Morbidity and mortality associated with obesity

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Abstract: Obesity and its repercussions constitute an important source of morbidity, impaired quality of life and its complications can have a major bearing on life expectancy. The present article summarizes the most important co-morbidities of obesity and their prevalence. Furthermore, it describes classification and grading systems that can be used to assess the individual and combined impact of co-morbid conditions on mortality risk. The literature was screened for assessment tools that can be deployed in the quantification of morbidity and mortality risk in individual patients. Thirteen specific domains have been identified that account for morbidity and mortality in obesity. Cardiovascular disease (CVD) and cancer account for the greatest mortality risk associated with obesity. The King's Criteria and Edmonton Obesity Staging System (EOSS) were identified as useful tools for the detection and monitoring of individual patient mortality risk in obesity care. The stark facts on the complications of obesity should be capitalized on to improve patient management and knowledge and referred to in the wider dissemination of public health messages aimed at improving primary prevention.

Keywords: Morbidity; mortality; obesity

Clinical context

Obesity and overweight are defined as a systemic disease that shows excessive and abnormal accumulation of body fat leading to adverse health effects. Obesity imposes devastating health and financial tolls on individuals and society. Despite significant efforts to increase awareness, the obesity epidemic continues at an alarming rate (1).

More than half of the European population is overweight and up to 30% is obese with prevalence worldwide doubling since 1980 [World Health Organization (WHO) 2011] (2). Obesity is associated with higher rates of death driven by comorbidities such as type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, obstructive sleep apnea (OSA), certain types of cancer, steatohepatitis, gastroesophageal reflux, arthritis, polycystic ovary syndrome (PCOS), and infertility (3).

Categorising of body weight

There are three measures of obesity often used in epidemiological studies: body mass index (BMI), waist circumference (WC) and waist to hip circumference ratio (WHR). The most commonly used is BMI which equals the ratio of weight in kilograms divided by height in meters squared (kg/m^2). The classes of BMI reported by the WHO are, 18.5–24.9 kg/m^2 for normal, 25.0–29.9 kg/m^2 for overweight and >30 kg/m^2 for obesity (*Table 1*) (4).

WC and WHR can be used to measure abdominal obesity (5) and its association with various metabolic risk

Table 1 Classification of overweight and obesity by BMI (4)

Classification	Obesity class	BMI (kg/m^2)
Underweight		<18.5
Normal		18.5–24.9
Overweight		25.0–29.9
Obesity	I	30.0–34.9
Severe obesity	II	35.0–39.9
Morbid obesity	III	40.0–49.9
Severe morbid obesity	III	>50

BMI, body mass index.

factors which appear more useful than the use of BMI alone (6,7). The cut-off of WC (>102 cm in men and >88 cm in women) is difficult to apply in all populations as people from Asia appear to have higher morbidity at lower cut-off for WC compared to White Caucasians (8).

Genes and environmental—the aetiology of obesity

Obesity is underpinned by positive energy balance believed to be driven by hyperphagia arising as a consequence of increased hunger, decreased satiety or both. Pathology of the subcortical areas of the brain that control appetite is influenced by environmental factors superimposed on genetically determined susceptibility. Although 'fatness' runs in families, it has been difficult to separate the influences of nature versus nurture. Heritable factors account for approximately 70% of the difference in BMI in adult life (9,10). Body composition, distribution of fat and visceral fat deposition after periods of overeating share a similar genetic component (11). Environmental factors include marketing, advertising, increasing portion sizes, accessibility and availability of calorie dense foods and increased automation, all of which have contributed to increased energy intake and reduced energy expenditure (12).

Obesity and its major co-morbidities

Diabetes

The term of "diabesity" is used to describe the overlap between T2DM and obesity (13). About 50% of diagnosed diabetic patients are obese, but only approximately 20% of patients seeking bariatric surgery are diabetic (14,15).

The risk of developing T2DM increases by 20% for each 1 kg/m^2 increased in the BMI (16). The risk of T2DM does not increase up to a BMI <27.2 kg/m^2. But a BMI of 27.2 to 29.4 kg/m^2 the risk will rise by 100% and increases by about 300% for BMI >29.4 kg/m^2 (5,16).

