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World Obesity Federation Position Statement

Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation

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Summary

This paper considers the argument for obesity as a chronic relapsing disease process. Obesity is viewed from an epidemiological model, with an agent affecting the host and producing disease. Food is the primary agent, particularly foods that are high in energy density such as fat, or in sugar-sweetened beverages. An abundance of food, low physical activity and several other environmental factors interact with the genetic susceptibility of the host to produce positive energy balance. The majority of this excess energy is stored as fat in enlarged, and often more numerous fat cells, but some lipid may infiltrate other organs such as the liver (ectopic fat). The enlarged fat cells and ectopic fat produce and secrete a variety of metabolic, hormonal and inflammatory products that produce damage in organs such as the arteries, heart, liver, muscle and pancreas. The magnitude of the obesity and its adverse effects in individuals may relate to the virulence or toxicity of the environment and its interaction with the host. Thus, obesity fits the epidemiological model of a disease process except that the toxic or pathological agent is food rather than a microbe. Reversing obesity will prevent most of its detrimental effects.

Keywords: Causes of obesity, epidemiology of obesity, pathophysiology, risks of obesity.

Introduction

The question of whether obesity, which affects a large fraction of the world's population, should be called a 'disease' has sparked controversy for most of the last century and into the 21st century (1–6). As Faber noted 70 years ago, 'All disease entities are abstract concepts created by the human mind' (7), and this would include obesity. A timeline for the differences of opinion about whether obesity is a disease process from 1977 shows gradual movement towards acceptance of the proposition that obesity is a disease process (5). In 1977, the American Health Care Financing Administration decided obesity was not a disease (5). In 2002, the Japanese Association for the Study of Obesity published criteria applicable to their population on criteria for obesity as a disease process (8). In 2004, the Centres for Medicare and Medicaid Services in the USA removed language saying obesity was not a disease (5). In 2010, the Scottish Intercollegiate Guideline (9) used these words to describe obesity, 'Obesity is defined as a disease process characterised by excessive body fat accumulation with multiple organ-specific consequences'. Only 3 years later, in 2013, The American Medical Association recognized obesity as a disease (5). This was followed in short order by a number of other health professional organizations recognizing obesity as a disease process, including The American Association of Clinical Endocrinologists, the American Academy of Family Physicians, the American College of Cardiology, the American College of Surgeons, the American Society for Reproductive Medicine, the American Urological Association, the Endocrine Society, the Obesity Society, the Society for Cardiovascular Angiography and Interventions (10) and by World Health Organization, the Food and Drug Administration and the National Institutes of Health (11,12). Finally, in 2015, the Nagoya Declaration identified 'obesity disease' as a pathological state caused by obesity and requiring clinical intervention (13).

The World Obesity Federation is an organization representing professional societies from many countries that focus on research, education and health care for people with obesity. The World Obesity Federation has commissioned this statement to argue for the position that 'Obesity is a chronic relapsing disease process' and to serve as the basis for their position on this issue.

The chronic and relapsing nature of obesity is illustrated in Fig. 1 redrawn from the Diabetes Prevention Programme and Outcomes Study, an on-going study of individuals with at risk for developing diabetes (14). The initial body mass index (BMI) of the placebo group was 30.4 kg m^{-2}, and it showed little change over the 10-year interval. The same is seen over a 15-year interval in the matched control group with

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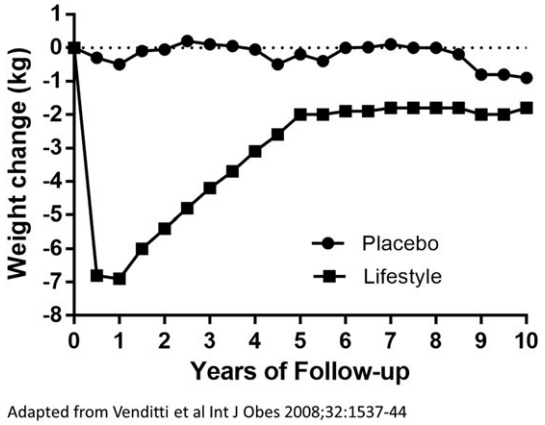

