Relationship between Substance use and Endocrine Disorders: A Narrative Review

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Abstract

INTRODUCTION

Substance use disorder is one of the significant public health concerns and the co-morbidity with endocrine disorders has a potential to cause adverse outcomes. There is a definite link between substance use and dysregulation of endocrine system at a level of causation, association, management and drug interaction. It has been seen that the screening of substance use while managing endocrine disorders is a must. Also, integrated management of both of these chronic condition with collaborative care approach can not only help in effective management but also improve the outcomes in terms of mortality, cost effectiveness, stigma and financial burden. Though considered important this common area seems to be understudied. Hence we recommend that this co-occurrence of substance use and endocrine disorders should be studied and guidelines be developed for the effective management.

KEYWORDS

Substance use disorder, Endocrine disorder, co-morbidity

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INTRODUCTION

Psychoactive substance (substance) use as a risk factor accounts for 11% of total health burden globally and is regarded as a major public health concern.[1] United Nations' Sustainable Development Goals for 2030 has featured prevention and treatment of substance use disorders (SUDs) in the targets highlighting the need to focus on these addictive disorders.[1] Substance use disorders pose additional challenges due to their intricate association with other medical disorders. Endocrine disorders are among such disorders that share a multifaceted interface with substance use disorders. A review from US states that the prevalence estimates of endocrine disorders even without co-morbidity have posed a significant public health burdens.[3] The co-occurrence of these conditions adds to the burden. Substance use disorder can present as co-morbid condition along with different endocrine disorders and also serve as a risk factor for emergence of endocrine disorders.[4] Substance use disorders can complicate the clinical presentation, diagnosis, management, course and outcome of the endocrine disorders when the two occur as comorbidity. More importantly, this interaction is not unidirectional and even the endocrine disorders impact the emergence, management, course and outcome of the substance use disorders in different ways. There is much higher expenditure for the patients who have comorbid substance use disorder and medical disorders like endocrine disorders due to hospitalization, prescription drugs, clinical visits than those without such comorbidities.[5] Also lack of screening services and integrated care tends to delay the management and impact the course and outcome adversely. This shortcoming of the clinical care delivery is partly attributable to limited

focus on this comorbidity in research studies For instance substance use in type 2 diabetes has been described as 'dangerous but understudied' problem.[6] It has been highlighted that SUDs in persons with complex healthcare needs, especially endocrine disorders are insufficiently studied and need systematic exploration to inform targeted screening and care-coordinating efforts.[7]

In this article we aim to provide a narrative overview of the co-morbidity of these two set of disorders and offer recommendations on assessment and management of the same. We also highlight the research need in this area going ahead.

Substance use as risk factor for endocrine disorder

Psychoactive substance use has been identified as a risk factor for emergence of certain endocrine disorders. Exogenous opioids when consumed as substance of abuse have effects on multiple levels of the endocrine system, although the mechanisms are not yet fully elucidated. There have been reports of chronic opioid use being implicated in adrenal sufficiency.[8] There is ample evidence that chronic opioid use can cause hypogonadotropic hypogonadism in both men and women. Although less frequent, cortisol deficiency can also be found among those with chronic opioid use. The data on the impact of opioids on GH and TSH are not much clear. Hyperprolactinaemia can be occasionally detected along with opioid use disorder. One of the important negative impacts mostly overlooked of opioids on endocrinology is the bone health.[9] Opioid administration leads to a metabolic state similar to diabetes and it can also worsen diabetes by decreasing insulin secretion in both humans and animal models. There is a role of opioids in glucose hemostasis and exogenous opioids might lead to higher chances of individuals having diabetes.[10]

