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CLINICAL PROBLEMS CAUSED BY OBESITY

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ABSTRACT

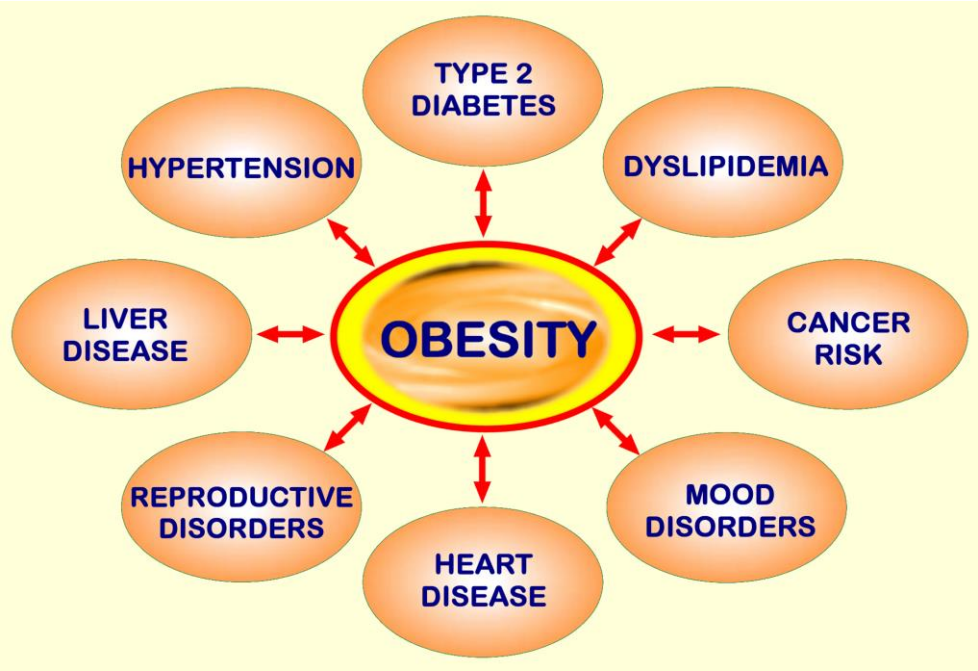
Obesity constitutes a worldwide epidemic with prevalence rates which are increasing in most Western societies and in the developing world. By 2025, if this trend continues, the global obesity prevalence will reach 18% in men and exceed 21% in women. Furthermore, it is now well-established that obesity (depending on the degree, duration, and distribution of the excess weight/adipose tissue) can progressively cause and/or exacerbate a wide spectrum of co-morbidities, including type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, non-alcoholic fatty liver disease, reproductive dysfunction, respiratory abnormalities, psychiatric conditions, and even increase the risk for certain types of cancer. This chapter presents an overview of these links focusing on the most common obesity-related co-morbidities.

INTRODUCTION

During the past few decades, the prevalence rates of obesity [defined as body mass index (BMI) over 30 kg/m^2] have been increasing at a rapid pace in both Western societies and the developing world (1), reaching 641 million adults being obese in 2014 [266 million men and 375 million women], compared to 105 million adults in 1975 [34 million men and 71 million women] (2). Notably, if this trend persists, the global obesity prevalence is predicted to rise to 18% in men and surpass 21% in women by 2025 (2). Overall, obesity can be considered a chronic relapsing and progressive disease (3) and a leading risk factor for global deaths. Furthermore, alarming trends of weight gain have also been documented for children and adolescents, undermining the present and future health status of the population (4-7). To highlight the related threat to public health, the World Health Organization (WHO) declared obesity a global epidemic, also stressing that in many cases it remains an under-recognized problem of the public health agenda (1, 8, 9).

Depending on the degree and duration of weight gain, obesity can progressively cause and/or exacerbate a wide spectrum of co-morbidities, including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, cardiovascular disease (CVD), liver dysfunction, respiratory and musculoskeletal disorders, sub-fertility, psychosocial problems, and certain types of cancer (**Figure 1**).

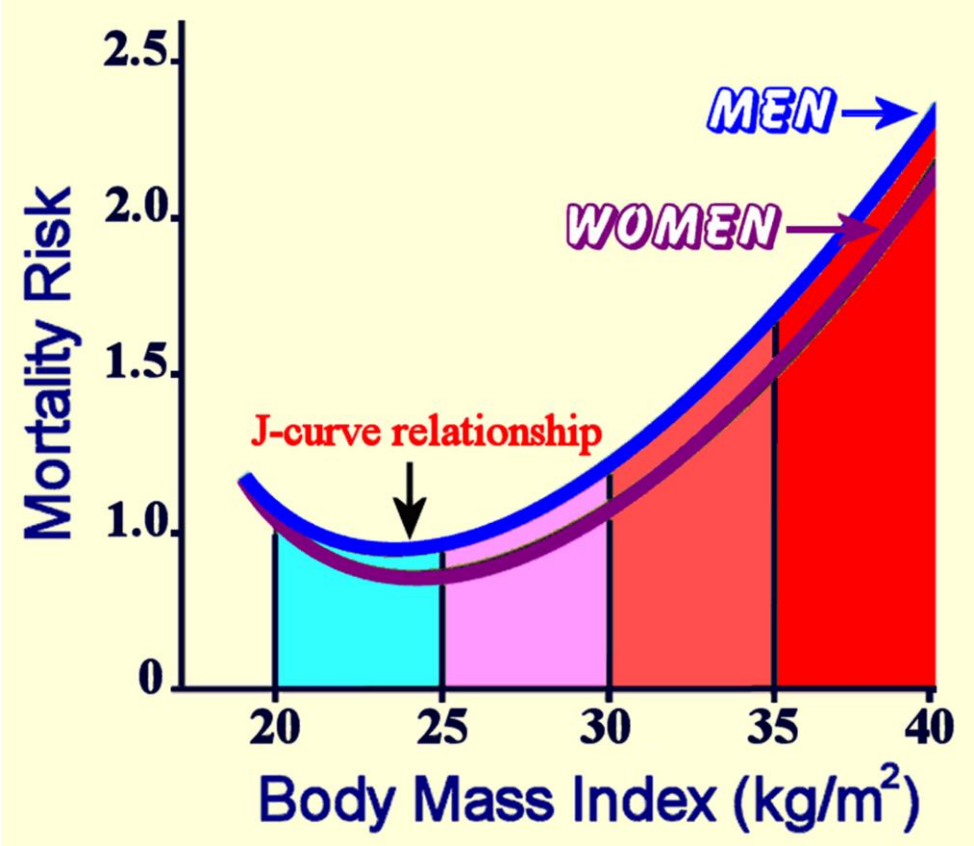
Figure 1. Co-Morbidities Associated with Overweight and Obesity.



These chronic diseases have been shown to have strong correlations with BMI, and closely follow the prevalence patterns of excessive body weight in all studied populations (10, 11). Notably, the risk of developing a number of obesity-related co-morbidities rises exponentially with increasing BMI over 30 kg/m^2, which is further associated with a graded increase in the relative risk of premature death, primarily from CVD (9, 10, 12). For individuals with BMI between 25 and 29.9 kg/m^2 (pre-obesity) the risk of premature mortality is weaker and appears to be influenced mainly by fat distribution (**Figure 2**). Indeed, fat accumulation intra-

abdominally and subcutaneously around the abdomen (central, abdominal, visceral, android, upper body or apple-shaped obesity) is associated with higher risk for cardiometabolic diseases, independent of BMI (13, 14). On the other hand, fat accumulation in the subcutaneous regions of hips, thighs and lower trunk (gluteofemoral, peripheral, gynoid, lower body or pear-shaped obesity) is considered less harmful or even protective against cardiometabolic complications (13, 15-17).

Figure 2. Relationship Between Body Mass Index (BMI) and Mortality (data from Calle *et al*. NEJM 1999 (12)).



Notably, individuals of certain ethnic backgrounds, regardless of the country of residence, are predisposed to central/abdominal obesity and more vulnerable to obesity-related complications (18-21). Indeed, studies in South Asian, Japanese, and Chinese populations have demonstrated significantly higher risk for insulin resistance, T2DM and CVD compared to matched overweight/obese Caucasians (22-24). Accordingly, rigorous cut-off points have been proposed for weight management among these populations, diagnosing obesity with BMI thresholds as low as 25 kg/m^2 and defining central obesity based on ethnicity specific cut-off values of waist circumference (22-27).

In any case, obesity should be recognized by the treating physician as a key risk factor for the health of the patient, and appropriate weight loss treatments should be offered to patients with obesity, independently of other related co-morbidities (28-30). Weight management is crucial and should be suggested promptly even when these individuals are otherwise healthy (*e.g.* metabolically healthy patients with obesity) to prevent and/or delay the onset of obesity-related complications. Interestingly, recent advances in treatment

options for CVD risk factors and acute coronary syndromes are now offering improved cardio-protection outcomes and appear to prolong life expectancy in patients with obesity. Indeed, epidemiologic data support the notion that, in developed societies increasing numbers of these patients are expected to live more than previously predicted, despite failing to reduce their excessive body weight (31, 32). As such, it is estimated that growing and progressively ageing populations in Western societies will continue to develop an increasing burden of obesity-related disease, including complications (e.g. chronic liver disease, respiratory or mobility problems) which were previously under-diagnosed or under-expressed due to earlier mortality (expansion of obesity-related morbidity) (31, 33, 34). Subsequently, the economic impact of obesity on health care costs is profound and will continue to increase, while the additional indirect costs (e.g. absence from work, reduced productivity and disability benefits) are also substantial. National surveys in the UK have shown that obesity is directly responsible for almost 7% of the overall morbidity and mortality, with a direct cost to the Neational Health System (NHS) that currently exceeds five billion pounds per year and could potentially rise to more than nine billion pounds by 2050 (35-37).

Childhood obesity also poses a significant burden due to a spectrum of complications both in the short term and later in life, highlighting the need for early intervention and prevention of obesity in children and adolescents (5, 38, 39). It should be noted that the absolute BMI is not an appropriate screen index to identify children with elevated body fat mass since BMI normative values differ based on age and gender. Hence, in the pediatric population BMI should be plotted on the Centers for Disease Control and Prevention's percentile curves to identify the corresponding BMI percentile category (www.cdc.gov/growthcharts) [obesity in children and adolescents will be reviewed in detail in the EndoText chapter dedicated to Pediatric Obesity].

OBESTITY-RELATED CO-MORBIDITIES RESULTING FROM FAT DISTRIBUTION AND FUNCTION

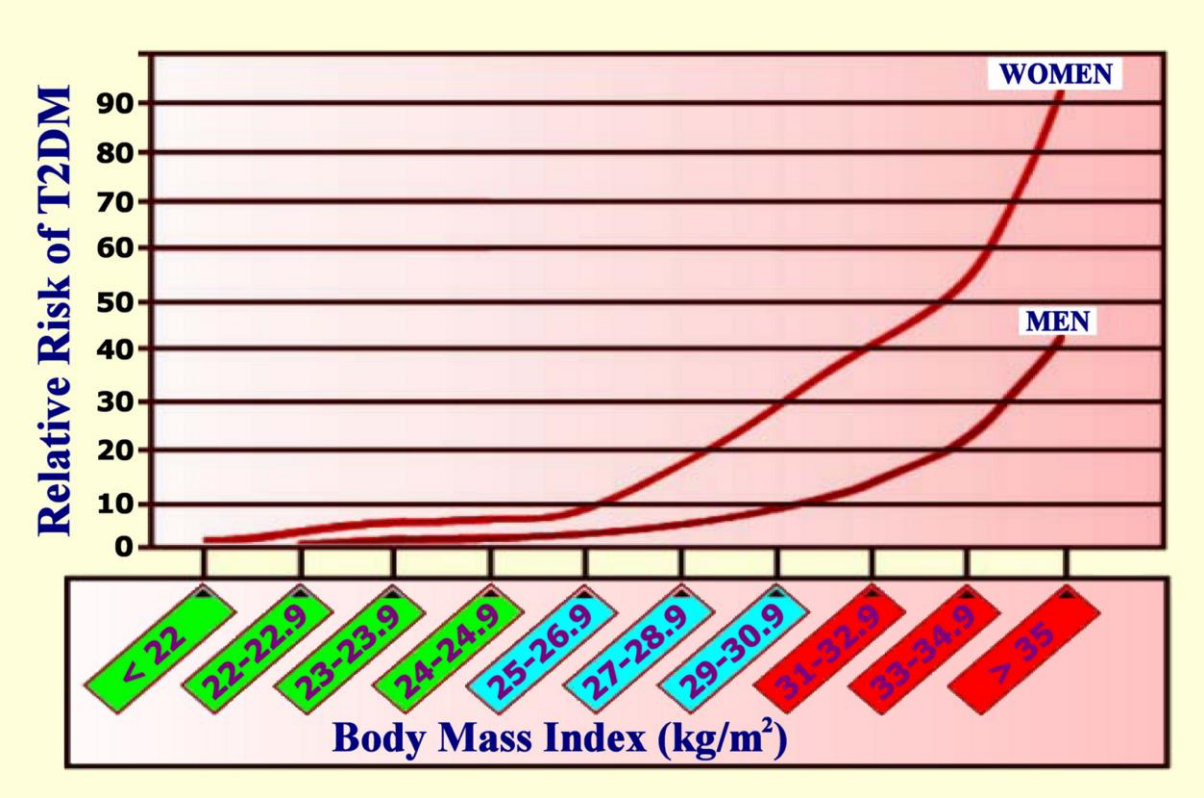
Obesity and Type 2 Diabetes Mellitus

Diabetes mellitus constitutes a rather diverse group of metabolic disorders which are characterized by hyperglycemia (e.g. type 1 diabetes, type 2 diabetes, gestational diabetes, maturity onset diabetes of the young, drug-induced diabetes, diabetes secondary to pancreatic damage) (40). Type 2 diabetes mellitus (T2DM) comprises up to 90% of all diagnosed diabetic cases in adults and is typically associated with presence of various degrees of obesity. Depending on ethnicity, age and gender, 50-90% of T2DM patients exhibit a BMI over 25 kg/m^2, while patients with BMI over 35 kg/m^2 are almost 20 times more likely to develop T2DM compared to individuals with BMI in the normal range (18.5-24.9 kg/m^2 for Caucasians) (40, 41). Indeed, T2DM rates have been increasing both in developed and developing countries following the documented prevalence trends of obesity (2, 42, 43); hence, the term "*diabesity"* has been introduced to describe this twin epidemic (43-45).

Large-scale population studies have shown that obesity is the most important independent risk factor for insulin resistance and T2DM (46-49). In adults, the relative risk for T2DM begins to increase even at BMI values within the normal weight range, 24 kg/m^2 for men and 22 kg/m^2 for women, while it rises exponentially with increasing BMI over 30 kg/m^2 (**Figure**

3). Thus, morbid obesity is associated with markedly high relative risk for T2DM in both genders, up to 90 and 40 for women and men, respectively (46, 47). Although visceral adiposity is more prominent in men, obesity appears associated with higher T2DM risk in women compared to men (50, 51). Moreover, T2DM increases the risk of CVD by three to four times in women and two to three times in men, after adjusting for other risk factors (52). Interestingly, impaired glucose homeostasis and T2DM have been linked to X-chromosomal loci (53); however, the relative contribution of these loci to the onset of T2DM is not fully clarified yet. Overall, it appears that an interplay exists between gender, ethnicity, and certain adipose tissue characteristics which plays an important role in the association between obesity and related cardiometabolic comorbidities, including T2DM (54). Moreover, children and adolescents with obesity are now increasingly diagnosed with impaired glucose tolerance and T2DM (55-58).

Figure 3. Body Mass Index (BMI) and Risk of Developing Type 2 Diabetes Mellitus (T2DM) in Male and Female Adults (based on data from Colditz GA *et al*. Ann Intern Med. 1995 (47) and Chan JM *et al*. Diabetes Care 1994 (46)).



Furthermore, a strong association exists between central obesity and T2DM, beyond the impact of BMI (13, 14, 59, 60). Both insulin resistance and hyperinsulinemia correlate positively to visceral fat accumulation which constitutes an independent risk factor for T2DM. Accordingly, anthropometric indices of central obesity (e.g. waist circumference, waist-to-height ratio and the visceral adiposity index) are utilized to better assess the obesity-related risk of T2DM and CVD (61-63). The higher cardiometabolic risk associated with central fat distribution is attributed to a combination of factors, relating mainly to a more deleterious adipocyte secretory profile in these fat depots. Indeed, visceral adipose tissue is more lipolytic (decreased insulin-mediated inhibition of the hormone-sensitive lipase and increased catecholamine-induced lipolysis) causing a greater flux of free fatty acids (FFA) into the

portal circulation with lipotoxic effects, primarily in the liver and skeletal muscle (64, 65). Additionally, adipocytes in visceral fat depots exhibit increased secretion of pro-inflammatory adipokines (e.g. tumor necrosis factor-α and intrerleukin-6) and decreased secretion of adiponectin, hence, leading to decreased insulin sensitivity and activation of pro-inflammatory pathways in the adipose tissue, liver, and skeletal muscle (66, 67). Hormonal changes either at the systemic level of various neuroendocrine axes (e.g. chronic mild hypercortisolemia and dysregulation of the hypothalamic-pituitary-adrenal axis, as seen in chronic stress) or at the local level of the visceral adipose tissue (e.g. increased conversion of cortisone to cortisol via type 1 11β-hydroxysteroid dehydrogenase, 11β-HSD1, in fat depots) may increase lipogenesis and thus contribute to adverse metabolic consequences of central obesity (68-70).

