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Understanding the pathophysiology of obesity—the relevance of weight loss strategies through behavior modification

Matthias Blüher[1,2]

[1] Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Zentrum München, University of Leipzig and University Hospital Leipzig, Leipzig, Germany

[2] Medical Department III—Endocrinology, Nephrology, Rheumatology, University of Leipzig Medical Center, Leipzig, Germany

Abstract

Obesity is a chronic, progressive, and relapsing disease that can contribute to morbidity, reduced life expectancy, and adverse health outcomes. The prevalence of obesity increased worldwide in the past 60 years, mainly because of changes in our environment and society. With the technical revolution of the last century, new modes of transportation and working conditions, automatization, and computerization, human energy demands have decreased. In parallel, the availability of energy-dense food, refined carbohydrates, and fat has markedly increased. These developments in society clash with biological factors that predispose humans to the development of obesity. At the individual level, obesity is the result of a long-term imbalance between too much energy consumed and too little energy expended. Therefore, lifestyle and behavior interventions aimed at reducing calorie intake and increasing energy expenditure target the root causes of obesity. However, both at the individual and population level, obesity prevention and treatment strategies that are based only on behavior modification are frequently not successful in the long term. The limited effectiveness of behavior interventions on weight loss are explained by complex and persistent hormonal, metabolic, and neurochemical adaptations that prevent weight loss and promote weight regain. However, behavior interventions lead to important health benefits beyond weight loss and are therefore an integral part of obesity management. This review discusses how a better understanding of the pathophysiology of obesity can influence weight loss strategies through behavioral modification. The complex factors contributing to the development of obesity require a multimodal long-term approach that is based on behavior interventions but may also include pharmacological or surgical approaches. The treatment paradigm has recently shifted from simple weight loss strategies towards treating obesity as a multisystem disease.

Keywords
Body mass index · Nutrition · Exercise · Lifestyle · Pathophysiology

Obesity is a chronic, relapsing, non-communicable multisystem disease characterized by an abnormal and/or excessive accumulation of body fat that presents a risk to health [1–4].

The World Health Organization (WHO) estimated that in 2022 there were 890 million people living with obesity worldwide (prevalence of 16%; [1]). The WHO announced that obesity leads to 5 million premature deaths per year and that 5% of

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worldwide mortality was attributable to obesity and its related diseases [1]. The prevalence of obesity in adults has more than doubled since 1990, and adolescent obesity has quadrupled [1]. Currently, over 160 million children are living with obesity [1]. The prevalence of obesity is generally higher in women than men, increasing with age after the age of 14 years, and it is higher in countries where there is greater social inequality [3, 5].

People living with obesity frequently have an impaired quality of life and may have a reduced life expectancy because of several obesity-related complications including type 2 diabetes, hypertension, fatty liver diseases, cardiovascular diseases (myocardial infarction, heart failure, atrial fibrillation, stroke), obstructive sleep apnea, osteoarthritis, mental disorders, and some types of cancer [6, 7]. As a result, obesity is associated with increased direct and indirect healthcare costs, a loss of productivity through sickness-related absence, slower economic growth, and increased disability rates, thereby constituting a large economic burden to society [1, 8]. The Global Burden of Disease Obesity Collaborators 2015 evaluated the health effects of overweight and obesity in 195 countries over 25 years with regard to body mass index (BMI)-related mortality and health outcomes [5]. Out of the impaired health conditions attributable to high BMI, cardiovascular diseases at 41% were the leading cause of mortality followed by diabetes, chronic kidney disease, and cancer [5]. Obesity-associated type 2 diabetes and musculoskeletal disorders were among the leading causes for years lived with disabilities [5]. Supporting the impact of obesity on cardiometabolic disease burden, a pooled cohort analysis involving 1.8 million participants showed that nearly half of the excess risk for ischemic heart disease and more than 75% of the excess risk for stroke that was related to high BMI were mediated through a combination of raised levels of blood pressure, total serum cholesterol, and fasting plasma glucose [9, 10]. Moreover, obesity-related cancers also significantly contribute to mortality associated with high BMI [10]. There is support from observational studies suggesting a causal relationship between obesity and cancers of the esophagus, colon and rectum, liver, gallbladder and biliary tract, pancreas, breast, uterus, ovary, kidney, and thyroid [10].

Although obesity is widely recognized as a disease [1, 2, 4] and our current understanding of the pathophysiology improved during the past few decades, there is still an unmet need to better assess individual obesogenic factors with the aim of offering personalized interventions that target the main causes of obesity.

