A Review of Posttraumatic Stress Disorder and Obesity: Exploring the Link

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ABSTRACT

Objective: The incidence of posttraumatic stress disorder (PTSD) and obesity are on the rise, and evidence continues to support the observation that individuals who have symptoms of PTSD are more likely to develop obesity in their lifetime. The incidence of obesity in individuals with PTSD, including war veterans, women, and children exposed to trauma, is not solely attributable to psychotropic medications, but actual pathophysiologic mechanisms have not been fully delineated. Additionally, there are no studies to date demonstrating that obese individuals are predisposed to developing PTSD compared to the general population. This review explores the pathogenic pathways common to both PTSD and obesity, which include inflammation, the renin-angiotensin-aldosterone system, cellular structures, and neuroendocrine activation.

Data Sources and Synthesis: A PubMed search for the years 2000–2015 with the keywords *PTSD* and *obesity* was performed. There were no language restrictions.

Results: More research is needed in human subjects to understand the pathogenic pathways common to both PTSD and obesity and to further clarify the direction of identified associations. Ideally, in the future, clinical interventions targeting these pathways may be able to modify the course of PTSD and obesity. The outcome of studies investigating the utility of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the treatment of PTSD symptoms will be relevant to control both PTSD and obesity. Importantly, outcomes assessing inflammation, obesity, and cardiac function in the same subjects also should be determined.

Conclusion: Research is needed to reveal the multidimensional and intricate relationship between PTSD and obesity. The implications of this research would be essential for treatment, prevention, and potential public health reforms.

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Posttraumatic stress disorder (PTSD) is a debilitating mental disorder that occurs following a trauma. Exposure to trauma is very common. In 2011, it was reported that approximately 240,000 Americans were exposed to sexual assault, and over 1,000,000 were exposed to aggravated assault.[1] In the United States, 7%–8% of the population will have symptoms of PTSD at some point in their lives, although this condition is underdiagnosed and lifetime prevalence is very likely much higher.[2] Similarly, in Europe, the prevalence of PTSD is 0.56%–6.67% of the population.[3] According to the Anxiety and Depression Association of America,[4] women are twice as likely as men to develop PTSD, possibly related to the increased likelihood of women experiencing traumatic events such as child abuse and sexual assault. PTSD also is commonly seen in war veterans.[4,5] Depending on the conflict and population studied, presence of PTSD in combat veterans is estimated to be between 10% and 15% in the previous year, and a lifetime prevalence is estimated at over 30%.[4]

PTSD is classified as a "trauma- and stressor-related" disorder in the *DSM-5*.[6] The following criteria for diagnosis of PTSD are applicable to adults, adolescents, and children older than 6 years of age[6(p271)]:

A. Exposure to actual or threatened death, serious injury, or sexual violence
B. Presence of intrusion symptoms, such as dissociative reactions
C. Persistent avoidance of stimuli associated with traumatic event
D. Negative changes in mood and cognition
E. Increased arousal and reactivity
F. Duration of symptoms is more than 1 month
G. Distress in social, occupational, and other areas of functioning
H. The disturbance is not due to the effects of a substance or another medical condition.

Obesity is a major epidemic. Obesity is defined as body mass index (BMI) ≥ 30 (kg/m^2) in adults and a BMI above the 95th percentile for children. Around one-third of adults and 17% of youths were considered obese in 2009–2010.[7] In the United States, the prevalence of obesity is similar in men and women. In some parts of the world, especially in areas with low and middle income, women were found to be 2 times more obese than men.[8]

Research demonstrates that individuals with PTSD have a predisposition to obesity. One study[9] found that obese individuals who lost weight had a parallel decrease in PTSD symptoms. This relationship is independent of the known metabolic side effects of the psychotropic medications used to treat PTSD symptoms.[10]

In this review, we discuss in detail how both PTSD and obesity manifest in affected individuals at the molecular, neuroendocrine system, and peripheral nervous system levels. On the basis of these findings, we discuss the possible cause-and-effect relationships between obesity and PTSD. We posit that because of similar mechanisms affected by either obesity or PTSD, there is a bidirectional relationship between these conditions:

Clinical Points

- Posttraumatic stress disorder (PTSD) and obesity are major epidemiologic problems that increase morbidity and mortality.
- A better understanding of the relationship between PTSD and obesity may lead to better treatment plans.

obese individuals may be predisposed to developing PTSD after trauma exposure, and those with PTSD are more likely to develop obesity. Clarifying these relationships may have pertinence for treatment and prevention of both conditions.