Figure 1 Weight change over 10 years in the Diabetes Prevention Programme. The lifestyle arm of this trial initially lost weight to reach a nadir at 1 year and then regain 70% of the lost weight compared with the nearly stable weight of the placebo group. Redrawn and adapted from Venditti *et al.* (14)

obesity from the Swedish Obese Subjects Study (15). In the Look AHEAD (Action for Health in Diabetes) Trial that enrolled people with diabetes and obesity, the initial BMI of 36.0 kg m^{-2} did not change more than 3% over 10 years (16)

The relapsing nature of this disease process is also seen in Fig. 1 where the treatment group initially lost over 7 kg and then slowly regained over 70% of the lost over the next 4 years. This long-term stability of body weight without treatment intervention suggests the existence of a set point or settling point mechanism where changes in food intake are a major driver of the change in body weight (17).

Not only does obesity relapse, but in the early years prior to the plateau seen in Fig. 1, there is progressive weight gain. In those who become obese, the increase in weight occurs over many years. In the The Coronary Artery Risk Development in Young Adults (CARDIA) Study, for instance, there was a weight gain of 7.8 kg over an 8-year period in individuals who were aged 18–30 years (18).

One difficulty with weight loss is that it activates a number of hormonal changes that favour weight regain (19). One of the most challenging questions remaining to be solved is why long-term weight loss is so difficult to sustain and how these compensatory mechanisms can be disabled or overcome.

Few will argue with the proposition that obesity, or excess body fatness, whether estimated by skin-fold thicknesses (20), by weight in relation to height (BMI) (21), by waist circumference (22) or by more sophisticated techniques including dual X-ray absorptiometry (23), magnetic resonance imaging (24) or computed tomography (25) or other measures poses an increased risk of mortality and morbidity in individuals with obesity (21,22,26–31). Obesity also increases healthcare costs for society (32–37).

We will argue that obesity is a disease process in the same sense that hypertension or hypercholesterolemia is a disease. Weight, like blood pressure and cholesterol are continuous variables (Fig. 2).

When each of these variables deviates sufficiently above the population mean as shown by the vertical dashed line, it produces a disease; this is called hypertension when blood pressure is too high, hypercholesterolemia when cholesterol is too high or obesity when body weight is too high. Obesity is no different from these other chronic diseases where short-term treatments do not change the underlying biology that drives and maintains them. Garrow caught the essence of obesity when he said that,

> Obesity is not a disease which you either do or do not have: rather it is a continuum, like baldness, in which the diagnosis is made when some arbitrary diagnostic boundary is exceeded (38)

The importance of this deviation was captured even earlier by Dr Malcolm Flemyng when he said more than 250 years ago:

> Corpulency, when in an extraordinary degree, may be reckoned as a disease, as it in some measure obstructs the free exercise of the animal functions; and hath a tendency to shorten life, by paving the way to dangerous distempers (39)

Over the years since then, obesity has been recognized as a disease process many, many times (1,3,4,40,41).

One concern about labelling obesity as a disease process is the finding that some people with obesity do not have any of the risk factors for associated diseases although they may be victims of stigmatization and at risk for orthopaedic problems. These so-called healthy obese have no 'associated' risk factors such as prediabetes, dyslipidemia, hypertension or other findings (42). However, it is now clear from long-term follow-up studies that half or more of these individuals will develop obesity-related disease during their lifetime (43). This effect of time on the expression of risk factors in people with higher body weight (i.e. obesity) is clearly seen in data from the Framingham study where the mortality was followed up in 6-year intervals for 30 years from the initial examinations in 1948–1950. The relative risk of mortality is plotted against the baseline relative weight (Fig. 3). For the first 12 years, the heavier group had a lower mortality than lighter individuals. As time passed, however, the curvilinear relationship between relative weight and mortality appeared at 18 years and got progressively stronger (44,45). Hubert *et al.* (46) could show that after 26 years, obesity was an independent risk factor for heart disease. Thus, quoting from Garrow again, we need to 'Treat Obesity Seriously' (38) and provide sufficient time for efforts at prevention and treatment to work.