It should be noted that, insulin resistance in patients with obesity leads to chronic compensatory hyperinsulinemia, which in turn may promote further weight gain (71). On the other hand, it is interesting that acute and short-term increases of circulating insulin levels can even reduce liver fat accumulation, at least in mice (72). This concept may contribute to the documented beneficial effects of dietary protein and certain insoluble cereal fibers which induce a short-term surge in insulin secretion (73-75). Several studies indicate that both dietary protein and cereal fiber intake are associated with beneficial effects on blood glucose regulation and body fat distribution in the long-term (76-86). With high protein diets, this appears to be mainly related to increased satiety and weight loss (86, 87). Intake of insoluble cereal fiber appears to improve insulin sensitivity and the risk of developing T2DM, with the only moderate weight loss involved unlikely being the driving factor (84, 85, 88, 89). Indeed, in an 18 week randomised controlled isoenergetic trial in 111 overweight or obese subjects, whole-body insulin sensitivity markedly improved with the intake of a diet high in cereal fiber (85). Interestingly, existing data also indicate that high protein intake in sedentary, at-risk subjects who typically fail to lose weight in the longer term regardless the diet (90) could have adverse effects on insulin resistance and T2DM risk. Of note, Wang et al. have investigated the metabolite profiles in 2,422 normoglycemic subjects who were followed for 12 years, with 201 of the subjects having developed T2DM (91). Five branched-chain and aromatic amino acids (isoleucine, leucine, valine, tyrosine, and phenylalanine) showed highly-significant associations with the future development of T2DM, with replication of the results in an independent, prospective cohort (91). The authors proposed amino acid profiling as a potential predictor for future diabetes, but a potential causal link between dietary protein intake and future diabetes cannot be excluded. Despite the widely claimed beneficial effects, there is increasing evidence that longer term high intake of both animal and total protein may have detrimental effects on insulin resistance (85, 86, 92-99), diabetes risk (100, 101) and the risk of developing CVD (102, 103). This could be especially detrimental in pre-diabetic subjects with obesity who already have impaired insulin secretion and may be resistant to the anabolic response to high protein intake (104), thus lacking several potentially important compensatory mechanisms for protein-induced worsening of insulin resistance (86). Furthermore, obese patients are typically sedentary, with potential additional unfavourable effects on protein-regulated mTOR/S6K1 signaling and the development of insulin resistance, as suggested by studies in rodents (105). Finally, whereas in elderly people low protein intake may have detrimental effects, recent studies have linked high protein intake to cancer risk and overall mortality in younger individuals (below the age of 65 years) (103). Given this evidence, further research is clearly needed before high protein diets should be widely proposed as a safe tool for weight loss in

sedentary subjects with obesity that typically fail in long-term weight maintenance after an initial diet-induced weight loss and are already at high-risk of developing T2DM.

Overall, in chronic hyperinsulinemia a vicious cycle is formed, where fat accumulation causes generalized insulin resistance (insulin resistance in adipose tissue, liver and skeletal muscle) combined with increased insulin secretion and *vice versa*. Decreased insulin sensitivity in adipose tissue is crucial for initiating and fuelling this vicious cycle (106, 107). Normally, insulin-mediated inhibition of hormone-sensitive lipase in adipocytes decreases FFA release from fat depots, leading to lower FFA plasma concentrations, inhibition of hepatic glucose production and increased muscle glucose uptake. However, in T2DM uninhibited lipolysis in insulin-resistant adipocytes causes persistently increased circulating FFA levels. In turn, this leads to reduced peripheral glucose utilization, increased hepatic glucose production and decreased insulin sensitivity in the liver and skeletal muscle (108, 109). Thus, adipocytes play a crucial role in the overall regulation of glycemia in T2DM, although the adipose tissue glucose uptake is less than 5% of the total glucose disposal (107).

In the liver, insulin regulates the hepatic glucose production rate by activating specific enzymes which induce glycogenesis and suppressing enzymes involved in gluconeogenesis. Hepatic insulin resistance can be defined as the failure of insulin to adequately suppress hepatic glucose production and is associated with fasting hyperglycemia in T2DM (110). Notably, the lipogenic actions of insulin do not appear to be compromised in insulin-resistant states, as will be further discussed in the following section of this chapter about obesity and fatty liver disease. Under normal fasting conditions, circulating levels of insulin are low and fasting hepatic glucose production matches the basal glucose utilization (equal gluconeogenesis and glycogenolysis rates). In T2DM, the fasting glucose production in the liver is increased due to hepatic insulin resistance despite compensatory hyperinsulinemia (107). Overall, the absolute amount of hepatic glucose production is moderately increased in T2DM patients compared to that of healthy controls, but is inadequately suppressed relative to the raised concentrations of glucose and insulin (111). This increased fasting hepatic glucose production exhibits a linear correlation with the degree of fasting hyperglycemia and is caused primarily by accelerated glucose synthesis through the gluconeogenic pathway (112). On the other hand, insulin resistance in skeletal muscle fuels postprandial hyperglycemia in T2DM, since skeletal muscles are responsible for most of the glucose disposal after meals. Decreased insulin sensitivity in skeletal muscles of T2DM patients causes impaired insulin-stimulated glucose uptake which is both reduced and delayed (113). This postprandial under-utilization of glucose by skeletal muscles is superimposed on increased hepatic glucose production rates, thus, compounding the magnitude and duration of postprandial hyperglycemia.

Although necessary, insulin resistance alone is not sufficient for T2DM development since the pancreas has the capacity to adapt by accordingly increasing both beta-cell mass and insulin secretion. Due to these compensatory mechanisms, normoglycemia can be maintained despite reduced insulin sensitivity in the periphery. Thus, inadequate insulin secretion is a crucial component of the T2DM pathophysiology (107). Obesity contributes to beta-cell decompensation and impaired insulin secretion through the related insulin resistant state and various glucotoxic and lipotoxic effects on the pancreas. Lipotoxicity can cause beta-cell dysfunction depending on the degree of exposure to FFA and on the underlying

genetic predisposition for T2DM. *In vitro*, prolonged exposure of beta-cells to high FFA concentrations increases FFA oxidation and causes accumulation of intracellular metabolites (e.g. citrate and ceramide) which impair glucose-stimulated insulin secretion and promote apoptosis (107, 114). Clinical studies have also confirmed that sustained high FFA plasma levels can impair insulin secretion in predisposed individuals (115). On the other hand, pharmacological inhibition of lipolysis in non-diabetic individuals with strong family history of T2DM can improve insulin secretion (116). Similarly, glucotoxicity can impair beta-cell function depending on the duration and degree of hyperglycemia. *In vitro*, prolonged beta-cell exposure to high glucose concentrations causes glucose desensitization, impairs insulin gene transcription and induces apoptosis (107). Clinical studies have also reported that reduced beta-cell sensitivity to glucose plays a predominant role in patients with impaired glucose tolerance (117, 118).

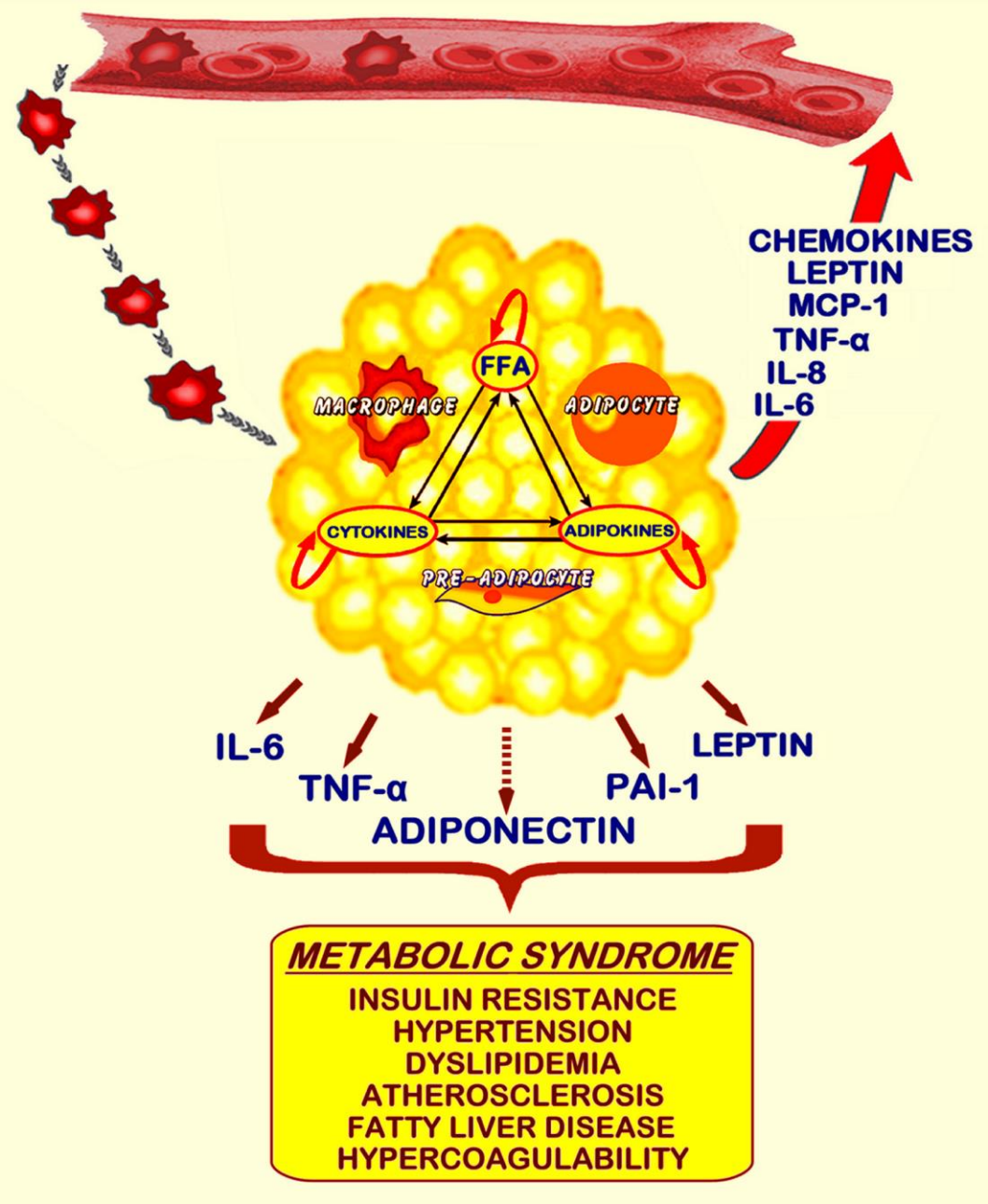
Finally, it should be emphasized that both the insulin resistant state in obesity and the related acquired beta-cell defects can be restored, at least in part, with weight loss and good glycemic control. Indeed, several studies have reported that even modest weight loss (*e.g.* weight loss achieved by lifestyle interventions, including diet and exercise to increase physical activity) is important for T2DM prevention, significantly reducing the risk and delaying the onset of the disease (14, 119-127).

Obesity-Related Inflammatory and Procoagulant State: Link to CVD and Metabolic Syndrome

Following the recognition of adipocytes as endocrine cells, research has further focused on studying the links between obesity-related complications and the development of a chronic low-grade inflammatory state in obesity. As such, it became evident that weight gain progressively promotes sub-clinical inflammation in patients with obesity, which is mainly attributed to secretion of various pro-inflammatory factors, including adipokines/cytokines and chemokines (e.g. leptin, TNF-α, IL-6, IL-1β) (128-140). The pro-inflammatory nature of adipose tissue is heightened in proportion to fat accumulation and exhibits positive correlations with increasing BMI and especially with visceral adiposity (65, 130-133, 141). Thus, central obesity appears to trigger and exacerbate an inflammatory cascade that initially evolves within fat depots. Over time, this exerts systemic effects, since enhanced adipose tissue secretion of pro-inflammatory adipokines persists for as long as the excess abdominal fat mass is maintained. Compiling evidence suggests that this obesity-related activation of pro-inflammatory signaling pathways is linked to key CVD risk factors (e.g. insulin resistance and T2DM), as well as to atherosclerosis and thrombosis (59, 142-146). Indeed, NLRP3 inflammasome activation appears to be a key underlying mechanism/link between obesity-related chronic inflammation and insulin resistance (129).

Obesity induces multiple constitutional alterations in the micro-environment and cellular content of adipose tissue depots, which collectively promote differentiation of pre-adipocytes, insulin resistance and pro-inflammatory responses (130-133). A closer look at the underlying molecular interplay unveils a vicious cycle between pre-adipocytes, mature adipocytes and macrophages, which reside in adipose tissue of patients with obesity (**Figure 4**).

Figure 4. Adipose Tissue and Low-Grade Inflammatory State in Obesity.



TNF-α: tumor necrosis factor-α, MCP-1: monocyte chemotactic protein-1, IL-8: interleukin 8, IL-1: interleukin-1, IL-6: interleukin-6.

Weight gain enhances both lipogenesis and adipogenesis inside fat depots, as well as secretion of pro-inflammatory adipokines and chemokines (e.g. monocyte chemotactic protein-1, MCP-1, and IL-8) into the circulation. In response to such chemotactic stimuli mononuclear cells are recruited from the circulation and transmigrate into adipose tissue depots, increasing the number of resident activated macrophages (147-149). In turn, this growing population of macrophages secretes cytokines, such as TNF-α, IL-1β and IL-6, which can potentially aggravate the pro-inflammatory and insulin resistant profile of adipocytes; although there is also a body of literature suggesting that IL-6 does not cause insulin resistance (133, 150, 151). Thus, sustained fat accumulation establishes an unremitting local pro-inflammatory response within the expanding adipose tissue. This cascade progresses to a chronic low-grade generalized inflammatory state in obesity,

mediated by persistent release of pro-inflammatory adipokines of adipocyte and/or macrophage origin and coupled with decreased adiponectin secretion (130-132, 152), with deleterious effects on peripheral tissues and organs (e.g. liver, skeletal muscles, vascular endothelium). These effects promote hepatic and skeletal muscle insulin resistance, hypertension, atherosclerosis, hypercoagulability, thrombosis and enhanced secretion of acute-phase reactants (e.g. C-reactive protein, fibrinogen, haptoglobin) (130-133, 153).

The procoagulant state in obesity is further characterized by increased levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1), which promote atherogenic processes and increase the related CVD risk (145, 154-157). Fibrinogen is synthesized by hepatocytes and holds a pivotal role in the coagulation cascade, being a major determinant of plasma viscosity and platelet aggregation, whilst also potentially playing a pro-inflammatory role in vascular wall disease (158). Expression of fibrinogen in the liver is up-regulated by IL-6 during the acute phase reaction, and various studies have documented an association between elevated fibrinogen levels and increasing BMI (159). Interestingly, fibrinogen has also been shown to predict weight gain in middle-aged adults (160). PAI-1 regulates the endogenous fibrinolytic system and constitutes the main inhibitor of fibrinolysis by binding and inactivating the tissue plasminogen activator, thus increased PAI-1 activity leads to decreased clearance of clots. Elevated PAI-1 levels have been associated with increased BMI, visceral adiposity and obesity-related cardiometabolic complications (145, 161-165). Enhanced adipose tissue expression of PAI-1 has been reported in obesity, particularly in visceral adipose tissue (166), while an inverse relationship was also demonstrated between PAI-1 activity and adiponectin in overweight and obese women (164, 165).