METHOD

A PubMed search for the years 2000–2015 with the keywords *PTSD* and *obesity* was performed. There were no language restrictions.

RESULTS

Studies in Veterans

An increasing number of studies[11] have shown that PTSD symptoms are associated with obesity and metabolic syndrome in veterans. PTSD was found to be associated with mortality related to heart disease.[12] Patients with PTSD are more likely to have an increased risk of developing obesity and cardiovascular illnesses due to poor health habits including substance abuse and lack of exercise.[12] In a study[13] involving returning veterans from Iran and Afghanistan, many veterans were found to be overweight and obese. Often, patients with PTSD are taking psychotropic medications, which have a potential to cause weight gain and may confound direct relationships between PTSD and obesity. To clarify this, a study[14] among veterans with PTSD showed that BMI was not correlated with psychotropic drug use alone. Of note, the degree of metabolic disturbance necessitated the use of medications to treat metabolic syndrome in these subjects.[14] In a study[15] reviewing local and national PTSD databases, PTSD was found to be a potential risk factor for obesity. In another study,[16] it was found that police officers with severe PTSD symptoms related to job stress had 3 times the risk of concurrent metabolic syndrome.

On the other hand, a study[17] in Iraqi veterans found that obesity in these veterans was not related to their PTSD symptoms. Furthermore, another clinical trial[11] found that obesity was present in veterans with PTSD, but PTSD symptoms were not related to obesity.

Studies in Women and Children

In addition to combat veterans, women and children are frequently exposed to trauma and abuse and are at risk for developing PTSD. In a cohort of obese women with binge-eating disorder, PTSD was commonly reported along with poorer psychological functioning.[18] Further, the National Women's Study[19] reported that 21% of women with binge-eating disorder met criteria for PTSD compared to 12% of women without an eating disorder, linking PTSD and a disorder leading to obesity.

PTSD has been shown to have significant correlations with increased BMI, central adiposity, and waist-to-hip ratio in US civilian women with PTSD related to childhood traumatic stress.[19] In contrast, Pederson and Wilson[24] noted a relationship between women reporting severe childhood emotional neglect and increased PTSD scores; however, no relationship with obesity was found when controlling for other variables. A study[20] involving female veterans in the VA Puget Sound Health Care System asked to complete a survey on health history habits identified that women who screened positive for PTSD symptoms had increased rates of obesity, cervical cancer, stroke, and polycystic-ovarian syndrome compared to women without PTSD. In addition to the possible relationship between obesity and PTSD symptoms, eating behaviors also may be related to traumatic experiences. In a study[21] of women with a history of past sexual and physical abuse who developed eating disorders between their 30s and 50s, food avoidance practices were identified as a mechanism to cope with PTSD symptoms.

Obesity and PTSD also are often associated in children and carry repercussions for their health, even into adulthood. A study[22] examining Kuwaiti children with a history of exposure to war trauma showed a relationship to PTSD, poor sleep, and increased BMI. A Danish study[23] demonstrated a relationship between PTSD symptoms, a history of childhood abuse, and both underweight and overweight status. Specifically, emotional abuse was related to underweight status and sexual/overall abuse was related to obesity/overweight status.[23] Similarly, research on childhood traumatic stress and obesity in women has shown significant effects of PTSD and depression on BMI and waist-hip ratio.[23] In contrast, one study[24] found that although women do have increased incidence of PTSD with a history of childhood sexual or emotional abuse, there was no significant relationship with obesity after controlling for other variables.

Predicting the effect of PTSD on BMI is challenging in human beings due to the complexity of individual coping mechanisms including overeating versus food restricting. Feeding and satiety behaviors may obscure directional correlations with other symptoms and disorders. Determining a direct correlation between traumatic experiences, presence of PTSD symptoms, and obesity remains a complex challenge. In the following sections, we discuss the pathophysiologic pathways and cellular structures affected by both PTSD and obesity, which may explain the relationship between obesity and PTSD.

Inflammation

Obesity has been shown to be associated with increased markers of inflammation. Overweight people tend to have increased levels of interleukin-6 (IL-6) and C-reactive protein (CRP), which are considered markers of inflammation associated with cardiovascular risk factors.[25] Obese subjects have increased CRP (>10 ng/mL) compared to nonobese subjects.[26] Studies[27] have demonstrated increased CRP in

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obese women and children. One study[28] reported weight loss led to a reduction in CRP levels. A Munich study[29] conducted in an outpatient gynecology clinic revealed elevated CRP levels in 139 women who experienced interpersonal violence. This study[29] indicates that CRP elevation is an independent pathway in PTSD, independent from obesity-associated elevation in CRP.

