INTRODUCTION

Obesity is a chronic, multifactorial and complex disease resulting from a long-term positive energy balance, in which both genetic and environmental factors are involved. It was recently suggested that some forms of obesity are associated with chronic low-grade inflammation. Overweight and obesity constitute the fifth leading risk for global deaths. In June 2013, the American Medical Association officially recognized obesity as a disease.[(1)] Obesity and its severity can be measured by several methods which include:

1. **Body mass index (BMI)** is the most common way of classifying obesity, and is also useful for the anaesthesiologists for classification, risk-stratifying and need of extra consults and measures. It is calculated as total body weight in kilograms divided by height in square meters. Based on BMI, body weight can be classified as follows:[(1-3)]

- Underweight - BMI <18.5 kg/m^2.
- Normal range - BMI of 18.5 - 24.9 kg/m^2.
- Overweight - BMI of 25-29.9 kg/m^2.
- Obesity - BMI of 30-39.9 kg/m^2.
- Morbid obesity - BMI ≥ 40 kg/m^2 or BMI ≥ 35kg/m^2 associated with ≥ comorbidity.
- Super obesity - BMI above 50 kg/m^2.
- Super super obesity - BMI above 60kg/m^2.
- Mega obesity (ultra obesity) - BMI above 70kg/m^2.

The cut-off for each grade varies according to an individual's ethnic background. For example, a BMI of 23 kg/m^2 or higher may define overweight and 27.5 kg/m^2 or higher may define obesity in many Asian populations. Other BMI cutoffs have been identified. These corroborate findings of studies which have documented high levels of %body fat for lower BMI in population samples from a number of countries, including China, Japan, Ethiopia, Indonesia, Thailand and Mexico.[(4)] Ethnicity, therefore, critically needs to be considered in identification of high-risk cases of obesity, especially in definition of cut-off values of anthropometric measurements.[(5)]

Despite its wide spread use, BMI has limited use in some populations, such as very muscular individuals. Moreover, BMI tends to reflect overall adiposity but not fat distribution whereas research suggests that abdominal adiposity may independently influence health outcomes. Consequently, the use of recommendations based on measurements that reflect abdominal adiposity, such as waist circumference (WC), is increasing. A striking example of the limitations of the BMI relates to the metabolically obese, normal-weight (MONW) subjects who have normal BMI values, nonetheless suffer from metabolic complications commonly found in obese people. These observations suggest that high cardiovascular disease risk may be observed even below the normal BMI cut-off of 25 kg/m^2 due to excess visceral adiposity.[(5)]

2. **Waist circumference (WC);**[(6)] measured with the subject standing, at the end of exhalation, at the midpoint between the lowest rib and top of the iliac crest. Two different cutoff points were used for establishing abnormal WC: a) ≥88 cm in women

and ≥102 cm in men (traditional criteria); and b) ≥ 80 cm in women and ≥90 cm in men (new criteria).

3. **Waist-Hip ratio (WHR):**[6] hip circumference is measured at the maximum circumference of the buttocks, with the subject standing and his feet placed together. WHR is defined as high if it is >0.9 in men and >0.85 in women.

4. **Waist to height ratio (WHtR)**[7] is strongly correlated with abdominal fat. WHtR increases the risk for co-morbidities if it is >0.5 in both males and females.

5. **Skin fold thickness**:[8] Biceps skin fold thickness measured at the level of the nipple line while triceps skin fold thickness measured midway between the acromion process of the scapula and the olecranon process. The subscapular and suprailiac skin fold thickness measured at the inferior angle of the scapula and superiorly on the iliac crest directly in the mid-axillary line respectively. The sum of skin fold thickness is defined as high when the value exceeds 50 mm.

6. **Body adiposity index (BAI)** has recently been strongly correlated with % body adiposity measured using dual energy x-ray absorptiometry (DXA) of differing ethnicities without numerical correction. It is calculated as **((hip circumference)/(height in meters)$^{1.5}$ – 18)**.[9]

7. **Body composition reference methods:** [8, 10]

- Hydrometry (underwater weighing) and densitometry (isotope dilution).
- Air-displacement plethysmography (ADP).
- Dual energy x-ray absorptiometry (DXA).
- Bioelectrical impedance analysis (BIA).
- Computed tomography (CT) and magnetic resonance imaging (MRI).

Epidemiology of obesity[11]

In 2005, world health organization (WHO) measured that 1.6 billion people were overweight and 400 million were obese. It estimates that by the year 2015, 2.3 billion people will be overweight and 700 million will be obese. The Middle East, including the Arabian Peninsula, Eastern Mediterranean, Turkey and Iran, and North Africa, are no exception to the worldwide increase in obesity. Subsequently, some call this trend the New World Syndrome. A national plan of action to overcome obesity is urgently needed to reduce the economic and health burden of obesity in this region. Obesity reached an alarming level in all age groups of the Eastern Mediterranean Region countries. Among preschool children, it ranged from 1.9% to 21.9%, while the prevalence among school children ranged from 7% to 45%. Among adults the prevalence of overweight and obesity ranged from 25% to 81.9%.

Etiology

Development of obesity involves interactions between excessive caloric intakes, inefficient use of food energy, reduced metabolic activity, reduced thermogenic response to meals, and an abnormally high set point for body weight. Hormonal, genetic, environmental and psychosocial factors all contribute to this problem.[12]

I. Hormonal influences on appetite[5, 13, 14]

The hypothalamus is the major site of integration of anorexigenic and orexigenic signaling. Peripheral satiety hormones, such as ghrelin from the stomach fundus and leptin from adipose tissue, primarily bind and activate their cognate receptors directly in hypothalamus or in the medulla. In hypothalamus, there exist two populations of neurons:[13, 14]

- Those expressing the orexigenic neuropeptide Y (NPY) or agouti-related peptide (AgRP).
- Those expressing the anorexigenic pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART).

Several satiety hormones induce their anorectic effects by either inhibiting the activity of NPY/AgRP neurons or activating POMC/CART neurons. These neurons project to second-order neurons in other hypothalamic nuclei which express anorexigenic neuropeptide (corticotrophin-releasing hormone, thyrotropin-releasing hormone, brain-derived neurotrophic factor and orexigenic neuropeptides (orexin and melanin concentrating hormone), which modulate appetite and energy homeostasis. Furthermore, the regulation of energy balance involves an integration of signaling from the hypothalamus, brain stem, and reward pathways of the mesolimbic system.[13, 14]

Melanocortin hormone acting through 5 melanocortin receptor (MCR) subtypes, with MC3R and MC4R primarily modifies appetite. Increased local cortisol synthesis in adipose tissue, without marked hypothalamic pituitary adrenal axis alterations, is now recognized as an important molecular etiologic factor for abdominal obesity.[5]

Endocannabinoids, through their effects on endocannabinoid receptors, increase appetite, enhance nutrient absorption, and stimulate lipogenesis. Evidence showed that endocannabinoid system is chronically activated in obese individuals and interacts with several major players in the multiple cascades of metabolic regulation. Other potent satiety hormones include glucagon like peptide-1, cholecystokinin and pancreatic amylin.[5, 13]

II. Genetics of obesity[15-17]

Genetic factors are presumed to explain 40-70% of the variance in obesity, within a limited range of BMI (18-30 kg/m^2). Mutations of the leptin receptor in the hypothalamus may occur. These mutations result in early onset obesity and hyperphagia despite normal or elevated leptin levels, along with hypogonadotropic hypogonadism, and defective thyrotropin secretion. Several Genome-wide association studies have found novel genes that may underlie obesity risk, such as insulin induced gene 2, fat mass and obesity associated gene, the melanocortin receptor genes, catenin beta like 1 gene, and phosphofructokinase platelet gene. Recently, single-nucleotide polymorphism plays an important role (it is a DNA sequence variation occurring when a single nucleotide A, T, C or G in the genome (or other shared sequence) differs between members of a biological species or paired chromosomes).

III. Environmental factors[11]

Many factors have been suggested as major causes of the obesity such as:

- Sedentary lifestyles and short sleep duration.
- Skipping breakfast.
- Breastfeeding has been reported as being a potentially protective factor against weight gain in childhood.
- High intake of energy-dense, micronutrient-poor foods.
- The heavy marketing of fast-food outlets and energy-dense, micronutrient-poor foods and beverages.
- A high intake of sugars-sweetened beverages and watching television.
- Adverse socioeconomic and cultural factors, especially for women in high-income countries.
- Food eaten outside the home.

IV. Psychological factors of obesity[12, 18]

Night eating syndrome, defined as ingestion of >25% of daily calories after dinner and nocturnal awakenings with ingestion, is more frequent among obese subjects. Indeed, such a disorder occurs at an incidence of 1.5% in the general public but at 9% in the obese and >25% in the morbidly obese populations.[12]

According to recent prevalence estimates, 33.7% of bariatric surgery candidates have a current Axis I disorder, and lifetime rates are even higher (67.8%). The most common current diagnoses are anxiety disorders (18.1%), affective disorders (11.6%), and binge eating disorder (compulsive overeating 10.1%). In addition to those meeting diagnostic criteria for an eating disorder, a much higher percentage endorse maladaptive eating behaviors such as emotional overeating, grazing, and loss of control over eating . Depressive symptoms account for significant variance in binge eating severity among bariatric surgery. Moreover, binge eating, grazing, uncontrolled eating and postoperative loss of control have been shown to predict poorer weight loss and greater weight regain following bariatric surgery.[18]

Pathophysiology of obesity[5, 19, 20]

White adipose tissue (WAT) is a dynamic and modifiable tissue that develops late during gestation in humans. It can account for as little as 3% of total body weight in elite athletes or as much as 70% in the morbidly obese. With the development of obesity, WAT undergoes a process of tissue remodeling in which adipocytes increase in both number (hyperplasia) and size (hypertrophy). Accordingly, hypertrophic adipocytes become overburdened with lipids, resulting in changes in the secreted hormonal milieu. Lipids that cannot be stored in the engorged adipocytes become ectopically deposited in organs such as the liver, muscle, and pancreas.[5]

Hypertrophic obesity, usually starting in adulthood, is associated with increased cardiovascular risk and responds quickly to weight reduction measures. In contrast, patients with hypercellular obesity may find it difficult to lose weight through nonsurgical interventions and occurs in persons who develop obesity in childhood or adolescence, but it is also invariably found in subjects with severe obesity.[5, 19]

Adipocytes are far more than storage vessels for lipids. They secrete a large number of physiologically active substances called ***adipokines*** that lead to inflammation, vascular and cardiac remodeling, airway inflammation, and altered microvascular flow patterns. They contribute to linked abnormalities, such as insulin resistance and the metabolic syndrome, and they attract and activate inflammatory cells such as macrophages. These changes can lead to organ dysfunction, especially cardiovascular and pulmonary tissues. These mediators include ***inflammation-related adipokines*** such as leptin, adiponectin, tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), ***procoagulant substances*** such as plasminogen activator inhibitor factor-1(PAI-1), ***vasoactive substances*** such as leptin, angiotensinogen and endothelin and molecules that may contribute to ***insulin resistance*** such as free fatty acids (FFA), TNF-α and resistin. These cytokines are released into the circulation, stimulating hepatic C-reactive protein (CRP) production.[5, 19, 20]

