European Review for Medical and Pharmacological Sciences 2021; 25: 5483-5489

Combined treatment of myo-inositol and D-chiro-inositol (80:1) as a therapeutic approach to restore inositol eumetabolism in patients with bipolar disorder taking lithium and valproic acid

L. JANIRI[1], F. D'AMBROSIO[2], C. DI LORENZO[3,4]

[1]Department of Neuroscience, Section of Psychiatry, Catholic University of the Sacred Heart of Rome, Rome, Italy
[2]Specialist in Psychotherapy and Clinical Psychology, University of Rome Tor Vergata, Rome, Italy
[3]Department of Medico-Surgical Sciences and Biotechnologies, La Sapienza University Polo Pontino, Latina, Italy
[4]The Experts Group on Inositol in Basic and Clinical Research (EGOI), Rome, Italy

Abstract. – OBJECTIVE: Patients with bipolar disorder (BD) experience a poor quality of life (QoL) and a weak adherence to the therapy due to the various side effects occurring during the pharmacological therapy. To date clinicians have no tools to intervene on such effects, considering them as an unavoidable part of the therapy. This review paves the way for a step forward in the management of patients with BD bridging the therapeutic gap in clinical practice.

MATERIALS AND METHODS: We reviewed the literature, searching through different databases (MEDLINE, Scopus, Google Scholar). We used different keywords, including bipolar disorder, lithium and valproic acid, inositol role in bipolar disorder, side effects, inositol depletion, supplementation of inositols under lithium treatment, inositol role in metabolism, hypothyroidism, renal and cardiac functionality. In particular, we narrowed the search down to English literature, excluding works before 1980s. Regarding clinical studies, we included case reports and both preclinical and clinical studies, especially only those exhibiting a control group. The outcome of the database search was to highlight the threat of side effects and the relationship with inositol lower levels, paving the way for a step forward in the management of patients with BD.

RESULTS: Based on the collected evidence, the combined administration of myo-inositol (myo-ins) and D-chiro-inositol (D-chiro-ins) is strongly recommended in order to restore levels and metabolism of inositols. Previous studies pointed out the beneficial effects of inositols in recovering pathological conditions, like polycystic ovary syndrome (PCOS), hypothyroidism, weight gain, cardiac functionality, being all these conditions related to the depletion of inositols. Furthermore, a controlled dosage of inositols, up to 6 grams/daily, may reduce the side effects caused by lithium therapy, without hindering its central therapeutic role on patients' mood.

CONCLUSIONS: Considering the iatrogenic depletion of inositols, the tailored ratio 80:1 in favour of myo-ins, may become a safe and effective strategy to counteract side effects, by providing a large amount of myo-ins and an adequate one of D-chiro-ins. The clinical dosage of inositols used as dietary supplementation is 4 grams/daily, and it may allow the recovery of the side effects and improve patients' QoL, without reducing the central therapeutic effect of the pharmacological therapy.

Key Words:
Myo-inositol, D-chiro-inositol, Iatrogenic depletion, Dietary supplementation, Valproic acid, Lithium, Bipolar disorder.

Introduction

The most used mood stabilizers and anticonvulsant drugs, like lithium (Li) and valproic acid (VA), share the depletion of inositols, especially myo-inositol (myo-ins), in the central nervous system (CNS) as a therapeutic outcome[1]. These drugs are targeted for the management of neurological diseases affecting brain functionality, including bipolar disorder (BD)[2,3]. Specifically, BD is a chronic psychiatric condition described as a disorder of mood and characterized by alternating episodes of mania and depression[2,4]. It is often ac-

Corresponding Author: Francesco D'Ambrosio, MD; e-mail: francescop.dambrosio@gmail.com

companied by increasing disability and reduced quality of life (QoL), involving both patients and their relatives[5,6].

Pathological mechanisms underlying the etiology of BD, include the excessive activation of the neuronal phosphoinositide signalling pathway[7], which is involved in firing manic phases in patients with BD. Previous evidence described altered levels of myo-ins in the CNS of patients with BD: higher levels underpin the manic phase, while lower levels characterize the depressive status[8,9]. In line with this, the above-mentioned drugs, even if structurally dissimilar, act on inositol metabolism by inducing a central depletion of myo-ins, thus dampening the overactive signalling and giving rise to the "inositol depletion hypothesis" as a therapeutic outcome[10].

