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Inositol treatment for psychological symptoms in Polycystic Ovary Syndrome women

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Abstract. – OBJECTIVE: PCOS women experience different discomfort as a consequence of the illness. During the years, several risk factors and treatments emerged. This review aims at underlining evidence on psychological symptoms in PCOS women and on the effectiveness of therapies.

MATERIALS AND METHODS: We reviewed literature searching through different databases. We used different keywords, including: PCOS, PCOS and depression, PCOS and anxiety, PCOS and psychological, PCOS depression and risk factors, PCOS depression therapies, depression and inositol.

RESULTS: Based on the collected evidence, PCOS women are more likely to develop psychological symptoms, like depression or anxiety disorders. Furthermore, several risk factors are associated with higher depression or worse psychological conditions. Particularly, the literature highlights BMI, hirsutism, insulin resistance, excess of androgens and lack of serum Vitamin D. Even though several pharmaceuticals find application in psychological symptoms, some of them can impair hormonal condition in PCOS women. Few molecules are able to improve psychological symptoms without impairing hormonal profiles. Among these, myo-inositol appears to be the most interesting, as it is also considered first-line therapy in PCOS women.

CONCLUSIONS: Psychological symptoms affect PCOS women more than healthy subjects. Among the different treatments, inositol emerges as a safe approach, being the first-line therapy in PCOS for hormonal improvement and having putative effects also in psychiatrists.

Key Words:
PCOS, Depression, Anxiety, Inositol.

Introduction

PCOS is a pathology affecting a significant proportion of women in reproductive age, from 6% to 28.5%[1]. Rotterdam diagnosis criteria is nowadays the most accepted among the scientific community. These criteria establish that a PCOS woman displays at least 2 out of 3 of the following: (1) Anovulation or irregular menstrual cycle; (2) ultrasound diagnosis of cystic ovaries; (3) biochemical or phenotypical hyperandrogenism[2]. Furthermore, insulin resistance proved to be a condition frequently occurring in PCOS women[2,3]. Hyperandrogenism is usually due to insulin resistance that leads to steroidogenesis alterations, which result in androgens overproduction. Symptoms often include infertility, hirsutism, acne, and weight gain[4].

Pcos and Depression

Psychological symptoms in women with PCOS are usually related to self-consciousness. Hyperandrogenism and phenotypical alterations such as acne or hirsutism can cause body image issues. Particularly, PCOS women display Body-Image Distress that contributes to increased anxiety and depression[5]. Indeed, in these patients, body image distress plays an important role in sleep quality, impairing sleep and dreams[6]. Perception of body image, furthermore, appears to affect sexuality, impairing sexual function and depression[7]. Sexuality and sex life seem to be really affected by PCOS psychological distress. Besides, PCOS women experience reduced fertility, and fertility-related stress appears to affect PCOS women more than infertile non-PCOS patients[8]. Furthermore, sexuality and sexual function appear altered, especially in some behavioral elements, including masturbation and erotic dreams frequency[9]. Sexual satisfaction also appears to be an important parameter to evaluate in PCOS women, among whom about 33% rate sexual satisfaction as low[10]. PCOS women additionally display lower orgasm score, indicating lower gratification[11].

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PCOS women show a broad spectrum of psychiatric symptoms, including depression and anxiety[10,12] and in general higher emotional distress compared to control populations[13]. Besides, affective temperament features are related to depression diagnosis in PCOS women. Indeed, these women display depressive, cyclothymic, irritable and anxious temperament, associated with higher depression and anxiety scores[14,15]. In fact, PCOS usually leads to worse symptoms of depression and anxiety and relates to some psychological conditions such as bipolar or obsessive-compulsive disorders[16]. Other symptoms reported having a higher incidence in the PCOS sub-population are personality and eating disorder, as well as schizophrenia[17] or, in general, psychotic symptoms[18]. PCOS women, indeed, are more likely to develop psychological symptoms as depression across the lifespan[19]. Starting from adolescence, PCOS women exhibit higher depression risk[20], which tends to decline over the years[21]. PCOS adolescents experience higher emotional distress related to some symptoms of the syndrome, such as hirsutism and obesity[22]. Really, all these symptoms and disorders compromise the quality of life of women[23] and, in fact, appropriate measures for assessing the quality of life have been studied for women with PCOS[24].

Risk Factors

Several factors can affect PCOS women's psychological picture, altering their perception and increasing their stress[25]. An intriguing factor can be represented by genetics, as Day et al[26] identified genetic loci associated with both PCOS and depression, highlighting putative genetical origins to the two pathologies. Besides, BMI and hirsutism seem to positively correlate with higher depression and anxiety scores, while insulin resistance relates to depression and free testosterone levels relate to anxiety[27]. Other factors related to higher depression and anxiety scores in PCOS women are excess of androgens, Vitamin D deficiency, obesity, and insulin resistance[28].

