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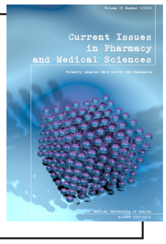

The impact of Body Mass Index (BMI) on mortality rates in patients with severe burns

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ABSTRACT

There is an increase in the number of obese patients in burn units. Obesity is strongly associated with metabolic syndrome and chronic diseases, including cardiovascular and gastrointestinal disorders and diabetes. However, there is evidence that moderate obesity and overweight have a potentially protective effect on mortality among severely burned patients. The "obesity paradox" may result from the protective effect of adipose tissue due to its thermal conductivity and the regenerative potential resulting from the presence of mesenchymal stem cells in the subcutaneous tissue. This review aims to summarize available data showing correlation between Body Mass Index (BMI; kg/m^2) and clinical outcome of the treatment of burns, including its impact on mortality. We pointed out direction of further research that should be conducted to more precisely examine the relationship between weight and course of treatment of burn patients. A systemic search was conducted of the relevant literature up to and including July 2024 – using database PubMed.

The presented articles confirm the J-shaped and U-shaped correlation between BMI and mortality in burn patients. Being overweight or moderately obese proved to be protective compared to having a normal BMI or more severe obesity. Obesity is undoubtedly associated with several adverse health effects and requires additional challenges for health care in the process of treating its undesirable effects. However, the presented articles prove that overweight and obesity can have a protective effect on patients with severe burns.

INTRODUCTION

Extensive burns are a life-threatening condition due to the loss of the skin barrier and, consequently, fluid loss, severe metabolic changes and infectious complications [1]. Burn injury is associated with a state of increased catabolism. Poor nutritional status and changes in the body composition of the burned patient may lead to impaired wound healing, organ dysfunction, increased susceptibility to infections and, ultimately, even to the death of the patient [2]. Hypermetabolism is a well-known but highly complex and multifaceted challenge to manage in patients with severe burns.

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While age and the extent of deep burns are key prognostic factors, outcomes can also be influenced by the patient's clinical condition and history of chronic diseases. According to the World Health Organization (WHO), 2.8 million deaths annually are linked to complications associated with being overweight or obese [3].

Obesity impacts quality of life and is associated with an increased risk of a wide range of health problems, including: diabetes mellitus type 2, insulin resistance, hypertension, cancers (colorectal cancer, breast cancer, kidney cancer), sleep apnea, infertility, renal disfunction. This list highlights the broad impact obesity can have on overall health. However, there is data to suggest that moderate obesity may have, paradoxically, a positive impact on mortality in ICU (Intensive Care Unit) patients and in patients with chronic illnesses. A J-shaped relationship between Body Mass Index (BMI) and mortality has been observed. Overweight and moderate obesity appear to offer a protective effect compared to a normal BMI or severe obesity, a phenomenon often referred to as the "obesity paradox", which remains debated and not fully understood [4]. The mechanisms behind the "obesity paradox" are not well understood, especially in burn patients, where data on the obesity paradox is limited.

BMI was introduced in 1972 as a standard indicator of body weight used for the comparative assessment of social groups and populations, because it correlates well with the body fat content and is rather independent of height [5]. WHO classification of BMI is presented in Table 1.

Table 1. WHO classification for obesity based on BMI [5]

Nutritional status	BMI Range (kg/m²)
Underweight	<18.5
Normal Weight	18.5-24.9
Pre-obesity	25.0-29.9
Obesity	30 or greater
Obesity Class I	30.0-34.9
Obesity Class II	35.0-39.9
Obesity Class III	>40.0

Explanations of the obesity paradox

The increased survival of patients classified as overweight and class I obese suggests a potential influence of adipose tissue on the treatment course and survival of burn patients [4]. Severe injuries, including burns, lead to elevation of catecholamines, which, in turn, stimulate lipolysis, which is proven by the increase in glycerol concentration [6]. Burns also induce a release of free fatty acids (FFAs), however, their level depends not only on lipolysis, but also on the rate of the re-estrification. Both FFAs and glycerol lead to the accumulation of fat in the liver and skeletal muscle [6]. Moreover, catabolism leads to transformation of subcutaneous white adipose tissue into brown adipose tissue (Browning effect) as mitochondrial uncoupling protein 1 (UCP-1) induces white adipocytes to adopt a brown adipocyte-like phenotype. Browning has negative consequences such as triggering futile triglyceride/FFA cycling, creating a lipotoxic environment, promoting insulin resistance and contributing to hypermetabolism and hepatic and skeletal muscle disfunction [7].

One of the explanation of better clinical outcome in obese and overweight is that a higher concentration of lipids could lead to increased binding of endotoxins or a greater reserve for adrenal steroid synthesis which help to overcome the hypercatabolic period [8].

