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The use of D-chiro-Inositol in clinical practice

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Abstract. – OBJECTIVE: D-chiro-Inositol has been widely used in clinical practice to induce ovulation in women with polycystic ovary syndrome. Only recent evidence established that this molecule acts through two different mechanisms, with potentially different outcomes. On the one hand, under a metabolic perspective, D-chiro-Inositol improves insulin signaling, thus restoring physiological insulin levels in resistant subjects. On the other hand, at a cellular level, it downregulates the expression of steroidogenic enzyme aromatase, which is responsible for the conversion of androgens to estrogens.

MATERIALS AND METHODS: We reviewed current literature in different databases, searching for D-chiro-Inositol in relation with one of the following keywords: myo-inositol, PCOS, infertility, insulin resistance, aromatase, androgen and inositol, testosterone, estrogen and inositol, estradiol, hypogonadotropic hypogonadism, fat tissue, estrogens and cancer, anovulation, uterine myoma, endometriosis, endometrial hyperplasia.

RESULTS: D-Chiro-Inositol treatment may be helpful in restoring physiological hormonal levels in various clinical disorders. However, D-Chiro-Inositol intervention should be carefully designed to avoid possible undesired side effects stemming from its multiple mechanisms of action.

CONCLUSIONS: We evaluated the optimal D Chiro-Inositol administration for different pathologies, defining dosages and timing. Even though further studies are required to validate our preliminary results, this paper is primarily intended to guide researchers through some of the pathways of D-Chiro-Inositol.

Key Words:
D-chiro-Inositol, Aromatase, Sex hormones, Fertility, PCOS.

Introduction

Inositols make up a family of six-membered cyclic polyols that naturally occur as five different stereoisomers. Myo-Inositol (myo-Ins) represents approximately 99% of mammalian inositol pool, and contributes to various functions in different tissues[1]; the remainder of inositol molecules in mammals consists of Dchiro-Inositol (Dchiro-Ins),which mediates different functions than those mediated by myo-Ins[2].

In human body, Inositols are commonly found in almost every tissue and their absolute and relative concentration can strongly differ, depending on the milieu[3]. Inositols exist either in their free form or as phosphate derivatives. Inositol-phosphates are the active molecules that participate to intracellular signaling pathways[4], being either components of cell membranes as phosphatidyl-inositol-phosphates (PIP) or water-soluble molecules (IP). Myo-Ins is involved in the Follicle-Stimulating-Hormone (FSH) and the Thyroid-Stimulating-Hormone (TSH) pathways, while both myo-Ins and Dchiro-Ins are insulin second messengers[1,5].

One of the first studies highlighting the importance of Inositols found out that a molecule called Ins-2 plays an important role in insulin signaling pathway[6]. Indeed, Ins-2 is a Dchiro-Ins-based phosphoglycan. Larner et al[7] later discovered that Dchiro-Ins acts as insulin sensitizer or insulin mimetic, and its administration can enhance the corresponding phosphoglycan pool, increasing intracellular insulin signaling. As a consequence, organs become sensitive to lower levels of insulin. Moreover, these studies[6,7] found out that Dchiro-Ins mediates glycogen synthesis and increases androgen production in the ovary. Specifically, Dchiro-Ins induces higher testosterone production in theca cells in a dose-dependent manner, even in the absence of insulin stimulation, making Dchiro-Ins an "androgen-raising" molecule[6]. Other

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studies observed higher content of Dchiro-Ins in tissues involved in energy storage and androgen production[3].

Myo-Ins participates in more processes than Dchiro-Ins, and it is also its precursor. Myo-Ins is synthesized through multiple steps, starting from glucose-6-phosphate[4]. Eventually, an enzyme of the epimerase family catalyzes the direct transformation of myo-Ins to Dchiro-Ins according to specific tissue requirements[8]. Thus, increased or decreased epimerase enzymatic activity can lead to Inositol unbalance, which alters the response of a given tissue to external stimuli. Indeed, the specific ratio between myo-Ins and Dchiro-Ins (M/D) is a highly preserved characteristic of each tissue or organ, and it contributes to maintain their physiological conditions. This may help understanding why it is possible to talk about Inositols ratios, instead of absolute concentrations.

