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REVIEW

Behavioral health disorders related to nonalcoholic steatohepatitis

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INTRODUCTION

The most common cause of chronic liver disease in the United States is nonalcoholic fatty liver disease (NAFLD), which is closely associated with excess body fat as a result of obesity.[1] Within NAFLD lies nonalcoholic steatohepatitis (NASH).[2] The latter includes steatosis and inflammation of the liver, and increased risks for liver failure, hepatocellular carcinoma, and cirrhosis. Present in approximately 2%–4% of the US population, NASH predominantly affects those with diabetes or obesity, and the prevalence rate in those populations may reach 20%.[3]

Obesity is classified as having a body mass index (BMI) ≥30, and it is a chronic disease that poses further health, social, and financial issues. Individuals with obesity are at risk for coronary heart disease, diabetes mellitus, cancer, stroke, and other comorbidities. Financially, by 2030, 16%–18% of health care costs will be attributed to obesity management.[4] Links between obesity and mental health have been explored in recent literature, and it has been found that those with a mental health disorder are two to three times more likely to suffer from obesity. With an estimated 18.6% of the United States suffering from mental health disorders, it is important to understand the connections, which may be attributed to a number of biological and psychosocial causal factors.

TYPES OF BEHAVIORAL PROBLEMS LINKED TO NASH

Mood disorders, attention deficit hyperactivity disorder, and schizophrenia are some mental health disorders most commonly associated with obesity.[4] More specific to NASH are higher incidences of major depressive disorder (MDD), generalized anxiety disorder, bipolar disorder, and schizophrenia (Table 1).[5] Insulin resistance, a common causal factor of NASH, is often present in patients with depression and anxiety.[6] Lack of treatment of patients with these risk factors may lead to inflammatory states, oxidative stress, aggravation of genetic predispositions, and eventually NASH.[7] The psychopathology associated with obesity and NAFLD, which can escalate to NASH, may not only contribute to behavior that promotes disease development and progression but may also impact the ability to adopt and maintain lifestyle changes needed to reverse the course of the disease. One study showed that patients with NASH were largely in a "pre-contemplation" state and did not consider they had a weight-related disorder despite being in a clinic with regular weight counseling being provided; such patients are unlikely to adopt behavior change to lose weight.[1] There is thus a need to better understand the psychopathology underlying NASH and integrate specific behavioral interventions based on the individual patient's determinants of health-related behavior in the treatment plan. TREATMENTS FOR OBESITY IN THE CONTEXT OF NASH AND MENTAL HEALTH.

MECHANISMS FOR THE LINK BETWEEN OBESITY, NASH, AND MENTAL HEALTH

Psychosocial links

Food choice can be influenced by one's mood, and mental disorders such as depression or anxiety may exacerbate overeating in an effort to dispel negative emotions

TABLE 1 Mental health disorders associated with NASH

Mental health disorder	Mechanisms for association with NASH
Depression	Insulin resistance,[6,22] inflammatory state[7,23]
Anxiety	Insulin resistance,[24] inflammatory state[7,25]
Bipolar disorder	PNPLA3,[26] HPA axis,[27] insulin resistance,[5,28] inflammation,[5,27,28] oxidative stress[5,27]
Schizophrenia	Inflammation,[29,30] metabolic dysfunction,[30,31] oxidative stress,[32] mitochondrial dysregulation[33]
Autism spectrum disorders	Metabolic dysregulation[34]

TABLE 2 Mechanisms driving mental health disorders in NASH

- Genetic
- Mitochondria, inflammation, and oxidative stress
- Hormonal
- Gut dysbiosis
- Psychological factors
- Lifestyle (diet and exercise)

(Table 2). Emotional eating–mediated weight gain has been noted in patients with depressive symptoms, and adoption of unhealthy eating behaviors as a result of undesirable emotional states is considered a coping mechanism.[8,9] "Coping foods" or calorie-dense meals are often preferred under these circumstances, leading to increased BMI[10] (Figure 1). Depressive symptoms may also be associated with a decline in cognitive restraint, a behavior that is generally responsible for weight maintenance or loss. Thus, those with depression often report changes in appetite, which can compel them to increase intake of coping foods. Moreover, it is believed that depression contributes to the dampening of self-efficacy, the belief in one's self to be able to accomplish a task.[8] Consequently, behaviors such as physical activity and controlled eating are diminished, leading to weight gain and, potentially, obesity.[8] Emotional eating in response to stress has also been described, with college students attributing it as a motivator to turn to comfort foods, thus leading to potential weight gain.[11] Similarly, excessive eating in patients with posttraumatic stress disorder (PTSD) is a likely response to stress.[4] In contrast, stopping a long-duration high-fat diet has been shown to lead to depressive symptoms in patients, suggesting that the diet itself may have hedonistic effects, with its withdrawal unmasking or precipitating depressive symptoms. All of these promote cycles of weight gain and depressive moods.[9]