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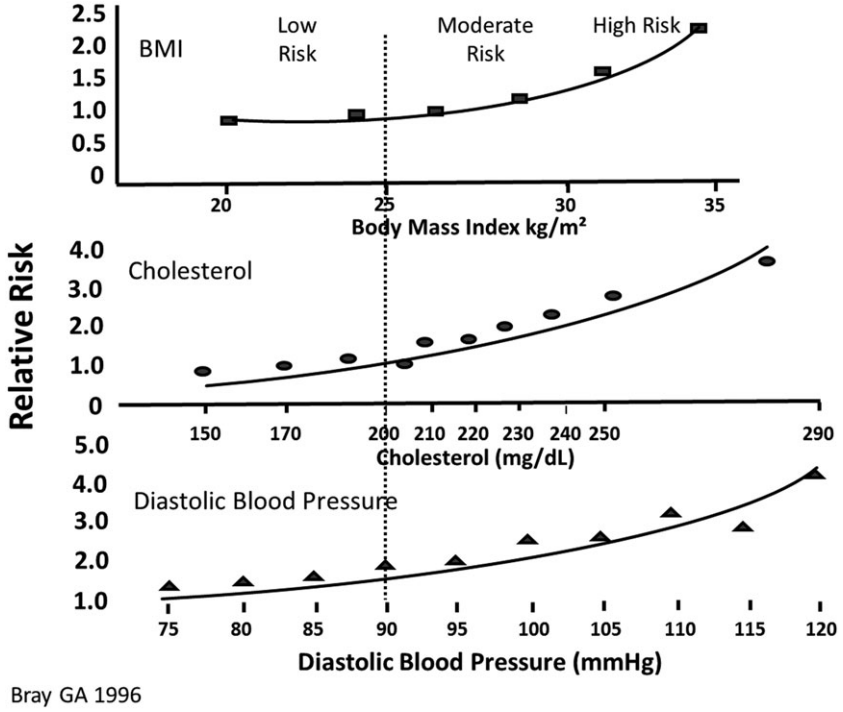

Figure 2 Relationship of body mass index (BMI), cholesterol and diastolic blood pressure to relative risk of mortality. Data from the American Cancer Society study (90) have been replotted for the BMI, and tables in papers by Stamler *et al.* (91,92) have been used to construct the relationship between cholesterol and blood pressure (93)

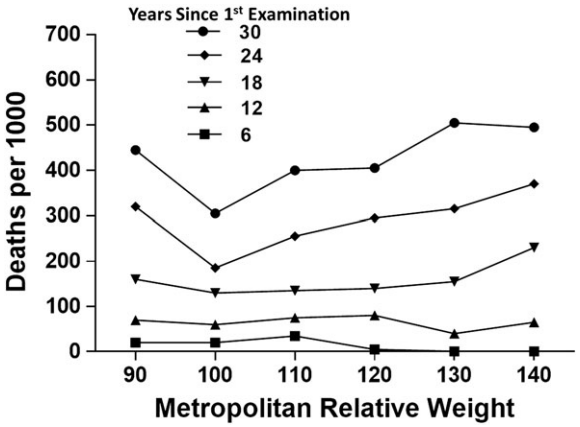

Figure 3 Mortality for women in the Framingham study in relation to initial relative weight plotted for each 6 years of observation.

The curvilinear relationship of BMI to body weight appears to be contradicted by the finding that elderly individuals and those with specific diseases such as chronic obstructive pulmonary disease or heart failure, obesity may contribute to longer life, a finding called the 'Obesity Paradox'. The explanation is probably a consequence of selection bias. A simple way to eliminate this bias is to ensure that the start of exposure and the start of follow-up coincide. This is precisely how randomized clinical trials are typically analyzed: an analysis that selects individuals free of coronary heart disease 5 years after randomization and then compares the coronary heart disease incidence between arms from year 5 onwards would be unacceptable; similarly for the effect of obesity (47).

An epidemiological model

An epidemiological model for obesity as a chronic progressive relapsing disease process is shown in Fig. 4 (48,49). An epidemiological model has an environmental agent that acts on a host to produce a disease. Disease is related to the virulence of the agent and the susceptibility of the host.

The agent

Food is the principal environmental agent for obesity, with a decline in the level of physical activity being second (50,51). Tasty, low cost, convenient foods are abundant in the western diet (52,53). These tasty foods can activate the so-called pleasure centres of the brain providing pleasurable rewards from eating (54,55). This centre is the same one that is activated by substances of abuse (56). At the same time that tasty foods have become less expensive and more abundant, physical activity has gradually declined (57) and together with the abundance of food provide the major drivers for obesity.

