first 2 years of life (role of the pediatrician).
- Legislative regulatory framework for the operation of nursery schools and kindergartens in terms of nutrition, play, and open spaces. Integrating 45

minutes of physical activity in the daily schedule.

- In primary school, complying with the school circular for canteens, daily non-competitive physical education class, active break, establishing a routine of having a healthy breakfast or brunch together with the teacher, identifying bullying and exclusionary behaviors towards children with obesity.
- Intervening in the food industry (avoiding the production of packaged foodstuffs with high calorific value, reducing sugar and trans-fat content, producing juices without added sugars, increasing soluble fibers in packaged snacks, promoting portioned packaging, applying labeling regarding nutritional value and content, which must be accurate and understandable, avoiding misleading indications, and avoiding advertisements that target children).
- Boosting physical activity (Cooperation with regions and municipalities to enable free or very affordable access to open spaces, parks, and sports facilities for exercise.); cooperation with regions and municipalities to enable safe walking access to schools; providing students the opportunity to have access to the schoolyard beyond school hours (security issues, supervision); special reference to rural areas; special provision for students with disabilities.

ACCEPTANCE OF OBESITY AS A DISEASE

Hippocrates wrote that "obesity is a disease itself and the harbinger of others", recognizing that obesity is a disease that leads to many other diseases. In 1948, the World Health Organization recognized obesity as a chronic disease and included it in the International Classification of Diseases. The World Health Organization defines obesity as the abnormal or excessive accumulation of fat in the human body, which presents risks to health. Accordingly, it becomes clear from the definition alone that obesity is a disease²⁶ and more specifically, as of 2000 the World Health Organization highlighted that obesity is a complex disease and continued by stating that obesity is a serious chronic disease that requires long-term strategies for its effective prevention and management.²⁷ Subsequently, Portugal in 2004 and Italy in 2019 recognized obesity as a disease. In 2013, the American Medical Association described obesity as "a disease with many pathophysiological aspects". Since then, several scientific societies (European Society for the Study of Obesity, Endocrine Society, American Association of Clinical Endocrinologists, Obesity Society, World Obesity Federation, The American Academy of Family Physicians, The Canadian Medical Association, etc.) recognized obesity as a chronic disease.²⁸

Nowadays, based on the plethora of scientific data

that are available, obesity is considered a multifactorial, chronic, difficult-to-treat and relapsing pathological condition. The European Union has accepted the European Commission’s report that was published on 4 March 2021, in which obesity is defined as a “chronic relapsing disease, which in turn causes a range of other non-communicable diseases, such as diabetes mellitus, cardiovascular diseases and neoplasms”²⁹ According to this description, the European Commission officially and bindingly classifies obesity into non-communicable diseases and recognizes it as a disease, accepting the definition of the World Health Organization, as declared on its official website,²⁹ and even emphasizes that obesity acts as a gateway to a range of other serious non-communicable diseases, such as diabetes, cardiovascular diseases and cancer.³⁰

According to Encyclopedia Britannica³¹, disease is defined as any harmful deviation from the normal state of an organism, which is generally associated with certain symptoms and commonly exhibits signs or symptoms indicative of its abnormal state. The concept of the disease comprises its causality, the comprehension of its development mechanisms, i.e. its pathogenesis, the structural changes that are associated with its existence (morphological changes), and the functional consequences of these changes.

Based on these data, obesity is a disease, since, firstly, the pathophysiological mechanisms that cause its occur-

rence are known, while the numerous anatomic changes and the various functional changes that it causes to the human organism are also known. Moreover, many of the mechanisms through which it causes a multitude of intercurrent pathological conditions have become known or some other are under investigation, and finally there are treatment solutions, as is the case with any other disease.

The most significant fact regarding obesity is that it adversely affects many tissues, as well as many organs of the human body, and as a result, obesity is nowadays considered a multisystem disease. Indicatively and briefly, obesity affects the entire human body, as depicted in Figure 1.

Therefore, these effects are expected to create many and varied health problems that will reduce the quality of life, with an increase in the days of illness and absence from work, but mainly they will considerably decrease life expectancy for both sexes, as will be analyzed below.

EFFECTS OF OBESITY ON HEALTH

Type 2 diabetes mellitus

Some of the most common and important effects of obesity are the metabolic ones. Obesity is the most crucial factor for the occurrence of metabolic diseases. The presence of an increased amount of fat, particularly visceral fat, has been recognized for many years as an

