14 Obesity and Diabetes

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Keypoints

- Obesity is characterized by an excess of body fat mass and is defined by a body mass index equal to or greater than 30 kg/m^2. Its prevalence has increased considerably over the past decades in all parts of the world and currently affects 15–30% of the adult populations in Western countries.
- Overweight and/or obesity represents by far the most important modifiable risk factor for type 2 diabetes mellitus (T2DM). An abdominal type of body fat distribution is also closely associated with T2DM, particularly in the lower body mass index categories.
- Both obesity and T2DM have a strong genetic background. The known susceptibility genes for obesity mainly affect central pathways of food intake, whereas most risk genes for T2DM compromise β-cell function.
- Important environmental factors contributing to the development of obesity include energy-dense diets including large portion sizes and permanent availability of foods, lack of physical activity and low socioeconomic status.

- An expanded adipose tissue impairs insulin action and causes insulin resistance in muscle, adipose tissue, liver and possibly other organs.
- Obesity is also characterized by subacute chronic inflammation in adipose tissue because of an impaired paracrine–endocrine function of adipose tissue, but also by mitochondrial dysfunction, local hypoxia and other still poorly understood disturbances at the cellular level.
- Weight loss in obese individuals is followed by rapid amelioration of all metabolic disturbances including chronic inflammation and insulin resistance. These improvements are brought about by caloric restriction rather than the macronutrient composition of the dietary intervention.
- Bariatric surgery is the most powerful approach to treat morbid obesity and may lead to a marked improvement of the metabolic disturbances if not the resolution of T2DM.

Introduction

Obesity is defined as a common chronic disorder of excessive body fat and has become a global epidemic which is present not only in the industrialized world but also in many developing and even in underdeveloped countries. At present, the prevalence of obesity (defined as body mass index [BMI] ≥30 kg/m^2) is in the range 15–30% in the adult populations in Europe, North America and in many Arabic countries, with an unequivocal trend for further increases [1]. This condition increases the risk of developing a variety of adverse consequences to human health ranging from metabolic disturbances including type 2 diabetes mellitus (T2DM) and cardiovascular complications to disorders of the locomotor system and many types of cancer [2]. In addition, obesity impairs the subjective quality of life in affected people and can reduce life expectancy [3]. Although there is a very specific close relationship between excessive body weight and the risk of diabetes, the presence of obesity may induce many other disturbances that may aggravate the diabetic state.

Definition of obesity and the body fat distribution pattern

The diagnosis and classification of obesity is usually based on the BMI. This simple anthropometric index can be calculated from body weight and height, is independent of body height and correlates reasonably well with body fat mass (r = 0.4–0.7). The current classification of body weight according to the World Health Organization (WHO) is presented in Table 14.1. A BMI greater than 30 kg/m^2 is considered to be the central formal criterion for the definition of obesity which is further subdivided into three classes depending on the severity of excessive body fat. The BMI range of 25–29.9 kg/m^2 represents the category of overweight or pre-obesity which requires additional criteria to assess the concomitant health risks. In Western countries, 30–50% of the population fall into the category of overweight [1].

Not only the extent of excessive body fat mass, but also the anatomic location of the body fat mass determines the risk for metabolic and cardiovascular complications. This is particularly

Table 14.1 Classification of human obesity based on body mass index (BMI) classification (kg/m²). Reproduced from World Health Organization [1] with permission.

Classification	kg/m²
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	≥25.0
Obesity	
grade I	30–34.9
grade II	35–39.9
grade III	≥40

Table 14.2 Classification of fat distribution pattern, threshold values for the moderately and markedly elevated risk for metabolic and cardiovascular diseases.

	Waist circumference (cm)	
	Elevated metabolic and cardiovascular risk	
	Moderately	Markedly
Men	>94	>102
Women	>80	>88

important for the category of moderate overweight and even in the upper normal range of BMI. At a defined BMI, the pattern of fat distribution can vary substantially. This has been most impressively shown using computed tomography (CT) or magnetic resonance imaging (MRI) scans which are the only imaging techniques to provide a direct assessment of the size of the intra-abdominal visceral adipose tissue. For practical means, waist circumference measured mid way between the lower rib margin and the upper iliac crest is used as a simple anthropometric measure to assess the fat distribution pattern. This variable has been used in many cross-sectional and longitudinal studies; therefore, the threshold levels demonstrated in Table 14.2 are now well based on human data sets concerning associated health risks. The waist circumference is closely correlated with BMI but cannot discriminate between subcutaneous and intra-abdominal fat depots.

Obesity is the most potent risk factor for type 2 diabetes

A large body of clinical data consistently demonstrates a close relationship between body fat mass and the risk of diabetes. It is noteworthy that in contrast to other obesity-associated metabolic disturbances, the diabetes risk already increases in the upper normal range of BMI. This has been shown for both men and women. In the prospective Nurses' Health Study, women in the upper normal range with a BMI of 23.0–24.9 kg/m² had a four- to fivefold increased risk of developing diabetes over a 14-year observation period compared with women with a BMI of <22 kg/m². In women with a BMI of 29.0–30.9 kg/m² the risk of diabetes was 27.6-fold higher than in the lean reference group. Almost two-thirds of newly diagnosed women with T2DM were obese at the time of diagnosis [4]. Similar observations were made for males in the Health Professionals' Study [5]. Moreover, changes in body weight also predicted the risk of diabetes. Weight gain in women after the age of 18 of 11.0–19.9 kg, which is the average range of weight change between adolescence and meno-

pause in industrialized countries, was found to be associated with a 5.5-fold higher risk of diabetes compared with weight-stable women, whereas weight reduction of the same extent reduced the risk of diabetes by about 80% [4]. Very similar data were reported for men [5]. A recent analysis of the EPIC Potsdam cohort revealed that a weight gain of 1 BMI unit between the age of 25 and 40 years increased the relative risk of T2DM by 25% and had a greater effect than the same weight gain between 40 and 55 years of age [6]. It is also important to note that the duration of obesity has a strong impact on the risk of developing T2DM.

In a recent analysis of the relative contributions of different levels of overweight and obesity to the prevalence of diabetes between 1976–1980 and 2000–2004 in the USA it was found that the increase in total diabetes prevalence from 5.08% to 8.83% was largely caused by the increase in obesity. Of the increased number, 81% was attributed to the different classes of obesity (Figure 14.1). The authors concluded that the increase in diabetes prevalence over recent decades has disproportionately included persons with extreme levels of obesity [7]. Thus, obesity appears to be the main environmental driving force for the manifestation of T2DM.

