Obesity

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1.1 Classification of Obesity

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Obesity is defined as an increase in fat mass beyond the normal level with unfavourable effects on health. Usually, the Body Mass Index (BMI) is used to classify overweight and obesity. It is the quotient of body weight and squared height (unit: kg/m^2). According to the WHO classification, overweight (preadiposity) is defined by a BMI of 25.0–29.9 kg/m^2. A BMI of ≥30 kg/m^2 and above is considered as obesity, which is subdivided into different degrees of severity (Table 1.1).

The BMI is easy to determine and is therefore a practical approach for a quick assessment of the nutritional status. However, BMI classification is not sufficient for the assessment of the burden of obesity; in particular, the pattern of fat distribution has to be taken into account. A particular high risk for the development of cardiovascular and metabolic diseases is present when the "visceral" fat mass increases in comparison to the subcutaneous fat mass. Abdominal (visceral or also central) obesity is also known as "apple shaped". In subcutaneous (gluteal-femoral or peripheral) obesity, there is an increase in fat mass mainly in the region of the hips and thighs; this form is also known as "pear type". The fat distribution pattern can be determined by circumferential measurements. If the waist-to-hip ratio is greater than 0.85 for women and greater than 0.90 for men, abdominal obesity is present; if the ratio is less, peripheral obesity is assumed.

Table 1.1 Classification of overweight according to body mass index

Classification	BMI (kg/m^2)	Risk of secondary disease
Underweight	<18.5	
Normal weight	18.5–24.9	
Overweight/ preadiposity	25.0–29.9	Slightly elevated
Obesity grade I	30.0–34.9	Increased
Obesity grade II	35.0–39.9	Significantly increased
Obesity grade III	≥40	Highly increased

1.2 "Globesity": The Current Pandemic

No other disease is spreading as strongly and as rapidly as obesity. The World Health Organization WHO refers to a worldwide epidemic of obesity. Obesity is no longer just a disease of the individual, but also socioeconomic problem for communities. In some countries, normal weight has now become the exception, and overweight and obesity are the rule. The consequences are catastrophic. Mortality is increasing and life expectancy is falling. As a result of obesity, not only diabetes mellitus type 2, cardiovascular diseases, sleep-related respiratory disorders, tumour diseases and infertility are on the rise, but also epigenetic changes caused by obesity will have an impact on future generations.

National and international health authorities are aware of this challenge and the global threat, but the necessary political consequences are still insufficient. The economic burden of the obesity epidemic on public health services is already considerable. In a study from 2015, the research unit of the management consultancy McKinsey estimates the costs of the obesity epidemic at approximately 1.6 trillion Euros per year—comparable to the costs caused by war and terror.

Epidemiological data on overweight and obesity impressively describe the dramatic increase. In large parts of the world, such as in Asia, the disease is progressing rapidly; as children and adolescents are particularly affected, the dynamics appear particularly threatening.

In a recently published analysis in the Lancet (Ng et al. 2014; Fig. 1.1) it is stated that currently one third of the world population is overweight or obese. The total number of all overweight or obese people worldwide has risen from 875 million in 1980 to 2.1 bil-

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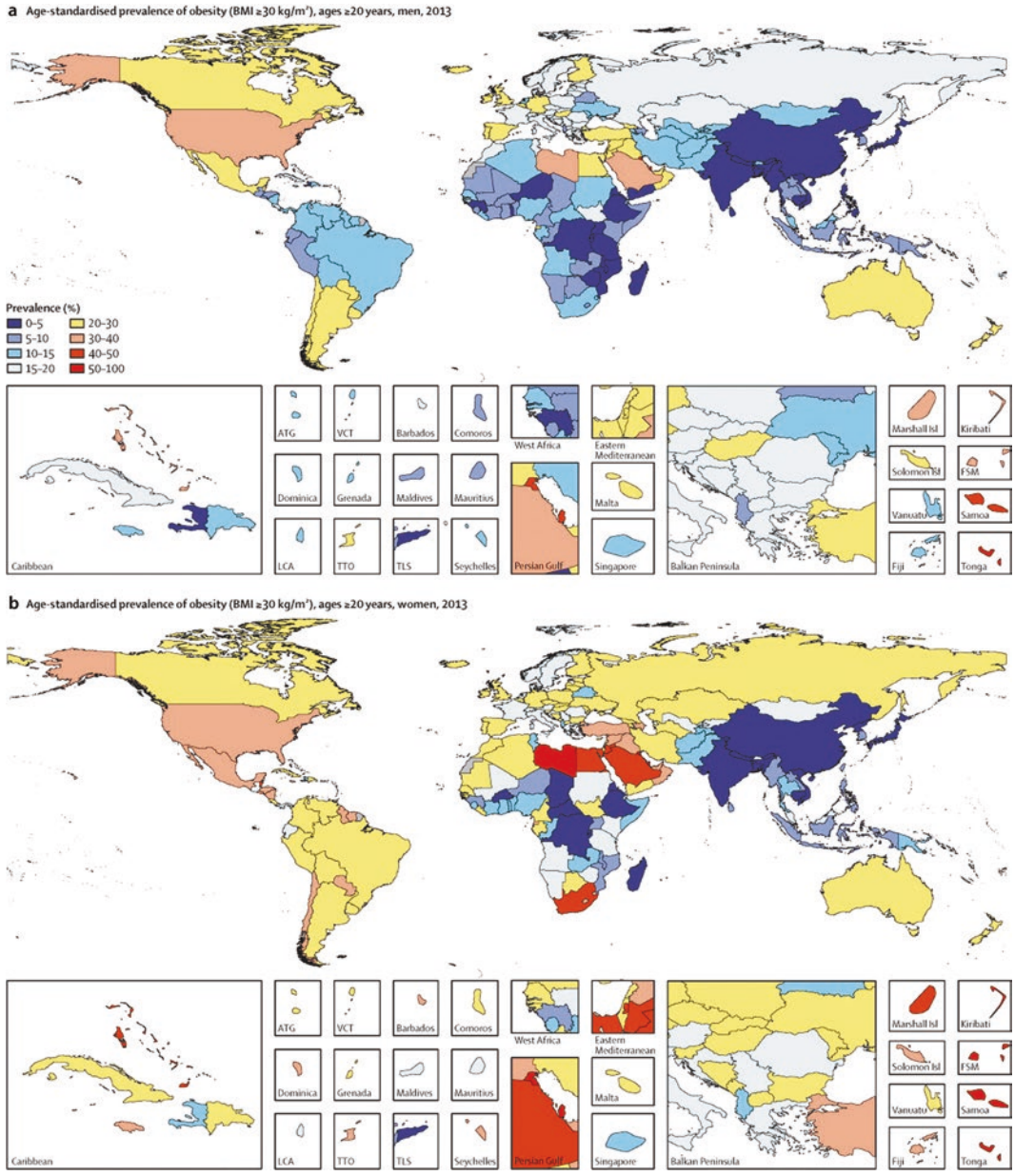


Fig. 1.1 Age-standardised prevalence of obesity (BMI ≥ 30 kg/m^2, age ≥20 years) in 2013: **a** men, **b** women. (From Ng et al. 2014, with kind permission)

lion. Furthermore, the number of overweight people is growing much faster than the world population as a whole. According to this study from Washington, most obese people live in a total of 10 countries. These include the USA, China, India and Germany.

The incidence of obesity reaches extreme levels in the southern and western Pacific islands. In Micronesia, Tonga or the Cook Islands, about 70% of the population is obese.

