Obesity and infection

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Obesity increases morbidity and mortality through its multiple effects on nearly every human system. However, the various aspects of the association between obesity and infection have not been reviewed. Thus, we reviewed the relevant literature focusing on clinical aspects of this association. Obesity has a clear but not yet precisely defined effect on the immune response through a variety of immune mediators, which leads to susceptibility to infections. Data on the incidence and outcome of specific infections, especially community-acquired infections, in obese people are so far limited. The available data suggest that obese people are more likely than people of normal weight to develop infections of various types including postoperative infections and other nosocomial infections, as well to develop serious complications of common infections. Large prospective studies are required to further define the burden of infectious morbidity and mortality conferred by obesity.

Introduction

The US National Institutes of Health and the WHO classify people regarding their body weight according to the body mass index (BMI), calculated as body weight (in kg) divided by the body height (in m) squared. Overweight, obese, and morbidly obese people are those with a BMI 25–30 kg/m², 30–40 kg/m², and greater than 40 kg/m², respectively. Normal weight and underweight people are those with BMI 20–25 kg/m² and less than 20 kg/m², respectively. Obesity, through various well-described pathophysiological interactions, increases the risk of cardiovascular and other diseases, compromises the quality of life, and increases overall mortality.[1,2] However, the various aspects of the association between obesity and infection have not been reviewed.

We review the available evidence regarding the various aspects of the association between obesity and infection, including obesity-related mechanisms that lead to predisposition to infections, the epidemiology of nosocomial and community-acquired infections in the obese population, and special issues related to the management of infections in the obese patient. We briefly review infections that are the result of procedures for the management of obesity. In addition, we mention the evidence for the reverse association between obesity and infection—namely, the possibility that infectious agents may have an aetiological role in obesity, an idea known as "infectobesity".

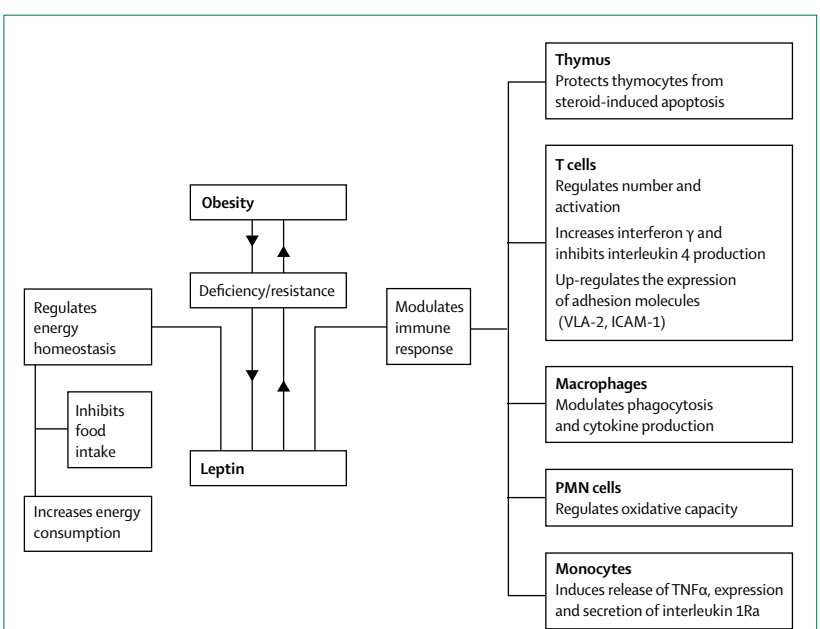

Figure: **Leptin has a key role in linking nutritional state to the immune response**
Leptin regulates energy homeostasis by reducing food intake and increasing energy consumption and modulates the immune response to inflammatory/infectious stimuli. Leptin deficiency has been associated with susceptibility to infections in animals as well as in human beings. PMN=polymorphonuclear, TNF=tumour necrosis factor.