Pathogenesis

Obesity is associated with elevated circulating free fatty acids (FFAs) (17), which induce oxidative stress by promoting the production of reactive oxygen species (ROS) to a level greater than their removal, and the high level of ROS is the main cause of insulin resistance (18,19). A high-fat diet is associated with a reduction in the hepatic levels of the antioxidant glutathione (GSH) and diminished activity of antioxidant enzymes, while the activity of some enzymes such as NADPH oxidase which produce ROS, is augmented (20,21). In skeletal muscle, markers of oxidative stress have also been reported to be increased by high-fat diet which leads to increased peripheral insulin resistance in association with ectopic fat storage in muscle (21,22). With time the pancreas becomes exhausted and blood glucose level begins to increase as not enough insulin is produced to overcome the resistance. Once hyperglycemia occurs, its toxic effect on islet cells (glucotoxicity) exacerbates the problem (23). Consequently, the increase in FFAs causes lipotoxicity. Insulin resistance at the muscular, hepatic and adipose tissues increases proinflammatory cytokines and decreases anti-inflammatory cytokines, resulting in chronic inflammation.

The long-term complications of T2DM include cardiovascular diseases (CVD), stroke, peripheral vascular diseases (PVD), retinopathy, nephropathy, neuropathy (23). Therefore, prevention or at least control of T2DM will

reduce complications and direct healthcare costs of obesity.

CVD

Obesity associated with the metabolic syndrome is associated with CVD (24). Metabolic syndrome is defined as a combination of at least three of the following features: central obesity, high serum triglyceride (TG) levels, low serum high-density lipoprotein (HDL), cholesterol levels, hypertension, and elevated fasting blood glucose levels. Cardiomyopathy associated with obesity is characterized by left ventricular hypertrophy and diastolic dysfunction (25). The prolonged exposure to obesity leads to worsening of cardiac function and larger ventricular mass (26), while left atrial dilatation and systolic dysfunction may also develop (27). Obesity also increases the risk of atrial fibrillation, but not stroke (28). Obese patients are 3.5 times more likely to have hypertension, while 60–70% of hypertension in adults may be attributable to adiposity (29). In a meta-analysis study of 2.88 million individuals, obesity was associated with an increase in mortality rate, with a hazard ratio of 1.18 (95% CI, 1.12–1.25) (30).

Airway

Severe obesity can be associated obesity-hypoventilation Syndrome (OHS) which defined as; the combination of obesity and chronic daytime hypercapnia [arterial carbon dioxide pressure $(PaCO_2) \geq 45$ mmHg] (31,32). The prevalence of OHS is 0.3–0.4% of the general population in Western countries (33,34) and 10–20% in patients with obesity associated obstructive sleep apnoea (35,36), to almost 50% of hospitalized patients with a BMI greater than 50 kg/m^2 (37). OHS associated with higher morbidity and mortality than either OSA or simple obesity (38). Using data from seven hospitals in Akashiba *et al.* study showed that hypercapnia was 9% in OSA non-obese patients and 32% in obese OSA patients (39). The survival rate for continuous positive airway pressure (CPAP)-treated obstructive sleep apnoea syndrome (OSAS) patients in the Campos-Rodriguez *et al.* study was 85.5% (40). However, it was 77.3% for the treated OHS patients in Priou *et al.* cohort study (41). So, we can conclude that mortality is higher in OHS than in OSAS as demonstrated by Castro-Añón *et al.* who showed that patients with OHS had a 2-fold increase in the risk of mortality compared with those with OSAS (42).

BMI showed a strong, independent and positive relation

with asthma possibly because of the impact of adipose tissue on the chest wall causing a restrictive lung disease, but also as obesity is associated with a chronic inflammatory state (43,44). The pulmonary function tests (PFTs) of obese patients often show impaired expiratory reserve volume (ERV), functional residual capacity (FRC) and total lung capacity (TLC), secondary to increased abdominal load and disturbed chest wall mechanics (45,46).

