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Article Title: CLINICAL PROBLEMS CAUSED BY OBESITY

Year of publication: 2010

Link to published article:

<http://www.endotext.org/obesity/obesity13/obesity13.htm>

Publisher statement: The original publication can be found at

<http://www.endotext.org/>

**OBESITEXT**

**CHAPTER 14: CLINICAL PROBLEMS CAUSED BY OBESITY**

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## **Clinical Problems Caused by Obesity**

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## **Introduction**

Over the past few decades the incidence of obesity has doubled worldwide and current estimates classify more than 1.5 billion adults as overweight and at least 500 million of them as clinically obese, with body mass index (BMI) over 25 kg/m<sup>2</sup> and 30 kg/m<sup>2</sup>, respectively [1]. Obesity prevalence rates are steadily rising in the majority of the modern Western societies, as well as in the developing world. Moreover, alarming trends of weight gain are reported for children and adolescents, undermining the present and future health status of the pediatric population [2]. To highlight the related threat to public health, the World Health Organization has declared obesity a global epidemic, also stressing that it remains an under-recognized problem of the public health agenda [3, 4].

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). These chronic diseases have been shown to hold strong correlations with BMI and closely follow the prevalence patterns of excessive body weight in all studied populations [5, 6]. Notably, the risk of developing a number of obesity-related co-morbidities rises exponentially with increasing BMI over 30 kg/m<sup>2</sup>, which is further associated with a graded increase in the relative risk of premature death, primarily from CVD [3, 6, 7]. In the overweight BMI range (25-30 kg/m<sup>2</sup>) the risk of premature mortality is weaker and appears to be influenced mainly by fat distribution (J-curve relationship, 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 metabolic and cardiovascular diseases, independent of BMI [8]. Conversely, 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 [9].

***FOR PEER REVIEW PLEASE SEE FIGURES 1 AND 2***

It must be noted that individuals of certain ethnic origins, regardless of the country of residence, are more predisposed to central obesity and more vulnerable to developing complications related to adiposity [10, 11]. Studies in South Asian, Japanese and Chinese populations have demonstrated significantly higher risk for insulin resistance, T2DM and CVD compared to matched overweight and obese Caucasians [12, 13]. Accordingly, rigorous cut-off points are being proposed for weight management among these populations, diagnosing obesity with BMI thresholds as low as 25 to 27.5 kg/m<sup>2</sup> and defining central obesity based on ethnicity specific cut-off values of waist circumference [13-15].

In any case, obesity must be recognized as a disease by the treating physician and appropriate weight loss treatments should be offered to obese patients, with or without related co-morbidities [16]. Weight management is crucial and should be promptly suggested even when these individuals are otherwise healthy (e.g. metabolically healthy obese patients) in order to prevent and/or delay the onset of complications. Interestingly, recent advances in treatments of cardiovascular risk factors and acute coronary syndromes are now offering improved cardio-protection options and appear to prolong life expectancy for obese patients. Indeed, current 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 significantly reduce their excessive body weight [17, 18]. Thus, it becomes evident that, growing and progressively ageing obese populations in Western societies will inevitably 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 morbidity) [18, 19]. Subsequently, the economic impact of obesity on health care costs is profound, while the additional indirect costs (e.g. absence from work, reduced productivity and disability benefits) are also substantial. National surveys in the UK reported that, obesity is directly responsible for almost 7% of the overall morbidity and mortality, with a direct cost to the NHS that reaches up to four billion pounds per year, while these figures are still considered to be an underestimate. [20-22].

## **Obesity and type 2 diabetes mellitus**

Diabetes mellitus represents a rather diverse group of metabolic disorders that are characterized by development of 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 etc). Type 2 diabetes mellitus (T2DM) comprises up to 90% of all diagnosed diabetic cases 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<sup>2</sup>, while patients with severe obesity (BMI > 35 kg/m<sup>2</sup>) are almost 20 times more likely to develop T2DM than individuals with normal BMI (18.5-24.9 kg/m<sup>2</sup>) [23]. Indeed, T2DM is steadily increasing both in developed and developing countries distinctively following the documented prevalence trends of obesity; hence, it is not surprising that, the term “*diabesity*” has been introduced to describe this twin epidemic [24, 25].

Large-scale population studies have shown that obesity constitutes the most important independent risk factor for insulin resistance and T2DM [26-29]. In adults, the relative risk for T2DM starts to increase even at BMI values within the normal weight range, 24 kg/m<sup>2</sup> for men and 22 kg/m<sup>2</sup> for women, while it rises exponentially with increasing BMI in the obese range (>30 kg/m<sup>2</sup>) (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 [27, 28]. Although visceral adiposity is more prominent in men, obesity appears associated with higher T2DM risk in women compared to men [30, 31]. Notably, impaired glucose homeostasis and T2DM have been linked to X-chromosomal loci [32], however the relative contribution of these loci to the onset of the disease is not fully clarified yet. In the pediatric population, T2DM constitutes a rather recent phenomenon and, even though type 1 diabetes accounts for most of the diabetic cases in young people, obese children and adolescents are now increasingly diagnosed with impaired glucose tolerance and T2DM [33, 34].

***FOR PEER REVIEW PLEASE SEE FIGURE 3***

Furthermore, a strong association is documented between central obesity and T2DM, beyond the impact of BMI [8, 35, 36]. Both insulin resistance and hyperinsulinemia correlate positively to visceral fat accumulation which is now regarded as an independent risk factor for T2DM and the hallmark of metabolic syndrome. Accordingly, anthropometric indices of central obesity (e.g. waist circumference and waist-to-height ratio) are utilized to better assess the risk for glucose intolerance and T2DM [37]. The higher cardiometabolic risk of central fat distribution is attributed to a combination of factors, relating mainly to a more deleterious biochemical profile of adipocytes in these fat depots. 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 [38, 39]. Additionally, adipocytes in visceral fat depots exhibit increased secretion of pro-inflammatory adipokines (e.g. tumor necrosis factor- $\alpha$ , interleukin-6) and decreased secretion of adiponectin, hence, leading to decreased insulin sensitivity and activation of inflammatory pathways in the adipose tissue, liver, and skeletal muscle [40, 41]. Hormonal changes either at the systemic level of various neuroendocrine axes (e.g. hypercortisolemia and dysregulation of the hypothalamic-pituitary-adrenal axis) or at the local level of the visceral adipose tissue (e.g. increased conversion of cortisone to cortisol via type 1 11 $\beta$ -hydroxysteroid dehydrogenase, 11 $\beta$ -HSD1, in fat depots) may also contribute to adverse metabolic consequences of central obesity [42-44].

Insulin resistance in obese patients stimulates insulin secretion and leads to chronic compensatory hyperinsulinemia which in turn may promote further weight gain. 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 [45]. 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 [46, 47]. Indeed, both dietary protein and cereal fiber intake are associated with beneficial effects on body fat distribution in the long-term [48-51]. However, 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 [52]. Normally, insulin-mediated inhibition of the 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 which in turn lead to reduced peripheral glucose utilization, increased hepatic glucose production and decreased insulin sensitivity in the liver and skeletal muscle [53, 54]. 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 [52].

In the liver insulin regulates the hepatic glucose production rate by activating 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 [55]. It must be noted that, 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. 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, fasting glucose production in the liver is increased due to hepatic insulin resistance despite compensatory hyperinsulinemia [52]. Notably, the absolute amount of hepatic glucose production is moderately increased in T2DM patients compared to that in healthy controls, but is inadequately suppressed relative to the raised concentrations of glucose and insulin [56]. 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 [57]. 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 [58]. This postprandial under-utilization of glucose by skeletal muscles is superimposed on increased hepatic glucose production rates, thus, regulating 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 T2DM pathophysiology [52]. 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 FFA exposure 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 [52, 59]. Clinical studies confirmed that, sustained high FFA plasma levels can impair insulin secretion in predisposed individuals (family history of T2DM) [60], while, on the contrary, pharmacological inhibition of lipolysis in non-diabetic individuals with strong family history of T2DM can improve insulin secretion [61]. 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. [52]. Clinical studies also reported that reduced beta-cell sensitivity to glucose plays a predominant role in patients with impaired glucose tolerance [62, 63].

It must be emphasized that the insulin resistant state in obesity and related acquired beta-cell defects can be, at least partially, restored with weight loss and tight glycaemic control. Indeed, several studies have reported that even modest weight loss is important for T2DM prevention, significantly reducing the risk and delaying the onset of the disease [64-70].

## **Obesity-related inflammatory and procoagulant state: link to CVD and metabolic syndrome**

### *Obesity as an inflammatory and procoagulant state*

Following the recognition of adipocytes as endocrine cells, one focus of research was studying the association between obesity and the development of a chronic low-grade inflammatory state. An impressive body of recent data strongly indicates that weight gain promotes an unconventional, sub-clinical inflammation, mainly due to secretion of a battery of pro-inflammatory factors (e.g. leptin, TNF- $\alpha$ , IL-6, IL-1 $\beta$ ) [71, 72]. The pro-inflammatory nature of adipose tissue is heightened in proportion to fat accumulation and exhibits consistent positive correlations with increasing BMI and especially with visceral adiposity [38, 71, 72]. Thus, central obesity appears to trigger and exacerbate an inflammatory cascade that initially evolves within fat depots, but eventually exerts systemic effects, since enhanced adipose tissue secretion of pro-inflammatory adipokines persists for as long as the excess abdominal fat mass is maintained. Indeed, current evidence suggests that this obesity-related activation of inflammatory signaling pathways is linked to major CVD risk factors (e.g. T2DM and atherosclerosis) [73, 74]. 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 [71, 72]. A closer look at the underlying molecular interplay unveils a vicious cycle between pre-adipocytes, mature adipocytes and macrophages that reside in adipose tissue of obese patients (Figure 4). Weight gain enhances both lipogenesis and adipogenesis inside fat depots, as well as secretion of pro-inflammatory adipokines and chemokines (e.g. monocyte chemoattractant protein-1, MCP-1, and IL-8) into the plasma. In response to such chemotactic stimuli mononuclear cells are recruited from the circulation and transmigrate into adipose tissue depots, increasing the number of resident macrophages [75, 76]. In turn, this growing local population of macrophages secretes cytokines, such as TNF- $\alpha$ , IL-1 $\beta$  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 [72, 77, 78]. Thus, sustained fat accumulation establishes an unremitting local inflammatory response within the expanding adipose tissue. Progressively this cascade transcends to a chronic low-grade generalized inflammatory state in obesity, mediated by persistent release of pro-inflammatory adipokines of either

adipocyte or macrophage origin [71, 79], with adverse effects on peripheral tissues and organs (e.g. liver, muscles, endothelium). These effects promote hepatic and skeletal muscle insulin resistance, hypertension, atherosclerosis, hypercoagulability and enhanced secretion of acute-phase reactants (e.g. C-reactive protein, fibrinogen haptoglobin) [72, 80].

***FOR PEER REVIEW PLEASE SEE FIGURE 4***

The procoagulant state in obesity is further characterized by increased levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) which both promote atherogenic processes and increase the risk of CVD [81-84]. Fibrinogen is synthesized by hepatocytes and holds a pivotal role in the coagulation cascade, being a major determinant of plasma viscosity and platelet aggregation. 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 [85]. Notably, fibrinogen has been also shown to predict weight gain in middle-aged adults [86]. 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 increasing BMI and visceral adiposity, as well as with metabolic syndrome components [87-90]. Enhanced adipose tissue expression of PAI-1 has been reported in obesity, particularly in visceral adipose tissue, while an inverse relationship was also demonstrated between PAI-1 activity and adiponectin in overweight and obese women [89, 90].

It is interesting to note 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, particular interest is also focused on inherent similarities between adipocytes and macrophages which are more apparent in obesity [72, 91, 92]. 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 that, under certain conditions, become committed to the adipocyte lineage and produce pre-

adipocytes. Notably, pre-adipocytes are reported to have the ability to differentiate into macrophages and to function as macrophage-like cells, developing phagocytic activity against microorganisms [93, 94]. 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- $\alpha$ ) which were typically associated to macrophages [95, 96]. Finally, both pre-adipocytes and adipocytes express Toll-like receptors (TLRs) which are cardinal regulators of innate and adaptive immune responses and, interestingly, have been proven to undergo direct activation by fatty acids [97]. This advocates a suspected role of the adipose tissue as an immune organ, with potential implications for treatment of obesity-related complications. Identifying common initial inflammatory mechanisms could lead to therapeutic interventions that may inhibit at an early stage the adipose-initiated inflammatory cascade, and, thus, prevent clinical complications (e.g. modulation of I $\kappa$ B kinase, IKK $\beta$ , and nuclear factor- $\kappa$ B, NF- $\kappa$ B, activity, which are pivotal signaling mediators that trigger intracellular inflammatory pathways).