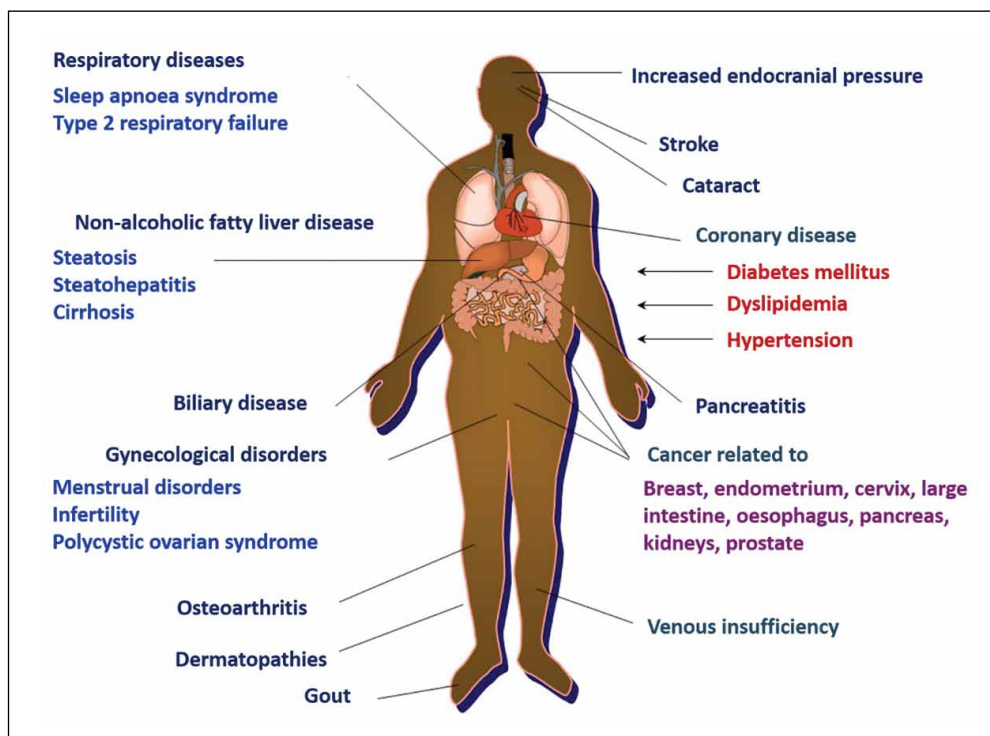


FIGURE 1. Schematic illustration of the most important and frequent effects of obesity on health.

independent risk factor for developing type 2 diabetes mellitus. Epidemiological data show that approximately 90% of patients with type 2 diabetes are overweight, and remarkably, 60% of them are obese. Studies indicate that men and women with BMI ≥ 35 kg/m², i.e. with moderate and severe obesity have a 42-fold and 93-fold higher relative risk for developing type 2 diabetes, compared to men with BMI < 23 kg/m² and women with BMI < 22 kg/m², respectively.^{32,33} For an obese person, the possibility of developing type 2 diabetes in their lifetime jumps to over 70% for both men and women, if moderate obesity is established by the age of 18 years.³⁴

Dyslipidaemia

Another important effect of obesity is dyslipidaemia.³⁵ Recent scientific evidence suggests that obesity-induced dyslipidaemia has distinct characteristics depending on many individual factors. The type of obesity-induced dyslipidaemia is characterized by high concentrations of triglycerides accompanied by reduced concentrations of high-density lipoprotein cholesterol (i.e., reduced HDL-C), and these are its main features. Concentrations of low-density lipoprotein cholesterol (i.e., LDL-C) are usually slightly elevated but may also be normal; however, the number of LDL particles is usually elevated.³⁶ It is known that elevated concentrations of LDL-C but also elevated triglycerides levels and decreased concentrations of HDL-C increase the risk of developing cardiovascular diseases. Therefore, dyslipidaemia constitutes an important link between obesity and the development of type 2 diabetes, cardiovascular diseases, and certain types of cancer, as well.

Hyperuricaemia

Hyperuricaemia, i.e. the abnormal increase of uric acid levels in the blood, may lead to complications, such as acute (podagra) or chronic gout, uric nephropathy, and nephrolithiasis. According to recent knowledge, hyperuricaemia is closely related to atherosclerosis and constitutes an early indicator or risk factor for its occurrence.³⁸ In obesity, there is often an increase, usually mild, in the uric acid levels, but several times this increase is pronounced, leading to the complications mentioned above. The risk of developing incredibly painful acute gout increases as the obesity degree increases.³⁹

Hypertension

Obesity has proved to be a significantly aggravating factor for the cardiovascular system. Epidemiological data clearly support the link between body weight and blood pressure, thus emphasizing that increased body weight is one of the main risk factors for developing hyperten-

sion.⁴⁰ In fact, the special mechanisms through which obesity causes hypertension lead to the so-called 'obesity hypertension'.⁴¹ It is remarkable that the relative prevalence of arterial hypertension increases as the obesity degree increases in both men and women, with a significantly upward-sloping increase in younger and middle-aged individuals compared to older adults.³⁵

Coronary artery disease

Atherosclerosis induced by obesity is one of its major impacts on health. The overwhelming evidence on the association of obesity with the occurrence of atherosclerosis through cardiovascular risk factors has become even stronger, as long-term follow-up studies have determined that obesity is associated with atherosclerosis, regardless of the presence or absence of other risk factors.⁴² Furthermore, the establishment of obesity during childhood and adolescence causes the onset of atherosclerosis at such young age.⁴³ Therefore, the association of obesity with the occurrence of coronary artery disease in middle and older age is expected for both sexes, irrespective of the coexistence of other predisposing factors.⁴⁴

Cerebrovascular diseases

Existing studies demonstrate a strong association between obesity and the occurrence of stroke, regardless of age, sex, and other major cardiovascular risk factors.⁴⁵ A study with 2.2 million participants and >30,000 ischemic stroke events showed a 22% increased risk for overweight subjects and a 64% increased risk for obese subjects compared to normal-weight subjects.⁴⁶ Many studies have established the association between BMI and stroke, as it has been proved that for each one-unit increase in BMI, there was a 4% increase in the risk of ischaemic stroke and a 6% increase in the risk of haemorrhagic stroke.⁴⁷ Based on the aforementioned data, there is no doubt that people whose body weight is increased beyond normal face an increased risk of having a stroke, at least an ischaemic one.