However, their administration is not devoid of risks, and it is often associated with the occurrence of several side effects, which may worsen patients' adherence to the therapy and their QoL, leading to a poor prognosis. Such effects are related to pathological conditions like weight gain, hypothyroidism, insulin resistance, hyperandrogenism, amenorrhea, polycystic ovary syndrome (PCOS), polyuria/polydipsia, cardiac alterations as the lengthening of QTc-interval, and dermatological problems like psoriasis, alopecia, acne, hirsutism. All these conditions were mostly associated with reduced levels of myo-ins in related peripheral tissues. Noteworthy, a recent marketing investigation revealed that clinicians do not intervene for counteracting side effects, they just change drugs' dosage and/or type of pharmacological treatment, considering the side effects as unavoidable part of the therapy itself[11]. These evidences highlighted the pressing need to bridge a therapeutic gap in clinical practice, paving the way for new strategies aiming to ameliorate the management of patients with BD and consequently their QoL.

Inositols are natural molecules involved in several biochemical and metabolic functions in different organs and tissues. Their altered levels may expose to several pathological conditions which correspond to the above-mentioned side effects. The reduced levels of myo-ins induced by Li and VA, also influence downstream processes, including myo-ins peripheral conversion into its stereoisomer, D-chiro-inositol (D-chiro-ins), determining an altered metabolism of inositols[12]. Physiologically, myo-ins is converted into D-chiro-ins via a unidirectional reaction mediated by an insulin dependent epimerase enzyme. For this reason, the administration of D-chiro-ins alone is not therapeutically effective, since it doesn't recover the reduced levels of myo-ins. Otherwise, the supplementation of myo-ins may positively impact on the levels of both stereoisomers, due to the above-mentioned physiological conversion.

Overall, the concomitant administration of both stereoisomers leads to a therapeutic advantage since the supplementation of small amounts of D-chiro-ins can immediately restore its altered levels, in addition to the biochemical conversion starting from myo-ins.

For this reason, the combined administration of myo-ins and D-chiro-ins seems to be the best choice to restore physiological levels of inositols and for recovering inositol depletion and the resulting side effects induced by mood stabilizer drugs[13].

Side Effects and Therapeutic Gap in the Treatment of Patients With BD

Considering the chronic course of BD, the affected patients require a long-term pharmacological therapy. However, the chronic use of drugs like Li and VA may expose patients to various side effects, worsening their QoL and weakening their adherence to the therapy. Most of such effects reflect pathological conditions characterized by lower levels of inositols in the related peripheral tissues. Indeed, a previous study indicated that the inositol depletion occurring in the CNS after Li administration correlates with reduced myo-ins levels in peripheral tissues, such as kidneys and testes[14]. The observed side effects include impairments in renal functionality with a consequent polyuria and polydipsia, occurring in up to 70% of patients taking Li[14,15]. A third of patients under Li treatment exhibit an altered cardiac functionality, especially regarding abnormalities of QTc-interval[16-18], along with the initiation and/or progression of arrhythmias, hypertrophy and heart failure[19,20]. In addition, about 20% of patients taking mood stabilizers develop hypothyroidism. Indeed, myo-ins plays a central role as second messenger of the thyroid stimulating hormone (TSH)[21] and Li, in particular, inhibits thyroid hormone release developing hypothyroidism[22].

Noteworthy, the reduction of myo-ins levels also implicates the reduction of D-chiro-ins levels, thus determining an altered metabolism of inositols. Both stereoisomers are involved as second messengers in the insulin signaling pathway, acting in different ways: myo-ins improves cellular uptake of glucose, while D-chiro-ins induces glycogen synthesis[23]. Their abnormal levels are involved in pathological contexts related to endo-

Table I. Key messages about the management of patients with BD.