Alcohol use is one of the important cause of pseudo-Cushing's syndrome.[11] The association between both acute and chronic alcohol consumption and lower testosterone levels have been demonstrated in research studies.[11] In a study comparing 66 men with alcohol use disorder with 30 controls without alcohol use disorder it was found that chronic alcohol consumption significantly increased FSH, LH, and estrogen levels.[12] This could lead to the symptoms of hypogonadism hypoactive sexual desire, erectile dysfunction, and reduced sperm quality and quantity in men. In case of female too the alcohol can cause the symptoms of hypomenorrhea, amenorrhea, and other menstrual irregularities due to the alteration of the hormonal levels. One of the mechanisms for hypogonadism due to alcohol use is via alcoholic liver disease, but it can also cause hypogonadism independently in the absence of severe liver disease. In addition, the people with alcohol dependence often show dysregulation of the hypothalamic-pituitary-thyroid axis. A study showed a significant reduction in T4 and T3 concentrations in the chronic alcohol using groups during withdrawal and early abstinence, compared to non-alcohol taking healthy groups.[13] Also there has been evidence of a blunted response of TSH to TRH in persons with alcohol use disorder during early withdrawal. This was found to be positively correlated with severity of withdrawal symptoms. However, after longer periods of abstinence, thyroid dysfunction was found to recover and thyroid hormones and TSH response to TRH returned to normal levels.[14] This, in turn, causes hormonal disturbances that leads to various disorders such as stress abnormalities, reproductive deficits, body growth defect, thyroid problems, immune dysfunction, cancers, bone disease and psychological and behavioral disorders.[15-16] One of the most important areas is the relationship between alcohol use and diabetes. Some evidence suggest that alcohol consumption reduces the incidence of type 2 diabetes mellitus especially in women and non-Asian populations whereas binge drinking seems to increase the incidence..[17-18] In a study with 4536 participants in China higher alcohol intake appeared to be causally associated with increased risk of diabetes, even for moderate alcohol use.[19] It has been seen that alcohol antagonizes the insulin-stimulated glucose disposal in peripheral tissues and suppress the hepatic glucose production via alcohol induced damage or alcohol induced liver disease. Also, chronic alcohol use leads to pancreatic β-cell dysfunction and apoptosis which may then lead to diabetes.2021

Smoking has been identified as a risk factor for Graves' disease and Graves ophthalmopathy. Moreover, this risk is reduced on tobacco cessation.[22] Another important effect of smoking is osteoporosis via its effects on various hormones especially anti-estrogenic effect in women. Smoking might also cause fertility problems and premature menopause.'23 Smoking causes changes in insulin secretion by the β cell of the pancreas and can mediate insulin resistance. This results in impaired glucose metabolism that can lead to development of diabetes. Also, smoking-induced endothelial dysfunction has a key role in the development of vascular complications of diabetes.[24] A meta-analysis of 22 eligible articles representing 343,573 subjects and 16,383 patients with type 2 DM from Japan estimated that 18.8% of DM cases in men and 5.4% of DM cases in women were attributable to smoking.[25] Maternal smoking and even passive smoking can delay growth of young children through decrease in Growth Hormone.[26]

Cannabis use can lead to subtle lowering of T4 hormone, decrease in testosterone, oligospermia and impotency in male, and inhibit the secretion of growth hormone especially impacting the fetal growth. Overall cannabis has a depressant effect on most of the hormones but their clinical implications are yet to be revealed clearly.[27-28]

The impact of use of substances like cocaine and inhalants on endocrine system are less studied. There are several effects of the short- and long-term of inhalant abuse mainly in energy and metabolic processes and glycemic control. It can cause dysfunction of metabolic homeostasis through altered adipose tissue, bone, and hypothalamic-pituitary-adrenal axis function.[29] Several hormonal effects are seen in cocaine abuse like disruption of HPA axis and gonadal axis hormones and need for further studies is highlighted to see the clinical implications..[30] There are very few studies that have looked

in the endocrine effects of Amphetamine-type stimulants (ATS), however3, 4-Methylenedioxymethamphetamine (MDMA) has been shown to increase plasma concentrations of cortisol, prolactin, and oxytocin compared with placebo.[31] There are case reports of ATS leading to dysregulation of blood glucose level in diabetes which needs further research.[32-33]

What makes it even more challenging clinically is the fact that the endocrine manifestations of substance use and SUDs are probably more often subclinical than clinically overt. The knowledge about the range and scope of these potential endocrine effects of substance use and SUDs can make a clinician more vigilant for clinically relevant disturbances whenever they tend to occur.