Burn injury affects adipose tissue functionally and morphologically through changes in the secretion of adipokines. White adipose tissue (WAT), which contains adipocytes, preadipocytes, macrophages, endothelial cells, fibroblasts and leukocytes, is extremely dynamic. The secretory function of WAT is realized through the production and secretion of, among others, leptin, adiponectin, resistin, visfatin, apelin, vaspin, hepcidin, chemerin, TNF-α, IL-6, MCP-1, plasminogen activator inhibitor 1 (PAI-1), retinol binding protein (RBP-4) and omentin [9]. Serum leptin levels increase significantly 30 minutes after a burn, as it acts as a chemokine for macrophages. Leptin is found in increased amounts in obese people. Its deficiency is associated with increased susceptibility to infections caused by bacteria and viruses and the toxic effects of proinflammatory factors. Additionally, it stimulates keratinocytes and the proliferation and differentiation of epidermal cells and angiogenesis in the connective tissue.

Potential influence of stem cells in Burn Wound Healing

Mesenchymal stem cells (MSCs) which are located in SWAT (subcutaneous white adipose tissue) and in dermis in the area of hair follicles, sweat glands and nerve endings, hold significant promise as a therapeutic option for treating burns. They possess the capability to differentiate into multiple cell types, such as muscle, cartilage, fat and bone. In the context of wound healing, MSCs can directly differentiate and regenerate missing tissue components, including fibroblasts, keratinocytes and skin appendages [10]. Following a severe burn, numerous cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, interferon (IFN-γ), IL-6, and IL-12, are released [11]. MSCs, by stimulation of secretion of anti-inflammatory TNF, can greatly reduce excessive inflammation by limiting the proliferation of immune effector cells and modifying their cytokine production profile. Moreover, they stimulate angiogenesis by secreting growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), fibroblast growth factor (b-FGF), SDF-1, transforming growth factor β (TGF-β), angiopoietin-1 and growth differentiation factor 11 (GDF11) [12].

An experimental study on rats where stem cells were administered intravenously revealed reduced inflammation by regulating liver secretion of proteins and cytokines. Indeed, research undertaken in the People's Republic of China has revealed improvement in skin graft healing and reduction of scarring [13].

In conclusion, the exceptional therapeutic potential of MSCs for treating burns has been demonstrated in various clinical studies and rodent models. The analyzed studies may be one of the explanations for the "obesity paradox" in burn patients. However, there is a need to deepen the available studies to more thoroughly investigate the observed phenomenon. These findings suggest that during periods of catabolic stress, having energy reserves may provide a survival advantage for patients with BMIs between 25 and 34.9.

There are several theories proposed to explain the mechanisms behind the Obesity Paradox. One suggests the influence of the cytokines – which still remains complex and conflicting. Particularly emphasized is the role of leptin, the levels of which are elevated in obese individuals, and its deficiency has been linked to increased vulnerability to viral and bacterial infections, as well as greater sensitivity to proinflammatory stimuli. Elevated leptin levels in obese patients could offer an advantage in combating infections, which is particularly beneficial for burn patients who are already at heightened risk for infections [14]. Ghrelin known as 'hunger hormone', for example, reduces thermogenesis to manage energy expenditure [15].

The metabolic response in burns is divided into two phases: ebb phase and flow phase. The first is related to decreased metabolism. This phase can last from several hours, to several days. The second, flow phase, describes high oxygen consumption, increased resting energy expenditure, accelerated potassium and nitrogen loss, increased splanchnic blood flow and visceral oxygen consumption, and enhanced total cardiac output. Moreover, the body temperature rises as central thermoregulation shifts upward. Severe burns cause a dramatic increase in metabolism that can persist for up to a year after the burn [2].

Another possible explanation for the Obesity Paradox is that obese individuals possess larger metabolic and energy reserves. Among burn patients, malnutrition is often observed especially in those requiring intensive care. Obese patients might cope better with temporary malnutrition due to their excess energy stores.

Although BMI is not the ideal tool for this purpose, it remains the most widely accepted method for classification despite its limitations. It does not consider differences in fat mass due to sex, race, age, or fitness level, even among individuals with the same body weight [16].

During hospitalization, the body composition of the burn patient potentially changes. The proportion of muscle mass, the amount of fat tissue, and the total water content change, which may directly affect the course of burn treatment and the prognosis of severely burned patients. Therefore, research on the influence of BMI on the course of burn treatment should be extended to include measurement of changes in body composition both during hospitalization and after discharge from hospital.

There are also other issues related to overweight and obesity among burn patients that require further discussion. The assessment of the burn area in obese patients may be unreliable, which may lead to inadequate fluid therapy [17] and burn wound treatment may be more demanding in terms of human resources and medical equipment [18].