In addition to the level and the duration of obesity, the risk of developing diabetes is also potently influenced by the fat distribution pattern. In an early study in humans, an abdominal pattern of fat distribution was found to be an independent risk factor for T2DM [8]. Subsequent studies confirmed this observation in many age groups and ethnic populations. Particularly at low degrees of overweight, and even in the upper normal range, the fat distribution pattern strongly predicts the risk for diabetes and the metabolic syndrome. Therefore, waist circumference should be routinely assessed when estimating the risk of diabetes even in normal-weight subjects. In the clinical setting, it is striking to observe that the majority of subjects with diabetes, particularly those of middle age, show a visible preferential truncal accumulation of excess body fat. It is also interesting to note that similar observations were made for the association between BMI and cardiovascular disease. Among overweight and obese subjects, only those with an abdominal type of fat distribution are at increased risk of coronary heart disease as recently documented in the INTERHEART study [9].
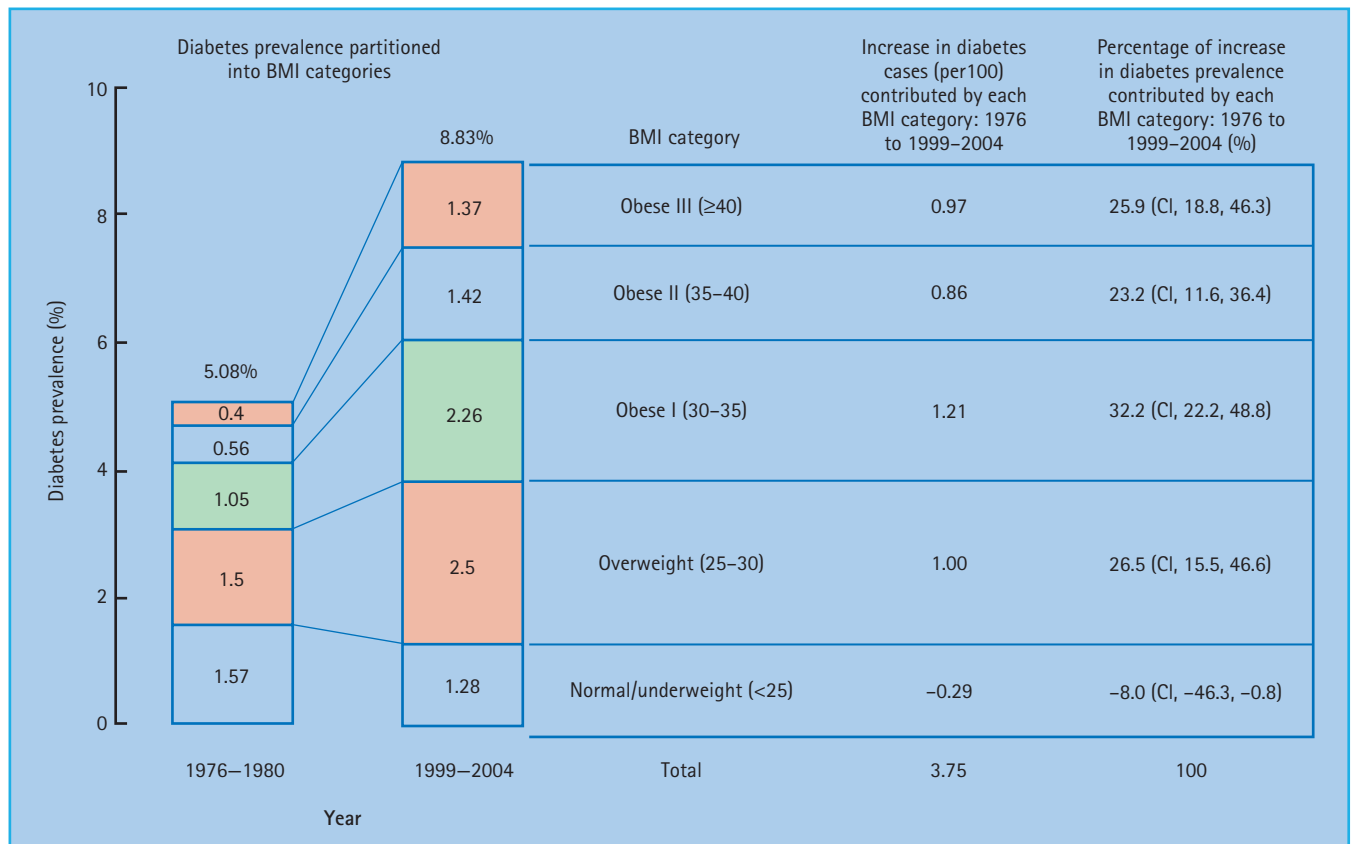
Figure 14.1 Contribution of five body mass index (BMI) categories to the overall prevalence of diabetes. National Health and Nutrition Examination Survey (NHANES) samples of 1976–1980 and 1999–2004 were compared. Reproduced from Gregg *et al.* [7], with permission from Elsevier.

Genetic predisposition for obesity and type 2 diabetes

It is well known from family, adoption and twin studies that obesity, like T2DM, has a strong genetic basis. In the classic adoption study by Stunkard *et al.* [10] there was no resemblance between the adult BMI of adopted Danish children and the BMI of the adopting parents, but a significant correlation to the BMI of the biologic parents, especially to the BMI class of the biologic mother. In a twin study of obesity, concordance rates for different degrees of overweight were twice as high for monozygotic twins as for dizygotic twins. This high heritability for BMI was seen at the age of 20 years and to a similar extent at a 25-year follow-up, suggesting that body fatness is under substantial genetic control [11]. There is also a very close correlation in monozygotic twins who were reared apart, also indicating a high heritability of the BMI trait. In a recent study of 5092 twins living in the London area, the authors estimated the heritability of BMI and waist circumference as 0.77, further supporting the strong effect of the genetic components irrespective of the force of the obesogenic environment [12].

During the last decade, a number of monogenic disorders that result in human obesity have been uncovered. These genetic dis-

orders were only found in rare cases, however, usually children and adolescents with early onset of obesity. At present, a variety of homozygous and compound heterozygous mutations have been described in the leptin–melanocortin signaling pathway, some of them with functional consequences resulting in human obesity. Functional mutations in the melanocortin-4-receptor gene are considered to be the most frequent cause of monogenic obesity in children with a frequency of 2–4% of all obese cases. It is striking that these defects affect genes that are involved in the central control of food intake [13].

Recent genome-wide association (GWA) studies in large cohorts with BMI as phenotype reported common genetic variants on various chromosomes. These polymorphisms predisposing to obesity at the population level are also largely related to central pathways of food intake [14–16]. Thus, human obesity may represent a heritable neurobehavioral disorder that is highly sensitive to environmental conditions, especially an energy-dense palatable foods which are abundantly available in many societies [13]. Despite these remarkable advances in our understanding of the genetic factors related to obesity, the effect size of most of the novel "obesity genes" is rather modest. Only individuals who are homozygous for the high-risk allele of the *FTO* gene weigh on average 3 kg more than individuals with two low-risk alleles [14]. The gene is encoding a 2-oxoglutarate-dependent nucleic acid

demethylase which is mainly expressed in the brain and in the arcuate nucleus of the hypothalamus [17]. Among the almost 20 gene variants found in GWA studies so far, variants near to the *FTO* and the *MC4R* gene appear to have the strongest effect size on body weight. All other recently discovered gene polymorphisms influence body weight by far less than 1 kg.

Thus, it is apparent from recent work that obesity represents a rather heterogeneous disorder in terms of genetic background and susceptibility to etiologic environmental factors. In addition, the risk for developing co-morbidities including T2DM may strongly depend on the individual genetic predisposition towards such diseases. In the case of T2DM, the lifetime risk of developing this disease is about 30% in the white North American population and similar in other ethnic groups [18]. It is currently assumed that only those obese subjects who exhibit a genetic failure of the pancreas to compensate for insulin resistance, which is a characteristic consequence of obesity, will develop T2DM [19]; even among severely obese subjects (BMI ≥40 kg/m^2) only 30–40% will develop diabetes throughout life. Thus, the development of T2DM requires the presence of "diabetes genes" which probably limit β-cell function.