Abbreviations

BMI	Body mass index
CV	Cardiovascular
DIRECT	Diabetes Remission Clinical Trial
EASO	European Association for the Study of Obesity
GWAS	Genome-wide association study
LOOK AHEAD trial	Look Action for Health in Diabetes
PREDIMED	Prevención con Dieta Mediterránea
THIN	The Health Improvement Network
WHO	World Health Organization

Pathophysiology of obesity

Obesity is the result of a long-term positive energy balance characterized by too high energy intake for the individual demands, low energy expenditure through intrinsic factors (basal metabolic rate, non-exercise-related energy expenditure), and low physical activity. However, the main question is not *whether* but *why* people with obesity have a chronic energy dysbalance [11]. The pathogenesis of obesity is complex and includes societal, environmental, and biological factors that interact at different levels and over the entire life span (**Fig. 1**; [3, 12]).

Biological factors

The brain seems to play a critical role in the pathogenesis of obesity because it regulates energy metabolism, food intake, and energy expenditure and integrates the response to an obesogenic environment with biological signals from peripheral organs (e.g., adipose tissue, liver, gut, pancreas; [13, 14]). Human obesity can therefore be viewed as a heritable disorder of the central control of energy balance [13]. The central role of the brain in body weight regulation was supported by observations that animals with lesions and humans with tumors affecting the hypothalamus develop abnormal food-seeking behavior and obesity [15]. With the discovery that a mutation in the *ob* gene causing a loss of the appetite-regulating adipokine leptin leads to severe obesity in *ob/ob* mice, it became clear that central neurocircuits receive signals on the peripheral energy status of the body that regulate energy homeostasis [16, 17]. In humans, mutations in genes coding for leptin, leptin receptor, melanocortin 4 receptor, pro-opiomelanocortin, agouti signaling protein, and others might cause severe monogenic obesity [18, 19]. However, monogenetic causes of obesity are rare and cannot explain the extent of the obesity pandemic. In addition, genome-wide association studies (GWAS) found that only ~2% of the BMI variability can be explained by common single-nucleotide polymorphisms [20], and population genetics cannot explain the obesity pandemic seen in the short span of the past 50 years.

Obesity in evolution

The pathophysiology of obesity should also be discussed in an evolutionary context. For thousands of years, humans and their predecessors had to survive periods of famine. Therefore, it is likely that evolution positively selected humans who could withstand longer periods of famine, who could store and mobilize energy more efficiently, and who might have reproduced better than those without these adaptations [14]. A genetic selection pressure could have contributed to a genotype that favors overeating, low energy expenditure, and physical inactivity and that is associated with the ability to eat more rapidly, to resorb calories to a higher degree, and to expand energy stores in adipose tissue more efficiently [3, 14].

Role of the environment and society in obesity development

The potential main drivers of the global rise in obesity prevalence must be those that have changed substantially preceding or coinciding with the simultaneous rise in obesity prevalence across countries [12]. In the 1970s, obesity rates started to in-