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.

***Metabolic syndrome: Definitions and quest for a single set of diagnostic criteria.***

Over two decades ago, Reaven proposed the term “Syndrome X” to describe a constellation of diseases, including obesity, T2DM, dyslipidemia and hypertension which exhibit a marked tendency to cluster together, revolving around insulin resistance [98]. All these metabolic disorders are established independent risk factors for cardiovascular complications and, indeed, their coexistence correlates with high CVD morbidity and mortality, an association that also aptly led to the description of the syndrome as the “deadly quartet” [99]. Since then, the term “Metabolic Syndrome” has been adopted to better illustrate this clustering of cardiometabolic risk factors, opening new vistas for the study of their interrelationships [100]. Data regarding the prevalence of the syndrome, based on large US, European and Australian cohorts, suggest that it affects over a quarter of the adult population in Western societies, conferring a five-fold increase in T2DM risk and twice greater relative risk for

CVD [101, 102]. Several prominent medical bodies, such as 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 in order to help identify individuals at high risk for T2DM and CVD in clinical practice (Figure 5) [103-105]. These definitions applied diagnostic criteria that varied significantly, limiting comparability between studies and creating some confusion regarding their use by clinicians. In order to address the need for widely accepted criteria that could be easily applied in different 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 and fasting glucose) (Figure 5). [106]. According to this consensus, central obesity becomes the hallmark of the metabolic syndrome and is a prerequisite for its diagnosis. To ensure applicability in various ethnic groups, central obesity diagnosis in the IDF definition relies on waist circumference measurements that put 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 more predisposed to central obesity and more susceptible to complications of visceral adiposity [10-15]. Overall, the IDF consensus represents a targeted effort to offer a metabolic syndrome definition set on criteria that are friendly to routine clinical practice and could be uniformly applied in different settings and patient groups. Moreover, the adopted rationale proceeds to embody a growing body of evidence which highlights the crucial role of central obesity in metabolic syndrome pathophysiology.

***FOR PEER REVIEW PLEASE SEE FIGURE 5***

Notably, 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 [106, 107]. Assessment of multiple metabolic parameters was proposed, including markers of adipocyte function (leptin, adiponectin), inflammatory markers (C-reactive protein, TNF- $\alpha$ , 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. Research into metabolic syndrome pathogenesis incorporating these complementary variables is expected to advance our understanding of underlying pathogenetic pathways and help identify even more precise criteria for the clinical diagnostic process.

It must be mentioned 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 [13, 106]. Further epidemiological studies are expected to continue to offer additional data which will supplement existing knowledge and help in recommending more accurate cut-off points for various populations (e.g. Sub-Saharan Africans, South and Central Americans, Asian, Eastern Mediterranean and Middle East populations). Indeed, recent studies have suggested cut-off points of over 85 to 90 cm for men and over 80 cm for women in Japan [108, 109]. In China threshold values of over 85 cm and over 80 cm have been proposed in men and women, respectively, while slightly lower values have been suggested in India [110]. Recently, another attempt was made to resolve the remaining differences between metabolic syndrome definitions which resulted into a joint interim statement from the IDF and the American Heart Association/National Heart, Lung, and Blood Institute [15]. In order to harmonize the criteria for metabolic syndrome diagnosis, 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 diagnosis is based on population- and country-specific thresholds of waist circumference with a recommendation that the IDF cut-off points should be used for non-Europeans, while either the IDF or the AHA/NHLBI cut-off points can be used for people of European origin until more data are available (Figure 6).

***FOR PEER REVIEW PLEASE SEE FIGURE 6***

To date, the IDF metabolic syndrome definition has contributed in setting widely accepted diagnostic criteria and emphasizing the significance of central adiposity, while it can be regarded as an

additional tool in forming and evaluating strategies for diagnosis and treatment [102, 106, 111]. However, there is still ongoing debate and controversy as to whether it adds more value in clinical decision making compared to its individual components and by many it is considered useful mainly as an educational concept [112-119]. Thus, 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 and low-density lipoprotein cholesterol plasma levels, substantially increase the risk of T2DM and CVD and must be also assessed in clinical practice, as will be further reviewed in the following chapter regarding the metabolic syndrome (chapter 23).

## **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 in order to regulate carbohydrate, lipid and protein metabolism. Obesity may cause hyperinsulinemia, hyperglycemia and ectopic fat accumulation in the liver which, in turn, can impair hepatic function and lead to a spectrum of abnormalities, ranging from steatosis and elevation of circulating liver enzyme levels to cirrhosis, liver failure and even liver cancer [120-123]. 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 [124]. Yet, it wasn't until 1980 that 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 [125]. Hepatocellular steatosis is the hallmark of the disease, defined as a triglyceride content higher than 5-10% of the total liver weight, although the minimum fat content which should be considered pathologic and uniform criteria for its assessment are still debated [126, 127]. This steatosis reflects ectopic fat deposition in the liver, usually starting from the less oxygenated zone of the acinus (zone 3), and is more frequently macrovesicular (one large intracellular fat droplet displacing the nucleus). Microvesicular steatosis may also occur (numerous small intracytoplasmic fat vesicles not displacing the nucleus) and is often underestimated due to limitations of routinely applied staining techniques [128, 129].

NAFLD pathology extends from steatosis to steatohepatitis and fibrosis. Matteoni *et al.* have proposed a histologic classification of NAFLD into four distinct types (Figure 7A) [130]. 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 [131]. It must be noted that, the exact histologic criteria for diagnosing and staging NASH are debated among pathologists and distinction between NASH and alcoholic hepatitis may not be possible at the histological level.



Accordingly, a detailed alcohol consumption history is crucial for differential diagnosis, while various scoring systems for grading and staging of NAFLD have been developed to consistently assess the disease and compare outcomes of therapeutic interventions, such as the proposed NAFLD activity score (NAS) which, however, requires repeated liver biopsies (Figure 7B) [132, 133].

***FOR PEER REVIEW PLEASE SEE FIGURE 7***

NAFLD is now recognized as one of the most common causes of chronic liver disease, exhibiting rising prevalence and worldwide distribution which follows the global trends of obesity and T2DM [134, 135]. Data on NAFLD prevalence in the general population vary depending on applied diagnostic criteria, while large-scale population studies are hindered by the fact that the disease can remain asymptomatic for years, may coincide with other chronic liver diseases and requires a liver biopsy for definite diagnosis [136]. Based on current evidence, the estimated overall NAFLD prevalence in several Western countries is approximately 20-30% [137-142], with a corresponding NASH prevalence of 2-3% [143, 144]. Particularly significant are reported data for obese and T2DM cohorts which consistently document a very high incidence of NAFLD, thus, suggesting strong pathogenetic links. Indeed, up to 75% of obese and T2DM patients appear to develop steatosis, while NASH can be diagnosed in 10-20% of these cases [144, 145]. Notably, even higher NAFLD incidence (90-95%) is documented among patients with morbid obesity and manifestations of the metabolic syndrome [145, 146]. NAFLD also exhibits increasing prevalence among the pediatric population (general prevalence of 2.6-10%) in close association with childhood obesity, since up to 80% of obese children are reported to present the disease [147].

Gender differences appear to exist, thus, NAFLD is considered more common in males, although initial data suggested female predominance, peaking during the fourth decade in men and postmenopausally in women (after the fifth decade) [134]. Furthermore, family clustering and significant ethnic variations have been documented, supporting the role of genetic predisposition [141, 148]. Indeed, NAFLD prevalence in India is estimated at 20-30%, despite lower reported obesity rates compared to Western societies [149]. Conversely, African Americans exhibit NAFLD less often than

expected based on their respective incidence of obesity and T2DM; while Hispanic and Asian populations overall tend to be more susceptible to steatosis and NASH [150, 151]. Notably, these ethnicity-related variations coincide with higher predisposition of specific ethnic groups for developing central obesity, insulin resistance and metabolic syndrome complications [10-15].

To date, a limited number of studies have described the natural history of NAFLD. However, it is now clear that NAFLD may lead to severe liver complications (Figure 7). The underlying histologic stage dictates NAFLD prognosis which appears to rely crucially on the presence of fibrosis [152]. It is generally accepted that absence of inflammation and fibrosis is associated with a stable and benign long-term course in approximately 95% of the cases [153]. On the other hand, NASH exhibits an increased risk for developing cirrhosis, liver failure and even hepatocellular carcinoma (HCC), with 3-15% of NASH cases progressing to cirrhosis over 10-20 years [154, 155]. The prognosis is poor once NASH-related cirrhosis is established and 30-40% of these cases will require liver transplantation. Furthermore, HCC appears to develop at an annual rate of 2-5% in NASH patients with cirrhosis (Figure 7) [156, 157]. Indeed, long-term follow-up of patients with biopsy-proven NAFLD (129 patients followed for 13.7 years) has shown that NASH patients had significantly reduced survival due to liver-related and cardiovascular causes [158]. Overall, the age and gender adjusted mortality rate in patients with NAFLD is significantly higher compared to the general population (both for overall and liver-related mortality) [152, 159]. NAFLD severity increases with age, however regression is also possible if effective weight management is applied before the stage of cirrhosis, thus, highlighting the need for prompt and aggressive weight loss treatment. Notably, signs of regression can be misleading since progressing fibrosis may be silent or even associated with normalization of circulating aminotransferases levels and improvement of steatosis and inflammation features particularly in older patients. This often reflects a transition of NASH to cryptogenic cirrhosis which is associated with high HCC risk [160].

NAFLD pathogenesis is strongly linked to obesity and obesity-related insulin resistance [120-123]. 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, current evidence

indicates that this usually follows insulin resistance in adipose tissue. It is now evident that, obesity-related insulin resistance can cause fatty liver, while, *vice versa*; excessive intrahepatic fat accumulation may promote insulin resistance and weight gain [55]. Notably, the lipogenic actions of insulin appear to remain uncompromised in insulin-resistant states, thus, *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). Day *et al.* have proposed a two stage hypothesis to describe the pathogenetic mechanisms leading from obesity to NAFLD (“two-hit” model), with development of steatosis at the initial stage (first “hit”) and subsequent progression to hepatic injury, inflammation and fibrosis (second “hit”) (Figure 9) [161-163]. Insulin resistance directly facilitates the first “hit” through decreased inhibition of lipolysis in adipocytes as well as decreased inhibition of gluconeogenesis and increased lipogenesis in the liver. Thus, steatosis appears primarily caused by an overall enhanced hepatic influx of circulating FFA which are released by insulin resistant adipocytes. It is important to highlight that, 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 [164].

***FOR PEER REVIEW PLEASE SEE FIGURES 8 AND 9***

Notably, there is also evidence that hepatic accumulation of previously stored body fat and saturated dietary fat may induce hepatic insulin resistance, whereas newly produced fat by the liver and mono- and poly-unsaturated dietary fat is likely to have less deleterious effects, thus suggesting compartmentalisation of fatty acid metabolism in hepatocytes [165]. In the context of hepatic insulin resistance, hyperinsulinemia and hyperglycemia can further increase the intrahepatic triglyceride content due to stimulated *de novo* lipogenesis (DNL), impaired hepatic fatty acid oxidation and decreased VLDL efflux, while dietary fatty acids also contribute to steatosis (Figure 10) [166, 167]. Indeed, it has been shown that of the triacylglycerol accounted for in the liver of NAFLD patients approximately 60% arose from serum FFA, while 26% from DNL and 15% from the diet [167]. A positive correlation is reported between the degree of insulin resistance and steatosis which is

considered to subsequently enhance the liver susceptibility to the second “hit” [163]. This second “hit” causes progression from steatosis to NASH and cirrhosis by inducing hepatocyte injury and formation of fibrotic tissue (Figure 9). Current evidence suggests that this process reflects a diffusion of detrimental effects from adipose tissue depots to the hepatic level [133, 168, 169]. Thus, NASH is regarded to result from a cascade inside the steatotic liver which involves escalating hepatic insulin resistance and lipid peroxidation, in combination with local pro-inflammatory, oxidative stress and endoplasmic reticulum stress responses [163, 164]. In obesity-related insulin resistance these pathways are triggered and continuously fuelled by hyperleptinemia, hypoadiponectinemia and increased circulating concentrations of adipose-derived cytokines, primarily TNF- $\alpha$  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 [162, 170, 171]. Hepatocytes are further stimulated to locally secrete pro-inflammatory cytokines and factors (e.g. TNF- $\alpha$ , IL-6, IL-1 $\beta$ ). Furthermore, Kupffer and hepatic stellate cells are potently activated, while circulating inflammatory cells are also chemo-attracted and infiltrate the liver [172, 173]. The final outcome of these processes is a chronic and progressive pro-inflammatory state inside the liver which bears striking resemblance to the low-grade inflammation within adipose tissue depots in obesity.