According to the Study on Adult Health in Germany (Studie zur Gesundheit

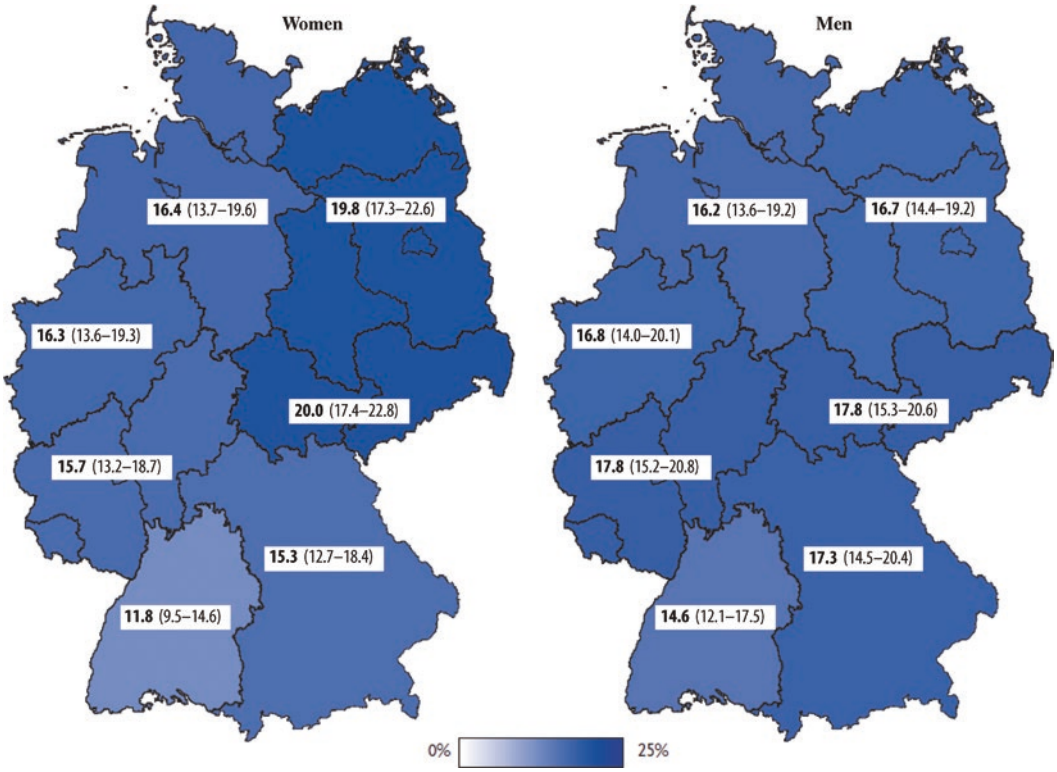


Fig. 1.2 Regional distribution of obesity among women and men. (Robert Koch Institute 2014, with kind permission)

Erwachsener in Deutschland, DEGS) by the Robert Koch Institute (2008–2011), 67% of men and 53% of women in Germany are overweight or obese (Fig. 1.2). 23% of men in Germany have a BMI above 30 kg/m^2 and are therefore obese. In 1998, the figure was 19%. The prevalence for women in Germany is 24%. Comparable data are found in the Health Survey (Gesundheitsbefragung, GEDA) of the Robert Koch Institute from the year 2012, according to which 17% of men and 16% of women are obese.

In particular, the situation of children and adolescents has worsened considerably in Germany over the recent years. According to the study on the Health of Children and Adolescents in Germany (Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland, KIGGS, 2003–2009)—also by the Robert Koch Institute—15% of children and adolescents are overweight or obese, which corresponds to approximately 800,000 obese children and adolescents.

1.3 Why Are We Getting More and More Obese? Etiology and Pathophysiology

J. Ordemann and U. Elbelt

Obesity is a chronic disease. It is based on a disturbed energy balance with a predominance of energy intake through food with insufficient energy expenditure.

The total energy expenditure consists of resting energy expenditure, the thermic effect of food, cold-induced thermogenesis and activity energy expenditure. The latter can be further divided into exercise-related activity thermogenesis (EAT) and non-exercise activity thermogenesis (NEAT). In obese people, the resting energy expenditure accounts for about 70% of the total energy expenditure; this component cannot be influenced deliberately and is mainly determined by age, sex and body weight. The percentage share of

activity energy expenditure decreases with increasing obesity (approx. 26% of the total energy expenditure in obese people with grade III obesity), whereas the share of EAT is only marginal at best. In this respect, everyday and spontaneous physical activity in obese people plays an important role in weight regulation. An additional role in thermogenesis is taken by the so-called brown adipose tissue (BAT). In contrast to white adipose tissue, this leads to energy expenditure in the form of heat. The brown adipose tissue contains a high number of mitochondria whose respiratory chain is "uncoupled". The brown adipose tissue initially described in newborns is also found to a lesser extent in adults. Experimental studies showed that the activity of brown adipose tissue decreases significantly with increasing body weight.

There are numerous factors that favour obesity (Fig. 1.3); taken together, they lead to a disturbance of the energy balance. They are briefly outlined below.

1.3.1 Food and Eating Habits

Since the industrial revolution, food composition and eating habits have changed significantly. While a long-lasting reduced food intake leads to a reduction of the resting energy expenditure, an increased food intake ("calorie intoxication") does not lead to an increase of the energy expenditure; this imbalance reflects a bias of the energy balance.

Today, food can be purchased permanently and for a cheap price. In addition, it has also become increasingly energy dense. The increase in calorie intake is exemplified by data from the National Health and Nutrition Examination Survey (NHANES) II (1976–1980) and NHANES III (1988–1991) in the USA. During the period 1976–1991, men increased their energy intake by about 5%, women by an average of 15%. In this respect the energy intake of women has converged to that of men. Other countries showed comparable increases in calorie intake (Fig. 1.4).

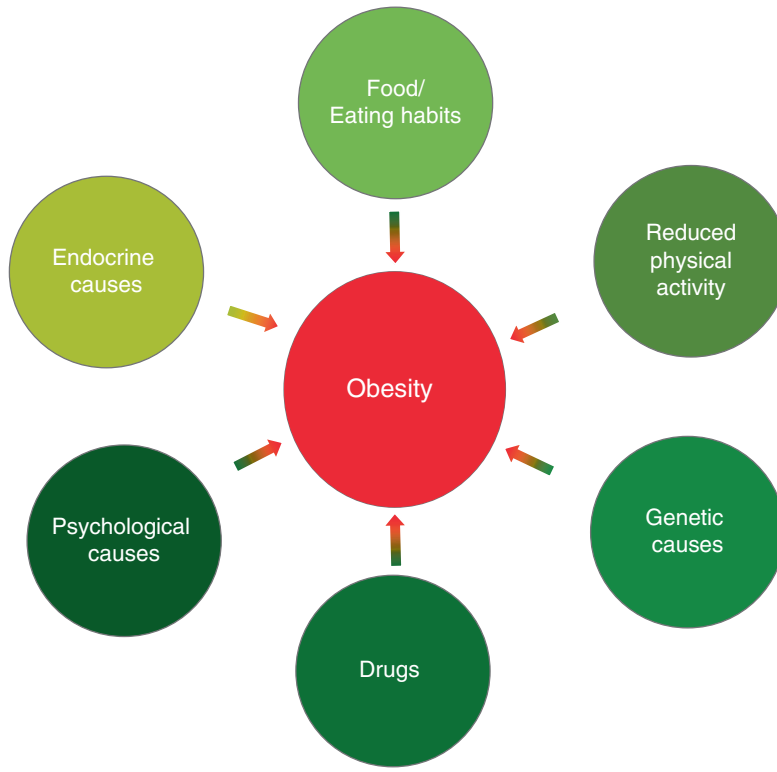


Fig. 1.3 Compilation of factors favouring obesity

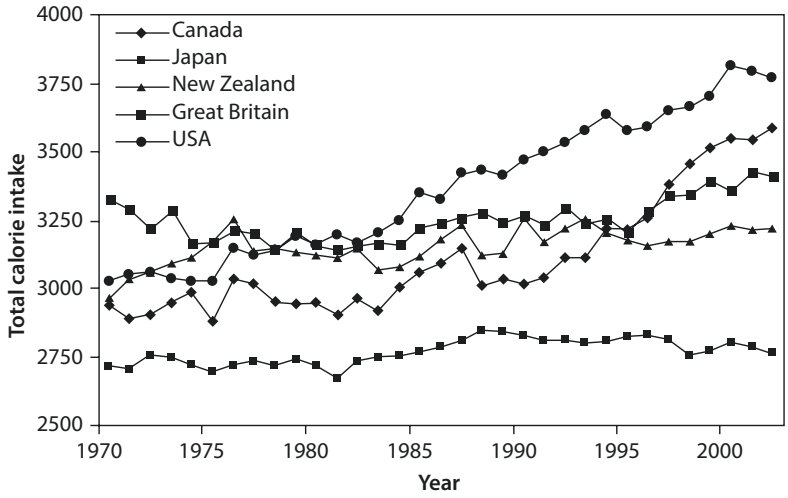


Fig. 1.4 Increase in daily calorie intake in different countries. (Adapted from Duffey and Popkin 2011)

