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Is there a relationship between PTSD and complicated obesity? A review of the literature

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ABSTRACT

Recent research strongly supports the hypothesis that posttraumatic stress disorder (PTSD) can be accompanied by obesity and related metabolic disturbances. The mechanisms of these associations are however still not well defined, although disturbed functions in the sympathetic-adrenergic nervous system together with the disturbed release of hormones via the endocrine HPA (hypothalamic-pituitary-adrenal) axis apparently play a role. Leptin resistance and ghrelin excesses might contribute to a disturbed hypothalamic function, and also disturb other cerebral functions, leading to dysfunctional reward signaling and uncontrolled appetite combined with a tendency to alcohol abuse. Secondarily, cortisol stimulation will contribute to the development of central obesity which is known to facilitate the development of metabolic syndrome, including slightly increased levels of inflammatory biomarkers such as C-reactive protein and fibrinogen. While previous therapeutic strategies have focused on early psychotherapeutic interventions in PTSD, the present review emphasizes the importance of better therapeutic approaches regarding the somatic correlates of the syndrome. Strict regulation of dietary meals and food composition with minimal intake of sweets and saturated fat, as well as alcohol avoidance, can provide a basic therapeutic framework. A cognitive psychotherapeutic approach with graduated desensitization toward trigging factors, combined with pharmacotherapy, is discussed in the present review.

1. Introduction

Today, obesity and its comorbidities represent a significant global health challenge, and the number of people with obesity is still increasing [1,2]. In Scandinavia and in the United States, the prevalences of obesity in the general populations are now about or above 25% and 35%, respectively [3,4]. And worldwide the obesity rates present an increasing trend [5]. Obesity has been attributed to a sedentary lifestyle together with affluent intake of energy-rich food with copious amounts of fat and sugar [6]. However, in recent years psychological factors including anxiety, emptiness feelings, and posttraumatic stress have emerged as possible background factors of obesity and its comorbidities [7,8]. Here, it is relevant that the prevalence rate of the severe variant of stress, posttraumatic stress disorder (PTSD), is also rather high, with variations around 8% in populations in the Western world [9–13]. PTSD is characterized by symptoms of relapse of the traumatic event (flashbacks), and symptoms of increased irritability together with concentration difficulties, and increased alertness to stimuli that reminds of the traumatic event [14]. Symptoms may occur early or a few weeks after the trauma, but in some cases, the latency time is considerably longer [15]. Anxiety, depression, suicidal thoughts, alcohol or drug abuse, can follow PTSD [16]. Also in uncomplicated cases, PTSD represents a significant burden on our society.

Of particular relevance is that PTSD in recent studies appears to be linked to obesity development and metabolic complications. The large health costs associated with complicated PTSD accompanied by comorbidities will give rise to a significant burden on health care systems and affected individuals [17]. A range of obesity-related diseases may accompany PTSD, such as type 2 diabetes (T2DM), insulin resistance, cardiovascular disease, and dyslipidemia [18,19]. But still, there is no current strategy for treating or preventing PTSD associated metabolic disturbances, and further research has been requested [20,21].

The present review aims at updating our knowledge on relations between obesity and PTSD, as well as clarifying the challenges related

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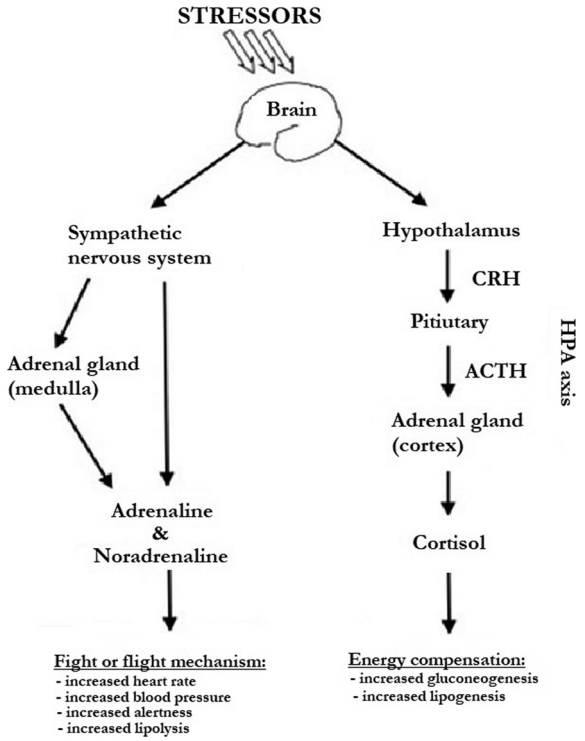

Fig. 1. Effects of PTSD via the sympathetic nervous system and via the hypothalamus-pituitary-adrenal axis (HPA axis). While the adrenaline and noradrenaline response gives rise to increased blood pressure, increased cortisol levels are associated with central obesity.

to the treatment of PTSD-associated metabolic dysfunctions with the purpose of improving therapeutic strategies.