***FOR PEER REVIEW PLEASE SEE FIGURE 10***

Research for specific therapeutic interventions regarding NAFLD and NASH is now focused on identifying critical steps of the aforementioned pathogenetic links which could be modulated in order to either prevent steatosis or stop/delay progression to steatohepatitis (e.g. targeting the peroxisome proliferator-activated receptor- $\gamma$  pathway, oxidative stress responses or the pro-inflammatory IKK $\beta$ /NF- $\kappa$ B pathway). It is important to mention that most of the existing evidence on NAFLD pathogenesis is derived from *in vitro* experiments and animal models and results cannot be necessarily extrapolated to other species, including humans. Yet, novel data indicate that at least some of the proposed molecular pathways are indeed relevant to the disease pathophysiology in humans [174]. To date, weight loss remains the only established treatment for NAFLD. Early and aggressive

weight management interventions should be offered to these patients, as well as appropriate treatment for coexisting metabolic syndrome manifestations (e.g. for T2DM, dyslipidemia and hypertension) in order not only to improve the underlying liver pathology, but to further address the associated high CVD morbidity and mortality [168, 169]. Notably, the role of insulin-sensitizing agents in NAFLD treatment appears promising even in non-diabetic patients [175, 176]. Although not consistently, metformin is shown to reduce steatosis, liver inflammation and hepatocellular injury [177-179], and trials with pioglitazone and rosiglitazone have also produced favorable results [180-182]. However, further long-term studies are required to establish their efficacy in NAFLD and NASH, while especially for glitazones their safety profile should be additionally established for these patients due to the associated risk of weight gain, osteoporosis and heart failure [183-190].

## **Obesity and gallbladder disease**

Gallbladder disease is a common gastrointestinal disorder in Western countries with cholelithiasis being the most frequent hepatobiliary pathology, primarily with gallstones composed of cholesterol. 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 dollars [191]. 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 [191-193]. Overall, cholelithiasis is strongly associated with overweight and obesity and a classic medical textbook mnemonic for gallstone risk factors is known as the "4 Fs" ("fat, female, fertile, and forty") [23, 193-198]. The relative risk of gallstone formation appears to rise as body weight increases exhibiting a positive correlation with increasing BMI which is more pronounced when BMI exceeds 30 kg/m<sup>2</sup> [23, 194-196]. In the Nurses' Health Study, women with BMI over 30 kg/m<sup>2</sup> had twice the risk of gallstones compared to non-obese women, while a seven-fold excess risk was noted in women with a BMI over 45 kg/m<sup>2</sup> compared to those with BMI less than 24 kg/m<sup>2</sup> [195]. It is interesting that obesity and female gender remain risk factors for gallstone disease even in children and adolescents [199]. Higher prevalence of cholelithiasis with increasing BMI is also reported in men, however this association appears less potent and is regarded to depend more on abdominal fat accumulation than on body weight alone [194, 200, 201]. Indeed, large prospective studies among US adults of both genders indicate that measures of central obesity, such as waist circumference and waist-to-hip ratio, can predict the risk of gallstones and cholecystectomy independent of BMI [202, 203]. In addition to higher prevalence of cholesterol gallstones, a recent study on gallbladder pathology in morbidly obese individuals has further documented significantly increased prevalence of cholecystitis and cholesterolosis [204]. Notably, current evidence suggests that obesity is associated with inflammation and fatty infiltration of the gallbladder, described as cholecystosteatosis, which results in abnormal wall structure and decreased contractility [205]. This bears resemblance to steatohepatitis and it has been reported that NASH prevalence in patients with morbid obesity and gallbladder disease can reach 18%, with insulin resistance being more common in concurrent NASH and gallbladder disease [206]. Finally, it is worth

mentioning that obesity increases the risk of hospital admission and prolongs the length of hospital stay for gallbladder disease [207].

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 [208-212]. 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. This leads to supersaturation of the bile which becomes more lithogenic with high cholesterol concentrations relative to bile acids and phospholipids. Notably, in obese patients the bile also remains supersaturated for much longer periods of time and not only during the fasting state. Furthermore, obesity is associated with gallbladder hypo-motility and stasis which predispose to gallstones formation. Increased fasting and residual volumes, as well as decreased fractional emptying of the gallbladder have been reported in obese patients [213-216]. Interestingly, hyperinsulinemia may cause both increased cholesterol supersaturation and gallbladder dysmotility [217-220].

Rapid weight loss in obese patients is additionally associated with increased risk of gallstone formation [221-226]. This is particularly significant following weight loss through surgical interventions and it is suggested that every morbidly obese patient undergoing bariatric surgery should be considered at high risk for developing gallstone disease independently of other risk factors [224-226]. Indeed, a recent retrospective study regarding predictors of gallstone formation after bariatric surgery reported that weight loss exceeding 25% of the initial body weight was the only post-operative factor that helped in selecting patients for postoperative ultrasound surveillance and subsequent cholecystectomy once gallstones were identified [226]. Notably, weight cycling is also shown to increase the risk of cholecystectomy, independent of BMI [227]. 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 [221-223]. Thus, diets with moderate levels of fat may reduce cholelithiasis risk by triggering gallbladder contractions and maintaining an adequate gallbladder emptying [222]. Use of ursodeoxycholic acid can also prevent gallstone formation after bariatric surgery [228]. Finally, several studies have

advocated concomitant prophylactic cholecystectomy with bariatric procedures in order to prevent post-operative gallstone formation [229, 230].

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 gall-bladder surgery is still inadequate) [231, 232]. Subsequently, studies on the relationship between obesity and gallbladder cancer are limited. Although restricted, available data are consistent in indicating that obesity is indeed associated with an increased risk of gallbladder cancer, attributed to higher risk of cholelithiasis and chronic inflammation [232]. A recent meta-analysis that included eleven studies (three case-control and eight cohort studies with a total of 3288 cases) confirmed that excess body weight could be considered a risk factor for gallbladder cancer based on existing evidence [233]. The summary relative risk of gallbladder cancer for overweight and obese individuals was 1.15 (95% CI, 1.01-1.30) and 1.66 (95% CI, 1.47-1.88), respectively, compared to normal weight persons. 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).



## **Obesity and reproduction**

Obesity can cause hypothalamic-pituitary-gonadal (HPG) axis dysfunction in both genders. 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, sub-fertility and more rarely hypogonadism [234]. Despite recent progress in our understanding regarding the role of adipose tissue in multiple neuro-endocrine networks, the exact pathogenetic mechanisms linking excess fat accumulation to HPG dysfunction remain unclear. Current research is focused on interactions between adipokines and the HPG axis, highlighting leptin as a pleiotropic modulator of energy homeostasis and reproduction [235-237]. 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 [238-240]. Sex hormone binding globulin (SHBG) also plays a crucial role in obesity-related dysfunction by regulating the bio-availability of sex steroids. Obese patients exhibit decreased circulating SHBG levels and thus higher bio-available sex-steroid levels and increased sex-steroid clearance. This appears related to direct suppression of SHBG synthesis in the liver by insulin which is more pronounced in central obesity due to related insulin resistance and hyperinsulinemia [239-241]. Finally, it must be noted that, a strong psychological component is also present, with clear reciprocal relationships between obesity and psychological comorbidities, especially anxiety and depression, which can significantly contribute to male and female sexual dysfunction manifested as decreased sexual desire, lack of sexual activity enjoyment, difficulties in sexual performance and avoidance of sexual encounters [242, 243].

### ***Female reproductive system and obesity***

In 1952, Rogers *et al.* first published a study documenting the relation of obesity to menstrual abnormalities [244]. Since then it has become evident that, in females a close link exists between body weight and reproductive health from menarche to menopause and beyond (Figure 11). From an evolutionary perspective, menarche marks the beginning of reproductive potential which requires sufficient energy stores to facilitate pregnancy and lactation. Thus, it is not surprising that the onset of

menstruation is considered related to the presence of a critical body fat mass [245, 246]. Recent epidemiological studies documented a clear correlation between obesity and earlier puberty onset in obese girls [247-250]. Indeed, 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 [251, 252]. However, this is often linked to decreased reproductive performance later in life and current evidence suggests that weight gain can also lead to earlier ovarian failure and menopause [253, 254].

***FOR PEER REVIEW PLEASE SEE FIGURE 11***

Menstrual disturbances are the most common manifestation of HPG dysfunction in obese women, extending from dysmenorrhea and dysfunctional uterine bleeding to amenorrhea [255, 256]. The degree of clinical manifestations is reported to have a strong correlation with BMI and, furthermore, appears related to fat distribution since central obesity commonly leads to more severe symptoms [234, 255-257]. Abnormal menstrual patterns in obese women are primarily attributed to altered androgen, estrogen and progesterone levels (Figure 11), and, indeed, weight loss can restore regular menstrual cycles by decreasing androgen aromatization to estrogens in adipose tissue depots. Obese women with polycystic ovary syndrome (PCOS) constitute a distinct category characterized by (1) polycystic ovaries; (2) oligo- or anovulation; and (3) clinical and/or biochemical signs of hyperandrogenism (2 out of 3 according to the Rotterdam consensus diagnostic criteria for PCOS - PCOS will be reviewed in detail in the relevant chapter in Endotext-Female Reproductive Endocrinology) [258]. Notably, obese PCOS women exhibit higher risk of menstrual abnormalities compared to BMI matched women without PCOS attributed to worse endocrine and metabolic profiles, involving various degrees of hyperinsulinemia and insulin resistance in combination with hyperandrogenism [259].

Female obesity is additionally associated with decreased fertility due to chronic anovulation [234, 255, 256]. Indeed, several studies have reported higher risk of anovulatory infertility with increasing BMI [260-264]. Central fat distribution is considered to play a crucial role in this

association through hyperinsulinemic hyperandrogenemia that disrupts ovulation, as also documented in PCOS [255, 256, 265]. Interestingly, prehistoric statuettes which are presumed to be fertility idols, including the famous “Venus of Willendorf”, depict rather obese women, yet characterized by pronounced buttocks and thighs [266, 267]. Furthermore, obesity can also decrease the success rate of assisted conception methods such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) [268-271]. Although additional data are still required, obese women 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 [255, 256, 271-275]. Thus, weight loss, even modest, is advised for obese women seeking fertility treatment in order to increase the chances of a favorable outcome [276]. Overall, pregnant obese women can be classified as having a high risk pregnancy associated to 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) risks [277, 278].

Finally, it must be noted that, obesity is a risk factor for endometrial, postmenopausal breast and ovarian cancer, although the data for the later are relatively limited [279, 280]. A higher risk for these hormone-sensitive gynecologic malignancies in obese women is attributed to elevated endogenous estrogen levels that persist even after menopause (adipose tissue consists the major source of postmenopausal estrogen production from androgens), while hyperinsulinemia appears to also independently contribute to carcinogenesis, as will be reviewed in the following section of this chapter about obesity and cancer [281, 282].

### ***Male reproductive system and obesity***

Men appear to exhibit clinical manifestations of obesity-related HPG axis dysfunction less frequently compared to obese women. However, research has been focused mainly on the impact of obesity on female reproductive health, thus, underestimating adverse effects on male reproduction. In recent years, following the increasing availability of assisted conception methods, a growing body of

evidence indicates that obesity can also impair male reproductive functions leading to decreased libido, sub-fertility and even infertility (Figure 12) [234, 239, 253].

***FOR PEER REVIEW PLEASE SEE FIGURE 12***

Data regarding secular trends of pubertal maturation in boys and possible relationships to obesity are less clear and partly conflicting [247, 249, 251, 252]. Indeed, 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 reported [247, 283-286]. Furthermore, assessing male puberty can be more subjective and unreliable due to lack of a landmark pubertal event such as menarche in girls. Thus, current evidence regarding the impact of childhood obesity on male sexual maturation is inconclusive and further data are required to clarify such potential associations.