Adipose tissue is known to produce IL-6. This marker of inflammation can promote atherosclerosis, insulin resistance, and type 2 diabetes mellitus.[30] IL-6 also is shown to be elevated in PTSD, especially in persistent PTSD.[31] Further studies are needed to demonstrate if obese individuals exposed to violence will develop PTSD symptoms due to increased IL-6 and CRP.

Neuropeptide Y (NPY) is released from the sympathetic nervous system, forebrain, and limbic system in response to stress. This peptide acts on fat tissue, stimulating adipogenesis and causing an increase in adiposity and thereby obesity. A high-fat diet as well as stress increases the levels of corticosterone, the primary corticosteroid released by adrenal fats. The glucocorticoids increase the expression of NPY, particularly in the abdominal fat.[32]

NPY acts as a regulator, which lowers the stress-signaling hormones norepinephrine and corticotropin-releasing hormone.[33] In a study[34] conducted among combat veterans with chronic PTSD, it was reported that these subjects had low concentrations of NPY in the cerebral spinal fluid. This relationship between low cerebral spinal fluid NPY and symptoms of PTSD was investigated. Low NPY can cause an increase in the sympathetic nervous system, leading to symptoms of hyperarousal. Additionally, in the hippocampus, low NPY levels can cause impaired cognition and response to fear. In the amygdala, low levels of NPY increased symptoms of fear and anxiety and decreased resilience to stress.[34] Further studies are needed to find a cause-and-effect relationship between PTSD and obesity mediated by NPY.

Brain-derived neurotrophic factor (BDNF) regulates neuronal development, and low levels are found in patients with obesity.[24] Similarly, low levels of BDNF are seen in subjects affected by PTSD. BDNF plays an important role in the limbic system regulating neuronal plasticity and memory. BDNF may be associated with the pathogenesis of both obesity and PTSD, but the role in their correlation and pathophysiology are not yet clearly defined.[35]

Renin-Angiotensin-Aldosterone System

In addition to the classic renal renin-angiotensin-aldosterone system (RAAS), studies[36] have shown that adipose tissue harbors its own local RAAS endocrine pathway. The RAAS is an important regulator of blood pressure. Adipose tissue locally generates angiotensin II from angiotensinogen, which is now known to be present in adipose tissue, and has additional local effects.[36] This process occurs through a series of reactions: angiotensinogen is converted to angiotensin I via renin enzyme and, finally, to angiotensin II via angiotensin-converting enzyme (ACE). The possible actions of angiotensin II in adipose tissue include preadipocyte differentiation, endothelial proliferation, angiogenesis, and sympathetic activation. These effects may further increase obesity as well as hypertension.[37] Due to these additional effects, ACE inhibitors are being studied to control obesity. Animal studies[38] have shown that inhibition of the RAAS causes weight loss and a reverse of inflammation related to obesity.

Another study[39] suggests that ACE inhibitors and angiotensin receptor blockers could possibly reduce PTSD symptoms. This finding supports the role of the renin-angiotensin pathway in PTSD-related symptoms. These facts support the possibility that obesity and symptoms of PTSD can be based on shared activation of similar pathways, particularly the renin-angiotensin system.

Telomere Length

Studies[40] indicate an association of both PTSD and obesity with shortened telomere length. Telomeres, tandem repeats of hexamers found at the ends of chromosomes, protect against spontaneous DNA damage and preserve genomic integrity. Normally, telomeres progressively shorten with each replication in human somatic cells. Telomere shortening can be accelerated, however, by conditions leading to oxidation and inflammation. These conditions include high BMI, hypertension, cholesterol, metabolic diseases, and cancer.[40]

The risk for remaining obese after a 5-year dietary intervention is lower in individuals having a longer baseline telomere length, suggesting longer telomeres are protective against obesity.[41] Similarly, obese children have significantly shorter telomere length (on average 23.9%) than nonobese children.[42] A London study[43] demonstrated that obese women have, on average, a telomere length 240 base pairs shorter than lean women, and shortened telomere length may contribute to an obese phenotype.