2. Stress, anxiety, PTSD, and somatic manifestations

Somatic manifestations of PTSD appear to occur through neuroendocrine links leading to activation of the sympathetic-adrenergic nervous system together with the release of hormones via the endocrine HPA (hypothalamic-pituitary-adrenal) axis [22]. Even anxiety and non-specific stress can affect neuroendocrine links and the HPA axis (Fig. 1), thereby leading to increased levels of circulating cortisol, and secondarily also the development of metabolic dysfunctions and central obesity [23,24]. PTSD has been linked to a significantly (about 1.5-fold) elevated risk to develop obesity [25]. Also, childhood adversity is considered to predispose individuals to the development of complex PTSD and secondarily to central obesity later in life [26]. Furthermore, childhood traumatic events have been linked with metabolic syndrome, and also the development of T2DM and cardiovascular disease [18]. High levels of stress-related hormones, especially catecholamines and cortisol, seem to predispose for altered adipokine profile accompanied by metabolic complications, in particular, if traumatic events occurred in early life, either childhood or adolescence [27,28]. Although the catecholamines and some other factors [29] may induce lipolysis (Fig. 1), this effect appears to be counteracted by hyperinsulinemia and the leptin resistance characterizing obesity [30–32].

Clinical practice suggests that stress often accompanies arterial hypertension. A meta-analysis of a large-scale population-based study performed in practically healthy young people showed that psychological factors like anxiety, anger, chronic stress, and post-traumatic stress disorder are connected with an elevated occurrence of cardiovascular pathology approximately 1.5 times, which indicates the causal role of psychological factors in these diseases [33].

Different hypotheses explain the connection between psychological stress and cardiovascular disease development. One of these hypotheses is that epigenetic programming of the hyperactive stress response system in a fetus of a mother under stress can lead to autonomic, neuroendocrine, and immune dysfunction. This subsequently leads to an atherosclerotic process and a negative effect on brain structures by transmitting negative signals through interoceptive pathways many years before the development of arterial hypertension or other cardiovascular diseases [34]. Moreover, adaptive changes in the cardiovascular system in response to external stressful situations can lead to cardiometabolic and structural changes in arteries, endothelial dysfunction, and development of hypertension. In turn, cardiovascular events can provoke psychological acute-phase reactions, which may lead to the development of depression, anxiety, and post-traumatic stress disorder [35].

Psychological factors and stress are usually associated with behavioral and lifestyle problems such as smoking, physical inactivity, poor nutrition, alcohol abuse, and sleep problems. Stress-related health behaviors contribute to the development of traditional cardiometabolic risk factors, including hypertension, dyslipidemia, insulin sensitivity, and increase in body mass index [36].

Inflammation characterized by increased levels of biomarkers such as CRP, tumor necrosis factor alpha (TNFα), and interleukin-6 (IL-6), also appear to occur more frequently in adults who have been exposed to adversity early in life [37]. Individuals with obesity and metabolic comorbidities, including T2DM and cardiovascular disease, have also often experienced other psychological stressors, such as social isolation or socioeconomic difficulties [38]. It is conceivable that constant stress related to lack of social contacts and emptiness feelings can lead to increased intake of fast-food with a high content of sugar and saturated fat [39].

3. Potential mechanisms in the links between chronic stress, PTSD, and obesity

By using a rat model of PTSD, Edwards et al. [40] found that the animals could use alcohol consumption in their strategies to deal with traumatic stress, and these investigators also reported altered cerebral activities in prefrontal and temporal loci of the animals. Secondarily, disturbances in neuro-endocrine links appear to lead to increased or uncontrolled consumption of high-fat foods, sugar and even alcohol in the animals [41]. It is known from observations in humans that severe PTSD symptoms to a significant degree are comorbid with alcohol misuse and dependence [42]. Increased PTSD symptoms are also linked to more frequent alcohol cravings, presumably through activation of reward systems in the amygdala or locus coeruleus [43]. Consumption of alcohol may also aggravate the impacts of stress-induced neuropsychiatric outcomes. For example, the volume of the hippocampus has been found to be reduced in patients with PTSD [44], and it is well known that alcohol abuse may exacerbate these deficits [45]. Ideally, alcohol or drug abuse should, therefore, be carefully monitored in future studies on PTSD.

PTSD also leads to disturbed functions of satiety hormones. During the vicious circle of affluent intake of high-fat food combined with sweets and alcohol abuse, comorbidities with hyperinsulinemia and leptin resistance, as well as ghrelin disturbances may develop. And severe PTSD symptoms have been linked to obsessive disorder with emotional eating [46].