Developmental programming of obesity and diabetes

A new component that may have a major role in the development of obesity and T2DM is the modification of gene expression by epigenetic mechanisms during fetal life. Although this is still a poorly defined phenomenon and it is rather unclear which mechanisms may underlie this association, there is some clue that epigenetics may also operate in this context. Observational studies suggest that infants of mothers with gestational diabetes are at increased risk of developing childhood obesity [20]. In another study, siblings born after the mother had developed gestational diabetes (i.e. exposed to diabetes *in utero*) have a much greater risk of T2DM in young adulthood than siblings not exposed to diabetes *in utero* (odds ratio 3.7; $P = 0.02$) [21].

Another interesting clinical observation is that excessive weight gain during pregnancy, independent of initial BMI, may also increase the risk of early development of obesity in the offspring [22,23]. It is speculated that both hyperglycemia and chronic overnutrition during pregnancy may cause fetal hyperinsulinemia, hypercortisolemia and hyperleptinemia. These hormonal changes may result in a persisting malprogramming of hypothalamic centers controlling energy homeostasis and metabolism, thereby increasing the lifetime risk for obesity and T2DM and possibly the risk for other adverse long-term health consequences [24]. The mechanisms mediating these effects are largely elusive, but it is speculated that epigenetic processes such as DNA methylation, histone modification and changes of the microRNA pattern are involved. Animal experiments suggest that this imprinting process may mainly affect central neuroendocrine pathways which may finally modify appetite regulation [24].

Pathophysiology of obesity

Irrespective of the strong genetic influence on body weight, there is also no doubt that the evolving worldwide epidemic of obesity is primarily a consequence of substantial changes in the environment and lifestyle (see Chapter 8). It is rather new to mankind that food is abundant in many countries and that physical activity is no longer a prerequisite for survival. These dramatic changes in environment and the subsequent changes in lifestyle have occurred within a few decades, a period probably too short to result in adaptations of the genetic background and biologic systems to optimize survival. To date, the relative contributions of the various environmental factors to the epidemic of obesity are hard to quantify in detail and there exist considerable differences between populations.

Humans, like other mammals, are characterized by a tight control of energy homeostasis allowing a stable body weight to be maintained. This setpoint of body weight can vary substantially among individuals and may also vary across lifetime. A complex regulatory system controls energy homeostasis which involves central pathways and peripheral components such as the size of adipose tissue which is sensed to the brain via the secretion of leptin. In addition, gut hormones, signals from the gastrointestinal nervous system and nutrients signal to the brain and induce a complex central integration according to the dietary intake and nutrient requirements of the organism. Central pathways are the anorexigenic leptin–melanocortin link and the orexigenic NPY–AgRP pathway. Many other factors such as insulin modify these signaling processes and thereby influence energy balance [25]. This complex and potent homeostatic system also serves to defend body weight against a critical energy deficiency but also against chronic overnutrition. Several adaptive systems are known to restore the initial body weight under such fluctuations of energy intake and expenditure. This may explain why obese humans exhibit a strong tendency to regain weight after intentional dietary weight reduction. The same tendency to return to initial body weight is observed after experimental overfeeding.

The role of energy homeostasis in the development of obesity has been elaborated by previous studies using indirect calorimetry to investigate the contribution of the resting metabolic rate (RMR) to the risk of obesity. In a study of Pima Indians, RMR was found to be a familial trait and to vary considerably across families [26]. In prospective studies in American Indians, a reduced rate of energy expenditure assessed in a respiratory chamber turned out to predict body weight gain over a 2-year follow-up period. This finding was confirmed in another group over a 4-year-follow-up period in the same paper, indicating that a low rate of energy expenditure may contribute to the aggregation of obesity in families [27]. At present, the genetic components for these differences in energy metabolism are still unknown.

Environmental factors promoting obesity and type 2 diabetes

It is now established that a complex gene–environment interaction determines the individual risk to develop obesity (Table 14.3). Even in societies with an abundance of affordable, highly palatable food there is a high variation in body weight across the populations ranging from lean individuals to extremely obese persons. Many other factors such as physical activity, education and socioeconomic status may also act as strong modifiers of body weight. After two to three decades of modern lifestyle the trend towards obesity appears to reach a plateau, as suggested by recent data from the USA and other Western countries. This observation also supports the concept that genetic and biologic factors contribute substantially to the susceptibility to develop obesity.

Despite the genetic predisposition it is widely accepted that the current worldwide epidemic of obesity is largely a consequence of dramatic changes in lifestyle and environment which emerged over the past 30–50 years. A dramatic change in eating habits and food selection took place, whereas physical activity decreased remarkably because of technologic development concerning transportation and workplaces. Although dietary abundance and sedentary lifestyles have multiple origins, both may equally contribute to a chronic positive energy balance which may result in energy storage in adipose tissue.

A rather novel phenomenon is the expansion of the fast-food culture characterized by high-fat, low-starch foods together with a high intake of sugar-sweetened beverages. In addition to having a high energy density, fast-food menus have large portion sizes. This combination has led to the assumption that frequent fast-food consumption is linked to body weight gain and maintenance of overweight and obesity in the population. Despite this popular explanation, there is rather limited evidence for this association in the scientific literature. Nevertheless, a recent systematic review of six cross-sectional and seven prospective cohort studies concluded that sufficient evidence exists, at least for the adult population [28]. In addition, a high intake of sugar-sweetened beverages is another part of the global fast-food culture. Another systematic review clearly concluded that a high intake of calorically sweetened beverages can be regarded as a determinant of

obesity, although there was no support that this association is mediated via increased energy intake, suggesting that alternative biologic explanations should be also explored [29]. In view of the expansive growth of the fast-food industry in many countries this is a critical issue and may require more intense public discussion on the health consequences of this policy. According to a recent survey, people from the USA obtain one-third of their daily caloric intake from restaurant meals, and one-third of customers of chain restaurants in New York purchased meals containing more than 1000 calories [30]. Thus, there is a growing need to develop new public health policies to limit fast-food consumption and to facilitate a healthier food selection.

Another aspect in the context of high fast-food consumption which may further explain the elevated risk of obesity is the energy density of modern foods. There is convincing evidence that energy density of foods is a key determinant of caloric intake. From an evolutionary point of view, the human regulatory system for energy intake is adapted to starchy foods with low caloric content which requires large volumes to obtain sufficient energy. Today, most fast-foods have a high energy density which may favor a passive overconsumption of calories. A recent study showed that the average energy density of fast-food menus is approximately 1100 kJ/100 g, which is 65% higher than the average British diet (approximately 670 kJ/100 g) and more than twice the energy density of recommended healthy diets (approximately 525 kJ/100 g). It is 145% higher than in traditional African diets (approximately 450 kJ/100 g) which represent the levels against which human weight regulatory mechanisms have evolved. The authors concluded that the high energy density of many fast foods challenges human appetite control systems with conditions for which they were never developed [31].

Another determinant of the obesity epidemic may be the persistent trend over the last decades towards increasing portion sizes. A study from the USA demonstrated that the average portion size for many food items increased markedly between 1977 and 1998, with greatest increases for food consumed at fast-food restaurants and at home [32]. Similar trends have been documented in other countries. Experimental human studies have clearly established that both increasing the portion size and the energy density of food is associated with an increase in caloric intake and, in the long run, may therefore promote weight gain and obesity [33].

Finally, socioeconomic status is a strong determinant of obesity and of T2DM. In most countries there is a gradient between education and household income and the prevalence of obesity. A low socioeconomic status is associated with an unfavorable lifestyle including poor nutrition, low leisure-time physical activity and low health consciousness. This gradient is usually greater in females than males. Thus, the association between low household income and obesity may be mediated by the low costs of energy-dense foods, whereas prudent healthy diets based on lean meats, fish, vegetables and fruit may be less affordable for those of lower socioeconomic status [34].