Mechanisms that predispose obese patients to infection

It has been recently recognised that the adipose tissue participates actively in inflammation and immunity, producing and releasing a variety of proinflammatory and anti-inflammatory factors, including the well-studied adipokines leptin and adiponectin, as well as cytokines and chemokines.[3] Adiponectin is potently immunosuppressive,[4] while leptin activates polymorphonuclear neutrophils,[5] exerts proliferative and anti-apoptotic activities on T lymphocytes, affects cytokine production, regulates the activation of monocytes/macrophages, and contributes to wound healing (figure).[6] Leptin induction seems to be a protective component of the immune response and genetic leptin deficiency in human beings has been associated with increased mortality due to infections.[7] The genetic defect of leptin-deficient *ob/ob* mice, which causes a severe obese phenotype, is associated with increased sensitivity to proinflammatory monocyte/macrophage-activating stimuli and impairment of phagocytic functions, as well as reduced T-cell function.[8] These mutant mice are highly susceptible to bacterial infections with, for example, *Listeria monocytogenes, Klebsiella pneumoniae*, etc.[9,10]

Adipocytes participate in fatty acid composition and control of lipolysis. Prolonged, low-level immune stimulation induces hypertrophy of adipose tissue that partly emancipates the immune system from fluctuations in the abundance and composition of dietary lipids.[11] Increased susceptibility to infections in obese patients may be related to decreased availability of arginine and

glutamine, resulting in decreased tumour necrosis factor (TNF)α production and increased nitric oxide release, as has been noted in obese rats.[12] On the other hand, sepsis-related morbidity in obese patients may reflect microvascular inflammation and thrombosis. In an experimental model, it was shown that obese mice exhibited an exaggerated proinflammatory and thrombogenic response to the same stimuli than their lean counterparts.[13]

In another animal model comparing the ability of obese and lean Zucker rats to clear candida from the circulation and tissues, it was shown that 9 days after intravenous injection of yeast suspension, obese rats carried a higher burden of yeasts, residing particularly in the kidney.[14] However, whether these findings apply to human beings remains to be studied.

The connection of proinflammatory states of obesity with the risk of infection has not been precisely determined, but leptin seems to have an important role in the immune response. Leptin deficiency has been associated with susceptibility to infections in animals as well as in human beings. More studies are needed in leptin-resistant obese human beings. Additional research is needed to clarify whether various interventions such as weight loss, exercise, or nutrient supplementation could help to ameliorate the alterations in immunity of obese individuals.[15]

Obesity and clinical infections

Nosocomial infections

The incidence of nosocomial infections in overweight and obese patients is increased compared with normal weight patients. Routine medical care of obese patients in everyday practice may present certain difficulties. In some instances usual diagnostic and treatment procedures must be modified. For example, some computed tomography equipment cannot accommodate obese patients above a certain weight limit. Routine care of non-ambulatory morbidly obese patients (eg, lifting and bathing) requires adequate and trained staff. Risk of skin breakdown is increased due to immobility caused by underlying disease, improperly sized rooms and equipment, and inadequate staff numbers or inadequately trained staff. Due to these difficulties, obese patients may experience a prolonged length of stay, thus increasing their risk of acquiring a nosocomial infection.[16–18] Most available data concern obese surgical patients and reveal a high incidence of clinically relevant nosocomial infections such as pneumonia, wound infection, bacteraemia, and *Clostridium difficile* colitis.[19]

Surgical site infections

Surgical-site infections following various surgical procedures are more common in obese compared with non-obese patients.[20] Local changes, such as an increase in adipose tissue, increase in local tissue trauma related to retraction, lengthened operative time, and disturbance of body homeostatic balance, may contribute to the increased incidence of surgical-site infections caused by obesity.[21] Subcutaneous tissue oxygenation is reduced in obese patients and this may predispose to wound infection, particularly after laparoscopic procedures.[22] Obesity was found to be independently associated with *Staphylococcus aureus* nasal carriage, which is a risk factor for surgical-site infections.[23] Obese women undergoing elective hysterectomy for benign conditions (dysfunctional bleeding or fibromas) had an increased risk of surgical-site infections, particularly if no antimicrobial prophylaxis had been administered.[24] Morbid obesity was recognised as an independent risk factor for surgical-site infections after spinal surgery (laminectomy or spinal fusion).[25,26]