Impaired male fertility is also associated with increasing BMI, especially in men with morbid obesity when BMI exceeds 40 kg/m<sup>2</sup> [234, 287-289]. 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 [290-293]. This is primarily attributed to decreased circulating testosterone levels due to higher aromatization of androgens to estrogens in adipose tissue depots, while SHBG levels can also be reduced (Figure 12) [239-241, 253, 294]. In addition to hormonal changes, obese men 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 [295]. Finally, morbid and longstanding obesity is often associated with comorbidities such as diabetes and macrovascular disease that increase the risk of sexual dysfunction in men and can lead to sub-fertility.

Evidence on the precise association between obesity and prostate cancer is inconsistent [296, 297]. Current data from large prospective studies indicate that obesity increases the risk of aggressive (high-grade) disease, while on the contrary is inversely associated with indolent (low-grade) tumors [298-300]. However, epidemiologic data on prostate cancer incidence should be interpreted with caution since obese men tend to exhibit larger sized prostates and lower prostate-specific antigen

(PSA) levels, parameters affecting the sensitivity and specificity of both PSA screening and prostate needle biopsy in this population [297, 301]. More consistently obesity has been associated with a higher risk of prostate cancer-specific mortality [296, 297, 302]. The underlying pathophysiologic mechanisms for these associations are considered multifactorial, including effects of decreased androgen levels, increased circulating adipokines, hyperinsulinemia and the low-grade chronic inflammation state in obesity [297, 303].

## **Obesity, stress and psychiatric co-morbidities**

A growing body of evidence indicates that depression and other common psychological disorders constitute independent risk factors for developing obesity and metabolic syndrome manifestations [304, 305]. Prospective data from the Whitehall II cohort documented that common mental disorders increase the risk of obesity in a dose-dependant manner (more episodes of the disorder correlated with higher future obesity risk) [306]. Notably, the odds of obesity in the presence of mental disorders tend to increase with age [307]. Indeed, in a large community-based cohort of elderly persons, 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 [308]. Furthermore, recent studies additionally report 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 [309]. Chronic work-related stress has also been identified as an independent predictive factor for general and central obesity during midlife [310, 311]. Interestingly, weight gain in female UK students during their first year at university was related to higher levels of perceived stress [312].

On the other hand, epidemiologic data further support positive correlations between obesity and both depression and anxiety disorders risk [313, 314]. These associations appear primarily concentrated among individuals with severe obesity and among obese females [315-319]. To date, the level of existing evidence is considered weak or moderate, since gender differences and multiple obesity-depression covariations are probable, while only a few high-quality prospective studies have been published [320-323]. However, the “jolly fat” hypothesis, associating obesity with decreased depression risk, should be, at least partially, revisited [324-327]. Notably, a U-shaped quadratic relationship between BMI and depression can be proposed [328]. In accord with available epidemiologic data, there is now an increasing number of prospective, controlled studies reporting remission of depressive symptoms and improved psychological functioning following weight loss through bariatric procedures [329-334]. Thus, reversibility is indeed noted regarding adverse effects of obesity on mental health. Conversely, it must be also stressed that, depressive and anxiety disorders

are shown to have strong predictive value for weight loss in obese patients even when surgical interventions are applied [335].

Overall, obesity can be considered to hold a bi-directional association with psychological well-being, especially with chronic stress and mood disorders [304]. This reciprocal relationship is complex and conclusions for causal effects cannot be drawn based on existing evidence. However, 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 13) [336-339].

***FOR PEER REVIEW PLEASE SEE FIGURE 13***

Obesity, particularly central, induces an unremitting low-grade inflammatory state, characterized by constantly high plasma levels of pro-inflammatory adipokines [71]. This adverse adipokine profile (decreased adiponectin and increased TNF- $\alpha$ , 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 [43]. Conversely, chronic stress and depression, associated with mild hypercortisolemia and increased sympathoadrenal activity, favor visceral fat accumulation and progressive obesity (e.g. favoring enhanced appetite, insulin resistance and increased adipogenesis) [340-343]. It is interesting to note that, sleep disorders, such as 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 adipokines (e.g. leptin, TNF- $\alpha$  and IL-6) and gut hormones (e.g. ghrelin) [344, 345]. Thus, a deleterious vicious cycle appears to be formed, where weight gain causes prolonged stress system activation (manifested with depression, anxiety and even sleep disorders) and *vice versa*, mediated through hormonal and adipokine effects on multiple endocrine axes and the central nervous system [336, 341, 342]. Furthermore, obesity is associated with sedentary lifestyle and socioeconomic disadvantage which increase the risk of depression [346]. In turn, over-nutrition, comfort eating, alcohol abuse and low physical activity are common features of depressive and anxiety

disorders promoting the development of obesity. Notably, even though obesity constitutes a chronic disease, obese individuals often additionally experience obesity-related stigma and discrimination that further contribute to clinical manifestations of depression and low self-esteem [347, 348]. The aforementioned associations highlight the importance of assessing and treating psychiatric comorbidity as part of weight management interventions [317, 335]. In the context of such 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) [349].



## **Obesity and cancer risk**

Over the last two decades, compelling data have accumulated indicating that obesity is associated with higher incidence, morbidity and mortality of several common cancers. Sufficient evidence is now available to support such associations between increasing BMI and endometrium cancer, post-menopausal breast cancer, colorectal cancer, kidney (renal cell) cancer, oesophageal and gastric cardia adenocarcinoma (Figure 14) [350-358]. Indeed, obese patients are shown to have approximately 1.5 to 3.5 higher risk of developing these cancers compared to normal-weight individuals [356]. Further studies have reported that excess body weight may also increase the risk of liver, pancreas and gallbladder cancers, as well as haematopoietic and lymphoid tissue malignancies [350-356]. In accord to what is noted for the majority of obesity-related co-morbidities, central obesity is identified as an independent, at least partially, predictor of increased cancer risk. Waist circumference correlates primarily with endometrium, breast, colon, pancreas and liver cancers, thus, suggesting pathogenetic links between visceral adiposity and carcinogenesis at these sites [359-361]. Pancreatic and hepatocellular cancer incidence is more distinctly related with T2DM, highlighting the adverse role of underlying insulin resistance and hyperinsulinemia [352, 362, 363]. Interestingly, some studies have also suggested that long-standing T2DM may diminish the increased risk of certain cancers, potentially due to progressive beta-cell failure and deteriorating insulin secretion over time [364, 365]. It is important to stress that, whether long-acting insulin analogs (particularly insulin glargine) exert an additional effect on cancer risk remains unproven based on available data and deserves further study, however treatment with high insulin doses can accelerate the growth of existing tumors [366-377]. On the other hand, metformin therapy appears to decrease colon and pancreas cancer risk in T2DM patients compared to treatment with insulin or insulin secretagogues [376, 377].

***FOR PEER REVIEW PLEASE SEE FIGURE 14***

Prospective studies have established that weight gain in adult life is a risk factor for colorectal cancer, while post-menopausal fat accumulation in women is associated with breast cancer [354, 378,

379]. Notably, obesity may protect pre-menopausal women against breast cancer, probably attributed to tendency for increased cycle length and decreased ovulation [353]. Both gender and ethnic differences appear to exist regarding the impact of obesity and weight gain on certain tumors, thus, significantly stronger association is documented between BMI and colon cancer in males, while correlations between BMI and breast cancer risk are more potent in the Asia-Pacific region compared to Europe, North America, and Australia [380]. Overall, cancer risk in adults increases when BMI exceeds 22 kg/m<sup>2</sup>, hence the current cancer prevention recommendation regarding body adiposity from the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) is 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<sup>2</sup> in adults depending on normal ranges for different ethnic populations) [353, 381, 382]. Childhood obesity is also implicated, since excess adiposity in adolescence tends to persist into adulthood and is shown to have long-term effects doubling the risk of death from colon cancer [383, 384]. Recent estimates in the European Union suggest that approximately 5% of all incident cancers can be attributed to excess body weight (3% and 6% in men and women, respectively) [385]. In US adults (50 years of age or older) the proportion of all deaths from cancer that is attributable to overweight and obesity may reach 14% in men and 20% in women [358]. Globally, obesity and physical inactivity are now recognized among the most important modifiable risk factors, together with tobacco control, for primary cancer prevention. Indeed, maintaining normal BMI in adulthood exerts a cancer-preventive effect on colorectal, endometrium, post-menopausal breast, renal cell and oesophageal cancers [350-353]. Furthermore, in clinical practice emphasis must be placed on growing evidence supporting the impact of weight loss in reducing obesity-related cancer risk [386, 387].

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 cancers [353]. Indeed, most studies associate increased BMI with breast cancer recurrence and compromised survival [388]. For colorectal cancer, increases in both adiposity and waist circumference have been shown to correlate to higher disease specific mortality [389]. Overall mortality and disease recurrence among

women with colon carcinoma (stage II-III) appears to increase with obesity [390]. Current data further relate excess body weight to increased prostate cancer-specific mortality and risk of aggressive prostate cancer [296-300, 302].

Notably, studies have suggested an association between obesity and delayed cancer detection in clinical practice 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 obese women or abdominal examination in central obesity) and diagnostic procedures (e.g. less accurate biopsy detection of prostate cancer in obese men due to larger sized prostates) [296, 391-394]. Furthermore, it is important to underline that the disease burden may be higher in obese cancer patients due to increased risk for both cardiometabolic comorbidity (e.g. T2DM and ischemic heart disease) and post-chemotherapy or postoperative complications.

Several mechanisms have been proposed to explain the described epidemiologic associations between obesity and cancer in addition to environmental factors and genetic predisposition. Insulin resistance and compensatory chronic hyperinsulinemia hold a cardinal role in proposed models for obesity-related carcinogenesis which may vary depending on cancer site (Figure 15) [351, 362, 395-397]. 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. Notably, hyperinsulinemia can 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 [398, 399]. Increased levels of estrogens and androgens are also considered to mediate carcinogenic effects, particularly for endometrium 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 [239-241]. Enhanced metabolism of sex steroids within adipose tissue depots can further contribute to

increased plasma levels of androgens and estrogens in obesity (Figure 15) [238-240]. Finally, current evidence suggests that adipokine changes (e.g. hypoadiponectinemia and hyperleptinemia) and the chronic low-grade inflammatory state in obesity may directly promote carcinogenesis [400].

***FOR PEER REVIEW PLEASE SEE FIGURE 15***

### **Various weight-related co-morbidities**

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 [401]. Indeed, enhanced local biomechanical stress due to accumulated fat and increased body weight (e.g. on joints, on the respiratory tract, on blood vessels or within the abdominal compartment) causes and/or exacerbates several co-morbidities which are common in obese patients, such as knee osteoarthritis, back pain, restrictive lung disease, obstructive sleep apnea, gastroesophageal reflux disease, hernias, and chronic venous insufficiency. Notably, even these complications are further aggravated by the adverse metabolic profile and chronic inflammatory state in obesity, multiplying the overall burden of the disease and creating a vicious cycle that can be broken only by weight loss.

#### ***Weight-related co-morbidities of the musculoskeletal system and skin***

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 [402]. 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 [403-407]. A recent prospective study in Finland (population-based with 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 obese persons compared to individuals with BMI less than 25 kg/m<sup>2</sup> [408]. Overall, each additional BMI unit above 27 kg/m<sup>2</sup> can lead to a 15% increase of the risk of knee OA, with the association being stronger in women compared to men and for bilateral than for unilateral disease [409, 410]. Obesity appears to also increase the risk of hip and hand osteoarthritis, although these associations are less consistent [411-416]. Furthermore, excess body weight is an important predictor of progressive knee and hip osteoarthritis with obese patients exhibiting higher risk for deteriorating disease and development of disability [401, 407, 417]. Notably, 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% [418]. Functional disability in obese patients diagnosed with knee osteoarthritis may also be improved with weight reduction over 5% or at the rate of more than 0.25% per week within a 20 week-period [419]. The association of obesity with OA of weight-bearing joints is primarily attributed to repetitive overloading during daily activities which progressively causes destruction of cartilage and damage to ligaments and other support structures, while muscle weakness, abnormal gait and alignment disorders may be further contributing factors [410, 420, 421]. It is interesting to note that increasing BMI is associated with higher injury rates, including those related to falls, sprains/strains, joint dislocations and lower extremity fractures [422]. In turn, joint injuries (e.g. meniscal ligament tears in the knee, fractures and dislocations) increase the risk of later development of OA in the injured joint [401, 423]. OA in non-weight-bearing joints (e.g. in the hand) and increased frequency of OA in obese women indicate that a metabolic component may also link obesity to OA, in addition to biomechanic causes. Indeed, current evidence suggests that adverse hormonal and metabolic profiles in obesity (e.g. changes in leptin, adiponectin, TNF- $\alpha$  and IL-6, as well as hyperglycemia, lipid abnormalities and chronic inflammation) can play a crucial role in the pathogenesis of OA [424-426]. Increasing attention is focused on leptin effects and local dysregulation of adipokine production in osteoarthritic joints [424-427], while recent data obtained from the cohort of the Chingford Study showed that individuals were more likely to be diagnosed as having radiographic knee OA if they had a higher BMI and increased circulating levels of IL-6, highlighting the potential implication of this pro-inflammatory cytokine in the disease process [428].

