Excess Body Weight and Pancreatic Disease

Mats L. Wiese  Ali A. Aghdassi  Markus M. Lerch  Antje Steveling

Department of Medicine A, University Medicine Greifswald, Greifswald, Germany

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Abstract
Background: Excess body weight (EBW) is a risk factor for various acute and chronic conditions. Conversely, the “obesity paradox” suggests a protective effect of higher body weight on some disease outcomes. This article discusses the role of EBW along the disease continuum of pancreatitis and pancreatic cancer (PC) in terms of incidence and outcome. Summary: Comparison of findings is hampered by the use of different methods to assess EBW. Nevertheless, in acute pancreatitis (AP) and PC, EBW, especially visceral obesity, presents a distinct risk factor and predictor of a negative outcome. Findings of a protective effect likely result from nonconsideration of fat distribution or other confounders. Regarding chronic pancreatitis (CP), few studies indicate lower incidence and a better outcome with higher body mass. However, there is insufficient evidence to confirm the existence of an obesity paradox. The precise mechanisms of how EBW affects the disease continuum require further elucidation but both common and disease-specific effects seem involved. Key Messages: EBW is associated with higher incidence and a negative outcome in AP and PC. The association with CP is less conclusive. Thus, maintaining normal weight is advisable at any stage of the disease continuum.

Introduction
Excess body weight (EBW) generally implies an excessive accumulation of body fat, resulting from prolonged positive energy balance, that is, energy intake exceeding expenditure. If not halted, this gain of body fat initially leads to the development of overweight, and eventually obesity, which has been a pandemic-scale health problem for decades [1]. Although in the past it has been controversially discussed whether obesity is a chronic condition in itself [2], there is consensus that both overweight and obesity increase the risk of numerous noncommunicable diseases, most prominently metabolic and cardiovascular diseases as well as various types of cancer [3].

Just as EBW has been a constantly growing health-care issue, also the global burden of pancreatic diseases has increased over the past decades [4, 5]. In this context, acute pancreatitis (AP) presents the most common pancreatic disease, while pancreatic cancer (PC) is the most lethal one [6]. Clinical data accumulated from human studies confirm that AP, recurrent AP, and chronic pancreatitis (CP) form a disease continuum [7, 8]. Likewise, CP is a well-established risk factor of PC [9, 10]. Because of the parallel trends in prevalence and the established role of overweight and obesity as risk factors for numerous conditions, EBW presumably also increases the risk and worsens the outcome in these pancreatic diseases. However, in the past, the existence of a phenomenon termed “obesity paradox,” that is, obesity exerting a protective effect on an outcome in several chronic and acute diseases, has been proposed. Since then, it has been controversially discussed whether the obesity paradox is real or simply a product of residual confounding [11]. Therefore, assessing the role of EBW in the continuum of pan-
Acute Pancreatitis

The most common causes of AP are gallstones and alcohol abuse, accounting for approximately 60–80% of all cases [23]. In the remaining cases, actual causes remain unknown. Hypertriglyceridemia and certain medications, including drugs used for the treatment of metabolic diseases, for example, diabetes mellitus, are considered potential triggers of AP [24]. As associations with overweight and obesity have been shown for all these factors, it is a key question whether EBW is an independent risk factor for AP.

While in the past contradictory findings have been reported on the association of BMI and risk of AP [25–32], higher WC has been consistently associated with an increased risk [27, 29]. A recent meta-analysis [33] showed that both BMI and WC are associated with an increased risk of AP in a dose-response-related manner, with a risk elevation of 18% per 5-unit increment in BMI and 36% per 10 cm increase in WC. While in case of WC, the association was linear, for BMI, a nonlinear association with a steeper risk increase when BMI exceeded 30 kg/m² was found.

With regard to the AP outcome, the relation with EBW is more complex. Several meta-analyses confirm obesity based on BMI as a relevant prognostic factor for local and systemic complications [34–38] as well as severity and mortality in AP [34–39]. According to the most recent meta-analysis [39], obese patients have a 3.6-fold risk of severe AP and a 2.9-fold mortality risk. Two meta-analyses [36, 39] also addressed overweight as a risk factor. Although a higher risk of local complications and mortality was found than in normal-weight patients, the strength of these associations was weaker than for obesity.

In contrast, findings from studies that applied multivariate analysis suggest that EBW may not necessarily be an independent predictor of outcome [40–44]. Findings of an individual patient data meta-analysis [45] corroborate these findings. After adjustment for confounding variables, an independent association of obesity was only seen with development of organ and multiple organ failure but neither with local nor systemic complications nor mortality.

Although these findings question BMI as a suitable parameter to reflect the risks inherent to EBW in AP, they do not support the concept of an obesity paradox either. Evidence for the existence of such phenomenon is scarce anyway. As of today, only few studies [46–48] have suggested that an obesity paradox may exist in AP. In fact, this may be true under certain conditions. Several studies [49–52] showed visceral fat to be a stronger predictor of severe AP than BMI. Assuming that excessive visceral fat causes negative outcomes in AP, high BMI, in the absence of abdominal obesity, could exert a protective effect. The
fair correlation between BMI and visceral fat might explain the association between obesity based on BMI and negative outcomes in AP seen in large population-based studies and meta-analyses.