Table 14.3 Environmental factors promoting the development of obesity.

Ready availability of food
High palatability of food
High energy density
Relatively low cost of foods
High consumption of sugar-sweetened beverages
Aggressive commercial food promotion
Low physical activity

Pathophysiologic links between obesity and type 2 diabetes

T2DM is characterized by an impaired insulin action or a defective secretion of insulin or both. Both defects are thought to be required for the manifestation of the disease and both are present many years before the clinical onset of the disease. To date, the mechanisms by which obesity increases the risk of developing T2DM are only partly understood and the evolving picture is getting more and more complex. The main adverse effect of obesity is on the action of insulin, particularly in liver, muscle and adipose tissue, but obesity also affects insulin secretion. Substantial advances have been made over recent years in our understanding how an excessive fat mass, but also chronic overnutrition, may cause metabolic disturbances resulting in overt T2DM in those with a genetic predisposition for the disease.

Lipids and insulin resistance

The earliest hypothesis to explain the relationship between obesity and T2DM is the "glucose–fatty acid cycle" which is based on the observation of a competition between glucose and fatty acid oxidation in the heart muscle and was introduced by Randle *et al.* [35]. The increased supply of non-esterified fatty acids from expanded adipose tissue depots competes with glucose utilization, particularly in muscle, which represents the organ that oxidizes the largest proportion of glucose. The proposed mechanism is an inhibition of the glycolytic enzymes pyruvate dehydrogenase, phosphofructokinase and hexokinase. As a consequence, the rate of glucose oxidation is reduced and glucose concentrations rise. The concomitant increased fatty acid turnover is accompanied by an increased release of glycerol from adipose tissue which is reutilized for hepatic glucose production, further augmenting the imbalance of glucose metabolism. Increased hepatic glucose output is another early disturbance contributing to glucose intolerance.

In addition, it was reported that elevated free fatty acids can directly impair insulin action. Recent studies suggested that obese subjects and those with T2DM have a high intramyocellular lipid accumulation which is an important feature of the insulin-resistant state. Exposure of skeletal muscle to an excessive lipid supply may lead to intramuscular accumulation, not only of neutral fatty acids, but also of lipid-derived metabolites such as ceramide, diacylglycerol and fatty acyl coenzyme A (CoA). This lipid accumulation is associated with coincident disturbances in insulin action mediated by an activation of a serine–threonine kinase cascade leading to serine–threonine phosphorylation of insulin receptor substrate 1 (IRS-1) and IRS-2 which may cause an impairment of insulin signaling including an impaired activation of phosphoinositol-3 kinase and other downstream elements [36]. This condition is also caused and exacerbated by chronic overnutrition with a high dietary fat intake. Thus, the increased availability of fatty acids may be the single most critical factor in disturbing insulin action in obesity.
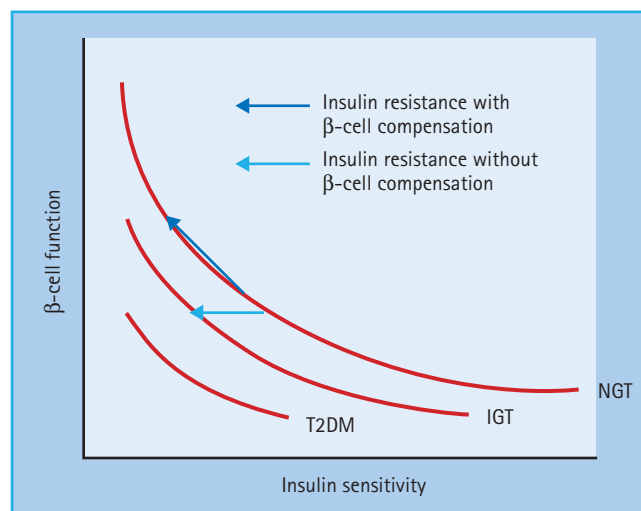

Figure 14.2 Hyperbolic relation between β-cell function and insulin sensitivity. IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus. Reproduced from Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005; **365**:1333–1346, with permission from Elsevier.

Lipids and β-cell function

Obesity is characterized by an elevated insulin secretion and a decreased hepatic insulin clearance. Human studies suggested that the β-cell volume is increased by about 50% in healthy obese subjects, probably because of hypertrophy of existing β-cells. Insulin release and insulin sensitivity are closely reciprocally related in a non-linear manner (Figure 14.2). Failure of this feedback system is known to result in a progressive decline in β-cell function and to underlie the development of T2DM. In addition to glucose, long-chain fatty acids may also exert a stimulatory effect on insulin secretion from the pancreatic β-cells via generation of fatty acyl CoA and activation of protein kinase C [36]. Another effect of fatty acids on insulin secretion is via binding to the G-protein-coupled receptor GPR 40 on the β-cell membrane which may result in a subsequent increase in intracellular calcium and secretory granule exocytosis [37]. Although fatty acids are critical for normal insulin secretion, a chronic exposure of β-cells to excessive fatty acids is associated with marked impairment of glucose-stimulated insulin secretion and decrease in insulin biosynthesis [38]. Another mechanism by which elevated fatty acids may impair insulin secretion in response to glucose is via an increased expression of uncoupling protein 2 (UCP-2) in β-cells. UCP-2 was found to be upregulated under glucolipotoxic conditions and mitochondrial superoxide has been identified as a post-translational negative regulator of UCP-2 activity in islets [39].

Glucose sensing of the pancreatic β-cells requires an intact oxidative mitochondrial metabolism to generate ATP. The resulting high ATP:ADP ratio is a prerequisite for normal insulin secretion. Studies in humans suggest that insulin resistance may
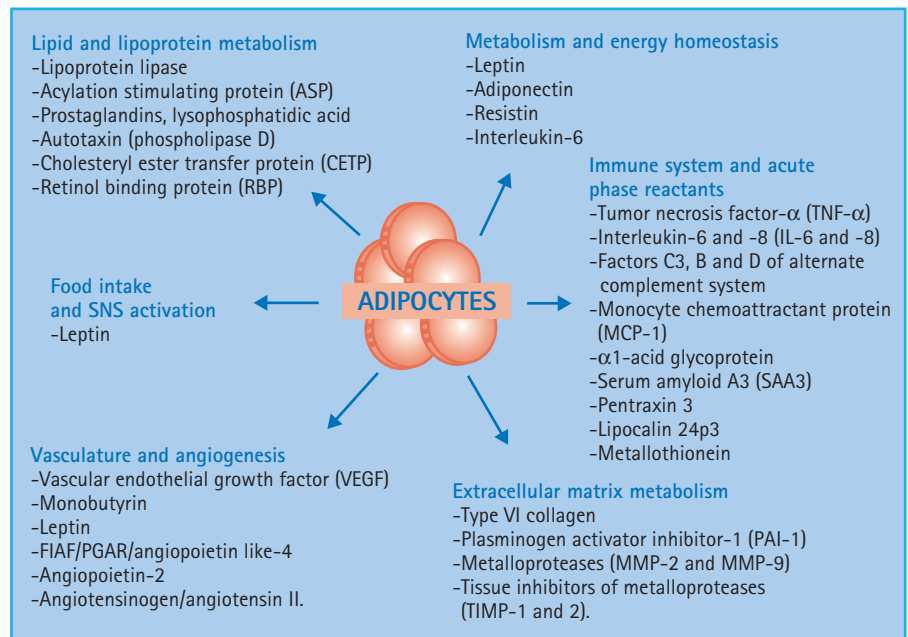
Figure 14.3 Secretory products from adipose tissue and functional relationship. Reproduced from Lafontan M. Fat cells: afferent and efferent messages define new approaches to treat obesity. *Annu Rev Pharmacol Toxicol* 2005; **45**:119–146, with permission from *Annual Reviews*.

also arise from defects in mitochondrial fatty acid oxidation which may lead to increased intracellular fatty acid metabolites (fatty acid CoA, diacylglycerol). It was recently shown that young insulin-resistant offspring of parents with T2DM have features of impaired mitochondrial function [40]. Furthermore, it was reported that obese individuals have smaller mitochondria with reduced bioenergetic capacity than lean controls [41]. Although studies on this topic are still limited, there is growing evidence that a defective mitochondrial function could be a prominent feature of disturbances in both insulin secretion and action [42].