Observed changes in cognition reported in patients with PTSD may be related to changes that lead to amplification of reward activation of consumptive behaviors. Earlier PTSD studies have reported various degrees of structural changes in amygdala and hippocampus, which may reflect the severity of PTSD symptoms [47]. These changes may also influence brain responses to food intake stimulants, and thereby contribute to the development of obesity [25].

4. Obesity, metabolic disorders, and leptin resistance

In addition to a dysfunctional endocrine HPA axis, patients with PTSD appear to have alterations of the cerebral reward systems, accompanied by enhanced dopamine release in nucleus accumbens, which is known to be a key aspect both of disturbed eating behaviors and drug, alcohol or gambling addiction [48]. Some studies of functional changes in the brain of PTSD patients have reported that these changes overlap with appetite-related brain areas. For example, a functional MRI study showed that PTSD patients tested during the performance of a cognitive task with an affective challenge had parietal and frontal activations [49]. These same areas are presumed to be implicated in the cognitive control of food intake.

Polypeptide leptin secreted by adipocytes plays a significant role in the regulation of lipid metabolism. In individuals with severe obesity, elevated leptin levels and leptin resistance are usually observed. Leptin can inhibit the transcription of the insulin gene and its secretion through the sympathetic nervous system [50]. Recent studies have shown that leptin contributes to the development of oxidative stress through enhancing the macrophages phagocytic activity and the induction of pro-inflammatory cytokine synthesis (TNF-a, IL-6, IL-2) and interferon-gamma. It leads to damage of endothelial cells, monocytes, neutrophils, and also increased levels of markers for endothelial cell dysfunction [51]. It has been suggested that the pro-inflammatory effects of leptin are associated with structural and functional similarity with the IL-6 cytokine [52]. Obesity can be characterized as chronic low-grade inflammation with an ever-increasing level of oxidative stress. After exceeding a certain level, oxidative stress damages cellular structures which lead to a decrease in the synthesis of antioxidant substances and the development of complications associated with obesity [53]. In a study conducted on rats with genetically determined obesity, it was shown that hyperphagia entailed hyperinsulinemia followed by increased lipogenesis. This leads to ectopic deposition of triacylglycerol outside adipocytes, increased formation of fatty acids, impaired non-oxidative metabolism, and ceramide synthesis, which causes functional changes and apoptosis in beta cells and cardiomyocytes with subsequent development of cardiomyopathy [54]. Increased size and number of adipocytes leads to hyperproduction of cytokines, decreases the sensitivity of the peripheral tissues to insulin, accelerates atherogenic processes, and increase the levels of free fatty acids, triglycerides, and low-density lipoproteins, hyperlipidemia, hyperglycemia, and hypertension.

It has been suggested that both hyperinsulinemia and leptin dysfunction are consequences of PTSD. Failure of increased leptin levels to suppress appetite and mediate weight loss characterizes a state of leptin resistance, which may be observed in morbidly obese individuals [55]. Today it is known that several mechanisms attenuate leptin signaling and promote hypothalamic leptin resistance. For instance, observations have indicated that hyperinsulinemia leads to leptin resistance [56,57]. Leptin and insulin appears to share a pathway in the central signaling. Research indicates that insulin has a role as an endogenous antagonist to leptin. Thus, normalization of hyperinsulinemia may ameliorate leptin resistance [58], and may thereby normalize the neuropeptide Y (NPY) response and secondarily also regulate the HPA-axis.

NPY levels seem to be consistently elevated in individuals who in their past have had PTSD, but not in currently suffering individuals. This suggests that NPY may have a function in stress recovery, which might regulate appetite and eating behaviors [59]. Other adipokines and appetite-regulating hormones, like adiponectin and ghrelin, need more research to fully understand their possible relationships with PTSD.

When using a rodent PTSD model Meyer et al. found that ghrelin, the hunger hormone, was upregulated by stress [59]. And increases in ghrelin appeared to be necessary for the implemented stress to increase the memory of fear since blocking the ghrelin receptor abolished the stress-related enhancement of fear memory [60]. However, human studies are indispensable to translate these observations into the therapeutic administration of anti-ghrelin drugs to prevent stress-induced psychiatric disorders like PTSD and accompanying feelings of hunger after energy-rich food and sweets.

