



Review Article

Psychiatric Manifestations of Endocrine Disorders

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Abstract

When studying different endocrine disorders, it has been customary to focus on the hypothalamic-pituitary axis in discussing certain aspects of these disorders. Much less attention has concentrated on the psychiatric symptoms commonly associated with these disorders, and the need for physicians to think with an interdisciplinary approach in achieving the best possible outcomes for their patients. It is our goal through this review to provide a comprehensive assessment of the psychological aspects associated with many of these endocrine disorders. Specifically, we will address the psychological characteristics associated with diabetes, Cushing's syndrome, Addison's disease, hyperthyroidism, hypothyroidism, hyperparathyroidism, hypoparathyroidism, pheochromocytoma, and androgen and estrogen disorders, as well as a discussion of selected psychiatric issues in transgender patients.

Introduction

The endocrine system has been studied extensively from physiological, biochemical, and molecular approaches. However, much less attention has concentrated on the psychological aspects associated with these different endocrine diseases, and the necessity of addressing these psychological issues in order to effectively treat endocrine patients. Often, there is a significant impairment in the quality of life when it comes to these different endocrine diseases, and an interdisciplinary approach is needed in order to achieve the best possible outcome for the patient. It is our goal through this review to provide a comprehensive assessment of the psychological implications associated with different endocrine disorders. Specifically, we will address the psychological aspects associated with diabetes, Cushing's syndrome, Addison's disease, hyperthyroidism, hypothyroidism, hyperparathyroidism, hypoparathyroidism, pheochromocytoma, and androgen and estrogen disorders, as well as a brief correlation of transgender adults.

Adrenal: Cushing's Syndrome and Addison's Disease

Over the past few decades, a number of authors have found a significant amount of psychological disorders associated with

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Cushing's syndrome. Sonino and Fava [1] found that major depression is a life-threatening complication, which may affect 50-60% of patients with Cushing's syndrome. They found that it occurs in both the pituitary dependent and independent forms of the disease. Kelly et al., [2] found a similar association with 57% of 209 Cushing's syndrome patients having a significant psychiatric illness, usually depression. A follow-up study by Sonino et al., [3] found that 54% of patients with pituitary-dependent Cushing disease had major depression according to DSM-IV criteria. They observed that the depression in Cushing's syndrome was significantly associated with female gender, older age, higher urinary cortisol levels, a relatively more severe clinical condition, and an absence of a pituitary adenoma. Other authors have also found the same correlation between depression and Cushing's syndrome [1,4-7]. While depression is one of the most important psychological symptoms associated with Cushing's syndrome, other symptoms have been noticed. Starkman et al., [8] and Starkman [9] reported that around 66% of their Cushing's syndrome patients experienced generalized anxiety or panic disorders. Sonino et al., [10] also found a significant association between anxiety and Cushing's syndrome. In this same particular study, the authors also saw there was a significant association in their Cushing's syndrome patients with increased irritable mood, higher levels of stress, and lower physical well-being. Mania and hypomania are other psychological symptoms that have been associated with Cushing's syndrome by a number of authors [11,12].

There has been a significant debate in the literature whether the psychological symptoms of Cushing's syndrome completely resolve after the remission of the disease. Several studies have found significant improvements or even complete remission of anxiety, hypomania, mania, depression, and mood irritability, after correction of the hypercortisolism [2,13-17]. In particular, Dorn et al., [6] found significant improvements of depression in patients after 3, 6, and 12 months, of treatment based on the Hamilton depression rating scale and depressed mood scale. Also of note, it has been postulated by a number of studies that inhibitors of corticosteroids like ketoconazole or metyrapone may be better in treating psychological symptoms of these patients, rather than the antidepressant drugs [9,18].