PTSD also has been shown to affect telomere length. A study[44] in southern Germany with a sample population of 3,000 demonstrated an association between PTSD and shorter telomere length. The researchers additionally found a dose-response effect of telomere length; individuals diagnosed with full PTSD versus partial PTSD had greater telomere attrition, suggesting that the effect of stress on telomere length is cumulative.[44] Supporting this point, a study by O'Donovan et al[45] found that young individuals with PTSD who had been exposed to multiple types of childhood trauma had significantly shorter leukocyte telomere length later in life compared to controls, with number of categories of trauma experienced varying linearly with telomere attrition.

A study[46] of combat veterans who served in Iraq or Afghanistan suggests that PTSD subjects with shorter telomeres may be more vulnerable to stress and thus to developing PTSD and stress-related cellular aging. Similarly, victims of rape who developed PTSD 3 months after the trauma compared to rape victims who did not develop PTSD have been shown to have shorter relative telomere

length, again suggesting that shorter telomere length may predispose to PTSD development.[47]

If shorter baseline telomere length may be associated with increased predisposition to PTSD, can obesity, which causes shortened telomere length, further predispose to PTSD? Further studies are required to answer this question.

Mitochondrial Dysfunction

Mitochondrial dysfunction has similarly been associated with obesity and PTSD. Mitochondria are cellular organelles that play a central role in adenosine triphosphatase production, energy expenditure, and the disposal of reactive oxygen species (ROS). Obesity can lead to increased ROS production via increased caloric intake. These calories are a substrate for mitochondria in the production of ROS. ROS cause cell damage, increased mutation rates of mitochondrial DNA, and apoptosis. Damaged mitochondria cause cell senescence and death, leading to age-dependent cardiometabolic diseases.[48]

PTSD also can induce cellular apoptosis via the release of cytochrome c, an apoptotic-signaling agent, from mitochondria. Stress induces the release of cortisol, which activates the glucocorticoid receptor. Glucocorticoid receptor binding leads to the release of cytochrome c to cytoplasm, leading to apoptosis. This cascade is thought to be responsible for the hippocampal atrophy associated with PTSD.[49] Additionally, exposure to chronic mild stress leads to mitochondrial dysfunction via the inhibition of mitochondrial respiration rates and activation of prooxidant and proinflammatory pathways.[50] Perhaps obesity-related mitochondrial damage and apoptosis also can be related to the hippocampal malformation associated with PTSD. Further research is needed in this arena.

Endoplasmic Reticulum

The endoplasmic reticulum is an organelle majorly involved in protein, lipid, and sterol synthesis. An early consequence of excess nutrient intake includes endoplasmic reticulum stress to meet the protein demands of expanding adipocytes. This leads to the development of insulin resistance and inflammation as shown in mouse studies.[51] Increased endoplasmic reticulum stress also has been demonstrated in the subcutaneous fat of obese human test subjects.[51]

A study[52] demonstrated that individuals with a recent history of PTSD show activation of endoplasmic reticulum stress-related genes and stress marker binding immunoglobulin protein (BIP). Increased endoplasmic reticulum stress could be associated with a higher risk of developing cardiovascular disease, diabetes, and obesity in individuals with PTSD.

Neuroendocrine Activation

The link between glucocorticoids and obesity has been well-studied. PTSD symptoms also have been linked to increased cortisol levels. Glucocorticoids, the body's "stress hormones," are key regulatory agents of energy and are responsible for releasing high-energy compounds (fatty acids and glycerol) from adipocytes when the body requires them, including during periods of fasting or exercise. Glucocorticoids, when elevated due to increased production (ie, Cushing's disease) or exogenous use, are linked to increased buildup of adipose tissue. An increased cortisol clearance and production rate with increased hypothalamic-pituitary-adrenal axis activation is seen in obese individuals.[53] A primate study[54] suggested an association between obesity and elevated urine catecholamines in both fasting and fed states.

Elevation in glucocorticoid levels is posited to influence the choice of high-caloric, sugary foods, logical in starvation but maladaptive in a nonfasting state such as psychological distress. Interestingly, it has been observed that individuals responding to stressful events with high cortisol levels are more likely to consume a greater number of calories from high-fat, sweet foods.[53]

Glucocorticoids also are necessary to cause differentiation of immature adipocytes to mature adipocytes, thereby causing adipogenesis and adipocyte hypertrophy. Glucocorticoids have a unique role in lipid storage via up-regulating the activity of lipoprotein lipase, which sequesters fatty acids and triglycerides from circulation to adipose tissue. There also is evidence that glucocorticoids may have an antilipolytic role.[53]