5. Cytokines

Potential modulators in the interplay between PTSD and obesity, in addition to leptin and NPY, may be certain cytokines and other adipokines [61] PTSD seems to impact inflammatory biomarkers, indirectly or directly [62]. Among observed alterations are increased IL-6 [63], and an increase in CRP and the intercellular adhesion molecule 1 (ICAM-1) [64]. A twofold increase in the CRP-value in PTSD has been observed [65], which is comparable to the CRP increases characterizing patients with metabolic syndrome [66]. The relationship between PTSD-associated obesity and T2DM may be mediated through the concomitantly increased levels of leptin and caveolin 1 [67] And the accompanying increased serum amyloid A levels together with a persistent elevation of leptin may reflect or contribute to a low-grade inflammation with raised cardiovascular risk [68,69]. Another inflammatory biomarker, namely fibrinogen, which also operates as a coagulation factor and thereby is considered a risk biomarker for cardiovascular disease, is also elevated in PTSD [70]. Thus, in a study examining, if present stress influences fibrinogen in patients or controls, the PTSD patients had higher concentrations of fibrinogen both at baseline and after stress in comparison with controls (persons without PTSD) [71]. Taken together, research indicates an association between PTSD and the development of inflammatory and metabolic conditions, although detailed mechanisms need to be outlined.

6. Discussion

It appears from the reviewed research that patients who have PTSD also are at increased risk for developing obesity, thereby linking PSTD to obesity comorbidities such as T2DM, cardiovascular disorders, and metabolic syndrome. Recent research has substantiated that PTSD increases the risk of metabolic and cardiovascular disorders. PTSD appears to be the psychiatric disease that most commonly is associated with obesity [72]. And when PTSD occurs together with depressive symptoms, it leads to especially high risk to develop metabolic syndrome [73], with cardiovascular disease being a frequently occurring endpoint. Thus, in a prospective study of survivors of the World Trade Center, persons with PTSD who had been physically injured during the attacks were found to have had three times increased the risk to develop cardiovascular disease in comparison with persons without PTSD or injuries [74]. In another prospective study of survivors of the World Trade Center attacks, PTSD was found to significantly predict T2DM-development [75]. Taken together, the studies reviewed in the present paper show obesity-related and metabolic comorbidities with PTSD. The suggested mechanisms include altered endocrine responses in the HPA axis together with functional alterations in the CNS and distortion of the adipokine interplay.

In this connection, a crucial aim is to address the challenges of implementing prophylaxis against the development of PTSD-associated obesity and metabolic dysfunctions. While previous therapeutic strategies have focused solely on psychotherapeutic interventions [76], it is clear that somatic PTSD correlates should not be neglected.

An appropriate psychotherapeutic approach in complicated PTSD appears to be a cognitive behavioral therapy combined with desensitization techniques [77]. Cognitive restructuring and psychoeducation under optimized therapeutic relationship, combined with exposure via narrative traumatic experiences as active ingredients may maximize treatment effects [78]. In addition, therapists should detect alcohol and drug misuse at an early stage, and dieticians should be part of the treatment team.

Regarding dietary approach, a rational approach is to recommend a

basic framework consisting of regular meals together with minimal intake of sweets and saturated fat. Adequacy with regard to minerals and trace nutrient appears to be of importance. It has been reported that magnesium deficiency can exacerbate anxiety and aggravate T2DM [79]. This may also occur for zinc deficiency [80]. Recent reports have outlined that a lack of vitamin D is associated with increased anxiety and pain [81]. When deficient, vitamin D supplementation may have a positive effect, as adequate vitamin D supplementation can have therapeutic importance in the treatment of anxiety [82]. Long-term dietary habits with low intake of sugar and adequate intake of mono-unsaturated and poly-unsaturated fat - from vegetables and fish - is recommended for the general population [83]. This is also because of the importance of adequate intake of fat-soluble vitamins. Several of these constituents may exert anti-inflammatory effects in metabolic syndrome [84].

As regards pharmacological approach, clinical use of anti-ghrelin treatments may become a successful approach in the future [59], but human studies are indispensable to translate the positive observations in animal experiments into therapeutic use for prevention of PTSD and metabolic complications. Other pharmaceuticals under investigation are a combination of bupropion and naltrexone, which appear promising [85]. Recently developments of GLP agonists with once-a-week administration bear promises with regard to improved prophylaxis of the pre-diabetic patients [86].

7. Conclusion

In summary, recent research strongly supports the hypothesis that PTSD leads to obesity and related metabolic disturbances. The mechanisms of these associations are however still not well defined. Further research should try to determine how the significant association between PTSD and metabolic risks may occur. The present evidence might suggest that PSTD is linked to altered brain and neuroendocrine activity leading to altered food consumption and altered food decisions that cause obesity. But this is not yet fully confirmed. It is also important in future research to explore the association between PSTD and altered inflammatory cytokines and adipokines. Of importance, as PTSD has a prevalence that remains high, this particular type of obesity needs specific and adequate treatments. Currently, there are not available any targeted and effective measures for obesity that is associated with PTSD. Therefore, it is a need to develop and test from bench-to-bed promising treatment strategies, which target this obesity type.

Conflicts of interests

The authors declare no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

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