However; as mentioned, other studies have found delayed treatment or continued presence of psychological symptoms after normalization of cortisol levels. Long-lasting effects of anxiety, depression, attention, and mood, have been seen to persist long after treatment of Cushing's syndrome [19-22]. The effect of excess glucocorticoids causing brain atrophy has been believed to be the mechanism causing the neurocognitive symptoms seen in Cushing's syndrome patients and has been thought to be partially irreversible even after the disease has remitted [23]. Through proton magnetic resonance spectroscopy, Resmini et al., [24] found there was neuronal dysfunction and persistence of neuronal damage in the hippocampus even after the remission of the disease. Dorn et al., [6] has even noted that psychiatric symptoms might even exacerbate after disease remission because of the cortisol decrease. Overall, with the discrepancies of this subject in the literature, it can be said that more long-term studies are needed to answer the question of whether or not there is a continued persistence of psychological symptoms even after the normalization of cortisol levels.

Addison's disease has been found to present with different psychological symptoms as well. The symptoms of irritability, mood behaviors, distress, depression, and to a minor extent psychosis, have been reported by a number of studies to be associated with the disease [25-27]. Anglin et al., [25] brings up the point that psychiatric symptoms may even be the only symptoms present in Addison's disease patients, so it is important when seeing these symptoms to maintain a high index of suspicion for this potentially fatal condition. Potential mechanisms that have been proposed to explain these neuropsychiatric symptoms of Addison's disease include: electrophysiological; glucocorticoid deficiency; electrolyte and metabolic abnormalities; increased endorphins; and an associated Hashimoto encephalopathy. However, the mechanism remains unknown [28]. Also, in a few studies, it has been found that there is a significant improvement in psychological symptoms once Addison's disease is corrected with appropriate corticosteroid therapy [3,27]. Iwata et al., [29] even suggests that performing blood work for ACTH and cortisol in the field of psychiatry is necessary because Addison's disease can often be overlooked when psychiatric features are present (Table 1).

Endocrine Condition	Psychiatric Symptoms
Hypercortisolism Depression	Anxiety, Panic disorders, Irritability, Mania, Hypomania, Poor self-image hypocortisolism irritability, Distress, Mood disorders, Depression
Type 1 Diabetes	Depression, Psychomotor agitation, Sleeping difficulty, Eating disorders
Type 2 Diabetes	Depression, Eating disorders, Poor self-image
Hyperthyroidism	Anxiety, Irritability, Mania, Hypomania, Psychosis, Insomnia, Attention and Overactivity problems, Depression, Restlessness, Fatigue, and Delirium
Hypothyroidism Depression	"Myxedema madness", Attention deficits and cognitive disturbances
Pheochromocytoma	Anxiety, Panic disorders, Tremulousness
Hyperparathyroidism	Anxiety, Depression, Personality changes, Psychosis
Hypoparathyroidism	Depression
Androgens	Increased aggression, Anger, Acting out, Dominant behavior, Antisocial behavior
Androgens	Increased sexual desire and Seductive behavior
Menopause	Depression

Table 1: Collective Review of Psychiatric Symptoms associated with Endocrine Conditions.

Type 1 and Type 2 Diabetes

Type 1 and type 2 diabetes are endocrine disorders, which are also associated with psychiatric symptoms. In a study of 330 type 2 diabetic patients, Derakhshanpour et al., [30] found a significant association with depression and poor self-image, which was noted as having a considerable impact on the consequences of diabetes and the quality of life in the patients. Semenkovich et al., [31] reported the statistic in his study that clinically significant depression is present in one out of every four patients with type 2 diabetes. A number of other authors have also found this association of depression and poor self-image with type 2 diabetic patients [32-34]. As Egede et al., [35] and Nicolau et al., [33] mentioned, physicians need to be aware of the psychiatric symptoms associated with diabetes because when the psychiatric issues of diabetes are not diagnosed and treated, the financial cost to society and the health care system is catastrophic.