As already observed, the content of Dchiro-Ins is higher in tissues that store glycogen, while it drastically falls in tissues with high consumption of energy, like the heart or the brain. For instance, tissues like fat or liver exhibit M/D of about 2:1, while the brain and the heart display a far different ratio of 200:1[3]. In the follicular fluid, researchers found that the average M/D ratio is equal to 100:1, higher than 40:1 normally occurring in the blood[9,10]. Insulin control upon epimerase is a key point in the maintenance of these physiological ratios. Indeed, insulin stimulates the enzyme activity, shifting the balance in favor of Dchiro-Ins[8]. This is crucial because deregulation of insulin levels is involved in several pathologies, and therefore Dchiro-Ins unbalance could be considered as an important factor in their etiology. An example is the hyperandrogenic phenotype in Polycystic Ovary Syndrome (PCOS) women with insulin resistance, where the compensatory hyperinsulinemia supposedly induces androgen overproduction via Dchiro-Ins unbalance.

A study[11] concerning the restoration of ovulation with Dchiro-Ins in hyperinsulinemic women demonstrated that Dchiro-Ins treatment reduced systemic insulin levels and thus androgen parameters, such as testosterone, androstenedione, or dehydroepiandrosterone sulphate. However, it seems unlikely that ovarian physiology may benefit from an androgen enhancer. In fact, a following study[12] found that Dchiro-Ins administration at a higher dosage (2400 mg/die) worsened the endocrinological parameters in obese anovulatory women, showing slightly higher testosterone levels (+15% Total T, +29% Free T). This evidence[13] finds explanation in the modulatory activity of Dchiro-Ins on the expression of the steroidogenic enzyme aromatase, which catalyzes the transformation of androgens to estrogens. Particularly, Dchiro-Ins lowers aromatase expression in a dose-response manner, thus increasing androgens levels at the expense of estrogens.

A singular phenomenon, that we can define as Dchiro-Ins Paradox, occurs in the ovary, a particular tissue with a unique environment. Indeed, the ovaries remain sensitive to insulin even in resistant subjects[14], resulting in M/D unbalance in the case of hyperinsulinemia. Dchiro-Ins treatment in such case leads to reduced systemic insulin levels and paradoxically to reduced intraovarian Dchiro-Ins content. As a consequence, intraovarian myo-Ins concentration increases, improving FSH sensitivity and restoring ovulation in the short term. However, Dchiro-Ins has a double role. Beside acting as insulin sensitizer, it has steroidogenic properties. Under normal insulin conditions, Dchiro-Ins treatment reduces aromatase expression and thus estradiol production, decreasing the negative feedback on the hypothalamus. The consequent increases in FSH release results in ovulation. We should emphasize that all the studies on ovulation induction with Dchiro-Ins featured 6 to 8 weeks treatment, and long-time data are not available. In longer treatment or higher dosages, Dchiro-Ins effects on steroidogenesis could become predominant, increasing androgen levels and worsening patients' clinical picture.

All these findings suggest that Dchiro-Ins administration must be well pondered because of its double mechanism of action, which depends on the dosage, likewise the dose-response behavior of many drugs. If on the one hand Dchiro-Ins improves insulin signaling, on the other hand it may inhibit estrogen synthesis in favor of androgens. The clinical effect of Dchiro-Ins depends on three parameters: (1) the insulinemic condition of the patients; (2) the dosage of Dchiro-Ins;)3) the treatment duration. Considering these parameters for each patient, the most suitable Dchiro-Ins therapy could be evaluated for treating estrogen sensitive pathologies or those involving impaired insulin signaling, hyperestrogenism, hypoandrogenism.

In the present paper, the authors try to evaluate the appropriate Dchiro-Ins dosages and duration of treatment for different clinical pictures, based on the literature collected so far on the topic and on the authors' clinical and experimental experience.