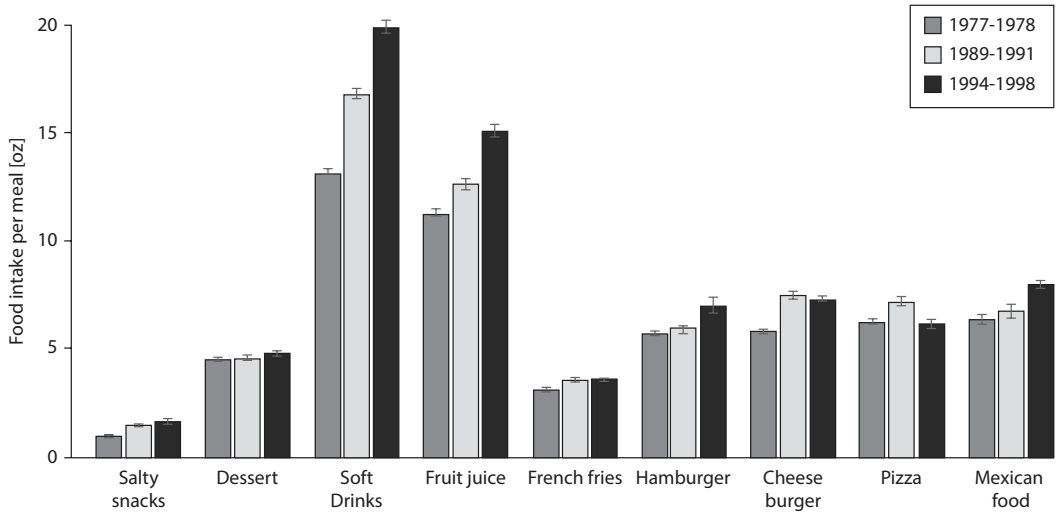


Fig. 1.5 Increase in portion sizes from 1977–1998. (Adapted from Nielsen and Popkin 2003)

An increase in the number of daily meals and portion sizes between the time periods 1977–1978 and 2003–2006 led to an increase in total daily energy intake of 570 kcal. This increase is mainly due to sugar consumption in the form of soft drinks and fruit juices (Fig. 1.5). In addition, traditional nutritional patterns are increasingly being abandoned and replaced by more frequent meals outside the home and the increased consumption of convenience foods with high energy density.

1.3.2 Lack of Physical Activity

In addition to the changes in dietary habits described above, the energy expenditure due to physical activity is dramatically declining. As an example of the traditional lifestyle, the exercise behaviour of the Amish religious community in the USA (Amish People) was investigated. There, women had an average daily number of 15,000 steps, men averaged 21,000 steps per day. In a population-based study of

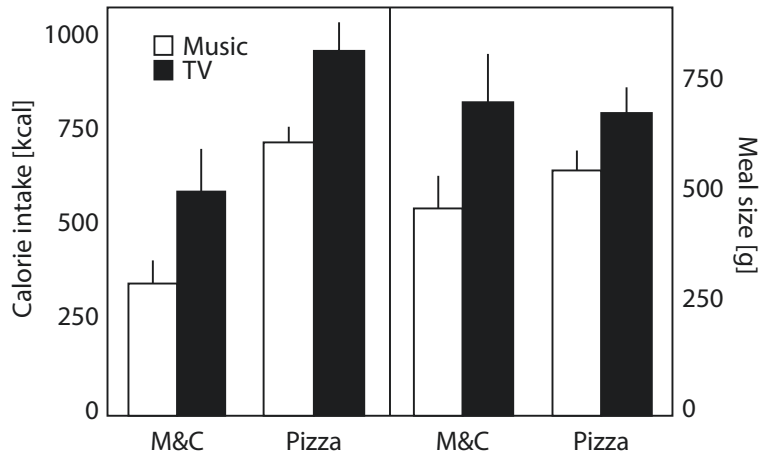


Fig. 1.6 Television consumption is accompanied by an increase in calorie intake. (Adapted from Blass et al. 2006)

physical activity in Colorado—representative of the Western lifestyle—the average number of steps per day was 6600 for women and just over 7000 for men. Thus, the number of steps has fallen to about a third under modern living conditions. This reduction corresponds to a daily deficit of about 500 kcal of energy expenditure. Furthermore, the population-based study by Wyatt et al. (2005) showed a highly significant correlation between weight category and daily step number. The number of steps per day in normal-weight persons (7259) decreased continuously with increasing weight category; it was 6704 for overweight persons and 4866 for obese persons.

Furthermore, the decrease in energy expenditure is caused by changing working conditions—a decrease in hard physical work due to mechanisation and an increase in office work—as well as changes in leisure time behaviour in the form of TV and computer consumption. Figure 1.6 illustrates that changed media behaviour leads not only to a decrease in physical activity but even to an increase in energy intake.

1.3.3 Genetic Causes

For the genetic predisposition of obesity development, various genetic variants have been identified in genome-wide association studies (e.g. in the FTO gene). However, these individual variants in themselves explain only small increases in weight, so that a polygenic predisposition can be assumed. So far, genetic testing has not been of high clinical relevance.

The monogenetic forms of obesity with mutations mainly in the leptin-melanocortin signalling pathway must be distinguished from the genetic predisposition described above. These forms of obesity are a rarity and occur in childhood. A more detailed description is given in ▶ Sect. 5.2. Furthermore, syndromic forms of obesity which also manifest in childhood and are associated with physical stigmas, endocrine disorders and sometimes mental retardation (e.g. Prader-Willi syndrome) must also be taken into account. In these cases, genetic testing is indicated and can be a relief for the affected persons and their families.

1.3.4 Psychological Causes

Psychosocial factors reinforce the development of obesity favoured by current dietary and exercise habits and should be adequately considered both in diagnosis and therapy.

A change in family structures and occupational demands—work intensification on the one hand and the burden of unemployment on the other—lead to an increased stress perception and social isolation with psychological effects that can further intensify the changes in food intake and eating behaviour described

above. Self-stigmatisation of obesity as well as stigmatisation by the social environment represent a further burden. A detailed description of obesity-related mental stressors and mental illness is given in ▶ Sect. 1.5.

1.3.5 Endocrine Causes

The effect of (sub-) clinical hypothyroidism on weight development is usually overestimated. The distinction between hypercortisolism (Cushing's syndrome) and common obesity is often difficult even for an experienced clinician. Although hypercortisolism is also rare in obese people, the individual benefit of early detection is high, so that testing for hypercortisolism should be performed at low-threshold. More on this in ▶ Sect. 5.2.