Obese patients, burdened with a high cardiovascular risk, frequently undergo cardiothoracic surgery. The incidence of mediastinitis as well as of deep and superficial sternal infection after coronary artery bypass grafting is increased in obese compared with normal weight patients.[27–29] In a large retrospective study of

Reference	Number of patients	Comparison groups according to BMI (kg/m²)	Type of infection	Odds ratio (95% CI)
Crabtree et al[28]	4004	Obese *vs* non-obese*	Superficial sternal infection Deep sternal infection	1·09 (1·06–1·12) 1·08 (1·04–1·11)
Löfgren et al[24]	3267	<25 25–28 >28	Postoperative infection	1·0 0·8 (0·6–1·1) 1·3 (1·0–1·8)
Lilienfeld et al[29]	1204	Obese *vs* non-obese*	Wound infection and/or endocarditis following coronary artery bypass grafting	6·2 (p<0·05)
Potapov et al[30]	22 666	26–26·9 28–28·9 34–34·9 ≥36	Infection following coronary artery bypass grafting	1·0 1·2 (1·1–1·7)† 1·8 (1·1–2·6) 3·7 (2·7–4·8)
Olsen et al[25]	222	Morbid obesity *vs* non-morbid obesity‡	Surgical-site infection following spinal surgery	5·2 (1·9–14·2)
Vilar-Compte et al[20]	3372	Obese *vs* non-obese*	Surgical-site infections	1·8 (1·1–2·7)
Harrington et al[31]	4474	Obese *vs* non-obese*	Surgical-site infection following coronary artery bypass grafting	1·8 (1·4–2·3)

*Obese=BMI≥30 kg/m². †Odds ratios were extracted from the relevant figure of the article (the exact odds ratios were not available). ‡Morbid obesity=BMI≥35kg/m².

Table: **Risk of nosocomial infections in obese surgical patients**

22 666 consecutive patients following coronary artery bypass grafting, the lowest risk for postoperative infection was recorded in patients with BMI between 26–27 kg/m², whereas in overweight patients (BMI≥28 kg/m²) the risk was significantly raised (p<0·01).[30] In addition, in an Australian large multicentre prospective study, obesity was found to be an independent predictor of surgical-site infections following coronary artery bypass grafting, conferring a higher risk even compared with diabetes mellitus (odds ratio [OR] 1·8 *vs* 1·6, respectively).[31] Reports regarding the comparative incidence of nosocomial infections in obese surgical patients are summarised in the table.

Odontogenic infections

Obesity may be associated with the acquisition and persistence of specific bacteria in the oral flora, since it is often related to increased sugar consumption and other comorbidities such as diabetes mellitus. It has been reported that obesity is a predisposing factor for periodontal disease, especially among young individuals.[32,33] An association between high body weight and dental caries was recorded even in elementary school children.[34] An experimental study found that there is a positive correlation between BMI and TNFα concentration in gingival crevicular fluid of young individuals; these data imply that obesity may contribute to periodontal inflammation through a systemic effect.[35] Given that suppurative orofacial infections are usually preceded by dental caries or periodontal disease, whether obese patients are predisposed to orofacial infections other than dental caries and periodontitis should be further examined.