D-Chiro-Ins Treatment in Men

Increase of Androgens

Hypogonadotropic hypogonadism

Hypogonadism affects up to 9.3% of men, depending on the age and other physiological factors. It is characterized by low testosterone levels and can be divided in: *primary*, displaying testicular dysfunction and high Luteinizing Hormone (LH) and FSH levels; *secondary*, unrelated to testicular dysfunction, usually derives from impaired Hypothalamic-Pituitary-gonadal (HPG) axis[15]. In secondary hypogonadism, also called hypogonadotropic, men usually develop symptoms like reduced libido, erectile dysfunction, fatigue, infertility, gynecomastia, weight gain, and psychological symptoms[16]. Aromatase inhibitors, like letrozole, improve testosterone values in men, even in the presence of hypogonadotropic hypogonadism[17]. Moreover, aromatase inhibitors reduce the estrogen negative feedback on HPG axis, increasing the production of LH and FSH in men with secondary hypogonadism[18]. In men with primary hypogonadism aromatase inhibitors must be avoided, because estrogens inhibit gonadotropin production and secretion[15]. Thus, Dchiro-Ins could be a suitable treatment in hypogonadal hypogonadotropic patients, inhibiting aromatase expression and naturally restoring physiological androgen levels. On the other hand, like aromatase inhibitors, Dchiro-Ins must be avoided in primary hypogonadal males, where it could worsen the already overburdened gonadotropin signaling. Our preliminary unpublished data support the use of Dchiro-Ins in hypogonadotropic hypogonadal males, showing that short-term administration of high dosages may improve hormonal parameters in these patients. We investigated the effects of 1200 mg/die Dchiro-Ins for 30 days in elderly hypogonadal male subjects. In patients currently enrolled, testosterone increased by approximately 20% after 30 days of Dchiro-Ins administration (Table I). We observed comparable results in androstenedione, while estradiol levels were significantly lower, by 20% on average. Furthermore, testosterone increase seems to be associated with improved erectile function. Thus, Dchiro-Ins treatment appears indicated to men who suffer from secondary hypogonadism, independently of their age.

Psychological symptoms

Low testosterone levels in serum and in saliva correlates with major depression disorder. The lower the testosterone, the more severe the clinical picture[19]. Testosterone administration can ameliorate psychological symptoms in males, particularly by reducing sadness and anger[20]. Interestingly, the therapy was more efficient in patients displaying lower testosterone levels, suggesting that the lack of androgens worsens depression in a dose-dependent manner[21]. In such clinical picture, androgen therapies seem to be the only ones that effectively restore normal mood, even if they come with multiple serious side effects. On this basis, Dchiro-Ins administration appears to be useful in male patients with depression to restore normal testosterone levels, improving mood and reducing psychological symptoms.

Decrease of Estrogens

Overweight and obese

Estrogens play an important role in male physiology, especially during the developmental phase of life, assisting the formation of testis efferent ducts. Moreover, estrogen receptors are necessary for male fertility and different male reproductive structures express them. High concentrations of estrogens occur in some districts of male body, like in rete testis fluid, but high systemic levels can be associated with various pathologies[22,23]. Obese men constitute a particular population that suffer from hyperestrogenism. Fat tissue, in fact, expresses aromatase enzyme, which produces estrogens at the expense of androgens. In obese men, estrogen signaling induces fat tissue accumulation, while testosterone administration leads to decreased waist circumference[24]. On such eviden-

Table I. Hypogonadal males hormones following D chiro-Ins high dose administration.

Cases Data	#1 Basal	#1 After	#2 Basal	#2 After	#3 Basal	#3 After
Testosterone	222 ng/dl	281 ng/dl	227 ng/dl	292 ng/dl	221 ng/dl	258 ng/dl
Estradiol	42.20 pg/ml	30.80 pg/ml	51.40 pg/ml	28.40 pg/ml	36.90 pg/ml	32.20 pg/ml
T/E2	5.60	9.10	3.30	10.30	6.00	8.00

ce, restoring physiological hormone balance is crucial for borderline overweight and obese patients, which are likely to develop insulin resistance. Due to its properties, Dchiro-Ins can be very helpful in such cases, lowering fat tissue accumulation and improving patients' metabolic condition. Based on our preliminary findings on male volunteers, administration of 1200 mg/die Dchiro-Ins for 30 days leads to a significant improvement in hormonal profile. After treatment, average testosterone increased 1 mg/ml, estradiol decreased, and testosterone-to-estradiol ratio was significantly higher (Table II). These parameters show that Dchiro-Ins impacts hormonal balance, resulting in improved metabolic profile.