Key messages	Mechanistic details
Inositol depletion hypothesis	Li and VA induce a depletion of myo-ins in the CNS
Poor adherence to the therapy	Li and VA administration is associated with the occurrence of side effects (hyperandrogenism, PCOS, hypothyroidism, weight gain, etc)
Side effects as unavoidable part of the therapy	Clinicians have no tools to intervene for counteracting side effects
Beneficial effects of inositols	Inositol supplementation recovers pathological side effects (hyperandrogenism, PCOS, hypothyroidism, weight gain, etc)
Inositol administration (up to 6 grams/daily) in patients taking lithium	Recovery of side effects (polyuria, psoriasis) without dampening the central therapeutic outcome
Myo-ins: D-chiro-ins as a safe and effective strategy	80:1 myo-ins: D-chiro-ins ratio seems to be the best choice for recovering inositol iatrogenic depletion

The 80:1 myo-ins: D-chiro-ins ratio is suggested as a safe and effective strategy to counteract the side effects and fill the therapeutical gap.

crine and metabolic imbalances, including weight gain, metabolic syndrome, obesity and PCOS.

Weight gain is reported as a common side effect by the majority of psychiatrists interviewed in a recently published survey[11]. A recent meta-analysis on 14 trials[16] confirmed that weight gain is highly common among patients taking Li and VA, occurring in up to 50% of patients, influencing treatment acceptability and causing pharmacological therapy dropouts[24].

Typical PCOS pathological features, like insulin resistance, hyperandrogenism, hirsutism, amenorrhea are other side effects commonly observed during VA treatment[1]. The endocrine and metabolic unbalances typically correlate with altered inositol metabolism in these patients, and indeed PCOS women exhibit an altered ratio between levels of myo-ins and D-chiro-ins. They also exhibit insulin resistance, resulting in a systemically reduced insulin-dependent conversion of myo-ins into D-chiro-ins[11,23,24]. On the contrary, the ovarian tissue does not become insulin resistant, always responding to insulin signaling that stimulates the activity of the epimerase enzyme[25]. In this way, the ovarian tissue undergoes depletion of myo-ins, which is involved as second messenger in the follicle-stimulating hormone (FSH) pathway. As a consequence, such tissue becomes enriched in D-chiro-ins, which is responsible for insulin-mediated androgens synthesis[26,27], thus promoting hyperandrogenism and related features (hirsutism, acne)[28].

Furthermore, Li administration may expose patients to dermatological problems, including the exacerbation of psoriasis. A recent work indeed suggested an intriguing role for inositols, especially D-chiro-ins, as adjuvant to the local treatment of mild plaque psoriasis[29]. In line with this, an *in vitro* study associated reduced skin elasticity with high expression of an enzyme called aromatase, which is involved in estrogen and inhibited by D-chiro-ins[30].

Finally, Li and VA may expose to teratogenic risk in fertile and/or pregnant women, increasing the incidence rate of neural tube defects (NTDs). Indeed, myo-ins plays a crucial role in preventing the risk of NTDs, especially for those NTDs resistant to folic acid[30,31]. Therefore, clinicians and women under VA are strongly encouraged to consult updated educational material to increase awareness about the risks of the therapy and to avoid the occurrence of pregnancies with defects and malformations.

A recently published marketing investigation, carried out in a small cohort of psychiatrists, confirmed that VA is highly used in clinical practice for the treatment of BD, followed by Li and other atypical antipsychotics[11]. Noteworthy, this survey indicated that clinicians do not intervene to counteract side effects, considering them as part of the pharmacological treatment, they just change therapies or dosages without a specific resolutive strategy[11].

For this reason, based on the chronic course of the disorder and the long-term therapies in pa-

tients with BD[4-6], providing a therapeutical strategy that can counteract, or altogether avoid, the side effects, is crucially important. An approach recovering the side effects may improve patients' QoL and fill the therapeutic gap in pharmacological therapy of BD.

The Tailored Ratio 80:1 As a Step Forward in the Management of Patients With BD

Inositol supplementation induces positive and beneficial effects in most of the previously reported pathological conditions, due to the crucial role played by inositols in the physiology of related tissue.