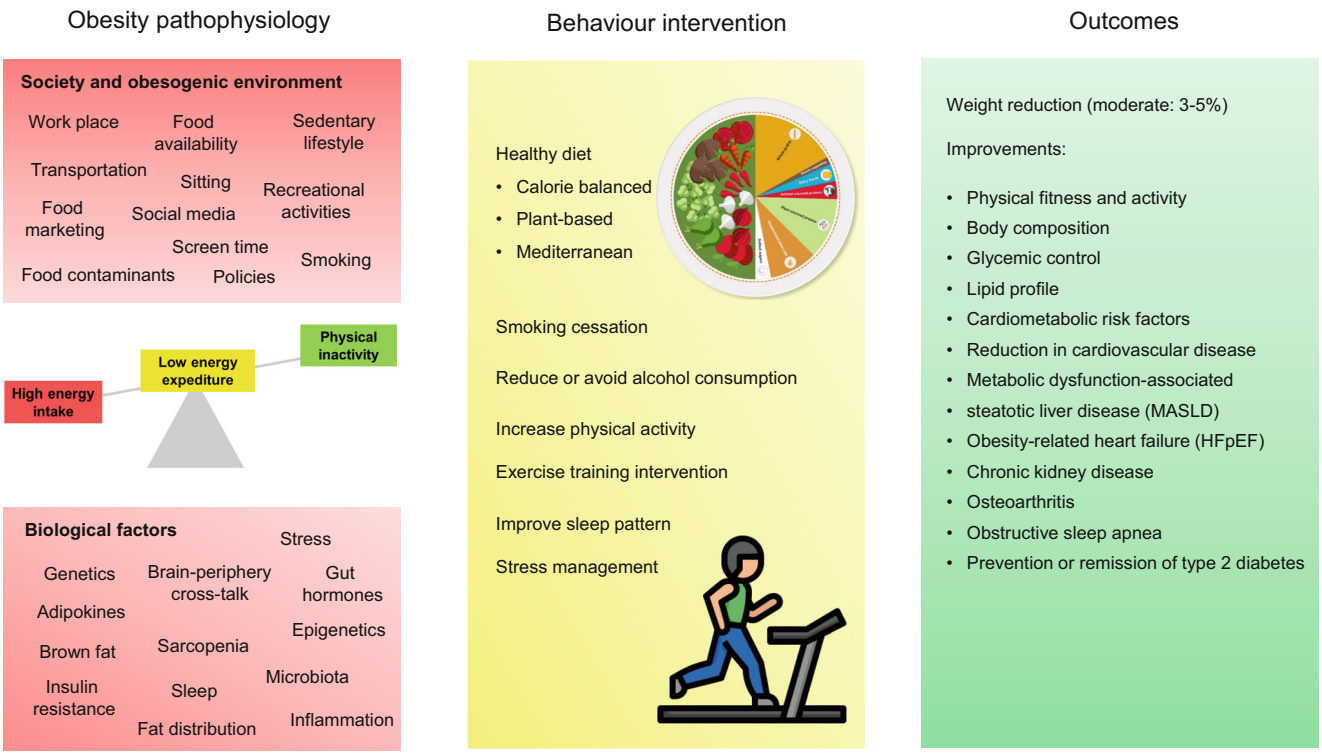

Fig. 1 ▲ Pathophysiology of obesity, behavioral intervention, and outcomes. Obesity can result from a combination of increased energy intake, low physical activity, and reduced energy expenditure. The main drivers causing a chronic positive energy balance subsequently leading to obesity are complex and include societal, environmental, and individual biological factors. Individual factors such as genetic background, epigenetic memory, microbiota, or the periphery (adipose tissue, gut)—brain cross-talk may increase susceptibility to obesity, which may develop in an obesogenic environment (e.g., food availability, eating culture, transportation modes, screen and sitting time). Behavior intervention including a balanced healthy diet, aerobic endurance and resistance training, reduction of alcohol consumption, and smoking cessation can improve several outcomes and cardiometabolic diseases. *HFpEF* heart failure with preserved ejection fraction

crease in high-income countries followed by most middle-income countries—and now also affecting low-income countries—suggesting that obesity prevalence is linked to improved economy and wealth [3, 12]. Therefore, changes in the global food system combined with sedentary behaviors seem to be the major drivers of obesity at the population level [12]. Supporting this notion, data from dietary surveys in the United Kingdom found that the increase in average body weight in men between 1986 and 2000 might be the result of both increased energy intake and reduced physical activity [21]. Our society and environment influence human behavior and lifestyle choices. The increasing prevalence of obesity is associated with a reduction in home cooking, greater reliance on convenience food, increased use of air conditioning causing reduced energy expenditure to maintain body temperature, reduced physical activity because of computer-based workplaces in most occupations, leisure time entertainment becoming dependent on information technology, a growing habit of snack consumption, more persuasive food marketing, and other changes [3, 12]. The inherited and biological factors underlying obesity development have to be considered in the context of obesogenic environments and societies when defining behavior interventions aimed at preventing or treating obesity.

Assessment of obesity and associated risks

In most current guidelines, the diagnosis of obesity is simply based on BMI, i.e., > 30 kg/m^2 and for Asian people >25 kg/m^2 [2, 4, 7]. This definition of obesity only incompletely reflects the health risks associated with increased fat mass, abdominal fat distribution, and adipose tissue dysfunction [22]. Therefore, the Lancet Commission on clinical obesity recently proposed new diagnostic criteria for obesity that pragmatically distinguish clinical obesity from preclinical obesity on the basis of the presence of objective clinical manifestations of altered organ function or impairment of an individual's ability to conduct daily activities [4]. Preclinical obesity is considered a state of excess fat mass with preserved function of other tissues and organs [4]. Clinical obesity reflects a disease state that can lead to severe end-organ damage, causing life-altering and potentially life-threatening complications [4]. Excess adipose tissue accumulation should be confirmed by either direct measurement of body fat or indirectly by measuring waist circumference, waist-to-hip ratio, or waist-to-height ratio [4]. Independently, the European Association for the Study of Obesity (EASO) proposed a new framework for the diagnosis, staging, and management of obesity in adults that reflects obesity as an adiposity-based chronic disease better than previous narratives [2].