Obesity is also associated with several dermatologic conditions [429-431]. Striae distensae (striae or stretch marks) is a common dermatosis in obese patients representing linear atrophic plaques which are created due to tension and skin stretching from expanding fat deposits. 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 than striae in Cushing's syndrome which are characterized by more intense color and inordinate breadth and depth. Acanthosis nigricans can be noted in obese patients with insulin resistance and hyperinsulinemia 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. Skin tags are also commonly associated with hyperinsulinemia and acanthosis nigricans. Obese women may exhibit hirsutism and acne vulgaris as a result of both hyperandrogenism and hyperinsulinemia. 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 intertrigo (inflammation-rash in body folds), candidiasis, candida folliculitis, folliculitis and less often cellulitis, erysipelas or fasciitis. Finally, obesity is a risk factor for lower limb lymphedema, chronic venous insufficiency and stasis pigmentation, while wound healing may be slower in obese patients.

#### ***Weight-related co-morbidities of 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 [432-434]. Although the effects on conventional respiratory function tests are often modest until BMI exceeds 40 kg/m<sup>2</sup>, obese patients may exhibit reductions in lung volumes and respiratory compliance, as well as in respiratory efficiency [434, 435]. Morbid 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 descent of the diaphragm [432-435]. Reduced FRC impairs the capacity to tolerate periods of apnea and represents the most consistently documented effect of obesity on respiratory function [435-437]. FRC can be reduced even in overweight individuals and declines exponentially with increasing BMI to the extent that it may approach residual volume (RV) [435, 436]. On the other hand, RV is usually found within the normal range in obese patients, but it can also be increased suggesting concurrent obstructive airway disease and gas trapping [435-437]. 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 obese adults and children [438, 439]. However, both FEV1 and FVC exhibit a tendency to decrease with weight gain and improvements have been reported following weight loss [439-442].

Longitudinal studies have demonstrated this inverse association between BMI and FEV1 [443, 444], while it is important to note that pulmonary function and FEV1 is regarded as an independent predictor of all-cause mortality and a risk factor for CVD, stroke and lung cancer [445, 446]. 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 also to reductions in chest wall compliance due to local fat accumulation [447, 448]. Decreased respiratory compliance is associated with FRC reductions and impaired gas exchange [437, 449]. Conversely, total respiratory resistance is increased in severe obesity mainly due to increases in lung resistance [447, 448]. 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 [434]. 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 [450-452]. Indeed, indices of visceral adiposity are considered better predictors of respiratory function than body weight or BMI and an inverse association exists between waist circumference and both FEV1 and FVC, with data showing 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 [452, 453]. Adverse effects on the lungs caused by circulating adipokines and chronic inflammation in central obesity are considered to mediate these heighten associations with respiratory dysfunction.

Obesity is further associated with a spectrum of distinct respiratory conditions including obstructive sleep apnea, obesity hypoventilation syndrome, asthma, and chronic obstructive pulmonary disease [432, 454-457].

Obstructive sleep apnea (OSA) is a common respiratory disorder 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) [454]. 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 unrefreshing sleep, daytime hypersomnolence and 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) and OSA diagnosis relies on polysomnography which remains the “gold standard” diagnostic method [454, 458, 459]. 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 [460]. A hypopnea is defined based on the presence of either (1) reduced airflow by  $\geq 30\%$  from baseline for at least 10 seconds with  $\geq 4\%$  desaturation from baseline or (2) reduced airflow by  $\geq 50\%$  for at least 10 seconds with  $\geq 3\%$  desaturation or an arousal [460]. 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) [461]. However, it must be noted that AHI does not necessarily reflect the severity of clinical symptoms and use of other indices has been suggested (e.g. based on hypoxemia) [462, 463]. 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 [464].

OSA prevalence is increasing in Western societies and appears to be higher in men and among the elderly [465]. 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 [466]. Obesity, especially central, is recognized as a major risk factor for OSA [454, 465, 467]. Several studies have reported a consistent association between increased BMI and OSA risk

with an extremely high OSA incidence among morbidly obese subjects (55-100% in patients evaluated for bariatric surgery) [468-470]. Notably, a prospective population-based study documented that even moderate weight gain can increase OSA risk with a 10% weight gain predicting a six-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 [471]. 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 [472]. Available data further suggest that waist circumference can exhibit a stronger association with OSA risk compared to BMI and even neck circumference, highlighting the role of upper body fat distribution in OSA pathophysiology [473].

Multiple mechanisms appear to mediate the association between obesity and OSA [454, 467]. 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 [454]. 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 [474-476]. Furthermore, impairment of upper airway dilator muscles is suggested in obese patients with data reporting increased genioglossus fatigability [477]. 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 [432-435]. Insulin resistance, circulating adipokines (e.g. leptin), pro-inflammatory cytokines (e.g. IL-6 and TNF- $\alpha$ ), reactive oxygen species (ROS) production and oxidative stress are also considered to further aggravate OSA, particularly in central obesity (Figure 16) [478-481]. Finally, research attention is focused on the role of increased SNS activity which appears implicated in the inter-relationships between weight gain, OSA and hypertension in obese patients [482-484].

***FOR PEER REVIEW PLEASE SEE FIGURE 16***

Weight loss can significantly reduce the AHI and improve clinical manifestations of OSA. Promising results are reported from studies on the impact of bariatric surgery and according to meta-analysis data up to 85% of OSA patients may exhibit remission and complete resolution of sleep-disordered breathing [485]. However, it is important to highlight that although weight reduction improves OSA, morbidly obese patients undergoing bariatric surgery should not necessarily expect to be cured of OSA following weight loss. Indeed, a recent meta-analysis regarding effects of surgical 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) [486]. Interestingly, recurrence of OSA can be noted following initial improvements with weight loss even without concomitant weight regain [487]. This can be attributed to variation in fat loss from different body sites with persisting fat deposition in the neck and to other mechanisms contributing to increased upper airway collapsibility, independent of body weight [467]. 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 excessive weight gain in the period preceding the diagnosis [488, 489]. Finally, a significant proportion of OSA patients remains undiagnosed and this poses an additional risk to bariatric surgery candidates since OSA is 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) [468, 490, 491].

## Conclusions

In this chapter we have discussed some of the key disorders that are associated with obesity and are potentially 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 cancers, as well as unfavorable outcomes regarding reproduction, stress levels, and psychiatric disorders.

However, it should be noted that obesity does not necessarily imply disease. Indeed, obese individuals often largely differ regarding manifestations of obesity-related morbidity [38] and it appears that patterns of lipid partitioning are a major determinant of the metabolic profile. Distribution of body fat appears to play an important role in this context. As such particularly visceral accumulation of excess body fat, clinically manifested with an increased waist circumference, is shown to be associated with most of the obesity-related disorders including insulin resistance [492], and T2DM [493], as well as with all-cause mortality [494], whereas increased subcutaneous fat depots can even have protective metabolic effects [495-497]. Although not all previous studies showed an independent effect of the subcutaneous abdominal fat on insulin sensitivity [498] and controversial findings have also been reported [499], a growing body of evidence suggests that an expanded fat mass particularly of subcutaneous adipose tissue may function as a sink for glucose uptake resulting in compensatory improvement of insulin sensitivity [496]. In agreement with this hypothesis, it was recently shown that enabling a massive expansion of the subcutaneous adipose tissue mass in the ob/ob mouse model potently counteracts the strong trends toward development of insulin resistance associated with excess caloric intake [500]. In conclusion the metabolically “healthy obese” individual with a predominantly female type of fat distribution appears to exist, but other parameters such as osteoarthritis, disability and effects on psychological well-being need to be further considered when discussing benefits of weight management interventions.

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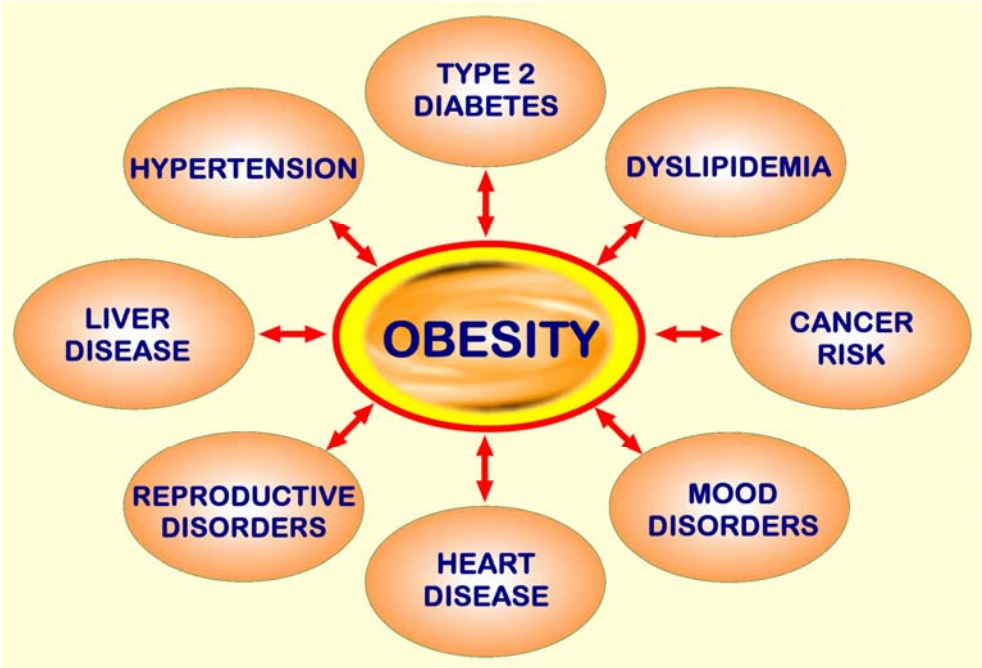
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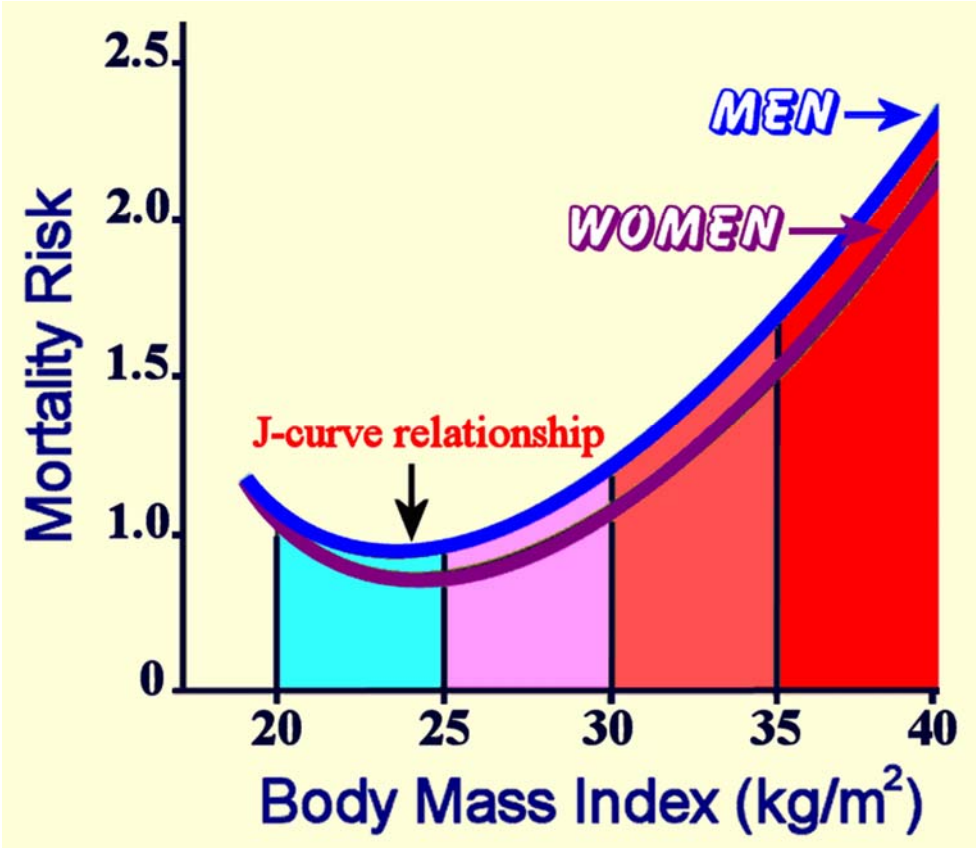
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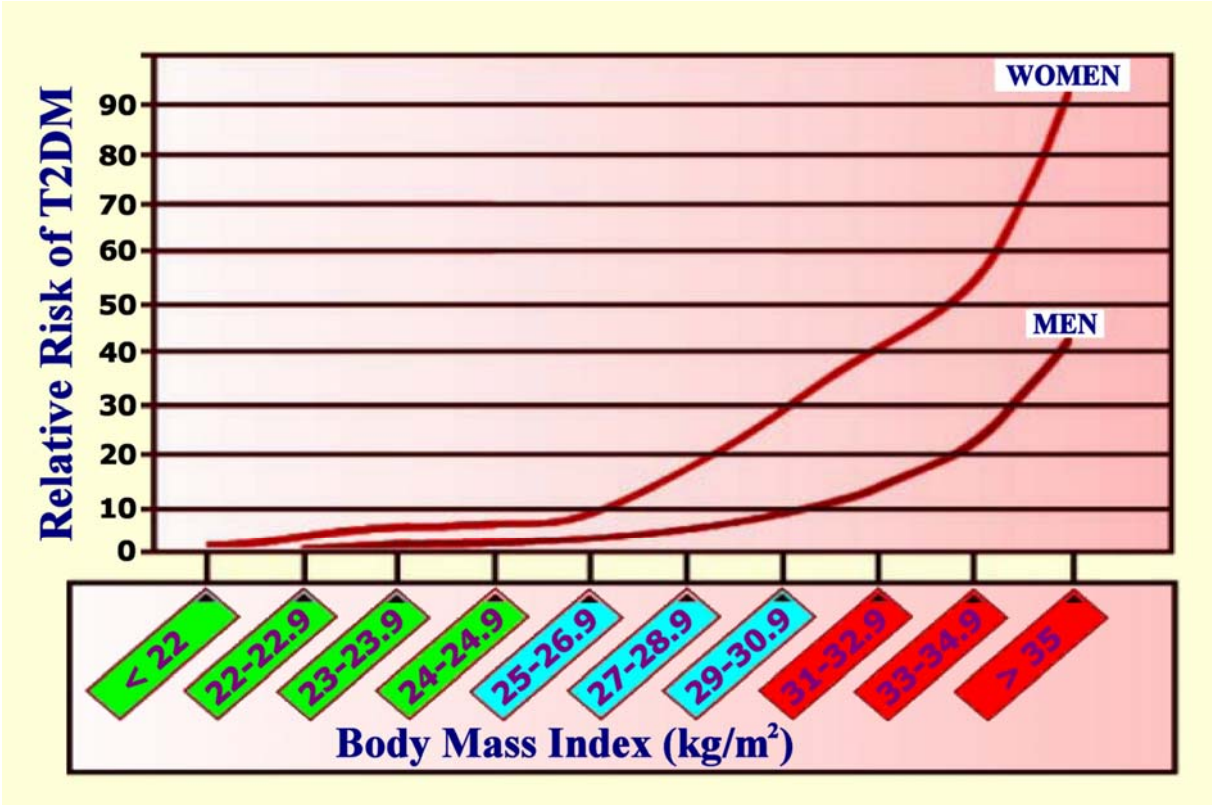
**Figure 1.** Co-morbidities associated with overweight and obesity.