Considering that myo-ins acts as second messenger of TSH, a recent study revealed that supplementation of myo-ins is significantly effective in restoring euthyroidism in patients with subclinical hypothyroidism or autoimmune thyroiditis[32].

Furthermore, based on the unbalance between myo-ins and D-chiro-ins occurring in PCOS women, clinical studies pointed out the beneficial effects of the treatment with the combined 40:1 ratio, in favour of myo-ins, in these patients[33-35].

Such ratio indeed is not random, but it reflects the myo-ins: D-chiro-ins plasma ratio which is around 40:1[36]. Several studies[31,37,38] highlighted that such ratio positively affects the hormonal profile in PCOS overweight women, improving also metabolic parameters like levels of insulin, triglycerides, lipids and weight gain[39]. The addition of α-lactalbumin (α-LA) to supplementation of inositols further optimized their beneficial effects, overcoming the problem of inositol resistance, which occurs in a moderate portion of patients that cannot absorb inositols[40].

Beside positive outcomes on metabolism and hormonal profile, a preclinical study revealed beneficial effects of the 40:1 ratio on cardiac functionality. The authors demonstrated that in a mouse model of obesity, with a phenotype of induced cardiac fibrosis, the administration of inositols restores cardiac functionality and morphology[41]. In particular, inositols counteract the lengthening of QT interval, preserve atrial morphology and improve ventricular and heart functionality.

Interestingly, a recent work pointed out an intriguing role for inositols, especially D-chiro-ins, as an adjuvant local treatment of mild psoriatic plaques[29]. A recent *in vitro* study[30] revealed that high expression of the aromatase enzyme correlates with lower levels of D-chiro-ins and reduced skin elasticity.

Overall, these evidences revealed the safety and the beneficial effects of myo-ins and D-chiro-ins combined supplementation on various pathological conditions, which occur as side effects during Li and VA therapy.

Noteworthy, supplementation of inositols in a controlled dosage may counteract these side conditions without dampening the central therapeutic effect of the pharmacological therapy and without raising inositol levels in brain. Indeed, the administration of 3 grams/daily of myo-ins in patients taking Li and exhibiting polyuria and polydipsia, confirmed positive effects on renal functionality without altering patients' mood[42]. Additional studies revealed that 6 grams/daily of myo-ins induce an improvement of psoriatic plaques in patients taking Li, without impinging the therapeutic effect of the pharmacological treatment[40,41]. Therefore, within the reported dosage, supplementation of inositols is an effective and safe tool in the management of patients with BD.

A combined supplementation of inositols in a controlled dosage is useful to recover, or altogether avoid, the side effects occurring during Li or VA pharmacological therapy. In addition, myo-ins safety is widely recognized. The U.S. Food and Drug Administration indicated myo-ins among the compounds generally recognized as safe (GRAS). Previous studies[43,44] reported that a dosage of myo-ins over 12 grams/daily can induce mild gastrointestinal symptoms only, experienced for the first month. In particular the dosage of 4 grams/daily of inositols commonly used in clinical practice as dietary supplementation is completely free of side effects[45]. Furthermore, 4 grams/daily have negligible effects on the levels of inositols in the CNS and on patients' mood, thus unaltering the pharmacological outcomes[43].

Considering that drug-induced depletion of myo-ins also influences D-chiro-ins levels, a combined administration is therapeutically more advantageous than myo-ins alone. The 40:1 combined ratio, in favour of myo-ins, is effective in recovering endogenous conditions including metabolic impairments and endocrine alterations both in PCOS women and in diabetic or overweight patients[27,35,46,47]. However, higher amounts of myo-ins are required to recover iatrogenic depletion of inositols. The tailored 80:1 combined ratio of myo-ins: D-chiro-ins seems to be the best choice to restore peripheral inositol lower levels, counteracting the side effects occurring during the pharmacological therapy. This ratio further provides the adequate amounts of D-chiro-ins im-

mediately available, which is needed for the metabolic boost and for recovering the altered ratio of inositols[13].