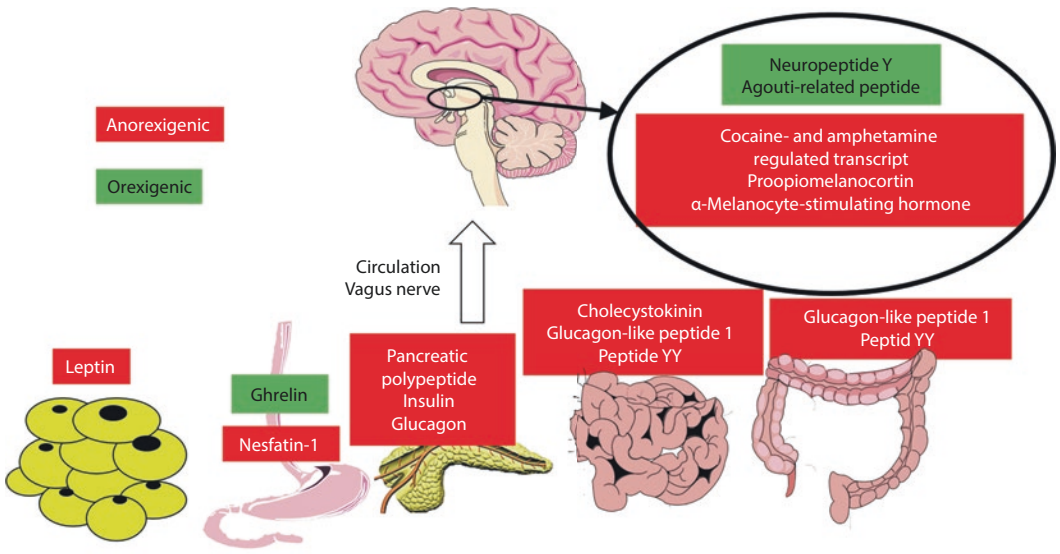
1.3.6 Drugs Promoting Weight Gain

Numerous drug classes promote weight gain. In particular, tricyclic antidepressants stimulate appetite and hunger and can therefore lead to considerable weight gain. Other weight gain promoting drugs are neuroleptics, glucocorticoids, insulins, sulfonylureas and thiazolidinediones.

1.4 Regulation of Hunger and Satiety in Obesity

A. Stengel

Contrary to the earlier assumption of a primary regulation of hunger and satiety at a central level in the brain, the current state of knowledge points primarily to a peripheral production of food-regulatory messenger substances. The main sources of these hormones are specialized cells in the gastrointestinal tract. The hormones act via the so-called gut-brain axis (◘ Fig. 1.7) to signal hunger or satiety in the brain and to keep body weight constant in a physiological way. In the following, these regulatory mechanisms, the pathophysiological changes of these systems in obesity as well as psychological factors are described in more detail.



◘ **Fig. 1.7** Hormones, which are involved in the regulation of food intake via the gut-brain axis

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1.4.1 Definition of Hunger and Satiety

The German language primarily distinguishes hunger (a sensation localised in the stomach area which causes the need for food intake; this can be further distinguished from appetite, which causes the same desire but can arise in the absence of hunger) from satiety (absence/disappearance of the need for food intake). The English language allows for a more complex understanding of satiety: on the one hand "satiation" (leads to the termination of a meal), on the other hand "satiety" (leads to a subsequent delay between meals). Both together contribute to the termination of the meal and prevent the next meal from being started immediately. In order to make these quantities measurable, the determination of the microstructure of food intake—i.e., meal size, duration, eating speed, interval between meals—is state of the art in animal research as well as in studies on humans.

1.4.2 Peripheral Mediators of Hunger and Satiety Regulation

During the gastrointestinal passage ingested food comes into contact with the gastric mucosa for a longer period of time. Specialised endocrine cells are located in the gastric mucosa, which secrete food-regulating peptides. Such cells (here called enteroendocrine cells) are also found further distal in the intestinal tract. Their hormonal release is induced by nervous stimuli, which in turn are triggered by stretch receptors that react to changes of volume and pressure in the stomach and intestine. Gut chemosensors also play a role: they detect food components and also cause neuronal activation. Recently, bile acids have also been attributed a function in the regulation of food intake; corresponding receptors have recently been identified in the enteric nervous system. In the following, the enteroendocrine cells and their peptide products will be described.

Ghrelin

Ghrelin was discovered in the stomach in 1999 and is the only known peripherally produced and centrally acting hormone that stimulates food intake. Ghrelin is produced in the X/A-like cell (called P/D1 cell in humans). The main source of production seems to be the stomach, as circulating ghrelin levels in patients after gastrectomy fall by 65%. The hormone carries a unique modification in the form of a fatty acid (acyl group) at the third amino acid. This modification is essential for binding to the ghrelin receptor. Recently, the enzyme that catalyses this acylation was identified and named ghrelin-*O*-acyltransferase (GOAT). Since GOAT is the only enzyme that controls this change, it could be a target molecule for the drug treatment of obesity.

Ghrelin was recognized early on as a food-regulating peptide that has a food-stimulating (orexigenic) function. The meal-dependent regulation supports the assumption that ghrelin is a physiological regulator of food intake. Circulating ghrelin levels rise before food intake and fall again after food intake. Interestingly, the presentation of images with food (during the cephalic phase) also leads to a change in ghrelin levels. Besides these directly food-associated changes, fasting leads to an increase in both the production and release of ghrelin. The ghrelin-activating enzyme GOAT also increases under fasting conditions both in the stomach and in the blood. This could contribute to an increased acylation/activation of ghrelin with the aim of stimulating food intake.

In addition to these short- and medium-term influences on ghrelin, long-term changes in body weight also lead to adaptive changes in ghrelin levels. While ghrelin circulates in higher levels under conditions of cachexia/anorexia, obese people show low ghrelin concentrations in the blood. This could be an attempt by the body to adapt in order to counteract further weight loss in the case of underweight or a further increase in body weight in the case of obesity. However, it should be noted that the postprandial decline of ghrelin in obesity is also attenuated. This could

contribute to a reduced feeling of satiety after food intake and thus play a pathophysiological role in the maintenance of obesity.

Nesfatin-1

Interestingly, another hormone has recently been described in the ghrelin-producing cells of the stomach. Nesfatin-1 was initially identified in the rat brain as an inhibitor of food intake (anorexigenic), but was detected shortly thereafter in significantly higher concentrations in the stomach. Here the peptide was localized in the same endocrine X/A-like cells as ghrelin, but in different vesicle populations. This co-localisation led to the concept of a differential regulation of food intake by this specific endocrine cell in the stomach: While food intake is stimulated by the release of ghrelin, it can be inhibited by the release of nesfatin-1. Like ghrelin, nesfatin-1 is also regulated by food intake. A fasting period of 24 h led to a decrease in circulating levels of nucleobindin-2 (NUCB2, the precursor protein of nesfatin-1) and nesfatin-1 in rats—an effect that could be reversed by feeding the animals. A change in nesfatin-1 levels was also observed under long-term changes in body weight: While anorexic patients showed lower levels, obese patients showed higher circulating NUCB2/nesfatin-1 concentrations. This change is opposite to that of ghrelin, which further supports the hypothesis that these two peptides differentially influence food intake. However, it has to be clarified to what extent nesfatin-1, as described in the animal model, also inhibits food intake in humans and thus represents a potential target molecule in pharmacological obesity therapy.

Cholecystokinin

Cholecystokinin (CCK) is produced in the enteroendocrine I-cells of the duodenum and jejunum and is released postprandially. CCK mediates a variety of digestive functions: the contraction of the gallbladder (which gave the hormone its name), the stimulation of exocrine pancreatic secretion, the increase in gastric accommodation and the reduction of food intake. These effects are mediated by two receptors—CCK1 and CCK2—with the peripheral reduction of food intake apparently being primarily induced by CCK1. CCK2 is primarily expressed in the brain, where it is involved in mediating the anorexigenic effect of CCK. The release of CCK is attenuated in obese people, which could lead to a reduced reduction in food intake. In addition to these short-term changes in food intake, CCK also appears to be involved in the regulation of body weight. For example, CCK knockout animals show a reduced body weight (despite unchanged food intake) due to impaired fat absorption in the intestine and increased energy expenditure. These changes led to a resistance to the development of diet-induced obesity and make CCK an interesting substance for pharmacologically influencing/treating obesity.

Pancreatic Polypeptide

Pancreatic polypeptide is released from pancreatic PP cells located within the endocrine islets of Langerhans. This hormone is released after meals, with an increase in circulating levels lasting several hours. In addition to this short-term regulation by food intake, the circulating levels of pancreatic polypeptide are also determined by body weight: While anorexic patients showed significantly increased levels, these were reduced in obese patients. Since pancreatic polypeptide reduces food intake, the changes described above could cause the pathologically altered body weight to be maintained or increased.

