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LETTER TO THE EDITOR

Argument for the need of investigation of the relationship between body fatness and experimental pain sensitivity

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In this communication, we argue about the need for an extensive investigation of the relationship between body fatness and fat distribution and experimental pain to explore the factors that might contribute to the increased prevalence of pain conditions in obese individuals.

Keywords: *obesity*; *chronic pain*; *experimental pain*; *body fat*; *cytokines*

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Obesityand pain are significant public health problems and contribute to significant disability worldwide (1). There appears to be tentative evidence that individuals with a high body mass index (BMI), which is often used as a proxy measure of obesity, report higher pain intensity compared with individuals with normal BMI (2). However, the relationship between obesity and pain has received little attention and the potential mechanisms underlying a putative relationship is not well understood (3, 4).

Obesity is defined as an increase in body weight as a result of an excessive accumulation of body fat and is associated with increased morbidity and mortality (5). Obesity is commonly measured using the BMI, with obesity characterised as a BMI greater than 30 kg/m^2, overweight between 25 and 29.9 kg/m^2, and normal weight from 18 to 24.9 kg/m^2 (6, 7). The World Health Organization (2013) reports that more than 1.5 billion adults worldwide are overweight and approximately 500 million adults meet the criteria for obesity. In the United States, approximately 78 million adults and 12.5 million children and adolescents are obese (8).

Obesity and chronic pain

Obesity is usually associated with comorbidities (9, 10) such as diabetes. There is very strong evidence that obesity is a high-risk factor for elevated cholesterol, heart disease, type 2 diabetes, cancer, and stroke (10). Obesity may be influenced by genetic and physiological factors, such as a thyroid disorder, growth hormone and leptin deficiency, and lifestyle factors including overeating, especially excess consumption of sugary and processed foods, and lack of exercise associated with a sedentary way of life (11).

Obesity is also associated with painful conditions, including low back pain, fibromyalgia headache, and osteoarthritis (12). It has been estimated that approximately 50% of people who are obese regularly experience pain (13). The International Association of the Study of Pain (IASP) defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (14). It is unclear whether obesity causes chronic pain or chronic pain could cause increased weight, or some other factor(s) cause both conditions concurrently (2, 15). It has been assumed that pain in obese people could be the result of the excessive weight, causing mechanical stress to weight-bearing structures, particularly joints of the back and lower limbs (16). More recently, attention has been on the possibility that obesity produces a pro-inflammatory state and that inflammatory substrates may contribute to the development of pain (2).

Body fatness and experimental pain

Laboratory investigations into the pain sensitivity response of healthy individuals has been used extensively in pain science to investigate relationships between pain sensitivity and sex, gender, ethnicity, and other factors that may influence pain experience. To date, the mechanisms underlying the supposed relationship between obesity and an individual's pain sensitivity response has received little attention (3, 4, 16, 17). Pain sensitivity is the level at which an individual reacts to a noxious stimulus and is measured using controlled experimental stimuli (18).

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Laboratory investigations into the pain sensitivity response of obese pain-free individuals would be useful to determine whether obesity contributes to pain experience, in addition to other factors already known to influence pain sensitivity response, including age, sex, gender, ethnicity, and psychological factors such as anxiety and catastrophising. These factors should be accounted for in any study of pain sensitivity (19).

The role of pro-inflammatory cytokines

Susceptibility to pain in obese individuals may be affected by increases in the concentrations of pro-inflammatory cytokines in the blood (2, 17). Cytokines are proteins secreted by cells to regulate the immune response to infection and trauma (17, 20, 21). Some cytokines promote the healing of wounds; pro-inflammatory cytokines increase inflammation and cause diseases to progress; anti-inflammatory cytokines suppress the activity of pro-inflammatory cytokines (20). Inflammatory responses in the peripheral and central nervous systems play key roles in the development and persistence of the hallmarks of pain: redness, swelling, temperature rise, and pain (22). Cytokines are regulators of adipose tissue metabolism and are secreted by many cells in the body. Pro-inflammatory cytokines are predominantly produced by activated macrophages and are involved in the up-regulation of inflammatory reactions. There is abundant evidence that certain pro-inflammatory cytokines such as IL-1β, interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) are involved in the process of pathological pain (23). The significance of cytokines in the development of pain and hyperalgesia as well as their mechanisms of action on nociceptors has been realised only during the last decade (24, 25). Adipose tissue releases inflammatory mediators, including prostaglandin, histamine, and interleukin (25). Visceral adipose tissue in particular is a rich source of pro-inflammatory cytokines, which appear to be major regulators of adipose tissue metabolism. There is evidence that obese individuals have elevated circulation levels of pro-inflammatory cytokines, such as TNF-α, IL-6, and C-reactive protein (CRP). IL-6 is a circulating cytokine secreted from different types of cells, including activated macrophages and lymphocytes. The biological activity of IL-6 is elevated in the presence of systemic infection or inflammation (26), and it is known that IL-6 and TNF-α play key roles in chronic pain conditions (27).

Obese individuals may be in a pro-inflammatory state (17). It is unclear whether an increased prevalence of pain conditions and pain sensitivity in obese individuals is the result of the inflammatory mediators associated with adipose tissue or else some other factors, such as body size and accumulation and distribution of fat, are also linked to pain sensitivity responses (28).

Conclusion

One way of investigating whether inflammatory mediators in obese people are associated with pain sensitivity is to correlate the concentrations of biomarkers of systemic inflammation in pain-free individuals using experimental pain induction techniques. However, before undertaking experimental studies, it is necessary to review the current status of research literature to contextualise the prevalence of chronic pain among obese individuals and the current understanding of the mechanism by which fat content of the body affects pain. It is also necessary to conduct a systematic review of research on experimental pain sensitivity response and body fatness to determine the status of current research on the topic and to inform the design of the experimental studies. Therefore, there is a need to investigate the relationship between pain sensitivity, body fat distribution, and levels of pro-inflammatory cytokines. Such a study should be based on an experimental investigation of the relationship between pain sensitivity, body fat distribution (measured by a state-of-the-art device), and blood levels of IL-6, CPR, TNF-α, and leptin.

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