It is also noteworthy that a putative integration of adipocytes into the innate immune system has been suggested, thus linking metabolic and inflammatory signaling pathways. Apart from their documented reciprocal interactions inside adipose tissue depots, the inherent similarities between adipocytes and macrophages are of particular interest (133, 167, 168). Although these cells clearly belong to distinct lines, they have a common ancestral origin from the mesoderm during early embryogenesis. Mature adipocytes differentiate from pluripotent mesenchymal stem cells which, under certain conditions, become committed to the adipocyte lineage and produce pre-adipocytes. Notably, pre-adipocytes appear to have the ability to differentiate into macrophages and to function as macrophage-like cells, developing phagocytic activity against microorganisms (169, 170). Furthermore, analysis of the adipocyte gene expression profile in obesity revealed striking resemblances to that of macrophages, with adipocytes expressing specific cytokine genes (e.g. IL-6, TNF-α) which were typically associated to macrophages (171, 172). Finally, both pre-adipocytes and mature adipocytes express Toll-like receptors (TLRs) which are cardinal regulators of innate and adaptive immune responses and can be directly activated by both lipopolysacharide (LPS) and fatty acids (173). This advocates the hypothesis that the adipose tissue may also play a role as an immune organ (174), with potential implications for treatment of obesity-related complications. Identifying common initial inflammatory mechanisms could lead to therapeutic interventions that may inhibit at earlier stages the adipose-initiated pro-inflammatory cascade and, thus, prevent the onset of clinical complications. Indeed, therapeutic interventions to inhibit inflammatory pathways in obesity have shown promising results with beneficial effects on insulin sensitivity in mouse models and human trials (130).

Metabolic Syndrome: Definitions and Quest for a Single Set of Diagnostic Criteria

All the aforementioned findings support the notion that obesity-related pro-inflammatory pathways mediate deleterious cardiometabolic effects which can lead to clinical manifestations of the metabolic syndrome. In 1988, Reaven proposed the term “Syndrome X” to describe a constellation of metabolic abnormalities, including glucose intolerance, dyslipidemia and hypertension, which frequently cluster together revolving around insulin resistance (175). All these metabolic disorders are established independent CVD risk factors and their coexistence correlates with high CVD morbidity and mortality, an association that aptly led to the description of the syndrome as the “deadly quartet” (176). Since then, the term “Metabolic Syndrome” has been adopted to better illustrate this clustering of cardiometabolic risk factors, opening new opportunities for the study of their interrelationships (177, 178). Existing evidence on the prevalence of the metabolic syndrome, based on large US, European, and Australian cohorts, indicate that, depending on the applied definition, it affects over a quarter of the adult population in Western societies (179-181). Furthermore, meta-analysis data have shown that the metabolic syndrome is associated with a 2-fold increase in CVD outcomes and a 1.5-fold increase in all-cause mortality (182). Several prominent medical bodies/scientific societies, including the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), and the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III), have proposed different metabolic syndrome definitions to help identify individuals at high risk for cardiometabolic complications in clinical practice (**Figure 5**) (183-185).

However, these definitions applied diagnostic criteria that varied significantly, thus limiting comparability between studies and creating confusion regarding their use by clinicians (177). In order to address the need for widely accepted criteria that could be easily applied in different settings and ethnic populations, in 2005 the International Diabetes Federation (IDF) issued a consensus statement introducing a worldwide metabolic syndrome definition based on assessment of simple anthropometric and plasma measurements [waist circumference, blood pressure and plasma levels of triglycerides, high-density lipoprotein cholesterol (HDL-C) and fasting glucose] (**Figure 5**) (186). This consensus identified central obesity as the hallmark of the metabolic syndrome and the prerequisite component for its diagnosis. Furthermore, to increase the applicability in various ethnic groups, central obesity diagnosis in the IDF definition relies on waist circumference measurements, which puts into practice a set of ethnic-specific cut-off values. Thus, an approach was adopted to take into account the fact that individuals of specific ethnic origin (e.g. South Asians), regardless of their country of residence, are predisposed to central obesity and more susceptible to complications of visceral adiposity (20-24, 26). Overall, the IDF consensus was a targeted effort to offer a metabolic syndrome definition set on criteria that would be friendly to routine clinical practice and could be uniformly applied in different settings and patient groups. Moreover, the adopted rationale for this definition took into account the growing body of evidence which supported the crucial role of central obesity in the pathophysiology of insulin resistance and the metabolic syndrome.

Of note, the published IDF consensus statement included a recommended “Platinum standard” list of additional criteria to be included in epidemiological and other research studies regarding the metabolic syndrome (186, 187). Assessment of multiple metabolic parameters was proposed, including markers of adipocyte function (leptin, adiponectin), inflammatory markers (C-reactive protein, TNF-α, IL-6), and coagulation markers (PAI-1,

fibrinogen), together with evaluation of fat distribution (visceral adiposity, liver fat), and precise measurements of insulin resistance, endothelial dysfunction, atherogenic dyslipidemia and urinary albumin. Incorporating these variables into comprehensive research on the pathophysiology of the metabolic syndrome components aimed to further advance the understanding of the underlying pathogenetic pathways/mechanisms.

Figure 5. Different Definitions of the Metabolic Syndrome.

DIFFERENT DEFINITIONS OF THE METABOLIC SYNDROME		
EGIR (1999)	**WHO (1999)**	**NCEP-ATP III (2001)**
Insulin resistance - hyperinsulinemia based on fasting insulin values (upper quartile of a non-diabetic population)	Diabetes, IFG, IGT or insulin resistance (by euglycemic hyperinsulinemic clamp - glucose uptake less than lowest quartile)	
Plus at least two of the following:	**Plus at least two of the following:**	**At least three of the following:**
1. Central obesity WC ≥94 cm (37 in) (M) WC ≥80 cm (31 in) (F)	1. Obesity with BMI >30 kg/m^2 or WHR >0.9 (M) WHR >0.85 (F)	1. Central obesity WC >102 cm (40 in) (M) WC >88 cm (35 in) (F)
2. TG >2.0 mmol/l (177 mg/dl) or HDL <1.0 (39 mg/dl) mmol/l	2. TG ≥1.7 mmol/l (150 mg/dl) or HDL-C <0.9 mmol/l (35 mg/dl) (M) HDL-C <1.0 mmol/l (39 mg/dl) (F)	2. TG ≥1.7 mmol/l (150 mg/dl) 3. HDL-C <1.04 mmol/l (40 mg/dl) (M) HDL-C <1.33 mmol/l (50 mg/dl) (F)
3. BP ≥140/90 mmHg or on antihypertensive medication	3. BP ≥140/90 mm Hg	4. BP ≥135/85 mmHg or on antihypertensive medication
4. FPG ≥6.1 mmol/l (110 mg/dl)	4. Albumin excretion rate ≥ 20 µg/min or albumin/creatinine ratio ≥ 30 mg/g	5. FPG ≥6.1 mmol/l (110 mg/dl)*
*changed to FPG ≥ 5.6 mmol/l (100 mg/dl) in 2004 EGIR: European Group for the Study of Insulin Resistance; WHO: World Health Organization; NCEP-ATP III: National Cholesterol Education Program-Adult Treatment Panel III; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; FPG: fasting plasma glucose; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; M: men; F: women		

METABOLIC SYNDROME - IDF DEFINITION (2005)			
I. CENTRAL OBESITY			
ETHNIC GROUP	**MEN**	**WOMEN**	**Until more specific data are available:** **Sub-Saharan Africans - Eastern Mediterranean - Middle East (Arab) populations**: use European data **Ethnic South and Central Americans:** use South Asian recommendations
Europids	≥ 94 cm	≥ 80 cm	
South Asians	≥ 90 cm	≥ 80 cm	
Chinese	≥ 90 cm	≥ 80 cm	
Japanese	≥ 85 cm	≥ 90 cm	
II. PLUS ANY TWO OF THE FOUR FOLLOWING FACTORS:			
A. ↑ TG levels: ≥ 150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality			
B. ↓ HDL-c levels: males ≤ 40 mg/dl (1.03 mmol/l), females ≤ 50 mg/dl (1.29 mmol/l) or specific treatment for this lipid abnormality			
C. ↑ Blood pressure: systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or Treatment of previously diagnosed hypertension			
D. ↑ FPG: ≥ 100 mg/dl (5.6 mmol/l) or previously diagnosed Type 2 Diabetes			
TG: triglycerides; HDL-c: high-density lipoprotein cholesterol; BP: blood pressure; FPG: fasting plasma glucose; **IDF: International Diabetes Federation**			

It is also important to mention that, the waist circumference values in the IDF definition were proposed as initial guidelines based on available evidence and, thus, were accepted as neither complete nor definite (23, 186). Further epidemiological studies are still required in this field in order to offer additional data and contribute to identify more accurate cut-off points for waist circumference in various populations (e.g. Sub-Saharan Africans, South and

Central Americans, Asian, Eastern Mediterranean and Middle East populations). Indeed, cut-off points of >85-90 cm for men and >80 cm for women have been suggested in Japan, while in China threshold values of >85 cm and >80 cm have been proposed in men and women, respectively, and slightly lower values in India (188-190).

Figure 6. Criteria for clinical diagnosis of the metabolic syndrome from the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and recommended waist circumference thresholds for abdominal obesity by organization (adopted from Alberti *et al*. Circulation 2009 (25)).

CRITERIA FOR CLINICAL DIAGNOSIS OF THE METABOLIC SYNDROME	
RISK FACTOR-MEASURE	**CATEGORICAL CUT-OFF POINTS**
1. Increased waist circumference *	Population- and country-specific definitions
2. Increased TG (drug treatment for increased triglycerides is an alternate indicator †)	≥150 mg/dL (1.7 mmol/L)
3. Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator †)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
4. Increased blood pressure (antihypertensive drug treatment in a patient with a hypertension history is an alternate indicator)	Systolic BP ≥130 mm Hg and/or Diastolic BP ≥85 mm Hg
5. Increased fasting plasma glucose ‡ (drug treatment of increased glucose is an alternate indicator)	≥100 mg/dL
Presence of any 3 of 5 risk factors constitutes a diagnosis of metabolic syndrome *: It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available. †: The most commonly used drugs for increased triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose of ω-3 fatty acids presumes high triglycerides. ‡: Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria HDL-C: high-density lipoprotein cholesterol; BP: blood pressure	

RECOMMENDED WAIST CIRCUMFERENCE THRESHOLDS FOR ABDOMINAL OBESITY			
POPULATION	**WC IN MEN**	**WC IN WOMEN**	**ORGANIZATION**
Europid	≥94 cm	≥80 cm	IDF
Caucasian	≥94 cm (increased risk) ≥102 cm (higher risk)	≥80 cm (increased risk) ≥88 cm (higher risk)	WHO
United States	≥102 cm	≥88 cm	AHA/NHLBI (ATP-III)
Canada	≥102 cm	≥88 cm	Health Canada
European	≥102 cm	≥88 cm	European CV Societies
Asian (including Japanese)	≥90 cm	≥80 cm	IDF
Asian	≥90 cm	≥80 cm	WHO
Japanese	≥85 cm	≥90 cm	Japanese Obesity Society
China	≥85 cm	≥80 cm	Cooperative Task Force
Middle East, Mediterranean	≥94 cm	≥80 cm	IDF
Sub-Saharan African	≥94 cm	≥80 cm	IDF
Ethnic Central & South American	≥90 cm	≥80 cm	IDF
WC: waist circumference; CV: cardiovascular; IDF: International Diabetes Federation; WHO: World Health Organization; AHA: American Heart Association; NHLBI: National Heart, Lung, and Blood Institute			

In 2009, another attempt was made to resolve the differences between metabolic syndrome definitions, which resulted in a joint interim statement from the American Heart

Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and the IDF (25). To harmonize the metabolic syndrome criteria, this statement accepted the previous five criteria of the IDF and ATP-III definitions and agreed that central obesity should not be a prerequisite for diagnosis, which instead should be confirmed by the presence of any 3 of the 5 accepted risk factors (**Figure 6**). In this joint definition, central obesity is defined based on population- and country-specific thresholds of waist circumference with a recommendation that the IDF cut-offs should be used for non-Europeans, while either the IDF or the AHA/NHLBI cut-offs can be used for people of European origin until more data become available (Figure 6).

The more recent metabolic syndrome definitions have contributed in setting more widely accepted diagnostic criteria for both research and clinical practice (25, 181, 186, 191). Despite these efforts, there has been significant debate and controversy as to whether the diagnosis of the metabolic syndrome adds more value compared to its individual components, especially in clinical decision making (177, 192-199). Indeed, based on a more recent report of a WHO Expert Consultation the metabolic syndrome is considered useful mainly as an educational concept with limited practical utility as a diagnostic or disease management tool (198, 199). However, the metabolic syndrome diagnosis and its definitions are still applied in research studies and in clinical practice, whilst both traditional and technology supported lifestyle interventions are utilized for the treatment of the metabolic syndrome and its components (200). As such, it is important to stress that, in parallel to the risk conferred by a metabolic syndrome diagnosis, additional risk factors, such as age, gender, smoking, low-density lipoprotein cholesterol (LDL-C) plasma levels and other obesity-related comorbidities (e.g. non-alcoholic fatty liver disease and obstructive sleep apnea), substantially increase the related CVD risk and must be comprehensively assessed and addressed in routine clinical practice, as will be further reviewed in the EndoText chapter dedicated to the metabolic syndrome and its treatment.

Obesity and Non-Alcoholic Fatty Liver Disease

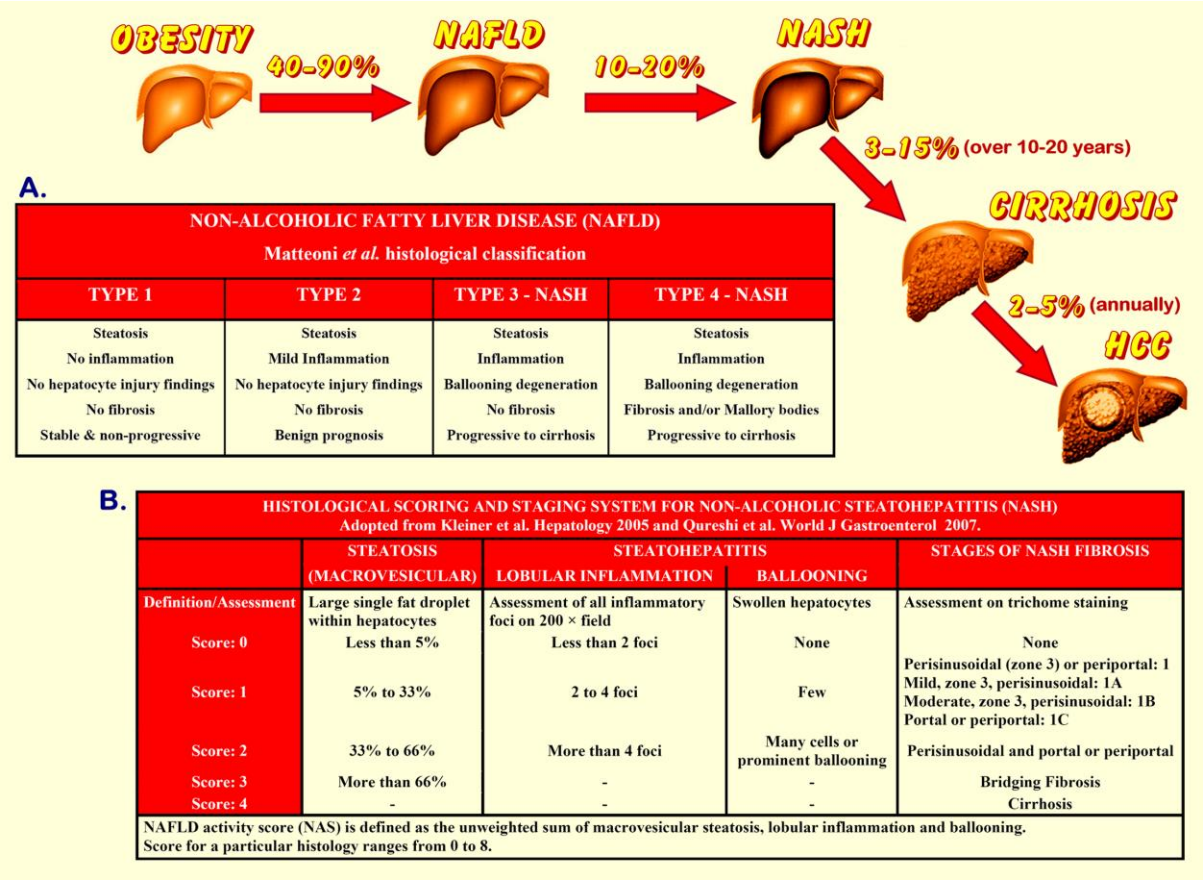
The liver is the largest solid organ in adults, constituting 2-3% of the body weight and accounting for 25-30% of the total oxygen consumption. Normal hepatic function is essential for preserving metabolic homeostasis and a dynamic crosstalk exists between the liver and adipose tissue to regulate carbohydrate, lipid, and protein metabolism. Obesity may cause hyperinsulinemia and hyperglycemia, as well as ectopic fat accumulation and insulin resistance in the liver. In turn, this can impair hepatic function and lead to a spectrum of abnormalities, ranging from elevation of circulating liver enzyme levels and steatosis to local inflammation (steatohepatitis), cirrhosis, liver failure and even liver cancer (201-208). The term non-alcoholic fatty liver disease (NAFLD) is now applied to describe this spectrum of hepatic abnormalities.