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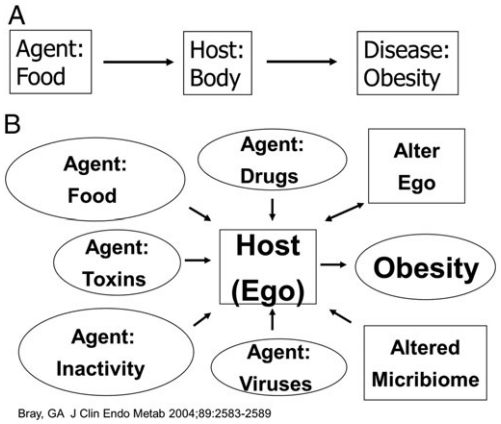

Figure 4 Panels A and B: an epidemiological model of obesity. Panel A shows the basic elements for an epidemiological model – agent, host and disease. Panel B shows the variety of environmental agents that have been related to the onset of obesity (29)

In addition to food and physical activity, a variety of other environmental factors such as less sleep time, endocrine disruptors (also called obesogens) (58), epigenetic and intergenerational effects, older parental age, certain medications and reduced smoking have all conspired to enhance the effects from the main causative agents – tasty and pleasurable food and low physical activity (59).

The host

Genetic factors

Genetic factors are a component of the host response to the environmental agents. There are some genes which have high penetrance and lead inevitably to massive obesity. Examples would be defects in the production of leptin or a defective leptin receptor, abnormalities in proopiomelanocortin gene, or in the melanocortin-4 receptor system (60,61). However, nearly 100 other genes have been identified that are related to obesity and fat distribution, but with a much smaller individual contribution (62,63). It is clear that in the same environment some people become obese and others do not. Many factors are involved in this differential response, and some of them have been noted earlier.

Fat cells

For the genetically susceptible host, excess energy from food leads to an accumulation of fat in fat cells (64,65). The enlargement and/or increase in number of fat cells to accommodate this storage of fat are the pathologic lesions of obesity. The distribution of fat in ectopic regions such as visceral fat, cardiac fat and fat in muscles may occur as fat cells reach their maximal storage capacity. Enlarging fat cells and the microbiome may interact to increase the inflammatory environment of the host (66).

As the fat cells increase in size, they produce increased amounts of a variety of peptides, including leptin, cytokines such as interleukin 6 and tumour necrosis factor alpha, angiotensinogen, adipsin (Complement D), metabolites such as free fatty acids and lactate; concentrations of the anti-inflammatory adipocyte product, adiponectin fall (67). The products of the fat cell in turn modify the metabolic and inflammatory processes in the host affecting the brain and peripheral systems alike (64). For the susceptible host, these metabolic changes lead in turn to a variety of other processes, including dyslipidaemia, hypertension hyperinsulinemia and diabetes, resulting in atherosclerosis, and physical stress on bones and joints (Fig. 5). However, not everyone with hypertension develops a stroke and not everyone who is obese develops serious outcomes. From this epidemiological perspective, we conclude that obesity is a disease process in the same way that atherosclerosis and hypertension are diseases and that like these diseases may require long-term treatment.

The pathologic changes associated with obesity: the disease process

The enlarged fat cells produce the physical signs of obesity. The metabolic consequences of obesity result from the cytokines released from fat cells and from the inflammatory environment in which they live.

Figure 5 provides a model of the intermediary mechanisms for each of the major manifestations of obesity that we will deal with subsequently, including diabetes mellitus, myocardial infarction, hypertension and stroke, some forms of cancer, sleep apnea, gallstone disease, osteoarthritis, neurodegenerative diseases and stigmatization.

Two types of functional impairments are associated with the increased size and mass of fat cells in obesity. The first are those related to the fat mass such as osteoarthritis (29), sleep apnea (68–70) and the psychosocial responses to the individual with obesity (29). The second are the metabolic and inflammatory consequences resulting from the excessive secretion of products by the enlarged fat cell (64) and ectopic deposition of lipid (71).

Leptin is one of many proteins secreted in larger amounts by enlarging fat cells. Leptin deficiency, a recessively inherited genetic disease, produces massive obesity in human beings and animals as its principal sign and symptom (60,61). The increased concentration of free fatty acids, which also rises as the size of the fat cell increases, probably produces alterations in insulin clearance by the liver and the altered metabolism of cholesterol in the liver that lead to the increasing risk of diabetes and gall bladder disease in the obese (72).