Both the Lancet Commission and the EASO highlight that abdominal fat accumulation is a stronger determinant of developing cardiometabolic complications than BMI [2, 4]. Indeed, waist circumference and/or waist-to-hip ratio are better predictors of mortality and cardiometabolic morbidity in people with obesity [23].

In the clinical setting, it is important that in addition to the assessment of body weight, BMI, and parameters of fat distribution, a systematic evaluation of medical, functional, and psychological impairments and obesity complications is performed. In general, the risk for obesity comorbidities increases with increasing BMI. The risk of developing type 2 diabetes, arterial hypertension, but also cardiovascular diseases increases with increasing categories of BMI [24, 25]. As an example, the obesity-related risk of developing type 2 diabetes increases from <5% to > 25% when comparing people with a BMI <25 kg/m^2 against people living with obesity (BMI >40 kg/m^2; [7]).

However, the relationship between BMI and cardiometabolic obesity complications is not always linear, and at any given BMI, the variation in obesity-related disorders is high [7]. Up to one fourth of people with obesity may be protected against premature cardiometabolic disease manifestations, an obesity phenotype that has been described as "metabolically healthy obesity" [26]. However, in The Health Improvement Network (THIN) including data from more than 3.5 million people in the United Kingdom, metabolically healthy obesity was still associated with a higher risk of myocardial infarction or heart failure outcomes compared to metabolically healthy lean persons [27].

Principles of behavior interventions

At the society level, interventions aimed at motivating behavior changes (such as education, health promotion, social marketing, and incentives for healthy living) and/or enforcing actions that reduce the effects of the main causes of obesity (e.g., laws, regulations, and policy changes) might help [12]. Suitable approaches may include policy interventions such as a tax on sugar-sweetened beverages, mandatory standards for meals at kindergartens and schools, or banning unhealthy food advertisements aimed at children [3].

At the individual level, prevention and treatment strategies are based on the concept that calorie intake must not exceed calories expended [28]. Treatment of obesity requires a comprehensive medical approach that includes behavioral strategies such as dietary, physical activity, and/or psychological interventions; pharmacotherapy; and bariatric surgery [28, 29]. Obesity management should include interventions from all appropriate categories designed to achieve the individually defined goals for weight loss, health status, and quality of life.

Behavior modification is particularly important in preventing cardiometabolic diseases and should start as early as in utero, since maternal pre-pregnancy weight, body weight dynamics during the pregnancy, nutrition, and physical activity significantly influence the future obesity risk in offspring [24, 30]. Breastfeeding has been shown to exert protective effects against obesity development during childhood and may benefit the cardiometabolic health of the mother [31].

The critical age for obesity development during childhood is as early as 3–6 years, and children with obesity at this age have a > 90% risk of obesity being transmitted into adulthood [32].

Behavior interventions should be initiated as early as possible and aim at changing the lifestyle to prevent cardiometabolic diseases.

Treatment of obesity with behavior interventions

Previously, the main aim of obesity treatment was defined by weight reduction targets [29]. Current guidelines for the treatment of obesity recommend weight loss of > 5% to > 10% for adults over a period of 6–12 months because this extent of weight reduction has been associated with relevant and meaningful health improvements and with a reduction in weight-related complications [33, 34]. More recently, the paradigm of obesity treatment shifted from a focus on weight loss towards improving health and treating obesity as a multisystem disease [29]. Importantly, it needs to be emphasized by healthcare professionals that obesity is a chronic and progressive disease that requires lifelong management [33, 34].

Behavior modification has been established as first-line and basic background treatment of obesity [34, 35]. Most guidelines recommend a multifactorial, comprehensive lifestyle program that includes a high-quality hypocaloric diet that should also involve a minimum of 150 min of moderate-intensity activity per week as well as behavior-changing strategies to foster adherence to dietary and physical activity [34–36].