Estrogen-sensitive conditions

Inflammation is a typical characteristic of adipose tissue that derives from metabolic and immune causes. Fat tissue secretes pro-inflammatory molecules, like leptin and Interleukin 6, that recruit macrophages and T cells[25]. This environment is prone to develop cancerous formations. Furthermore, leptin acts as a positive genetic regulator for estrogen receptor and aromatase. Estrogens play an important role in the progression of some tumoral species progression, leading to mass growth and more severe symptoms[26]. Male Breast Cancer (MBC) is an important estrogen-sensitive cancer, representing about 1% of total breast cancers. Despite MBC is known to respond to estrogens, current studies on aromatase expression remain controversial. Feminizing Adrenocortical Tumors are other important male cancerous formations that usually produce massive amounts of estrogens and androgens, which are later aromatized in other tissues. The resulting steroidal unbalance causes hyperestrogenism and related diseases, such as gynecomastia[27]. In these clinical pictures, Dchiro-Ins adjuvant treatment could be very useful to reduce aromatase expression and thus estrogen production, restoring the physiological ratio between estrogens and androgens.

D-Chiro-Ins Treatment in Women

Increase of Androgens

Anovulation

Dchiro-Ins administration can be useful in restoring ovulation under certain conditions. If the patient is a hyperinsulinemic anovulatory woman, Dchiro-Ins proved to behave primarily as insulin sensitizer, leading to better insulin signaling in the whole body and thus lowering systemic insulin levels. On the contrary, literature data concerning non-hyperinsulinemic women are unavailable. Other our unpublished data indicate that six-week treatment with 1200 mg/die Dchiro-Ins induces ovulation in non-PCOS lean women, as indicated by progesterone increase from 0.5 ng/ml to 12 ng/ml. In this case, Dchiro-Ins is likely to act mainly on aromatase expression, reducing estradiol production and increasing FSH release. However, due to the androgen-raising effect of Dchiro-Ins, long-term treatments with high dosages should be avoided because of potential negative impact on the ovary. In fact, our above data suggest that high dosages of Dchiro-Ins induce histological PCOS-like phenotype in a mouse model, with cystic tertiary follicles with atretic oocytes or altogether devoid of oocytes.

On the other hand, long-term treatments with myo-Ins proved safe in ameliorating ovarian conditions in PCOS women. An interesting review gathers several papers that demonstrated that myo-Ins induces ovulation by improving FSH signaling, thus normalizing menstrual cycle[28]. Of the two stereoisomers, myo-Ins is both insulin and FSH second messenger, and thus it can be considered as the first line therapy in PCOS patients[1]. These women usually develop insulin-resistance and therefore respond to insulin-sensitizing compounds. Among them, overweight and obese patients represent a particular subpopulation. A study on obese PCOS women compared myo-Ins to myo-Ins plus Dchiro-Ins at the physiological serum ratio of 40:1. The results demonstrated that these patients better respond to the combined therapy[10,29].

Table II. Hormonal and metabolic data following D chiro-Ins high dose administration to overweight men.

Cases Data	#1 Basal	#1 After	#2 Basal	#2 After	#3 Basal	#3 After
Glycemia	117 mg/dl	101 mg/dl	109 mg/dl	101 mg/dl	110 mg/dl	92 mg/dl
Insulinemia	32.16 µUI/ml	21.31 µUI/ml	5.60 µUI/ml	5.4 µUI/ml	4.18 µUI/ml	4.02 µUI/ml
Testosterone	457 ng/dl	561 ng/dl	462 ng/dl	516 ng/dl	452 ng/dl	575 ng/dl
Estradiol	30.04 pg/ml	27.8 pg/ml	26.8 pg/ml	23.4 pg/ml	41.4 pg/ml	46.4 pg/ml
T/E2	15	20.2	17.2	22.1	10.9	12.4

Although useful in the short term to restore ovulation, high dosages of Dchiro-Ins find no application rationale in longer-term treatments, especially for PCOS women. Indeed, Bevilacqua et al[30] highlighted that PCOS murine models differently respond to different ratios of myo-Ins plus Dchiro-Ins. After inducing a PCOS-like phenotype by constant light exposition for 10 weeks, mice were divided in groups and treated with various M/D ratios or water. After 10 days of treatment, they analyzed the uteri and the ovaries. Mice treated with M/D ratio equal to 40:1 displayed normal ovaries, physiological thickness of theca and granulosa cells and follicles corresponding at every maturation stage, including enlarged Graafian follicles. Among other formulas, 80:1 seemed to be the more effective, even if only a partial normalization of the uterus and the ovaries was achieved. Higher Dchiro-Ins amounts led to unrestored ovarian condition, showing scattered primary and secondary follicles and atypical and disorganized ovarian tissues. The more the Dchiro-Ins administrated, the more severe the ovarian and uterine conditions. This finding underlines that high dosages of Dchiro-Ins lead to a general impairment of the ovaries, the uterus and the fertility in PCOS women, worsening their clinical picture.