**Figure 2.** Relationship between body mass index (BMI) and mortality (data adopted from Calle et al. NEJM 1999 [7]).

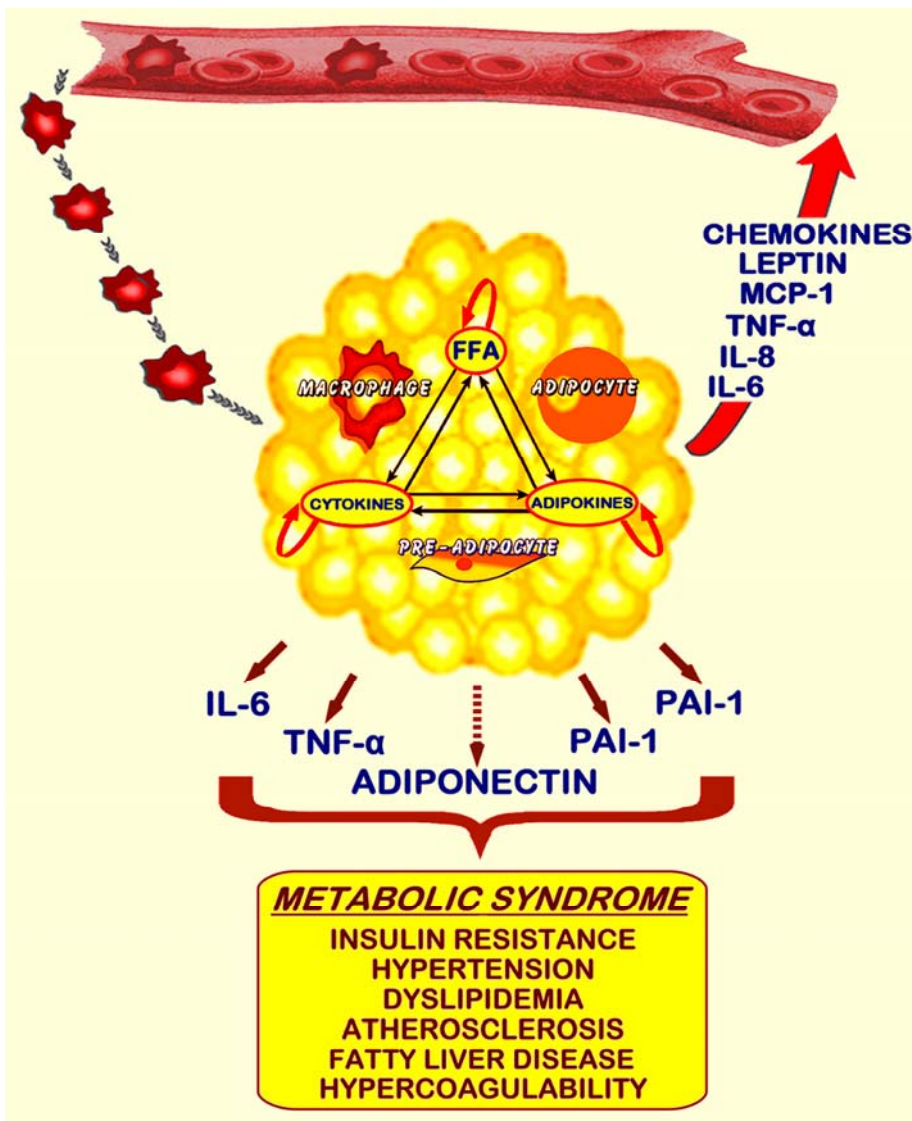


**Figure 3.** Risk of developing type 2 diabetes and body mass index (BMI) in male and female adults (based on data from Colditz GA et al. Ann Intern Med. 1995 [27] and Chan JM et al. Diabetes Care 1994 [28]).





**Figure 4.** Adipose tissue and low-grade inflammatory state in obesity. Excess fat accumulation induces increasing secretion of pro-inflammatory adipokines and chemokines particularly by visceral adipose tissue depots into the circulation. In response to chemotactic stimuli, circulating mononuclear cells are recruited and transmigrate into the expanding adipose tissue, creating a growing population of resident macrophages. In turn, these adipose tissue macrophages are the major source of local cytokine secretion (e.g. TNF- $\alpha$ , IL1 and IL-6). It is evident that a vicious cycle is formed locally with adipocyte-derived free fatty acids (FFA) and adipokines stimulating macrophages to secrete cytokines and *vice versa*. The result is chronic sub-clinical inflammation within adipose tissue depots which persists for as long as the excess fat mass is maintained and leads to generalized inflammation and a procoagulant state due to unremitting release of pro-inflammatory adipokines. This finally can result in deleterious systemic cardiometabolic effects and clinical manifestations of the metabolic syndrome. TNF- $\alpha$ : tumor necrosis factor- $\alpha$ , MCP-1: monocyte chemotactic protein-1, IL-8: interleukin 8, IL-1: interleukin-1, IL-6: interleukin-6.



**Figure 5.** Different definitions of the metabolic syndrome.

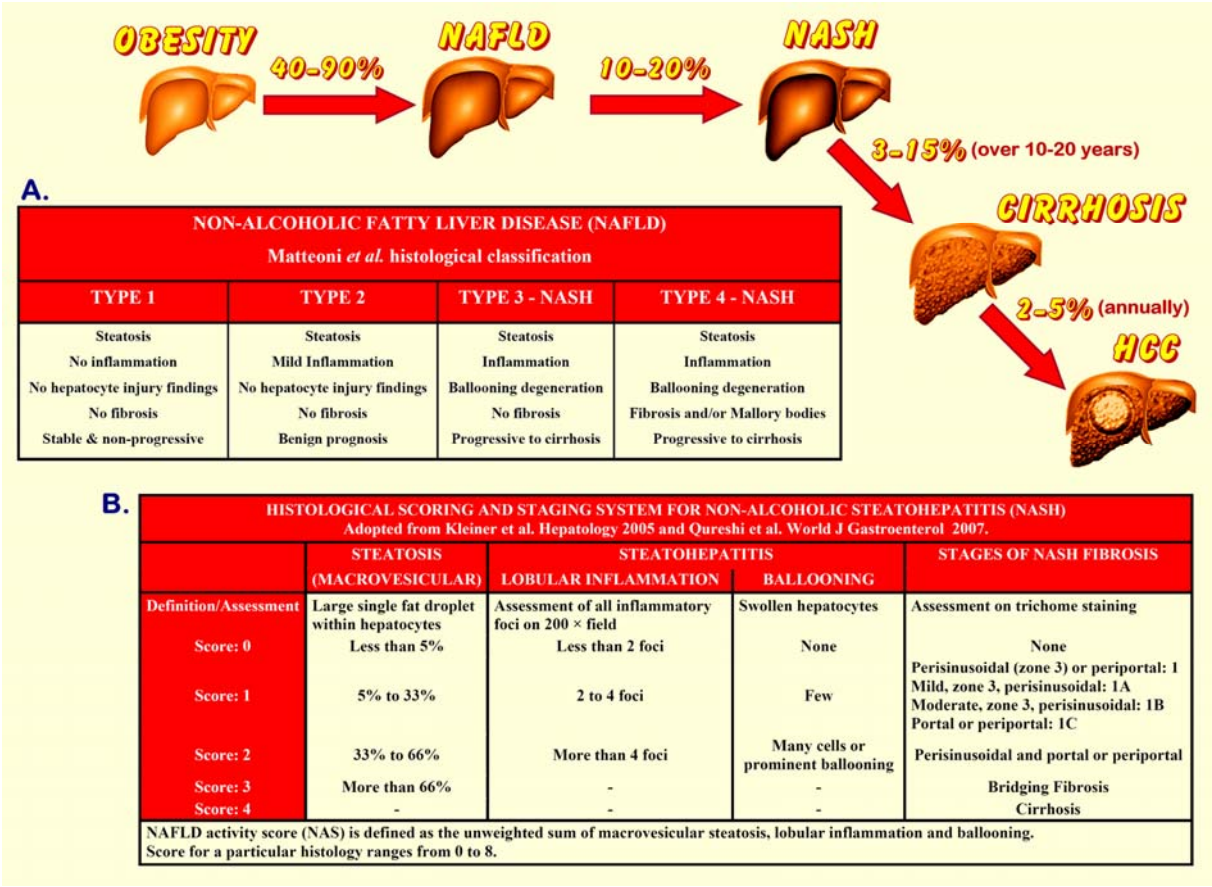
<b>DIFFERENT DEFINITIONS OF THE METABOLIC SYNDROME</b>		
<b>EGIR (1999)</b>	<b>WHO (1999)</b>	<b>NCEP-ATP III (2001)</b>
Insulin resistance - hyperinsulinemia based on fasting insulin values (upper quartile of a non-diabetic population)	Diabetes, IFG, IGT or insulin resistance (by euglycemic hyperinsulinemic clamp - glucose uptake less than lowest quartile)	
<b>Plus at least two of the following:</b>	<b>Plus at least two of the following:</b>	<b>At least three of the following:</b>
1. Central obesity WC ≥94 cm (37 in) (M) WC ≥80 cm (31 in) (F) 2. TG >2.0 mmol/l (177 mg/dl) or HDL <1.0 (39 mg/dl) mmol/l 3. BP ≥140/90 mmHg or on antihypertensive medication 4. FPG ≥6.1 mmol/l (110 mg/dl)	1. Obesity with BMI >30 kg/m <sup>2</sup> or WHR >0.9 (M) WHR >0.85 (F) 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) 3. BP ≥140/90 mm Hg 4. Albumin excretion rate ≥ 20 µg/min or albumin/creatinine ratio ≥ 30 mg/g	1. Central obesity WC >102 cm (40 in) (M) WC >88 cm (35 in) (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) 4. BP ≥135/85 mmHg or on antihypertensive medication 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		