Respiratory infections

Obesity can profoundly alter lung mechanics, diminish exercise capacity, augment airway resistance resulting in an increased work of breathing, and influence respiratory muscle function, control of breathing, and gas exchange. Moreover, obesity is closely associated with obstructive sleep apnoea, a syndrome often accompanied by an increased risk for aspiration[36,37] as well as chronic inflammation of the upper and the lower respiratory tract.[38,39]

The risk for aspiration pneumonia is increased in hospitalised obese compared with normal weight patients, especially in the postoperative period. This is postulated to be due to the higher volume of gastric fluid, lower pH of the gastric fluid in the fasting state, increased intra-abdominal pressure, and higher incidence of gastro-oesophageal reflux in obese patients compared with normal weight patients.[40,41] These data suggest that there is need of positioning the obese patient in the semi-upright position during hospitalisation.[42]

In addition, there are interesting published data about the incidence of community-acquired respiratory tract infections in obese patients. In a large population study of 26 429 men aged 44–79 years from the Health Professionals Follow-up Study[43] and 78 062 women aged 27–44 years from the Nurses' Health Study II,[44] the BMI was shown to be directly associated with an increased risk of community-acquired pneumonia among women. Additionally, women who gained weight (18 kg or more) during follow-up had a nearly two-fold increase of the risk for community-acquired pneumonia than those who maintained their weight.[45]

Less information can be found in the literature about the incidence of respiratory tract infections in obese children. The factors predisposing to recurrent acute respiratory infections were investigated in a Polish cross-sectional field study of 1129 9-year-old school children. Susceptibility to acute respiratory infections was significantly associated with BMI: overweight children (BMI≥20 kg/m²) had twice the risk of infection than children with a lower BMI (OR 2·02, 95% CI 1·13–3·59).[46] In another report by the same authors, it was shown that, apart from BMI, low or moderate physical exercise was independently associated with recurrent respiratory tract infections in children.[47]

Gastrointestinal, liver, and biliary infections

It might be expected that accumulated fat, with its mechanical and endocrine properties, may influence gastrointestinal, liver, and biliary functions in the obese patient, in turn leading to predisposition to infection. Obesity has been suggested to be associated with *Helicobacter pylori* colonisation,[48] but in more recent reports, the observed difference did not reach statistical significance after adjustment for age.[49]

Obesity is a well-recognised risk factor for the development of steatosis in patients with chronic hepatitis C infection and markers of obesity such as the BMI and waist-to-hip ratio correlate with the extent of steatosis in this population[50,51] independently of the presence of diabetes.[52] Steatosis is probably associated with decreased plasma adiponectin levels.[53,54] The degree of steatosis and fibrosis both tend to increase with increasing BMI, independently of the presence of diabetes mellitus.[51,52] Steatosis affects the natural course of hepatitis C infection: it is associated with fibrosis, it impairs the response to antiviral treatment, and might constitute a risk factor for the development of hepatocellular carcinoma. Consequently, hepatitis C infection progresses more rapidly in obese compared with non-obese patients.[54,55]

Obese patients are also at increased risk for biliary disease and its infectious complications both by being overweight and by reducing their body weight with extreme diets.[56,57] However, whether the incidence of biliary tract infections is higher in obese compared with non-obese patients with biliary disease remains to be studied. The available data suggest that acute pancreatitis is more often complicated by infection in obese than non-obese patients.[58]

Also, in a large cohort study comprising 10 709 peritoneal dialysis patients with a 12-year follow-

up, a higher BMI was associated with a shorter time to first peritonitis episode, independent of other risk factors (hazard ratio 1·08 for each 5 kg/m² increase in BMI, 95%CI 1·04–1·12, p<0·001).[59] Nevertheless, it has been debated in several reports whether obesity has an independent effect on the overall outcome in peritoneal dialysis patients.[60–62]