Endocrine disorders as a risk factor for SUDs

It is seen that endocrine disorder could be a risk factor for substance use. An electronic health record data of 211880 from USA showed that substance use (tobacco, alcohol, any drug) was significantly more prevalent among patients with diabetes than those without it (22.5% vs 11.9%)[34]. Another study among 166 adults with type 1 diabetes showed frequencies of substance similar or more that of the general population, fairly high misuse of prescription opioid and sedatives, and frequent drinking.[35] It is usually seen that youths with chronic medical condition have a higher tendency to have substance use problems which could be a form of self-medication for disease symptoms or comorbid depression or anxiety.[36] On the basis of pathophysiological mechanism it is seen that any event that leads to change in HPA activity like stress leads the patient with substance use disorder to relapse.[37] The onset and continuation of an endocrine disorder is stressful for the patient. It has been seen that situations causing stress can increase the vulnerability to substance use disorder both in terms of development of dependence and risk of relapse. The psychological theories view substance use as a coping strategy to deal with stress or reduce tension. The neurological theories explain this in terms of involvement of the mesolimbic dopamine, glutamate, and gamma-amino-butyric acid (GABA) pathways.[38] One of the neurobiological hypothesis states that in patients with diabetes the disruption in insulin signaling causes suppression in the dopamine system. This can enhance substance reward and thus explain higher prevalence of substance like nicotine in diabetes.[39]

Impact of Substance use on management of endocrine disorder

When we look at diabetes as a prototype endocrine disorder it can be seen that the patients who have comorbid substance use disorder present with more adverse outcomes and poorer adherence to diabetes care than those without a substance use disorder.[40] A randomized controlled trial showed that diabetes could significantly increase the likelihood of premature death among people with co-occurring substance use disorders at the end of 12 years (41% with diabetes compared to 10% without diabetes).[41] Apart from that there are many consequences of untreated substance use disorders on the medical complications of diabetes as well. The substance use might also hamper the implementation and completion of structured education which is underpinning component of successful management of Type 2 DM.[42] When we look at the financial burden, a study done from the Veteran Health Administration and Medicare fee-for-service claims database (fiscal years 1999 and 2000) with sample size of 390,253 showed that the total average expenditure was highest among the patient who had co-morbid diabetes and substance use as compared to only diabetes group.[43] There are many substances that may interact with the drugs given for endocrine disorders. For example sulfonylureas used in the treatment of diabetes has an interaction with alcohol where alcohol inhibits hepatic gluconeogenesis and increases the risk of developing hypoglycemia during sulfonylureas treatment and even may cause disulfiram-like flushing reaction.[44] Both endocrine disorders and substance use involve a wide range of neurotransmitters, hormones, and different other biological systems, the treatment of one can influence the other which are yet to be delineated. Some of the examples are mentioned in Table 1.

Screening and integrated management:

Like most of the endocrine disorders, substance use disorder is also a chronic condition that needs to be monitored and managed clinically over a long period of time in order to reduce the risk of relapse and promote full recovery. In the time where psychosocial aspects of different endocrine disorders are being highlighted in causation, association and management .[45], the integration of substance use disorder in the form of screening, brief intervention and referral to specialist can be done along with the treatment of endocrine disorders. Endocrine clinics as well as primary health care centers can present as a unique opportunity in this regards. There are two major models with which we might be able to link the substance use disorders and endocrine disorders. The first model known as centralized model brings primary care, mental health, and/or substance abuse services together at a single site. This is also known as one-stop shopping model that has been implemented in primary care clinics and substance use disorder treatment programs. This model helps to overcome the substantial political, bureaucratic, attitudinal, geographical and financial barriers that separate substance-dependent persons from needed services.[46] A randomized controlled trial among 592 adults from a large health maintenance organization chemical dependency program in Sacramento, Calif showed that the individuals having substance abuse related medical condition benefit from integrated medical and substance abuse treatment, and such an approach can be cost-effective.[47] Another model for linking is a distributive model. Here the sites providing care for endocrine disorders can be linked by effective systems to refer patients with substance use disorder to the specialized site. Successful referral is the core task of the distributive model. However, evidence suggest that referral alone cannot

integrate the care of patients with substance use disorder in primary care settings. Collaborative care model incorporating evidence-based integrative medicine interventions that includes care coordination, enhancing inter professional communication, non-pharmacological interventions/ complementary therapy and physical integration of primary and secondary health care have been proposed to adequately address mental health problems with comorbid medical conditions.[48] Similar approach can be applied in case of coexisting substance use and endocrine disorders.