Eating disorders are commonly seen in type 2 diabetic patients as well. In a study of 320 type 2 diabetic patients, Nicolau et al., [33] found that 16% had eating disorders and 12.2% had binge eating

disorders. In their study of 152 type 2 diabetic patients, Celik et al., [36] found similar findings. Eating disorders are also seen in type 1 diabetics where patients will intentionally omit their insulin to induce hyperglycemia and induce loss of glucose in the urine in order to lose weight [37,38]. The common denominators for the development of eating disorders in type 1 and type 2 diabetic patients are increased body weight, body dissatisfaction, female gender, a history of dieting, and a history of depression. Clinical signs that should raise suspicion to the physician include poor glycemic control, recurrent episodes of diabetic ketoacidosis, recurrent hypoglycemia secondary to intentional overdose, missed clinical appointments, poor self-esteem, and dietary manipulation [38].

With type 1 diabetes and psychiatric symptoms, Raymond [39] makes the plea that, "Additional research, specifically interventions successfully addressing the behavioral and psychosocial issues in this population, is desperately needed," because, "Behavioral and psychosocial issues in adolescents with DM1 greatly impact their diabetes and general life outcomes." In their study of 295 adolescents with type 1 diabetes, Adal et al., [40] found a significant correlation with depression and anxiety with a reported depression rate of 12.9%. A number of other authors have also found these correlations of psychiatric symptoms with type 1 diabetes including the issue of psychomotor agitation, sleep difficulty, and eating disorders [34,41-44]. Cox et al., [46] brings up the point that type 1 diabetes can be difficult to manage for patients because of three contributing themes. These themes are parental influence, peer influence, and depression, which all can lead to non-compliance in type 1 diabetic patients.

Thyroid: Hyperthyroidism and Hypothyroidism

When it comes to the subject of hyperthyroidism and hypothyroidism, there have been a number of studies that have found psychological symptoms associated with both hormone imbalances. Stern et al., [47] found in their study of 137 patients with Grave's disease that the psychiatric symptoms of anxiety and irritability were strongly correlated with the disease. Kathol and Delahunt [48] reported that 60% of their hyperthyroid patients were found to have an anxiety disorder. Furthermore, several other studies have found these symptoms as well as other psychiatric symptoms associated with Grave's disease which include hypomania, mania, depression, psychosis, insomnia, attention and over activity problems, restlessness, fatigue, and delirium [26,49-58]. As far as treatment, there are discrepancies with some studies that have found that psychiatric symptoms like anxiety generally improve with the treatment of hyperthyroidism [26,48,59]. However, other studies have reported that psychiatric symptoms persisted despite appropriate anti-thyroid treatment [47,60-63].

As alluded to earlier, hypothyroidism has been associated with a number of psychiatric disorders. As early as 1888, the effects of hypothyroidism on the psychological state were recognized by the Clinical Society of London in their study of 109 cases with myxedema. They reported that, "delusions and hallucinations occur in nearly half the cases, mainly when the disease is advanced [64]." In 1949, Asher reiterated this relationship of psychosis and hypothyroidism, and coined the infamous term, "myxedematous madness" [28]. Since then, numerous studies have been working to characterize the psychological symptoms associated with hypothyroidism. In a study of 2,142 individuals diagnosed with thyroid disorders, Ittermann et al., [65] found substantial evidence that untreated hypothyroidism is significantly associated with depression. A number of other studies have found this correlation in hypothyroid patients and have observed additional

psychological problems associated with hypothyroidism including attention deficits and cognitive disturbances [26,50,66-68].