The relationship between obesity and liver dysfunction has been noted in the literature since the first half of the past century (209). In 1980, the term non-alcoholic steatohepatitis (NASH) was introduced by Ludwig *et al.* to describe findings in 20 patients at the Mayo clinic exhibiting a non-alcohol related liver disease which was histologically similar to alcoholic hepatitis (210). Hepatocellular steatosis is the hallmark of the disease (triglyceride deposition in the liver higher than 5% of the total liver weight), and the presence of more than 5% of steatotic hepatocytes in a liver tissue section is now regarded as the minimum criterion for

the histological diagnosis of NAFLD (211-213). This steatosis reflects ectopic fat deposition in the liver which is more frequently macrovesicular (one large intracellular fat droplet displacing the nucleus). Microvesicular steatosis (numerous small intracytoplasmic fat vesicles not displacing the nucleus) may also occur, but is less frequent and it can be underestimated due to limitations of routinely applied staining techniques (211-213).

Non-alcoholic fatty liver disease pathology extends from steatosis to steatohepatitis and fibrosis. In 1999, Matteoni *et al.* proposed a histologic classification of NAFLD into four distinct types (**Figure 7**) (214).

Figure 7. Natural History of Non-Alcoholic Fatty Liver Disease (NAFLD). **A.** Histological classification as proposed by Matteoni *et al.* (214). Non-alcoholic steatohepatitis (NASH) represents the most severe form of NAFLD (NAFLD types 3 and 4) and can progress to cirrhosis and hepatocellular carcinoma (HCC). **B.** NAFLD activity score (NAS) proposed for histological scoring and staging of NAFLD in order to consistently assess the disease and compare outcomes of therapeutic interventions (adopted from Kleiner *et al*. Hepatology 2005 (206, 215)).



A.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) Matteoni *et al.* histological classification			
TYPE 1	TYPE 2	TYPE 3 - NASH	TYPE 4 - NASH
Steatosis No inflammation No hepatocyte injury findings No fibrosis Stable & non-progressive	Steatosis Mild Inflammation No hepatocyte injury findings No fibrosis Benign prognosis	Steatosis Inflammation Ballooning degeneration No fibrosis Progressive to cirrhosis	Steatosis Inflammation Ballooning degeneration Fibrosis and/or Mallory bodies Progressive to cirrhosis

B.

HISTOLOGICAL SCORING AND STAGING SYSTEM FOR NON-ALCOHOLIC STEATOHEPATITIS (NASH) Adopted from Kleiner et al. Hepatology 2005 and Qureshi et al. World J Gastroenterol 2007.				
	STEATOSIS (MACROVESICULAR)	STEATOHEPATITIS		STAGES OF NASH FIBROSIS
		LOBULAR INFLAMMATION	BALLOONING	
Definition/Assessment	Large single fat droplet within hepatocytes	Assessment of all inflammatory foci on 200 × field	Swollen hepatocytes	Assessment on trichome staining
Score: 0	Less than 5%	Less than 2 foci	None	None
Score: 1	5% to 33%	2 to 4 foci	Few	Perisinusoidal (zone 3) or periportal: 1 Mild, zone 3, perisinusoidal: 1A Moderate, zone 3, perisinusoidal: 1B Portal or periportal: 1C
Score: 2	33% to 66%	More than 4 foci	Many cells or prominent ballooning	Perisinusoidal and portal or periportal
Score: 3	More than 66%	-	-	Bridging Fibrosis
Score: 4	-	-	-	Cirrhosis
NAFLD activity score (NAS) is defined as the unweighted sum of macrovesicular steatosis, lobular inflammation and ballooning. Score for a particular histology ranges from 0 to 8.				

Non-alcoholic steatohepatitis(NASH) corresponds to types 3 and 4 of this classification, representing the most severe histologic form of NAFLD. In addition to steatosis, NASH is characterized by various degrees of inflammation, hepatocyte injury and fibrosis which may gradually lead to cirrhosis (211-213). Subsequently, various scoring systems for grading and staging of NAFLD have been developed to assess the disease and compare outcomes of therapeutic interventions. The Pathology Committee of the NASH Clinical Research Network

designed and validated a histological feature scoring system for the entire spectrum of NAFLD lesions and proposed the NAFLD activity score (NAS) which was developed as a tool to measure changes in NAFLD during therapeutic trials (Figure 7) (212, 213, 215). It must be noted that distinction between NASH and alcoholic hepatitis may be difficult at the histological level, and, thus, a detailed alcohol consumption history is always crucial when evaluating patients with suspected NAFLD in clinical practice (203). Indeed, according to the recent clinical practice guidelines for the management of NAFLD by the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO), the interaction between moderate alcohol intake and various metabolic factors in fatty liver must always be considered (216). Non-invasive scoring systems and methods have also been proposed in order to identify advanced fibrosis in NAFLD patients, including the NAFLD Fibrosis Score (NFS), the Enhanced Liver Fibrosis (ELF) panel and transient elastography which measures liver stiffness non-invasively (203, 216-218).

Non-alcoholic fatty liver disease is now recognized as the most common cause of chronic liver disease, with rising prevalence and worldwide distribution which follows the global trends of obesity and T2DM (201-203, 208, 219, 220). Data on NAFLD prevalence in the general adult population vary depending on the applied diagnostic criteria and the population studied. Moreover, large-scale population studies are generally hindered by the fact that this liver disease can remain asymptomatic for years, may coincide with other chronic liver diseases and requires a liver biopsy for definite diagnosis (203, 221). Non-alcoholic fatty liver disease is thought to be present in approximately 25% of the Asian population, and in 25% to over 30% of the US population with a corresponding NASH prevalence of 3-6% in the US (201, 203, 208, 219). Moreover, in the US it is estimated that the prevalent NAFLD cases will increase by 21%, from an estimated 83.1 million cases in 2015 (25.8% prevalence among all ages, and 30% prevalence among individuals aged ≥ 15 years) to 100.9 million cases in 2030, whilst, in parallel, the prevalent NASH cases will increase by 63%, from 16.52 to 27 million cases (222). Estimates of the NAFLD prevalence worldwide, based on a variety of assessment/diagnosis methods, range from 6.3% to 33%, with a median of 20% in the general adult population, whilst the estimated NASH prevalence ranges from 3% to 5% (203). Recently, the pooled overall global prevalence of NAFLD diagnosed by imaging has been estimated at 25.24% (95% CI: 22.10-28.65), with the highest prevalence rates in the Middle East and South America and the lowest in Africa (223). Particularly significant are also the reported data in cohorts with T2DM and/or obesity which consistently document very high NAFLD prevalence rates, thus suggesting strong pathogenetic links. Indeed, the majority of patients with T2DM and/or obesity appear to develop steatosis, while NASH can be diagnosed in 10-20% of these cases (203, 208, 220). Of note, NAFLD prevalence is even higher among patients with severe obesity, since the reported prevalence of NAFLD in bariatric surgery patients can exceed 90%, whilst up to 5% of these patients may have unsuspected cirrhosis (203, 220, 224, 225). It must be highlighted that NAFLD is not restricted to adults, but also exhibits increasing prevalence among the pediatric population (estimated pediatric NAFLD prevalence of 3-10%), with reported NAFLD prevalence rates of up to 80% in children with obesity based on studies from the US, Europe and Japan (203, 226).

Gender, age and ethnicity are associated with the prevalence of NAFLD (203, 220). As such, gender differences appear to exist, and, although the initially available data suggested

female predominance, male gender is now considered a risk factor for NAFLD (220). Furthermore, several studies have shown that NAFLD prevalence increases with age, although relevant studies on individuals older than 70 years remain rather limited (203, 223, 227). Family clustering and significant ethnic variations have also been documented, supporting the role of genetic predisposition (203, 219, 228, 229). Asian populations are considered particularly susceptible to NAFLD, partly due to body composition differences, with NAFLD prevalence rates that range between 20% in China and 15-45% in South Asia and Japan (219, 230). In addition, Hispanic individuals have significantly higher, and non-Hispanic blacks have significantly lower, NAFLD prevalence, compared to non-Hispanic whites (203, 229).

Studies on the natural history of NAFLD have shown that the underlying histologic stage dictates the prognosis of the disease, which appears to rely crucially on the presence of fibrosis (Figure 7) (201, 203, 208, 218, 220, 231-233). It is generally accepted that simple steatosis with absence of inflammation and fibrosis is associated with a benign and stable long-term course in the vast majority of the cases, exhibiting no or very slow histological progression (203, 218, 220). On the other hand, patients with NASH can exhibit histological progression to cirrhotic-stage disease (203, 218, 220). Indeed, NASH is associated with an increased risk for developing cirrhosis, liver failure and even hepatocellular carcinoma (HCC), with studies indicating that 3-15% of NASH cases can progress to cirrhosis over 10-20 years (234, 235). The prognosis is poor once NASH-related cirrhosis is established and a high proportion of these cases will require liver transplantation. Furthermore, HCC has been reported to develop at an annual rate of 2-5% in NASH patients with cirrhosis (236, 237). In a study with long-term follow-up of a small cohort with biopsy-proven NAFLD (129 patients followed for 13.7 years) NASH patients had significantly reduced survival due to liver-related and CVD causes (238). Overall, the age and gender adjusted mortality rate in NAFLD patients is significantly higher compared to the general population (both for overall and liver-related mortality) (203, 232, 239). A meta-analysis by Musso *et al.* reported that NAFLD has a 2-fold risk of T2DM and an increased overall mortality (OR: 1.57, 95% CI: 1.18-2.10) due to liver-related problems and CVD, with the odds ratio of liver-related mortality in the presence of advanced fibrosis being 10.06 (95% CI: 4.35-23.25; p=0.00001) compared with less advanced fibrosis stages (218). Non-alcoholic fatty liver disease severity tends to increase with age, but regression is also possible if prompt and effective weight loss interventions are applied before the stage of cirrhosis. However, signs of regression can be misleading, particularly in older patients, since progressing fibrosis may be silent or even associated with normalization of aminotransferases levels and improvement of steatosis and inflammation features. This often reflects a transition of NASH to cryptogenic cirrhosis which is associated with high HCC risk (203, 233, 240, 241).

The pathogenesis of NAFLD has been the subject of intense research in recent years (201). Initially, Day *et al*. first proposed a two stage hypothesis/model in order to provide a pathophysiological rationale (“two-hit” model), describing steatosis (reversible intracellular deposition of triacylglycerols) as the initial stage (first “hit”) that sensitizes the liver to the “second hit” (generation of free radicals, oxidative stress and cytokine-induced hepatic injury) which induces progression to fibrosis (242). This model offered an initial framework to study NAFLD pathogenesis; however, it is now regarded that progression to steatohepatitis is not limited to a “two-hit” process, but rather involves multiple interacting mechanisms occuring in parallel (208, 233, 243). Indeed, the pathogenesis of NAFLD appears to involve

a complex interplay between genetic predisposition, environmental factors (e.g. diet composition, sedentary lifestyle, smoking), metabolic dysregulation (e.g. dyslipidemia, lipotoxicity and hyperglycemia) and other contributors, such as dysbiosis of the gut microbiota (201, 207, 208, 228, 233, 243-247).

In the context of this chapter, we will briefly highlight crucial pathophysiologic processes linking obesity (especially central/visceral obesity) and obesity-related insulin resistance with NAFLD and its progression to NASH. Fat accumulation in adipose tissue depots is typically followed by ectopic fat deposition in the liver and skeletal muscle and by insulin resistance in these tissues. Although hepatic insulin resistance can develop independently as a result of increased hepatocyte triglyceride content, growing evidence indicates that this usually follows insulin resistance in adipose tissue (207, 208, 245). Thus, obesity-related insulin resistance can cause fatty liver and, *vice versa,* excessive intrahepatic fat accumulation may promote insulin resistance and weight gain (110). However, the lipogenic actions of insulin appear to remain uncompromised in insulin-resistant states; hence, *de novo* fatty acid synthesis is undeterred even in the presence of marked insulin resistance (e.g. hepatic transcription of the gene encoding SREBP-1c remains stimulated by both insulin and glucose; **Figure 8**). Insulin resistance induces decreased inhibition of lipolysis in adipocytes, as well as decreased inhibition of gluconeogenesis and increased lipogenesis in the liver. Thus, steatosis is closely associated with an overall enhanced hepatic influx of circulating FFA that have been released by insulin resistant adipocytes. Importantly, in central obesity visceral fat depots exhibit a higher lipolysis turnover creating an amplified direct supply of FFA to the liver via the portal vein, which can account for 20-30% of the total hepatic FFA influx (248). Moreover, there is also evidence that hepatic accumulation of previously stored body fat and saturated dietary fat may induce hepatic insulin resistance (249).

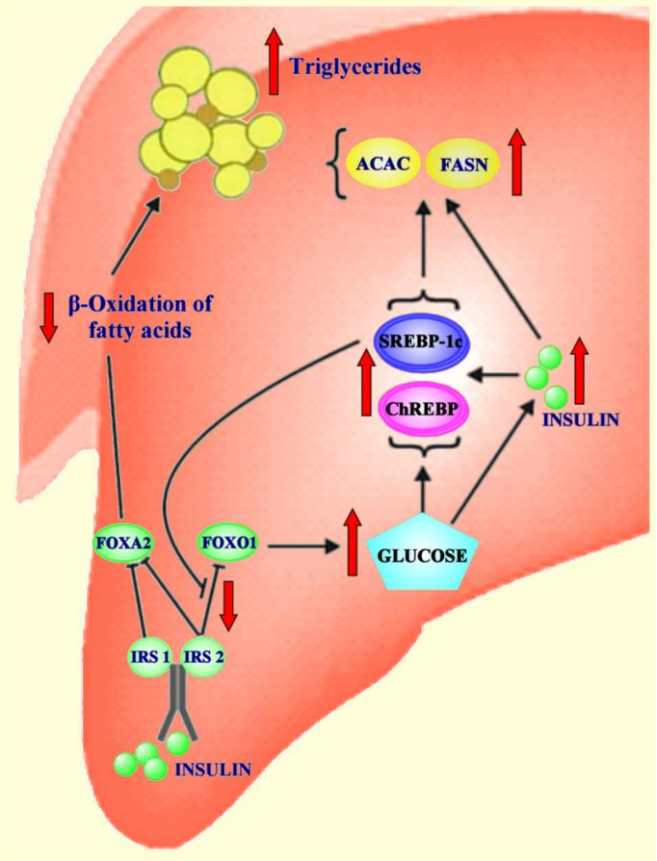


Figure 8. Signaling Pathways Leading to Hepatic Triglyceride Accumulation in Insulin-Resistant States. In insulin sensitive states, insulin binds to its receptor and activates IRS1 and IRS2 which, via PKB/Akt, block gluconeogenesis (FOXO1) and fatty acid oxidation (FOXA2). In insulin resistance, the FOXA2 pathway may remain responsive to insulin when inhibition of FOXO1 is impaired, resulting in decreased fatty acid oxidation. In turn, elevated glucose activates both SREBP-1c and ChREBP, enhancing pancreatic insulin secretion (compensatory hyperinsulinemia). SREBP-1c blocks IRS2 signaling in the liver, further promoting hepatic glucose production, and probably counteracting the suppressive effect

of SREBP-1c on gluconeogenic genes. Insulin, ChREBP and SREBP-1c also induce FASN and ACAC, leading to increased production of fatty acids. Thus, in insulin-resistant states hepatic triglycerides accumulate as a result of both reduced fatty acid oxidation and increased fatty acid production. Red arrows indicate the direction of changes in insulin-resistant states. ACAC: Acetyl-CoA carboxylase; ChREBP: carbohydrate response element-binding protein; FASN: fatty acid synthase; FOX: forkhead transcription factor; PKB: protein kinase B/Akt; SREBP: sterol response element-binding protein (adopted from Weickert *et al*. Diabetologia 2006 (110)).

On the other hand, newly produced fat by the liver, as well as mono- and poly-unsaturated dietary fat are likely to have less deleterious or even beneficial effects, suggesting compartmentalization of fatty acid metabolism in hepatocytes (249). In the context of hepatic insulin resistance, hyperinsulinemia and hyperglycemia can further increase the intrahepatic triglyceride content by stimulating *de novo* lipogenesis (DNL), impaired hepatic fatty acid oxidation and decreased VLDL efflux, while dietary fatty acids also contribute to steatosis (**Figure 9**) (250, 251). Indeed, it has been shown that of the triacylglycerol accounted for in the liver of NAFLD patients approximately 60% originates from serum FFA, 26% from DNL, and 15% from the diet (250). Moreover, a positive correlation is reported between the degree of insulin resistance and steatosis (252).