Kidney

Obesity is associated with abnormal renal parameters, obesity-related glomerulopathy, and chronic kidney disease (CKD). Obese patients often have increased albumin excretion rates (AER) that indicate early renal impairment and elevated risk of cardiovascular (CV) morbidity and mortality (47-49). Microalbuminuria prevalence correlates positively with total and central adiposity even in the absence of diabetes and hypertension (50,51). For each 5 kg/m^2 increase in BMI, mortality associated with kidney diseases increases by 60% (52). Furthermore, the dyslipidemia which associated with obesity leading to progressive CKD by promoting inflammation and endothelial dysfunction (53). Lower concentrations of HDL, are associated with a higher incidence of CKD in the general population (54). Evidence for a link between dyslipidemia and reduced renal function in children was demonstrated in a population-based study from Turkey (CREDIT-C study), where both hypercholesterolaemia and a higher BMI were associated with a lower glomerular filtration rate (47).

Liver

Nonalcoholic fatty liver disease (NAFLD) includes hepatic steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. NAFLD is the most common cause of chronic liver disease in the United States (55,56). Obesity and insulin resistance are considered to be the main causative factors of NAFLD; the percentage of obese patients seeking bariatric surgery that have steatosis is 91%; 37% have NASH and 10% show cirrhosis (57). Hepatic steatosis arises from an imbalance between TG production and utilization. The FFAs used for the hepatic production of TG are derived from diet, *de novo* lipogenesis (DNL) and adipose tissue lipolysis. Approximately 60% of accumulated TG in the livers of NAFLD patients are derived from FFAs mobilized from peripheral adipose depots, 25% from DNL,

and the remaining 15% from dietary lipids (58).

Based on the Argo and colleagues analysis of ten studies, 37.6% of NAFL patients have progressive fibrosis over 5.3 years (59). The incidences of hepatocellular carcinoma were 4%, 10%, 3.6%, and 8.9% in Ascha *et al.*, Ratziu *et al.*, Bugianesi *et al.*, and Hashimoto *et al.* studies respectively (60-63).

Gonadal

Obesity is associated with subfertility (64) with up to 41.9% of women seeking obesity surgery suffering from subfertility, the subfertility in obese patients in this cohort study attributed to androgen excess, insulin resistance, and hyperinsulinism (65). Obesity has marked effects on sex hormone secretion and metabolism changing the bioavailability of estrogen and androgens.

With increasing adiposity, there is an increase in peripheral aromatization of androgens to estrogens associated with a decrease in the hepatic synthesis of sex hormone-binding globulin (SHBG), which cause an increase in free oestradiol and testosterone. This is further exacerbated by an associated hyperinsulinemia resulting in decreased SHBG and stimulation of ovarian androgen production. Excess secretion of luteinizing hormone (LH) and the increased androgen to estrogen ratio and the overall altered endocrine milieu, in turn, lead to abnormal folliculogenesis and follicular atresia (66). Analysis of follicular fluid assayed for various hormones and metabolites from patients undergoing *in vitro* fertilization (IVF) cycles demonstrate marked differences between obese and non-obese patients. High level of mediators such as C-reactive protein, interleukin-6, tumor necrosis factor-α and plasminogen activator inhibitor type-1 in obese patients have a deleterious effect on the reproductive cycle (67).

Gastroesophageal reflux

The prevalence of gastroesophageal reflux disease (GERD) is estimated to be 20–44% in the Western countries, with a lower frequency in Asia (68). In particular, this escalation is suggested to be related to the global rise in obesity (69,70). The cause for this increasing prevalence is uncertain. Dietary changes with increasing fat intake, smoking, alcohol use, and possibly decrease in the prevalence of Helicobacter pylori infection are possibilities (71). Hampel *et al.* study which analyzed nine different studies reported that there are statistically significant associations between BMI and GERD

in six studies, significant associations of BMI with erosive esophagitis in six studies, and significant associations of BMI with gastric cardia adenocarcinoma in four studies (72).

BMI >30 kg/m^2 (as compared with BMI <25) is associated with increased acid reflux episodes, long reflux episodes (>5 min), pH <4 in the oesophagus, and a calculated summary score. The association between reflux parameters and BMI was largely mediated by WC (71).