Nutrition

Nutrition recommendations for adults of all body sizes should be personalized to meet individual values, preferences, and treatment goals in order to support a dietary approach that is safe, effective, nutritionally adequate, culturally acceptable, and affordable for long-term adherence [36]. To achieve clinically significant weight loss, most international guidelines recommend a daily energy deficit of at least 500 kcal that should be adjusted for individual body weight and physical activity [34–36]. The energy deficit can be achieved by specific strategies including portion size control, reduction or elimination of ultraprocessed foods such as sugar-sweetened beverages, reduction of alcohol consumption, and increased fruit and vegetable intake. Healthy eating approaches can be selected based on individual preference, metabolic risk, and likelihood of long-term adherence [28, 37]. Targeted weight reduction can also be achieved by specific dietary approaches including low-fat, vegan, vegetarian-style, low-carbohydrate, and Mediterranean diets [24, 28, 37]. For short-term use of less than 12 weeks, very low calorie diets (≤ 800 kcal/day) could support more rapid weight loss, but they require close medical supervision [38]. While some evidence demonstrates weight loss and improved cardiometabolic risk factors with other popular weight-loss approaches including time-restricted eating, intermittent fasting, or a ketogenic diet, clinical practice guidelines have not endorsed these strategies, and they may require dietitian support [36, 37].

In a meta-analysis comparing dietary macronutrient patterns of 14 popular dietary programs for weight and cardiovascular risk factor reduction in adults, most dietary patterns resulted in similar and only modest short-term weight loss but with substantial improvements in cardiovascular risk factors [39]. As an example, the PREDIMED-Plus intensive lifestyle intervention for 12 months effectively reduced adiposity by −3.2 kg and improved cardiovascular risk factors. However, there is no evidence that caloric restriction alone or in combination with increasing physical activity significantly reduces cardiovascular events or mortality in people living with obesity.

Physical activity

Obesity treatment should include increasing physical activity with a weekly exercise target of more than 150 min of accumulated moderate-intensity endurance exercise, in combination with strength training [33–38]. Ideally, the physical activity intervention should be performed under the supervision of experienced trainers to avoid injuries or exercise-related adverse events. Following weight loss, weight maintenance remains a major challenge in obesity management. Therefore, after successful weight reduction, exercise programs should be increased to 300 min of moderate-intensity activity every week and be tailored to individual physical capabilities and preferences [33–38]. Behavior modification needs to further aim at reducing sedentary behavior (sitting time, computer use, gaming etc.) and increasing daily activities such as walking, cycling, or gardening [34]. Importantly, increasing physical activity without additional nutrition intervention has only modest effects on reducing weight. However, the benefits of increased physical activity, exercise, and a better cardiopulmonary fitness have health gains beyond weight-modulating effects and include significant improvements in cardiometabolic health [41]. Muscle strength or resistance training has the potential to reduce visceral adiposity and improve cardiovascular risk factors, while endurance training increases physical fitness and exercise programs in general increase muscle strength [42].

Multicomponent behavior interventions

Evidence-based commercial multimodal behavioral interventions represent an important strategy of obesity management within primary care or community settings [28, 37]. Moderate- to high-intensity programs typically include 12 or more sessions in the first year, followed by a maintenance phase for up to 24 months, and may facilitate 5–10% weight loss with maximal loss achieved between 6 and 12 months [38]. Multimodal interventions include group, individual, or technology-based delivery for lifestyle changes, education, peer support, self-weighing, coaching, self-monitoring, cognitive restructuring, and goal setting [28, 37]. Multimodal interventions include recommendations for self-monitoring (e.g., regular weighing) as well as tracking dietary intake and physical activity levels. Additional behavioral strategies include learning to improve stimulus control, modifying existing dietary and fitness habits, and setting reasonable and individualized weight loss targets. The main aim of the multimodal approach in obesity treatment is to provide support to achieve weight loss goals and enhance patients' adherence to their individual behavior modification program [29].

Benefits of behavior interventions

The weight loss effects of behavioral interventions are only moderate. However, the health benefits that can be achieved by lifestyle modifications are relevant for the prevention, treatment, and even remission of obesity-related diseases (◘ **Fig. 1**; [7, 24]). In prospective clinical trials such as the Diabetes Preventions Study and the Finnish Diabetes Prevention Study, behavior interventions were demonstrated to reduce the risk of developing type 2 diabetes in individuals with prediabetes [43, 44]. The weight loss that was associated with type 2 diabetes prevention was only 3–7%, but the diabetes risk reduction was sustained up to the 15-year follow-up recall [45]. While moderate weight loss in people with obesity and prediabetes appears to be sufficient to prevent or delay type 2 diabetes, greater weight loss of > 15% is required to achieve remission of type 2 diabetes, including diet interventions (DIRECT trial; [46]), bariatric surgery [47], or pharmacotherapy [48]. The health benefits of obesity treatment may be related to the extent of weight loss. As an example, an average weight loss of 7% was not sufficient to significantly improve cardiovascular endpoints in the Look AHEAD trial [49]. In the Look AHEAD trial, 5145 patients with overweight/obesity and type 2 diabetes were randomized to an intensive lifestyle intervention (weight loss promotion through reduced caloric intake and increased physical activity) or regular care [49]. Despite greater weight loss (−8.6 vs. −0.7%) and greater reduction in HbA1c and blood pressure levels, the intensive lifestyle intervention did not reduce the rate of cardiovascular events [49]. Importantly, study participants who achieved ≥ 10% weight loss in the first year of the intervention had a significant improvement in the cardiovascular outcome [50]. Beyond weight loss, behavioral interventions are associated with several clinically relevant improvements in the health status of people with obesity (◘ **Fig. 1**).