Pheochromocytoma

In adults and children, psychiatric symptoms like anxiety are known to be associated with pheochromocytoma patients and patients with increased catecholamines. In their study of 93 patients with pheochromocytoma, Anderson et al., [69] found a significant association with the symptoms of anxiety and tremulousness in their patients, which resembled a panic attack. Lenders et al., [70] report that psychological symptoms like anxiety and panic are common in pheochromocytomas and say that these symptoms are seen in 20-40% of pheochromocytoma patients. In their epidemiological study of 284 patients with pheochromocytoma, Mannelli et al., [71] found a similar percentage of patients with anxiety with 35% having the symptom. A number of other studies in the literature have furthermore found a significant correlation with psychiatric symptoms like anxiety in pheochromocytoma patients, and it has been reported that anxiety is the fourth most common symptom seen in pheochromocytomas [72]. As a number of authors have pointed out, it is easy for physicians to confuse psychiatric symptoms of pheochromocytomas with other neuropsychiatric disorders, so it is imperative that they keep this diagnosis in mind, especially if a pattern of hypertensive episodes persists or worsens in the patient [73,74].

Parathyroid: Hyperparathyroidism and Hypoparathyroidism

Psychiatric disorders have been found to be connected with parathyroid disorders. In his study of 169 hyperparathyroid patients, Espiritu et al., [75] found a significant association between depression and hyperthyroidism. They observed that hyperparathyroid patients were twice as common in developing depression compared to controls, and the severity of hyperparathyroidism as reflected by the serum calcium level is related to depression. Weber et al., [76] also found a significant correlation with 23% of hyperparathyroid patients having depressive symptoms, and Wilhelm et al., [77] found that 10% of his 360 hyperparathyroid patients met the DSM-IV criteria for major depression. The literature has further reported that hyperparathyroid patients have a reduced quality of life [78], and Pasiaka et al., [79] found a significant improvement in quality of life of patients after parathyroid surgery. Joborn et al., [80] found that out of their 441 hyperparathyroid patients that 23% had psychiatric symptoms with the most common being anxiety and depression. But, they also reported a number of patients with psychosis. Other studies have confirmed the relationship of hyperparathyroidism to anxiety and depression and in addition have seen an association with personality changes in these patients [81,82]. As far as the mechanisms, Espiritu et al., [75] report, "The mechanism by which PHP (hyperparathyroidism) leads to depression is unclear," and all the psychiatric symptoms associated with hyperparathyroidism for that matter. It has been popular in the literature to see if the psychiatric symptoms of hyperparathyroidism disappear after parathyroidectomy. Wilhelm et al., [77] reported that 90% of patients, who had depression before the parathyroidectomy, no longer had any depression after the surgery. Also, they reported that a parathyroidectomy in hyperparathyroid patients saves an estimated 700 to 3,000 dollars per patient per year in anti-depressant medication alone.

Psychiatric symptoms are also evident in hypoparathyroidism. In a study of 62 hypoparathyroid patients, Aggarwal et al., [83] found that

neuropsychological dysfunctions were present in one-third of their patients, and these dysfunctions correlated with duration of illness, female gender, serum calcium, and calcium-phosphorus product during follow-up but not with intracranial calcification. Also, Bohrer et al., [84] and Rosa et al., [85] both supported the claim that depression is associated with hypoparathyroidism and that psychiatric disorders seemed predominant in the setting of long-term hypoparathyroidism. As Bohrer et al., [84] mentioned concerning the potential proposed mechanisms of depression with hypoparathyroidism, "The exact cause of depression in cases of hypoparathyroidism is not known." Furthermore, it was found that psychiatric symptoms did not improve with conventional antidepressants and antipsychotics until the serum calcium levels were corrected [34,85].