The 80:1 combined administration may guarantee a recovery of inositol eumetabolism in patients taking Li or VA, improving such pathological conditions reported as side effects of pharmacological therapies. This supplementation may restore the altered metabolic profile, improving body weight and insulin resistance, thus enhancing treatment acceptability. It also likely guarantees positive effects on cardiac functionality, by counteracting the lengthening of QTc interval induced by Li, and by preserving atrial and ventricular morphology. The recovery of myo-ins levels provides an improvement in thyroid functionality and in hypothyroidism-related symptoms, as reported in clinical studies[22]. In addition, considering previous studies and the physiological conversion of myo-ins into D-chiro-ins, this combined administration can further improve plaque psoriasis, recovering skin elasticity in these patients[29]. Based on previous evidence on the effectiveness of the 40:1 ratio in recovering depletion of inositols in endogenous pathological conditions like PCOS, weight gain, insulin resistance and heart defects, the tailored 80:1 ratio may provide larger amounts of myo-ins for recovering iatrogenic depletion. It also ensures the adequate amounts of D-chiro-ins immediately available, recovering in this way the altered metabolism of inositols (Table 1).

This therapeutic strategy may overcome inositol depletion induced by drugs, bridging the gap in clinical practice and providing the opportunity to ameliorate patients' QoL. Such treatment may further improve adherence to the therapy, by recovering or altogether avoiding side effects of therapies based on mood stabilizers.

Conclusions

The management of patients with BD is principally based on the administration of Li or VA as pharmacological therapies. However, both these drugs share the depletion of inositols, especially myo-ins, in the central nervous system as a therapeutic outcome, exposing patients to several side effects, due to the depletion of inositols in peripheral tissues. Such pathological conditions are related to an altered metabolism of inositols and they include insulin resistance and weight gain, hyperandrogenism, hirsutism, amenorrhea, PCOS, hypothyroidism, cardiac and renal alterations, along with dermatological problems, like psoriatic plaques. These effects strongly weaken patients' adherence to the therapy and negatively impact their QoL.

To date clinicians have no tools to counteract the above-mentioned pathological effects and they can just accept them as unavoidable part of the therapy. Therefore, the urgent need to fill this therapeutical gap is clear. Considering the iatrogenic depletion of inositols, the tailored ratio 80:1 in favour of myo-ins, may become a safe and effective strategy to counteract side effects, providing larger amounts of myo-ins and adequate quantities of D-chiro-ins. A clinical dosage of 4 grams/daily, used as dietary supplementation, may restore the side effects and improve patients' QoL, without hindering the central therapeutic effect of the pharmacological therapy.

Conflict of Interest

There are no conflicts of interests and non-financial competing interests in all of authors.

References

1) Murru A, Popovic D, Pacchiarotti I, Hidalgo D, León-Caballero J, Vieta E. Management of adverse effects of mood stabilizers. Curr Psychiatry Rep 2015; 17: 603.
2) American Psychiatric Association. Diagnostic And Statistical Manual Of Mental Disorders, Fifth Edition. 2013.
3) Chiu CT, Wang Z, Hunsberger JG, Chuang DM. Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder. Pharmacol Rev 2013; 65: 105-142.
4) DelBello MP, Adler CM, Cerullo MA, Fleck DE, Strakowski SM. Bipolar Disord 2014; 16: 703-712.
5) Fajutrao L, Locklear J, Priaulx J, Heyes A. A systematic review of the evidence of the burden of bipolar disorder in Europe. Clin Pract Epidemiol Ment Health 2009; 5: 3.
6) Oldis M, Murray G, Macneil CA, Hasty MK, Daglas R, Berk M, Conus P, Cotton SM. Trajectory and predictors of quality of life in first episode psychotic mania. J Affect Disord 2016; 195: 148-155.
7) Berridge MJ. The inositol trisphosphate/calcium signaling pathway in health and disease. Physiol Rev 2016; 96: 1261-1296.
8) Davanzo P, Thomas MA, Yue K, Oshiro T, Belin T, Strober M, McCracken J. Decreased anterior cingulate myo-inositol/creatine spectroscopy resonance with lithium treatment in children with bipolar disorder. Neuropsychopharmacology 2001; 24: 359-369.

