Chapter

Obesity: A Risk Factor for Infection after Surgery

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Abstract

Obesity is a prevalent health problem all over the world. It is associated with several diseases including infections. It impairs the immune system function by plenty of mechanisms. For instance, leptin and adiponectin are cytokines produced by the adipose tissue, both participating in immunity, but their effects are impaired in obese patients. Moreover, immune cells also show defects in their functions. They produce a pro-inflammatory state and contribute to obesity-related diseases. Innate immune system and adaptive immunity are both impaired in obese patients which causes a poor response to infections. In addition, in surgical site infections (SSI), there are local factors that must be considered. The large adipose panicle and visceral adipose tissue increase the surgical technique difficulty and extend the operative time. Besides, the adipose tissue has poor oxygenation and reduces operative field. It has been proven that obesity is associated to surgical site infection irrespective of type of surgery. However, minimal invasive surgery has demonstrated that reducing surgical trauma can diminish the risk for surgical site infection.

Keywords: obesity, surgery, surgical site infection, immune deficiency, surgical complication

1. Introduction

Nowadays, obesity is a serious health problem which affects all countries irrespective of economic status. It is produced by an energy imbalance, and then there is an increase in body-fat mass. A body mass index (BMI) more than 30 kg/m^2 is defined as obesity [1].

There are plenty of diseases that are linked to obesity; the most common are metabolic syndrome, type 2 diabetes mellitus, coronary disease, and hyperlipidemia. Despite not being as well-known as the previous examples, obesity is strongly associated with infection [2].

Obese patients have a higher risk of nosocomial infections because medical care of these patients requires special procedures, equipment, and staff. Moreover, obese patients are usually immobilized which is a risk factor for decubitus ulcers and contributes to increase length of stay [3].

Although there are some controversial studies, an association between caries rates and elevated BMI has been proven. Dietary habits characterized by high consumption of soft drinks, fast food, and refined sugar contribute to dental caries as well as obesity [4]. In addition, it is well-known that severe infections in the face and neck usually have an odontogenic origin and obesity is a risk factor for the infection progression. Besides, an association has been described between the levels

of tumor necrosis factor alpha in gingival crevicular fluid and BMI [5]; therefore, there is a systemic effect of obesity in oral health.

Obesity is related to respiratory diseases including nosocomial pneumonia and community-acquired respiratory tract infections [3]. In these patients, a decreased lung volume and a restrictive ventilatory pattern have been noticed. Excess weight on the anterior chest wall, abdominal obesity, and the presence of the adipose tissue in the intra-abdominal visceral tissue increase muscle work in breathing, diminish lung expansion, and increase airway resistance. These mechanical changes and augmented adipose tissue produce an inflammatory state that contributes to metabolic disease [6]. Other respiratory diseases associated to obesity are obstructive sleep apnea, chronic obstructive pulmonary disease, and asthma [6, 7].

On the other hand, obesity is a risk factor for the development of steatosis in patients with chronic hepatitis C infection and biliary disease with infectious complications [3]. Skin and soft tissue infections are also more prevalent in obese patients [2, 3]. The adipose tissue affects the pharmacokinetics and pharmacodynamics of antibiotics. Therefore, some special considerations must be taken when treating an obese patient [8, 9].

Even though there are some important studies that demonstrate obesity is not a risk factor for surgical complications [10], there are still some evidence that contrast with these researches [11]. On the other side, it is well-known that obese patients have a higher risk for surgical site infections (SSI) particularly when open surgery is performed. This phenomenon has been associated to low oxygen tension in the adipose tissue as well as a poor immune response observed in obese patients [3, 10, 11].

In this chapter we will review the available evidence about obesity as a risk factor for surgical infections in most common surgical procedures, considering pathophysiology as well as relevant clinical information.

2. Pathophysiology of infection in obese patients

There are several mechanisms that cause immune dysfunction in obese patients. The adipose tissue produces some cytokines which have effects on immune cells. There are other mechanisms that explain the altered immune response in obese patients.