Neurocircuitry

Neurobiological processes of the brain responsible for drug addiction have been hypothesized to play a role in food addiction.[12] Addiction follows a three-stage cycle consisting of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. During the first stage, the patient experiences a rewarding feeling via the mesocorticostriatal dopamine pathways, which release dopamine and opioid peptides. Conditioned reinforcement through repeated drug use may occur through the mesocorticolimbic dopamine system, where neurons begin to fire during a specific stimulus prior to reward delivery. This process, referred to as incentive salience, leads to specific cues that cause cravings and desire for the drug, particularly during stressful situations. During withdrawal, decreased sensitivity to the drug leads to emotional dysregulation that can manifest as stress, irritability, and malaise, in part because of reduced dopamine and serotonin in the nucleus accumbens, in addition to disruption of the hypothalamic-pituitary-adrenal (HPA) axis. Aversive emotional states worsened by changes in release of corticotropin-releasing factor perpetuates negative reinforcement, which leads to drug-seeking behavior. Finally, relapse after drug avoidance occurs in the preoccupation stage.[12,13] This cycle is highlighted in food addiction, where repeat exposure triggers reward mechanisms releasing dopamine into the nucleus accumbens. Over time, dopamine D2 receptors decline so a greater intake is required for the same level of reward response.[13] Most who have food addiction often have a family history of addiction, and a genetic component is possible. Binge eating disorder (BED), a diagnosis of food addiction, is often associated with risk factors present in NASH and NAFLD. Development of type 2 diabetes is 13 times more likely in patients with BED, and obesity is present in more than 40% of patients.[14,15] Thus, treatment of BED can help minimize the risk for NASH development.

Biological links

A number of biological factors, such as genetics, disturbances in the HPA axis, inflammatory pathways, and other hormonal imbalances, have been implicated in the genesis of psychopathology related to obesity and NAFLD (Table 2, Figure 1).

Genetics

Approximately 200 genetic loci linked to obesity and weight gain have been described. Many of these genes are expressed in the hypothalamus, pituitary gland, hippocampus, and limbic system, with the former being responsible for appetite and the latter for mood regulation. Of the 50 loci found to be responsible for MDD, genes that contributed the greatest to depressive phenotypes overlapped with genes responsible for

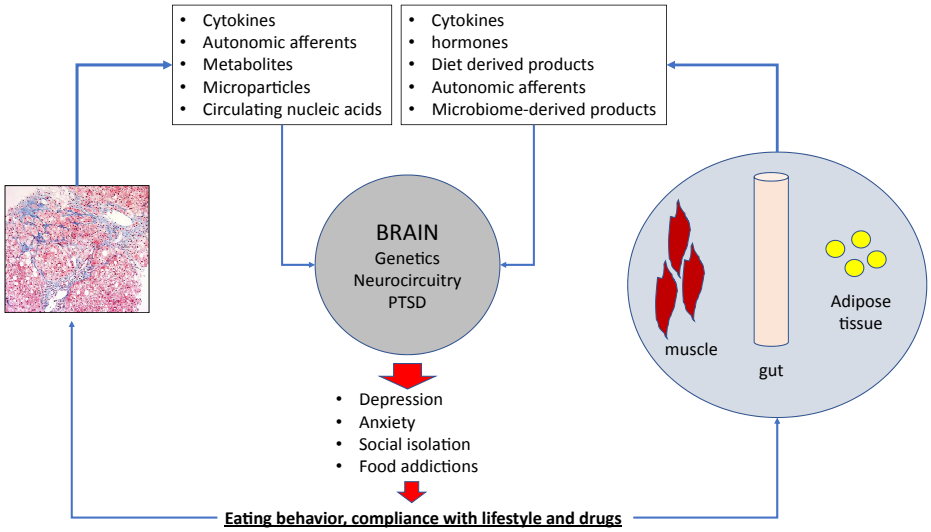

FIGURE 1 Biological and psychosocial factors linking NASH with psychiatric disorders. A number of biological, behavioral, and psychosocial factors have been implicated in the pathophysiological links between obesity, NASH, and mental health. Biological factors such as genetics, disturbances in the HPA axis, inflammatory pathways, and microbiome and other hormonal imbalances closely interact with psychosocial factors such as eating behaviors, perpetuating a vicious cycle of obesity, NASH, and psychiatric disorders

BMI determination, such as neuronal growth regulator 1 (NEGR1). NEGR1 has been specifically identified as a modulator for appetite and mood, with higher hypothalamic expression being linked to restricted feeding.[16] Dysfunctions with the gene have demonstrated correlations with both obesity and MDD. The recessive variant of another gene, patatin-like phospholipase domain-containing protein 3 (PNPLA3), responsible for glucose and fatty acid regulation, has been found more often in individuals with bipolar disorder and obesity.[5] Genome-wide association studies have indicated that PNPLA3 has NAFLD predisposing variants that may lead to NASH.[17] Beyond common genetic loci between NAFLD and mental disorders, it is hypothesized that microRNAs have some role in progression of NAFLD and mental disorders. miR-34a, responsible for lipid secretion and hepatic lipogenesis, is found to be elevated in patients with bipolar disorder, as well as patients with NAFLD.[5]