Peptide YY

Peptide YY (PYY) is produced by the endocrine L-cells of the distal intestinal tract (decrease from the rectum to the jejunum) and is secreted after a meal. $PYY_{1–36}$ represents the biologically active form, which is activated by dipeptidyl peptidase 4 by cleavage and binds to Y_1 and Y_2 receptors. An anorexigenic role of PYY in the regulation of food intake was postulated—an effect that was also observed in obese patients. However, it should be noted that several follow-up studies could not confirm this effect, so that the role of PYY in the regulation of food intake is considered uncertain or should at least be viewed critically. The body weight-dependent regulation of PYY has also not yet been clarified conclusively.

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Glucagon-Like Peptide 1

Glucagon-like peptide 1 (GLP-1) is also produced in the enteroendocrine L-cells of the small intestine and is released postprandially. Interestingly, the expectation of a meal also leads to an increase in circulating GLP-1 levels, so that stimulation of the release already in the cephalic phase is obvious. GLP-1 also led to a reduction in food intake, an effect that was also observed in obese patients. In addition, repetitive subcutaneous injections of GLP-1 resulted in a decrease in body weight in obese patients. In addition to its anorexigenic property, GLP-1 leads to an inhibition of glucagon secretion and stimulates insulin secretion (so-called incretin effect). Incretin-based therapies already play a major role in diabetes therapy and are now also approved for the medical therapy (see also ▶ Sect. 2.3).

Leptin

For a long time, adipose tissue was considered to be solely a storage place for energy. According to current knowledge, this tissue is also endocrine active and produces adipokines. The most prominent representative of this group is leptin, which is produced in adipose tissue in dependence of fat mass. Circulating leptin levels also increase with increasing body weight. Leptin leads mainly to a negative energy balance by reducing food intake and by increasing energy expenditure. In addition, leptin is involved in the long-term regulation of body weight. Despite the pronounced effects of leptin administration on body weight regulation in children with congenital leptin deficiency, the effects of such leptin administration in common obesity are small due to the already high leptin levels and the resulting reduced leptin sensitivity. Therefore, leptin does not appear to be a suitable target molecule for the drug treatment of common obesity.

Hormones, which are primarily involved in the regulation of glucose metabolism, also influence food intake and are described below.

Insulin

In addition to the well-described effect on glucose metabolism (leading to a reduction in blood glucose levels via various mechanisms), insulin produced in the beta cells of the endocrine pancreas is also involved in the regulation of food intake and energy balance. The circulating insulin levels correlate—similar to leptin—with the body mass index. In the animal model, the central application of insulin acutely led to a reduction in food intake and, with repetitive administration, also to a reduced increase in body weight. Since insulin can cross the blood-brain barrier, such a regulation is also conceivable under physiological conditions. Whether insulin also plays a significant role in the regulation of hunger and satiety as well as in the regulation of body weight in humans needs further investigation.

Glucagon

Glucagon is produced in the alpha cells of the islets of Langerhans of the endocrine pancreas and, like GLP-1 described above, is a member of the glucagon family. In addition to its well characterized effect on glucose homeostasis (elevation of blood glucose levels in hypoglycemia), glucagon also plays a role in the regulation of food intake. A reduction of food intake by peripheral administration of glucagon has been reported early on, an effect that is likely to be transmitted via the vagus nerve and may be associated with a reduction in gastric emptying. Inhibition of the orexigenic hormone ghrelin may also play a role in mediating the inhibition of food intake by glucagon. In addition, glucagon stimulates thermogenesis and thus leads to an increase in energy expenditure, which could contribute to the observed reduction in body weight in humans after repeated administration of glucagon. Interestingly, glucagon also stimulates the activity of brown adipose tissue in animal models. It has to be clarified whether this signalling pathway is also relevant for the glucagon-induced increase in energy expenditure in humans. In the context of these effects

a therapeutic impact of glucagon is discussed, especially in combination with GLP-1 as a dual or co-agonist.

1.4.3 Signalling from the Periphery to the Brain

Various peptide hormones act directly on the brain, in particular on hypothalamic structures. They are often transported across the blood-brain barrier or in the area of the circumventricular organs which is characterized by a lack of the blood-brain barrier. Furthermore, signals are transmitted via the vagus nerve. The vagus nerve has numerous receptors for peptide hormones and transmits the neuronal signal to higher regulatory centres, particularly in the hypothalamus, via the brain stem.

1.4.4 Central Nervous Signal Integration

Specific regions in the brain integrate the signals coming from the periphery and mediate weight-increasing (orexigenic) or weight-reducing (anorexigenic) effects. The most important of these are the nucleus tractus solitarius in the brain stem and various nuclei in the hypothalamus, especially the nucleus arcuatus (in humans called nucleus infundibularis, but in literature often referred to as nucleus arcuatus) and the nucleus paraventricularis. In the nucleus arcuatus two populations of neurons can be distinguished: One contains neuropeptide Y and agouti-related peptide, two strongly orexigenic signals, and the other co-expresses cocaine and amphetamine regulated transcript (CART) and proopiomelanocortin, both of which have anorexic effects. Proopiomelanocortin is also a precursor protein for other biologically active peptides, including α melanocyte-stimulating hormone, which itself also has anorexic effects. These signals are transferred via projections from the nucleus arcuatus to other nuclei, in particular the nucleus paraventricularis. Next to pharmacological interventions on these central signalling pathways other interventions such as deep brain stimulation represent promising strategies for obesity therapy.

1.4.5 Psychological Constructs

The regulatory mechanisms mentioned above are classically attributed to the homeostatic control of hunger and satiety. This has long been contrasted with the so-called hedonic control of hunger and satiety, which is influenced by reward system, desire and palatability of food. Today, these different systems are perceived less isolated and there is increasing evidence for the involvement of the peptide outlined above in both systems. Various psychological constructs of eating behaviour have been developed considering these influencing factors. These include:

- the food responsiveness (interest in food),
- the liking of food (enjoyment),
- the satiation response (e.g. leaving food on the plate),
- eating in the absence of hunger,
- the relative reinforcing value of food (this describes the effort to gain access to food opposed to the effort to achieve other rewards, such as reading a book)
- the disinhibition of eating (e.g. increased eating in social situations) and
- impulsiveness and self-control.

It is important to note that these constructs overlap and cannot be viewed independently of each other. They can be studied under specialised study conditions and with the help of questionnaires and allow a better characterisation of eating behaviour under various metabolic conditions.

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Conclusion

A large number of hormones is involved in the regulation of hunger and satiety. Most of them come from the gastrointestinal tract and act via the gut-brain axis on the brain stem and hypothalamus to signal hunger or satiety. Interestingly, so far only one peripherally produced and centrally acting hormone is known to stimulate food intake: ghrelin. In contrast, there are several anorexigenic hormones (Fig. 1.7). Despite increasing knowledge of the regulatory mechanisms of food intake, pharmacological modulation of high-grade obesity has so far been insufficient.

1.5 Secondary Diseases of Obesity

U. Elbelt

The health-related consequences of obesity are numerous. In addition to joint and pulmonary diseases, the unfavourable influence of cardiovascular risk factors such as diabetes mellitus type 2, arterial hypertension and dyslipidaemia are of decisive importance. Furthermore, the risk of developing carcinomas is also increased in the presence of obesity. The life expectancy of obese people is shortened. In 40-year-old obese people, for example, it is reduced by about 7 years. The increased mortality is mostly due to cardiovascular diseases and a higher prevalence of malignancies.