Leptin is one of the key vasoactive substances produced by adipocytes, which signal satiety to the hypothalamus and thus reduce dietary intake and fat storage while modulating energy expenditure and carbohydrate metabolism, preventing further weight gain. Most humans who are obese are leptin resistant. Other adipocyte-derived molecules, including prostaglandins, adiponectin, and the more recently discovered resistin, affect metabolic function and might play a role in causing cardiovascular end-organ damage. Visceral fat appears to produce several adipokines more actively than subcutaneous adipose tissue, and an increased visceral adiposity renders these individuals more prone to metabolic and cardiovascular problems.[5, 20]

Recent evidence indicates that overweight and obesity may result from alterations in ***gut microflora*** that is suggested to result in the increased efficiency of caloric extraction from food, enhanced lipogenesis, and impaired central and peripheral regulation of energy balance. Other studies revealed an excessive weight gain in a significant percentage of people infected with certain species of human adenoviruses that cause dysregulation of adipocyte function. High-fat diet is thought to trigger the inflammatory response in the hypothalamus, an event that promotes weight gain and further defends elevated body weight through the initiation of central leptin and insulin resistance and impairment of regenerative capacity of hypothalamic neurons.[21]

Complications of obesity

Obesity shortens the life span of those who suffer with it. The mortality rate is known to be doubled when BMI ≥ 40 kg/m^2. It is estimated that a man in his 20s, with a BMI ≥ 45 kg/m^2 has a 22% reduction in life expectancy, a decrease of 13 years.[22]

Obesity increases the risk of morbidity from hypertension, dyslipidemia, type II diabetes, coronary artery disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, as well as cancers of the endometrium, breast, prostate, and colon. Higher body weights are also associated with an increased mortality from all causes. Obese individuals may also suffer from social stigmatization and discrimination.[5, 23]

Cardiovascular system complications

Obesity is a major risk factor for cardiovascular disease. The extent and severity of these effects in obese patient is highly variable, but important factors include both BMI and duration of obesity. This is mediated in part through traditional risk factors, such as hypertension, dyslipidemia and insulin resistance/glucose intolerance. Recently, the low-grade inflammatory state associated with morbid obesity has been implicated in the development of vascular and coronary artery disease and the hypercoagulable state seen in these patients.[24-26] Common features, include an increased blood volume compared with non obese subjects, together with a raised cardiac output. Morbid obese patients typically exhibit splanchnic blood flow 20% greater than that of lean individuals. [24-26]

Hypertension[27]

It is estimated that at least 75% of the incidence of hypertension is related directly to obesity. Between 5 and 10% of subjects suffer severe hypertension, and up to 50% have moderate hypertension. Pathogenesis of obesity-related hypertension may be due to:

- Central obesity which increases insulin resistance and leptin levels.
- Increased sympathetic nervous system (SNS) activity by insulin and leptin.
- Increased renin-angiotensin-aldosterone system activity due to:
  - SNS stimulation of renin release.
  - Increased angiotensinogen from intra-abdominal adipocytes
  - Increased aldosterone production (in excess of angiotensin stimulation)
- Salt sensitivity (increased renal sodium reabsorption) by SNS, insulin, angiotensin, aldosterone and intra-renal blood flow redistribution.

Arrhythmias[28]

Obesity is a risk factor for atrial fibrillation because of increased atrial dilatation. Myocardial fat accumulation is associated with conduction defects as lipid can accumulate in the SA node, AV node, and right bundle branch. [28]

Atherothrombotic risk[29]

Adipocytes secrete numerous hormones and adipokines which influence gene expression and cell functions in endothelial cells, arterial smooth muscle cells, and monocytes/macrophages favoring development of an atherosclerotic vulnerable plaque. Moreover, the release of such molecules also promotes endothelial dysfunction, disturbs haemostasis and fibrinolysis, and produces platelet dysfunction affecting initiation, progression and stabilization of thrombus formation upon atherosclerotic plaque rupture. A link between obesity and coronary artery disease development has been repeatedly proposed, possibly due to a proinflammatory-prothrombotic state and dyslipidemia. Central obesity independently predisposes not only to atherothrombosis but also to venous thrombosis due to added effect of increased intraabdominal pressure and that limits venous return and decreases blood velocity through femoral veins.[29]

Myocardium[30-33]

Obesity (abdominal obesity in particular), is an independent risk factor for the development of heart failure (HF). Higher cardiac oxidative stress is the early stage of heart dysfunction due to obesity, and it is the result of insulin resistance, altered fatty acid and glucose metabolism, and impaired mitochondrial biogenesis. Myocyte hypertrophy and myocardial fibrosis are early microscopic changes in patients with HF, whereas circumferential strain during systole and left ventricular hypertrophy (LVH) and dilatation are the early macroscopic and functional alterations in obese developing HF. LVH leads to diastolic dysfunction and subendocardial ischemia in obesity and pericardial fat has been shown to be significantly associated with LV diastolic dysfunction. Evolving abnormalities of diastolic dysfunction may include progressive hypertrophy and systolic dysfunction, and various degrees of eccentric and/or concentric LVH may be present with time. [(30)]

Obesity paradox states that overweight and obese have a better prognosis than do their lean counterparts with the same level of cardiovascular disease. It is mainly due to lower muscle protein degradation, brain natriuretic peptide circulating levels and cardio-respiratory fitness than normal weight patients with HF. However, dilated cardiomyopathy may in part, be responsible for the increased incidence of unexplained sudden death in persons with severe obesity.[(31)]

Neurohormonal and metabolic abnormalities as well as cardiovascular co-morbidities may facilitate this process. Many obese patients develop right heart complications as a consequence of obstructive sleep apnea and the obesity hypoventilation syndrome. Weight loss is capable of reversing most of the alterations in cardiac performance and morphology and may improve functional capacity and quality of life in patients with obesity cardiomyopathy.[(32, 33)]

Respiratory complications [(34-41)]

Excess weight on the anterior chest wall due to obesity lowers chest wall compliance and respiratory muscle endurance with increase in work of breathing and airway resistance. Furthermore, obesity hinders diaphragmatic movement, diminishes basal lung expansion during inspiration, and with the closure of peripheral lung units, causes ventilation–perfusion abnormalities and arterial hypoxemia. An increased metabolic need is another cause of hypoxemia added to decreased lung volumes.[(34, 35)].

Weight gain is associated with decreases in lung volumes reflected by restrictive pattern on spirometry. Rise in BMI lowers forced expiratory volume-1 second (FEV1), forced vital capacity (FVC), functional residual capacity (FRC), and the expiratory reserve volume (ERV). In morbid obesity, there is also a modest decrease in residual volume (RV), total lung capacity (TLC) and FRC approaches RV.[(36)]

Obesity and obesity-related reductions in lung volumes play a large part in increasing the passive mechanical pressures, which contribute to upper airway obstruction. This increases fat deposition around the soft tissues of the neck and tongue, contributing to an increase in extra-luminal pressures in the pharynx that elevates critical closing pressure (Pcrit), thereby increasing the chances of repeated airway collapse. Airway obstruction causes cessation of air flow (apnea) or shallow breaths (hypopnea). This leads to hypoxia and hypercarbia that stimulates repeated arousals from sleep to reestablish breathing. The disturbed sleep produces daytime somnolence. Sleep apnea, with chronic hypoxia and hypercarbia can stimulate pulmonary vasoconstriction, pulmonary hypertension, and arrhythmia or HF.[(31, 37)]

Leptin-deficient obese mice were observed to have a reduced ventilatory drive in response to hypercapnia, which subsequently improved on administration leptin proposing its role in maintaining adequate minute ventilation in obese subjects.[38, 39, 41]

The deleterious pulmonary effects of morbid obesity are reversible with weight loss and patients can show significant improvement even with small amounts of weight loss and complete resolution is seen in many by the end of one year.[40]

Risk of cancer [5, 42, 43]

Obesity is associated with increased risk of developing leukaemia and cancer of breast, gallbladder, ovaries, pancreas, prostate, colon, oesophagus, endometrium, renal cells as well as non-Hodgkin's lymphoma and myeloma. Insulin resistance is a major mechanism, but there are several other factors including insulin-like growth factors, sex steroids, adipokines, obesity-related inflammatory markers, the nuclear factor kappa beta (NF-κ B) system and oxidative stress represented by increased TNF-alpha and IL-6 in fat rich adipocytes. While public health strategies to curb the spread of the obesity epidemic appear ineffective, there is a need to better understand the processes linking obesity and cancer as a pre-requisite to the development of new approaches to the prevention and treatment of obesity-related cancers.[5, 42, 43]

Gastrointestinal complications [5, 44-47]

There are numerous gastrointestinal changes associated with obesity. Many of these have pathological significance, and some are of immediate relevance in perioperative period. There are specific intra- abdominal changes, particularly in those with android fat distribution. This result in increased intra-abdominal pressure, which of significance both in terms of cardio-respiratory effects and in term of end organ effects. These include reduced tissue perfusion and potential for abdominal compartmental syndrome following major surgery.

There is involvement of liver in large number of morbidly obese patients coming to surgery. The prevalence of fatty liver is up to 90%. In addition to steatosis, some patients develop inflammatory changes and progress to clinically significant cirrhosis.