Cancer

Obesity increases cancer incidence (73) partly by converting high-fat diet supplied fatty acids or *de novo* synthesized fatty acids into protumorigenic signaling lipids. Signaling lipids then signal onto the cancer cell through paracrine or autocrine interactions, while aggressive cancer cells upregulate monoacylglycerol lipase to generate fatty acids. These are incorporated in oncogenic signaling lipids that in-turn drives cancer pathogenicity (74).

Obesity is associated with an increased risk of developing insulin resistance which considered a major metabolic abnormality in most patients with type 2 diabetes characterized by elevated levels of circulating insulin (75). A recent meta-analysis of observational studies has revealed that insulin resistance and hyperinsulinemia is a significant risk factor for endometrial cancer (76).

Premenopausal women mainly synthesize estrogens in the ovary. However, in postmenopausal women ovarian biosynthesis is replaced by peripheral site synthesis, and in obese postmenopausal women, adipose tissue is the main source of estrogen biosynthesis. So, obese postmenopausal women have significant increases in estrone, estradiol, and free estradiol (77,78). This mechanism of estrogen production can lead to local estrogen levels in breast tumors that are as much as 10-fold higher compared with the circulation. In fact, a recent publication assessing breast cancer risk factors listed BMI and weight gain between the ages of 20 and 50 years as second only to Gail Model parameters [quantitative breast density, free estradiol, parity (yes/no), and age of menopause] in importance (79). The association between obesity and breast cancer risk is complex, varying by breast cancer subtype and by menopausal status. Although obesity is associated with reduced breast cancer incidence in premenopausal women (80), it is associated with increased breast cancer incidence in postmenopausal women (80,81). Obesity acts as a protective factor for premenopausal breast cancer, but it is associated with increased risk of breast cancer

subtypes such as triple negative and basal-like disease (82). Obesity is associated with increased risk of breast cancer recurrence and mortality in both pre and postmenopausal women (83,84). Multiple studies have demonstrated that this association may be stronger in women with hormone receptor-positive tumors (85-87).

Medication

The comorbidities of obesity necessitate an increase in drug prescriptions for CVD, pain, psychiatric disorders, diabetes mellitus, and asthma (88). Narbro *et al.*'s study demonstrates that 52% of the obese individuals were taking medications compared with only 36% of the randomly selected reference populations (89). Physiological changes such as increased muscle mass, connective tissue, and total body water in obese patients alter pharmacokinetics and pharmacodynamics of medications (90).

Functional (physical functioning)

The severely obese patient shows marked impairment in their activities of daily living such as walking, climbing stairs, and bathing. These problems are often very distressing (91,92), which leading to increasing the risk of musculoskeletal pain and osteoarthritis (93). *Figure 1* illustrates how mobility disability and functioning are viewed as an outcome of the interactions between obesity, body functions, structures, personal and environmental factors (94). Obesity is associated with decreased postural control and stability which hinders the individual's ability to adapt to changes in terrain or grades during walking. One of the etiological factors for this is the abnormal distribution of body fat in the abdominal area. This leads to a forward anterior-posterior (AP) center of pressure; meaning that they carry their weight toward the front of their feet, and AP instability during static and dynamic balance (95). The instability created by abnormal body fat distribution mainly compensated by the changes to temporospatial gait parameters (distance between steps and number of steps per minute) (96).

Perceived health status

Around 25–30% of obese patients seeking bariatric surgery show marked clinical symptoms of depression. According to the WHO, depression is considered one of the main causes of disability, affecting about 121 million people all over the world (97).

Body image

Defined as the mental image a person has about the size, shape, and form of his/her body, as well as the feelings about these characteristics and constituent body parts. Body dissatisfaction (BD) is the discrepancy between the real and an individual's idealized body image (98,99). Decreased physical activities in obese patients make them depressed, socially isolated, or discriminated against; resulting in poor self-esteem, body image distortions, and making them more likely to be the targets of teasing or bullying (100,101).

Economic repercussions

Reduced productivity, unemployment, and direct healthcare costs are the main economic repercussions of obesity (102). In the UK, healthcare costs associated with obesity account for 2.3–2.6% of all public health spending (103), Studies of the economic impact of obesity sometimes examine direct costs, while others focus on indirect costs or both. Direct costs refer to money consumed to treat obesity-related health problems such as hospitalization, medical consultations in outpatient clinics and the consumption of medications, while indirect costs refer to lost productivity or costs to the economy outside of the health sector.