Summarizing the cited studies, the outcomes for obese burn patients vary based on the degree of obesity. Patients with mild obesity showed the most favorable outcomes, while those with morbid obesity experienced the poorest results. Although mild obesity appears to have a positive effect on recovery after a burn, morbid obesity has a harmful impact, worsening the prognosis for patients with severe thermal injuries.

MATERIAL AND METHODS

A search for the literature up to and including July 2024 was performed using PubMed. No language restrictions were placed on the search. The search terms were "burns" + "obesity paradox" and "BMI" and "stem cells". Titles, abstracts and full texts were filtered to select original articles and reviews describing relationship between patients' weight, course of treatment of burn patients and their mortality.

A total of 3173 papers were identified with the searching strategy. The records came from PubMed. Of these, 8 records were identified for quote "obesity paradox + burns" but only 3 met the criteria; "BMI + burns" found 645 articles with 10 relevant to the topic; for "stem cells + burns", there were 2520 matches and we included 7. Many records did not meet the inclusion criteria. 20 papers were included in the scoping review. Figure 1 is a graphical presentation of the screening process according to the PRISMA guidelines.

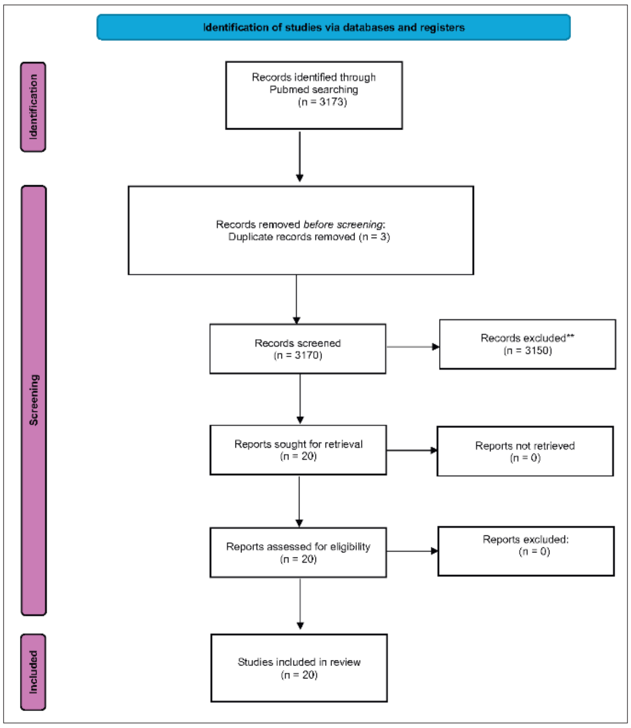

Figure 1. Graphical presentation of the screening process according to the PRISMA guidelines

The most important data from the articles are presented in the tables below. They describe the most crucial demographics, as well as burn and mortality data of the sub-groups defined by the BMI cut points (Table 2, Table 3, Table 5, Table 6) or by division into non-obese and obese (Table 4, Table 7). Due to the lack of uniform division and the variety of data presentation, each of the articles discussing the obesity paradox is presented in a separate table.

Table 2. Demographical, burn and mortality data of the sub-groups defined by the BMI cut points

Parameter	Burn patients with BMI <25 kg/m²	Burn patients with BMI 25-29,9 kg/m²	Burn patients with BMI 30-34,9 kg/m²	Burn patients with BMI 35-39,9 kg/m²	Burn patients with BMI >=40 kg/m²
Number of patients	30	65	35	14	4
Age (years)	42±24	42±19	40±16	42±18	51±12
Mortality (%)	13%	22%	20%	43%	75%
ABSI score	8±2	8±2	8±2	9±2	10±2
TBSA (%)	34±15%	33±16%	35±18%	43±20%	48±16%

Study conducted by Ghanem *et al.* [21]

Table 3. Demographical, burn and mortality data of the obese and nonobese patients

Parameter	Burn patients with BMI >=35 kg/m²	Burn patients with BMI <35 kg/m²
Number of patients	11	190
Age (years)	48.27 (30-78)	47.7 (17-89)
Mortality (%)	36.4	7.0
ABSI score	6.9 (3-10)	6.37 (2-16)
Baux index	70.5 (39-109)	65.4 (20-167)
TBSA (%)	22.3 (9-40)	18.49 (1-95)

Study conducted by Liodaki *et al.* [18]

Table 4. Number of patients included and mortality data of the obese and nonobese patients

Parameter	Nonobese	Obese
Number of patients	100,778	672
Mortality (%)	4%	10%

Study conducted by Carpenter *et al.* [22]

Table 5. Demographical, burn and mortality data of the sub-groups defined by the BMI cut points

