Depression Can Beget Obesity Can Beget Depression

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Many patients suffering from depression are also overweight, or even obese,[1–3] and the comorbidity of depression and diabetes—frequently caused by obesity—is even greater.[4] This association has raised the possibility that a particular gene can, in some patients, confer vulnerability to both conditions.[5] Some evidence supports this hypothesis.[5] In the present issue of the *Journal*, Samaan and associates[5] confirmed that a high body mass index was positively correlated with depression status and found that 1 of 21 genetic variants (single nucleotide polymorphisms) was associated with both obesity and major depression. In an earlier study in twins,[6] the authors found that 12% of the genetic component of depression was shared with obesity. This indicates that the relationship between depression and obesity must also be generated by nongenetic factors, probably including the following 3 groups proposed:

1. iatrogenic mechanisms; for example, the administration of antidepressant, mood-stabilizing, or antipsychotic drugs may promote weight gain by suppressing satiety, diminishing physical activity, or increasing consumption of calorie-rich meals or snacks[7,8];
2. psychological inputs, in which the impairment in self-esteem, social isolation, and even chronic unemployment among many obese patients may in themselves promote feelings of depression[9,10]; and
3. metabolic/neurochemical processes through which the production and release of serotonin, a brain neurotransmitter implicated in the control of both mood and satiety, are impaired due to insulin resistance and to other metabolic consequences of obesity.[11,12]

Iatrogenic Obesity in Depressed Patients

The use of antidepressants—particularly paroxetine[7]—or of the mood stabilizers and antipsychotic agents administered to patients with bipolar depression—is often associated with weight gain. Although the increase may be limited to 15–20 pounds, this weight gain may be sufficient to change the individual's classification from overweight to obese. The mood stabilizers and antipsychotic agents can promote weight gain both by suppressing satiety and by diminishing physical activity[8]; these effects are especially troublesome for patients who are receiving several medications, each with its own potential for increasing body weight. Patients complain of an inability to feel satiated following meal consumption, even though portion sizes were satiating prior to treatment. Excessive snacking, or even consumption of a second meal soon after the first, is common, and often the foods chosen are high in fats and carbohydrates.[13] Some of these drugs decrease motor activity in normal experimental animals[8]; in depressed human subjects, the fatigue often produced as a drug side effect also increases weight by decreasing physical activity.

In our experience directing a weight-management center at a psychiatric hospital, we have found that many patients who gained weight while taking psychotropic drugs had not been overweight prior to treatment. Unlike the general population of obese individuals who struggle with weight control throughout their adult lives, many of these individuals, prior to treatment for depression, followed a healthy diet and exercised routinely. Now obese, they sometimes describe themselves as living in an alien body, embarrassed at no longer being slim and fit, and bewildered as to how to respond to remarks about their enlarged size. As one patient commented, "I can't stand up at a Weight Watchers meeting and tell everyone that I'm fat because I have been taking Paxil." When such patients discontinue treatment in order to avoid further weight gain, they risk remaining depressed or becoming depressed again. Their obesity, a side effect of their prior treatment for depression, may now prolong and amplify their continued depressed state.

Psychological Factors Promoting Obesity in Depressed Patients

The depressed mood seen among obese patients may result in part from situational stresses. A patient whose weight increased by 125 pounds while taking an atypical antipsychotic medication and who, as a consequence, developed diabetes, orthopedic restrictions, sleep disruptions, the inability to find employment, and social isolation volunteered that she became depressed because of the perceived hopelessness of changing her life. Another patient explained that she obtained solace only by ordering large quantities of take-out foods to "keep me company at night." Bariatric surgery had been suggested; however, her depression and obesity-related orthopedic problems made it impossible for her to adhere to the required preoperative weight-loss regimen. The weight gain does not have to be massive in order to contribute to the depression; it needs only to be sufficient to make the individual "hate her body" but feel incapable of improving it.

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Often, changing the situational or psychological environment is more effective in facilitating weight loss and improving mood than dieting or treatment for depression. A young law associate who was overloaded with work and often stayed in the office overnight to complete it fed herself from the candy machine to keep awake. A change in law firms solved her obesity problem.