Urogenital infections

The available data regarding urinary tract infections in obese patients mainly concern women, probably because of the increased incidence of urinary tract infections in this population. 1732 white, married 25–39-year-old women were studied throughout England and Scotland in the period 1968–74 to assess the possible association between various factors including obesity and urinary tract infections.[63] This study showed that the risk of first referral to hospital for a urinary tract infection decreased with age, while it was higher in non-obese than in obese women, in nulliparous compared with parous women, and in current users of the diaphragm compared with current users of other methods or no method of contraception. The observed negative association between obesity and urinary tract infection was unexpected and independent of the effect of age, parity, and diaphragm use. To explain these findings, it has been postulated that obese women may be less susceptible to trauma to the genital area during sex because the adipose tissue offers them protection. Furthermore, increased oestrogenisation in obese women, resulting from peripheral conversion of androstenedione to estrone, may exert some beneficial effect on the urinary tract, thus reducing the susceptibility to infection.[63] However, it should be emphasised that a lower frequency of intercourse in obese compared with lean women[64] could, at least in part, account for the above-mentioned negative association between obesity and incidence of urinary tract infections.

As far as obesity during pregnancy and the postpartum period is concerned, women with BMI over 30 kg/m² are at an increased risk of postpartum urinary tract infections. In a large population-based observational study of 60 167 deliveries in Wales, it was shown that postpartum urinary tract infections are nearly twice more common in obese than non-obese women (OR 1·9, 95% CI 1·1–3·4).[65]

Skin infections

A higher incidence of cutaneous infections has been reported in obese compared with non-obese patients. Intertigo, candidiasis, furunculosis, erythrasma, tinea cruris, and folliculitis are frequent skin infections among obese patients, while cellulitis, necrotising fasciitis, and gas gangrene are also occasionally encountered.[66,67] Fungal foot infections—eg, tinea pedis and toenail onychomycosis—are more common in obese than non-obese patients[68] and in the long run may predispose the affected patients to acute bacterial cellulitis of the lower extremities.[69] Hidradenitis suppurativa is more prevalent in obese than normal weight patients.[70]

Pilonidal sinus disease is common in adults, but it may also develop in adolescents and children. Although there is not enough evidence that obesity predisposes to pilonidal sinus disease,[71,72] it appears that obesity is a risk factor for wound infection after surgical management of pilonidal sinus.[73]

According to observations in human beings and experiments in animals, wound healing is partly regulated by leptin. Chronic wounds are associated with prolonged and dysregulated inflammation and macrophages infiltrating these lesions seem to be only partly activated. However, it remains unclear whether topical or systemic leptin administration in chronic wounds would accelerate healing and limit bacterial colonisation and infection.[74–76] Clinical observations in diabetic patients imply a strong correlation between morbid obesity and infected foot ulcers.[77] Furthermore, it was shown in a prospective observational study of 330 patients with venous stasis leg ulcers that a high BMI was linearly associated with poor healing of the ulcers.[78]

Bone and joint infections

There are no published data regarding the comparative incidence of bacterial bone and joint infections in obese and non-obese patients. However, there are data suggesting that these infections can become rapidly progressive, involving adjacent structures, and become life threatening in obese patients, especially if diabetes mellitus is an associated comorbidity.[79] Whether obesity is independently associated with serious bone and joint infections after adjustment for diabetes needs to be clarified.

Obesity and infections in special populations

Infections in critically ill patients

Obese and morbidly obese patients in the intensive care unit setting are reported to have higher mortality compared with normal weight patients.[80,81] A matched cohort study compared 170 mechanically ventilated patients with BMI over 30 kg/m² with 170 normal weight mechanically ventilated patients. The obese patients had increased intensive care unit mortality (OR 2·1, 95% CI 1·2–3·6), explained by a higher risk of complications (OR 4·0, 95% CI 1·4–11·8), including sepsis, ventilator-associated pneumonia, and central venous catheter-related infections.[80] Another retrospective study, which compared 117 morbidly obese patients with BMI over 40 kg/m² with 132 non-obese patients (BMI<30 kg/m²), showed an increased morbidity and mortality in the morbidly obese group. There was a trend for a higher rate of catheter-related infections in the morbidly obese compared with the non-obese group, but the difference did not reach statistical significance (10% *vs* 3%, respectively, p=0·1).[80] However, the extent to which diabetes contributed to the reported mortality, and particularly its infectious part, was not clarified in the above studies.[80,81]