Thrombosis

Many clinical studies have indicated that obesity increases the risk of thrombotic complications, including heart attack, cerebrovascular disease, venous thrombosis, and probably peripheral artery disease. In people with obesity, the tendency of forming arterial clots is 1.5-fold to 2.5-fold higher compared to normal weight people.⁴⁸ The pathophysiological pathways that are mainly responsible for obesity-related thrombosis are chronic low-activity inflammation and reduced fibrinolysis, which are induced by obesity.⁴⁹ Today, based on a specific meta-analysis, it appears that obese people have a 2.4-fold higher relative

risk of experiencing a venous thromboembolic event in comparison with normal-weight people.⁵⁰

Neoplasms

Among the multiple effects of obesity, there is a relatively unacknowledged though extremely important effect, which is the increased incidence of many forms of cancer. A meta-analysis of 239 studies from all over the world, with more than 10 million participants and a median follow-up of 13.7 years, confirmed the association of obesity with various types of cancer.⁵¹ It is also impressive that with regard to the age of onset of obesity-related and non-obesity related cancers, in more than 6 million people during a follow-up period of 16 years, the meta-analysis showed a clear tendency for the occurrence of obesity-related cancers in younger people.⁵² Nowadays, it is accepted that obesity is associated with an increased risk of developing 13 types of neoplasms. The types of neoplasms causally related to obesity are presented in Figure 2. These are meningioma, multiple myeloma, oesophageal adenocarcinoma, adenocarcinoma of kidney, uterus, ovary, thyroid, and breast in postmenopausal women, as well as adenocarcinoma of liver, gallbladder, stomach, pancreas, colon and rectum.⁵³

These types of neoplasms account for approximately 40% of all neoplasms diagnosed in the United States in

2014. The mortality of the obese individuals due to the occurrence of malignancies is significantly increased compared to that of non-obese individuals for both men and women.⁵⁴

Respiratory disorders

Mechanical stress incurred by increased body fat to the respiratory system mainly leads to reduced expiratory reserve volume, reduced residual static pulmonary volumes and reduced lung extensibility.⁵⁵ Furthermore, obesity, depending on its severity, causes moderate or severe respiratory restrictive disorder. In addition, obesity is often observed to form a risk factor for some of the most common respiratory diseases, such as the obstructive sleep apnoea syndrome,⁵⁶ the obesity- hypoventilation syndrome,⁵⁷ chronic obstructive pulmonary disease,⁵⁸ and bronchial asthma⁵⁹.

Gastrointestinal disease

Obesity forms a significant predisposing factor for many abnormal conditions and digestive system diseases.⁶⁰ The incidence of oesophagus motility disorders in obese individuals is increased. The most common disorder is oesophagus hypokinesia whereas disorders related to the function of the lower esophageal sphincter⁶¹ leading to

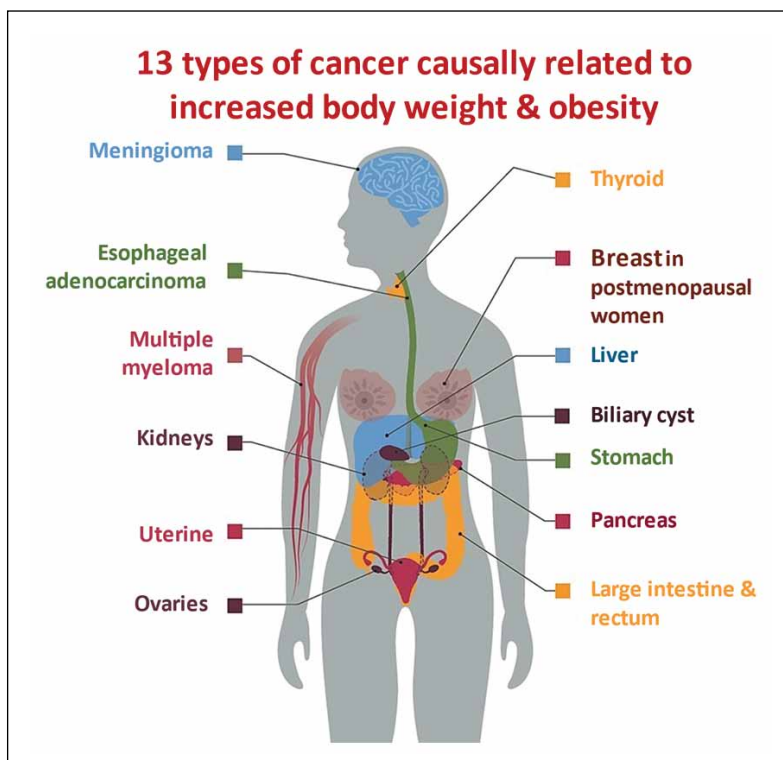


FIGURE 2. Types of neoplasms that have been proven to be causally related with obesity.