Obesity has been proven to be a significant independent risk factor for development of gastro esophageal reflux disease (GERD) and/or hiatal hernia (HH). About 50–70% of patients undergoing bariatric surgery for morbid obesity have a symptomatic reflux, while symptomatic HH is present in 15% of patients with BMI >35 kg/m2. So, bariatric procedures have been proposed by several authors for the synchronous treatment of morbid obesity and GERD with or without HH, providing good results in terms of excess weight loss and reflux symptoms improvement.[47]

Genitourinary complications[48-51]

Obesity has been recognized as an independent risk factor for developing chronic or end-stage renal disease. Several risk factors for chronic kidney disease (hypertension, dyslipidemia, and diabetes mellitus) also are common in obesity. In addition, obesity amplifies the impact of hypertension on albuminuria. Hyperfiltration is the hallmark of obesity-associated kidney dysfunction because it increases physical stress on the glomerular wall and results in proteinuria, even before major structural damage occurs. Structural damage includes enlarged glomeruli, mesangial hypercellularity, podocyte hypertrophy, and/or focal segmental glomerulosclerosis. How obesity affects the kidney is not completely understood. Potential mechanisms include inflammatory cytokines, renal lipotoxicity, and hemodynamic factors.[50, 51]

More recently, there has been greater interest in the effects of obesity and metabolic syndrome on a variety of benign and malignant urologic conditions. Obesity/metabolic syndrome has been shown to have an effect on urolithiasis, benign prostatic hyperplasia, lower urinary tract symptoms, female incontinence and pelvic prolapse, male hypogonadism, and male sexual dysfunction and infertility. These diseases have a considerable impact on patients' quality of life.[51]

Obesity/metabolic syndrome have been demonstrated to play a role in prostate cancer and in renal cell cancer; its role in bladder cancer remains ill defined. Furthermore, dietary or lifestyle modifications may improve outcomes in many of these urologic disease processes. Inflammatory abnormalities and oxidative stress are characteristic findings of obesity and play important roles in the renal damage associated with obesity. Thus, it is imperative for physicians to understand these relationships in order to better screen obese patients and be aware of the potential impact of weight loss on affected benign and malignant urologic conditions.[48, 49]

Obesity and osteoarthritis (OA) [52, 53]

Obesity is a major risk factor for OA. Traditionally, it has been thought to contribute to the development of OA by increasing the load on weight-bearing joints. However, this appears to be an over-simplification, because obesity is also linked to OA in the hand and finger joints. Recent studies have shown that leptin is a possible link between obesity and OA. Leptin levels in synovial fluid are increased in obese patients, leptin receptor (Ob-R) is expressed in cartilage, and leptin induces the production of matrix metalloproteinases, pro-inflammatory mediators and nitric oxide in chondrocytes. Furthermore, according to the very recent findings, not only leptin levels in the joint but also leptin sensitivity in the cartilage is enhanced in obese OA patients. The findings supporting leptin as a causative link between obesity and OA offer leptin as a potential target to the development of disease-modifying drugs for osteoarthritis, especially for obese patients.[52, 53]

Management of obesity

Weight management programmes should include physical activity, dietary change and behavioural components.

I. **Dietary interventions:**[5, 54] A variety of dietary approaches can produce weight loss in obese adults if reduction in dietary energy intake is achieved. Diet is modified to achieve reduced calorie intake as part of a comprehensive lifestyle intervention by one of the following prescriptions:
   a) 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men (kcal levels are usually adjusted for the individual's body weight);
   b) 500 kcal/day or 750 kcal/day energy deficit; or

c) Prescribe one of the evidence-based diets that restricts certain food types (such as high-carbohydrate foods, low-fiber foods, or high-fat foods) in order to create an energy deficit by reduced food intake.

II. Physical activity:[55] Overweight and obese individuals should be prescribed a volume of physical activity equal to approximately 1,800-2,500 kcal/week. This corresponds to approximately 225-300 min/week of moderate intensity physical activity (it may be achieved through five sessions of 45-60 minutes per week, or lesser amounts of vigorous physical activity).

III. Cognitive behavioral therapy(CBT):[18] is a skills-based psychosocial intervention shown to improve binge eating and promote short-term weight loss in obese individuals; however, weight loss is modest (typically less than 10% of body weight) and it is not typically sustained during the follow-up period. Several key components of an effective behavior modification program should include self monitoring, goal setting, stimulus control, reinforcement, social support and cognitive change.[18]

Despite psychological factors contributing to obesity, psychosocial interventions are not routinely offered in bariatric surgery programs. Approximately 20% to 50% of patients begin to regain their weight within the first 1.5 to 2 years following bariatric surgery. Untreated psychological factors might be one of the contributing factors to weight regain. In order to improve psychosocial functioning and maintain weight loss, individuals need to learn coping skills such as scheduling healthy meals and snacks at regular time intervals, planning pleasurable alternative activities to overeating, planning for difficult eating situations, and reducing vulnerability to emotional overeating by solving problems and challenging negative, counterproductive thoughts.[12,18]

IV. Pharmacological treatment in adults

- ***Orlistat;*** [14, 56] is a potent inhibitor of pancreatic lipase, reducing the absorption of dietary fats. Patients with BMI ≥28 kg/m2 (with comorbidities) or BMI ≥30 kg/m^2 should be considered on an individual case basis following assessment of risk and benefit. Most common adverse effects are steatorrhea, oily spotting, fecal incontinence and urgency, increased frequency of bowel movements, fat soluble vitamins deficiency, headache, back pain, flu like symptoms, gallbladder disease, nausea, abdominal pain or discomfort and anxiety . Despite its approved status, orlistat may cause hepatotoxicity, nephrotoxicity, pancreatitis and kidney stones.

- **Appetite suppressants**[14, 56]

a) **Phentermine**, FDA-approved for obesity management for not >12 weeks. It stimulates anorexic signaling in hypothalamus or dopamine receptor in the hippocampus. Side effects include dizziness, dry mouth, sleeping difficulty, irritability, nausea, vomiting, diarrhea, constipation and withdrawal symptoms.

b) **Topiramate**, Enhances GABA signaling to promote anorexigenic signaling, inhibiting voltage-gated channels and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor in the orexigenic neurons. Side effects include fatigue, drowsiness, dizziness, loss of coordination, tingling of the hands/feet, bad taste, and diarrhea. Mental problems such as confusion, slowed thinking, trouble concentrating or paying attention, nervousness, memory problems, or speech/language problems may also occur. Rare side effects include kidney stones, depression, suicidal thoughts, and vision loss.

c) **Sibutramine**: is a noradrenaline and serotonin reuptake inhibitor which causes weight loss via effects on both food intake and metabolic rate. It stimulates thermogenesis via central activation of efferent sympathetic activity. Sibutramine was withdrawn in 2010 due to increased cardiovascular events.

- **Other drugs:**[14] **Aminorex** caused chronic pulmonary hypertension with 50% mortality. **Ephedrine** caused heart attacks, hypertension, palpitations, strokes, and sudden death. **Phenylpropanolamine** caused intracranial bleeding and strokes. **Rimonabant**, caused increased depression and suicide. These unsafe drugs have been withdrawn, although their unregulated use may continue to some extent.

- **Herbal products and plant extracts**[57]

Understanding the key factors affecting pharmacological effects and clinical outcomes has been a critical theme of natural product research. However, well-controlled scientific and validation studies are needed before herbal therapeutics can be introduced into the global market.

- **Off Label medications for Obesity Prevention or Treatment**[14, 56, 58]

Medications that are FDA approved for other conditions and found to result in weight loss have been tested as potential obesity treatments. Some, such as **fluoxetine**, were found to promote weight loss for not longer than 6 months. **Bupropion**, a norepinephrine and dopamine reuptake inhibitor, was tested as monotherapy for as long as one year as a weight loss medication. **Metformin**, increasingly used off label in patients with prediabetes and other insulin-resistant states, produces small sustained weight losses. **Zonisamide**, an antiepileptic medication, also induces weight loss however, adverse effects were limiting.

As of September 2013, only three drugs are approved by the FDA as adjunctive therapy for *chronic weight management*: orlistat, approved in 1999; lorcaserin, approved in 2012; and Phentermine/topiramate extended-release formulation, also approved in 2012. However, European Medicines Agency (EMA) has rejected both lorcaserin and Phentermine/topiramate. The EMA rejected lorcaserin due to its opinion that the drug's benefits did not outweigh its risks, particularly the potential risk for tumors, and rejected Phentermine/topiramate due to concerns over the potential cardiovascular and central nervous system effects associated with its long-term use, its teratogenic potential, and its use by patients for whom it is not indicated.[14]

- **Future studies:**[14, 56, 58] A host of new drugs are in the pipeline, designed to minimize risk and maximize efficacy targeting endogenous endocrine circuits regulating energy homeostasis and metabolism; and combination therapy with monotherapeutic agents to elicit improved safety and efficacy, with potential synergy. Discoveries in the molecular mechanisms regulating adipose metabolism and satiety signaling have opened the door for targeting guanosine 3,5-cyclic monophosphate (cGMP) signaling as a future antiobesity strategy.

a) Incretins[56, 58] increase insulin release from pancreatic b-cells and suppress glucagon release from pancreatic a-cells. Glucagon-like peptide-1(GLP-1) is a major endogenous incretin, but it is not useful therapeutically as it is rapidly metabolized by dipeptidyl peptidase-4(DPP-4). Exenatide along with its extended-release form Bydureon liraglutide are injectable GLP-1 agonists that mimic endogenous GLP-1 but have a longer duration of action, making them suitable therapies for type 2 diabetes. GLP-1 agonists enhance glucose dependent insulin secretion, suppress inappropriate glucagon secretion (leading to decreased insulin demand and hepatic glucose output), slow gastric emptying, improve glycemic control, decrease food intake and enhance satiety. DPP-4 inhibitors prolong the half-life of endogenous GLP-1 and approved for use in the United States such as: sitagliptin, saxagliptin, and linagliptin.

b) Pramlintide[56, 58] is a synthetic injectable congener that mimics the actions of amylin. Amylin is a B-cell polypeptide co-stored and co-released with insulin in response to meals. In diabetic patients, amylin, as well as insulin secretion, is deficient. Pramlintide promotes weight loss by slowing gastric emptying, increasing satiety, decreasing postprandial glucagon secretion and centrally decreasing appetite and total caloric intake.

c) Cetilistat,[56, 58] a lipase inhibitor is claimed to have superior safety profile to orlistat and is in phase 3 clinical trials.

d) Combination Therapies:[56, 58] Low-dose, controlled-release phentermine plus topiramate have recently been approved for the treatment of obesity. A sustained-release combination of naltrexone and bupropion is currently under investigation. Naltrexone is an opioid antagonist used for the treatment of opioid addiction and alcohol dependence. Bupropion is a norepinephrine and dopamine reuptake inhibitor used as an antidepressant and assists in smoking cessation.

V. Surgical intervention [51, 59, 60]

Obesity surgery is indicated via a group decision, made after multidisciplinary discussion and consensus, in adult patients presenting all of the following conditions:

1. BMI ≥40 kg/m2 or a BMI ≥35 kg/m2 combined with at least one co-morbidity that is likely to improve following surgery (in particular CVD including hypertension, OSA and other severe breathing disorders, severe metabolic disorders, in particular type 2 diabetes, incapacitating joint disorders, non-alcoholic steatohepatitis).

2. Failed non operative means properly conducted for 6-12 months to lose weight (medical, nutritional, dietetic and psychotherapeutic treatment).

3. Well-informed patients, having undergone multidisciplinary preoperative assessment and management.

4. Patients have accepted the need for lifelong medical and surgical follow-up.

5. Acceptable operating risk.

Bariatric surgery procedures currently used[61]

1. Restrictive:

- **Adjustable gastric banding(AGB)**;[62] figure (1-A): an inflatable silicone device placed around the top portion of the stomach to create a small pouch that holds 8-10% of the stomach capacity. The pouch fills with food quickly, and the band slows the passage of food from the pouch to the lower part of the stomach leading to early satiety and less frequent hunger.
- **Sleeve gastrectomy (SG);** figure (1-B):[63] most of the stomach is removed, leaving a sleeve-shaped cylinder with reduced capacity.

2. Malabsorptive:[51, 64]

- **Biliopancreatic diversion**; figure (2A): a portion of the stomach is removed. The remaining portion is connected to the lower portion of the small intestine.
- **Biliopancreatic diversion with duodenal switch**; figure (2B): the remaining stomach remains attached to the duodenum which is connected to the lower part of the small intestine.

