DISCOVER THE RELATIONSHIP BETWEEN EXCESS BODY WEIGHT AND THE DEVELOPMENT OF PANCREATITIS, INCLUDING THE MECHANISMS THROUGH WHICH EXCESS ADIPOSE TISSUE MAY LEAD TO PANCREATIC INFLAMMATION

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ABSTRACT

Background: A number of acute and chronic illnesses are at risk due to excess body weight (EBW). On the other hand, the "obesity paradox" contends that larger body weight may protect against some illness outcomes.
Objective: The impact of EBW on the incidence and course of the pancreatitis and the pancreatic cancer (PC) is discussed in this article. The use of several EBW assessment techniques makes it difficult to compare results. However, EBW, particularly the visceral obesity, is separate risk factor and the predictor of the poor outcome in the acute pancreatitis (AP) and the PC.
Results: Findings suggesting a protective effect are probably the result of not taking fat distribution or other variables into account. Few research on chronic pancreatitis (CP) suggest that increased body mass is associated with a lower incidence and better prognosis. To prove the existence of an obesity paradox, however, there is not enough supporting data. It is yet unclear exactly how EBW influences the disease continuum, although both general and disease-specific effects appear to be at play.
Conclusion: In AP and PC, EBW is linked to a higher incidence and a bad result. Less proof exists for the CP connection. Therefore, it is advised to maintain a healthy weight throughout the course of the condition.

Keywords: Pancreatitis, Excess Adipose Tissue, Excess Body Weight, EBW Pancreatic Inflammation

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INTRODUCTION

A prolonged positive energy balance, or when energy intake exceeds energy expenditure, results in an abnormal buildup of body fat, which is what is meant by the term "excess body weight" (EBW). If the increase in body fat is not stopped, it first results in the overweight and then the obesity, which had been the major public health issue from the decades.[1] There was agreement that both the obesity and overweight increase risk of the wide range of the noncommunicable diseases, mostly cardiovascular and metabolic diseases and different types of the cancer.[2] Obesity has historically debated as to whether it is a chronic condition in and of itself.[3] The burden globally of pancreatic illnesses had grown over from few decades, just like EBW had been a continuously expanding issue of health care.[4] Acute pancreatitis is most prevalent pancreatic disease in this situation, whereas pancreatic cancer is most fatal one.[5] The existence of a continuum between acute pancreatitis (AP), recurrent AP, and chronic pancreatitis (CP) is confirmed by clinical data gathered from human research.[6] Similarly, CP is the recognised risk factor for the PC.[7] EBW certainly also worsens the results and raises the risk in various pancreatic disorders due to concurrent growth in the prevalence and documented involvement of the overweight and the obesity as the risk factors for the several conditions.[8] A phenomenon known as the "obesity paradox," in which obesity protects against the outcomes of various chronic and the acute diseases, had been hypothesised in the past. Since then, there has been debate about whether the obesity paradox actually exists or if it is just a result of the residual confounding.[9] Evaluating the involvement of the EBW in spectrum of the pancreatic disorders is therefore quite appealing. What are incidence and outcome effects, as well as the underlying mechanisms? This paper answers these queries by summarising the data supporting the involvement of the EBW in the AP, the CP, and the PC respectively.

MEASURES OF THE EBW

As the use of various approaches can make it difficult to compare the results of different studies, certain methodological issues regarding the assessment of EBW are suggested. In addition, the method used and the disease being studied may have an impact on how the results are interpreted. How to most effectively assess EBW is a question that has no clear solution. There are numerous approaches, and each has advantages and disadvantages. The Body mass index is arguably most established metric because it is simple to measure, even in the large-scale research studies, and have shown to be reliable indicator of unfavourable results connected to the EBW in numerous studies.[10] Overweight was indicated by the BMI between 25.0 and 30.0 kg/m2, and the obesity is indicated by the values higher than 30 kgm^{-2}. However, lower cutoff criteria for Asian populations, i.e., 23 and 27.50 kgm^{-2}, has been determined to signify the enhanced risk of the EBW.[11] Aside from challenge of the establishing suitable cut-off points for the certain populations, the BMI falls short while failing to take into consideration fat distribution or body composition. Regarding latter, visceral fat, or much more specifically abdominal fat, is associated with both chronic disorders as well as unfavourable outcomes in the conditions that are currently being treated.[12] Therefore, other anthropometric measurements, such as waist-to-hip ratio, or waist circumference (WC) which had demonstrated an extra predictive value for the variety of diseases, were usually used in investigations on large-scale for a more precise assessment.[11] These techniques, however, do not offer a precise estimation of the body fat stores. Although there were non-invasive approaches for the assessments, such as hydrostatic weighing or bioelectrical impedance analysis, these methods have drawbacks that prevent their use in settings of the larger study. Additionally, none of these techniques adequately account for visceral obesity in terms of fat distribution.[13] In contrast, imaging methods including computed tomography, magnetic resonance imaging, and dual-energy X-ray absorptiometry measure both the amount and the distribution of the body fat. Though, because the imaging methods also have the drawbacks, such as radiation exposure, the need for highly skilled operators, or expensive costs, they have only lately become increasingly prevalent outside of clinical settings.[14]