9) Frey R, Metzler D, Fischer P, Heiden A, Scharfetter J, Moser E, Kasper S. Myo-inositol in depressive and healthy subjects determined by frontal 1H-magnetic resonance spectroscopy at 1.5 tesla. J Psychiatr Res 1998; 32: 411-420.
10) Williams RSB, Cheng L, Mudge AW, Harwood AJ. A common mechanism of action for three mood-stabilizing drugs. Nature 2002; 417: 292-295.
11) Giannunzio L, Lista P, Lepore E, Logoteta P. A survey on the management of bipolar disorders. IJMDAT 2021; 4: e330.
12) Sun TH, Heimark DB, Nguygen T, Nadler JL, Larner J. Both myo-inositol to chiro-inositol epimerase activities and chiro-inositol to myo-inositol ratios are decreased in tissues of GK type 2 diabetic rats compared to Wistar controls. Biochem Biophys Res Commun 2002; 293: 1092-1098.
13) Lepore E, Lauretta R, Bianchini M, Mormando M, Di Lorenzo C, Unfer V. Inositols depletion and resistance: principal mechanisms and therapeutic strategies. Int J Mol Sci 2021; 22: 6796.
14) Sherman WR, Munsell LY, Gish BG, Honchar MP. Effects of systemically administered lithium on phosphoinositide metabolism in rat brain, kidney, and testis. J Neurochem 1985; 44: 798-807.
15) Bone S, Roose SP, Dunner DL, Fieve RR. Incidence of side effects in patients on long-term lithium therapy. Am J Psychiatry 1980; 137: 103-104.
16) Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord 2016; 4: 27.
17) Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000; 355: 1048-1052.
18) Menegueti M, Basile-Filho A, Martins-Filho O, Auxiliadora-Martins M. Severe arrhythmia after lithium intoxication in a patient with bipolar disorder admitted to the intensive care unit. Indian J Crit Care Med 2012; 16: 109-111.
19) Swedberg K, Winblad B. Heart failure as complication of lithium treatment. Acta Med Scand 2009; 196: 279-280.
20) Kockskämper J, Zima AV, Roderick HL, Pieske B, Blatter LA, Bootman MD. Emerging roles of inositol 1,4,5-trisphosphate signaling in cardiac myocytes. J Mol Cell Cardiol 2008; 45: 128-147.
21) Lazarus JH. Lithium and thyroid. Best Pract Res Clin Endocrinol Metab 2009; 23: 723-733.
22) Nordio M, Pajalich R. Combined treatment with Myo-inositol and selenium ensures euthyroidism in subclinical hypothyroidism patients with autoimmune thyroiditis. J Thyroid Res 2013; 2013: 424163.
23) Bevilacqua A, Bizzarri M. Inositols in insulin signaling and glucose metabolism. Int J Endocrinol 2018; 2018: 1968450.
24) Verrotti A, D'Egidio C, Mohn A, Coppola G, Chiarelli F. Weight gain following treatment with valproic acid: pathogenetic mechanisms and clinical implications. Obes Rev 2011; 12: e32-43.
25) Carlomagno G, Unfer V, Roseff S. The D-chiro-inositol paradox in the ovary. Fertil Steril 2011; 95: 2515-2516.
26) Larner J, Craig JW. Urinary myo-inositol-to-chiro-inositol ratios and insulin resistance. Diabetes Care 1996; 19: 76-78.
27) Sortino MA, Salomone S, Carruba MO, Drago F. Polycystic ovary syndrome: insights into the therapeutic approach with inositols. Front Pharmacol 2017; 8: 341.
28) Kamenov Z, Gateva A. Inositols in PCOS. Molecules 2020; 25: 5566.
29) Owczarczyk-Saczonek A, Czerwińska J, Wygonowska E, Kasprowicz-Furmańczyk M, Placek W. D-chiro-inositol as a treatment in plaque psoriasis: a randomized placebo-controlled clinical trial. Dermatol Ther 2021; 34: e14538.
30) Inoue T, Miki Y, Abe K, Hatori M, Hosaka M, Kariya Y, Kakuo S, Fujimura T, Hachiya A, Honma S, Aiba S, Sasano H. Sex steroid synthesis in human skin in situ: the roles of aromatase and steroidogenic acute regulatory protein in the homeostasis of human skin. Mol Cell Endocrinol 2012; 362: 19-28.
31) Beckner ME, Gobbel GT, Abounader R, Burovic F, Agostino NR, Laterra J, Pollack IF. Glycolytic glioma cells with active glycogen synthase are sensitive to PTEN and inhibitors of PI3K and gluconeogenesis. Lab Investig 2005; 85: 1457-1470.
32) Nordio M, Basciani S. Treatment with myo-inositol and selenium ensures euthyroidism in patients with autoimmune thyroiditis. Int J Endocrinol 2017; 2017: 2549491.
33) Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M. A combined therapy with myo-inositol and D-chiro-inositol improves endocrine parameters and insulin resistance in PCOS young overweight women. Int J Endocrinol 2016; 2016: 3204083.
34) Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials. Endocr Connect 2017; 6: 647-658.
35) Monastra G, Unfer V, Harrath AH, Bizzarri M. Combining treatment with myo-inositol and D-chiro-inositol (40:1) is effective in restoring ovary function and metabolic balance in PCOS patients. Gynecol Endocrinol 2017; 33: 1-9.
36) Facchinetti F, Dante G, Neri I. The ratio of MI to DCI and its impact in the treatment of polycystic ovary syndrome: Experimental and Literature Evidences 2016; pp. 103-109.
37) Gambioli R, Forte G, Buzzaccarini G, Unfer V, Laganà AS. Myo-inositol as a key supporter of fertility and physiological gestation. Pharmaceuticals 2021; 14: 504.
38) Unfer V, Porcaro G. Updates on the myo-inositol plus D-chiro-inositol combined therapy in polycystic ovary syndrome. Expert Rev Clin Pharmacol 2014; 7: 623-631.
39) Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an