Inflammation

Obesity is a state of inflammation marked by the release of inflammatory markers, such as tumor necrosis factor (TNF) alpha, interleukins, and inflammatory cytokines. The inflammatory markers can disrupt negative feedback suppression of HPA activity by hindering glucocorticoid receptor (GR) function, preventing cortisol binding, and demonstrating shared links between obesity and mental health disorders.[16] In addition, secretion of inflammatory cytokines and adipokines contributes to insulin resistance and drives steatosis and lipotoxicity, a central feature of NASH.[5] The secretory protein, adiponectin, responsible for glucose and lipid homeostasis, shares links with both obesity and MDD. Adiponectin inhibits the secretion of cytokines such as TNF and interleukins, and a decrease in the anti-inflammatory protein has been found in patients with depression. Lower levels of circulating adiponectin are present in overweight patients, as well as those with NASH.[18] Moreover, under normal conditions, leptin mediates food intake, regulates mood via antidepressive properties, and is responsible for some immune function, such as producing inflammatory cytokines, TNF, and interleukins. However, disruption through loss-of-function mutations or leptin resistance may be risk factors for depression and weight gain.[16,19] A study investigating the relationship between inflammation and NAFLD, as well as NASH, reported finding elevated levels of TNF and interleukins.[20] Overall, the hepatic lipogenesis present in NAFLD is consistent with the secretion of inflammatory cytokines and adipokines present in obesity and mental health disorders.[10] The links between obesity, NASH, and mental health disorders are evident through inflammation and support a relationship in which one illness can lead to the others.

Microbiome

Buildup of fat in the liver through increased intestinal absorption and development of NAFLD and NASH has been attributed to a change in gut microbiota. Relationships between inflammation of hepatic and

adipose tissue, as well as steatosis, and alterations in intestinal flora are continuously being investigated, as are treatments. In addition, there is some evidence of a correlation among variations in the microbiota and mental health disorders. For example, inflammatory dysregulation by bacterial products has been linked to depression, dementia, and autism.[5] Human metabolism is directly impacted by the hundreds of species found in the gut. Bacteroidetes and firmicutes are two phyla of gastrointestinal bacteria responsible for energy production, and imbalances in the Bacteroidetes/firmicutes ratio have been attributed to obesity.[16] Milaneschi et al.[16] note that experimental manipulations of the ratio may lead to inflammation through an increase in gut permeability, and they can alter mood through depression-specific pathways. Specifically, a smaller ratio has been found in patients with MDD, and depression-like symptoms have been induced in rats via microbiota transplantation from depressed patients.

HPA axis

Dysregulation of the HPA axis leads to extended release of cortisol, leading to damage in brain areas responsible for mood and inhibition of lipid-mobilizing enzymes.[21] This has similar outcomes to Cushing syndrome, an endocrine illness that leads to weight gain via prolonged release of cortisol and shares similarities with defects in the HPA axis as seen in depression, thereby linking obesity with psychiatric disorders.[4] Hypercortisolism is common in obesity and often associated with changes in mood.[18] Excessive exposure to psychological stressors elevates cortisol levels via the initial release of corticotropin-releasing hormone and arginine vasopressin, followed by the release of adrenocorticotropic hormone.[18] Cortisol may promote obesity by promoting adipogenesis in visceral fat, increasing appetite, or suppressing thermogenesis in brown fat. The inflammatory characteristics of obesity can inhibit the negative feedback of cortisol release by interfering with the GR.[16]

CONCLUSION

The relationship between NASH, obesity, and mental health disorders is dependent on various biological elements and psychosocial factors. Elevated stress leading to emotional eating, genetics, dysfunction of the HPA axis, inflammation, and microbiome and hormonal imbalances all play significant roles. Despite the current understanding of the onset of the diseases, more research is required to understand the bidirectional correlation between obesity and mental health, as well as the specific pathways.

CONFLICT OF INTEREST

Dr. Sanyal is President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect, Exhalenz, and Hemoshear. He has served as a consultant to Astra Zeneca, Conatus, Coherus, Bristol Myers Squibb, Blade, Tobira, Takeda, Siemens, Merck, Genentech, Tern, Gilead, Lilly, Poxel, Artham, Boehringer Ingelhiem, Novo Nordisk, NGM Bio, Birdrock, Novartis, Pfizer, and Genfit. He has been an unpaid consultant to Intercept, Echosens, Perspectum, Immuron, Galectin, Fractyl, Affimune, Chemomab, and Nordic Bioscience. His institution has received grant support from Gilead, Salix, Tobira, Intercept, Bristol Myers, Shire, Merck, Astra Zeneca, Malinckrodt, Cumberland, and Novartis. He receives royalties from Elsevier and UptoDate.

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