Milman et al[29] identified an excess of serum testosterone as strongly related to depression insurgence in perimenopausal women. Barry et al[30] found out few linear correlations between serum testosterone and mood variables, suggesting a weak connection between androgens and depression in PCOS women.

Serum Vitamin D proved to be an interesting marker in depression diagnosis, either in PCOS or in non-PCOS women[31]. Further studies identified serum Vitamin D threshold below which depression is strongly related to PCOS, establishing 20 ng/mL as limit value[32]. Liu et al[33] identified a lower threshold, bringing to 10.89 ng/mL the value. Furthermore, they identified familiar history of depression as a risk factor for developing lower serum Vitamin D values, finding the higher relationship between the familiar history of depression and lower Vitamin D in PCOS patients compared to non-PCOS women. Therefore, both low serum Vitamin D and familiar history of depression represent a higher risk factor in PCOS women for depression insurgence rather than in non-PCOS subjects.

Although obesity should not be considered as a risk factor for depression in PCOS women, it characterizes in a particular way the complex interaction between the gynecological syndrome and the psychological illness. PCOS women have the higher chance to develop depression and anxiety behaviors when compared to non-PCOS women[10]. Comparing PCOS to non-PCOS and considering also BMI, researchers observed that lower BMI groups have closer anxiety and depression scores, while in higher BMI groups, the gap between the scores increased[34]. Furthermore, higher BMI seems to negatively affect sexual function among PCOS women[10], especially in terms of orgasms and satisfaction[11].

Hollinrake et al[35] highlighted that insulin resistance is significantly associated with depression in PCOS women. Due to the reduced insulin sensitivity in PCOS women, this should represent an intriguing factor in depression etiology. Greenwood et al[36] suggested that cortisol, serotonin, and inflammation markers can represent a strong link between insulin resistance and depression, other than elevated sympathetic response. Furthermore, they observed an interesting phenomenon. Several PCOS women lost weight after depression incidence, improving insulin sensitivity and BMI, processes that would normally improve the syndrome's condition. Nevertheless, these women did not experience PCOS improvement[36]. In a further study, the same group found twice the risk of depression insurgence in PCOS women when compared to non-PCOS[37]. Furthermore, they reported risk increase based on HOMA-IR, calculating each point on HOMA-IR as a 7% higher depression risk.

Therapies

Even though PCOS women generally try different pharmaceuticals to improve their condition, lifestyle seems to affect the syndrome's symp-

toms. A balanced diet combined with physical activity improves the symptomatology[4,10,11,34,35]. Even so, PCOS women usually display complex clinical pictures, which lead the physician to recommend pharmaceutical or nutraceuticals intake. Pharmaceutical treatments proposed to PCOS women include oral contraceptives such as progestins, androgens receptor antagonists like spironolactone, progesterone derivatives, and aromatase inhibitors like letrozole[4]. Despite this, a significant portion of PCOS women prefers improving their health condition in a natural way. Workout and correct food intake combined with specific nutraceuticals proved to improve the condition of these women without troublesome side effects. Among nutraceuticals commonly used against PCOS, inositol represents intriguing and long-studied molecules. Inositol is the commonly given name to a family of nine stereoisomer, with myo-inositol and d-chiro-inositol the most abundant[38]. In the human body, they both play the role of the second messenger in several pathways. Although they have a similar structure and share some biological activities, they seem to exert different and specific individual functions[39].

Low inositol is a condition that characterize also several psychological issues. Particularly, low inositol in different brain areas is related to different psychopathologies. Patients with schizoaffective disorders or major depressive disorder display lower levels of myo-inositol in the anterior cingulate cortex[40]. Furthermore, low myo-inositol levels in the frontal cortex may indicate depression and sleep symptoms. This is probably through altered second messenger system in those brain areas, being myo-inositol the component of membranes implied in signal transduction[41]. Particularly, myo-inositol is involved in signaling pathways concerning different stimuli, such as hormonal. These stimuli are of primary importance in the whole brain, influencing behavior and psychological condition. Thus, patients suffering from psychological disorders may benefit from inositol therapy, including gynecological patients with psychological symptoms. In fact, women suffering from PCOS may experience pre-menstrual syndrome (PMS). PMS is a common psychological issue related to hormone alteration during the menstrual cycle. PCOS women experience hormonal unbalance as a consequence of the syndrome, that can alter also neurophysiology[42]. Mukai et al[43] highlighted that patients suffering from depression and anxiety disorders may benefit from inositol. Besides, they evidenced that inositol may represent also the first-line therapy in women suffering from PMS. These findings suggest that myo-inositol may positively influence psychological conditions related to depressive and anxious moods.