Parameter	Burn patients with BMI <18,5 kg/m²	Burn patients with BMI 18,5-24,9 kg/m²	Burn patients with BMI 25-29,9 kg/m²	Burn patients with BMI 30-34,9 kg/m²	Burn patients with BMI >35 kg/m²
Number of patients	2.46%	28.31%	33.54%	20.92%	14.77%
Age (years)	50.56 (23.45)	46.72 (18.63)	48.72 (15.75)	46.63 (15.61)	42.87 (16.35)
TBSA (%)	9.50 (14.40)	8.03 (15.27)	7.50 (11.03)	7.84 (14.87)	8.06 (12.62)

Study conducted by Lester *et al.* [4]

Table 6. Number of patients included in the study and mortality data of the sub-groups defined by the BMI and age

Parameter	Burn patients with normal weight	Burn patients with obesity		
Number of patients	273	116		
Age (years)	28±21	28±20		
Mortality (%) Among adults	23%	Obese I	Obese II	Obese III
		12%	32%	64%
TBSA (%)	49±21	50±20		

Study conducted by Lin *et al.* [26]

Table 7. Demographical, burn and mortality data of the sub-groups defined by the BMI cut points

Parameter	Age <65 years		Age ≥65 years	
	Burn patients with BMI ≥ 25 kg/m²	Burn patients with BMI < 25 kg/m²	Burn patients with BMI ≥25 kg/m²	Burn patients with BMI <25 kg/m²
Number of patients	422		68	
Mortality (%)	9.2%	17.4%	33.3%	19.5%

Study conducted by Jeschke *et al.* [27]

DISCUSSION

Despite progress in prevention and treatment, burns remain a significant cause of morbidity and mortality globally. Several indices of burn severity are available. The most commonly used in clinical setting is the abbreviated burn severity index (ABSI) which consists of five variables: sex of patient, age, presence of inhalation injury, presence of full thickness burn, percentage of total body surface area burned [19]. However, this scale does not take into account the patient's body weight, while in surgical patients, obesity is recognized for elevating the risk of morbidity and mortality during the post-operative period [20]. In researching this issue, Ghanem *et al*. recorded ABSI score among patients assigned to the corresponding BMI group and then compared these with the observed mortality within that group. Following a burn with a TBSA greater than 15%, patients with a BMI of 35 kg/m² and 40 kg/m² had odds of death that were 3 times and 20 times higher, respectively, compared to patients with a normal BMI (less than 25 kg/m²). Their retrospective study revealed that a BMI of 35 kg/m² is a tilt point, beyond which mortality is higher than predicted [21]. Carpenter *et al*. found that obese patients were 2.6 times more likely to die as compared to those not classified as obese in the national burn database [22]. However, numerous studies have shown an “obesity paradox”, in which a higher Body Mass Index (BMI) seems to provide a protective effect on mortality. The “obesity paradox” or otherwise known as “reverse epidemiology” was initially identified by Fleischmann *et al*. in 1999. His study of 1,346 hemodialysis patients revealed that the 1-year survival rate was significantly higher in patients with a BMI over 27.5 kg/m² and lower in those with a BMI under 20, compared to patients of normal weight [23]. Research in Scotland demonstrated that that patients with class II obesity or higher and those with a normal weight (BMI between 20 and 25 kg/m²) face an increased risk of mortality within two years after a type 2 diabetes diagnosis, compared to those with a BMI in the overweight range (25 to 30 kg/m²) [24]. Bijjani, in turn, observed a comparative relationship where overweight and obesity significantly reduced the risk of mortality in elderly diabetic patients, although central obesity (waist circumference ≥95 cm) still remained a significant risk factor [25]. Similarly, there is evidence indicating a survival benefit for burn patients classified as overweight or obese. A retrospective study at American Burn Association Verified Burn Center on 519 adult patients indicated, for example, that the underweight patient group had higher odds of death compared to those of normal weight, while patients with class 1 obesity showed a statistically significant mortality benefit [4].

Another study conducted by scientists at the Fujian Medical University Union Hospital evidenced that the obesity paradox is present, but needs further clinical trials stratified by age. They divided patients into a younger group (18≤ age <65 years) and an older group (age ≥ 65 years). Accordingly, overweight and obesity provided a protective effect against burn injury in the younger group, but not in the older group [26]. Prospective research by Jeschke *et al*. revealed that patients with mild obesity had the best survival rates, while those who were morbidly obese experienced the highest mortality. Underweight patients were excluded from the analysis due to an insufficient number of participants [27].

CONCLUSIONS

The “obesity paradox” and the protective effect of higher BMI may be related to the content of white adipose tissue and adipose tissue-derived hormones, cytokines and chemokines. It may also result from the protective effect of adipose tissue due to its thermal conductivity (the body's thermal insulator) and the regenerative potential resulting from the presence of mesenchymal stem cells in the subcutaneous tissue. We conclude that further research on the observed correlation is necessary.

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