The greater number of skin punctures during central venous catheter insertion and, in particular, the extended duration of the presence of central venous catheters due to the difficulty in obtaining and maintaining peripheral venous access seem to account for the higher frequency of catheter-related infections in obese critically ill patients.[82] In addition, a prospective study of 1772 critically ill trauma patients showed that obesity is highly predictive of increased duration of the presence of a urinary catheter and thus urinary tract infections.[83]

Infections in patients with malignancy

There are only a few reports regarding the influence of the body weight on the incidence of neutropenia-related infections. A retrospective study of 768 children with acute myeloid leukaemia compared survival rates in children who at diagnosis were underweight (BMI≤10th percentile), overweight (BMI≥95th percentile), or middleweight (BMI between the 11th and 94th percentiles). It was shown that overweight children experienced excess treatment-related mortality compared with middleweight ones (hazard ratio 3·49, 95% CI 1·99–6·10, p<0·001). Mortality was particularly due to infections occurring after the first two courses of chemotherapy.[84]

Another relevant issue that may lead to problems in obese patients with malignant diseases is that most chemotherapy trials specify doses of cytotoxic drugs normalised to the body surface area. However, the use of the body surface area in determining chemotherapy dosing, particularly in obese patients, remains controversial. Subsequently, there is need for prospective studies of chemotherapy pharmacokinetics addressing the issue of optimal chemotherapy dosing, with implications regarding effectiveness and toxicity, including infectious complications, in the obese population.[85]

Post-transplant infections

Obesity seems to have an effect on the incidence of infections after solid organ or bone marrow transplantation. Pancreas transplantation is more often complicated by intra-abdominal infection if the donor is obese. Pancreas grafts from obese donors are postulated to be more susceptible to ischaemia-reperfusion injury, resulting in abscess formation.[86,87] In addition, simultaneous pancreas and kidney transplantation in obese recipients was associated with a significantly higher incidence of duodenojejunal anastomotic leaks (p=0·012).[88]

Of interest, obesity appears to favour prognosis in recipients of allogeneic stem cell transplantation. In a Swedish study of 544 patients with haematological malignancies, it was observed that allogeneic stem cell recipients with BMI under 20 kg/m² had a higher incidence of alpha-haemolytic streptococcal septicaemia (p=0·005) than patients with BMI of 20 kg/m² or over, but the groups had a similar incidence of overall bacteraemia. The 5-year survival was 36%, 47%, and 55% in patients with low, normal, and high BMI, respectively. In this study, it was also shown with multivariate analysis that death was associated with BMI under 20 kg/m² (p=0·023).[89]

Obesity and HIV infection

Only a few studies have addressed the association of baseline obesity with the natural progression of HIV infection, the response to antiretroviral treatment, and other outcomes in HIV-infected patients. The effects of obesity on immune function, disease progression, and mortality were evaluated longitudinally in 125 HIV-1-seropositive drug users and 148 HIV-1-seronegative controls followed at a community clinic from 1992 to 1996, before administration of highly active antiretroviral therapy (HAART). At baseline, no significant immunological differences were observed among lean, non-obese, and obese groups. Over an 18-month period, an at least 25% decline in CD4 cell count was recorded in 60·5% of the non-obese HIV-1 seropositive patients compared with 18% of the obese patients (p<0·004). It should be noted that BMI was inversely associated with progression to death, an association that was found to be independent of the baseline CD4 count (p<0·02). These data suggest that mild-to-moderate obesity in HIV-1-infected chronic intravenous drug users favours survival.[90]

Another study in 871 HIV-infected women showed that a higher baseline BMI was inversely associated with a drop of the CD4 cell count below 200 cells per µL. Moreover, in analyses that incorporated time-varying BMI, underweight and normal weight women had an increased risk of development of clinical AIDS. In addition, underweight women had an increased risk of HIV-related death compared with obese women. These findings indicate that higher baseline BMI and increases in BMI are associated with less progression of the HIV infection.[91]

Infections following procedures for the management of obesity

Several procedures have been used in obese patients for the management of obesity itself and for the restoration of the accompanying cosmetic deformities. These procedures are sometimes complicated by infections caused by common or rare microorganisms.