gastroesophageal reflux disease⁶², erosive esophagitis and Barrett's esophagus that are considered to be a pre-cancer condition are equally common. The prevalence of idiopathic inflammatory bowel disease continues to increase in parallel to obesity increase and approximately 15-40% of the patients are obese.⁶³ Epidemiology studies have shown increased incidence of diverticulitis in obese individuals. All obesity indexes relate to diverticula development as well as with their sequela, including diverticulitis and hemorrhagic bleeding.⁶⁴ Non-alcoholic fatty liver disease is considered to be very closely related to obesity in terms of epidemiology and demographics.⁶⁵ Obesity is most commonly related to non-alcoholic fatty liver disease since in most studies 70-100% of these patients are obese.⁶⁶ Steatosis and/or steatohepatitis severity is related to the extent of obesity. Obesity and increased waist circumference have been proved to be strong predisposing factors for the development of gallstones and individuals with obesity often develop gallstones and cholecystitis.⁶⁷ Pancreatic fatty liver increases in frequency and is now recognized as an obesity complication and may increase the severity of acute pancreatitis and pancreatic dysfunction.⁶⁸ Studies have shown that obesity relates to increased risk of acute pancreatitis.⁶⁹

Renal effects

The adverse effect of obesity to the kidneys is impressive, including a wide range of signature pathophysiological disorders ranging from increased albumin secretion, reduced glomerular filtration, chronic kidney disease to end-stage renal impairment. A number of population studies have proven the relation between obesity and the development or deterioration of chronic renal disease.⁷⁰ Obesity, including abdominal obesity in particular, have been related to relevantly early kidney parenchyma damages, ranging from microalbuminuria to more advanced damages such albuminuria⁷¹, GFR decline rate⁷², development or deterioration of known chronic renal disease,⁷³ as well as adverse transplanted liver outcome. Obesity is also related to increased kidney store prevalence.⁷⁴

Infertility

Obesity also causes hypogonadism and reproductive disorders both in males and females. A number of studies have shown the inverse relationship between fat tissue and testosterone in men. Abdominal obesity, meaning increased visceral fat, leads to testosterone reduction and increased estrogen transformation. These, combined with increased leptin, insulin and inflammatory cytokines levels, cause the inhibition of the hypothalamo-pituitary-adrenal axis and secondary gonadal insufficiency.⁷⁵ Approximately

40% of men with obesity develops secondary gonadal insufficiency that has been shown to relate to increased morbidity and mortality.⁷⁶

Overweight and obese women commonly present with menstrual cycle disorders, anovulation, sexual dysfunction, infertility and abortions, compared to normal-weight women. Menstrual cycle frequency disorders are positively related to BMI and central fat distribution whereas it is three times higher in obese women with central obesity compared to those with fat accumulation at the periphery.⁷⁷ Polycystic ovary syndrome is more common in obesity and its incidence increased as per obesity severity.⁷⁸ Menstrual cycle disorders, infertility and metabolic disorders are more common in obese women with polycystic ovary syndrome compared to obese women without polycystic ovary syndrome.

Immune effects

Excessive nutrients intake may reinforce immune system dysfunction and cause certain immunodeficiencies.⁷⁹ Obesity-caused inflammation adds up to the development of many chronic diseases. Interactions among the metabolic systems and certain subsets of immune system cells play a crucial role in the pathogenesis of obesity-related diseases.

However, there are published data suggesting that obesity may also have an adverse effect on the adaptive immune responses.⁸¹ Published studies have shown that obesity leads to mortality and morbidity aggravation following flu infection.⁸² In addition, as far as obesity effect is concerned in terms of immune response to the adult population, it seems that obesity is related to an increased number of WBC and lymphocytes (excluding the natural killer cells and the cytotoxic/suppressor T-cells) and lower T- and B-cells induced- lymphocyte proliferation, accompanied by increased phagocytosis of monocytes and granulocytes.⁸³ Obesity affects specific immunological functions and special immune responses mediated by chemical and cellular mechanisms. There is documented proof of the connection between the liver tissue and the immune cells, whereas in obesity there is impaired immune system function. In general, clinical and epidemiological data support the fact that the incidence and severity of certain types of infectious diseases is higher in obese compared to normal-weight individuals, as well as that obese individuals have a poorer antibody response to vaccinations (Figure 3).⁸⁴

Factors for severe COVID-19 disease

The pandemic caused by the new SARS-CoV-2 virus caused increased number of hospitalizations, admission to Intensive Care Units (ICU) and millions of deaths through-