Furthermore, progression from steatosis to NASH and cirrhosis also appears connected to a diffusion of detrimental effects from adipose tissue depots to the hepatic cellular level (203-208). Indeed, NASH development in the steatotic liver involves increased hepatic insulin resistance and lipid peroxidation, in combination with local pro-inflammatory, oxidative stress, and endoplasmic reticulum stress responses. In obesity-related insulin resistance these pathways are triggered and fuelled by hyperleptinemia, hypoadiponectinemia and increased circulating concentrations of adipose-derived cytokines (e.g. TNF-α and IL-6). Intermittent exposure of the steatotic liver to this adverse adipokine profile increases hepatic insulin resistance and leads to mitochondrial dysfunction, inflammation, cell injury, apoptosis and fibrosis (203-208). Hepatocytes are also stimulated to locally secrete pro-inflammatory cytokines and factors (e.g. TNF-α, IL-6, IL-1β). In addition, hepatic stellate cells and Kupffer cells are activated, while circulating inflammatory cells are chemo-attracted and infiltrate the liver (253, 254). The outcome of these processes is a chronic pro-inflammatory state inside the liver, which bears resemblance to the low-grade inflammation within adipose tissue depots in obesity. Further research in the pathophysiology of NAFLD is required to fully clarify these underlying pathogenetic mechanisms, and lead to targeted therapeutic interventions which could either prevent steatosis or stop/delay progression to steatohepatitis.

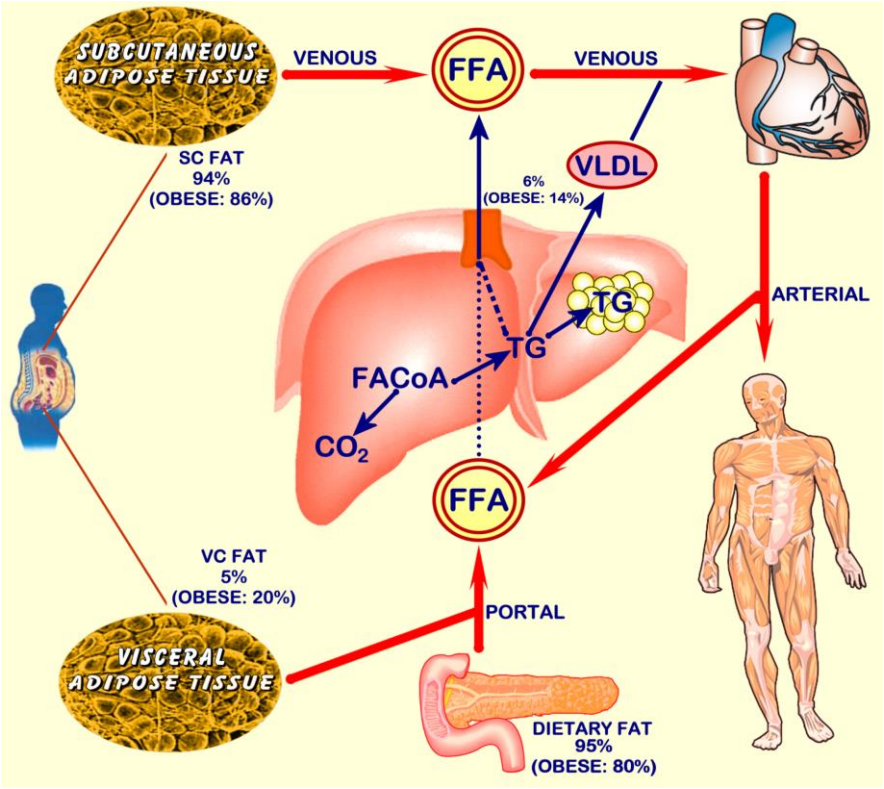


Figure 9. Free Fatty Acid (FFA) Circulation Through the Liver (adopted from Roden *et al*. Nat Clin Pract Endocrinol Metab 2006 (251) with data from Nielsen *et al*. J Clin Invest 2004 (248). Adipose tissue delivers approximately 80% of circulating FFA in the fasted state, reduced to 60% postprandially. In normal-weight persons dietary fat is responsible for the bulk of the portal supply to hepatic FFA, with the remaining proportion being derived mainly from subcutaneous fat. The contribution of FFA supplied from visceral adipose tissue increases in individuals with obesity, whereas a lower percentage of FFA is supplied from both subcutaneous fat depots and dietary fat. This could be important given that the source of FFA might be relevant for metabolic effects of hepatic lipid accumulation (reviewed in Weickert *et al*. Diabetologia 2006 (110)). FACoA: long-chain fatty acids bound to coenzyme A.

Detailed description of the treatment options for NAFLD is beyond the scope of this chapter. Various position papers and clinical practice guidelines have been published by international and national scientific societies (216, 255). As such, EASL, EASD, and EASO have recently issued clinical practice guidelines for the management of NAFLD (216). It must be noted that, while several clinical trials are exploring the safety and efficacy of various agents for the treatment of NASH and hepatic fibrosis, no agent is specifically approved by regulatory agencies for NASH treatment (201, 216). Thus, weight loss remains vital for the management of NAFLD patients with obesity. Evidence suggests that weight loss of at least 3-5% of the body weight appears necessary to improve steatosis, while greater weight loss (up to 10%) may be required to improve necroinflammation (203). Therefore, pragmatic approaches should be discussed with NAFLD patients with overweight/obesity in order to adhere to lifestyle modifications combining dietary interventions and increased physical activity (e.g. aerobic exercise or resistance training), aiming to achieve and maintain a meaningful weight loss (201, 216). In addition to weight loss interventions, appropriate treatment for any coexisting metabolic syndrome manifestation (e.g. for T2DM, dyslipidemia and hypertension) should be also offered in order to both improve the underlying liver pathology, and to further address the associated high CVD morbidity and mortality.

Obesity and Gallbladder Disease

Gallbladder disease is a common gastrointestinal disorder in Western countries and cholelithiasis represents the most frequent hepatobiliary pathology, primarily with gallstones composed of cholesterol (approximately 80% of gallstones are cholesterol stones) (256, 257). The prevalence of gallstones reaches 10-20% in the adult population in developed countries and it is estimated that in the US alone more than 700,000 cholecystectomies are performed per year with annual costs of approximately 6.5 billion US dollars (257, 258). Female gender, increasing age, and family history are typical risk factors for gallstones, while the main modifiable risk factors include obesity, metabolic syndrome, and high caloric intake (257-260). Overall, cholelithiasis is strongly associated with being overweight and obese and a classic medical textbook mnemonic for gallstone risk factors is known as the "*4 Fs*" ("*fat, female, fertile, and forty*") (41, 260-265). The relative risk of gallstone formation rises as body weight increases, exhibiting a positive correlation with increasing BMI which is more pronounced when BMI exceeds 30 kg/m^2 (41, 261-263). In the Nurses' Health Study women with BMI over 30 kg/m^2 had twice the risk of gallstones compared to non-obese women, while a 7-fold excess risk was noted in women with BMI over 45 kg/m^2 compared to those with BMI less than 24 kg/m^2 (263). Obesity and female gender remain risk factors for gallstone disease even in children and adolescents (266-268). Higher prevalence of cholelithiasis with increasing BMI is also reported in men; however, this association appears less potent and appears to depend more on abdominal fat accumulation than on body weight alone (262, 269, 270). Indeed, large prospective studies among US adults of both genders indicate that indices of central obesity (e.g. waist circumference and waist-to-hip ratio) can predict the risk of gallstones and cholecystectomy independent of BMI (271, 272).

In addition to a higher prevalence of cholesterol gallstones, a study on gallbladder pathology in morbidly obese individuals has further documented significantly increased prevalence of cholecystitis and cholesterolosis (273). Interestingly, obesity may be also associated with inflammation and fatty infiltration of the gallbladder (fatty gallbladder disease, including cholecystosteatosis and steatocholecystitis), which results in abnormal wall structure and decreased gallbladder contractility (274, 275). Of note, it has been reported that NASH prevalence in patients with morbid obesity and gallbladder disease can be as high as 18%, with insulin resistance being more common in concurrent NASH and gallbladder disease (276). Moreover, another study reported cholelithiasis as an independent risk factor of NAFLD (277). Finally, obesity appears to increase both the risk of hospital admission and the length of hospital stay for gallbladder disease (278), as well as the conversion rate from laparoscopic cholecystectomy to open surgery in patients with symptomatic gallstone disease (279).

Several mechanisms have been proposed to explain the association between excess body weight and formation of cholesterol gallstones, focusing primarily on secretion of supersaturated bile and gallbladder stasis (256, 280-284). Thus, obesity is characterized by a high daily cholesterol turnover which is proportional to the total body fat mass and can result in elevated biliary cholesterol secretion (256, 280-282). This leads to supersaturation of the bile which becomes more lithogenic with high cholesterol concentrations relative to bile acids and phospholipids. Notably, in patients with obesity the bile also remains supersaturated for much longer periods of time and not only during the fasting state. Furthermore, obesity is associated with gallbladder hypomotility and stasis which predispose to gallstones formation. Increased fasting and residual volumes, as well as decreased fractional emptying of the gallbladder have also been reported in patients with obesity (285-

288). Interestingly, hyperinsulinemia may cause both increased cholesterol supersaturation and gallbladder dysmotility (289-292).

Rapid weight loss in patients with obesity is also associated with increased risk of gallstone formation (293-300). Of note, weight cycling has been also shown to increase the risk of cholecystectomy, independent of BMI (301). Increased bile lithogenicity during weight loss is potentially attributed to an enhanced flux of cholesterol through the biliary system, while low intake of dietary fat may further impair gallbladder motility and cause stasis (293, 294, 300). Thus, diets with moderate levels of fat may reduce cholelithiasis risk by triggering gallbladder contractions and maintaining an adequate gallbladder emptying (293). A meta-analysis has also indicated that use of ursodeoxycholic acid can also prevent gallstone formation after surgical weight loss interventions (302).

The increased risk of gallstone formation with rapid weight loss is of particular significance following bariatric surgery. It is suggested that patients with severe obesity undergoing bariatric surgery should be considered at high risk for developing gallstone disease independently of other risk factors (295-299). Indeed, a retrospective study regarding predictors of gallstone formation after bariatric surgery reported that weight loss exceeding 25% of the initial body weight was the only postoperative factor that helped in selecting patients for postoperative ultrasound surveillance and subsequent cholecystectomy once gallstones were identified (296). Another study comparing cholecystectomy cases after Roux-en-Y gastric bypass, sleeve gastrectomy, and gastric banding reported that the frequency of symptomatic gallstones did not differ significantly between the first two procedures, while it was significantly lower after gastric banding potentially due to lower and slower weight loss (298). Concomitant prophylactic cholecystectomy with bariatric procedures has been suggested in order to prevent postoperative gallstone formation (303, 304). However, there is no clinical consensus on this point, while a growing body of evidence suggests that concomitant cholecystectomy should not be routinely performed during bariatric surgery, but only in bariatric patients with symptomatic gallbladder disease or at a second stage after the bariatric operation in patients who had or developed asymptomatic gall stones (305-310).

Gallstones are the major risk factor for biliary tract cancers and particularly for gallbladder cancer; however, gallbladder cancer is rare in Europe and North America reflecting the widespread and earlier adoption of cholecystectomy (high-risk areas remain mainly in South America and India where access to gallbladder surgery is still inadequate) (311-313). Subsequently, studies on the relationship between obesity and gallbladder cancer are limited. However, the available data are consistent in indicating that obesity is indeed associated with increased risk of gallbladder cancer, potentially attributed to higher risk of cholelithiasis and chronic inflammation (305, 311). Meta-analysis data that included eleven studies (three case-control and eight cohort studies with a total of 3288 cases) have also confirmed that excess body weight could be considered a risk factor for gallbladder cancer (314). In this meta-analysis, compared to normal weight individuals, the summary relative risk of gallbladder cancer for overweight and obese subjects was 1.15 (95% CI, 1.01-1.30) and 1.66 (95% CI, 1.47-1.88), respectively. Notably, the documented association with obesity was stronger for women (relative risk of 1.88; 95% CI, 1.66-2.13) than for men (1.35; 95% CI, 1.09-1.68). Accordingly, the 2016 working group of the International Agency for

Research on Cancer (IARC) has concluded that there is sufficient evidence to support that excess body fatness causes gallbladder cancer (315, 316).

Obesity and Reproduction

Obesity can cause dysfunction of the hypothalamic-pituitary-gonadal (HPG) axis in both genders (317-319) (see also corresponding chapter in EndoText on Endocrine Consequences of Obesity). Reproductive disorders are more frequent in obese women, presenting with a wide range of manifestations that extend from menstrual abnormalities to infertility, while obese men can exhibit decreased libido, erectile dysfunction, sub-fertility and more rarely hypogonadism (318, 320-324). Despite recent progress in understanding the role of adipose tissue in multiple neuro-endocrine networks, the exact pathogenetic mechanisms linking excess fat accumulation to HPG dysfunction have not been fully elucidated. As such, current research is focused on interactions between adipokines and the HPG (325), with leptin being the prototype adipokine which plays a vital role as a pleiotropic modulator of energy homeostasis and reproduction (318, 319, 326-331). Furthermore, increased metabolism of sex steroids within adipose tissue depots can lead to abnormal plasma levels of androgens and estrogens, thus, potentially affecting the reproductive axis in obesity (332-335). Sex hormone binding globulin (SHBG) is also implicated in obesity-related reproductive dysfunction by regulating the bio-availability of sex steroids (336). Patients with obesity tend to exhibit decreased circulating SHBG levels, with higher bio-available sex-steroid levels and increased sex-steroid clearance. This results from direct suppression of SHBG synthesis in the liver by insulin, which is apparently more potent in central obesity due to more pronounced insulin resistance and compensatory hyperinsulinemia (332-334, 337). Finally, it must be noted that a psychological component may also frequently be present, with reciprocal relationships between obesity and psychological comorbidities, especially anxiety and depression. This can significantly contribute to male and female impairment in sexual functioning, which may manifest as decreased sexual desire, lack of sexual activity enjoyment, difficulties in sexual performance and avoidance of sexual encounters (338-340).

Female Reproductive System and Obesity:

In 1952, Rogers *et al.* first published a study documenting the relation of obesity to menstrual abnormalities (341). Since then it has become evident that, a close link exists between body weight and reproductive health in females from menarche to menopause and beyond (**Figure 10**).

Figure 10. Hormonal Changes and Clinical Manifestations of Hypothalamic-Pituitary-Gonadal (HPG) Axis Dysfunction in Females with Obesity.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS IN OBESE FEMALES	
Hormonal changes	**Clinical manifestations**
↑/↔ Estrogen & ↓/↔ Progesterone	Early menarche - Early menopause
↑ Testosterone	Menstrual disorders
↓ SHBG	Chronic oligo- anovulation
↔ basal FSH	Increased risk of miscarriage & pregnancy complications
↔ basal LH	Impaired fertility - Poor response to fertility treatment
↔ FSH after stimulation	Decreased contraceptive efficacy
↔ LH after stimulation	Increased risk of endometrial, ovarian & postmenopausal breast cancer
↔: normal levels; ↓: decreased levels; ↑: increased levels	

From an evolutionary perspective, menarche marks the beginning of the reproductive potential, which requires sufficient energy stores to facilitate pregnancy and lactation. Thus, it is not surprising that the onset of menstruation is closely related to the presence of a critical body fat mass (342-344). Of note, leptin links energy homeostasis to female reproductive function and appears to act as a metabolic gate to gonadotropin secretion, with minimum critical leptin levels and/or receptor signally being necessary to initiate and maintain the menstrual cycle (318, 319, 325, 328, 342, 345). Indeed, in female patients with anorexia nervosa low leptin levels are associated with amenorrhea and decreased LH and FSH, while regain of fat mass stimulates LH and FSH leading to resumption of menstrual function (345). Several epidemiological studies report a clear correlation between obesity and earlier puberty onset in girls with increased BMI (346-348). In Western societies, the age of pubertal maturation appears to be decreasing among girls in relation to increased prevalence rates of childhood and adolescent obesity (349, 350). However, this is often linked to decreased reproductive performance later in life and growing evidence suggests that weight gain can also lead to earlier ovarian failure and menopause (351, 352).

Menstrual disturbances are the most common manifestation of HPG dysfunction in women with obesity, extending from dysmenorrhea and dysfunctional uterine bleeding to amenorrhea (318, 323, 353, 354). The degree of clinical manifestations is reported to have a strong correlation with BMI and appears related to body fat distribution, since central obesity commonly leads to more severe symptoms (323, 324, 353-355). Abnormal menstrual patterns in women with obesity are primarily attributed to altered androgen, estrogen and progesterone levels (Figure 10), whilst weight loss can restore menstrual regularity, in part, by decreasing androgen aromatization to estrogens in adipose tissue depots (318, 353, 354). Women with obesity and polycystic ovary syndrome (PCOS) constitute a distinct category characterized by (i) polycystic ovaries; (ii) oligo- or anovulation; and (iii) clinical and/or biochemical signs of hyperandrogenism (2 out of 3 criteria according to the Rotterdam consensus for PCOS) (356). Notably, PCOS women with obesity exhibit higher risk of menstrual abnormalities compared to BMI matched women without PCOS, attributed to worse endocrine/metabolic profiles involving various degrees of hyperinsulinemia accompanying insulin resistance that lead to enhance ovarian-stimulated hyperandrogenism (134, 137, 357).