Adipose tissue as a secretory organ

Another hypothesis that may explain the association between obesity and T2DM is the observation that adipose tissue is a secretory organ that produces and releases a variety of factors that may contribute to the development of insulin resistance and other health risks (Figure 14.3; Table 14.4). Among these factors most data have been collected for a mediator role of tumor necrosis factor α (TNF-α). TNF-α is a multifunctional cytokine which was the first found to be expressed in adipose tissue [43]. It was subsequently shown that TNF-α exerts a variety of catabolic effects in adipose tissue. In addition to TNF-α, it was reported that its two receptor subtypes are overexpressed in adipose tissue from obese subjects [44–46]. The upregulated TNF-α system induces multiple adverse effects at the local organ level such as inhibition of glucose uptake because of an impairment of insulin signaling and suppression of GLUT 4 expression, a reduction of lipoprotein lipase expression and activity, and an increase in lipolysis [47]. Moreover, TNF-α activates the NF-κB pathway in adipose tissue which leads to an increased expression of many proinflammatory proteins such as interleukin 6 (IL-6), IL-8 and monocyte chemotactic protein 1 (MCP-1) among others. Finally,

Table 14.4 Secretory function of adipose tissue in obesity and potential clinical consequences.

Product	Secretion	Consequence
Free fatty acids	↑	Dyslipidemia (TG ↑), insulin resistance
TNF-α, IL-6, MCP-1 and other cytokines/chemokines	↑	Insulin resistance, type 2 diabetes
Angiotensinogen, angiotensin II and other vasoactive factors	↑	Hypertension
PAI-1	↑	Thrombembolic complications
CETP	↑	Low HDL cholesterol
Adiponectin	↓	Insulin resistance, atherosclerosis
Estrogens	↑	Endometrial and breast cancer

CETP, cholesterol ester transfer protein; HDL, high density lipoprotein; IL, interleukin; MCP, monocyte chemotactic protein; PAI, plasminogen activator inhibitor; TG, triglycerides; TNF, tumor necrosis factor.

TNF-α was demonstrated to reduce the expression of adiponectin, a protein that is abundantly expressed in fat cells and exerts direct antidiabetic and anti-atherosclerotic actions. A key mechanism by which TNF-α causes insulin resistance may be that this cytokine stimulates the phosphorylation of IRS-1 at the serine residue 307 which inhibits the transduction of the insulin signal to downstream elements [48].

Using an *in vitro* co-culture model of human adipocytes and muscle cells it was recently demonstrated that other fat cell secre-

tory products, in addition to TNF-α, are also involved in the development of muscle insulin resistance [49]. Thus, it is likely that the negative effect on muscle insulin action is brought about by a combination of adipokines. Although we have currently little information on the nature and the complex interplay of such proinflammatory and anti-inflammatory factors, a few relevant players have been identified. One such element may be MCP-1 [50]. Other potential candidates with a prodiabetic action may include plasminogen activator inhibitor 1 (PAI-1), but also lipid metabolites such as ceramide. Retinol-binding protein 4 (RBP-4) was also shown to contribute to insulin resistance via reduced PI_3 kinase signaling and enhanced hepatic expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase. An interesting observation in this context is that adiponectin may be able to antagonize the insulin resistance-promoting activity of proinflammatory cytokines released from adipose tissue in an autocrine fashion [51].

Adipocytes are also able to release products with anti-inflammatory properties including factors such as adiponectin, IL-1 receptor antagonist and IL-10. By far the most interesting component is adiponectin, which is the most abundantly expressed protein in adipose tissue. It was shown in a number of clinical studies that circulating adiponectin levels are inversely associated with BMI and that low concentrations predict the development of T2DM [52,53]. Adiponectin is now known to exert a variety of antidiabetic and anti-atherosclerotic effects (e.g. adiponectin stimulates fatty acid oxidation in an AMP-activated protein kinase-dependent manner) [54].

Signaling pathways of inflammation in adipose tissue

Current research has shown that the inflammatory response in human obesity is mediated via activation of the c-Jun N-terminal kinase (JNK) and IKKβ–NF-κB pathways. Both pathways are simultaneously stimulated by cytokines such as TNF-α and IL-6, but also by lipids. It has been convincingly demonstrated in experimental studies that genetic or chemical inhibition of these pathways can reduce inflammation and improve insulin resistance (for review see [55]) (Figure 14.4). In obesity, JNK activity is elevated not only in adipose tissue, but also in liver and muscle. Loss of JNK1 prevents the development of insulin resistance and diabetes in both genetic and dietary mouse models of obesity [56]. IKKβ can act on insulin signaling through at least two pathways. First, it can directly phosphorylate IRS-1 on serine residues and, second, it can phosphorylate the inhibitor of NF-κB (IκB) thus activating NK-κB, a transcription factor that stimulates the production of many proinflammatory mediators including TNF-α and IL-6 [57]. Mice heterozygous for IKKβ are partially protected against insulin resistance caused by lipid infusion, high-fat diet or genetic obesity [58]. Both the JNK and the IKKβ–NF-κB pathways are activated via pattern recognition receptors that function as membrane receptors for a variety of external signals. It is interesting to note that endogenous lipids and lipid conjugates were found to activate toll-like receptors (TLRs) in obesity. It was recently reported that saturated fatty
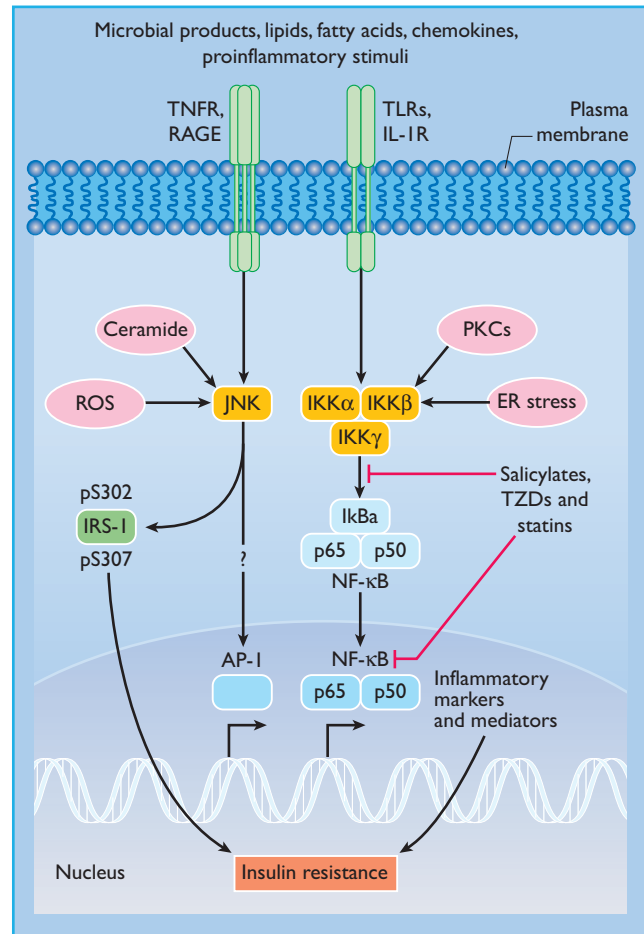