**Chronic Pancreatitis**

The number of studies investigating the association of EBW with the incidence of CP is very limited. A recent meta-analysis of prospective studies [33] found that a 5-unit increase in BMI lowered the risk of CP by 22%. Because only 2 studies [27, 28] were included in this analysis, with one [27] showing only a trend for this association, this finding should be considered with caution. Also, despite prospective study designs, it cannot be ruled out that reduced body weight at baseline might be the result of an early form of CP rather than a risk factor for disease.

Regarding the disease outcome, EBW may also have a protective effect, which is suggested for that reason alone that malnutrition, associated with increased morbidity and mortality, in CP is common and still challenging to treat [53]. However, there are only a few studies to actually support this hypothesis. For instance, a cohort study with a 30-year follow-up [54] found that CP patients with a BMI ≥25 kg/m² had a 40% lower mortality rate than patients with BMI <20 kg/m². In another study [55], BMI ≥23 kg/m² was associated with higher islet yields and better clinical outcomes in autologous islet cell transplantation. Last, a prospective investigation in pediatric patients [56] showed that overweight or obese children with CP were less likely to undergo medical or endoscopic treatment, develop exocrine pancreatic insufficiency, and require total pancreatectomy with islet autotransplantation. Despite these findings and the lack of data revealing an association of EBW with negative outcomes or mortality, there is insufficient evidence to confirm an obesity paradox in CP.

**Pancreatic Cancer**

The role of EBW in the development of PC presents as a clear-cut case. Several meta-analyses [57–59] and large pooled analyses [60–62] showed a dose-dependent association between BMI and PC risk, with a risk increase of approximately 10% per 5-unit increment in BMI. Among studies that also looked at anthropometric parameters, significant associations were found with WC [57] and waist-to-hip ratio [61, 62], especially in women, indicating a relevance of body fat distribution.

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**Fig. 1.** Biochemical mechanisms of how EBW affects pathogenesis and outcome in AP, CP, and PC. AP, acute pancreatitis; CP, chronic pancreatitis; PC, pancreatic cancer; EBW, excess body weight.
With respect to mortality, the association between EBW and PC is less conclusive. A recent meta-analysis [63] indicated that EBW at diagnosis or before PC surgery is not associated with survival. On the other hand, the same study found a dose-response relationship between adult BMI and mortality resulting in an 11% higher mortality risk per 5-unit increase in BMI. These findings could be explained by the rapid progression of PC accompanied by drastic weight loss commonly occurring before diagnosis or surgery. Unfortunately, weight loss as a confounding factor has not been included in the studies looking at BMI at diagnosis or before surgery. Another study [64] also investigated the effect of body fat distribution but found no association for either BMI or visceral fat with overall survival. For now, the effect of EBW on outcome in PC remains unclear. Despite its consuming character, so far, there is no evidence for the existence of an obesity paradox in PC.

**Mechanisms**

The mechanisms of how EBW effect pathogenesis and outcome in pancreatic diseases are still not fully understood. The most commonly proposed biochemical mechanisms are associated with an excessive accumulation of both visceral and intra-pancreatic fat (shown in Fig. 1). Low-grade inflammation and immune dysfunction mediated by adipokines, both locally and systemically, is likely to contribute to the pathogenesis of all 3 diseases [65]. Moreover, especially in AP, increased lipolysis seems to account for adverse outcomes by setting free unsaturated fatty acids that potentiate necrosis and worsen local and systemic inflammation [66] mediated by a storm of cytokines, predominantly IL-6, IL-8, and IL-10 [67]. Diet-induced visceral fat unsaturation has therefore recently been suggested as a driver of AP severity and potential explanation for an obesity paradox [68]. By contrast, in CP, intra-pancreatic adipocytes are surrounded by fibrotic tissue, which limits lipolysis and, thus, ameliorates severity of acute exacerbations in CP [69]. This could at least partially explain the observation of an improved outcome in patients with EBW. Last, especially in PC, hormonal effects of adipose tissue seem to be involved in pathogenesis. Obesity and BMI have been associated with increased levels of insulin and insulin-like growth factor 1, which may promote pancreatic carcinogenesis by modulation of cell proliferation, apoptosis, and angiogenesis [70]. In addition, also leptin, primarily synthesized in adipocytes, has been found to enhance the invasion of PC through an increase in matrix metalloproteinase-13 production [71]. Pancreatic steatosis, resulting from progressive fatty infiltration, may also contribute to carcinogenesis by tissue remodeling and fibroinflammatory reactions [72].

Overall, the observed associations of EBW with both AP and PC suggest similar mechanisms caused by EBW that include the induction of a pro-inflammatory microenvironment in both diseases. Although CP is a known risk factor of PC, there are only a relatively small number of CP patients who eventually develop PC, which may explain that pathogenic factors for cancer development are different to chronic inflammation. However, acknowledging the lack of convincing mechanistic explanations, the alleged inverse association between EBW and CP should be considered even more cautiously.

**Conclusion**

The role of EBW along the continuum of pancreatic diseases is ambiguous. For AP and PC, there is convincing evidence that EBW, especially in the form of visceral obesity, increases risk and worsens the outcome. Conversely, limited data on CP suggest a protective effect. The precise mechanisms of how EBW impacts pancreatic disease require further investigation, but there seem to be both common and disease-specific effects. To reduce the risk of progression, prevention should start at the earliest stage of disease. Therefore, maintaining normal-weight stands as a recommendation that is universally applicable along the continuum of pancreatic disease.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

M.L.W., A.A.A., M.M.L., and A.S. conceived and drafted the manuscript. All the authors approved the final version of the manuscript, including the authorship list.
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