ACUTE PANCREATITIS

Gallstones and alcohol consumption are the most frequent causes of AP, accounting for 60–80% of all cases.[15] The real causes of the remaining cases are frequently still a mystery. Potential AP triggers include hypertriglyceridemia and a few medicines, such as those prescribed to treat metabolic disorders like diabetes mellitus.[16] The question of whether the EBW is the independent risk factor for the AP is crucial given that relationships with overweight and/or obesity have been demonstrated for all of these categories.[17] While conflicting results on the relationship between the BMI and the risk of AP have previously been reported, enhance the WC had consistently been linked to the enhance

risk.[18] According to the previous meta-analysis, there is dose-related relationship between the WC and BMI and an elevated risk of AP, with the risk rising by 18% for the every 5-unit increment in the BMI and by 36% for every 10 cm rise in the WC. While the relationship between WC and BMI was linear in the case of WC, a nonlinear relationship was discovered with the higher risk rise when the BMI had exceeded 30 kgm^{-2}. The relationship between the AP result and EBW is more complicated. Numerous meta-analyses support the predictive value of obesity based on BMI for mortality and severity in the AP as well as for systemic and local complications.[18,19] The previous meta-analysis found that the obese patients had 3.6-fold increased chance of developing the severe AP and the 2.9-fold increased risk of dying. As a risk factor, overweight was also discussed in two meta-analyses.[18,20] Despite the fact that patients who were normal weight had the higher risk of the mortality and local complications these relationships were not as strong as those for obese patients.

Figure 1. Pancreatitis

The results of the studies that used the multi-variate analysis, however, indicate that the EBW might not always be the independent predictor of the outcome. These findings are supported by the results of the meta-analysis data of individual patient.[19,20] After adjusting for the confounding factors, the independent connection between the obesity and the development of the organ and the multiple organ failure was only seen; neither systemic nor local complications nor death were linked to obesity. These data do not support the idea of an obese paradox, even though they cast doubt on BMI as a metric that accurately reflects the dangers associated with EBW in AP. Even still, there isn't much evidence to support its existence. Only a few research to date have raised the possibility that the obesity paradox could be exist in the AP. In truth, depending on the situation, this might be accurate. Visceral fat was found to be the better predictor of the severe AP than the BMI in several trials.[17] High BMI may act as a protective factor in absence of the abdominal obesity, assuming that substantial visceral fat has detrimental effects on AP.

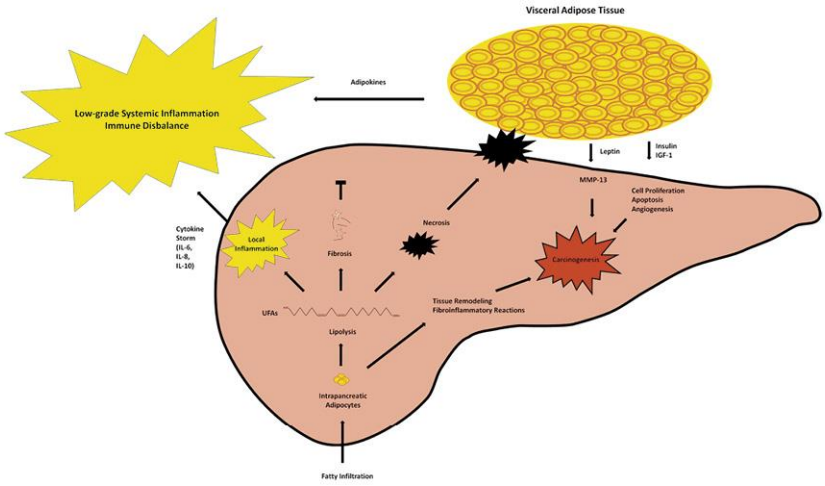

Figure 2. Mechanism

The link between the obesity which is based on the BMI and the poor outcomes in the AP shown in significant population-based meta-analyses and study may be explained by fair correlation between the visceral fat and BMI.