Figure 14.4 Potential cellular mechanisms for inflammation and development of insulin resistance. AP-1, activator protein 1; ER, endoplasmic reticulum; IKK, Iκ kinase; IL, interleukin; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; NF-κB, nuclear transcription factor κB; PKC, protein kinase C; ROS, reactive oxygen species; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor; TZD, thiazolidinedione. Reproduced from Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006; **116**:1793–801, with permission from the American Society for Clinical Investigation.

acids bind and activate TLR-4 on adipocytes, thereby suggesting a direct link between exogenous nutrients that are redundant in the obese state and inflammation [59]. Mice with a loss-of-function mutation of TLR-4 were found to be protected from diet-induced obesity and insulin resistance. These mice also showed a reduced NF-κB and JNK activity under a high-fat diet compared to wild-type control mice [60]. In a similar model, markedly lower circulating levels of MCP-1 were measured. TLR-4 deficiency, however, did not attenuate the induction of TNF-α and IL-6 expression [61].

It is noteworthy that most proteins released from adipose tissue are not produced by fat cells but rather by pre-adipocytes and invading immune cells such as activated macrophages. While leptin and adiponectin are true adipokines which are almost exclusively produced by adipocytes, TNF-α, IL-6, IL-8, MCP-1,

visfatin, PAI-1 and others are mainly expressed by pre-adipocytes, macrophages resident in adipose tissue and possibly other cells. The relative contributions of the various cellular components in adipose tissue to the secretion of these products remains unknown and may vary substantially according to depot and model. Nevertheless, all these locally secreted factors appear to participate in the induction and maintenance of the subacute inflammatory state associated with obesity. It is also important to mention that the invading macrophages release factors that substantially augment adipocyte inflammation and insulin resistance [62]. Another interesting observation in this context is that pre-adipocytes and macrophages share many common features [57].

The regulation and biologic functions of the secretory products are diverse and only poorly understood. In addition to the direct effects of fatty acids and their intracellular products, other factors may also contribute to the chronic inflammatory state in adipose tissue. It was recently shown that fat cell size may be a critical determinant of the production of proinflammatory and anti-inflammatory factors. Enlarged hypertrophic fat cells are characterized by a shift towards a proinflammatory state [63], thereby promoting insulin resistance. This is in agreement with clinical data showing that fat cell hypertrophy is associated with an increased risk of developing T2DM [64].

Obesity and endoplasmic reticulum stress

A recent observation suggests that obesity and chronic overnutrition overload the functional capacity of the endoplasmic reticulum (ER) and that the resulting ER stress contributes to the activation of the inflammatory signaling pathways including the JNK pathway. In both high-fat diet induced and genetic obesity models, obesity was shown to cause ER stress with inositol-requiring kinase-1α (IRE-1α) having a crucial role in insulin receptor signaling as a mediator of JNK activation [65]. In a mouse model of type 2 diabetes, systemic overexpression of 150-kDa oxygen-regulated protein (ORP150), a molecular chaperone located in the ER, improved insulin intolerance and enhanced glucose uptake indicating that this chaperone has an important role in insulin sensitivity and is a potential target for the treatment of T2DM [66].

Obesity and oxidative stress

A study from Japan demonstrated that fat accumulation is associated with systemic oxidative stress in humans and mice [67]. There was a selective production of reactive oxygen species (ROS) in adipose tissue of obese mice, accompanied by an increased expression of NADPH oxidase and a decreased expression of anti-oxidative enzymes. The authors also showed that fatty acids increased oxidative stress in cultured adipocytes via NADPH oxidase activation which was followed by dysregulated production of adipokines such as adiponectin, PAI-1, IL-6 and MCP-1. In addition, treatment with an NADPH oxidase inhibitor reduced ROS production, restored the dysregulation of adipokines in adipose tissue and improved diabetes, dyslipidemia and hepatic steatosis, indicating that the redox status in adipose tissue is a critical factor in the development of the metabolic syndrome [67].

Adipose tissue hypoxia

An expansion of the adipose tissue mass leads to fat cell hypertrophy and subsequent hypoxia of the tissue. Recent studies convincingly support the concept that hypoxia has an important if not central role in the development of chronic inflammation, macrophage infiltration, impaired adipokine secretion, ER stress and mitochondrial dysfunction in white adipose tissue in obesity [68,69]. These consequences are also accompanied by an inhibition of adipogenesis and triglyceride synthesis and elevated circulating free fatty acid concentrations. Measurement of the interstitial partial oxygen pressure (PO_2) in adipose tissue showed a reduction of up to 70% leading to oxygen levels of about 2% in obese animals compared to lean controls [69]. This observation was further substantiated by the determination of hypoxia response genes such as hypoxia-inducible factor 1α (HIF-1α), vascular endothelial growth factor (VEGF), heme oxygenase 1 (HO-1) and others. The low oxygen pressure may also contribute to a reduced mitochondrial respiration with a consecutive increase in lactate production. In humans, HIF-1α was also shown to be increased in white adipose tissue of obese patients and its expression was reduced after surgery-induced weight loss [70]. Hypoxia was also demonstrated to decrease adiponectin expression in adipocytes [71].

The physiologic basis of adipose tissue hypoxia may be related to a reduction in adipose tissue blood flow and capillary density which has been reported in both obese humans and animals. Although the hypoxic state leads to an increased production and release of pro-angiogenic factors from adipose tissue such as VEGF and others, this compensatory mechanism may not be sufficient to keep the PO_2 at a normal level as the free diffusion of oxygen in the adipose tissue may be limited [69].

Accumulation of immune cells

Leptin, TNF-α, MCP-1 and other chemokines have an essential role in the recruitment of macrophages to adipose tissue. The secretory profile of both pre-adipocytes and adipocytes includes a variety of chemoattractants for immune cells. It was recently reported that the attraction of T-lymphocytes possibly caused by stromal cell-derived factor 1 (SDF-1) represents the initial step which subsequently leads to the invasion and activation of circulating monocytes–macrophages resembling the scheme originally described for atherosclerosis [72]. Such accumulation of immune cells and inflammation of adipose tissue has been shown in obese humans [73] and appears to be more pronounced in omental than subcutaneous adipose tissue [74], which would also fit with the concept that the amount of visceral fat is the culprit for the metabolic and cardiovascular complications of obesity.