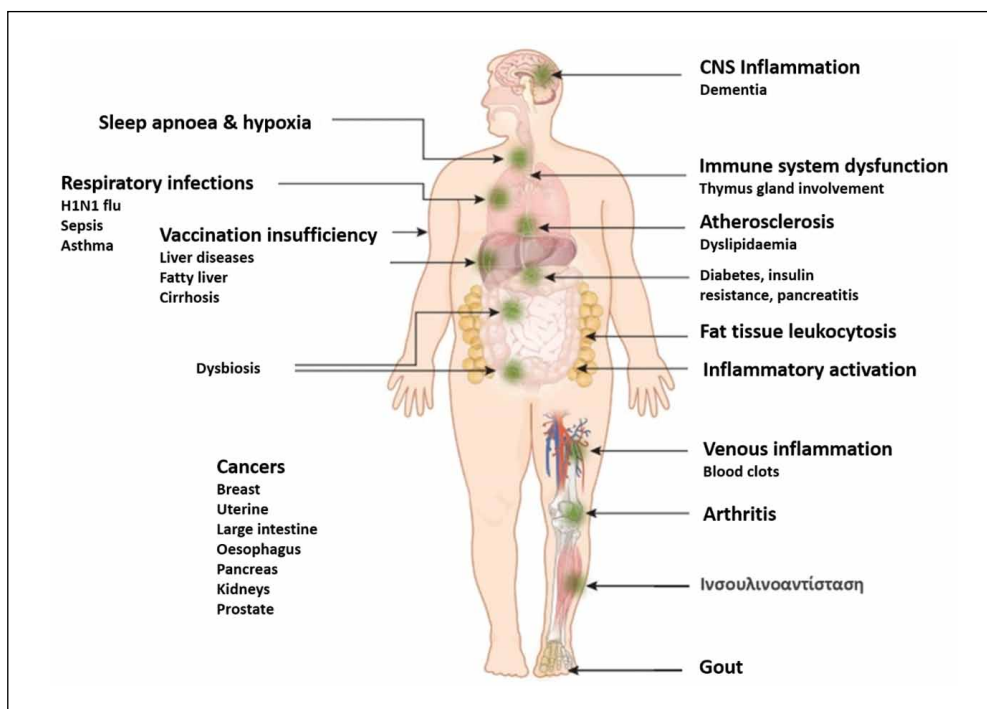


FIGURE 3. Obesity effects to the metabolic systems and the immune system.

out the planet. Obese individuals run an increased risk of being found positive, i.e. being infected, getting sick, being admitted in the ICU and dying from SARS-CoV-2.⁸⁵ It is important to note that obesity increases the incidence of serious disease and death from COVID-19 in younger ages, under the age of 65 years old and even younger adults,⁸⁶ even in adolescents and children!⁸⁷ In our days, obesity is considered one of most important factors of severe COVID-19 disease, if not the most important aggravating factor.⁸⁸

Musculoskeletal effects

The relationship between obesity and musculoskeletal diseases is complicated and involves the interaction of mechanical, dietary, genetic and metabolic factors.⁸⁹ Large long-term trials have shown that obesity is a major risk factor related mostly to the development and progression of clinical and radiology knee and other joints' osteoarthritis, such as the hip, the upper arms, the patellofemoral joint etc. suggesting that its relationship with obesity may be related to mechanical, metabolic and other factors, as it does not only involve weight-carrying joints.⁹⁰ Diffuse idiopathic skeletal osteoporosis, a degenerative disease of the spine seems to relate to obesity and is characterized by the development of osteophytes in entheses sites. Studies have shown that patients with diffuse idiopathic skeletal osteoporosis are more likely to have an increased BMI.⁹¹ Obesity seems to also affect and limit in terms of func-

tioning and structure normal gait further leveling the arch of the foot and causing ankle supination.⁹² Obesity seems to be related to patients with rheumatoid arthritis as well. Its presence relates to increased risk of disease development and it is mostly correlated with seronegative rheumatoid arthritis. Increased bodyweight also reduces the quality of Life of patients with rheumatoid arthritis.⁹³

Neurological effects

Obesity is also a risk factor for cognitive impairment and dementia, including Alzheimer's disease.⁹⁴ An additional risk may be mediated by diabetes mellitus type 2 that is quite often a consequence of obesity and that also relates to a higher development rate. Previous studies, mostly in people under the age of 65 years' old, indicate that increased body fat (obesity) relates to temporal cortex, frontal lobe, pole and caudate, thalamus and white matter atrophy.⁹⁵ In this way, obese individuals present with increased risk for dementia, as a high BMI in an adult's middle age or central fat accumulation more than doubles the risk of dementia development,⁹⁶ further reducing global cognitive abilities and executive function.⁹⁷ A completed study determined the relationship between obesity and multiple sclerosis in two groups of women from the Health Nursing Study since obese women aged 18 years' old presented with 2.25 times the risk of developing multiple sclerosis compared to those with normal weight and others followed with similar findings.⁹⁸

Mental Health effects

Psychopathology prevalence estimates are generally higher in the samples of obese individuals seeking treatment compared to the general population. Clearly, there are robust data on depression; most of the studies indicate a significant bidirectional relation between depression and obesity.⁹⁹ Prospective studies show that depression precedes obesity in girls, yet not boys,¹⁰⁰ whereas obesity precedes depression in older adult women.⁹⁹ The risk of developing depression in obese individuals is increasing with the severity of obesity, showing a major increase in severe obesity.¹⁰¹ Episodic hyperphagia disorders have been shown to present more commonly in obesity since this particular disorder shows a prevalence lower than 5% in the general population whereas in studies in obese individuals requesting help a prevalence increase has been shown reaching up to 30%.¹⁰²

Other less known or important effects

Obesity is a causal factor relating to the development of many and various abnormal conditions, such as idiopathic endocranial hypertension,¹⁰³ cataract development,¹⁰⁴ obesity-hypoventilation syndrome,¹⁰⁵ atrial fibrillation,¹⁰⁶ carpal tunnel syndrome,⁹⁰ plantar fasciitis,⁹¹ psoriasis,¹⁰⁷ headaches,¹⁰⁸ migraine,¹⁰⁹ pregnancy and labor complications¹¹⁰ and many other.