1.5.1 Metabolic Syndrome

For the extent of secondary diseases of obesity, not only the fat mass, but above all the distribution of fat tissue plays a decisive role. In comparison to subcutaneous fat deposits, for example in the buttock and thigh area, the abdominal (or visceral) fat distribution is an essential factor in the development of insulin resistance. Insulin resistance is defined as an impaired response of the body to insulin that leads to reduced glucose uptake in the muscles and reduced hepatic glycogen synthesis. The resulting increased glucose supply to the liver maintains these pathophysiological changes by increasing hepatic de novo lipogenesis. The joint occurrence of cardiovascular risk factors such as impaired glucose tolerance or diabetes mellitus type 2, dyslipidemia (with reduced HDL cholesterol and increased triglycerides) and arterial hypertension with abdominal obesity as a result of insulin resistance is called metabolic syndrome.

However, the metabolic syndrome has not yet been uniformly defined. At a consensus conference of the International Diabetes Federation (IDF), a standardization of these definitions was carried out (Table 1.2). In

Table 1.2 Diagnostic criteria of the metabolic syndrome according to the consensus conference of the International Diabetes Federation (IDF)

Criteria	Values
Presence of central (abdominal or visceral) **obesity** and at least two more of the following criteria	Abdominal girth[a] of European men ≥94 cm, of European women ≥80 cm
Triglycerides	>150 mg/dl (1.7 mmol/L) or specific triglyceride-lowering medication
HDL cholesterol	<40 mg/dl (1.03 mmol/L) for men, <50 mg/dl (1.29 mmol/L) for women or specific HDL-raising medication
High blood pressure	Systolic ≥130 mmHg and/or diastolic ≥85 mmHg or specific antihypertensive medication
Fasting plasma glucose	≥100 mg/dl (5.6 mmol/L) or diagnosed diabetes mellitus type 2

[a]With specific reference values of abdominal girth according to ethnicity, whereby from a BMI > 30 kg/m^2 onwards, the presence of abdominal obesity is to be assumed:
- for Arab and African men/women: ≥94 cm/80 cm
- for Asian and Chinese men/women: ≥90 cm/80 cm
- for South and Central American men/women: ≥90 cm/80 cm
- for Japanese men/women: ≥85 cm/90 cm

doing so, different risks for the development of cardiovascular secondary diseases, which are largely determined by ethnic origin, were taken into account.

Other components of the metabolic syndrome are hyperuricemia, impaired fibrinolysis and in women hyperandrogenemia. Patients with a metabolic syndrome must be considered as high-risk cardiovascular patients. Medical treatment of patients with a metabolic syndrome should particularly address dyslipidemia, arterial hypertension and diabetes mellitus type 2.

Practical Tip

The presence of a metabolic syndrome should be documented in order to classify the patient as a cardiovascular high-risk patient.

1.5.2 Diabetes Mellitus Type 2

Numerous epidemiological studies describe abdominal obesity as an important risk factor for the manifestation of type 2 diabetes mellitus. An example is the Nurses' Health Study: This study showed a 6.2-fold increase in the relative risk for the manifestation of diabetes mellitus type 2 with an abdominal girth of >96.4 cm compared to an abdominal girth of <71 cm within 8 years (Carey et al. 1997). Conversely, a moderate weight reduction—in the case of proven insulin resistance, possibly in combination with the intake of metformin in off-label use—can reduce the risk of diabetes manifestation (Knowler et al. 2002; Tuomilehto et al. 2001). Of importance for this interrelation is the secretion of proinflammatory adipokines by the visceral fatty tissue, which leads to an increase in insulin resistance as a major pathogenetic factor of diabetes mellitus type 2.

Table 1.3 shows the diagnostic criteria for diabetes mellitus type 2.

This interrelation does not apply to autoimmune diabetes mellitus type 1 and pancreoprive diabetes mellitus type 3.

Table 1.3 Diagnostic criteria for diabetes mellitus type 2

HbA_{1c} [a]	≥6.5% or ≥48 mmol/L
Random plasma glucose value	≥200 mg/dl (≥11.1 mmol/L)
Fasting plasma glucose value	≥126 mg/dl (≥7.0 mmol/L)
2-h plasma glucose value in an oral glucose tolerance test with 75 g	≥200 mg/dl (≥11.1 mmol/L)

[a]Diseases that lead to a falsification of the HbA_{1c} value have to be taken into account, in particular those with an altered red blood cell lifespan (anaemia, liver and kidney diseases)

1.5.3 Arterial Hypertension

Arterial hypertension is the most common concomitant disease of obesity (Table 1.4). Its prevalence increases up to five times in obese people. Key factors are the increased secretion of angiotensinogen from adipocytes, which is accompanied by activation of the renin-angiotensin-aldosterone system, and an increased tone of the sympathetic nervous system. Again, weight loss leads to a reduction of systolic and diastolic blood pressure.

Practical Tip

Attention has to be paid to the use of sufficiently large cuffs for blood pressure measurement in obese patients, as otherwise incorrectly high blood pressure values will be measured.

1.5.4 Dyslipidemia

There is a well-documented correlation between obesity and altered lipid patterns. The increase in triglycerides with simultaneously decreased HDL-cholesterol is called dyslipidemia. The level of LDL cholesterol is less affected by the extent of obesity, but the composition of LDL cholesterol is altered in

Table 1.4 Graduation of arterial hypertension

Blood pressure (mmHg)	High normal	Hypertension grade 1	Hypertension grade 2	hypertension grade 3
Systolic blood pressure	130–139	140–159	160–179	≥180
or				
Diastolic blood pressure	85–89	90–99	100–109	≥110

obesity. This leads to an increase in the highly artherogenic small-dense LDL particles.

1.5.5 Cardiovascular Complications

Obesity is now considered an independent risk factor for heart attack, (diastolic) heart failure (also known as obesity cardiomyopathy) and sudden cardiac death. The risk of cerebrovascular events also increases (probably mainly mediated by concomitant arterial hypertension).

Obesity also leads to disorders of clotting and fibrinolysis. The release of fibrinogen and plasminogen activator-inhibitor-1 (PAI-1) is increased in obesity, resulting in hypercoagulability with increased risk of thrombosis.

1.5.6 Liver Disease

Visceral obesity is considered to be a significant factor for the development of non-alcoholic fatty liver disease. The fatty degeneration of the liver (steatosis hepatis) can progress via inflammatory non-alcoholic steatohepatitis ("non-alcoholic steatohepatits", NASH) to liver cirrhosis and promote the development of hepatocellular carcinoma. Here, too, insulin resistance is regarded as a central pathogenetic factor, so that the liver changes must be regarded as a hepatic manifestation of the metabolic syndrome. The increase of γ-glutamyl-transferase (γ-GT) and alanine-aminotransferase (ALT) as well as—less pronounced—of aspartate-aminotransferase (AST) and alkaline phosphatase (AP) may indicate NASH at an early stage.

1.5.7 Obesity and Sleep-Related Breathing Disorders

Obesity increases the risk of developing a mostly obstructive (but also central or mixed) sleep apnea syndrome (OSA). A neck circumference of more than 43 cm in men or 40.5 cm in women is associated with a significantly increased frequency of nocturnal apneas. Men are four times more frequently affected than women. The leading clinical sign is increased daytime fatigue. Another manifestation is obesity hypoventilation syndrome (OHS), formerly known as "Pickwick's syndrome". It is defined as alveolar hypoventilation with hypercapnia (arterial $pCO_2 \geq 45$ mmHg), mainly during sleep but also in the waking state, with a BMI ≥ 30 kg/m^2, excluding other causes leading to hypoventilation. It often occurs together with obstructive sleep apnea syndrome. The prevalence correlates with the degree of obesity and is given as 3.7/1000 persons for the USA. OHS is considered underdiagnosed, the diagnosis is often made late in the course of acute respiratory insufficiency. Patients predominantly require night-time CPAP ("continuous positive airway pressure") ventilation.

Practical Tip

Obesity and sleep-related breathing disorders are often insufficiently diagnosed. Symptoms should be explicitly asked for in the anamnesis interview. The use of questionnaires can be helpful. Attentive preoperative diagnostics should be carried out to improve the patient's operability by initiating ventilation therapy.