Liposuction is a common cosmetic procedure. Infectious complications following liposuction have occasionally been reported and include subcutaneous abscesses, herpes zoster virus infection, necrotising fasciitis, and wound infection caused by rapidly growing mycobacteria.[92–100] Rare cases of toxic-shock syndrome have also been reported.[101]

Laparoscopic adjustable gastric banding is quite a popular surgical technique for the treatment of morbid obesity. Band infection is a relatively rare complication of this procedure that is usually secondary to band erosion. Moreover, severe band infection can be caused by any intra-abdominal source of sepsis (eg, diverticulitis) or by any infection causing bacteraemia. The treatment of choice

consists of band removal and antimicrobials, and is usually effective.[102–104]

Gastric bypass surgery done either as an open procedure or laparoscopically may be complicated by infection. Routine intra-operative peritoneal cultures have demonstrated frequent peritoneal contamination during laparoscopic gastric bypass.[105] Rare infections (eg, gastric actinomycosis[106]), or severe ones (eg, fulminant pneumococcal sepsis[107]) have occasionally been reported.

From the 1950s to the 1980s, many morbidly obese patients underwent jejunoileal bypass procedures for weight reduction. Bacterial overgrowth in the blind bowel loop caused secondary, extra-intestinal complications such as arthritis and vasculitis. The so-called "intestinal bypass syndrome" affected about 20% of patients treated with this surgical procedure. The underlying mechanisms of the syndrome are autoimmune, but it became apparent that enteric bacteria (eg, *Escherichia coli*) had an important role in tissue injury, the event initiating the autoimmune cascade.[108–110] Reduction of the intestinal flora with tetracycline or metronidazole has been proposed as therapy for the syndrome.[111] Apart from the well-characterised intestinal bypass syndrome, occasional pathogens can colonise the blind bowel loop and induce rare manifestations such as botulism.[112]

Management of infection in obese patients

Despite the growing prevalence of obesity worldwide, there are no well-established guidelines about the management of infections in obese patients, including specific recommendations regarding adjustment of dosage of therapy with antimicrobial agents, when necessary.

Several variables related to body weight have been used in pharmacokinetic studies in obese individuals, including body weight, lean body weight, ideal body weight, body surface area, BMI, fat-free mass, percent ideal body weight, adjusted body weight, and predicted normal body weight. However, there is still controversy regarding the single best descriptor of the influence of body size on both clearance and volume of distribution of various medications, including antimicrobial agents.[113]

The pharmacokinetics of many antimicrobials, including vancomycin and aminoglycosides, appears to be altered in obese patients. Obese patients show increased volume distribution and clearance for vancomycin, which correlate better with total body weight than with ideal body weight. Thus, vancomycin serum concentrations should be obtained in morbidly obese patients to ensure that the administered doses are adequate, because of the considerable pharmacokinetic variation in this population.[114] Dosage adjustments of vancomycin for morbidly obese patients with renal dysfunction require further study.[114] The volume distribution of aminoglycosides is also increased in obese compared with normal weight patients.[115] Thus, dosages of vancomycin and aminoglycosides may require an adjustment in obese patients, based on the estimated fraction of the excess body weight.