Female obesity is additionally associated with decreased fertility due to chronic anovulation (318, 324, 353, 354). Several studies have reported higher risk of anovulatory infertility with

increasing BMI (358-362). Central fat distribution is considered to play a crucial role in this association through hyperinsulinemic hyperandrogenemia that disrupts ovulation, as also documented in PCOS (353, 354, 363). Interestingly, prehistoric statuettes that are presumed to be fertility idols, including the famous “Venus of Willendorf”, depict women with obesity characterized by pronounced buttocks and thighs (364, 365). Furthermore, obesity can also decrease the success rate of assisted conception methods such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (366-371). Although additional data are still required, women with obesity appear to require higher doses of ovarian stimulation drugs and have increased risk of cycle cancellation and fewer oocytes collected, as well as lower pregnancy and live birth rates compared to normal-weight women (353, 354, 366, 371-375). Thus, weight loss (even modest weight loss of 5-10%) is advised for women with obesity that seek fertility treatment in order to increase the chances of a favorable outcome (376, 377). However, despite good evidence supporting the role of diet, physical activity/exercise, and behavior changes regarding optimal weight gain during pregnancy (378), there is clearly a need for further research into preconception weight loss interventions in order to study the effects of these interventions on key related outcomes (e.g. on live birth rates and the health of both the infant and the mother) and establish better evidence-based guidelines (321). Overall, pregnant women with obesity can be classified as having a high-risk pregnancy associated with increased rates of miscarriage, in addition to a spectrum of both maternal (e.g. gestational diabetes, hypertension and pre-eclampsia, urinary tract infections, thromboembolism, increased incidence of operative delivery, anesthetic risks and postpartum hemorrhage) and fetal (e.g. macrosomia, neural-tube defects and stillbirth) complications (379, 380).

Finally, obesity is also a risk factor for endometrial, postmenopausal breast and ovarian cancer (315, 316, 381-383). The higher risk of these hormone-sensitive gynecologic malignancies in women with obesity is attributed to elevated endogenous estrogen levels that persist even after menopause (adipose tissue consists the major source of postmenopausal estrogen production from androgens) (384, 385). Hyperinsulinemia appears to independently contribute to carcinogenesis, as will be reviewed in the following section of this chapter on obesity and cancer (384-386).

Male Reproductive System and Obesity:

Clinical manifestations of obesity-related HPG axis dysfunction exist also in men, although these appear to be less frequent compared to those in women (320, 323, 325). However, research has been focused mainly on the impact of obesity on the female reproductive health. Thus, it is plausible that the adverse effects of obesity on reproduction in men have been underestimated. Indeed, in recent years, following the increasing availability of assisted conception methods, a growing body of evidence indicates that obesity can significantly impair the male reproductive health, leading to decreased libido, erectile dysfunction, and sub-fertility/infertility (**Figure 11**) (318, 320, 323-325, 333, 351).

Figure 11. Hormonal Changes and Clinical Manifestations of Hypothalamic-Pituitary-Gonadal (HPG) Axis Dysfunction in Male Patients with Obesity.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS IN OBESE MALES	
Hormonal changes	**Clinical manifestations**
↓ Testosterone ↑ Estrogen ↓ SHBG ↓ / ↔ basal FSH ↓ / ↔ basal LH ↔ FSH after stimulation ↔ LH after stimulation	Reduced libido Impaired fertility Erectile dysfunction Potentially increased risk of high-grade prostate cancer and prostate cancer mortality
↔: normal levels; ↓: decreased levels; ↑: increased levels	

Data on secular trends of pubertal maturation in boys and potential relationships to obesity are less clear and partly conflicting (346, 348-350, 387). As such, various studies have reported that increasing BMI and adiposity can be associated with either earlier or later pubertal onset in boys, while lack of correlation has also been documented (348, 387-391). Furthermore, assessing male puberty can be more subjective and unreliable due to lack of a landmark pubertal event similar to menarche in girls. Thus, further data are required to clarify the impact of childhood obesity on male sexual maturation.

Impaired male fertility is also associated with increasing BMI, especially in men with severe obesity when BMI exceeds 40 kg/m^2 (318, 323, 324, 392-394). Semen quality can be significantly affected, and it is reported that both overweight and obese men exhibit markedly higher incidence of oligozoospermia and asthenospermia compared to normal-weight men (320, 323, 325, 392, 395-397). This is primarily attributed to decreased circulating testosterone levels due to higher aromatization of androgens to estrogens in adipose tissue depots, thus suppressing gonadotrohin levels; while SHBG levels can also be decreased (Figure 11) (333, 334, 337, 351, 398). In addition to hormonal changes, men with obesity are predisposed to elevated scrotal temperature, since the scrotum remains in close contact with surrounding tissues, which can potentially increase the risk of altered semen parameters and infertility (318, 323, 399). Finally, severe and longstanding obesity is associated with other comorbidities (e.g. T2DM and macrovascular disease), which further increase the risk of sexual dysfunction in men and can lead to sub-fertility.

In addition, both epidemiologic and mechanistic evidence indicates that there is an association between obesity and prostate cancer, although the data are relatively limited and have been inconsistent (315, 400-406). Large prospective studies link obesity with an increased risk of aggressive (high-grade) prostate cancer, while, on the other hand, obesity is inversely associated with indolent (low-grade) tumors (407-409). Of note, early data also suggest that obesity may be more closely linked to prostate cancer depending on race and molecular subtyping (e.g. in African American patients and in patients with TMPRSS2-ERG-positive tumors) (402). However, it must be highlighted that epidemiologic data on prostate cancer incidence should be interpreted with caution because men with obesity tend to have larger prostate size and lower circulating prostate-specific antigen (PSA) levels (lower PSA due to either lower androgen levels or hemodilution effects); parameters affecting the sensitivity and specificity of both prostate needle biopsy and PSA screening in this population (403-405, 410, 411). Interestingly, it has been reported that the accuracy of PSA

in predicting prostate cancer did not change by BMI category in Asian men (411, 412). More consistently obesity has been associated with a higher risk of prostate cancer-specific mortality (401, 404, 405, 413). For the clinical practice, it has been suggested that men with obesity and prostate cancer should continue to be offered active surveillance as a management option, since their risk of competing mortality is higher compared to normal-weight men (402). Overall, the underlying pathophysiologic mechanisms for the associations between obesity and prostate cancer are considered multifactorial, including changes in androgen levels, increased circulating adipokines, hyperinsulinemia and the low-grade chronic inflammation state in obesity (403, 405, 406, 414).

Obesity, Stress and Psychiatric Co-Morbidities

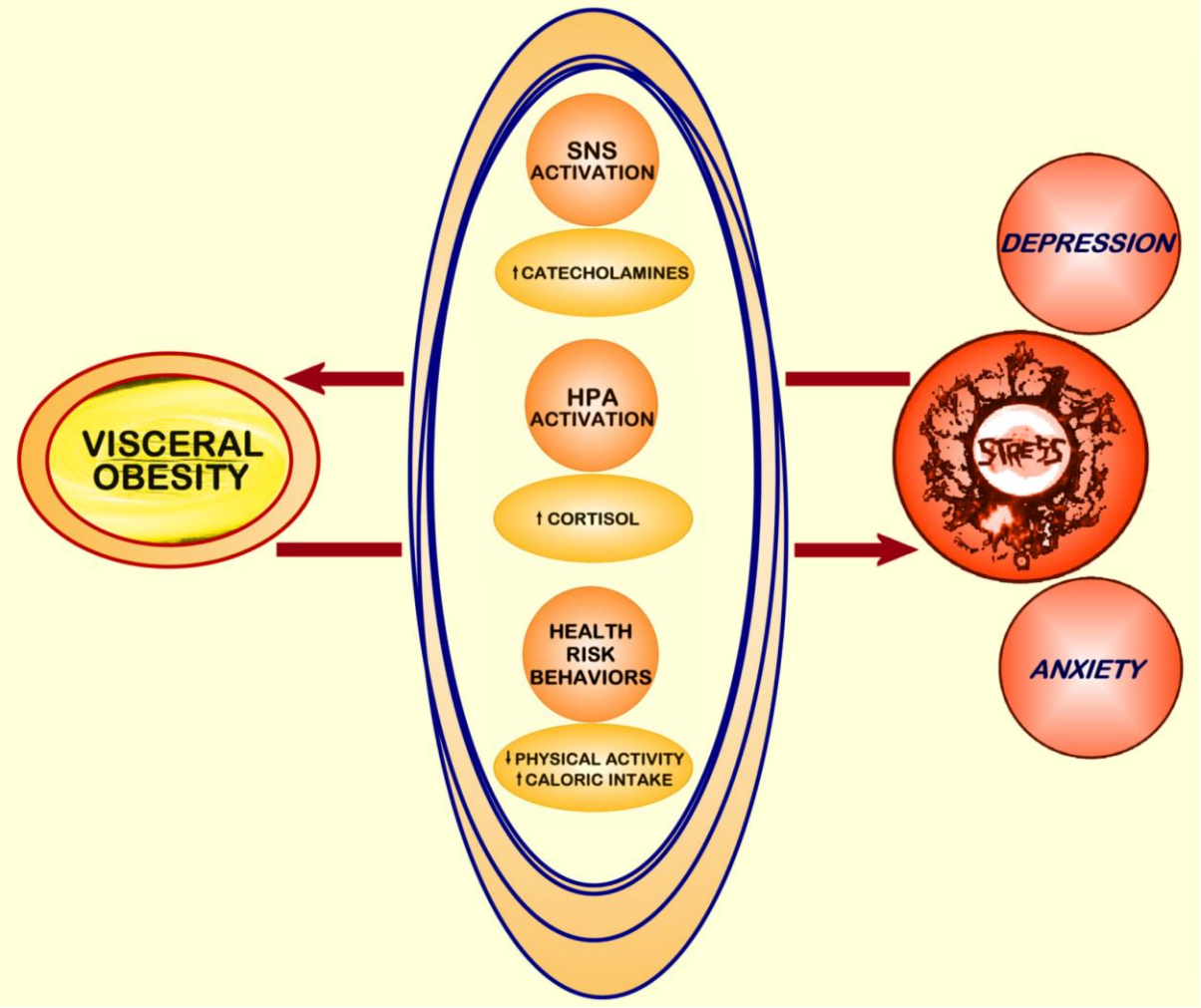
A growing body of evidence indicates that common psychological disorders, such as depression, anxiety and chronic stress, constitute risk factors for developing obesity, metabolic syndrome manifestations, and CVD (415-419). Indeed, prospective data from the Whitehall II cohort documented that common mental disorders increase the risk of obesity in a dose-dependent manner (more episodes of the disorder correlated with higher future obesity risk) (420). Moreover, the odds of obesity in the presence of mental disorders tend to increase with age (421). As such, in a large community-based cohort of elderly persons that was followed for 5 years, baseline depression was associated with increased abdominal fat accumulation independent of overall obesity, suggesting pathogenetic links between depression and central obesity (422). In addition, existing evidence indicates that prolonged and/or intense stress can lead to subsequent weight gain. In the Hoorn Study, enhanced visceral adiposity and higher probability of previously undiagnosed T2DM were associated to the number of major stressful life events during a 5-year preceding period (423). Chronic work-related stress has also been identified as an independent predictive factor for general and central obesity during midlife (424, 425). Interestingly, weight gain in female UK students during their first year at university was related to higher levels of perceived stress (426).

On the other hand, epidemiologic data further support positive correlations between obesity and both depression and anxiety disorders risk (427, 428). These associations appear primarily concentrated among individuals with severe obesity and among females (429-434). The level of existing evidence on these associations is considered relatively moderate, since gender differences and multiple obesity-depression covariations (moderating/mediating factors) are probable, while a limited number of high-quality prospective studies have been published (435-439). However, the “jolly fat” hypothesis, associating obesity with decreased depression risk, should be revisited (440-443). Of note, a U-shaped quadratic relationship between BMI and depression can be proposed (444). In accord with epidemiologic data, there is also an increasing number of prospective, controlled studies reporting remission of depressive symptoms and improved psychological functioning following weight loss through bariatric procedures (445-450). Thus, reversibility is noted regarding adverse effects of obesity on mental health. Conversely, it must be also highlighted that depressive and anxiety disorders are shown to have strong predictive value for reduced weight loss in patients with obesity even when surgical interventions are applied (451).

Overall, obesity can be considered to hold a bi-directional association with psychological well-being, especially with chronic stress and mood disorders (416, 429, 435). This

reciprocal relationship is complex and the underlying pathogenetic interplay has not been fully elucidated. Several mechanisms have been proposed to explain links between obesity and mental health in both directions, mainly focusing on over-activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), as well as on the role of health risk behaviors (**Figure 12**) (452-457).

Figure 12. Reciprocal Relations Between Obesity (Mainly Visceral) and Stress. Chronic stress, manifested with depressive and/or anxiety symptoms, can induce prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) which, together with health risk behaviors, can progressively lead to visceral obesity and *vice versa* (adopted from Kyrou *et al*. Curr Opin Pharmacol. 2009 (457)).



As aforementioned, particularly central obesity induces an unremitting low-grade inflammatory state that is characterized by high plasma levels of pro-inflammatory adipokines (131, 132). This adverse adipokine profile (decreased adiponectin and increased TNF-α, IL-6, and leptin levels) can act as a persistent stress stimulus, leading to chronic hypercortisolemia and SNS activation which predispose to depression and anxiety (454, 458). Conversely, chronic stress and depression, associated with mild hypercortisolemia and increased sympathoadrenal activity, favor visceral fat accumulation and obesity (e.g. favoring enhanced appetite, insulin resistance and increased adipogenesis) (459-463). Interestingly, sleep disorders (e.g. chronic insomnia, inadequate sleep or poor sleep quality)

are also shown to exhibit associations with dysregulated energy balance, obesity and T2DM, mediated through SNS activation and changes in circulating adipokines (e.g. leptin, TNF-α and IL-6) and gut hormones (e.g. ghrelin, glucagon) (464-467). Thus, a deleterious vicious cycle appears to be formed, where weight gain causes prolonged stress system activation (manifested with depression and/or anxiety and/or sleep disorders) and *vice versa*, mediated through hormonal and adipokine effects on multiple endocrine axes and the central nervous system (457, 461, 462). Furthermore, obesity is associated with sedentary lifestyle and socioeconomic disadvantage which increase the risk of depression (468). In turn, over-nutrition, comfort eating, alcohol abuse, and low physical activity are common features of depression and anxiety disorders, promoting the development of obesity. Moreover, patients with obesity often experience obesity-related stigma and discrimination, which further contribute to clinical manifestations of depression and low self-esteem (427, 469). The aforementioned associations highlight the importance of assessing and treating psychiatric co-morbidity as part of weight management interventions (431, 451). In the context of a multidisciplinary approach, clinicians should also take into consideration that several widely prescribed antidepressants and antipsychotic agents can induce weight gain (e.g. tricyclic antidepressants, paroxetine, mirtazapine, monoamine oxidase inhibitors, lithium, clozapine, olanzapine, risperidone) (470, 471).

Obesity and Cancer Risk

Compelling evidence over the past years indicates that obesity and obesity-related diabetes are associated with higher incidence of certain types of cancer (315, 316, 472-484). Indeed, excess adiposity is now considered a key cancer risk factor, so that obesity and physical inactivity are currently recognized among the most important modifiable risk factors for primary cancer prevention, together with tobacco use (316, 484, 485). In 2016, a working group of the International Agency for Research on Cancer (IARC) reassessed the preventive effects of weight control on cancer risk, reviewing the existing epidemiological evidence, as well as mechanistic data and studies in experimental animal models (315, 316). The special report on the findings of this IARC working group concluded that there is sufficient evidence that excess body fatness causes cancer of the esophagus (adenocarcinoma), gastric cardia, colon and rectum, liver, gallbladder, pancreas, breast (postmenopausal), corpus uteri (endometrium), ovary, kidney (renal-cell), meningioma, thyroid, and multiple myeloma (315, 316) (Figure 13). Moreover, according to this IARC working group, currently there is limited evidence to support this link for male breast cancer, fatal prostate cancer, and diffuse large B-cell lymphoma, whilst inadequate relevant evidence exists for squamous-cell carcinoma of the esophagus, and cancer of the gastric noncardia, extrahepatic biliary tract, lung, skin (cutaneous melanoma), testis, urinary bladder, and brain or spinal cord (glioma) (**Figure 13**).