2.1 Leptin and adiponectin

Nowadays, it is well-known that the adipose tissue has an active role in immunity by producing factors like leptin and adiponectin [3].

Leptin influences hematopoiesis, angiogenesis, and immune homeostasis. It stimulates proliferation and activation of monocytes in vitro and also increases the expression of surface markers. Leptin affects maturation of dendritic cells; deficiency of this cytokine is related to lower levels of tumor necrosis factor alpha and interleukins 12 and 6. It prevents neutrophil apoptosis and stimulates their chemotaxes. Leptin affects immune function of natural killer (NK) cells and T cells. It promotes T-cell proliferation, cytokine secretion, and migration of these cells. Th1-cell immune response is also stimulated by leptin. In addition, B lymphocytes are affected by leptin. It controls their development and can augment their population by suppressing apoptosis and stimulating proliferation of these cells [12–14]. Leptin also plays a role in wound healing. An experimental study has proved that leptin accelerates skin wound healing by increasing proliferation and differentiation of epidermal keratinocytes as well as promoting angiogenesis [15].

Congenital leptin deficiency is rare in humans. Diet-induced obesity is related to high levels of circulating leptin; however, it has been hypothesized that obesity causes some resistance in leptin receptors similar to what happens with insulin resistance [16]. Therefore, in obese patients, leptin cannot produce its effect on the immune system despite high levels of this cytokine.

Adiponectin is another important circulating adipocytokine that plays a role in immunity. It has anti-angiogenic, anti-inflammatory, and anti-apoptotic effects. Adiponectin can inhibit the phagocytic activity of macrophages, reduce the production of tumor necrosis factor alpha and gamma interferon, as well as induce the production of interleukin 10 and interleukin 1 receptor antagonists which are anti-inflammatory molecules. However, serum/plasma levels of adiponectin are higher in immune-mediated diseases [17, 18]. In contrast, in obese patients, adiponectin levels are lower than controls, and it has been observed that production of this adipocytokine increases after weight loss [19].

2.2 Immune cells

Although, in diabetic patients, neutrophils show defects in their functions, in obese patients this phenomenon has not been noticed. Indeed, these cells seem to be chronically primed and contribute to the development of obesity-related diseases [1].

Monocytes and macrophages also take part in immune response. They can change their phenotype getting a pro-inflammatory form (M1 CD11c+) or an anti-inflammatory form (M2 CD11c-) [1]. In obesity, a pro-inflammatory state, adipose tissue macrophages are more prevalent, these cells have M1 phenotype and are considered a factor that increases sepsis mortality. In addition, the percentage of macrophages in the adipose tissue is directly proportional to the adipocyte size [20]. Current evidence suggest that overnutrition causes adipocyte hypertrophy which leads to hypoxia and stimulates macrophage activity [21].

Natural killer cells are lymphocytes of the innate immune system. They are defined as CD3-/CD56+ granular lymphocytes and can be subcategorized based on the level of CD56 expression. $CD56^{dim}$ NK cell (or low density) subset can produce granzymes and perforins and is more cytotoxic than $CD56^{bright}$ (or high density) subset. On the other way, $CD56^{bright}$ NK cells have immunoregulatory effects. In obesity, there is no clear consensus about the effects on peripheral NK cell number. However, there is a study that demonstrates a significant more prevalence of $CD56^{bright}$ NK cells in obese patients as well as these patients also show a decreased percentage of $CD56^{dim}$ NK cells. Therefore, the predominance of $CD56^{bright}$ NK cells could be a cause for the impaired lytic activity NK cells against virus-infected and tumor cells observed in obese patients [22]. Several other studies have shown the impact of obesity on NK cells. An increased expression of activation markers such as CD69 and a decreased expression of other molecules such as NKp30 and NKp44 have been observed. Moreover, NK cells isolated from obese patients fail to engage glycolytic metabolism. They also lose the ability to kill macrophages and augment expression of gamma interferon which stimulates the migration of macrophages [23].