Mood disorder

Testosterone plays an important role in women's behavior, as its concentrations are tenfold higher than estrogens' in some brain areas, like the hypothalamus[31]. Lower testosterone levels influence mood and libido. In fact, testosterone administration can restore normal libido in women with low free testosterone levels associated with low libido[32]. Interestingly, after surgical menopause, women with low testosterone levels treated with testosterone in combination with estrogens felt more composed, elated, and energetic than the control group and the one treated only with estrogens[33]. Moreover, testosterone administration positively influenced the quality of life of perimenopausal women with climacteric psychological symptoms[34,35]. This allows us to speculate that the "androgens-raising" properties of Dchiro-Ins could be helpful in mood disorders or psychological symptoms associated with low testosterone levels. Moreover, Dchiro-Ins has negligible side effects compared with testosterone, allowing women to physiologically restore their own hormonal balance.

Decrease of Estrogens

Uterine myoma

Uterine myoma affects up to 70% of women in the fertile age. It is also called fibroid or leiomyoma and is a benign neoplasia of myometrium smooth muscle cells. In most cases, fibroids are asymptomatic and spontaneously disappear after menopause[36]. However, symptomatic fibroids lead to pelvic pain, dysmenorrhea, and metrorrhagia. Estrogens play an important role in myoma growth, acting as positive regulators of cell proliferation. *In-vitro* studies demonstrated that aromatase is upregulated in myoma cells[37], thus lowering estrogen levels can be an important therapeutical strategy[38]. Ulipristal Acetate (UPA), a Selective Progesterone Receptor Modulator (SPRM), was the first line therapy against myoma, silencing progesterone signaling[39]. However, because of serious adverse effects that include liver failure, UPA was withdrawn from the market, leaving a therapeutic gap[40]. In light of this, several natural molecules have been investigated as safe alternatives to treat myomas. Studies reported that uterine myomas are highly responsive to natural molecules such as Epigallocatechin gallate (EGCG)[41] and Vitamin D_3 (cholecalciferol)[42]. The combination of these two molecules achieved good results in arresting myoma growth and in reducing myoma size[43]. Co-administration of Dchiro-Ins may improve the efficacy of EGCG and Vitamin D_3 in two different ways. Dchiro-Ins-induced aromatase downregulation can lead to lower systemic estrogen levels. Furthermore, Dchiro-Ins can negatively modulate aromatase expression directly in myoma cells, lowering estrogen production *in situ* and slowing down tumor growth. Thus, the combination of Dchiro-Ins with EGCG and Vitamin D_3 may represent a safe and natural treatment in myoma management, reducing the associated symptomatology and facilitating following surgery. Furthermore, Dchiro-Ins can be used in low dosages, avoiding possible side effects. Considering these properties, low-dose Dchiro-Ins co-administration with EGCG and Vitamin D_3 appears ideal in complex clinical pictures, such as multiple myomas or myomas with diameter greater than 4 cm.

Endometriosis

Endometriosis is another common estrogen-sensitive pathology[44], that affects approximately 10% of women in the reproductive age. It consists of uterine endometrial tissue that

grows outside the uterine cavity[45]. Although about 25% of women are asymptomatic, severe symptoms appear in the majority of cases, and include dysmenorrhea, menorrhagia, pelvic pain, and chronic fatigue[46]. Endometriosis often leads to reduced fertility. While healthy couples have fecundity of 0.15-0.20 per month, couples including women with endometriosis have a tenfold lower fecundity[47]. Endometriotic tissue expresses aromatase, that guarantees local estrogen production to self-sustain growth[48]. Following studies proved that aromatase inhibitors like letrozole reduce the pain score in women with endometriosis under therapy with gonadotropin suppressors[49]. On these premises, Dchiro-Ins administration should be considered as adjuvant treatment to ameliorate endometriosis symptoms in combination with pharmaceutical therapies.