<b>METABOLIC SYNDROME - IDF DEFINITION (2005)</b>			
<b>I. CENTRAL OBESITY</b>			
<b>ETHNIC GROUP</b>	<b>MEN</b>	<b>WOMEN</b>	<b>Until more specific data are available:</b> 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	
<b>II. PLUS ANY TWO OF THE FOUR FOLLOWING FACTORS:</b>			
<b>A. ↑ TG levels:</b> ≥ 150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality			
<b>B. ↓ HDL-c levels:</b> males ≤ 40 mg/dl (1.03 mmol/l), females ≤ 50 mg/dl (1.29 mmol/l) or specific treatment for this lipid abnormality			
<b>C. ↑ Blood pressure:</b> systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or Treatment of previously diagnosed hypertension			
<b>D. ↑ FPG:</b> ≥ 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			

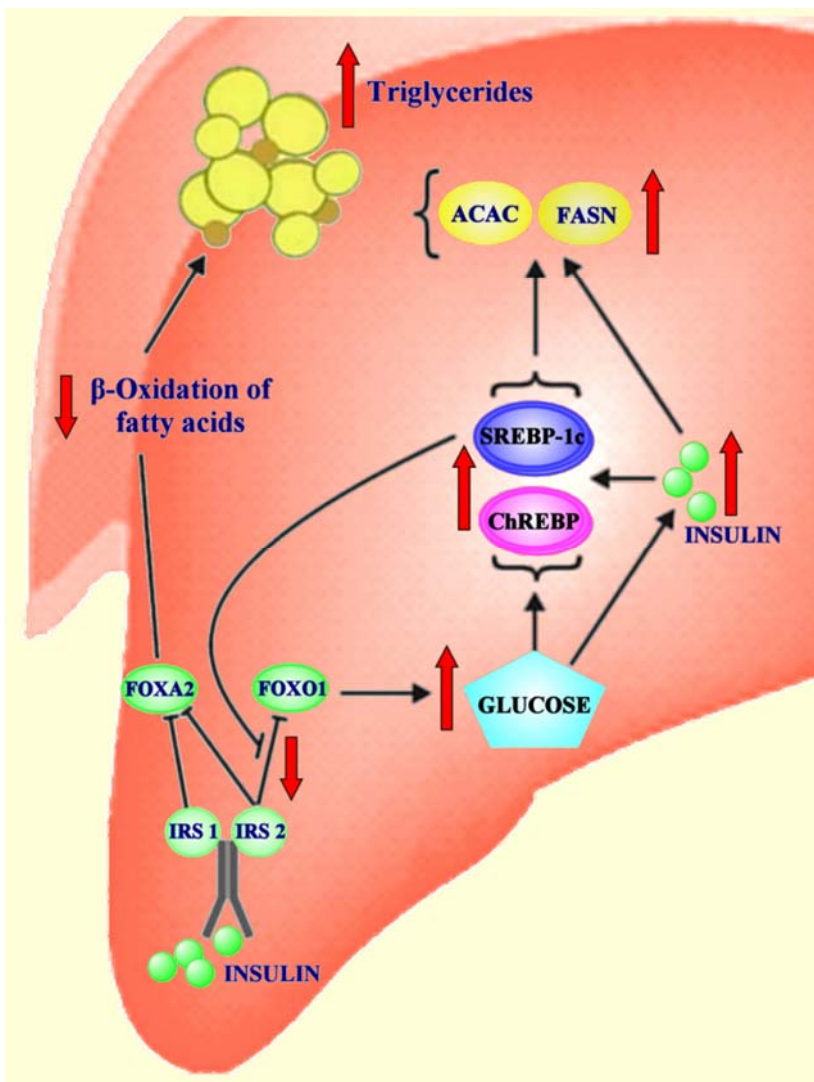
**Figure 6.** Criteria for clinical diagnosis of the metabolic syndrome proposed by a joint interim statement from the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and current recommended waist circumference thresholds for abdominal obesity by organization (adopted from Alberti et al. Circulation 2009 [15]).

<b>CRITERIA FOR CLINICAL DIAGNOSIS OF THE METABOLIC SYNDROME</b>			
<b>RISK FACTOR-MEASURE</b>		<b>CATEGORICAL CUT-OFF POINTS</b>	
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	
<p>Presence of any 3 of 5 risk factors constitutes a diagnosis of metabolic syndrome</p> <p>*: 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.</p> <p>†: 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.</p> <p>‡: Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria</p> <p>HDL-C: high-density lipoprotein cholesterol; BP: blood pressure</p>			
<b>RECOMMENDED WAIST CIRCUMFERENCE THRESHOLDS FOR ABDOMINAL OBESITY</b>			
<b>POPULATION</b>	<b>WC IN MEN</b>	<b>WC IN WOMEN</b>	<b>ORGANIZATION</b>
Euroid	≥94 cm	≥80 cm	IDF
Caucasian	≥94 cm (increased risk)	≥80 cm (increased risk)	WHO
	≥102 cm (higher risk)	≥88 cm (higher risk)	
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			

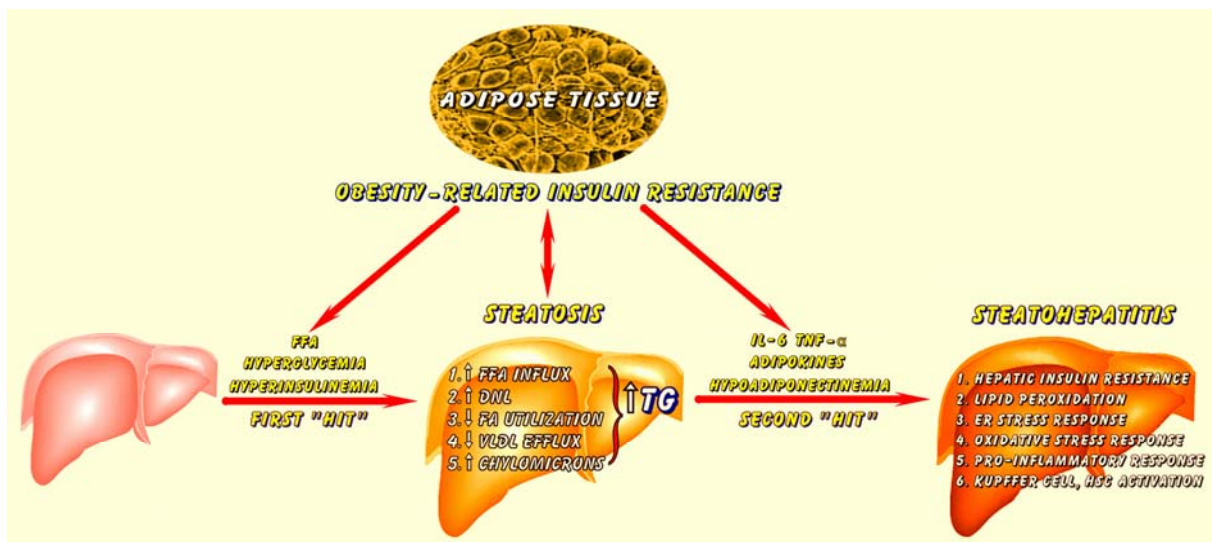
**Figure 7.** Natural history of non-alcoholic fatty liver disease (NAFLD). **A.** Histological classification as proposed by Matteoni *et al.* [130]. Non-alcoholic steatohepatitis (NASH) represents the most severe form of NAFLD (NAFLD types 3 and 4) and can progress to cirrhosis and hepatocellular carcinoma (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 and Qureshi *et al.* World J Gastroenterol 2007 [132, 133]).



**Figure 8.** Signaling pathways leading to hepatic triglyceride accumulation in insulin-resistant states. In 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 already impaired, resulting in decreased fatty acid oxidation. In turn, elevated glucose activates both SREBP-1c and ChREBP, and causes enhanced 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 [55]).

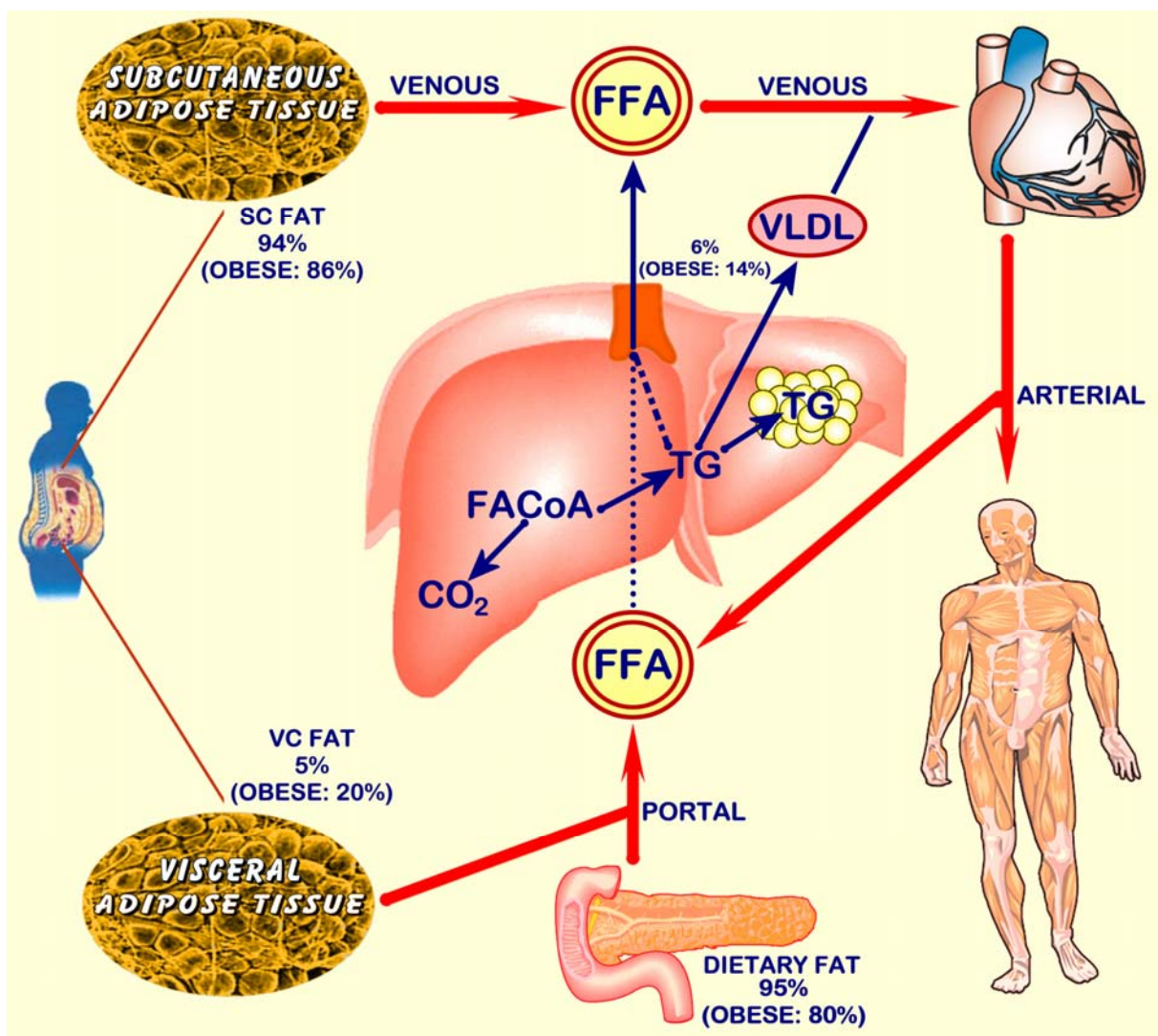


**Figure 9.** Pathogenesis of non-alcoholic fatty liver disease (NAFLD) based on the “two hit” model proposed by Day *et al.* [161-163]. The first “hit” induces steatosis primarily caused by increased circulating hepatic free fatty acids (FFA) released from insulin resistant adipocytes. Furthermore, due to hepatic insulin resistance, hyperinsulinemia and hyperglycemia also induce increased *de novo* lipogenesis (DNL), suppressed VLDL efflux and impaired fatty acid oxidation. Dietary fat may also increase hepatic triglycerides (TG) through delivery of chylomicrons from the intestines. The second “hit” is promoted by hyperleptinemia, hypoadiponectinemia and increased circulating levels of tumor necrosis- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), causing progression to steatohepatitis (NASH). Steatosis and the adverse adipokine profile in obesity further induce hepatic insulin resistance, hepatic lipid peroxidation, oxidative stress responses and endoplasmic reticulum (ER) stress responses, as well as activation of Kupffer and hepatic stellate cells. Thus, a chronic pro-inflammatory state develops inside the steatotic liver, progressively leading to hepatic cell injury, inflammation, apoptosis and fibrosis.