Dendritic cells (DCs) are also affected by obesity. They can activate or suppress immune responses and are characterized as conventional, inflammatory, or plasmacytoid dendritic cells. An increase in inflammatory DCs in the adipose tissue has been described. These cells are created from inflammatory monocytes and contribute to adipose tissue inflammation. However, there is evidence suggesting that conventional dendritic cells also take part in adipose tissue inflammation.

In addition, this study points out that dendritic cells could act independently of monocytes [24]. On the other hand, in obesity DCs failed to upregulate CD83, a marker for maturity. Besides, they produce less IL-12 and more IL-10, suggesting an inability to stimulate T cells [25].

Adaptive immunity is impaired too. Gamma delta T cells, a subset of T cells that takes part in repairing tissue and inducing inflammation, are diminished in obese patients and secrete less gamma interferon, contributing to the persistence of chronic, non-healing wounds [1, 26]. On the other side, memory T cells in the adipose tissue overexpress some cytokines while underexpress other ones. Moreover, obesity increases memory T-cell number which can be related to leptin production. Under healthy circumstances, memory T cells contribute to control infections; however, they can also mediate the pathogenesis in other conditions such as obesity [27]. In contrast, the number of regulatory T cells is reduced in the adipose tissue which promotes inflammation and insulin resistance [1, 26] because these cells participate actively maintaining self-tolerance and suppressing activity of effector T cells. This reduction can be partially explained by the levels of leptin which decreases the proliferation of regulatory T cells [28]. Other affected T cells are Th1 and Th17 cells. The first ones are increased in the visceral adipose tissue of obese patients contributing to inflammation, whereas Th17 cells are increased in the subcutaneous adipose tissue of obese patients and produce IL-17 which promotes inflammation and insulin resistance as well [26].

Relating to humoral immunity, there is no clear consensus. However, there is some evidence that it is impaired in obese patients. Obesity induces pro-inflammatory B cell subsets [29]. In spite of hyperstimulation of B cells and increased number of these, they function suboptimally and antibody production is modified. The most important factors that influence B-cell antibody production are leptin effect and essential fatty acid status [30].

3. Obesity and infection after surgery

Surgical site infection (SSI) is a serious complication that increases morbidity and mortality as well as extends postoperative stay and rises healthcare costs. Indeed, one observational study performed in 7020 patients who underwent colon surgery finds an increased rate of SSI in obese patients (14.5% vs. 9.5%; $p < 0.001$). In this study SSI increases costs in $17,000 because these patients have longer stays and higher rates of hospital readmission [31]. This increased risk for SSI is especially noticeable in clean and clean-contaminated surgeries. In addition, a study described a relation between BMI and the risks for SSI, and then overweight could just be a risk factor for SSI in some kinds of surgery [32].

There are several mechanisms that explain this increased risk. Some of them have already been mentioned. However, there are other ones that are important in surgical site infection. The most important factor is hypoperfusion of adipose tissue which is due to less vascularization of adipose tissue. It causes poor tissue oxygenation and extends wound healing. Moreover, there is more dead space, and antibiotics might not get adequate concentrations in the wound [32, 33].

Other important factors are related to surgery. Obese patients have great adipose panicle which makes open surgery more difficult. In addition, the visceral abdominal tissue is also increased and obligates surgeons to take special considerations on the surgical technique such as longer incisions, prolonged surgery time, and increased mean operative blood loss [32, 33]. Both are known risk factors for surgical site infection.

3.1 Obesity and gastrointestinal surgery

A large study performed in the Netherlands evaluated the relation between obesity and several types of surgery. Laparoscopic appendectomy, laparoscopic cholecystectomy, open colectomy, and laparoscopic colectomy were considered gastrointestinal surgery. The study revealed that the risk of superficial SSI gradually increased with increasing BMI, except in laparoscopic appendectomy. However, deep SSI did not seem related to BMI [32].

A meta-analysis also showed that overweight and obese patients have a 1.2- to 1.5-fold higher odds of developing SSI after colorectal surgery. Moreover, the same study performed a subgroup analysis that included only elective surgery cases, and then the results were similar. The authors highlighted the suboptimal tissue concentrations of antibiotics in obese patients. It is not only related to the increased volume of distribution and altered plasma protein binding; indeed, obese patients have changes in hepatic metabolism and renal excretion, and the prevalence of diabetes is higher in these patients [34].