Metabolic/Neurochemical Factors Promoting Obesity in Depressed Patients

Obesity, per se, can diminish the brain's ability to produce and release serotonin,[11] a neurotransmitter critically involved in sustaining mood and satiety. The insulin resistance of obesity impairs the ability of circulating tryptophan, serotonin's amino acid precursor, to enter the brain.[12] Tryptophan's passage across the blood-brain barrier is competitive with a number of other large neutral amino acids (LNAAs), principally, the branched-chain compounds leucine, isoleucine, and valine, and the 2 other aromatic amino acids, tyrosine and phenylalanine.[14,15] In normal individuals, the consumption of relatively small quantities of carbohydrates (eg, 25–30 g of carbohydrate in a snack, without protein[16]) induces sufficient insulin secretion to lower plasma levels of these other LNAAs by promoting their uptake into skeletal muscle. This enhances tryptophan's entry into the brain, where it can be converted to serotonin. In obese individuals, however, insulin resistance diminishes the fall in plasma LNAAs after carbohydrate ingestion, and thus decreases brain tryptophan uptake.[17] Moreover, basal plasma tryptophan levels also tend to be low. (Diabetes similarly reduces brain tryptophan and serotonin in rats.[18])

Attempts to treat obesity by decreasing carbohydrate intake (as with the high-protein Atkins Diet or South Beach Diet) only exacerbate the reduction in brain serotonin, often leading to carbohydrate craving, deterioration of mood (anger, depression), and insomnia.[19] Paradoxically, the consumption of dietary proteins—all of which, unlike carbohydrates, contain tryptophan—fails to elevate and may actually reduce brain tryptophan levels and serotonin synthesis. This is because tryptophan is a very minor constituent of dietary proteins (1%–1.5%) whereas the LNAAs that compete with tryptophan for brain uptake make up 20%–25% of most dietary proteins.[20] Hence the more protein in a meal or snack, the *less* brain serotonin levels may rise.

Often overlooked in understanding the overeating that accompanies depressed mood is that patients may overeat carbohydrates, usually as snacks, *in order* to enjoy a temporary respite from their painful mood state, ie, as an edible tranquilizer. Advertisers understand this very well; television ads show allegedly stressed models consuming chocolate candy, chocolate-coated ice cream, or gourmet cookies and, soon thereafter, displaying visible emotional relief. However exaggerated the depiction on television, the carbohydrate effect is real. A subset of obese individuals with pronounced carbohydrate craving routinely consume carbohydrate-rich, protein-poor snacks during the late afternoon, claiming that doing so improves their mood. When such patients were given beverages covertly containing carbohydrate or protein and their moods were assessed using standardized psychological tests, significant improvement followed carbohydrate but not protein ingestion.[21] Presumably the change in mood was linked to increased serotonin synthesis.

Women experiencing premenstrual syndrome[22] and those suffering from months' long seasonal affective disorder (SAD)[23] have also been shown to consume elevated quantities of carbohydrate-rich foods. We made direct measurements of their calorie and macronutrient intakes when they were not depressed (ie, during the follicular phase of the menstrual cycle in patients with premenstrual syndrome [PMS][2] or in late spring for those with SAD) and when they were depressed (ie, during the premenstrual phase or in November or December). Both diagnostic groups markedly increased their daily consumption of carbohydrate calories, in meals or as snacks, when depressed. The "I could kill for chocolate" admission attributed to mythical PMS patients is probably an overstatement, however, one of our subjects went out in a blizzard to buy chocolate ice cream. A woman suffering from SAD consumed only a very large bag of potato chips and orange juice every night for dinner for months over the late fall and winter.

The consumption of carbohydrate-rich foods by these groups was not simply due to their taste or mouthfeel. As with the studies on carbohydrate cravers, when women with PMS were given a beverage containing sufficient carbohydrate to elevate serotonin, their mood scores, control over appetite, and even ability to concentrate improved significantly.[22] Similar observations were made with individuals who experienced SAD over the long New England winter.[24]

Obesity, however, may be an unwelcome consequence of using foods as a form of self-medication because many of the foods usually selected may be rich in both carbohydrates and fats. Indeed, more than 50% of the calories in many pastries, doughnuts, chips, muffins, cookies, ice cream, chocolate, and bagels with cream cheese come from fat. Moreover, these snacks do not come with instructions to "eat one ounce and wait 30 minutes for your mood to improve." Unless taught otherwise, the moody, angry, anxious patient will continue to consume the carbohydrate-and-fat-rich foods until she or he feels better. Thus, considerably more than the needed 25–30 g of carbohydrate[16] may be ingested. And if the snack happens also to be consumed along with or soon after a protein-rich food, the increase in brain serotonin may be blocked, and the eater may consume additional calorie-rich snacks an hour or so later.

Unfortunately, the weight gain that follows unrestrained eating of high fat/high carbohydrate snacks may exacerbate the depression, as described above. Should the obese/depressed individual want to lose weight, the health caregiver may conclude, erroneously, that the dietary carbohydrates, and not the fat that accompanied them, must have been responsible for the weight gain and advise the patient to minimize carbohydrate consumption. This effect of consuming protein, in turn, may decrease brain serotonin synthesis, thus exacerbating the depression, causing carbohydrate craving, and extending the cycle of depression-obesity-depression.

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