Endometrial hyperplasia

Endometrial hyperplasia is a pre-cancerous lesion of the endometrium, showing high proliferative cells that may lead to endometrial carcinoma under certain conditions. It can be divided into Atypical and Typical, depending respectively on the presence or absence of single cell structure modifications[50]. Risk factors associated with endometrial hyperplasia include age, nulliparity, bodyweight, perimenopause, anovulatory cycles and high estrogen levels[51]. The latter is critical because estrogens can stimulate endometrial proliferation, and about 80% of endometrial carcinomas is responsive to estrogens, especially to estradiol[52]. Moreover, aromatase is expressed in endometrial cells, inducing a substantial increase in local estrogen levels, which provide the growth stimulus[53]. Aromatase inhibitors, like anastrozole, proved to play an important role in lowering local estrogen signaling, thus improving health conditions in patients displaying this type of lesion[54]. Thus, Dchiro-Ins administration can be a suitable adjunctive therapy in cases of endometrial hyperplasia and may represent a replacement treatment for poor-responder patients to aromatase inhibitors. In addition, Dchiro-Ins could be an important adjuvant treatment to other pharmaceutical therapies against endometrial carcinomas and other estrogen-sensitive malignant tumors, like some types of breast cancer. In conclusion, perimenopausal women may benefit from Dchiro-Ins as preventive treatment against estrogen-sensitive conditions.

Discussion

The properties of Dchiro-Ins have recently come forth in the spotlight, due to several processes in which the molecule is involved. Dchiro-Ins intervenes in multiple cell-signaling pathways, and its administration proved to exert two principal effects. In fact, Dchiro-Ins was first characterized as insulin mimicking molecule and mediator, then its role in steroidogenesis as aromatase modulator emerged. To identify the most appropriate Dchiro-Ins intervention, physicians must keep in mind this double behavior, taking into account patients' insulin and hormonal conditions. Dchiro-Ins administration, due to its mechanisms of action, can improve some conditions, but can also softly worsen other physiological ones. The best option when administrating Dchiro-Ins is to evaluate the metabolic profile of the patients.

In men with normal testosterone values, testosterone administration proved to induce important side effects. As stated by FDA, exogenous testosterone may cause testicular atrophy and sterility due to decreased systemic FSH and LH levels[55,56]. Thus, testosterone administration is likely to reduce male fertility. Analogously, long-term administration of Dchiro-Ins causes endogenous testosterone levels to raise, producing an androgen boost also in normo-androgenic patients, who may potentially experience reduced fertility as a result. Short-term treatments with low dosages of Dchiro-Ins, on the other hand, can be considered safe in man with normal testosterone levels. Even though endogenous testosterone should not impair HPG axis at all, data regarding the effects of Dchiro-Ins administration are still unavailable in such cases, and physicians should take these considerations into account when prescribing Dchiro-Ins-containing products.

Dchiro-Ins administration should also be avoided in women with PCOS, who may experience worsening of their symptoms. In these patients, long-term treatments with high doses of Dchiro-Ins may deteriorate the ovaries and the uterus. Furthermore, as they also seem to induce a PCOS-like phenotype in female mice, affecting oocytes' quality, clinical treatments with large amounts of Dchiro-Ins should always be carefully evaluated. Based on our preliminary studies, here we report the dosages of Dchiro-Ins that we recommend for the different clinical pictures taken into consideration (Table III).

Table III. D chiro-Ins recommended daily doses and timing of administration.

Dose	Mg/die	Time	Pathologies
Very Low	0-300	12+ months	Low testosterone-associated mood disorder or reduced libido; Endometriosis; Endometrial hyperplasia
Low	300-600	6 months	Endometriosis; Endometrial hyperplasia; Hypogonadotropic hypogonadal men; Estrogens responsive formations
Medium	600-1200	3 months	Endometriosis; Endometrial hyperplasia
High	1200+	30 days	Non-PCOS anovulatory women; Endometriosis; Endometrial hyperplasia; Hypogonadotropic hypogonadal men; Overweight and obese man

Conclusions

Briefly, this paper aims to spread knowledge on Dchiro-Ins use in medical treatments, collecting the most advanced experimental evidence to date. At the same time, we hope that it prompts researchers to undertake randomized, placebo-controlled, double-blind studies with greater sample size to confirm our preliminary findings and to better understand Dchiro-Ins pharmacokinetics.

Conflict of Interest

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

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