In accord with what is noted for the majority of obesity-related co-morbidities, central obesity is identified as an independent, at least in part, predictor of increased cancer risk. Waist circumference correlates primarily with cancer of the endometrium, breast, colon, pancreas and liver, suggesting pathogenetic links between visceral adiposity and carcinogenesis at these sites/organs (486-488). Overall, the risk of cancer in adults appears to increase when BMI exceeds 22 kg/m^2, and, thus, there is a cancer prevention recommendation regarding body adiposity from the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) to stay as lean as possible within the normal BMI range (recommended public health goal for a median BMI between 21 and 23 kg/m^2 in adults,

depending on normal ranges for different ethnic populations) (489-491). Moreover, emphasis must also be placed on the increasing evidence supporting the impact of weight loss in reducing the obesity-related cancer risk (492-495). Of note, gender and ethnic differences appear to exist regarding the impact of obesity and weight gain on certain types of cancer. Thus, significantly stronger association is documented between BMI and colon cancer in males, whilst correlations between BMI and breast cancer risk appear more potent in the Asia-Pacific region compared to Europe, North America, and Australia (496, 497). Furthermore, the prospective, controlled Swedish Obese Subjects (SOS) study showed that bariatric surgery was associated with a reduction in the cancer incidence among women by 42%, while there was no effect on the cancer incidence among men (492, 494). In addition, the duration of obesity appears to be another significant parameter in the association between increased BMI and cancer risk, with data from the Women's Health Initiative showing that a longer duration of overweight/obesity is associated with higher risk of developing several types of cancer (e.g. the risk of endometrial cancer increased by 17% for every 10-year increase in the duration of overweight in adulthood) (498). Accordingly, childhood obesity may also be associated with increased cancer risk and is suggested to have long-term consequences (e.g. increased risk of death from colon cancer), although further research is required to clarify the exact links between childhood obesity and different types of cancer (39, 499, 500).

Figure 13. Level of evidence regarding the cancer-preventive effect of the absence of excess body fatness according to cancer site/type, based on the special report of the 2016 working group of the International Agency for Research on Cancer (IARC).

Cancer-Preventive Effect of the Absence of Excess Body Fatness & Cancer Site / Type		
SUFFICIENT EVIDENCE	**LIMITED EVIDENCE**	**INADEQUATE EVIDENCE**
Esophagus: adenocarcinoma	Male breast cancer	Esophagus: squamous-cell carcinoma
Gastric cardia	Fatal prostate cancer	Gastric noncardia
Colon and rectum	Diffuse large B-cell lymphoma	Extrahepatic biliary tract
Liver		Lung
Gallbladder		Skin: cutaneous melanoma
Pancreas		Testis
Breast: postmenopausal		Urinary bladder
Corpus uteri		Brain or spinal cord: glioma
Ovary		
Kidney: renal-cell		
Meningioma		
Thyroid		
Multiple myeloma		

Adapted from: International Agency for Research on Cancer Handbook Working Group. N Engl J Med. 2016 Aug 25;375(8):794-8

[Adopted from: International Agency for Research on Cancer Handbook Working Group. N Engl J Med. 2016 Aug 25;375(8):794-8. (315)].

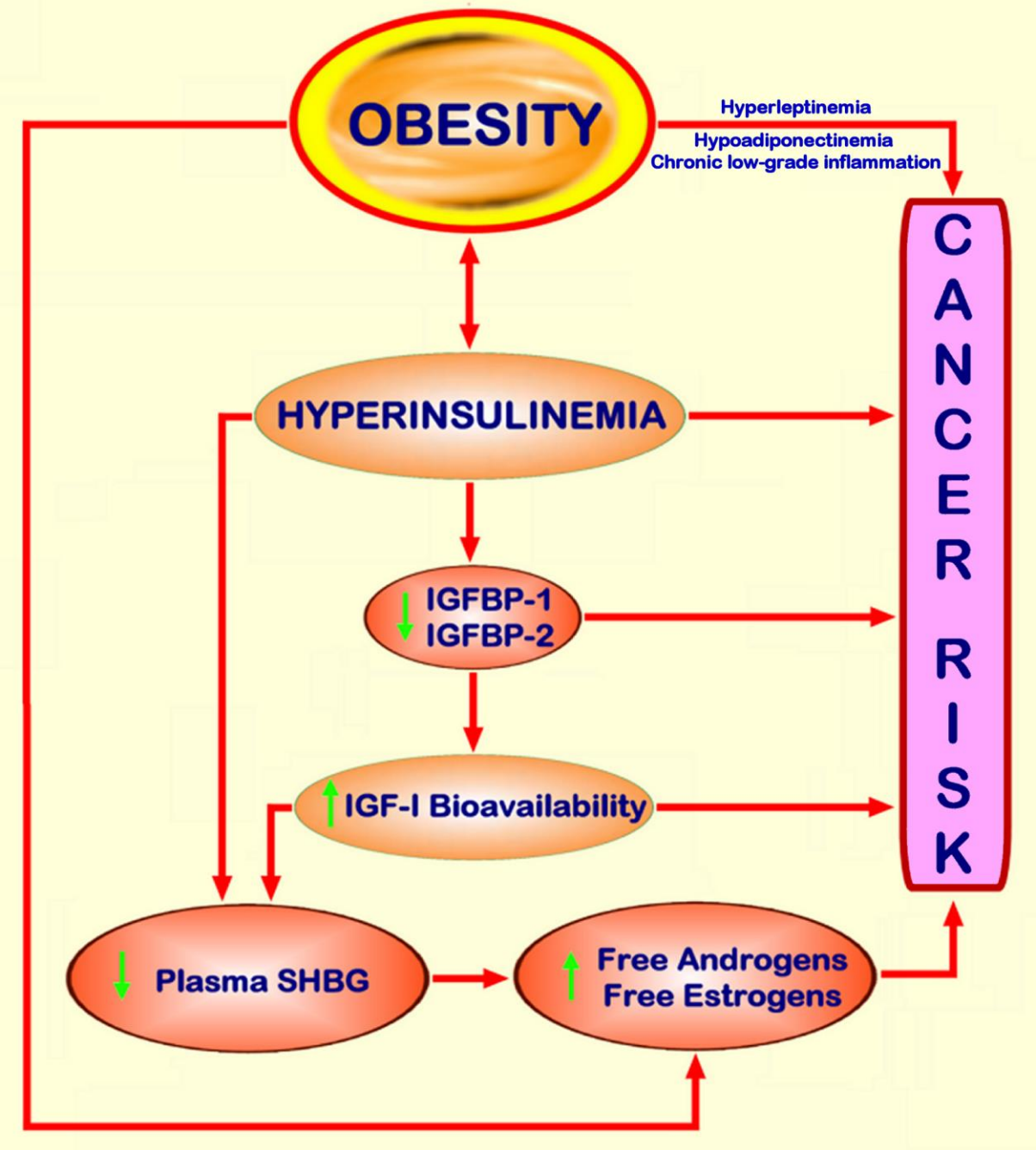
In general, overweight and obesity also constitute adverse prognostic factors among cancer survivors (individuals who are living with a diagnosis of cancer or have recovered from the

disease), associated with worse survival rates and increased recurrence risk for several types of cancer (489-491). Indeed, existing evidence links increased BMI with recurrence and compromised survival in women with breast cancer (501, 502). Furthermore, data on colon cancer survival suggest that patients with obesity have greater overall mortality and shorter disease-free survival intervals, although more evidence is required (503-506). Finally, as aforementioned, obesity appears associated to higher prostate cancer-specific mortality and risk of aggressive prostate cancer (403-409, 413).

It is also interesting to note that, various studies have suggested an association between obesity and delayed cancer detection in clinical practice. This may be attributed either to weight-related barriers and patient delay (the period from first onset of symptoms to first medical consultation) or to greater difficulty in performing clinical examinations (e.g. examination of larger breasts in women with obesity or abdominal examination in central obesity) and diagnostic procedures (e.g. less accurate biopsy detection of prostate cancer in men with obesity due to larger size of the prostate) (404, 507-510). Furthermore, it is important to emphasize that the disease burden may be higher in patients with obesity and cancer due to increased risk for both cardiometabolic co-morbidity (e.g. T2DM and ischemic heart disease) and post-chemotherapy or postoperative complications.

In addition to environmental factors and genetic predisposition, multiple mechanisms have been proposed to explain the epidemiologic associations between obesity and cancer (511-514). Insulin resistance and chronic compensatory hyperinsulinemia appear to play a crucial role in the pathophysiology of obesity-related carcinogenesis, which may vary depending on the cancer type/site (**Figure 14**) (386, 483, 515-518).

Figure 14. Overview of Proposed Mechanisms that Link Obesity and Increased Cancer Risk.



Obesity, particularly central/visceral, causes insulin resistance and chronic compensatory hyperinsulinemia. Increased insulin levels have been shown to induce mitogenic effects and contribute to tumorigenesis through activation of both the insulin receptor and the insulin-like growth factor 1 (IGF-1) receptor. Hyperinsulinemia can also suppress the synthesis of insulin-like growth factor binding protein 1 (IGFBP-1) in the liver and locally in other tissues, while is also associated with reduced plasma IGFBP-2. In turn, this decrease in IGFBP-1 and IGFBP-2 levels leads to increased bio-availability of IGF-1 which promotes cellular proliferation and inhibits apoptosis through its receptor in several tissues (386, 483, 515, 519, 520). Increased levels of estrogens and androgens are also considered to mediate carcinogenic effects, particularly for endometrial and post-menopausal breast cancers. Circulating SHBG levels are markedly decreased in patients with central obesity and hyperinsulinemia due to suppression of SHBG synthesis in the liver by insulin. Thus, higher

free sex-steroid levels are present in the circulation increasing the risk for hormone-sensitive gynecologic malignancies (333, 334, 337, 515). Enhanced metabolism of sex steroids within adipose tissue depots can further contribute to increased plasma levels of androgens and estrogens in obesity (**Figure 14**) (332-334). Finally, existing evidence suggests that changes in circulating adipokines (e.g. hypoadiponectinemia and hyperleptinemia) and the chronic low-grade inflammatory state in obesity may also directly promote carcinogenesis (386, 483, 511-514, 517, 521).

OBESITY-RELATED CO-MORBIDITIES DUE TO MECHANO-PHYSICAL EFFECTS

The aforementioned co-morbidities are closely related to adipose tissue secretion of multiple adipokines, hormones and factors that induce deleterious autocrine, paracrine and endocrine effects. A second principal mechanism leading to obesity-related disease reflects increased physical burdens imposed by excess fat mass to various body sites (522). Indeed, enhanced local biomechanic stress due to accumulated fat and increased body weight (e.g. on the joints, respiratory tract, blood vessels or within the abdominal compartment) causes and/or exacerbates several co-morbidities which are common in patients with obesity, such as knee osteoarthritis, back pain, restrictive lung disease, obstructive sleep apnea, gastroesophageal reflux disease, hernias, and chronic venous insufficiency. Of note, even these complications are further aggravated by the adverse metabolic profile and chronic inflammatory state in obesity, amplifying the overall burden of the disease and creating a vicious cycle which can be effectively broken only by sustained weight loss.

Obesity and Osteoarthritis

Osteoarthritis (OA) is the most frequent joint disorder worldwide and one of the leading causes of chronic pain and disability in the adult population of Western societies, particularly among the elderly (523). Obesity is a major risk factor for knee OA, with available data indicating that weight gain can precede the disease onset by several years and that this increased risk begins as early as the third decade of life (524-530). Indeed, a systematic review by Blagojevic *et al*. reported obesity as one of the main factors consistently associated with knee OA (pooled odds ratio of 2.63, 95% CI: 2.28-3.05) (525). Moreover, a prospective population-based study in Finland with a follow-up of 22 years documented a strong association between BMI and risk of knee OA, with relative odds ratio of 7.0 (95% CI: 3.5-14.10; adjusted for age, gender and other covariates) for individuals with obesity compared to those with BMI less than 25 kg/m^2 (531). Overall, the lifetime risk of symptomatic knee OA increases with increasing BMI and it is suggested that each additional BMI unit above 27 kg/m^2 can lead to a 15% increase of this risk, with the association being more prominent in women compared to men and for bilateral than for unilateral disease (529, 530, 532-534).

Obesity appears to also increase the risk of hip and hand osteoarthritis, although these associations are less consistent (523, 535-540). Furthermore, excess body weight is an important predictor of progressive knee and hip OA with patients with obesity exhibiting higher risk for deteriorating disease and development of disability (522, 523, 529, 530). Of note, it has been shown that weight loss of approximately 5.1 kg over a 10-year period can reduce the odds of developing symptomatic knee OA by more than 50% (541). Functional disability in patients with obesity diagnosed with knee OA may also be improved with weight

loss over 5% or at the rate of more than 0.25% per week within a 20 week-period (542). Finally, a growing body of evidence indicates that bariatric surgery may benefit patients with obesity and knee or hip OA, although further high-quality randomized studies assessing the impact of bariatric surgery and subsequent weight loss on these conditions are still required (543, 544).

The association of obesity with OA of weight-bearing joints is primarily attributed to repetitive over-loading during daily activities, which progressively causes cartilage destruction and damage to ligaments and other support structures (529, 530, 533, 545, 546). Abnormal gait, muscle weakness and alignment disorders may be further contributing factors for development of OA in patients with obesity. It is important to note that, increasing BMI is also associated with higher injury rates, including those related to falls, sprains/strains, joint dislocations and lower extremity fractures (547). In turn, joint injuries (e.g. meniscal ligament tears in the knee, fractures and dislocations) increase the risk of later developing OA in the injured joint (548). However, OA in non-weight-bearing joints (e.g. in the hand) and increased frequency of OA in women with obesity indicate that a metabolic/hormonal component may also link obesity to OA, in addition to biomechanic causes (549-551). Current evidence suggests that adverse hormonal and metabolic profiles in obesity (e.g. changes in leptin, adiponectin, TNF-α and IL-6, as well as hyperglycemia, lipid abnormalities and chronic inflammation) can play a role in the pathogenesis of OA. Indeed, increasing attention is now focused on the effects of leptin and the local dysregulation of adipokine production in osteoarthritic joints, while adipokines are also suggested as surrogate biomarkers for the severity of OA (529, 530, 533, 549-556).

Obesity and the Skin

Obesity is associated with several dermatologic conditions (557-562). Striae distensae (striae or stretch marks) is a common dermatosis in patients with obesity, representing linear atrophic plaques which are created due to tension and skin stretching from expanding fat deposits (557, 560, 561). Obesity-related striae are distributed primarily in the abdomen, breasts, buttocks, and thighs and pose more of a cosmetic problem. Clinically, these striae appear to be lighter, narrower, and less atrophic compared to striae in Cushing's syndrome which are characterized by more intense (purple) color and inordinate breadth (> 1 cm) and depth. Acanthosis nigricans can be also noted in patients with obesity and hyperinsulinemia due to insulin resistance and is manifested with hyperpigmented, velvety, irregular plaques often in the folds of the back of the neck, axilla and groin, as well as on knuckles, extensor surfaces, and face (558, 560, 561). Skin tags are also commonly associated with hyperinsulinemia and acanthosis nigricans (557). Of note, women with obesity may also exhibit hirsutism and acne vulgaris as a result of both hyperandrogenism and hyperinsulinemia. Furthermore, weight gain is also associated with cellulite due to changes in the epidermis and dermis mostly in women and in areas such as the thighs, buttocks and abdomen. Due to excessive sweating and increased friction between skin surfaces, a number of skin infections are more frequent in obesity including oppositional intertrigo (inflammation-rash in body folds), candidiasis, candida folliculitis, folliculitis and less often cellulitis, erysipelas or fasciitis. Moreover, obesity is a risk factor for lower limb lymphedema, chronic venous insufficiency and stasis pigmentation, while wound healing tends to be slower in patients with obesity (557). Growing evidence also indicate that patients with obesity are at increased risk of inflammatory dermatoses, such as psoriasis (557, 560).

Finally, although the currently available evidence has been regarded as inadequate by the 2016 IARC working group (315), there are data indicating the obesity may also be associated with increased risk of skin cancer (particularly malignant melanoma) (557, 560, 563).