3. Both restrictive and malabsorptive:

- **Roux-en-Y gastric bypass (RYGB)**;[65] figure (3A): It involves stapling of the lower part of the stomach and connecting the upper part to the small intestine. This skips the absorption of the nutrients and other food items that are supposedly brought to the lower part of the stomach as a result, capacity for food and drink is reduced to as little as 15 to 30 ml.
- **Mini-gastric bypass**; figure (3B):[66] creates a small gastric pouch (restrictive) joined to the jejunum, bypassing the duodenum and proximal jejunum (malabsorptive).

4. Endoscopic approaches:[67]

Primarily include **restrictive** (e.g. intragastric balloons, gastric stapling) or **malabsorptive** (e.g., duodenal-jejunal sleeve) devices and procedures. These less invasive approaches allow for outpatient or short-stay procedures and allow for treatment of individuals with comorbidities, older age, and super or mild obesity that are often excluded from surgical procedures. Efficacy observed with endoscopic methods typically lies between that observed for conservative and surgical approaches, with an improved safety profile over surgery.

- **Intragastric balloon**:[68, 69] is an endoscopic procedure, placing a silicone balloon filled with air and fluid in the stomach. It is not purely restrictive as it has a positive effect on glucose homeostasis and molecules regulating lipid and energy metabolism. Intragastric balloon has been shown to be a safe and effective procedure for **temporary** weight reduction in the preoperative treatment of morbidly obese patients who are scheduled to undergo bariatric or other elective surgery by minimizing mortality and morbidity risks.
- **Gastric stimulation**:[70] uses an implanted pacemaker-type device to produce electrical gastric stimulation.

figure (1-A): adjustable gastric banding

figure (1-B): sleeve gastrectomy

figure (2A): Biliopancreatic diversion

figure (2B): Bilio-pancreatic diversion with duodenal switch

figure (3A): Roux-en-Y divided gastric bypass

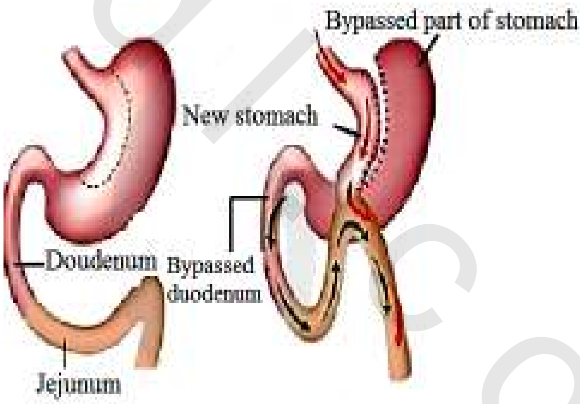

figure (3B): Minigastric bypass

Benefits of bariatric surgery [62, 71-77]

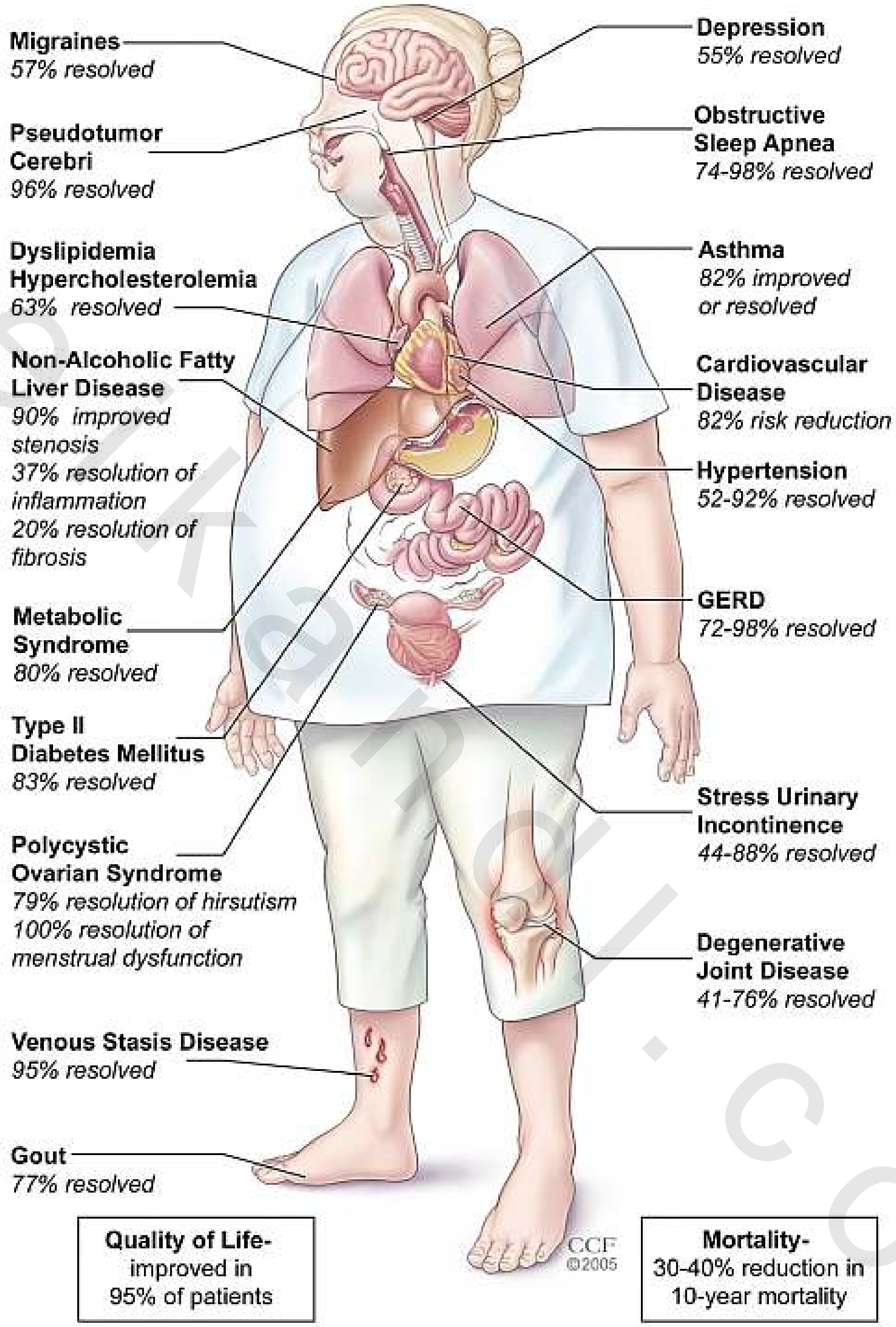

Figure (4): Resolution of obesity-related comorbidities after bariatric surgery. [62, 71-77]

Anaesthetic management of obese patients

Preoperative evaluation [78-80]

Patients should be assessed by a multidisciplinary team, which may include endocrinologists, dieticians, psychologists, specialist nurses, and experienced surgeons and anaesthetists. It is crucial in identifying and stratifying risk to ascertain the level of perioperative care required, and also each individual's suitability for surgery. In addition to a detailed history and examination, Patients should be evaluated for indicators of systemic or pulmonary hypertension, ischaemic heart disease, and heart failure. ECG may demonstrate signs of right ventricular hypertrophy. Further cardiac evaluation may include stress echocardiography and cardiopulmonary exercise testing.

Obesity with large neck circumference and a Mallampati score >3 are predictors of a potentially difficult intubation, whereas BMI or weight per se did not predict difficult intubation. The probability of a problematic intubation was ~5% with a 40 cm neck circumference and 35% with a 60 cm neck circumference. Approximately 5% of morbidly obese patients will have OSA. In patients who give a history of such snoring, apnoeic periods during sleep and day-time somnolence should be considered for overnight *polysomnography*. This can define the type and severity of OSA and also whether continuous positive airway pressure (CPAP) or bi-level positive airway pressure is required before operation. The *STOP-BANG questionnaire*[78, 79] can help to spot unrecognized OSA and guide patients to diagnosis and treatment in order that they avoid long term complications of OSA as well as reducing the associated peri-operative risks. Score ≥ 3 indicates high risk of OSA especially when accompanied by serum $HCO3^-$ level ≥ 28 mmol/L

- S - (Snore) "Have you been told that you snore?".
- T - (Tired) "Are you often tired during the day?".
- O - (Observed) "Has anyone observed you stop breathing while sleeping?".
- P - (Pressure) Hypertension (treated or not?).
- B - (BMI) BMI >35 kg/m^2.
- A - (Age) Age >50 years.
- N - (Neck) Neck circumference >40 cm.
- G - (Gender) Male.

It has been recommended that prophylaxis against aspiration be considered in all patients 12 and 2 hours before surgery, even if they do not declare any symptoms of heartburn or reflux. Examining the potential site for venous access is quite important as it may be problematic. Examination of the spine for regional block should be complemented. An anxiolytic can be given, but heavy sedation or opioid premedication should be used with caution and perhaps avoided.[79]

Pharmacokinetics (PK) and pharmacodynamics (PD) of obesity[81-86]

The main factors that affect the tissue distribution of drugs are body composition, regional blood flow and affinity of the drug for plasma proteins and/or tissue components. Changes in any of these factors may alter the volume of distribution. Therefore, a drug dosing based on a total body weight (TBW) may result in overdose in an obese individual.

- **Induction agents**:[81, 82, 84]

Thiopental dose is based on lean body weight (LBW) as it is highly lipophilic with a large volume of distribution in obese patients and a longer elimination half life. However, increased cardiac output can result in a more rapid redistribution of thiopental from the effect site into the plasma, resulting in more rapid awakening after a single bolus dose. However; in a continuous infusion dose should be adjusted to IBW, because the total clearance is not substantially changed compared with lean subjects.

Propofol is highly lipophilic, and distributes rapidly from the plasma into peripheral tissues. Redistribution into the plasma, and subsequently into peripheral tissues, accounts for its short duration of action after a single bolus dose. Like thiopental, cardiac output is a significant determinant of peak plasma concentration. The volume of distribution and clearance correlates with TBW. Elimination half-life is similar in obese and lean patients without signs of accumulation. For induction of anaesthesia, LBW is a more appropriate dosing scalar to avoid negative cardiovascular effects of large doses. Obese subjects who were administered a rapid propofol infusion based on LBW for induction of anaesthesia required similar doses and had similar times to loss of consciousness as lean control subjects who were administered propofol based on TBW. In addition, induction dose requirement was related to cardiac output, which is correlated to LBW.

Etomidate pharmacokinetic properties have not been established in obese subjects. However, since etomidate has similar pharmacokinetic and physicochemical properties as propofol, its pharmacokinetic profile is likely to behave similarly.