1.5.8 Diseases of the Musculoskeletal System

A common problem is degenerative joint disease, which occurs more frequently and also earlier in obesity. In particular, gonarthrosis and coxarthrosis form an obstacle to the desired increase of physical activity for the treatment of obesity. Furthermore, dorsopathies occur also more frequently. The activation of inflammatory signalling pathways may promote synovial damage.

1.5.9 Malignant Diseases

The carcinoma risk of obese people is increased. For every 5 kg/m^2 increase in BMI, the risk of developing a malignant disease increases by 12–51%, depending on the tumour entity. There is convincing evidence for the more frequent occurrence of colorectal carcinomas, renal cell carcinomas, adenocarcinomas of the esophagus and cardia, and pancreatic carcinomas. The increase in relative risk per 5 kg/m^2 higher BMI is stated to be 18% for colorectal carcinomas; mainly due to the increased risk in men. The extent of insulin resistance also seems to play an additional role. Hyperinsulinemia enhances mitogenic processes by influencing natural cell death (apoptosis) and cell proliferation, probably by binding to the receptor for "insulin-like growth factor 1" (IGF-1R). However, an increase of unbound IGF-1 in serum and tissue as well as effects mediated by elevated leptin levels and inflammation are also described. The reduced secretion of adiponectin with antiproliferative and anti-angiogenic effects in obese patients seems to be of additional importance for the development of malignancies. The increased rate of adenocarcinoma of the oesophagus is thought to be caused by the increased incidence of gastroesophageal reflux in obese patients. An increased incidence of hepatocellular carcinomas due to NASH and of prostate carcinomas is also reported. Women have a higher risk of developing carcinomas of the gallbladder and bile ducts as well as oestrogen-dependent tumours such as breast, endometrial, cervical and ovarian carcinomas. For postmenopausal breast carcinoma, an increase of 12% in the relative risk per 5 kg/m^2 higher BMI is stated. The cause seems to be the increased conversion of androgens to oestrogen through increased aromatase activity in visceral fatty tissue. A reduced risk of breast cancer is reported for obese women before menopause. The association of obesity and endometrial carcinoma is more pronounced. Here, a relative risk increase of 50% per 5 kg/m^2 higher BMI is stated. The relative risk of renal cell carcinoma is reported to increase by 24% for men and 34% for women per 5 kg/m^2. So far, there are hardly any reliable findings on the underlying mechanisms for the development of renal cell carcinomas.

1.5.10 Other Obesity-Related Diseases

The occurrence of gastroesophageal reflux disease is also associated with obesity. The increased intra-abdominal pressure in obesity is discussed as causative. Obese people show an increased biliary cholesterol secretion, which significantly promotes the development of chole(cysto)lithiasis—depending on the extent of obesity (for obesity grade I approx. threefold risk, for obesity grade III approx. sevenfold risk)—and increases the incidence of cholesterol stones. Pronounced conservative weight loss or weight reduction achieved by bariatric surgery further increases the risk of gallstone formation. In addition, obese people have an increased risk of developing diverticulitis.

Polycystic ovary syndrome (PCOS) is a common endocrinological disease of premenopausal women and a cause of unfulfilled wish to have a child. It is defined by the occurrence of at least two of the following criteria:

- hyperandrogenism (clinical and/or biochemical),
- menstrual disorder (oligo- or anovulation) and
- polycystic ovaries (ultrasonography).

Other causes have to be excluded before the diagnosis is made. Insulin resistance is also a decisive pathogenetic factor for PCOS. The diagnosis of PCOS enables the early identification of patients at high risk of developing a metabolic syndrome. Therapy with metformin in off-label use—combined with a change in diet and increased physical activity—can lead to an attenuation of the clinical manifestations.

In obese women, the risk of gestational diabetes is increased during pregnancy, and there is also a higher rate of complications during childbirth, making caesarean section more often necessary. The newborns of obese mothers have an increased risk of neural tube defects and macrosomia.

In case of pronounced cephalgia, the presence of a pseudotumour cerebri (idiopathic intracranial hypertension) should also be considered and appropriate diagnostic procedures should be initiated. In particular, obese women are affected, and a dreaded complication is the loss of vision caused by papilledema.

1.6 Psychosocial Aspects of Obesity

T. Hofmann

Obesity is higher-than-average associated with mental disorders. In this context, it was often assumed in the past that obesity was caused by mental disorders. Currently, however, the prevailing view is that massive overweight on the one hand and psychological problems on the other hand are interrelated both bi-directionally and multi-causally.

However, the prevalence rates of mental disorders in obese populations with no desire for treatment are not, or only slightly, higher than those of the general population. This changes in populations with a desire for treatment. Here, the more invasive the intended intervention is (nutrition/exercise, medication, surgery), the more pronounced the psychopathology appears to be. In preoperative cohorts the prevalence is higher than in obese patients with a wish of conservative treatment, which illustrates both the considerable psychological comorbidity and the increased suffering of patients seeking bariatric surgery. In up to 73% of all preoperative obesity patients at least one mental illness can be identified in their preoperative life span, and up to 56% of all obesity patients suffer from at least one mental illness at the time of preoperative evaluation. More pronounced psychopathology is often associated with female gender, higher BMI and especially lower socioeconomic status.

In comparison to the data given above, 38% of the German general population reported having suffered from a mental disorder in their lifetime; among obese people who had no intention of undergoing weight loss treatment, the figure was 48%.

Reasons for the higher prevalence of mental disorders in cohorts with a desire for surgical treatment are therefore probably primarily due to patient selection. Due to the indication criteria for surgical intervention, these patients have a higher BMI and—as a result—a higher risk of somatic comorbidities and a higher rate of mental disorders. Furthermore, the proportion of patients who hope that a surgical procedure will provide them with a kind of "quick fix", a quick solution to their entire life situation and thus also to their psychological burden, should not be underestimated.

1.6.1 Stigmatisation of Obese People

Stigma refers to characteristics or attributes of persons that are associated with negative evaluations and discredit the person concerned. Stigmatising attitudes towards obese people due to their body weight are widespread in our society. By attributing them as voracious, lazy, weak-willed or undisciplined, obese people are held individually responsible for their weight. Moreover, overweight is devalued in the context of the culturally hegemonic ideal of slimness. Obese people are therefore often affected by disparaging to aggressive statements in everyday life, in the media, and also

in their personal relationships. In addition, they often face disadvantages in educational institutions, in professional life and last but not least in the health care system. The stigmatisation seems to increase to the extent that it is assumed that the overweight is due to individual misconduct.

The effects of everyday stigmatisation are manifested for those affected in the psychological sphere by a negative body image, a lower self-esteem, and increasing social isolation. The latter being associated with an increased risk of depression, anxiety disorders and even suicidal thoughts. In addition, stigmatisation favours hunger pangs and even the occurrence of binge-eating disorders. All these interrelations seem to be even more pronounced for children, especially for girls. Furthermore, there are first indications that stigmatisation due to body weight could also be associated with physiological parameters such as elevated blood pressure and poor blood sugar control.

1.6.2 Quality of Life

Health-related quality of life, as part of the overall quality of life, plays a role in assessing the impairment of patients as the immediate life threat of a disease decreases and chronicity increases. Against this background, health-related quality of life is of great importance in assessing the need for treatment and in the choice of treatment methods for obesity. Health-related quality of life is generally worse in obese people than in the general population. Patients who undergo bariatric surgery are reported to have an even worse health-related quality of life than BMI-matched patients who do not wish to undergo surgery. This is probably not insignificant for the desire for surgery, since an operative procedure is often associated with a rapid and marked improvement in general well-being. Obese women seem to be more affected by limited health-related quality of life than obese men.

1.6.3 Stress

Stress is generally understood to be the physiological and psychological reactions of an organism to challenging environmental conditions (stressors). While stress can lead to reduced body weight, for example in the context of depression, a connection between chronic stress and obesity has been repeatedly postulated. In this context, psychosocial stress has mostly been understood as a consequence of stigmatisation or disadvantages in everyday life. In fact, especially for higher levels of obesity, there are links between the perception of stress and increased body weight.