According to Mukai et al[43], inositol proves efficiency in some fields of application. First, in depressive patients, inositol proved superior to placebo in response rate. Secondary, inositol showed a trend toward superior efficiency in reducing depressive symptoms in subjects suffering from Pre-Menstrual Depressive Disorder, a condition occurring as a symptom of PMS. Particularly, inositol seemed to be more effective in women suffering from PMS. Carlomagno et al[44] previously identified inositol as a novel treatment in PMS patients, assessing inositol as a good treatment against psychological symptoms related to PMS. Furthermore, Levine[45] identified inositol as a putative treatment against depressive symptoms due to the absence of manic episodes in bipolar depressed patients taking it. Besides, Benjamin et al[46] compared inositol to placebo in the management of the panic disorder, obtaining meaningful results, suggesting the efficiency of inositol in psychiatric symptoms management. Palatnik et al[47] highlighted another evidence on inositol's importance in the treatment of psychological symptoms. They compared fluvoxamine with inositol in patients suffering from panic disorder[47]. Fluvoxamine is an antidepressant belonging to the selective serotonin reuptake inhibitors class, used to treat major depressive, anxiety, panic, post-traumatic, and obsessive-compulsive disorders[48]. Palatnik et al[47] found out that inositol treatment is as effective as fluvoxamine in patients suffering from panic disorder, highlighting that a nutraceutical can outperform a pharmaceutical in terms of number of panic attacks. In fact, inositol supplemented patients displayed fewer panic attacks compared to fluvoxamine treated subjects, indicating myo-inositol as a better option to reduce panic seizures in these patients. In a recent meta-analysis, Solmi et al[49] evaluated the effects of lamotrigine, a pharmaceutical widely used in the treatment of epilepsy with good anti-depressant efficiency, with other pharmaceuticals and nutraceuticals, assessing lamotrigine efficiency similar to other pharmaceutical and to myo-inositol. Another important study, carried out by Nierenberg et al[50], compared lamotrigine, risperidone and inositol in management of treatment-resistant bipolar depression, highlighting interesting data. Particularly, they evidenced the equal efficiency of the

Table I. Evidence on myo-inositol pharmacological properties.

Reference	Dosage	Pathologies	Results
In Human			
Carlomagno et al 2011	12 g/day powder or 3.6 g/day soft-gel caps	PMDD	Reduction in DSR; improvement in HAM-D and CGI-SI
Benjamin et al 1995	12 g/day powder	Panic Disorder	Reduction in frequency and severity of panic attacks; reduction in agoraphobia
Palatnik et al 2001	up to 18 g/day powder	Panic Disorder	Improvement in HAM-A, agoraphobia score, and Clinical Global Impressions Scale
Nierenberg et al 2006	2.5 g/day increasing weekly up to 25 g/day	Treatment-resistant Bipolar Depression	Recovery rate comparable to lamotrigine, superior to risperidone
In Rats			
Patishi et al 1996	10 mg injection	Lithium-Pilocarpine-induced Status epilepticus	Prevention of seizures
Kotaria et al 2013	30 mg/kg injection	Kainic-acid-induced epilepsy	Prevention of neuronal loss and neuronal damage

PMDD: Premenstrual Dysphoric Disorder; DSR: Daily Symptoms Records; HAM-D: Hamilton Depression Rating; CGI-SI: Clinical Global Impression-Severity of Illness; HAM-A: Hamilton Anxiety Rating.

three treatments in the management of depressive symptoms. Moreover, they found out that inositol achieved recovery rate similar to lamotrigine, four-fold higher than risperidone.

Considering pharmaceutical normally used in psychiatry, some of them should be avoided in PCOS patients, due to their ability to induce modification in hormonal profile, increasing androgens production in normal women's thecal cells[51]. Particularly, valproate, a pharmaceutical used to treat several psychiatric pathologies such as epilepsy, is able to induce important side effects. Among the known side effects of valproate, particular cases are represented by weight gain, the development of oligomenorrhea, hyperandrogenism and cystic ovaries[51]. Furthermore, an intriguing evidence highlighted that myo-inositol is able to block epilepsy seizures induced in rat model by lithium-pilocarpine injections[52]. Besides, myo-inositol administration in rats exercises a protective effect against hippocampal cell loss and morphological and structural alterations in neurons and synapses typically observed in epilepsy during or as a consequence of seizures[53] (Table I).

Conclusions

Nowadays, psychological symptoms are often associated with a number of pathologies and syndromes. Due to the complex heterogeneity of the human brain, highlighting correlations between pathology and psychological symptoms is not always a certainty. Even so, in the present paper, the authors provide a critical review of the literature on the association evidenced so far between PCOS and depression. PCOS seems to be a risk factor in developing depression symptoms, and some PCOS features are likely to influence its appearance. Particularly, BMI, androgens excess, low Vitamin D, and insulin resistance appear to play a role in PCOS-related depression etiology. Even if the best option for PCOS and depression management is represented by lifestyle changes, some molecules proved efficient and safe in improving conditions and facilitating the recovery. Particularly, inositol proved safe and really efficient either in PCOS or in depression, and so its use in psychological issues related to PCOS could represent a novel approach, able to restore normal physiology and helping in recovering from a severe malady.

Conflict of Interest

RG and VU are employed at Lo.Li. Pharma srl. All other authors declare that they have no conflict of interest.

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