Role of body fat distribution pattern

Another important issue in this context is the distribution of body fat. It has long been known from early clinical studies that
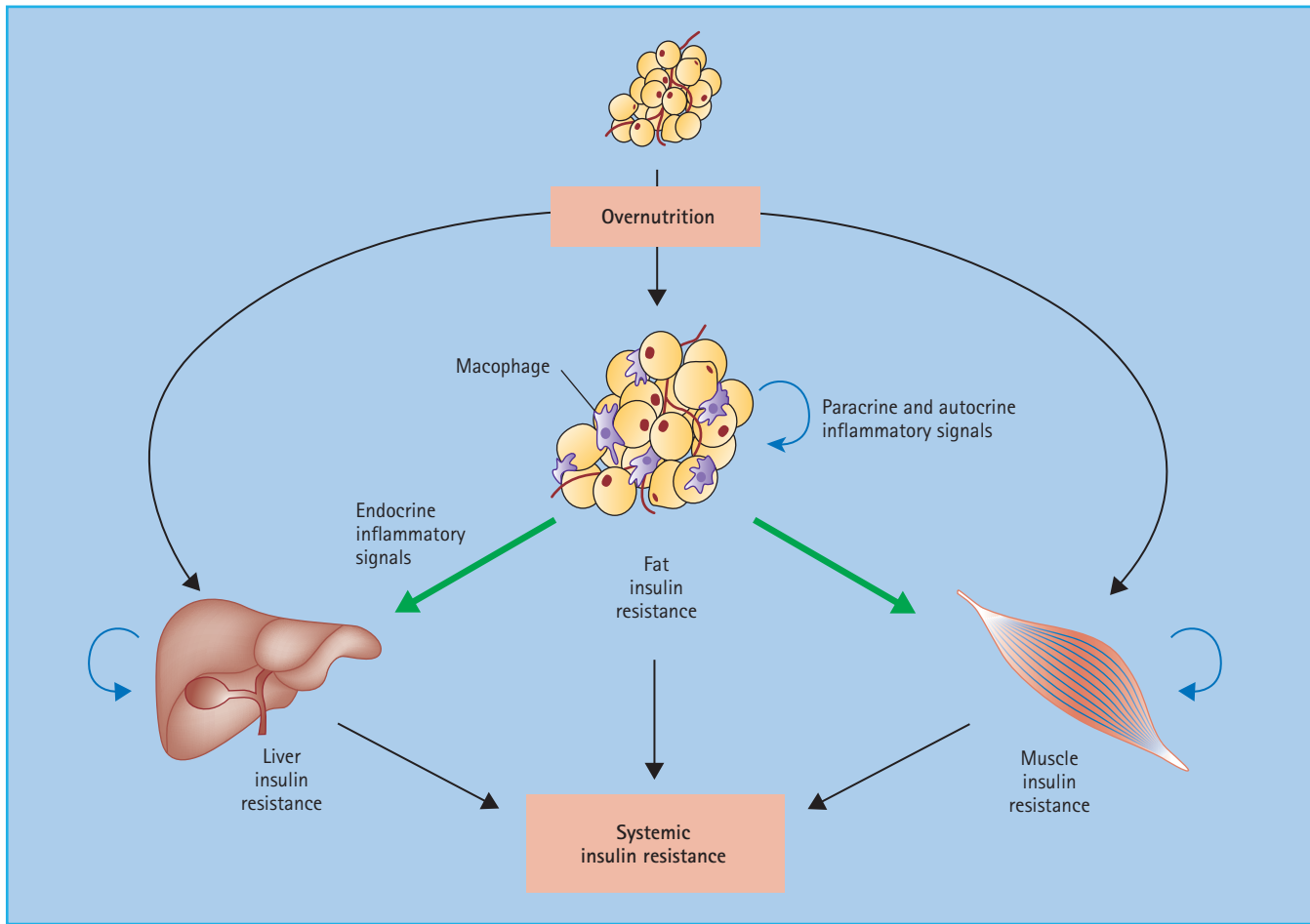
Figure 14.5 Nutrition and obesity-induced inflammation and development of systemic insulin resistance. Reproduced from De Luca C, Olefsky JM. Stressed out about obesity and insulin resistance. *Nat Med* 2006; **12**:41–42, with permission from Nature Publishing Group.

subjects with a more abdominal type of body fat distribution are at increased risk of developing T2DM and other metabolic and cardiovascular complications [75–77]; however, the underlying cause has only recently become evident. Intra-abdominal fat cells exhibit a differing expression profile and are lipolytically more active than subcutaneous adipocytes. Moreover, they show a greater accumulation of lymphocytes and macrophages, indicating greater proinflammatory activity. Visceral adipose tissue also has a much higher blood vessel and nerve density leading to a much greater metabolic activity. Visceral adipose tissue drains into the portal vein and thus the liver is directly exposed to fatty acids and proteins released from this active fat depot promoting insulin resistance in the liver. Thus, the inflammatory process is detected, not only at the level of adipose tissue, but may also affect the liver and possibly other organs. As enlarged visceral fat depots are frequently associated with fat accumulation in the liver, it was also hypothesized that secretory products from the visceral adipose tissue may directly cause hepatic insulin resistance.

In summary, a variety of data suggests that chronic overnutrition with a high-fat, high-sugar diet and as a consequence an accumulation of body fat is the primary cause of chronic inflam-

mation in obesity and may promote the development of systemic insulin resistance which affects many tissue including liver, muscle and the brain (Figure 14.5). It should not be neglected that apart from an unhealthy diet, other lifestyle factors such as lack of physical activity may substantially contribute to these pathologic processes.

Treatment of obesity in the context of the metabolic syndrome and type 2 diabetes

The fact that obesity is the most powerful driving force for the development of T2DM provides the rationale to consider weight management as the most important initial treatment step. Numerous studies have consistently shown that weight loss is not only an effective means to prevent the development of T2DM in those at increased risk, but may also improve the metabolic disturbances and associated risk factors in those with overt T2DM. In addition, weight reduction facilitates reaching the primary treatment goal of a metabolic control close to normal. Interestingly, almost all disturbances mentioned above are potentially reversi-

ble by weight loss. This was particularly demonstrated for elevated circulating adipokines. A modest to moderate weight reduction was found to reduce significantly the concentrations of circulating factors such as leptin, C-reactive protein, PAI-1, IL-6, IL-8, MCP-1 and others by 10–50%. By contrast, adiponectin levels are known to rise in relation to weight reduction. In a recent study in surgically treated morbidly obese subjects a significant reduction in macrophage infiltration was documented in adipose tissue samples after a mean weight loss of 22 kg within 3 months [70].

Management of obesity in subjects with type 2 diabetes

For the reasons outlined, management of obesity should represent a central component in the treatment strategy for T2DM. Although currently available weight reduction programs for patients with diabetes have only limited success rates, particularly in the long run, in contrast to previous beliefs, recent studies show that obese subjects with T2DM can achieve clinically significant weight loss. In the prospective Look AHEAD study, the average weight loss in obese subjects with T2DM in the intensive lifestyle intervention group after 1 year of treatment was 8.6% of the initial body weight and was accompanied by substantial improvements of all weight-associated risk factors. Mean HbA$_{1c}$ fell from 7.3% (56 mmol/mol) to 6.2% (44 mmol/mol) despite reductions in the dosage of glucose-lowering agents [78].

Despite this positive development, treatment of obese subjects with T2DM is usually considered to be more difficult than treating obese subjects without diabetes for several reasons. People with T2DM are usually older than obese subjects without diabetes, which may mean a smaller weight loss as energy expenditure decreases with age. Another reason is that subjects with diabetes focus more on blood glucose control which could result in neglecting other health problems. Finally, the effect of various antidiabetic agents to increase weight or prevent weight loss has to be considered [79].

Dietary approaches

The cornerstones of a weight reduction program for obese patients with diabetes include a moderately hypocaloric diet, an increase in physical activity and behavior modification, very similar to the recommendations for obese subjects without diabetes. Numerous studies have applied and examined such concepts and have been critically evaluated in reviews [80–82].