There is well-established literature[55] on the association of elevated cortisol levels and depression; similarly, PTSD symptoms have been linked to hypercortisolism. In a study[56] conducted at the University of Alabama at Birmingham, mothers meeting criteria for PTSD due to having a child with a life-threatening illness underwent salivary cortisol sampling 1 hour before and 24 hours after their child's medical checkup. It was found that mothers with PTSD had significantly higher saliva cortisol levels 1 hour before the appointment compared to controls without PTSD.[56]

Further strengthening the connection of PTSD with neuroendocrine activation is a study[57] comparing the 24-hour urine cortisol and urine 17-ketosteroids (major metabolite of dehydroepiandrosterone sulfate [DHEA-S], an androgen synthesized by the adrenal cortex) in women with PTSD due to childhood sexual abuse to controls without PTSD and to the neuroendocrine profiles of combat veterans with PTSD. The researchers found increased levels of neuroendocrine activation versus controls, with a high correlation between cortisol and 17-ketosteroids. In their sample, 50% of subjects with prior abuse were overweight, which was double the national rate.[57]

Interestingly, another study[58] found that individuals with chronic PTSD had lower levels of plasma cortisol due to an increased responsivity of glucocorticoid receptors. Low cortisol levels may be unable to "turn off" the sympathetic nervous system, leading to autonomic hyperactivation and an increase in level of catecholamines (failure of negative feedback). This increase could be partly responsible for the insomnia, irritability, lack of concentration, hyperarousal, and exaggerated startle found in patients with PTSD.[58]

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DHEA is an androgen associated with increased adrenocortical activity. Studies[59] suggest that obesity has a negative correlation with circulating DHEA. A Scandinavian study[60] of war veterans with PTSD demonstrated higher levels of DHEA in subjects with PTSD as a measure of coping. Low cortisol/DHEA ratio was found to predict severity of PTSD.[60]

Adrenal Hormones

The neurotransmitters epinephrine and norepinephrine, secreted by the adrenal medulla, are the mediators of the "fight or flight" response. The effects of this response may play an important role in the development of hypertension, obesity, and metabolic syndrome.[61] PTSD is associated with elevated resting heart rate, blood pressure, eye blinking, and skin conductance to startle. In adults, epinephrine and norepinephrine levels were found to positively correlate with PTSD symptoms.[62] As obesity can lead to increased adrenal activation, further research is required to assess if this regulatory pathway sensitizes one to develop PTSD.

CONCLUSION

PTSD and obesity are 2 major epidemiologic problems worldwide. PTSD is associated with increased coronary heart disease, thromboembolic stroke, diabetes, metabolic syndrome, substance abuse, and diabetes.[63] Similarly, obesity is associated with hypertension, metabolic syndrome, heart disease, and cerebral vascular accidents.[64] The combination of both of these conditions very likely increases morbidity, mortality, and disability. However, as both conditions are complex and related to appetitive behaviors around food and other substances, establishing direct correlations remains elusive and challenging. This review presents our attempt to identify mechanisms common to both PTSD and obesity that may be related to shared pathophysiology. Mechanisms at the genetic (eg, telomere length), growth and inflammatory mediator (eg, IL-6, BDNF), cellular (eg, mitochondrial and endoplasmic reticulum function), and endocrine (eg, glucocorticoid and RAAS pathways) levels have been discussed. Thus far, studies present associations in human subjects or preliminary studies of implicated pathways in animal models. More research is needed in human subjects to understand these mechanisms and to further clarify the direction of identified associations. Ideally, in the future, clinical interventions targeting these pathways may be able to modify the course of PTSD and obesity. The outcome of studies investigating the utility of ACE inhibitors and angiotensin receptor blockers in the treatment of PTSD symptoms will be relevant to control both PTSD and obesity. Importantly, outcomes assessing inflammation, obesity, and cardiac function in the same subjects also should be determined.

Essential questions that remain unanswered and require further exploration include the following:

1. Why do individuals with PTSD symptoms have a higher propensity to develop obesity?
2. Is there a possibility that obese individuals are more likely to develop PTSD when exposed to trauma?
3. Are these common pathways accurate for explaining the cause-and-effect relationship between PTSD and obesity?

In conclusion, our review offers a detailed exploration of the relationship between obesity and PTSD. We have summarized the potential pathways common to PTSD and obesity. The implications of understanding the associations between PTSD and obesity, particularly in vulnerable populations, may lead to better treatment options for these common and disabling conditions. Successful clinical approaches also could influence public health reforms and disease-prevention strategies.

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