- **Premedications**:[84]There have been no studies to date analyzing the effects of obesity on the PK/PD of dexmedetomidine. An infusion rate of (0.2 μg/kg/h LBW) has been recommended to avoid bradycardia and hypotension. Benzodiazepines doses are based on LBW as Thiopental**.**

- **Opioids; Fentanyl**[84] has numerous PK/PD models however none of these have been validated in obese individuals. When these models were scaled to TBW, they have been shown to overpredict fentanyl plasma concentrations. Fentanyl has a large volume of distribution due mainly to its high lipophilicity. Theoretically, obese subjects would have a larger volume of distribution due to their larger amount of adipose tissue, effectively lowering the plasma concentration after a single bolus dose. While obese subjects do have a lower plasma concentration during the early distribution phase, this is related to their higher cardiac output, rather than an increased volume of distribution. The clearance of fentanyl is significantly increased in obese subjects in nonlinear manner; however, fentanyl clearance increases linearly with “pharmacokinetic mass”, which is highly correlated to LBW. These data suggest that fentanyl administration for morbidly obese individuals be based on LBW.

Doses of **alfentanil** and **sufentanil**[84] should be calculated according to LBW. Although this restriction doesn't apply to other opioids, careful titration of all opioids is warranted because of their respiratory depressant effects. In patients with OSA, **remifentanil** decreases the number of obstructive apnoeas but markedly increases the number of central apneas. Arterial haemoglobin oxygen saturation was also significantly lower in OSA patients receiving remifentanil.

➢ **Inhalational agents [84, 85]**

Isoflurane is more lipophilic than **sevoflurane** and **desflurane**,[84] and therefore has fallen out of favour for use in obese patients. Yet, after administration of 0.6minimal alveolar concentration (MAC) of isoflurane for procedures lasting 2–4 h, obese and non-obese subjects had similar times to recovery.

Sevoflurane is less lipophilic and less soluble than isoflurane, which results in a slightly more rapid uptake and elimination in obese subjects when compared with isoflurane. However, the observed differences were only significant 30–60 s after discontinuation of the drugs.[85]

Desflurane has been advocated for use in obese patients because it is the least lipophilic and least-soluble volatile anaesthetic available, and theoretically has limited distribution to adipose tissue. However, the effect of BMI on desflurane uptake is not significant. Emergence and recovery is faster with desflurane than isoflurane in both obese and nonobese subjects. Some authors have demonstrated that obese subjects have faster emergence from desflurane when compared with sevoflurane, while others have shown no difference in times-to awakening between the two drugs.[84, 85]

Muscle relaxants

Succinylcholine administration should be based on TBW as in morbidly obese subjects, **pseudo cholinesterase** and extracellular fluid amounts are increased as both of these factors determine the duration of action of **Succinylcholine**. When compared with administration based on 1mg/kg IBW or LBW, 1mg/kg TBW administration results in a more profound block and better tracheal intubating conditions, with clinically insignificant postoperative myalgia.[83, 84]

The kidneys excrete the majority of **pancuronium** and its metabolites. Respiratory acidosis enhances its action and this must be considered as many morbidly obese patients present with some hypercapnia. Obese subjects require significantly more **pancuronium** than lean subjects to maintain constant twitch depression and pancuronium dosing regimen based on IBW.[86]

With smaller doses of ***vecuronium***, recovery from drug effect is secondary to distribution rather than metabolism. Doses based on IBW are recommended to avoid drug overdose in the obese.[83]

Rocuronium is a weak lipophilic. Its quaternary ammonium group makes it highly ionized, limiting its distribution outside the extracellular fluid. Although obese subjects have increased extracellular fluid volume, it is not entirely understood how this affects rocuronium dosing. The duration of action of rocuronium was doubled when the drug was given based on TBW versus IBW. In contrast, another study demonstrated a similar time to recovery in both obese and non-obese subjects after a dose of 0.6 mg/kg based on TBW with no differences in the PK parameters between the groups. Despite these conflicting results, administration based on IBW is prudent to avoid prolonged recovery.[84]

Both **cisatracurium** and **atracurium** are eliminated by Hoffman degradation. The duration of cisatracurium and atracurium are prolonged in obese subjects when given on the basis of TBW versus IBW.[(84)]

Obesity is associated with a number of anaesthetic-related risks. **Regional anaesthesia** may offer potential advantages for the obese surgical patient. Advantages include a reduction in systemic opioid requirements and their associated side effects, and possible avoidance of general anaesthesia in select circumstances, with a lower rate of complications especially that are related to airway. However, performing regional anaesthesia procedures in the obese has presented challenges due to difficulty in identifying surface landmarks and availability of appropriate equipment. Fatty infiltration, as well as increased blood volume of epidural space caused by increased intra-abdominal pressure, may reduce the volume of epidural space resulting in unpredictable spread of *local anaesthetic* solution and block height.[(87, 88)]

It is obvious that obesity was associated with higher block failure and complication rates in surgical regional anesthesia in the ambulatory setting. Often, patients with obesity have more fat in their lower limbs, thus lower limb blocks may be technically more challenging with landmark techniques, and one may have to resort to neuraxial blockade in such cases. Portable ultrasound has shown to improve accuracy of interscalene block similar to that seen in nonobese patients. Preferably newer ultrasound machines should be capable of visualizing deeper tissue than that used conventionally (i.e., lower frequency probe may be needed) or by using 3D ultrasound reconstruction technology if available. Further research is needed to determine optimal regional anaesthesia techniques, local anaesthetic dosage and perioperative outcomes in obese patients.[(87, 88)]

To overcome the limitations of James' empirical LBW equations, a semi-mechanistic model for LBW, based on bioimpedance, was developed in 2005. Male LBW (kg) = 9270×WT (kg) /(6680 + (216×BMI (kg/m^2)) while, Female LBW (kg) = 8780 × WT (kg) /(6680 + (244 × BMI (kg/m^2)).[(89)]

Intraoperative considerations and maintenance of anaesthesia[(88, 90, 91)]

Appropriate operating tables that are electrically powered should be used. The patient may position themselves comfortably on the operating table before induction. This avoids unnecessary manual handling of large patients by staff and may reduce the risk of nerve injury. Laparoscopic bariatric surgery is generally carried out in a ***modified Lloyd Davis*** position[(91)] (steep reverse Trendelenburg position with legs spread apart and both arms out on arm boards), although positioning may vary according to surgical preference. To prevent slipping down, a foot-rest is placed at the foot of the table and the patient is strapped and secured on the table. Arm gutters and beanbags may also be used if available. Close attention should be paid to protecting pressure areas. Invasive arterial monitoring should be directed by the patient's co-morbidities and the accuracy and reliability of the non-invasive arterial pressure cuff. Central venous access may be limited to patients with poor peripheral access, significant co-morbidity, or repeat surgery.[(88)]

Induction of anaesthesia is likely to be particularly hazardous in patients with increased risk of difficult or failed intubation. Bag and mask ventilation may be difficult because of upper airway obstruction and reduced pulmonary compliance. Gastric insufflations during ineffective mask ventilation will further increase the risk of regurgitation and aspiration of stomach contents. If the patient is considered to be at risk of regurgitation or aspiration at induction, a rapid sequence induction using succinylcholine following a period of adequate preoxygenation should be considered. Awake fibreoptic intubation may be required in those at risk of difficult intubation. Patient positioning is vital to improve laryngeal visualization and facilitate tracheal intubation during laryngoscopy, by elevating head, neck, shoulders and upper body to align their sternum and ear in a horizontal line ***(Blanket ramp position)***[90]. However, difficult intubation equipments and a range of face masks, laryngoscope blades, bougie, and other adjuncts must always be available. In suspected difficult cases, two anaesthetists and an experienced assistant should be present. Orogastric tube is usually inserted to decompress the stomach. This will need to be manipulated during surgery to assist the surgeon to optimize the surgical conditions. This will also need to be withdrawn proximally before formation of the anastomosis. The choice of agent used to maintain anaesthesia depends on the patient's comorbidities and duration of surgery. Desflurane has been suggested because of its low blood:gas partition coefficient which results in a more rapid and consistent recovery profile.[91]

Laparoscopy in obese patient [1, 78, 92-95]

The widespread introduction of laparoscopic gastric bypass has led to extensive experience with laparoscopy in morbid obesity. Laparoscopic bariatric surgery is a less invasive procedure and causes less postoperative pain, thus interfering less with the respiratory mechanics and shows reduction in overall morbidity.[1]

Laparoscopy requires insufflation of a gas, usually carbon dioxide, to provide a pneumoperitoneum to visualize an access to intra-abdominal structures. Lung compliance is decreased due to increased pulmonary blood volume, and chest wall compliance is reduced due to weight of adipose tissue around the thoracic cage. Small airways collapse, cephalad displacement of abdominal contents and increased pulmonary blood volume contribute to a reduced functional residual capacity and a linear increase in alveolar – arterial (A-a) oxygen tension gradient with increasing BMI. Therefore, normal tidal volume ventilation is leading to airway closure, ventilation-perfusion mismatching and increased intrapulmonary shunt. All these changes may be accentuated during laparoscopic surgery and render the morbidly obese patient at risk of rapid desaturation, increased airway resistance, reduced functional residual capacity and increased incidence of atelectasis. Hypercarbia and hypoxemia may be caused by ventilation – perfusion mismatch due to restriction of diaphragmatic mobility from pneumoperitoneum, which leads to distribution of the ventilation volume to the non dependent part of the lung.[92, 93]

Absorption of carbon dioxide can worsen hypercarbia and acidosis, which can be offset by hyperventilation. Catastrophic complications that should be kept in mind include massive gas embolism, pneumothorax and mediastinal emphysema.[93]

Tidal volume of 10 - 12 mL/kg LBW to avoid barotrauma, respiratory frequency of 12 - 14/min to maintain normocapnia, and moderate PEEP of 5 cmH_2O with preservation of hemodynamic stability have been applied to all patients. Mild low level of intra-abdominal pressure (IAP) increases vascular resistance systemic, increases venous blood return and blood pressure while a high level of IAP causes decreased venous return and cardiac output.[94]

Increased IAP > 20 mmHg decreases renal blood flow and glomerular filtration rate. As regard intravenous fluids estimated for this procedure, high-volume (10 ml/kg/hr) fluid therapy versus low-volume (4ml/kg/hr) therapy were compared in laparoscopic bariatric surgery patients and there was no significant difference between these two groups in postoperative renal function. Both groups had intraoperative oliguria, which was unresponsive to fluid administration. Despite these problems, laparoscopy is usually well tolerated as long as IAP is maintained at less than 15mmHg.[78, 95]

Postoperative care after bariatric surgery[96, 98]

The modified Montefiore Obesity Surgery Score (MOSS)[96] states that if patients have four or more of the following seven criteria, they are classified as moderate to high risk and are managed on the HDU or ICU.

1. Gastric bypass surgery.
2. Male gender.
3. BMI >50 kg m^{-2}.
4. Age >50 yr old.
5. A confirmed diagnosis of OSA.
6. Significant medical or surgical co-morbidity.
7. Previous abdominal surgery.