The so-called "modern lifestyle" with increasingly less physical activity and better availability of high-calorie and energy-dense food (so-called "comfort food") is primarily blamed for the continued rise in the prevalence of, in particular, high-grade obesity. In this context, the increased stress levels in industrialised countries, for example due to higher work density or the overall increasing demands on the individual when reliable social structures dissolve, are less frequently taken into account as another aspect of modern lifestyle. However, there are now plausible psychobiological concepts that conceive the development of obesity also as an adaptation of the organism to chronic psychosocial stress. Thus, in addition to the hypothalamus-pituitary-adrenal cortex axis, cerebral glucose and insulin metabolism as well as other endocrine signals such as ghrelin could play a decisive role.

1.6.4 Depression

Depression is characterized by depressed mood and a reduction in drive and activity. In addition, the ability to feel enjoyment, interest and concentration are reduced. Depression is an independent risk factor for several somatic diseases, and this relationship is well documented, especially for coronary heart disease and diabetes mellitus.

The link between obesity and depression has been repeatedly confirmed. However, it seems to be minimal or even non-existent in cohorts without a desire for treatment. This changes in patients with a desire for treatment. According to a meta-analysis of longitudinal studies, obese people, for example, have a 55% higher risk of developing depression than healthy people; conversely, the probability of developing obesity is 58% higher in people suffering from depression.

Practical Tip

The preoperative diagnosis of depression seems to be associated with less weight loss after bariatric surgery. On the other hand, the depressive symptoms seem to be significantly reduced in the majority of patients after surgery, although in some cases this success may weaken over the following years.

1.6.5 Anxiety Disorders

Anxiety disorders include

1. the generalised anxiety disorder with persistent, quasi "free-floating" fears that are not limited to certain environmental conditions,
2. panic disorder with recurrent severe anxiety attacks that are not limited to a specific situation or circumstances, and
3. phobias, where the fears are caused by clearly defined, actually harmless situations. A frequent phobic disorder, even in obese patients, is the social phobia with the fear of being judged by other people, which leads to the avoidance of social situations.

Anxiety disorders are the most common mental disorders in developed countries. Up to 25% of the population are affected within their lifetime. In addition, anxiety disorders generally have a negative impact on the course of chronic diseases. However, the connection between anxiety disorders and obesity is less clear than that for depression. In a meta-analysis, obese people were found to be 40% more at risk of having a concurrent anxiety disorder. This interrelation seems to increase with higher BMI and is most pronounced in anxiety in the context of post-traumatic stress disorders and social anxiety. No statement can be made about the direction of a possible causality or bidirectionality on the basis of the studies available to date.

1.6.6 Neglect, Abuse and Post-traumatic Stress Disorder

There is a well-established link between child abuse and the development of chronic physical illness. Accordingly, the connection between physical and sexual abuse in childhood and the development of obesity is well established. A meta-analysis showed a 36% increased risk for the development of obesity.

Post-traumatic stress disorder (PTSD) is characterized by psychological reactions that occur against the background of a stressful event with exceptional threat. Typical characteristics are re-experiencing of the traumatic event through intrusive thoughts, nightmares and flashbacks, vegetative hyperexcitability and often pronounced avoidance behaviour. Fifty percent of all patients with PTSD show abdominal obesity. The probability of obesity is significantly higher in these patients than in healthy people. In a German prospective longitudinal study, the risk of developing obesity in women, but not in men, was associated with the presence of manifest or subsyndromal PTSD.

1.6.7 Eating Disorders

Disturbed eating behaviour has often been associated with the development of overweight and obesity. Relevant eating disorders associated with obesity include binge-eating disorder and bulimia nervosa. Binge-eating disorder is defined by eating large quantities of food much faster than usual without a physiological feeling of hunger, associated

with a loss of control. At least one attack per week over a period of 3 months is required for diagnosis. In addition, feelings of shame or guilt usually occur as a consequence. In contrast to bulimia nervosa, whose core criterion is also eating attacks, there is no regular compensatory behaviour such as vomiting, taking laxatives or pronounced food restriction.

Binge-eating disorder is the most common eating disorder with a prevalence of about 1–3%. In obese cohorts with a desire for surgical treatment, however, the prevalence is significantly higher at up to 50%, which in turn points to an increased psychological comorbidity in this patient group. In contrast to anorexia and bulimia nervosa, binge-eating disorder also affects men to a relevant extent, accounting for about one third of cases.

In a population-based study in 14 countries, it was shown that 33% of all patients with bulimia nervosa and 42% of all patients with binge-eating disorder are obese. In addition, the proportion of patients with binge-eating disorder seems to increase in higher BMI ranges.

Other unfavourable eating habits relevant for the care of obese patients are

- Night-eating syndrome, which is characterised by an intake of food in the evening or at night,
- Sweet-eating syndrome, characterized by excessive consumption of sweet foods, and
- the so-called "grazing" with a repeated and unplanned intake of small amounts of food between regular meals.

However, these definitions are inconsistent and their character as independent diseases is currently under discussion.

1.6.8 Personality and Personality Disorders

Personality traits can be both protective and risk factors for the development of obesity. For example, obsessive-compulsive disorders can be associated with restrictive eating habits and reduced body weight. In contrast, personality traits such as neuroticism (emotional vulnerability, often associated with anxiety, depression, hostility and annoyance), increased impulsiveness or dependence on rewards have been shown to increase the likelihood of obesity. Neuroticism also appears to be associated with a more frequent occurrence of eating attacks in the context of emotional eating. Reward dependency appears to be associated with binge-eating disorder. In contrast, protective effects have been found for characteristics such as conscientiousness or self-control with regard to increasing body weight.

Eating disorders can also be associated with disorders of affect regulation and impulse control, as found in emotionally unstable personality disorders (so-called borderline personality disorders). The prevalence in various clinical obesity populations varies widely, averaging about 25%. In addition, up to about 30% of all obese patients with a binge-eating disorder appear to have a borderline personality disorder, again with large fluctuations in frequency.

1.6.9 Substance Abuse

Alcohol abuse seems to occur in obese patients with a desire for obesity surgery treatment with a frequency comparable to that of the general population. There is currently no reliable interrelation between postoperative weight loss and the development of alcohol abuse. According to the few studies available to date, patients with an alcohol abuse in their preoperative history are apparently at increased risk of relapse after bariatric surgery (and especially after a gastric bypass). This could apply not only to alcohol abuse and addiction, but also to other substance-bound and behavioural addictions.

1.6.10 Suicidal Tendencies

While an increased BMI is associated with the increased incidence of mental disorders, various studies suggest that there is an inverse relationship between increased BMI and the risk of a completed suicide. However, the findings are very inconsistent with regard to the

risk of suicide attempts and suicidal thoughts or tendencies, and may depend on subgroup characteristics such as psychological comorbidity, age, gender, and country of origin.

Even if the frequency and severity of psychological problems and illnesses initially decrease significantly after bariatric surgical procedures, the suicide risk after bariatric surgery seems to increase slightly overall. In a review, possible factors that could mediate an increased suicide risk after surgery were discussed. Reasons could be the persistence of somatic comorbidities, insufficient weight loss or the (re)appearance of psychological symptoms. Biological aspects of altered gastrointestinal anatomy, such as increased alcohol sensitivity or postprandial hyperinsulinemic hypoglycaemia, and factors that are difficult to modify, such as genetic variations, are also possible.

1.6.11 Social Inequality

Like other chronic diseases and life expectancy in general, obesity is associated with socioeconomic parameters, with a higher social position being associated with a lower BMI. This correlation is more pronounced in women than in men. In addition, it is interesting to note that studies have shown that a higher prevalence of obesity is associated with more pronounced social injustice in the form of income inequality, but not with the average income of an economy. Furthermore, an American prospective social-epidemiological study showed that moving from one neighbourhood with a high poverty index to another with a low poverty index led to reductions in pronounced obesity and diabetes. Psychosocial stress associated with social disadvantage is commonly cited as the mediating variable for this interrelation.

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