Mortality associated with obesity

Obesity is associated with an increased risk of disease and death, particularly from CVD and cancer (52,104). The Association between BMI and mortality substantially varies between populations and causes of death (52,105) and can change over time (106,107).

Regarding the study of Flegal *et al.*: relative to normal weight, grade 2 and 3 obesity were both associated with significantly higher all-cause mortality. Grade 1 obesity was not associated with higher mortality, suggesting that the excess mortality in obesity may predominantly be due to elevated mortality at higher BMI levels (108).

Kings Obesity Staging Criteria (KOSC)

The KOSC (109) was designed to allow a practical and simplified assessment of obesity-related complications and risk of mortality to minimize inter-operator variability. It grades 12 aspects of obesity-related morbidity in line with
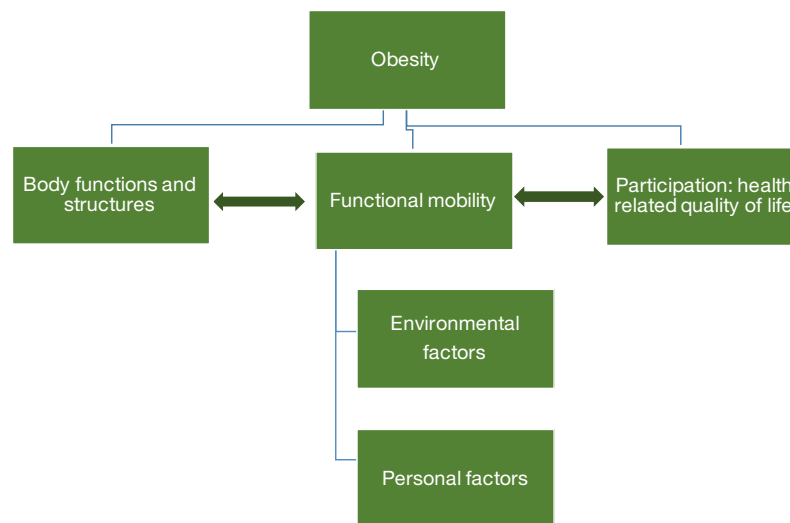
Figure 1 Illustration of how mobility disability and functioning and health-related quality of life are viewed as an outcome of the interactions between obesity, body functions and structures, environmental factors and personal factors.

those described above, and indexed in alphabetical order to improve ease of use: airways, BMI, CVD, diabetes, economic complications, functional limitations, gonadal axis, health status (perceived), body image, junction gastro-oesophagus, kidney disease, and liver disease (*Table 2*). For each domain, a person's health is assigned a score of 0 (normal health), 1 (at risk), 2 (established disease) or 3 (advanced disease). The KOSC use quantifiable measures where possible to reduce the bias of subjective measures. A benefit of the King's Criteria is that separate scores can be tracked for each domain, which allows for a more holistic and specific assessment of treatment benefit. So, patients with score 2 and 3 for each domain have increased all-cause mortality compared to stages 0 or 1 associated increase mortality rates (109).

Edmonton Obesity Staging System (EOSS)

The EOSS classifies the impact of obesity on an individual into five stages of severity (110). Stage 0 represents the obese phenotype with no co-morbidities. Stage 1 represents subclinical disease whereby medical management is favored. Patients in stages 2 and 3 of EOSS are candidates for medical and surgical intervention for obesity. Stage 4 represents end-stage disease and implies that surgical intervention is less likely to improve long-term prognosis and may be harmful (111).

Retrospective application of the EOSS to the National Health and Nutrition Examination Survey (NHANES) data showed that patients in stages 2–4 of EOSS have increased all-cause mortality compared to stages 0 or 1. The severity of the medical complication(s) had a far greater effect on survival than the BMI (111). The EOSS can also refine predictions of all-cause mortality within BMI categories of obesity.