In our days, abnormal conditions related to obesity rise to the astonishing number of 236 showcasing the major impact of obesity to health.¹¹¹

INCREASED HEALTH COST

Apart from the obvious burden of obesity to the overall morbidity load, being a major risk factor to health, the disease affects to a major extent health-related expenditure as a result of the increased care needs of the patients from the causally related to obesity diseases.

The financial impact of obesity to the health care system and society in general typically involves both direct and indirect costs. The first category exclusively relates to expenses incurred by patients' treatment (healthcare or other care expenses) and add an additional load either to the health system and social security or patients themselves. The second category relates to productivity loss due to the disease or even death and adds an additional load to the total of society, as a whole.

Based on the available literature estimates¹¹² and adjustments made to accommodate for the Greek reality, total financial burden from obesity in our country amounts to 2.4% of the GDP or, in monetary values, to 4.3 billion Euros on an annual basis. More than 50% of

this expenditure relates to productivity loss whereas it is worth noting that the quantification of the relationship between bodyweight and mean health care expenditure per individual indicates that individuals with BMI over 40 kg/m² present with 80% higher health care expenditure compared to normal weight individuals.^{113,114}

The need for action relating to limiting obesity becomes even more imperative when taking under consideration the long-term effects of this phenomenon for the health care system and the financial activity. As per the OOSA,¹¹⁵ in case active measures for limiting the exposure to risk factors are not taken, GDP change for the period 2020-2050 will be -3%, whereas mean health care expenditure for obesity will amount to approximately 10% of the total expenditure. On the contrary, taking up targeted and specific actions for limiting obesity is expected to have major benefits at a disease and financial level: based on the OOSA estimates, for each Euro spend on obesity prevention, approximately six Euros are being returned to society in terms of financial benefit.

DECREASE TO QUALITY OF LIFE

Quality of Life is a vast, multi-dimensional concept that includes the objective assessment of the positive and negative aspects of life, through specific questionnaires.¹¹⁶ Physical and mental health form significant negative factors relating to quality of life estimation.

Obesity has been characterized as a disease because its complications extend beyond the aesthetic and many medical complications¹¹⁷ and there is a linear relation between the BMI and the number of comorbidities.¹¹⁸ In addition, obesity relates to mental health disorders such as sleep disorders, anxiety, depression, dietary disorders, and severe psychiatric diseases.¹¹⁹

Apart from its purely medical extensions, obesity and excessive bodyweight relate to a documented reduction in the patient's quality of life. Quality of life does not directly affect health, but it affects many other parameters that can be demonstrated as low hygiene and mostly mental aggravation with a clear correlation.¹²⁰

Everyday life of an overweight or obese individual has major differences to the one of a normal individual. The body of an overweight or obese individual supports more kilos and thus carries additional stress. It is the knees and joints that are mostly affected and this creates a vicious cycle, during which the obese individual, owing to pain and difficulty is forced to limit his/her motility and exercise, which dramatically reduces calories' burning and then leads to metabolism decline. The same applies to the spine and then leads to muscle tissue loss and fat tissue increase, making the body weaker and less strong.

Everyday activities, such as walking up the stairs, cleaning the house and even bathing and hygiene routines end up being not applicable and accompanied by infections.¹²¹ Obese patients find it hard to get out of the house, even for their everyday shopping. This is mostly the case over the past few years during which on line shopping and home delivery can be easily taken care of. Although it may sound convenient, this leads to social isolation and home staying which consequently leads to depression and social isolation further reinforcing polyphagia as a means of comfort.

The social stigma through which society categorized individuals based on their body shape practically condemns obese individuals to a feeling of shame making them feel uncomfortable. A consequence of the above would be the very high levels of low self-esteem among the obese that have been recorded in many studies through questionnaires from major psychiatric trials. Poor self-image discourages individuals from being social, traveling, participating in group activities and ends up leading to reduced self-esteem even when it comes to completing a task or evolving professionally.¹²²

According to studies relating to documenting information for overweight or obese patients, the frequency of fatigue or feeling sick is more common on a daily basis, but is mostly related to physiological rather than physical causes.¹²³ At the same time, increase level of stress has been observed on the rest of the family, including reduced ability of adopting to changes, more stress on financial affairs, difficulty in managing everyday issues as well as a direct effect on their sexual life since their image is a major inhibition factor for their coming out and feeling accepted by their partner.^{120,124}

INCREASED MORTALITY AND REDUCED LIFE EXPECTANCY

It is normal and expected for such a multi-systematic disease with consequences to so many organs causing disturbed function in so many systems and metabolic routes to cause increased risk of morbidity and thus mortality leading to reduced life expectancy. Undoubtedly, obesity relates to increased risk of morbidity, as evidenced by many scientific studies.¹²⁵⁻¹²⁸ The undisputed relation between increased bodyweight and increased mortality always takes the form of the “J” curve, as evidence by Figure 4, meaning that more severe obesity is accompanied by a multiple risk of death.

There is increased risk of morbidity and it relates to cardiovascular diseases, cancer and all-cause mortality overall. Increased mortality among obese patients has a natural consequence relating to reduced life expectancy.