Androgens

Androgen disorders have been found to have psychiatric symptoms associated with them as well. In the large study of 4,179 veterans, Mazur et al., [86] found that basal testosterone levels were positively correlated with aggression and antisocial behavior. Archer [87] found through his study that androgen levels have an influence on aggression, and Mazur et al., [86] discovered that androgens are furthermore positively linked to dominant behavior. In the literature, there has been a popular trend to look at prisoners who have committed violent crimes and see if there are any irregularities in hormone levels that might explain their criminal history. Kreuz and Rose [88] found in their assessment of the young criminal population that criminals who committed violent crimes during their adolescence had higher testosterone levels. Dabbs et al., [89] proceeded to measure the free testosterone levels in saliva of 89 prisoners and found a strong association with higher testosterone levels in the prisoners who committed violent crimes versus those who committed non-violent crimes. These studies of criminals; however, should be taken with some reservation though because of the smaller sample sizes and unnatural conditions associated with these studies. In addition to the above literature, a number of other studies have found this association between aggression and androgens and have seen that androgens are associated with other psychiatric symptoms including anger, impulsivity, competitive traits, and violence [90-93]. When looking at adolescents, a number of studies have found a positive correlation of aggression, anger, and acting out, with the contribution of different forms of androgens like testosterone, androstenedione, and DHEA [94-96].

Patients with an androgen deficiency have been found to be associated with psychiatric symptoms. Aydogan et al., [97] is quoted as saying, "Anxiety and depression are the most common and frequently undiagnosed psychological problems associated with male hypogonadism." In their study of 4,393 Vietnam veterans, Booth et al., [98] had their patients' free testosterone levels and depressive symptoms tested. From their study, it was found that there was a significant association between low testosterone levels and depression, and in another study of 869 men over the age of 60, Kurita et al., [99] found this correlation as well. Others have also seen this link between depression and androgen deficiency in their studies [100,101]. As far as treatment, Khara [102] proposes that testosterone deficient patients should be given a trial of testosterone replacement therapy for at least 3 months as testosterone replacement therapy alone may improve clinical symptoms of depression. In the meta-analysis of 355 depressed patients with hypogonadism, Zarrouf et al., [101] further supported testosterone treatment when reporting that there was a significant improvement of the Hamilton depression rating scale among patients who were administered testosterone replacement therapy.

Menopausae, Estrogen, and Progesterone

In women, the transition to menopause and its hormonal alterations has been associated with increased depression. In a study of 376 women near menopause, Mauas et al., [103] found a high prevalence of a newly depressed mood among these women, who had no history of depression before menopause. The authors attributed these findings to the ever changing hormonal setting seen during menopause. In addition, their study made the claim that a diagnosis of depressive disorder was 2.5 times more likely to occur in the menopausal transition than premenopausal. Freeman et al., [104] and Gordon et al., [105] both found similar findings saying that the menopause transition is associated with a two to fourfold increased risk of major depressive disorder. These findings are consistent with the results of the SWAN (Study of Women's Health across the Nation) of 3,302 women aged 42 to 52 [106]. The study showed that the odds of depressive symptoms significantly increased as women progressed through the menopausal transition. As far as the mechanism to explain the increased risk of depressive symptoms in menopause, a number of mechanisms have been proposed, but the exact cause is still unknown [105,107]. It has been found by a number of studies that hormonal therapies like estrogen are extremely effective in all menopausal symptoms including depression [13,108,109]. Dibonaventura et al., [110] brings up an important point in his paper saying that depression around the menopausal period worsens a patient's quality of life but also causes more of a burden on health care resources and increases costs, so physicians need to be aware of the potential development of depression in women going through menopause.

Estrogen and progesterone also influence the psychological behavior of an individual. In a study of 48 menopausal women, Sherwin [111] gave treatments of estrogen and progestin to her patients. She found that sexual desire and arousal were significantly higher in her treatment group compared with her placebo group. Nathorst-Boos et al., [112] did a similar study giving their patients treatments of transdermal estradiol and found that the frequencies of sexual activity, sexual fantasies, and degree of sexual enjoyment were increased. Wiklund et al., [113] further showed, in their study with transdermal estradiol, that there was an increase in feelings of physical attraction and sexual satisfaction compared to their placebo group. In addition, drugs like tibolone, which is a second generation SERM (selective estrogen receptor modulator), may even be beneficial after surgical menopause because of its effects in improving mood and sexual behavior [114,115].