Another study performed a separate analysis for right colectomy, left colectomy, and rectal resection. Obesity did not affect morbidity and mortality after right colectomy. However, the rate of postoperative intra-abdominal collections was higher in obese patients after left colectomy. Moreover, the study showed that obesity was a risk factor for anastomotic leakage after rectal resection. Therefore, the authors recommended the use of a defunctioning stoma in obese patients when diabetes or ASA > 2 is present [35].

On the other hand, laparoscopic surgery has brought to table other considerations. A meta-analysis showed that the incidence of SSI is significantly less after laparoscopic surgery than after open surgery (70–80% lower risk). These findings could be related to less surgical trauma and smaller incisions that are used in laparoscopic surgery. However, conversion to open surgery has the worst outcomes [36]. Despite the advantages of laparoscopic surgery, it is not always easy to perform it in obese patients. A meta-analysis demonstrated that visceral obesity is associated to longer operative time, less lymph node harvest, and higher conversion rate. Moreover, laparoscopic surgery in obese patients requires technical expertise because of the limited exposure of the surgical field and the thickened mesentery which is difficult to maneuver [37].

In obese children the problem is similar, and there is some evidence that demonstrates that laparoscopy is safe in these patients, although it is related to longer operative time [38].

Laparoscopic surgery is safe in obese patients. However, there are some special considerations: adequate position to expand the surgical field avoiding pressure sores and minimizing nerve compression, adequate entry technique, longer operative time, and thromboprophylaxis [39].

Although there are few studies about obesity and robotic surgery, it has been suggested that it could bring more benefits for obese patients. It has been observed that the length of stay and 30-day readmission rate were lower in patients who underwent robotic surgery than in patients who underwent laparoscopic surgery. It probably happens because of superior stable 3D views and ergonomic wristed instruments that robotic surgery offers [40]. However, it must be considered that robotic surgery is more expensive than laparoscopic surgery and requires appropriate training.

3.2 Obesity and gynecological surgery

In gynecological surgery there is some controversy. Overweight could be a protective factor for SSI in vaginal hysterectomy. However, there is an increased

risk for deep SSI in morbidly obese patients [32]. In abdominal hysterectomy, the findings are similar, and the risk for SSI increases linearly with increasing BMI. The same study showed a nonsignificant prevalence of *Enterobacteriaceae* in obese or overweight patients with SSI after abdominal hysterectomy [33].

A large study that included 18,810 patients who underwent hysterectomy for benign indications demonstrated that the risk for superficial and deep wound infection was higher with increasing BMI after total abdominal hysterectomy. However, the risk was not different when minimally invasive surgery (total vaginal hysterectomy, laparoscopic assisted vaginal hysterectomy, total laparoscopic hysterectomy) was performed. In contrast, the operative time was longer with increasing BMI irrespective of the surgical approach [41].

Obesity is a risk factor for leiomyomata, ovulatory dysfunction, and endometrial cancer. All of them are common indications for hysterectomy. Therefore, hysterectomy is a common surgical procedure performed in obese women. In that way, it is recommended to prefer a minimal invasive approach because of its reduced rate of complications. Other aspects to be considered are adequate thromboembolism prophylaxis, antibiotic prophylaxis, and adequate surgical technique [42].

In cesarean section, maternal obesity is also associated with surgical and postoperative risks such as endometritis, intra-abdominal collection, and surgical wound complications. In that way, antibiotic prophylaxis in these patients is different, and the actual recommendation is to administer at least 2 g of cefazolin some 60 minutes before the cesarean section. Another recommendation is to close the subcutaneous tissue layer in obese patients particularly when its depth exceeds 2 cm [43].

Finally, for mastectomy and lumpectomy, it has been observed that the risk of developing SSI augmented with increasing BMI. Moreover, obesity is a risk factor for major and minor complications after mastectomy irrespective of being unilateral or performing reconstruction [44].