Obesity and the Respiratory System

Increased body weight and fat accumulation in the abdomen and chest wall can have a significant impact on respiratory physiology leading to deterioration of pulmonary function, attributed primarily to increased mechanical pressure on the thoracic cage and trunk (564-567). Although the detrimental effects on conventional respiratory function tests are often modest until BMI exceeds 40 kg/m^2, patients with obesity may exhibit reductions in lung volumes and respiratory compliance, as well as in respiratory efficiency (566-568). Severe obesity is associated with decreased total lung capacity (TLC), expiratory reserve volume (ERV) and functional residual capacity (FRC), as a result of mass loading, splinting and restricted decent of the diaphragm (564-568). Reduced FRC impairs the capacity to tolerate periods of apnea and represents the most consistently documented effect of obesity on respiratory function (568-570). Functional residual capacity can be reduced even in overweight individuals and declines exponentially with increasing BMI to the extent that it may approach residual volume (RV) (568, 570). On the other hand, RV is usually within the normal range in patients with obesity but can also be increased, suggesting concurrent obstructive airway disease and gas trapping (568-570). Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) are also modestly affected in obesity and, thus, these spirometric variables frequently remain within normal limits in otherwise healthy adults and children with increased BMI (571, 572). However, both FEV1 and FVC exhibit a tendency to decrease with weight gain and improvements have been reported following weight loss (572-575). Longitudinal studies have aslo demonstrated an inverse association between BMI and FEV1 (576, 577). It is important to note that FEV1 is regarded as an independent predictor of all-cause mortality and a risk factor for CVD (e.g. ischemic heart disease and stroke) and lung cancer (578, 579). Furthermore, increasing BMI is related to an exponential decline in respiratory compliance, which is attributed primarily to reduced lung compliance due to increased pulmonary blood volume and to reductions in chest wall compliance due to local fat accumulation (580, 581). Decreased respiratory compliance is associated with FRC reductions and impaired gas exchange (569, 582). Conversely, total respiratory resistance is increased in severe obesity mainly due to increases in lung resistance (580, 581). These changes in respiratory compliance and resistance are more marked in the supine position and can affect the breathing pattern which becomes shallow and rapid. Overall, the work of breathing is enhanced and can lead to restricted maximum ventilatory capacity and respiratory muscle inefficiency with heightened demand for ventilation and relative hypoventilation during activity (566). The impact of obesity on respiratory function is generally greater in men compared to women, probably attributed to gender-related differences in fat distribution, highlighting the crucial role of central obesity (583-585). Indeed, indices of central/visceral adiposity are considered better predictors of respiratory function than body weight or BMI, whilst an inverse association exists between waist circumference and both FEV1 and FVC (585, 586). Data show that, on average, an increase in waist circumference of 1 cm is associated with reductions of 13 ml and 11 ml in FVC and FEV1, respectively, after adjustment for gender, age, height, weight and pack-years of smoking (585, 586). Adverse effects on the lungs caused by circulating adipokines

and chronic inflammation in central obesity are also considered to mediate these heighten associations with respiratory dysfunction (567, 568).

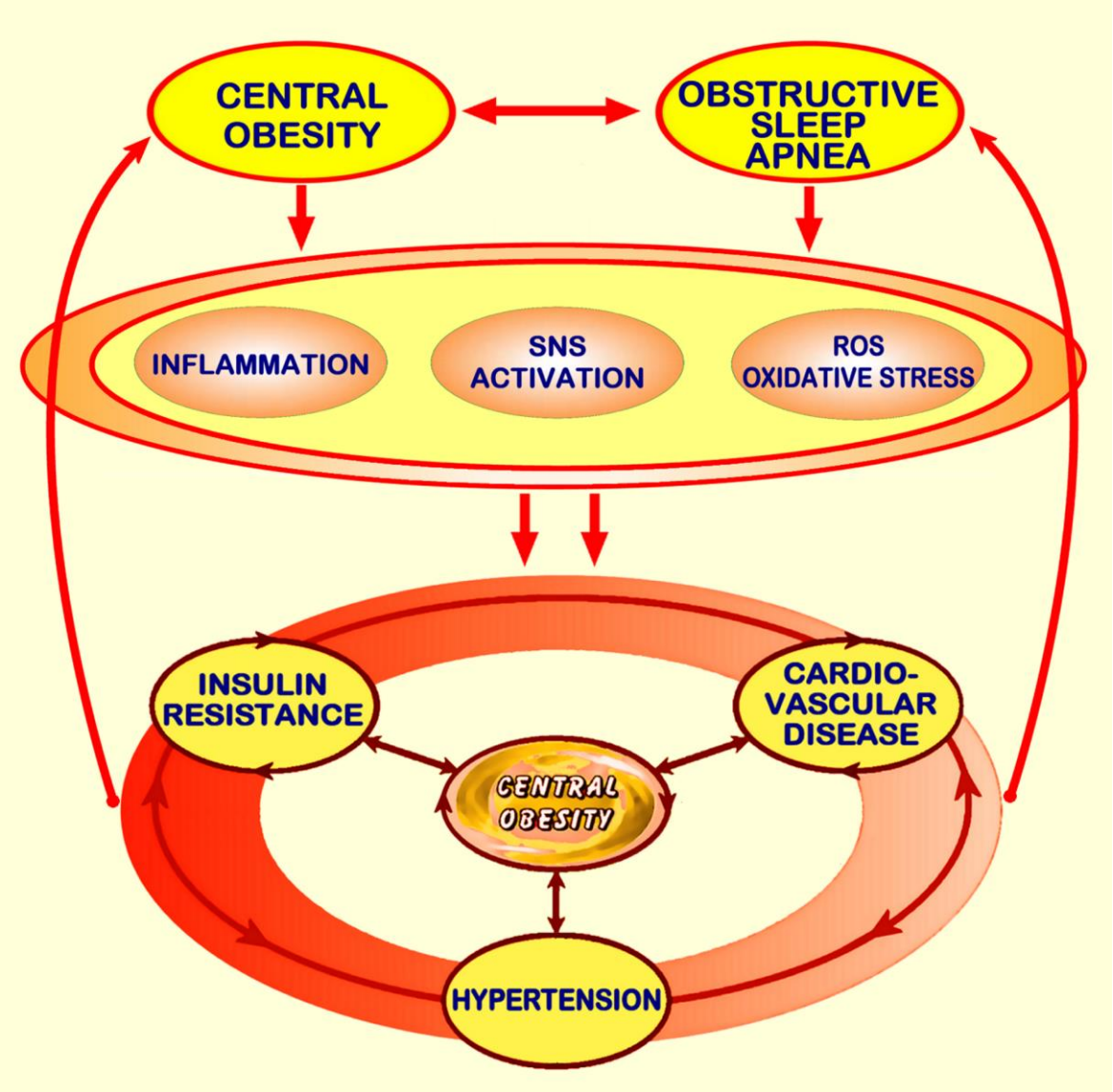
Obesity is further associated with a spectrum of distinct respiratory conditions, including obstructive sleep apnea, obesity hypoventilation syndrome, asthma, and chronic obstructive pulmonary disease (564, 587-592). Obstructive sleep apnea (OSA) is a prevalent respiratory disorder in the general population, and is shown to be particularly common in men and women with obesity (593). Obstructive sleep apnea is characterized by recurrent episodes of temporary airflow cessation (apnea) or reduction (hypopnea) during sleep, which are caused by total or partial upper airway collapse and result in decreased oxygen saturation (repeated episodes of hypoxemia and hypercapnia) (587, 594). Airflow is restored with arousal, thus disrupting the normal sleep pattern and adversely affecting sleep quality. Subsequently, OSA can lead to various clinical manifestations including snoring, choking episodes during sleep, nocturia, restless and un-refreshing sleep, daytime fatigue and hypersomnolence, impaired concentration, hypertension, decreased libido, irritability and personality changes, while it is also distinctly associated with increased incidence of motor vehicle accidents. Screening for OSA can be performed through validated questionnaires (e.g. the Epworth Sleepiness Scale and the Berlin Questionnaire) (587, 595, 596), and is particularly important for the clinical practice in patients with obesity and/or other obesity-related cardiometabolic disease (e.g. in patients with T2DM or PCOS) (597, 598), while the diagnosis of OSA relies on polysomnography which remains the “gold standard” diagnostic method (587, 595, 596). By consensus, an apnea is defined as airflow cessation for at least 10 seconds and is classified as obstructive or central based on presence or absence of respiratory effort, respectively (599). Accordingly an episode of hypopnea is defined based on the presence of either (i) reduced airflow by ≥30% from baseline for at least 10 seconds with ≥4% desaturation from baseline or (ii) reduced airflow by ≥50% for at least 10 seconds with ≥3% desaturation or an arousal (599). OSA severity is usually defined by the apnea-hypopnea index (AHI) which represents the number of apneas plus hypopneas per hour of documented sleep (mild OSA: AHI of 5 to 15; moderate OSA: AHI of more than 15 to 30; and severe OSA: AHI of more than 30 (600) However, it must be noted that AHI does not necessarily reflect the severity of clinical symptoms and use of other indices has also been suggested (e.g. based on hypoxemia) (601, 602). Of note, a long-term consequence of OSA is alterations in the central control of breathing, with episodes of central apnea due to progressive desensitization of respiratory centers to hypercapnia. These episodes are initially limited during sleep, but eventually can lead to the obesity-hypoventilation syndrome (Pickwickian syndrome), which is characterized by obesity, sleep disordered breathing, alveolar hypoventilation, chronic hypercapnia and hypoxia, hypersomnolence, right ventricular failure, and polycythemia (603).

Obstructive sleep apnea prevalence is increasing in Western societies and appears to be higher in men and among the elderly (593, 604). US data from the Wisconsin Sleep Cohort Study reported that the estimated population prevalence of OSA (AHI of 5 or more) in middle-aged men and women (30-60 years old) was 24% and 9%, respectively, with 4% of men and 2% of women also presenting daytime hypersomnolence (605). Obesity, especially central, is recognized as a major risk factor for OSA (587, 594, 604, 606, 607). Several studies have reported a consistent association between increased BMI and OSA risk, with an extremely high OSA incidence among subjects with severe obesity (55-100% in patients evaluated for bariatric surgery) (594, 608-610). Notably, a prospective population-based

study documented that even moderate weight gain can increase the risk of OSA, with a 10% weight gain predicting a 6-fold (95% CI, 2.2-17.0) increase in the odds of developing moderate to severe sleep-disordered breathing, while a 10% weight loss predicted a 26% (95% CI, 18%-34%) decrease in the AHI (611). Neck circumference, reflecting central obesity and fat deposition around the upper airways, is regarded as a better predictor of OSA risk compared to body weight and BMI (612, 613). Indeed, it has been shown that neck circumference is associated with the severity of OSA independently of visceral obesity, especially in non-obese patients (614). Finally, available data also suggest that waist circumference can exhibit a stronger association with OSA risk compared to BMI, highlighting the role of upper body fat distribution in the pathophysiology of OSA (615).

Multiple mechanisms appear to mediate the association between obesity and OSA (587, 594, 606, 607). Existing evidence suggests both direct genetic contribution to OSA susceptibility, as well as indirect genetic contribution implicated through obesity, craniofacial structure features, regulation of sleep and circadian rhythms, and neurological control of upper airway muscles (616). Overall, contributing factors for development of sleep-disordered breathing include older age, male gender, anatomically narrow upper airways, increased tendency for upper airway collapse, and variations in neuromuscular control of upper airway muscles and in ventilatory control mechanisms (587). Cervical fat deposition in obesity with fat deposits in the lateral wall of the pharynx may decrease the caliber of the upper airways and increase their collapsibility, mainly due to increased thickness of the lateral pharyngeal muscle wall (617-619). Furthermore, in patients with obesity impairment of the upper airway dilator muscles has been also suggested, with data showing increased genioglossus fatigability (620). Abdominal fat accumulation also leads to decreased longitudinal upper airway tension and increased upper airway collapsibility due to the aforementioned changes in respiratory function and lung volumes (564-568). Chronic intermittent hypoxia in OSA appears to increase reactive oxygen species (ROS) production and oxidative stress (**Figure 15**). In addition, insulin resistance, circulating adipokines (e.g. leptin), pro-inflammatory cytokines (e.g. IL-6 and TNF-α), are also considered to further aggravate OSA, particularly in central obesity (594, 606, 621-624). Finally, research has been recently focused on the role of increased SNS activity, which is thought to result from chronic intermittent hypoxia and disruption of normal sleep patterns (sleep fragmentation and recurrent arousals), on insulin resistance and HTN. In turn, insulin resistance promotes further central fat accumulation and CVD risk, which aggravate OSA, thereby forming a vicious cycle (625-627).

Figure 15. Potential mechanisms linking weight gain, insulin resistance, cardiovascular disease (CVD) and hypertension in patients with obesity and obstructive sleep apnea (OSA) (adopted from Arnarsdottir *et al*. Sleep 2009 (623)).



Sustained weight loss (e.g. by lifestyle modification with diet and exercise) can significantly reduce the AHI and improve the clinical manifestations of OSA (594, 628). Promising results have been also reported from studies exploring the impact of bariatric surgery on OSA (628), with meta-analysis data showing that up to 85% of OSA patients may exhibit remission and complete resolution of sleep-disordered breathing (629). However, it is important to note that although weight reduction improves OSA, patients with severe obesity undergoing bariatric surgery should not necessarily expect to be cured of OSA following weight loss. Indeed, another meta-analysis regarding the effect of bariatric-induced weight loss on measures of OSA demonstrated that the mean AHI after weight loss with bariatric procedures was consistent with moderately severe OSA (a pooled baseline AHI of 54.7 events per hour was reduced to a final value of 15.8 events per hour) (630). Nevertheless, a more recent systematic review performed to determine which of the common available bariatric procedures (i.e. Roux-en-Y gastric bypass, sleeve gastrectomy, gastric banding or biliopancreatic diversion) is the most effective for the treatment of OSA reported that all these procedures had significant beneficial effects on OSA (over 75% of the bariatric patients exhibited at least improvement), with biliopancreatic diversion being the most successful and gastric banding being the least successful in improving or resolving OSA

(631). Interestingly, recurrence of OSA has been reported following initial improvements with weight loss even without concomitant weight regain (632). This can be attributed to variation in fat loss from different body sites with persisting fat deposition in the neck, and to other mechanisms which contribute to increased upper airway collapsibility independent of body weight (607).

In clinical practice, physicians should also be reminded that the link between OSA and obesity is bi-directional, with untreated OSA predisposing to weight gain and obesity. Short sleep duration predicts future obesity and newly diagnosed OSA patients often experience a history of recent weight gain in the period preceding the diagnosis (633, 634). Finally, a significant proportion of OSA patients remains undiagnosed and this potentially poses an additional risk to bariatric surgery candidates, since OSA appears associated with higher risk of adverse outcomes occurring within 30 days after surgery (e.g. death, deep-vein thrombosis or venous thromboembolism, reintervention with percutaneous, endoscopic or operative techniques and failure to be discharged from the hospital within 30 days after surgery) (609, 635-638). Of note, it has been reported that OSA screening prior to bariatric surgery identifies an additional 25% of patients as having OSA; although, in this study, unscreened patients with severe obesity did not exhibit an increased incidence of cardiopulmonary complications after surgery compared to screened patients (639). To address this point for the clinical practice, in 2016 a consensus meeting was held in Amsterdam that issued a consensus guideline that, based on the existing evidence, comprehensively addressed the issue of perioperative management of OSA in bariatric surgery (640).

CONCLUSION

In this chapter, we have discussed major disorders/diseases that are associated with obesity and are caused, at least in part, by adipose tissue accumulation. These include disturbances of glucose metabolism, manifestations of the metabolic syndrome, non-alcoholic fatty liver disease, gallbladder disease, osteoarthritis, obstructive sleep apnea, and various types of cancer, as well as unfavorable outcomes regarding reproduction, stress levels, and psychiatric disorders.

In clinical practice it should be noted that individuals with obesity often vary significantly regarding clinical manifestations of obesity-related morbidity, and it appears that patterns of lipid partitioning are a major determinant of their metabolic profile (65). Distribution of body fat plays an important role in this context (65, 641). As such, visceral accumulation of excess body fat is shown to be strongly associated with most of the obesity-related disorders including insulin resistance (642), and T2DM (643), as well as with all-cause mortality (644). On the other hand, increased subcutaneous fat depots can even have protective metabolic effects (645-647). Although not all previous studies have shown an independent effect of the subcutaneous abdominal fat on insulin sensitivity (646) and controversial findings have also been reported (648), data suggest that an expanded fat mass, particularly of subcutaneous adipose tissue, may function as a sink for glucose uptake and triglyceride accumulation resulting in compensatory improvement of insulin sensitivity (647). In agreement with this hypothesis, it has been shown that enabling a massive expansion of the subcutaneous adipose tissue mass in the ob/ob mouse model potently counteracts the development of insulin resistance associated with excess caloric intake (649). Importantly, evidence from

rodent models of obesity and research into the genetic basis of human obesity have started to provide novel insight into the predisposition to weight gain and the pathophysiology of obesity-associated co-morbidity [rodent models of obesity and the genetics of obesity in humans will be reviewed in detail in the corresponding EndoText chapters].

In conclusion, obesity constitutes a complex, multifactorial disease associated with a wide spectrum of comorbidities due to both a deleterious endocrine/metabolic profile of the expanded/accumulated adipose tissue, and an increased physical burden imposed on various body sites/organs. Thus, even in cases of “metabolically healthy” obese individuals (presenting with a predominantly female type of fat distribution and absence of metabolic abnormalities) multiple other parameters and the risk of long-term adverse outcomes (e.g. risk of CVD, osteoarthritis, disability, psychological comorbidity) need to be seriously considered when discussing the benefits of various weight management interventions (28, 650, 651).

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