Correlate: Transgender Adults and Endocrinological Aspects

Through their work reviewing ten different studies from eight different countries spanning over forty years, De Cuypere et al., [116] provided the most accurate statistics available of prevalence in transgender adults. They reported the prevalence from these studies ranged from 1:11,900 to 1:45,000 for Male-to-Female individuals (MtF) and 1:30,400 to 1:200,000 for Female-to-Male (FtM) individuals. As rare as these statistics might seem, it is still important for healthcare professionals to know the best way to assist transgender adults in order to maximize the overall health of these individuals. This is where the World Professional Association for Transgender Health (WPATH) comes into play who is an international, multidisciplinary, professional association whose mission is to promote evidence-based care and respect for transsexual and transgender health. One of their main goals is to provide guidance to health professionals in how to provide

the best care possible for transgender patients through their Standards of Care manual [117].

The importance of effective hormonal treatment in transgender patients is made evident through the study of Murad et al., [118] He found that gender dysphoria can mostly be alleviated by treatment, and many individuals will find a gender role that is comfortable for them as a result, even if it differs from their gender assigned at birth. Green et al., [119] found across different studies that satisfaction rates of sexual reassignment patients ranged from 87% of Male to Female (MtF) patients to 97% of Female to Male (FtM) patients, and regrets were extremely rare [120]. Medical interventions carry risks however, and physicians must weigh the risks and benefits when considering hormonal therapy in transgender patients. Estrogens of feminizing hormone therapy significantly increase the risk of venous thromboembolic events, particularly in patients who smoke and patients who are over 40. Furthermore, estrogens significantly increase the risk of developing cardiovascular events, high triglycerides levels, and high liver enzyme levels, in MtF patients. Also, estrogens have been found to increase the risk of type 2 diabetes, hypertension, and prolactinoma [117]. In FtM patients, masculinizing hormone therapy involving testosterone and other steroids is known to significantly increase the risk of polycythemia and weight gain. In addition, testosterone therapy in FtM patients has been linked to increasing the risk of lipid disorders, liver enzyme elevations, and psychiatric symptoms in patients with underlying psychiatric disorders. These psychiatric symptoms include bipolar, schizoaffective, and other disorders that may include manic or psychotic symptoms [117]. Fertility is another issue endocrinologists must keep in mind before starting hormonal therapy. Masculinizing and feminizing hormones affects fertility, so the endocrinologist should discuss these issues with the patient and provide information on sperm-preservation and embryo freezing options if needed.

The World Professional Association for Transgender Health also provides guidelines to physicians for treating transgender adolescents with hormonal therapy if they meet a particular set of criteria and their parents or caretakers give consent. The goal is to suppress puberty through hormonal treatment with GnRH analogues to stop the production of testosterone secretion in males or estrogen and progesterone secretion in females. This is done in order to prevent the development of secondary sexual characteristics that are not desired which would lead to more years of intense gender dysphoria. The adolescent's physical development as well as the hormonal regimen should be under strict supervision by a pediatric endocrinologist. This hormonal therapy given to the youth differs substantially from adults and is adapted to take into account the somatic, emotional, and mental development that occurs throughout adolescence [121].

Conclusion

As outlined through this extensive review of the literature, psychological symptoms are an important aspect in a variety of endocrine conditions. It is our hope that physicians will now be more aware of these psychological issues so that they are able to treat their patients in a more concise and effective manner. In the future, further research and studies need to be performed because most of the mechanisms to explain how psychiatric symptoms, in patients with different endocrine disorders, arise are still unknown. In addition, treatment aspects of some of the different endocrine disorders need to be further investigated because there are discrepancies in the literature as to what degree correction of the hormonal issues will alleviate the psychiatric symptoms associated with the disorder. In summary and as

emphasized throughout this literature review, we believe it is vital for the physicians to think with an interdisciplinary approach when treating endocrine disorders, in order to provide the best quality of life and achieve the best possible outcomes for their patients.

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