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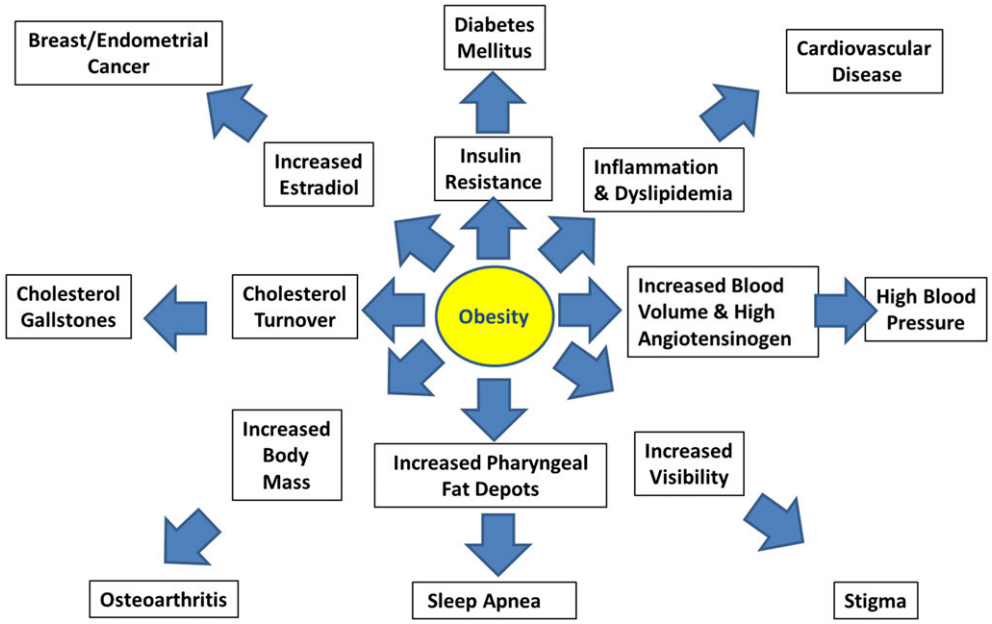

Figure 5 A model showing the relation of obesity in the centre and the diseases with which it is associated. The intermediate boxes show the pathophysiological factors that are principally involved with the development of disease; many of these pathophysiological factors may interact and be involved in more complex causal pathways, but potential interactions have been omitted for clarity. [Colour figure can be viewed at wileyonlinelibrary.com]

For all of these pathologic states, the relationship between increasing body weight or BMI and disease is curvilinear. That is, as body weight or BMI increase, the risk for diabetes (73,74), gall bladder disease (29,72), cardiovascular disease and cancer increases as the excess weight deviates ever more from the median (Fig. 2). A study of BMI and mortality carried out by pooling many studies, mainly from Europe (26), showed that the optimal BMI for lowest mortality was between 22.5 and 25 kg m^{-2}. For each increase of 5 BMI units, total mortality rose by 30%, chronic kidney disease by 60% and diabetes mellitus by 120%. This relationship between BMI and risk for death has been confirmed repeatedly (27,28). BMI is one predictor of risk and body fat another. When these two were examined together in a large Canadian population assembled from people who had dual X-ray absorptiometry to measure bone mineral density, Padwal *et al.* (75) found that low BMI and high body fat percentage are independently associated with increased mortality that may help explain the counterintuitive relationship between overweight and obesity.

Diabetes mellitus

Obesity is one of the strongest predictors of type 2 diabetes (76). Development of type 2 diabetes thus depends on changes in one or both of these two principal variables – insulin sensitivity and insulin secretion. Obesity can modify one or both of these variables (73).

In the individual with diabetes, the mass of beta-cells is reduced, probably by apoptosis. In addition, chronic exposure to high levels of glucose may blunt the responsiveness of these cells to incretins (73) and thus their ability to keep up with the demand for insulin to facilitate glucose uptake peripherally. Multiple factors contribute to the failure of the beta-cell including resistance to incretin hormones (GIP and GLP-1), lipotoxicity, glucotoxicity, ageing, genetic abnormalities, increased secretion of islet amyloid polypeptide, reactive oxygen stress and inflammation (73).