The prospective study “Framingham Heart Study” that included 3,457 individuals of mean age 40 years old analyzed the reduced life expectancy and the increased early death related to obesity. In 40-year-old non-smokers, men lost 3.1 years and women lost 3.3 years from the life expectancy for being overweight; they’ve also lost 5.8 years and 7.1 years, for being obese. Compared to normal-weight smokers, obese men smokers lost 6.7 years of life expectancy and obese smokers lost 7.2 years. Obese men smokers lost 13.7 years of life expectancy and obese smokers lost 13.3 years of life expectancy, compared to normal-weight non-smokers.¹²⁹ Data from the US survival tables and material from the NHANES I, NHANES II and NHANES III studies were used in order to estimate the life years lost in adults 18 to 85 years’ old. The best BMI related to less lost years of survival and thus more life longevity is 23-25 kg/m² for the white race. Maximum survival reduction for men aged 20–30 years with BMI > 45 kg/m² is 13 years and 8 years for Caucasian women. For men, this represents a 22% reduction and for women this represents a 17% reduction in the expected remaining life expectancy!¹³⁰ It is important to note that the younger the individual is and the higher the BMI is, the more the lost years of survival are, meaning that obesity should be treated more effectively and radically in the younger ages.

Quoting Hippocrates (460-370 B.C.), father of medicine “*Those fat by nature are to meet death sooner than the thin*”. And he was absolutely right as evidenced by nowadays scientific documentation!

MAJOR BENEFITS OF WEIGHT LOSS

Considering obesity a chronic medical condition helps in determining the concept of its therapeutic approach and increased body weight management aiming at weight loss. To begin with, all overweight and obese individuals should be given instructions on a healthier lifestyle based on nutrition, bodily activity and attitude change. At a

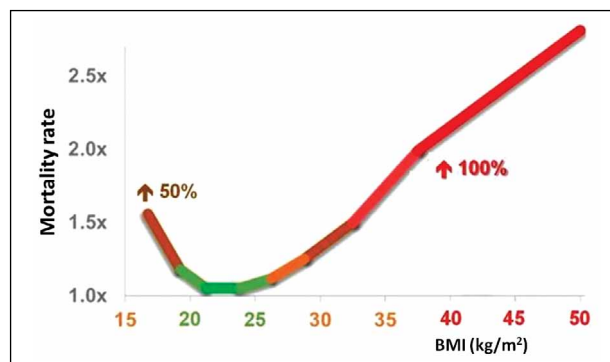


FIGURE 4. “J” curve of mortality relative to BMI, where increased mortality changes exponentially to increased obesity.

second level, medication is added to complement lifestyle adjustments, and as a third step surgical management is recommended.

Robust documented scientific data show that voluntary weight loss leads to improvement, even remission, of all health-related obesity effects. It has been known for quite a few decades now that weight loss reduces glycaemia, as well as metabolic factors in type 2 diabetes obese individuals¹³¹; if significant weight loss is observed, i.e. exceeding 15% from the baseline weight, either through diet and exercise¹³² or through bariatric surgery,¹³³ then this may lead to diabetes remission. Voluntary weight loss seems not only to lead to regulated glycaemia and reduced diabetes complications, but it is also related to a 28% reduction in the number of CV and diabetes-related deaths as well as a 25% reduction in the number of deaths from any cause if achieved with diet and exercise¹³⁴ and increased survival by 9.3 years in obese diabetics following bariatric surgery.¹³⁵

Similar favorable results in reducing hypertension,¹³⁶ improving the lipid profile¹³⁷, improving hyperuricaemia¹³⁸, having beneficial effects in female period, ovulation and fertility and improving male fertility¹³⁹ are achieved by weight loss.

As far as the cardiovascular system is concerned, weight loss is accompanied by reduced frequency in the development of angina episodes in obese angina patients and improvement of the thrombosis and fibrinolysis parameters.¹⁴⁰ In the digestive system, weight loss is accompanied by a significant reduction in gastro-oesophageal reflux,¹⁴¹ and reduced liver lipomatosis.¹⁴² As far as the respiratory system is concerned, weight loss leads to improvement and even resolution of sleep obstructive apnoea,¹⁴³ improvements in the asthma-related quality of life and to some extent to asthma control¹⁴⁴ and major weight loss leads to beneficial improvement in the obesity-hypoventilation syndrome.¹⁴⁵ A major kidney finding related to weight loss is significant reduction in albuminuria.¹⁴⁶

The scientific data relating to weight loss and cancer are encouraging. In addition, it should be stated that voluntary weight loss through diet change and physical activity is possible and may further reduce the risk of cancer development.¹⁴⁷ In particular, weight loss effect is more prominent in obesity-related cancers.¹⁴⁸ Definite details on the favorable effect of extended and long-term weight loss in reducing the risk of cancer stem from studies shown to have achieved major weight loss, i.e. bariatric surgery studies. In a study being considered a milestone for the favorable effects of bariatric surgery, the Swedish Obese Subjects Study, in 16 years' of follow-up, the risk for developing fatal or non-fatal cancer was reduced by 42% in women.¹⁴⁹