In recovery, patients should be nursed 45^0 with continuous pulse oximetry and invasive arterial pressure (if in situ). Continuous ECG monitoring is only required in patients at risk of arrhythmias which is more likely to occur in patients with cardio-respiratory disease. Supplemental humidified oxygen should be administered at an appropriate fraction of inspired oxygen (FIO2). There is evidence that postoperative incentive spirometry or CPAP started in recovery may accelerate the return to preoperative pulmonary function. Adequate thrombo-embolic prophylaxis is essential and early mobilization should be encouraged. Several studies found adjusted dose unfractionated heparin and low molecular weight heparin effective in bariatric surgery patients. Antibiotic prophylaxis is important because of the increased risks of postoperative wound and chest infection.[96]

Postoperative pain is a real challenge. Management of postoperative pain relieves suffering and leads to earlier mobilization, shortened hospital stay, reduced hospital costs, and increased patient satisfaction. Optimal analgesia ensures adequate ventilation and pulmonary mechanics and reduces the risk of postoperative chest infections. Pain control regimens should not be standardized; rather, they are tailored to the needs of the individual patient, taking into account medical, psychological, and physical condition; age; level of fear or anxiety; surgical procedure; personal preference; and response to agents given.[97] The major goal in the management of postoperative pain is minimizing the dose of medications to lessen side effects while still providing adequate analgesia. This goal is best accomplished with multimodal and preemptive analgesia.[98]

Obesity and pain

According to International Association for the Study of Pain, stating that it is an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage. There is a general agreement, that pain bears physical, psychosocial & psychological distress, to the unfortunate victim.[99]

Pain is classified depending on which region of the body is involved, which system dysfunction is causing the pain, by which etiology is it precipitated, by which neurochemical modulation is it provoked, by which character pattern and intensity is it presenting and by which time since onset and length of duration does it prevail.[100]

Summing all these variables into a single classification seems impossible but simply pain can be arbitrary divided into two main types;[99]

Acute Pain: is of sudden onset, transitory, lasting less than 30 days but can turn to subacute if it lasts up to six months. It resolves quickly once the underlying cause is cured. It is of a clear cause, most often nociceptive (i.e. resulting from injury or inflammation of somatic or visceral tissue). It is considered as a protective response; accordingly, the therapeutic objective is focused to treat the underlying cause.

Chronic Pain: is of insidious onset, lasting usually more than six months, yet can last for years or forever. It can either start as acute pain and continues beyond the normal time expected for resolution, persists, recurs for various other reasons or can even arise in absence of any detectable cause. It may be nociceptive or neuropathic. It is considered as a maladaptive response to injury so, therapeutic objective emphasis upon reducing the pain intensity to give relief, limit disability and improve function.

Theories of pain:[101, 102]

Gate Control Theory postulates that nociceptive pain is gated by non-nociceptive stimuli. For instance, neural mechanisms in dorsal horn neurons (DHN) act like a gate opening and closing i.e. permitting or shutting down flow of impulses, thus altering level of firing projected via ascending tracts that are perceived. This is controlled by ramifications from small adjacent cells which tend to either excite or inhibit DHN. It accounts for the clinically recognized importance of brain and mind in pain perception. [102]

Neuromatrix Theory states that each individual has a genetically built-in network of neurons called the "body-self neuromatrix" that is unique to him and is affected by all facets of the person's physical, psychological, and cognitive makeup, as well as his experience. As a subsequence, pain perception will not reflect a simple one-to-one relationship between tissue damage and nociceptive firing but that individual’s set-up will also have a role.

Pain perception

Pain is a complex phenomenon. The unique way each individual perceives pain and its severity, how it evolves, and the effectiveness of treatment depend on a constellation of factors such as the following:[99]

1. **Biological:** the extent of an illness or injury and whether the person has other illnesses, is under stress, or has specific genes or predisposing factors that affect pain tolerance or thresholds.

2. **Psychological:** anxiety, fear, guilt, anger, depression, and thinking the pain represents something worse than it does and that the person is helpless to manage it.

3. **Social:** the response of significant others to the pain whether support, criticism, enabling behavior, or withdrawal the demands of the work environment, access to medical care, culture, and family attitudes and beliefs.

In order that a noxious stimulus transforms into a painful perception, a group of highly specialized structures are set into a sequential cascade of functional changes:[102-104]

a. **Recognition** of the stimulus by nociceptors when its intensity reaches certain threshold. They possess specific biophysical and molecular properties for differential coding of noxious submodalities depending on the differential expression of selective channels that confer sensitivity to heat as Transient receptor potential cation channel subfamily V member 1(TRPV1), cold (as TRPM8), acids as acid-sensing ion channels (ASICs), and chemicals (as TRPA1). Figure (5).

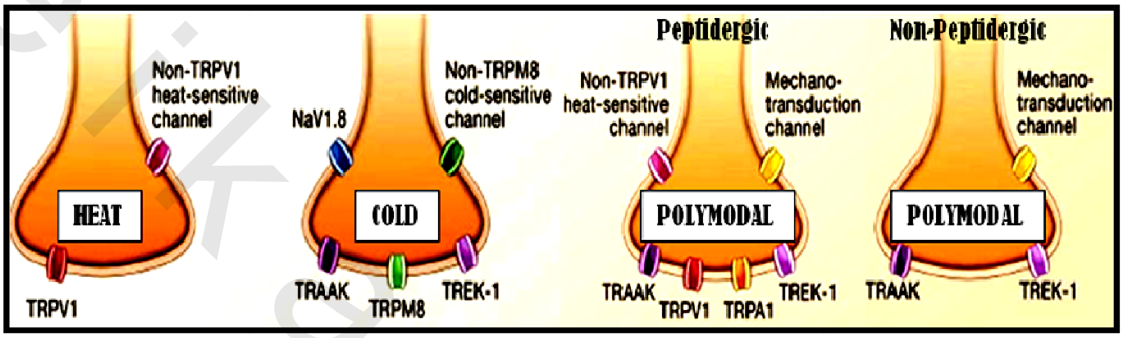

Figure (5): Transient receptor potential cation channel subfamily V member 1 (TRPV1), subfamily M member 8 (TRPM8) and subfamily A member 1 (TRPA1)

b. **Transduction** of stimulus via converting it into a depolarizing current that signal via specific ion channels only expressed within those specialized peripheral terminals. These seem to be activated by a variety of released molecules as; bradykinins, histamine, prostaglandins, leukotrienes, purines …etc.

c. **Conduction** refers to the passage of the action potential along the peripheral afferent terminals of nociceptors via voltage gated Na channels. These head towards their cell bodies located in dorsal root ganglia (for the body) and in trigeminal ganglion (for the face). From there, signals are further conducted along their central afferent terminal to project to different laminae of the dorsal horn of the spinal cord, where they relay, Figure (6). Fibers that carry such electrical activity are either;[99, 102]
   - **Myelinated (Aδ) afferents**: large diameter fibers that conduct at fast rate (5-20 m/s). They mediate well-localized acute, brief, sharp, pricking, fast pain sensations. They project to lamina I as well as to deeper dorsal horn (lamina V).
   - **Unmyelinated "C" fibers**: small diameter fibers that conduct at low rate (0.5–2.0 m/s). They convey poor localized, slow, 'dull' burning, aching, and longer lasting pain sensations. They project more superficially to laminae I (most peptidergic C fibers) and II (nonpeptidergic afferents).

d. **Transmission** is the process of synaptic transfer of signals from primary to secondary afferent projection neurons within the dorsal horn. It involves the release of neurotransmitters as glutamates (by Aδ fast fibers), substance P (by C slow fibers) and other tachykinins as neurokinin A and B …etc.

Signals further ***project*** from these dorsal horn neurons (DHN), as major outputs that constitute the ascending pain pathways, to finally relay supraspinal where their information is processed and perceived, figure(6). After these ascending pathways comprise:[102]

1. **Neospinothalamic tract;** arise from laminae I and V where Aδ carry "fast spontaneous pain" to somatosensory area in the cerebral cortex.
2. **Paleospinothalamic tract;** arise indirectly from laminae II and III (substancia geletinosa) that has inter-neuronal connections with lamina V from where C fibers carry "slow increasing dull pain" to thalamus and lower brainstem regions (medulla, pons, periaquidactal grey matter, midbrain tectum).

e. ***Perception*** is the process of integrating the relayed signals and translating them to actual sensory experience of conscious awareness. It occurs either within the somatosensory cortex or within the thalamus and lower brain stem areas.

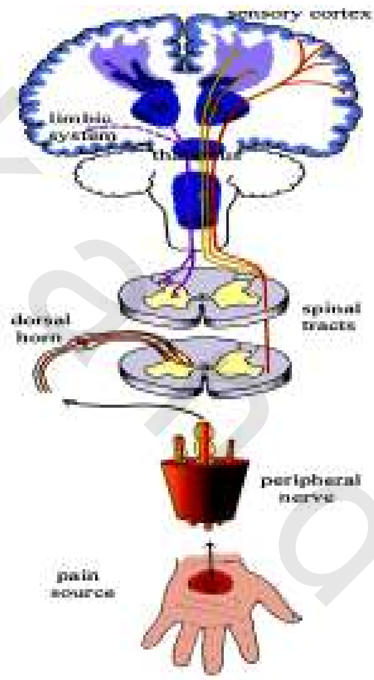

Figure (6): Pain pathway

Pain regulation and modulation[104, 105]

a. Facilitation and Sensitization; this can be achieved through increased firing of peripheral or central nociceptor terminals to modulate the ascending nociceptive pathways. It can be also achieved by suppressing inhibitory or activating excitatory interneurones or via activating DHN firing by descending facilitatory pathways.

- Peripheral sensitization;[106] is the increase in sensitivity of peripheral terminals of nociceptors caused either by inflammatory molecules released during tissue damage, or by persistence of noxious stimulation allowing C fibres to release neuropeptides creating neurogenic inflammation. This will activate "silent" neurons and sensitize nociceptors. The downstream signaling cascade of such triggers will increase concentration of both sodium and calcium ion channels within the plasma membrane of nociceptors and lowers their threshold for activation and increasing their rate of firing. This phenomenon is a pathophysiological mechanisms underlying inflammatory and neuropathic pain perception i.e. ***in hyperalgesia*** (painful stimuli are perceived more intensely) and ***in allodynia*** (normally non-painful stimuli are experienced as pain).