Conclusion

The pathophysiology of obesity is complex and therefore requires a comprehensive multimodal long-term treatment approach. Obesity management should include behavior interventions as foundation but, if required, also pharmacotherapy and surgery to achieve the individually defined goals for weight loss, health status, and quality of life.

Corresponding address

Prof. Dr. med. Matthias Blüher, MD
Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Zentrum München, University of Leipzig and University Hospital Leipzig
Philipp-Rosenthal-Str. 27, 04103 Leipzig, Germany
bluma@medizin.uni-leipzig.de

Declarations

Conflict of interest. M. Blüher received honoraria as a consultant and speaker from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, MSD, Novo Nordisk, Novartis, and Sanofi.

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Zusammenfassung

Verständnis der Pathophysiologie der Adipositas – Bedeutung gewichtsreduzierender Strategien durch Verhaltensintervention

Adipositas ist eine chronisch fortschreitende und rezidivierende Erkrankung, die zu Morbidität, reduzierter Lebenserwartung und negativen gesundheitlichen Folgen beitragen kann. Die Prävalenz von Adipositas hat in den letzten 60 Jahren weltweit zugenommen, hauptsächlich aufgrund von Veränderungen in unserer Umwelt und Gesellschaft. Mit der technischen Revolution des letzten Jahrhunderts, neuen Transportmitteln und Arbeitsbedingungen sowie Automatisierung und Computerisierung sinkt der Energiebedarf beim Menschen. Parallel dazu nahm die Verfügbarkeit von energiedichten Lebensmitteln, raffinierten Kohlenhydraten und Fetten deutlich zu. Diese gesellschaftlichen Entwicklungen treffen auf biologischen Faktoren, die Menschen für Adipositas prädisponieren. Auf individueller Ebene entsteht Adipositas durch ein langfristiges Ungleichgewicht zwischen zu hoher Energieaufnahme und zu geringem Energieverbrauch. Daher können Lebensstil- und Verhaltensinterventionen, die auf eine Reduzierung der Kalorienaufnahme und eine Erhöhung des Energieverbrauchs abzielen, als ätiologiebasierte Adipositastherapie angesehen werden. Allerdings sind sowohl auf individueller als auch auf Bevölkerungsebene die Adipositas-Präventions- und -Behandlungsstrategien, die ausschließlich auf Verhaltensänderungen basieren, langfristig nicht besonders erfolgreich. Die begrenzte Wirksamkeit von Verhaltensinterventionen erklärt sich durch komplexe und anhaltende hormonelle, metabolische und neurobiologische Anpassungen, die Gewichtsverlust verhindern und eine erneute Gewichtszunahme fördern. Verhaltensinterventionen führen jedoch über die Gewichtsabnahme hinaus zu Verbesserungen des Gesundheitszustands und sind daher ein integraler Bestandteil der Adipositasbehandlung. Im vorliegenden Übersichtsartikel wird diskutiert, wie ein besseres Verständnis der Pathophysiologie von Adipositas zu Empfehlungen für Gewichtsreduktionsstrategien durch Verhaltensmodifikation führen kann. Die komplexen Faktoren, die zur Entwicklung von Adipositas beitragen, erfordern einen multimodalen, langfristigen Ansatz, der auf Verhaltensinterventionen basiert, aber auch pharmakologische oder chirurgische Maßnahmen umfassen kann. Die Sichtweise auf die Therapie von Menschen mit Adipositas hat sich von der reinen Empfehlung zur Gewichtsreduktion zur Behandlung von Adipositas als Multisystemerkrankung gewandelt.

Schlüsselwörter
Body-Mass-Index · Ernährung · Bewegung · Lebensstil · Pathophysiologie

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