CHRONIC PANCREATITIS

There are very few research examining the relationship between EBW and the prevalence of CP. According to a previous meta-analysis of the prospective research studies, the 5-unit rise in the BMI decreased incidence of the CP by the 22%.[21] This finding needs to be interpreted cautiously because the two studies were comprised in the analysis, and one only revealed the trend for this relation. Additionally, despite of the prospective designs of study, it cann't be completely ruled out that the lower baseline body weight can be a marker of the earlier stage of the CP rather than the risk factor of the disease.[22] It is hypothesised for this reason alone—that malnutrition, which is prevalent and yet difficult to cure in CP and is related with higher morbidity and mortality—alone that EBW may also have a protective impact with regard to the course of the disease. However, there aren't many research that genuinely back up this theory.[23] For example, cohort research with a 30-year follow-up discovered that the death rate for CP patients with a BMI of 25 $kgm^{-2}$was 40% lower than that of patients with a BMI of 20 kgm^{-2}. In a different study, BMI 23.0 kgm^{-2} was linked to better clinical outcomes and higher islet yields in autologous islet cell transplants. The last finding was that the obese and the overweight children having CP are less likely to get the endoscopic or medical care, develop the exocrine pancreatic insufficiency, or need a total pancreas-tectomy having islet auto-transplantation. In spite of these results and dearth of the information linking EBW to unfavourable outcomes or death, there is inadequate proof of the obesity paradox in the CP.

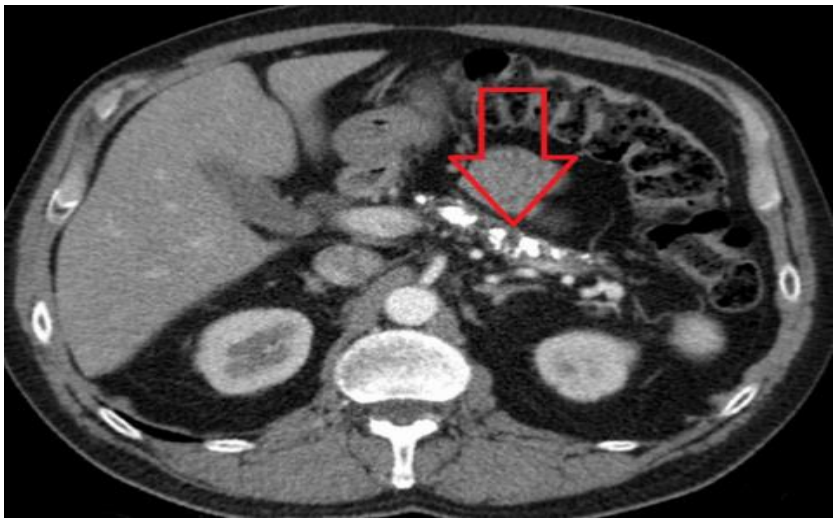

Figure 3. Chronic pancreatitis

PANCREATIC CANCER

The contribution of the EBW to creation of the PC is an obvious example. The dose-dependent link between the PC and BMI risk was shown in the various meta-analyses as well as sizable pooled analyses, along with a risk increase of the roughly 10% increment per 5-unit in the BMI.[24] Significant correlations with the waist-to-hip ratio and the WC, particularly in the women, were reported in studies that additionally included anthropometric characteristics, demonstrating the significance of body fat distribution. The relationship between EBW and PC in terms of mortality is less clear. According to the previous meta-analysis, the EBW prior to the PC surgery or at diagnosis is not related to survival. However, the similar study also discovered the dose response link in between the adult mortality and BMI, with the 5-unit increase in the BMI being related with the 11-percent increased risk of the mortality.[24] These results might be explained by the quick development of PC and the frequent occurrence of dramatic weight loss prior to diagnosis or surgery. Unfortunately, the studies looking on BMI at the diagnosis or prior to the surgery have not taken weight reduction as a confounding factor into account. The study also looked into how body fat was distributed, however neither BMI nor visceral fat were linked to overall survival.[24] The impact of EBW on the final result in PC is yet unknown at this time. Despite its consuming nature, there is currently no proof that the obesity paradox in PC exists.