- Central sensitization (called windup);[102, 106] is the increased efficiency of transferring action potentials at the synapse between nociceptors and DHN or supraspinal neurons. It may be initiated by a brief but intense nociceptive signal or it may be caused by sensitized nociceptors that fire ectopically. In such a cascade nociceptors initiate the drive by increasing glutamate release that is coupled with a concomitant increase in N-methyl d-aspartate (NMDA) receptors density within post-synaptic membranes of DHN. Also there is downstream alteration in Na, Ca influx and K outflux allowing more depolarization with release of Mg block to later permit subthreshold inputs from nociceptors to continue exciting DHN. The increased glutamates may also reduce opioid responsiveness (e.g. analgesic tolerance and/or opioid hyperalgesia).
- Descending facilitatory pathways; arise mainly from rostral ventromedial medulla in response to nociceptive firing projecting to it from damaged nerves directly or indirectly. This leads to the release of many substances as glutamates, SP, purines, tachykinins that lead to activation microglial cells there. The latter respond by IL-18 release to activate astrocytes to produce more cytokines that in turn activate a subset of descending 5-hydroxy tryptamine (5HT) neurons that project as descending facilitatory fibres back to the spinal cord or trigeminal nucleus where they activate 5-HT3 receptors and thereby enhance pain transmission. This descending facilitatory activation is incriminated in the pathophysiology of neuropathic pain perception.

b. Inhibitory Modulation; that decreases firing along ascending pathways via:

Inhibition of transmitter release by peripheral or central terminal of nociceptors, excitation of inhibitory interneurons, inhibition of excitatory interneurons or Inhibition of projection neurons firing by descending inhibitory pathways.

- Descending inhibitory pathways; arise mainly from periaqueductal grey matter to project downstream to nucleus raphe magnus (release 5HT) or locus ceruleus and nucleus reticularis giganto cellularis (release NE) to synapse on DHN or block signals sent by excitatory neurons to the dorsal horn via nociceptors. Endorphines acting on opioid receptor is the main modulator of this natural analgesic system by releasing the descending pathways from their GABAergic inhibition to allow NE and 5HT to suppress the DHN. However GABA reigns supreme within the spinal cord as it is the transmitter released by the inhibitory interneurones.

Pain management

A multidisciplinary team approach (eg, acute pain service) is useful for formulating a plan for pain relief, particularly in complicated patients, such as those who have undergone extensive surgery, chronically use narcotics, or have medical comorbidities that could increase their risk of analgesia-related complications or side effects as in case of obesity. Acute pain usually resolves by drugs that are prescribed by the treating physician, while chronic pain needs an interdisciplinary approach conducted by a team that work together not only to relieve the pain but to improve the quality of life of those living with pain. The typical pain management team includes medical practitioners, clinical psychologists, physiotherapists, occupational therapists, and nurse practitioners.[107]

Drugs that are used to treat pain fall under 2 major groups;[108]

- Analgesics; whether opioids or non-opioids (Acetaminophen, Nonsteroidal anti-inflammatory drugs (NSAIDs), Coxibs)
- Other pain controlling drugs; Antiepileptics, Antidepressants, Local anesthetics, α_2 adrenergic agonist, N-methyl d-aspartate (NMDA) receptor antagonists, Cannabinoid antagonists, Capsaicin,…..etc.

Other approaches to treat pain, some of which have sound medical reference standards while others do not. The commonest that are enrolled include;[109]

- Physiotherapy; Cryotherapy, Exercise, Occupational therapy, Physical therapy, Hot packs, neurostimulation and transcutaneous electrical nerve stimulation.
- Acupuncture; application of needles to precise points on the body according to Chinese Oriental Medicine.
- Cognitive-Behavioral Therapy.
- Prolotherapy; injecting an otherwise non-pharmacological and non-active irritant solution into the body for the purpose of strengthening weakened tissue.
- Biofeedback; the use of special electronic machine to train patients to become aware of, to follow, and to gain control over certain functions including pain.

Increased BMI is associated with different forms of pain mechanisms by which this link is hypothesized to develop generally include mechanical, structural, metabolic and behavioral changes. Most likely, a combination of factors is responsible for the relationship and these factors may contribute differently depending on the particular disorder. Weight loss appears to positively affect pain outcomes both in terms of lowering the risk of developing problems, such as musculoskeletal pain and OA, and reducing pain-related distress and disability.[109, 110]

Patients with morbid obesity pose a challenge for perioperative pain management. High ceiling analgesics-opioids have limited role due to safety concerns for patients with or without obstructive sleep apnea. More surgeries are being performed laparoscopically over the last couple of decades. This has led to decreased analgesic requirements and promoted expedited recovery. Despite this, postoperative pain still remains the prime factor of patient dissatisfaction toward surgical experience. Postoperative complications in patients with morbid obesity have been consistently linked to increasing BMI, and the use of opioids.[110]

Opioids[84, 110] being central depressants diminish the action of the pharyngeal dilator muscles in obesity and OSA. During the initial three days postoperatively, pain scores are highest. This high pain suppresses Stages 3 and 4 of both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Opioids promote deep sleep if used during the first three postoperative days (by direct central action), and apnea during drug-induced sleep is increased. Opioids also alter the natural sleep architecture by promoting NREM and REM phase of sleep. Subsequently during the next three days, natural deep REM sleep rebounds. In this phase of recovery, the danger of life-threatening natural deep sleep-induced apnea again increases. Opioids also increase sensitivity to therapeutic doses producing unpredictable results. Similarly, increased central sensitivity has also been confirmed in animal studies.(111)

Systemic analgesics other than opioids

Nonsteroidal anti-inflammatory drugs:(110, 112) In patients with morbid obesity, pain is best treated with IV rather than IM medication. Unless extra-long needles are used, medications intended for the muscle are often delivered instead into the more superficial adipose tissue. Drug absorption is inconsistent from fatty tissue thus possibly leading to inadequate pain control. For short-term postoperative use in bariatric surgery, NSAIDs have shown to be fairly safe with minimal platelet dysfunction or renal/gastrointestinal adverse effects. Some studies have demonstrated favorability of perioperative ketorolac in comparison to remifentanil for analgesia, early discharge, and better intraoperative hemodynamic stability in patients with morbid obesity undergoing abdominal laparoscopic surgeries.

Paracetamol : N-acetyl-p-aminophenol.

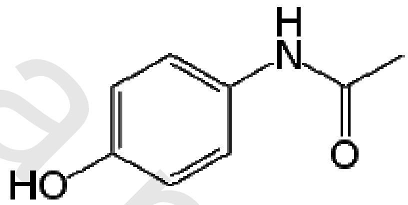

Figure (7): N-acetyl-p-aminophenol

Mechanism of action: (113, 114)

It inhibits phenoxyl radical formation from a critical tyrosine residue essential for the cyclooxygenase activity of COX-1 and COX-2 and prostaglandin (PG) synthesis. Its peripheral anti-inflammatory activity is usually limited by high level of peroxides present in inflammatory lesions. However, in some circumstances, even peripheral anti-inflammatory activity can be observed when low levels of arachidonic acid and peroxides are available. The result is that paracetamol does not suppress the severe inflammation but does inhibit the lesser one. Paracetamol often appears to have COX-2 selectivity that is shown by its poor anti-platelet activity and good gastrointestinal tolerance. Paracetamol inhibits other peroxidase enzymes including myeloperoxidase which decreases formation of halogenating oxidants (e.g. hypochlorous acid, hypobromous acid) that may be associated with multiple inflammatory pathologies including atherosclerosis and rheumatic diseases.

The metabolites of paracetamol e.g. NAPQI (N-acetyl-p-benzoquinone imine), are thought to act on TRPA1-receptors (figure 5) in the spinal cord to suppress the signal transduction from the superficial layers of the dorsal horn, to alleviate pain. It is suggested that thiol groups in cysteine proteases, e.g. the proteases that take part in the processing of procytokines, such as those generating IL-1β and IL-6, might be the targets giving rise to overall analgesic effects. Paracetamol also modulates the endogenous cannabinoid system and it has a serotonergic agonism action.

Pharmacokinetics:[113]

It is rapidly absorbed from the gastrointestinal tract with onset 11-29.5minutes after oral ingestion, its systemic bioavailability being dose-dependent and ranging from 70 to 90%. It is delayed by food, propantheline, pethidine and diamorphine and enhanced by metoclopramide. Paracetamol is also well absorbed from the rectum. It distributes rapidly and evenly throughout most tissues and fluids and has a volume of distribution of 0.9L/kg. 10 to 20% of the drug is bound to red blood cells. Paracetamol is extensively metabolised (predominantly in the liver), the major metabolites being the sulphate and glucuronide conjugates. A minor fraction of drug is converted to a highly reactive alkylating metabolite which is inactivated with reduced glutathione and excreted in the urine as cysteine and mercapturic acid conjugates. In healthy subjects 85 to 95% of a therapeutic dose is excreted in the urine within 24 hours with about 4, 55, 30, 4 and 4% appearing as unchanged paracetamol and its glucuronide, sulphate, mercapturic acid and cysteine conjugates, respectively. The plasma half-life in such subjects ranges from 1.9 to 2.5 hours which is prolonged in those with decompensated liver disease and the total body clearance from 4.5 to 5.5 ml/kg/min.

Clinical uses: intravenous paracetamol is FDA approved for the management of mild to moderate perioperative pain alone; the management of moderate to severe pain with adjunctive opioid medication. It is a commonly used antipyretic agent.[115]

Dose: For patients (⩾ 13 years) weighing ⩾ 50 kg, the dose is 1g every 6 hours (maximum single dose) and a total maximum daily dose of acetaminophen (any route) is 4g/day. This dose has generally been used for 24 to 48 hours postoperatively, but has been tested for as long as 7 days postoperatively. For patients (⩾ 13 years) weighing <50 kg, the dose is 15 mg/kg every 6 hours (maximum single dose is 750 mg) and a total maximum dose of 75 mg/kg (up to 3750 mg) in 24 hours. For children ages 2 to 12 years, the dose is 15 mg/kg and the maximum daily dose is 75 mg/kg. No adjustment in dosing is needed for obese or morbidly obese patients.[115, 116]

Side effects;[116] It is a safe and well tolerated drug in recommended doses and limited course. Most side effects are due to chronic use or overdose. It is hepatotoxic and side effects are very likely in chronic alcoholics or patients with liver damage. Prolonged daily use increases the risk of upper gastrointestinal bleeding, and may cause kidney or liver damage, nausea (34%) and vomiting (15%). headache (10%), insomnia (7%), and fatigue. On August, 2013, FDA issued a new warning about paracetamol that the drug could cause rare, and possibly fatal, skin reactions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis.

Paracetamol toxicity:[116] may result from a single toxic dose, from repeated ingestion of large doses (7.5-10 g daily for 1-2 days), or from chronic ingestion of the drug. Dose-dependent, hepatic necrosis is the most serious acute toxic effect and is potentially fatal which occurs as a result of depletion of glutathione and of binding of the excess reactive metabolite to vital cell constituents. Paracetamol toxicity usually involves 4 phases: ***phase 1***:anorexia, nausea, vomiting, malaise, and diaphoresis; ***phase 2***: resolution of phase-1 manifestations and replacement with right upper quadrant pain or tenderness, liver enlargement, elevated bilirubin and hepatic enzymes, prolongation of prothrombin time, and occasionally oliguria; ***phase 3***: anorexia, nausea, vomiting, and malaise recur (usually 3-5 days after initial symptom onset) and signs of hepatic failure and possibly renal failure and cardiomyopathy develop; and ***phase 4***: recovery or progression to fatal complete liver failure.