There are limited data regarding the pharmacokinetics of other classes of antimicrobial agents in obese individuals. The available information for cephalosporins suggests that dosages may need to be increased in obese compared with non-obese patients to attain similar serum and tissue concentrations in the two populations.[115] Serum concentrations of oral linezolid in obese patients with cellulitis were lower compared with those of healthy volunteers.[116]

As far as the management of viral infections in obese individuals are concerned, besides HIV infection, there are some published data regarding hepatitis C. Obesity seems to influence not only the progression but also the response to treatment of hepatitis C. Specifically, a BMI greater than 30 kg/m² was found to be an independent negative predictor of response to treatment of hepatitis C viral infection.[117] In particular, obesity-related insulin resistance correlated negatively with response to pegylated interferon plus ribavirin treatment for chronic hepatitis C.[118]

Obesity of infectious origin

Obesity of infectious origin is a concept that has been studied in animal models during the past two decades. Seven different pathogens (canine distemper virus, Rous-associated virus 7, Borna disease virus, scrapie agent, SMAM-1 avian adenovirus, and human adenoviruses Ad36 and Ad37) have been reported to cause obesity in animal models.[119,120] Canine distemper virus, a morbillivirus closely related to the human measles virus, was the first reported obesity-promoting virus, inducing hypothalamic damage to experimentally infected mice and leading to a significant increase in their body weight ($p<0·001$).[121–123] Rous-associated virus 7, an avian retrovirus, caused stunted growth, obesity, and hyperlipidaemia accompanied with fatty liver in chickens.[124]

Experimental infection with Borna disease virus, an RNA virus causing encephalomyelitis in horses and sheep, induced obesity in rats.[125] Scrapie agents, primarily causing a neurodegenerative disease in sheep and goats, were reported to induce obesity in mice and hamsters probably by interacting with the hypothalamic-pituitary-adrenal axis.[126,127] Additionally, three adenoviruses were reported to promote obesity through, at present, undefined mechanisms. Animals experimentally infected with SMAM-1, an avian adenovirus, or two human adenoviruses, Ad36 and Ad37, developed adiposity.[128] Notably, SMAM-1 and Ad36 were associated with obesity in human beings.[128,129] However, the relative contribution of these pathogens to human obesity is unknown. These data give a new perspective to the pathogenesis of obesity and imply an infectious origin, at least in some human beings.

Conclusions

Although obesity is a well-known risk factor for several morbid conditions, its relation to infection has not been adequately studied. The available evidence suggests that

Search strategy and selection criteria

We searched PubMed to identify English language articles on the association between obesity and infection. Relevant articles published between 1975 and 2005 were sought using the term "obesity" in combination with other terms including "immune system", "cellular immunity", "humoral immunity", "sepsis", "white blood cell", "cytokine", "chemotaxis", or "transplantation", as well as "obesity" in combination with various specific organ and system infections. To expand our search strategy, we repeated the above search by replacing the term "obesity" with the terms "BMI", "diabetes mellitus", and "metabolic syndrome". We also reviewed selected references contained in the identified articles. We focused on papers comparing the incidence of specific infections in obese and non-obese patients after adjustment for crucial confounding factors, especially diabetes mellitus. This was done because diabetes contributes to a large part of the overall morbidity and mortality of obese individuals and this might apply to infections as well.

infections of several organs and systems are more common in obese people than those of normal weight. However, the literature is so far lacking large epidemiological studies that could verify obvious or expected associations between obesity and infection and reject biased assumptions. In addition, it should be noted that several different definitions regarding the classification of the population in groups based on the BMI are used in the relevant publications, a fact that causes considerable problems in the synthesis of published data.

The question of whether the relation between obesity and infection is causal or simply an association generated by confounding factors such as diabetes mellitus cannot be easily answered. Large prospective studies are needed to further clarify which infections are related to obesity, and to what extent. Adjustment for confounding factors, especially diabetes mellitus, is essential. Moreover, relevant research efforts should also focus on obese children, where the available data are even more scarce compared with the adult population. Since obesity is a major epidemic of our times, preventing and treating at least the related infectious morbidity and mortality may be feasible and cost-effective.

Conflicts of interest

We declare that we have no conflicts of interest.

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