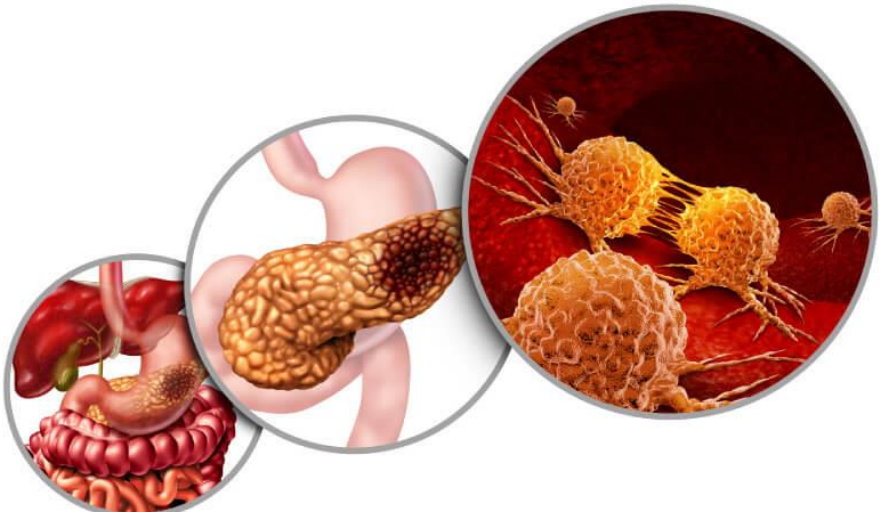

Figure 4. Pancreatic cancer

MECHANISMS

We still don't fully understand the processes by which EBW affect aetiology and prognosis in pancreatic disorders. The most frequent molecular pathways put forth are linked to the excessive buildup of the intra-pancreatic and visceral fat as shown in the Figure 2. All three disorders are probably characterised by the inflammation of low-grade and the immunological dysfunction that are both systemically and locally mediated by adipokines.[25] Additionally, increased lipolysis, particularly in AP, appears to be responsible for undesirable results by releasing fatty acids unsaturated that potentiate the necrosis and exacerbate the systemic and local inflammation, which is facilitated by a flurry of the cytokines, primarily, IL-10, IL-8, and IL-6.[26] Therefore, it has recently been proposed that dietary-induced visceral fat unsaturation serves as the driver of the AP severity and the potential justification for the obesity paradox. Contrarily, intrapancreatic adipocytes in the CP are surrounded by the fibrotic tissue, which limits the lipolysis and lessens the severity of the acute exacerbations.[27] Which may might partially account for observation of a better prognosis in the patients of EBW. Finally, hormonal actions of adipose tissue appear to play a role in pathogenesis, particularly in PC. Increased insulin and the levels of insulin-like the growth factor 1 have been linked to obesity and BMI, and these factors may encourage the pancreatic carcinogenesis via altering the apoptosis, angiogenesis, and cell proliferation.[28] Additionally, it has been discovered that leptin, which is largely produced in adipocytes, promotes PC invasion by increasing the production of matrix metalloproteinase-13.[25] Through tissue remodelling and fibroinflammatory responses, pancreatic steatosis, which results from increasing fatty infiltration, may also aid in the development of cancer.[29] Overall, observed correlations of the EBW with both PC and AP point to processes common to both diseases that include creation of the pro-inflammatory milieu. Although the CP is well known risk factor for the PC, relatively few CP patients actually go on to develop the PC, which

might help to explain why the pathogenic mechanisms for the cancer formation is distinct from those for chronic inflammation. The apparent negative connection between the CP and EBW should treated even the more cautiously given paucity of compelling mechanistic explanations.

CONCLUSION

The function of the EBW in spectrum of the pancreatic disorders is unclear. There is strong proof that that EBW, particularly in form of the visceral obesity, worsens outcomes and raises risk for AP and PC. Contrarily, the scant evidence available on CP point to a protective impact. Further research is necessary to determine the particular pathways by which EBW affects pancreatic illness, however there appear to be both general effects and disease-specific effects. The earliest stages of the disease should be targeted for prevention in order to lower the likelihood of progression. As a result, keeping a healthy weight is a suggestion that may be applied to anyone suffering from pancreatic disease.

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