Epigenetic factors

The intrauterine environment provides a mechanism that predisposes some people with obesity to develop diabetes later in life. Individuals who were malnourished while *in utero* may be more prone to weight gain, insulin resistance, beta-cell failure and hence diabetes than those who are well nourished, a hypothesis known as the 'Developmental Origin of Disease' or the 'Barker Hypothesis' (77). Maternal undernutrition forces the fetus to adapt during its intrauterine development and drives a reprogramming of its endocrine–metabolic state to produce permanent changes in the structure and the physiology of key organ systems (77,78). These changes in low-birth-weight infants (normal range, 3,000–4,000 g) contribute factors to chronic diseases such as type 2 diabetes, coronary heart disease, stroke and hypertension in adult life (79).

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Cancer

Obesity predicts the development of some forms of cancer, particularly in women (80). Oestrogen production by adipose tissue and the associated risk of endometrial and breast cancer is well known. In post-menopausal women, adipose tissue is the major source of oestrogenic compounds because the ovaries no longer produce oestrogens (Fig. 5). In addition, the growth factors produced by adipose tissue such as fibroblast growth factor-21, nerve growth factor, transforming growth factor-β and vascular endothelial growth factor, as well as insulin, may also participate in the growth of cells that eventually become malignant contributing another component to the risk for diverse forms of cancer in the individual who is obese (81)

Hypertension, stroke and cardiovascular disease

Hypertension, stroke and cardiovascular diseases are also increased in obesity (82). Several mechanisms may be involved in the development of hypertension, stroke and cardiovascular disease in these patients. The pro-inflammatory and pro-thrombotic adipokines may contribute to increased cardiovascular disease risk (83). Increased vascular volume, greater arterial resistance and the release of angiotensinogen from enlarged fat cells may contribute to the higher blood pressure.

Sleep apnea

The prevalence of sleep apnea is increased in the patient with obesity (69). Accumulation of fat in the pharynx is a major risk factor for development of sleep apnea that occurred in 80% of the participants enrolled in the Sleep AHEAD sub-study of the Look AHEAD Trial (84). In severe cases, 'obesity hypoventilation' can develop, which is a debilitating state of intermittently impaired consciousness, exemplified by Joe in Dickens' Pickwick papers.

Gallstone disease

Gallstone disease is more prevalent in the patient with obesity. Increasing body fat increases the turnover of cholesterol (85) such that each kilogramme of extra body fat produces an extra 20 mg of cholesterol each day that must be secreted through the biliary tree. For individuals with a tendency to gall stone formation, this extra load of cholesterol from increased fat may be the tipping point for the development of stone formation and gall bladder disease (86).

Osteoarthritis

Osteoarthritis is more prevalent in people who are obese (87). This can involve both weight bearing and non-weight bearing joints, suggesting that the pathophysiology must involve both the increased body mass (Fig. 5), circulating adipokines, inflammatory factors or other pathophysiologic mechanisms.

Stigmatization

Body size provides a visual read-out to the observing individual about the size of the person they are seeing. Many people with obesity do not perceive their enlarged size, but this is readily perceived by external observers and plays a dominant role in the stigmatization of obesity in children (88) and adults (89) by both the general public and by health professionals alike. This may lead to discrimination and contribute to depression and anxiety.

Conclusions

Although obesity is a non-communicable disease process, the epidemiological model of obesity described earlier tells us that it has a number of features in common with a 'communicable disease' including environmental agents, and the host responses to these agents. Just as infectious diseases have been controlled primarily by change in the environment such as improved sanitation, control of the obesity epidemic should start by controlling the virulence of environmental agents, which can be carried out by a collaboration of obesity professionals, local health environmental authorities and industry. Early diagnosis and treatment of childhood obesity could be considered similar to vaccination, by targeting individuals from the day of birth. A healthy body weight and healthy lifestyle should be implemented from early stages in life. For preventing damage to the host from obesity, medical personnel play an important role in the evaluation and treatment of the comorbidities in people with obesity.

Continuous effort is needed to control obesity because it is a relapsing disease process. There are many background genetic factors related to body weight and body fat that modify the responses to the tasty, inexpensive and convenient food in the environment. Removing barriers to physical activity provides an additional approach that may be analogous to the use of antibiotics for infectious diseases. With continuous and comprehensive efforts, the obesity epidemic will be gradually brought under control.

The World Obesity Federation takes the position that obesity is a chronic, relapsing, progressive disease process and emphasizes the need for immediate action for prevention and control of this global epidemic.

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