**Figure 10.** Free fatty acid (FFA) circulation through the liver (adapted from Roden et al. *Nat Clin Pract Endocrinol Metab* 2006 [166] with data from Nielsen et al. *J Clin Invest* 2004 [164]). Adipose tissue delivers approximately 80 percent of circulating free fatty acids (FFA) in the fasted state, with this proportion being reduced to 60 percent 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 obese persons, whereas a lower percentage of FFA is supplied both from 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 [55]).

FACoA: long-chain fatty acids bound to coenzyme A.



**Figure 11.** Hormonal changes and clinical manifestations of hypothalamic-pituitary-gonadal (HPG) axis dysfunction in obese females.

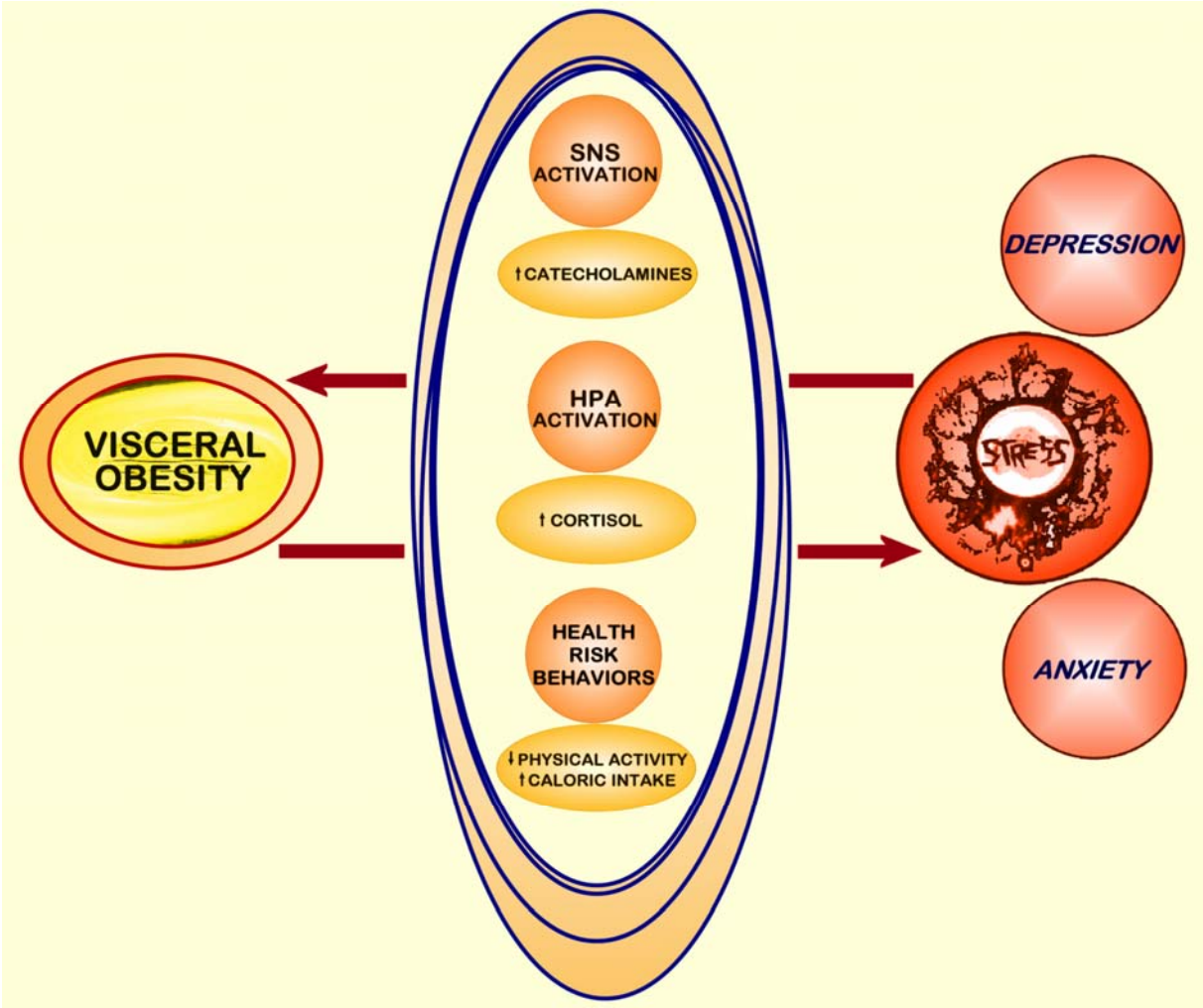
<b>HYPOTHALAMIC-PITUITARY-GONADAL AXIS IN OBESE FEMALES</b>	
<b>Hormonal changes</b>	<b>Clinical manifestations</b>
↑/↔ Estrogen & ↓/↔ Progesterone ↑ Testosterone ↓ SHBG ↔ basal FSH ↔ basal LH ↔ FSH after stimulation ↔ LH after stimulation	Early menarche - Early menopause Menstrual disorders Chronic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



**Figure 12.** Hormonal changes and clinical manifestations of hypothalamic-pituitary-gonadal (HPG) axis dysfunction in obese males.

<b>HYPOTHALAMIC-PITUITARY-GONADAL AXIS IN OBESE MALES</b>	
<b>Hormonal changes</b>	<b>Clinical manifestations</b>
↓ 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	

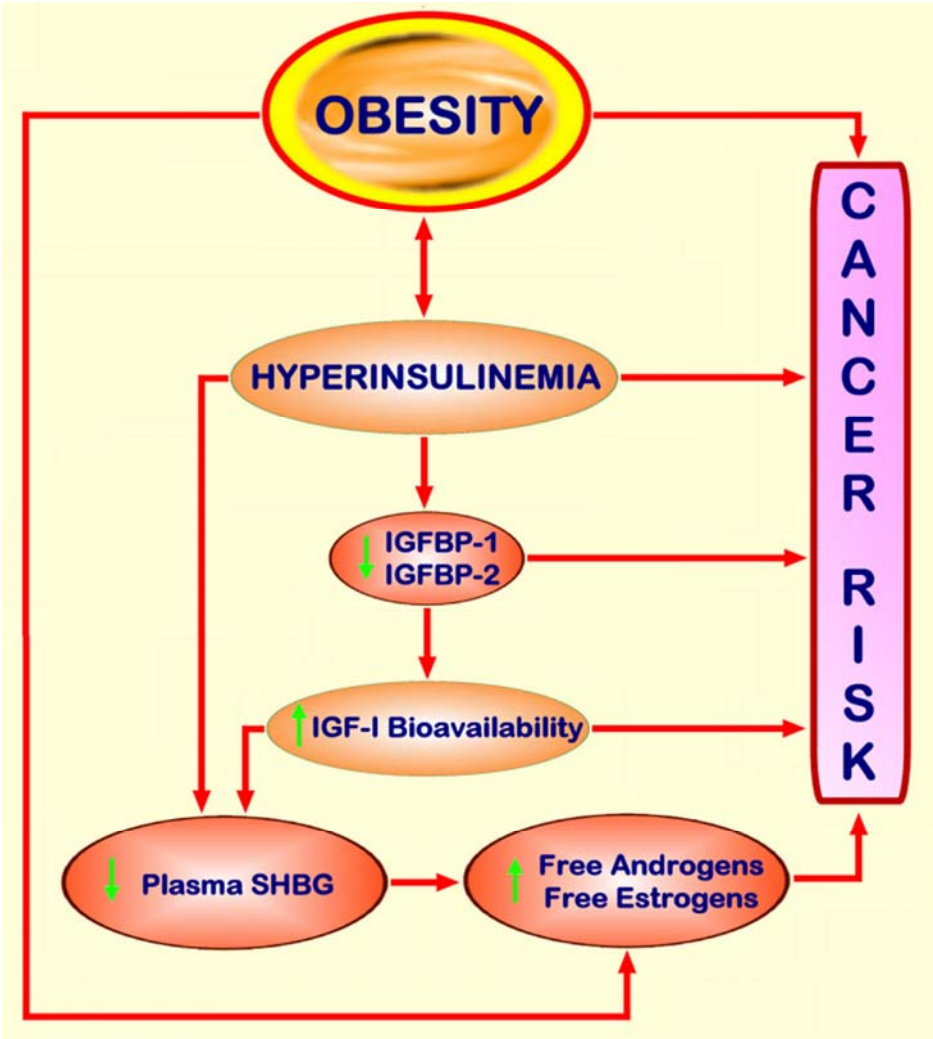
**Figure 13.** Reciprocal relations between obesity and stress. Chronic stress, manifested with depressive or anxiety symptoms, can induce prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) which together with health risk behaviors, can progressively lead to visceral obesity and *vice versa* (adopted from Kyrou et al. Curr Opin Pharmacol. 2009 [33]).



**Figure 14.** Level of evidence regarding obesity and risk of various cancers.

<b>OBESITY AND INCREASED CANCER RISK</b>		
<b>SUFFICIENT EVIDENCE</b>	<b>SUPPORTIVE DATA</b>	<b>INSUFFICIENT DATA</b>
Endometrial cancer Post-menopausal breast cancer Kidney (renal cell) cancer Colorectal cancer Oesophageal adenocarcinoma Gastric cardia adenocarcinoma	Pancreatic cancer Liver cancer Gallbladder cancer Lymphoid malignancies Haematopoietic malignancies	Lung cancer Thyroid cancer Bladder cancer Cervix cancer Ovarian cancer Prostate cancer Testicular cancer Malignant melanoma Noncardia gastric cancer

**Figure 15.** Proposed mechanisms linking obesity and increased cancer risk. Obesity, particularly central, causes insulin resistance and compensatory chronic hyperinsulinemia. Increased insulin levels directly induce mitogenic effects and contribute to tumorigenesis. Hyperinsulinemia can also suppress insulin-like growth factor binding protein 1 (IGFBP-1) and IGFBP-2 levels which, in turn, lead to increased insulin-like growth factor 1 (IGF-1) bio-availability. IGF-1 promotes cellular proliferation and inhibits apoptosis through its receptor in several tissues. Increased levels of estrogens and androgens additionally mediate carcinogenic effects, particularly for endometrium and post-menopausal breast cancers. Circulating SHBG levels are decreased in 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. Enhanced metabolism of sex steroids within adipose tissue depots can further contribute to increased plasma levels of androgens and estrogens in obesity. Finally, obesity may directly promote carcinogenesis due to adipokine changes (e.g. hypoadiponectinemia and hyperleptinemia) and development of a chronic low-grade inflammatory state (adopted from Bianchini et al. *Obes Rev.* 2002 [351]).



**Figure 16.** Potential mechanisms linking weight gain, insulin resistance, cardiovascular disease and hypertension in obese patients with obstructive sleep apnea (OSA). Chronic intermittent hypoxia in OSA may increase reactive oxygen species (ROS) production and oxidative stress. In addition, inflammatory pathways and activation of the sympathetic nervous system (SNS) are stimulated due to both chronic intermittent hypoxia and disruption of normal sleep patterns (sleep fragmentation and recurrent arousals). In turn, this induces progressive adverse effects on insulin sensitivity and cardiovascular risk mediated via circulating adipokines (e.g. leptin) and pro-inflammatory factors (e.g. IL-6 and TNF- $\alpha$ ). Conversely, insulin resistance promotes further central fat accumulation and cardiovascular disease which aggravate OSA, thereby closing a viscous cycle (adapted from Arnarsdottir et al. Sleep 2009 [481]).