3.3 Obesity and orthopedic surgery

Obesity is an important risk factor for SSI after total hip prosthesis. It has been observed that the rate of SSI increased gradually with increasing BMI. Moreover, this association was present in both superficial and deep SSI. However, in partial hip prosthesis, obesity was related to superficial and deep SSI, but overweight only was a risk factor for deep SSI [32]. Another study had similar findings. It showed that members of the *Enterobacteriaceae* were more common among normal-weight patients with hip replacement [33].

On the other hand, among the total knee replacement patients, obesity was a risk factor for deep SSI but not for superficial SSI. Indeed, only a BMI > 40 was a risk factor for superficial SSI [32].

A meta-analysis also demonstrated that the risk of periprosthetic joint infection in obese patients was 1.9-fold higher than non-obese patients. The authors mentioned that this increased risk could be related to prolonged operative time, an increased rate of wound complications, and the presence of medical comorbidities [45].

Finally, a large study that included 161,785 patients showed that obesity was associated to higher rates of complications after total hip arthroplasty than after total knee arthroplasty. The study demonstrated that among the obese and morbidly obese patients who underwent primary total hip replacement, the risk of total complications, wound complications, deep infection, and reoperation was higher than for similar weighted patients who underwent primary total knee arthroplasty. This observed difference would be due to the tendency of the adipose tissue to deposit in the gluteal region [46].

3.4 Obesity and cardiothoracic surgery

Among the patients who undergo cardiothoracic surgery, obesity is a risk factor for SSI. Several studies have shown that the risk for SSI augmented gradually with increasing BMI [32, 33]. In cardiac surgery, however, an obesity paradox has been described. It means that mildly obese or overweight patients may have some benefit instead of an increased risk. Indeed, a large study that included 4740 patients who underwent cardiac surgery demonstrated that extremely obese (BMI > 40 kg/m^2) patients had an increased risk for deep sternal infection, prolonged ventilation after cardiac surgery, and postoperative renal dialysis requirement. In contrast, mildly obese or overweight patients had minor in-hospital mortality, minor operative mortality, and less ICU hours [47]. Another study showed that obesity and underweight were both associated to postoperative adverse events. However, this study did not show differences between extremely and mildly obese patients probably because both studies used different ways to categorize BMI [48].

3.5 Obesity and neurosurgery

A large study performed in the Netherlands failed to demonstrate an association between obesity and surgical site infection after laminectomy [32]. However, another study which included 31,763 patients demonstrated that complications after lumbar spine surgery were associated to obesity. The stratification by BMI established five categories: underweight (BMI < 18.5), normal-overweight (BMI 20.0–29.9), obesity class I (BMI 30.0–34.9), obesity class II (35.0–39.9). and obesity class III (BMI > 40). The study evaluated airway, cardiopulmonary, and infectious complications. They found that obese class I was associated to 4 of the 11 complications analyzed; obesity class II was associated to 6 of the 11 complications analyzed; and obesity class III was associated to 9 of the 11 complications analyzed. In addition, the rate of surgical site infection increased with increasing obesity class [49].

The effect of obesity on cranial surgery is similar to spinal surgery, but the impact on surgical outcomes is lower on cranial surgery. It increases the risk of major medical complications and may increase the risk for SSI after craniotomy. On the other side, in spinal surgery, obesity increases the risk of SSI, venous thromboembolism, and major medical complications [50].

4. Conclusion

Although obesity leads to a pro-inflammatory state, it impairs the immune system and is a risk factor for several infections. Moreover, in surgical site infection, there are local factors related to obesity that must be taken into account: a large adipose panicle with poor oxygenation, a reduced operative field, difficulties in technique, and increased operative time. Therefore, obesity is a proven risk factor for surgical site infection in plenty of surgeries. However, there are some actions that we could take to reduce this risk: performing minimal invasive surgery, ensuring adequate surgical technique, prescribing adequate antibiotic doses, and recommending weight loss.

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Conflict of interest

The authors declare no conflict of interest.

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