One direction in this regards could be utilization of a chronic care management model which have the standards for patient-centered medical homes, the one devised by the National Committee for Quality Assurance. These standards provide the criteria for guiding and measuring quality of health care and coordination, involving team management of chronic diseases among primary and behavioral health care providers. This may be relevant for patients with coexisting substance use disorders and endocrine disorders.[49-50] These standards are defined across six categories:

- Enhancing care access and continuity of care both of which are important to patients with coexisting disorders such as endocrine and substance use disorder
- Collecting data for identifying and managing patient at population level
- Planning and managing care using evidence-based guidelines for preventive, acute, and chronic care (including medications) management and identifying patients with high-risk conditions, such as endocrine disorders or substance abuse problems
- Providing self-care support and community resources including assessing and providing treatment for patients with substance abuse comorbid with endocrine disorders
- Utilizing health information technology like electronic health records, to track, follow up on, and coordinate medical tests, referrals, and transitions of care
- Evaluating performance using measures for continuous quality improvement

There is a public health need of integration of preventive screening and substance use disorder treatment into community diabetes care or other endocrine disorders. However this area of integration needs research in different domains to assess the outcomes and cost-effectiveness of integrated treatment in terms of durability and performance (e.g. clinical quality measures), implementation strategies, sustainability, comparative effectiveness.[51]

We emphasize that any person newly diagnosed with endocrine disorder or coming to endocrine clinic for follow-up must be asked about psychoactive substance use. Detailed evaluation regarding history of psychoactive substance use mainly duration, quantity, frequency, last dose, usual dose should be enquired systematically. If time permits the diagnosis can be made using The International Statistical Classification of Diseases and Related Health Conditions (ICD)-10 or the Diagnostic and Statistical Manual of Mental Disorders-5 but this might not be always practical considering the constraints of time and expertise hence simple screening for substance abuse should be made mandatory. There are various screening tools available which are valid and take short time to assess substance use problems.[52] [Box 1].

It is important to identify some red flag signs for substance use among the patient with endocrine disorder. Regular screening and high index of suspicion based on "red flags" can be done in primary care setting or endocrine clinic. [Box 2]. It should be noted that the presence even one sign should raise suspicion but none of the red flags is pathognomonic for substance use.[53]

Box 1: Screening tools

- WHO-ASSIST
- CAGE questionnaire
- Alcohol Use Disorders Identification Test (AUDIT)
- Fagerström Test for Nicotine Dependence (FTND)
- Opioid Risk Tool
- Drug Abuse Screening Test (DAST)

Table 1: Interaction between drugs used in endocrine and substance use disorder

SN	Drugs	Disorder	Interaction
I.	**Used in Endocrine Disorder**[54]		
.	a. Chlorpropamide (sulfonylurea)	Alcohol	Disulfiram-ethanol type of reaction
	b. Metformin	Alcohol	Contraindicated considering Lactic Acidosis
	c. Drugs metabolized by Cytochrome-P450	Tobacco	Enzyme Induction
II.	**Used in Substance Use**		
	a. Methadone[55]	Diabetes	Change in glucose hemostasis by methadone, Caution warranted
	b. Varenicline[56]	Diabetes	Varenicline induced hypoglycemia, Caution warranted

Box 2: Red flag signs for substance use in endocrine disorders

- Problems in Sleep
- Patients with comorbid mental disorder and self-harm
- Signs of chronic obstructive pulmonary disease, hepatitis B or C, HIV infection
- Any physical finding not consistent with the endocrine disorder
- Any lab parameters that is not consistent with the endocrine disorder
- Atypical feature of endocrine disorder
- Endocrine disorder failing to respond in the expected manner to treatment
- History of relationship difficulties, poorly explained trauma etc

CONCLUSION

It is a known fact that the incidence of both substance related disorders and endocrine disorders are on a rise. There is a definite association between the two at a level of causation, association, management and drug interaction. The endocrine clinics can act as an important place to screen and

intervene for substance use disorder for which a collaborative and integrative approach is a must. Major clinical treatment guidelines for endocrine disorders and substance use disorders do not address the patients who have coexistence of both the conditions. Hence, it has been deemed necessary to focus in this special co-occurring conditions. Also, when we make permutations and combinations of different disorders between these two vast areas, we will definitely find different areas of concern and many clinical implications. The large population-based epidemiological studies in people with both substance use and endocrine disorders are needed. The longitudinal studies should be conducted to better understand the time course of onset and outcomes of endocrine disorders in relation to SUDs and randomized controlled trials are needed to assess safety and efficacy of promising psychosocial and pharmacological interventions for this common area.

CONFLICT OF INTEREST

None

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