Antidote: N-acetylcysteine(116) that replenishes hepatic glutathione stores and increases sulfate conjugation, preventing accumulation of NAPQI. Acetylcysteine may prevent hepatic failure from an acetaminophen overdose when administered early enough (within 8-10 hours following an acute overdose) but may still be of value up to 48 hours after ingestion.

Peripheral nerve blocks(87, 117)

It is obvious that obesity was associated with higher block failure and complication rates in surgical regional anesthesia in the ambulatory setting. Often, patients with obesity have more fat in their lower limbs, thus lower limb blocks may be technically more challenging with landmark techniques, and one may have to resort to neuraxial blockade in such cases. Portable ultrasound has shown to improve accuracy of interscalene block similar to that seen in nonobese patients. Preferably newer ultrasound machines should be capable of visualizing deeper tissue than that used conventionally (i.e., lower frequency probe may be needed) or by using three dimensions ultrasound reconstruction technology if available.(118)

Neuraxial nerve blocks in obese patient(88, 119)

Successful regional anesthesia in morbid obesity as a component of multimodal analgesia has potential advantages of avoiding risks of OSA, difficult airway, and pulmonary complications associated with general anesthesia. Technical difficulties, positioning and risk of local anaesthetic overdose associated with regional anesthesia are real challenges. Regional anesthetic techniques have been clearly linked to better pain relief and early discharge in patients with morbid obesity. These techniques can be either used to provide surgical anesthesia or aid in postoperative opioid-free analgesia. Continuous epidural techniques using local anesthetics via a catheter have shown favorable results in terms of respiratory function and return of bowel function. As per ASA practice guidelines, wherever possible intrathecal water-soluble opioids should be avoided in patients with morbid obesity. Many adjuvants have been used to prolong the analgesia in both general and regional anaesthesia. These adjuvants include: (110, 120, 121)

a. Synthetic opioids: eg. Tramadol and tapentadol.
b. N-Methyl D-aspartate (NMDA) antagonist: eg. Ketamine
c. Alpha-2a receptors antagonists eg. Dexmedetomidine and clonidine.
d. Corticosteroids; Single IV preoperative dose Dexamethasone has been shown not only to be effective in reducing postoperative nausea and vomiting but also to improve recovery, reduce pain and improve satisfaction.(122)
e. Gabapentinoids; eg. Gabapentin and pergabalin**.**(121)

Gabapentin (GBP): 1-aminomethyl cyclohexane acetic acid.

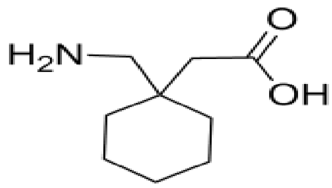

Figure (8): 1-aminomethyl cyclohexane acetic acid

Mechanism of Action:

A number of mechanisms may be involved in the actions of gabapentin. Alpha-2delta-1, an auxillary subunit of voltage gated calcium channels, has been documented as its main target. The binding to alpha2delta-1 subunits inhibits nerve injury-induced trafficking of alpha1 pore forming units of calcium channels (particularly N-type) from cytoplasm to plasma membrane (membrane trafficking) of pre-synaptic terminals of DRG neurons and dorsal horn neurons. Furthermore, the axoplasmic transport of alpha2delta-1 subunits from DRG to dorsal horns neurons in the form of anterograde trafficking is also inhibited. Gabapentin has also been shown modulate other targets including TRP channels, NMDA receptors, protein kinase C and inflammatory cytokines. It may also act on supra-spinal region to stimulate noradrenaline mediated descending inhibition, which contributes to its anti-hypersensitivity action in neuropathic pain. Gabapentin has been shown to inhibit glutamate release, increase the activity of NMDA receptors, inhibit the activity of voltage-gated sodium channels, and enhance the activity of voltage-gated potassium channels. Prolonged exposure to gabapentin can increase the amplitude of a tonic inhibitory GABAergic conductance that may also regulate pain processes.(123, 124)

Therapeutic Uses:

Pain: Gabapentin provides significant pain relief in people suffering fibromyalgia or neuropathic pain (eg. diabetic peripheral polyneuropathy, post herpetic neuralgia, trigeminal neuralgia, multiple Sclerosis, complex regional pain syndrome, HIV neuropathy, peripheral nerve injury and neuropathy and cancer pain). It appears as effective as pregabalin and costs less. It provides some benefit for migraine prevention and hot fluhes in post menopausal women. Gabapentin use has more recently extended into the management of more acute conditions, particularly in the perioperative period. More than 30 clinical trials evaluating the potential roles of gabapentin for postoperative analgesia and for reducing opioids consumption, preoperative anxiolysis, prevention of chronic post-surgical pain, attenuation of haemodynamic response to direct laryngoscopy and intubation, prevention of postoperative nausea and vomiting (PONV), and postoperative delirium have been published.(124, 125)

Seizures:(126) Gabapentin is approved for treatment of focal seizures in a number of countries but not for generalized epilepsy. There is little data to support its initial use over older anticonvulsant medications for any type of seizure disorder.

Other:[126] There is some evidence of benefit in acquired pendular and infantile nystagmus, menopausal symptoms and may be effective in reducing pain and spasticity in multiple sclerosis. Gabapentin helps with itching due to renal failure.

Off-label uses:[126] Numerous trials show that it is not effective alone as a mood-stabilizing treatment for bipolar disorder and so has no therapeutic advantage in having fewer side effects over better established bipolar drugs. Gabapentin is useful in the treatment of anxiety associated with bipolar disorder and restless leg syndrome, but has limited usefulness in social anxiety disorder, obsessive-compulsive disorder, in treatment-resistant depression, and for insomnia.

Absorption, Distribution & Excretion:[126]

Volume of distribution of gabapentin is approximately 50 to 60 L. It is highly ionized at physiological pH; therefore, concentrations in adipose tissue are low. GBP penetrates the blood-brain barrier, yielding cerebrospinal fluid (CSF) concentrations approximately equal to 20% of corresponding steady-state plasma concentrations in patients with epilepsy. Brain tissue concentrations in one patient undergoing temporal lobectomy were approximately 80% of corresponding plasma concentrations. Gabapentin is absorbed in part by the L-amino and acid transport system, which is a carrier-mediated, saturable transport system; as the dose increase, bioavailability decreases. Bioavailability ranges from approximately 60% for a 900 mg dose per day to approximately 27% for a 4800 mg dose per day. Food has a slight effect on the rate and extent of absorption of gabapentin.

Time to peak concentration: 2-4 hours.[126]

Protein binding: less than 3% circulates bound to plasma protein.[123]

Metabolism: Gabapentin is not metabolized and does not induce hepatic microsomal enzymes. It is eliminated unchanged in the urine and faeces.[123]

Elimination:[123]

- Normal renal function: 5 to 7 hours.
- Impaired renal function (creatinine clearance < 30 mL/minute): 52 hours.

Dose: 300-3600mg in 3 divided doses, increased in some cases to 4800mg/day. [125]

Side-effects: Gabapentin is generally well tolerated. Reported adverse effects mostly were observed in patients with chronic pain treated with gabapentin such as somnolence (15.2%), dizziness (10.9%), asthenia (6%), headache (4.8%), nausea (3.2%), ataxia (2.6%), weight gain (2.6%), and amblyopia (2.1%), and convulsions (0.9%).[125]

Interactions:[124, 125] Gabapentin neither induces nor inhibits hepatic microsomal enzymes; neither does it affect the plasma concentration of the most concurrently administered antiepileptic drugs (AEDs). Other AEDs have no effect on the GBP pharmacokinetics. Gabapentin shows low protein binding in hepatic cells and also lacks any sort of hepatic metabolism. Cimetidine, decreases the clearance of gabapentin by 12% by decreasing the glomerular filtration rate. Naproxen may increase gabapentin absorption by 12 to 15%; no dosing recommendations. Morphine increases mean gabapentin area under the curve (AUC) values by 44%; patients may experience increased CNS depression; decreases in dosing of either agent may be necessary. Gabapentin decreases hydrocodone Cmax and AUC values in a dose-dependent manner while gabapentin AUC values are increased by 14%. Antacids taken within 2 hours of gabapentin intake reduce gabapentin bioavailability by 20%. Additive CNS depression may occur when used with other CNS depressants

Pain control regimens should not be standardized; rather, they are tailored to the needs of the individual patient, taking into account medical, psychological, and physical condition; age; level of fear or anxiety; surgical procedure; personal preference; and response to agents given. The major goal in the management of postoperative pain is minimizing the dose of medications to lessen side effects while still providing adequate analgesia especially in obese patients. This goal is best accomplished with multimodal and preemptive analgesia.(115)

Pre-emptive and multimodal analgesia(98, 127, 128)

Pre-emptive analgesia is the administration of analgesics prior to onset of noxious stimuli that modifies peripheral and central nervous system processing of these stimuli, thereby reducing hyperalgesia and allodynia. Analgesic therapy has traditionally targeted central mechanisms involved in pain perception using opioids; however, a better approach uses several agents, each acting at different sites of the pain pathway. This approach lessens the dependence on a given medication and mechanism. Preemptive analgesia reduces postoperative opioid use and side effects. (98)

Effective preemptive analgesic techniques use multiple pharmacological agents to reduce nociceptor activation by blocking or decreasing receptor activation, and inhibiting the production or activity of pain neurotransmitters. Synergism between medications decreases the doses needed and helps avoid the unwanted effects associated with the higher doses that would be required if only a single agent was used. So, multimodal analgesia is considered to be a part of preemptive analgesia; an approach to prevent postoperative pain that involves administering a combination of analgesics that act at different sites within the central and peripheral nervous systems in an effort to improve pain control while eliminating opioid-related side-effects. Use of multimodal analgesia for the prevention of pain in the ambulatory setting is one of the keys to improving the recovery process, reducing delayed discharges from hospital and surgery centers, and most importantly, facilitating the ability of patients to resume their activities of daily living after day surgery.(98, 128).

The concept of pre-emptive analgesia is based on advances and research in the basic science of pain and evidence-based clinical research. It has now been refined and evolved to a broader concept that surgical incision alone is not the trigger for central sensitization. Other factors, such as preoperative pain and additional painful noxious intraoperative inputs such as retraction, as well as postoperative inflammatory processes, related peripheral and central neuromodulators and ectopic neural activity can all cause an intensification of acute pain and long-term postoperative pain as a result of central sensitization.(127)

At present, there are several multimodal strategies covering the perioperative period that can help to decrease postoperative pain and minimize consumption of analgesics.

Preventive analgesia is now considered a more appropriate term because it encompasses all perioperative efforts to decrease postoperative pain and decrease consumption of analgesics. This treatment can be given at any time in the perioperative period, including the preoperative period, which results in a duration of action greater than that expected for the particular intervention given to decrease postoperative pain and to reduce consumption of analgesics. The molecular basis of central sensitization is an important concept for the understanding of pre-emptive analgesia and preventive analgesia. Central sensitization provides the neurobiological basis for much of the pain suffered by patients long after normal tissue healing has occurred.[127]