Prospective observational studies show that voluntary weight loss increases survival in obese individuals. A recent meta-analysis including 17,186 participants of mean age 52 years' old, mean observation time of 27 months and mean weight loss of 5.5 ± 4.0 kg, when the BMI range was 30-46 kg/m² recorded a 15% lower all-causes mortality risk form in the weight loss groups compared to non-weight loss groups.¹⁵⁰ A higher rate, i.e. 16% reduction in the relevant mortality risk following voluntary weight loss was observed in obese individuals with comorbidities.¹⁵¹ Impressive rates in mortality reduction are observed in studies relating to the follow-up of individuals having suffered a bariatric surgery and thus having achieved a significantly higher weight loss. Thus, in the Swedish Obese Subjects Study mentioned above, in the 24 years of follow-up, individuals having lost weight through bariatric surgery had 30% reduced mortality and increased survival by 3 years.¹⁵² Even more impressive results in terms of reducing mortality are being achieved through newer bariatric techniques, where recently, in a meta-analysis of studies with 174.772 individuals under study, a 49% mortality reduction was found in the group of patients under surgery as well as a 6.1 years' survival extension!¹⁵³ More recently, weight loss with bariatric surgery showed reduced incidence of obesity-related new cancers by 32%, as well as reduced development of all types of cancer by 17%; it should also be noted that reduced mortality is related to cancer by 48%!¹⁵⁴

CONCLUSION

Obesity is a multifactorial, chronic and relapsing disease that can be treated. Primary prevention is of major importance and may lead to significant savings on resources. Upon establishment, it should be treated as a severe disease, the management of which may prevent the development of severe and life-threatening complications. It is considered a disease by the World Health Organisation as well as the medical and scientific world. As a disease, it should stop being so underestimated and take the important part that it should be occupying in the private and mostly in the public health and, once its importance has been recognised, it should be given the opportunity of being correctly treated in a medically and scientifically documented way for the benefit of the Greek citizens, the Greek society, and the Greek state.

Funding

There is no funding for this work.

Conflicts of interest

The authors report no conflicts of interest.

ΠΕΡΙΛΗΨΗ

Η παχυσαρκία ως νόσος: Συναινετική δήλωση της συμμαχίας για την καταπολέμηση της παχυσαρκίας στην Ελλάδα

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Η παχυσαρκία ορίζεται ως μια χρόνια ασθένεια που χαρακτηρίζεται από μη φυσιολογική ή υπερβολική συσσώρευση λίπους στο σώμα. Η παχυσαρκία έχει λάβει διαστάσεις επιδημίας, καθώς ο επιπολασμός των υπέρβαρων ατόμων παγκοσμίως είναι σχεδόν 30%. Η παθογένεια της παχυσαρκίας είναι πολυπαραγοντική. Σε αυτή εμπλέκονται η αυξημένη πρόσληψη τροφής, γενετικοί παράγοντες, ενδοκρινικές παθήσεις, φάρμακα και διαταραχές της πρόσληψης τροφής. Ο Ιπποκράτης έγραψε ότι «η παχυσαρκία είναι μια ασθένεια η ίδια και ο προάγγελος των άλλων», αναγνωρίζοντας ότι η παχυσαρκία όχι μόνο είναι ασθένεια η ίδια, αλλά προκαλεί και πολλές άλλες ασθένειες. Πολλές επιστημονικές εταιρείες και ο Παγκόσμιος Οργανισμός Υγείας αναγνώρισαν την παχυσαρκία ως χρόνια νόσο. Η παχυσαρκία επηρεάζει αρνητικά πολλά όργανα του ανθρώπινου σώματος και θεωρείται ως πολυσυστημική ασθένεια. Η παχυσαρκία σχετίζεται με αυξημένη θνησιμότητα, ανάπτυξη σακχαρώδους διαβήτη τύπου 2, υπέρτασης, αθηροσκληρωτικών και θρομβωτικών επεισοδίων, νεφροπάθων, αναπνευστικών, νεφρολογικών, νευρολογικών, μυοσκελετικών και γαστρεντερικών διαταραχών και επηρεάζει το ανοσοποιητικό σύστημα και τη γονιμότητα. Η παχυσαρκία σχετίζεται με υψηλό υγειονομικό κόστος και επηρεάζει την ποιότητα ζωής. Η πρωτογενής πρόληψη της νόσου είναι μείζονος σημασίας και μπορεί να οδηγήσει σε σημαντική εξοικονόμηση πόρων για το σύστημα υγείας. Η παχυσαρκία πρέπει να αντιμετωπίζεται ως σοβαρή ασθένεια, η διαχείριση της οποίας μειώνει τη θνησιμότητα και μπορεί να αποτρέψει την ανάπτυξη σοβαρών και απειλητικών για τη ζωή επιπλοκών. Ως νόσος, πρέπει να πάψει να υποτιμάται και πρέπει να απασχολήσει σοβαρά τους ασχολούμενους με τη δημόσια υγεία, ώστε να αναγνωριστεί η σημασία της παχυσαρκίας και των συνεπειών της και να αντιμετωπίζεται με επιστημονικό τρόπο προς όφελος τόσο των ατόμων με παχυσαρκία όσο και της κοινωνίας.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: Παχυσαρκία, δείκτης μάζας σώματος, συννοσηρότητες, επιβίωση, κόστος υγείας

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