The gold standard in the dietary treatment of obese patients with T2DM is a balanced moderately energy-restricted diet with an energy deficit of at least 500 kcal/day (see Chapter 22). The most important single measure is the reduction in fat intake, particularly in saturated fatty acids. A low-fat, high carbohydrate diet is generally recommended. As shown recently, a diet rich in fiber and complex carbohydrates has some beneficial effects on measures of glucose and lipid metabolism but these effects may be small and possibly of limited clinical importance [83]. The concept of a high-carbohydrate, low-fat diet was challenged by clinical studies showing that replacement of saturated fat by monounsaturated fat compared to high-carbohydrate intake is equally favorable or even has advantages with regard to glycemic

response and lipids [84]. More importantly, recent studies using a low-carbohydrate, high-protein diet were at least equally effective. In a recent meta-analysis of such studies, HbA$_{1c}$, fasting glucose and some lipid fractions improved with lower carbohydrate content diets [85]. In a study from Israel, a Mediterranean type of weight loss diet showed small advantages in comparison to the classic low-fat, low-carbohydrate diet in a subgroup of overweight participants with diabetes [86]. The message from this and other studies [87,88] is that the macronutrient composition of the diet is secondary for weight reduction. In patients with nephropathy, however, protein intake remains a critical issue and should be limited in accordance with current recommendations [89].

From a practical point of view it is extremely important to assess the habitual diet of patients with T2DM and to focus counseling on timely changes of their eating habits in order to approach current dietary recommendations [89]. It should be stressed that all efforts for dietary changes should be made as simple as possible for patients as they may also be burdened by many requirements to manage their diabetes. For obese subjects with T2DM the frequent recommendation to distribute their allowed calories over 5–6 meals is difficult to meet and may even hinder weight loss without being of any advantage for metabolic control [90]. Therefore, in patients without insulin, three meals a day may be more appropriate and advantageous to reach the individual dietary and weight goals.

Another possible dietary approach is the use of a very low calorie diet (VLCD) for initial weight loss. This option may be particularly valuable for patients with poor metabolic control. Dietary restriction is known to be associated with a rapid improvement of insulin resistance and glycemic control after even short periods of VLCD. There is also evidence that the pattern of adipokines and macrophage-associated gene expression can change dramatically under such conditions [91]. This approach, however, can only be applied for a limited period of time and requires intensive medical surveillance. The long-term results of VLCD are moderately better than those of conventional diets, although there is considerable weight regain under the former [92]. Therefore, there is need for new sophisticated solutions such as intermittent VLCD in combination with conventional hypocaloric diets to obtain better long-term results [93]. Another possibility is to change the pattern of nutrient intake to modify adipose tissue inflammation. To date, there is little practical information available to indicate whether specific effects of single components in the diet can ameliorate adipose tissue inflammation independent of calorie restriction. There is no doubt that more research is urgently required to explore the potential of dietary components and to develop novel strategies that may help to provide better dietary solutions for the management of obesity.

Antidiabetic drugs and body weight

It has long been recognized that antidiabetic drugs can promote weight gain in subjects with T2DM (see Chapters 27 and 29). The strongest weight-promoting effect is exerted by insulin. In the Diabetes Control and Complications Trial (DCCT), intensified

insulin treatment was associated with substantial weight gain that resulted in unfavorable changes of lipid levels and blood pressure similar to those seen in the insulin resistance syndrome [94]. In the UK Prospective Diabetes Study (UKPDS), insulin treatment caused a mean weight gain of approximately 7 kg over 12 years of treatment in newly diagnosed subjects with T2DM [95]. In addition, sulfonylureas are known to promote weight gain because of their action to promote insulin secretion. In the UKPDS, the average weight gain under glibenclamide treatment amounted to about 5 kg [95].

Administration of glitazones, a relatively new class of PPAR-γ agonists with insulin sensitizing activity, leads to substantial weight gain of 4–5 kg on average. There is growing evidence, however, that weight gain under glitazone treatment occurs mainly in subcutaneous depots, not in the visceral depot, which should have less deleterious metabolic consequences. Furthermore, weight gain under administration of glitazones is not only caused by an increase in fat mass, but also by enhanced fluid retention. In contrast, metformin and α-glucosidase inhibitors have a modest weight lowering potential [79].

Recent data for the DPP-4 inhibitors show that these new drugs are weight neutral, whereas the administration of GLP-1 mimetics, such as exenatide, results in a substantial weight loss in a high proportion of patients [96].

Weight lowering drugs

Another component in the treatment of obesity is the adjunct administration of weight lowering drugs. As the efficacy of currently approved drugs is limited, drug treatment is only recommended if the non-pharmacologic treatment program is not sufficiently successful and if the benefit:risk ratio justifies drug administration [97]. At present, only two compounds are available that have demonstrated efficacy and safety in obese subjects with and without T2DM.

Orlistat is a gastric and pancreatic lipase inhibitor that impairs the intestinal absorption of ingested fat. In a recent systematic review of clinical studies over at least 12 weeks in obese subjects with T2DM, orlistat treatment produced a greater weight loss than placebo treatment by 2.0 kg on average, associated with a small improvement in HbA$_{1c}$ compared with controls [98]. Furthermore, orlistat moderately decreases low density lipoprotein (LDL) cholesterol concentrations.

Sibutramine is a selective serotonin and noradrenaline reuptake inhibitor that enhances satiety and slightly increases thermogenesis.[*] The same systematic review showed an average weight loss of 5.1 kg in obese patients with T2DM, also accompanied by

improvements of glycemic and lipid measures [98]. As sibutramine is known to activate the sympathetic nervous system, this drug should not be used in patients with diabetes and poorly controlled hypertension or coronary artery disease.

Bariatric surgery

Bariatric surgery is now an established method to reduce body weight in subjects with extreme obesity (≥40 kg/m^2), but there is growing consensus that this method can also be applied in subjects with T2DM at a BMI ≥35 kg/m^2. In this group of patients surgery is by far the most effective treatment mode with excellent long-term results compared to all other methods. In the Swedish Obese Subjects study, a large prospective trial comparing bariatric surgery with conventional dietary treatment, sustained weight loss ≥20 kg was achieved in the surgically treated subjects with practically no significant weight change in the control group. The surgical intervention not only reduced the incidence of T2DM, but also significantly reduced total mortality [99]. A recent meta-analysis of studies on the effect of bariatric surgery in obese patients with T2DM demonstrated that 78% had a complete remission of diabetes. Weight loss and diabetes resolution was greatest in patients undergoing combined restrictive and malabsorptive surgical methods [100]. The majority of insulin-treated patients can stop insulin treatment within a few months after surgery and all other medications for diabetes and other cardiovascular risk factors can be considerably reduced or discontinued. There are also many studies indicating how rapidly most circulating adipokines are normalized in relation to the degree of weight loss in these patients.

Conclusions

There is now growing information on how obesity is increasing the risk of developing T2DM. It is apparent that an excess of body fat promotes insulin resistance and impairs insulin secretion. As most patients with T2DM are overweight or obese, weight management must be a central component of any treatment strategy, as weight loss has been convincingly shown to provide a marked improvement in metabolic control. In parallel, most if not all underlying disturbances benefit from weight loss or dietary interventions. As conventional concepts combining an energy-reduced diet and an increase in physical activity frequently have poor long-term results, however, more effective weight loss strategies should be developed and evaluated.

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[*]The marketing authorization for sibutramine has recently been withdrawn in Europe following the publication of the SCOUT trial. In this trial which included 9,800 overweight or obese individuals at high risk of CVD events, treatment with sibutramine was associated with a 16% increased risk of non-fatal MI, non-fatal stroke, resuscitated cardiac arrest or CVD death. This result was driven by an increased incidence of non-fatal MI and stroke.

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