update on mechanisms and implications. Endocr Rev 2012; 33: 981-1030.

40) Montanino Oliva M, Buonomo G, Calcagno M, Unfer V. Effects of myo-inositol plus alpha-lactalbumin in myo-inositol-resistant PCOS women. J Ovarian Res 2018; 11: 38.

41) L'Abbate S, Nicolini G, Forini F, Marchetti S, Di Lascio N, Faita F, Kusmic C. Myo-inositol and D-Chiro-inositol oral supplementation ameliorate cardiac dysfunction and remodeling in a mouse model of diet-induced obesity. Pharmacol Res 2020; 159: 105047.

42) Bersudsky Y, Vinnitsky I, Grisaru N, Yaroslavsky U, Gheorghiu S, Ivgi D, Kofman O, Belmaker RH. The effect of inositol on lithium-induced polyuria? Polydipsia in rats and humans. Hum Psychopharmacol Clin Exp 1992; 7: 403-407.

43) Allan SJR, Kavanagh GM, Herd RM, Savin JA. The effect of inositol supplements on the psoriasis of patients taking lithium: a randomized, placebo-controlled trial. Br J Dermatol 2004; 150: 966-969.

44) Kontoangelos K, Vaidakis N, Zervas I, Thomadaki O, Christaki S, Stavrianeas NG, Papadimitriou GN. Administration of inositol to a patient with bipolar disorder and psoriasis: a case report. Cases J 2010; 3: 69.

45) Carlomagno G, Unfer V. Inositol safety: clinical evidences. Eur Rev Med Pharmacol Sci 2011; 15: 931-936.

46) Iervolino M, Lepore E, Forte G, Laganà AS, Buzzaccarini G, Unfer V. Natural molecules in the management of Polycystic Ovary Syndrome (PCOS): an analytical review. Nutrients 2021; 13: 1677.

47) Dinicola S, Chiu TTY, Unfer V, Carlomagno G, Bizzarri M. The rationale of the myo-inositol and D-chiro-inositol combined treatment for polycystic ovary syndrome. J Clin Pharmacol 2014; 54: 1079-1092.