Comparison of KOSC and EOSS

KOSC grades 12 domains of obesity-related morbidity arranged in an alphabetical manner each of them has scores 0–3, but EOSS classifies obese patients into five graded categories, based on their morbidity and health-risk profile. In KOSC separate scores can be tracked for each domain which allows for a more holistic and specific assessment for the risk of complications and mortality, which is not applicable in EOSS. The EOSS provides prognostic information that can assist clinicians in tailoring interventions in a simple manner; Stage 0 no need for treatment, Stage 1 represents subclinical disease whereby medical management is favored. Patients in stages 2 and 3 of EOSS are candidates for medical and surgical intervention for obesity. Stage 4 represents end-stage disease and implies that surgical intervention is the only feasible remaining option. However in KOSC tailoring of intervention is more complicated.

Table 2 The summarization of Modified King's criteria (109)

Criteria	Stage 0	Stage 1	Stage 2	Stage 3
Airway sleep	Normal	Snoring	Apnea require CPAP	Cor pulmonale
BMI (kg/m^2)	<30	30–35	35–50	>50
Cardiovascular	<25% risk	>25% risk	Heart disease	Heart failure
Diabetes	Normal	Impaired fasting glycemia	Type 2 diabetes	Uncontrolled type 2 diabetes
Economic	Normal	Suffered discrimination	Unemployed due to obesity	Requires financial support
Functional	Can manage 3 flights of stairs	Manage 1 or 2 flights of stairs	Manage <1 flight of stairs or requires walking aids	Housebound
Gonadal	Normal	Irregular periods	PCOS/impotence	Infertility
Health status	Normal	Low mood or QoL	Moderate depression or poor QoL	Severe depression
Image	Normal	Does not like looking in mirror	Avoid mirrors/body image dysphoria	Severe eating disorder
Junction gastroesophageal	Normal	Heartburn	Esophagitis	Barrett esophagus
Kidney	Normal	Proteinuria	GFR <60 mL/min	GFR <30 mL/min
Liver	Normal	Raised LFT/NAFLD	NASH	Liver failure

CPAP, continuous positive airway pressure; BMI, body mass index; PCOS, polycystic ovary syndrome; QoL, quality of life; GFR, glomerular filtration rate; LFT, liver function test; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Weight loss impact on morbidity and mortality

The life expectancy of a severely obese person is reduced by an estimated 5–20 years (112). A large cohort prospective study and other retrospective cohort studies suggested that bariatric surgery reduces mortality considerably. In the Swedish Obese Subjects (SOS) study, during a period of up to 15 years, the overall mortality was 30.7% lower among the bariatric group compared with control subjects, and the most common causes of death were myocardial infarction and cancer with much of surgery-induced reductions in the latter accounted for by diminished incidence of female cancers, particularly endometrial cancer (113).

In a large retrospective cohort study, during a mean follow-up of 7.1 years, adjusted long-term mortality from any cause in the surgery group decreased by 40% compared with the control group. The cause-specific mortality rate in the surgery group decreased by 56% for coronary artery disease, by 92% for diabetes, and by 60% for cancer (114).

Moreover, Flum and Dellinger reported a 33% reduction in the rate of death due to any cause after gastric bypass surgery as compared with the rate among control subjects after a mean follow-up of 4.4 years (115). Finally, Christou *et al.*, at a mean follow-up of 2.6 years, reported that among patients who had undergone gastric bypass surgery, the rate of death due to any cause decreased by 89% compared with control subjects (116). So, weight loss associated with decrease morbidity and mortality.

Conclusions

The epidemic of obesity has highlighted the extent of the risks associated with this disease. The risks arise from the increased mass of fat tissue, as well as the products produced by the increased number and size of adipocytes in obese individuals. Psychosocial dysfunction, OSA, and osteoarthritis can be a direct result of increased fat mass. Other diseases associated with obesity result from the metabolic consequences of enlarged fat cells. Diabetes, gallbladder stones, high blood pressure, liver disease, coronary artery disease, cerebrovascular disease, certain types of cancers, and infertility can all be traced in part to the increased secretion of inflammatory and coagulation

molecules from adipocytes. Finally, obesity also increases overall mortality. It is clear from this review that the morbidity and increased mortality of overweight and obesity are substantial and should prompt further attention towards the need for appropriate weight management in health care.

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Footnote

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