THE INTERNATIONAL CONFERENCE
PCOS – UNDERSTANDING THE SCIENCE AND PRACTICE

Jointly Organized by
The PCOS Society (India)
&
The Androgen Excess & PCOS Society (International)

THE PCOS SOCIETY

AE-PCOS
ANDROGEN EXCESS & PCOS SOCIETY

PCOS-Understanding the Science and Practice

Inositols

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PCOS and insulin

- It is well known that a strong relationship exists between PCOS and metabolic disruption, the latter being considered one of the most important traits of PCOS.

- In particular, insulin resistance has become a distinctive pattern of the syndrome and its incidence is progressively increasing, together with type II diabetes risk.

- The consequent hyperinsulinemia (65-70%) has a direct stimulating effect on ovarian androgens, besides a series of important modifications of body functioning, as increased abdominal fat deposition, dyslipidaemia, increased blood pressure, atherosclerosis and CV diseases risks .

- In addition, it is important to consider other factors, such as ethnicity, genetic polymorphisms, thyroid autoimmunity, when evaluating PCOS.

(Int. J. Fertil. Steril., 2016)

Insulin resistance

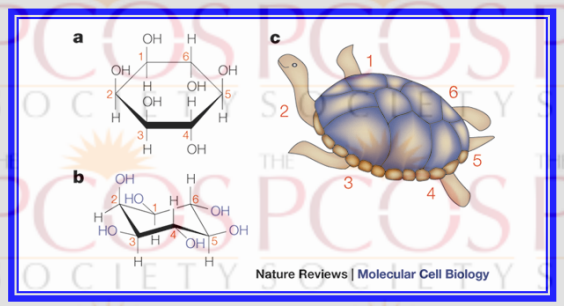
- Insulin regulates blood glucose through 2 main actions: the promotion of glucose cell uptake and glycogen synthesis.

- These activities are performed at post-receptor level, via the second messengers MYO-inositol (MYO) and D-chiro-inositol (DCI).

- MYO is able to promote glucose cell intake, while DCI stimulates glycogen synthesis.

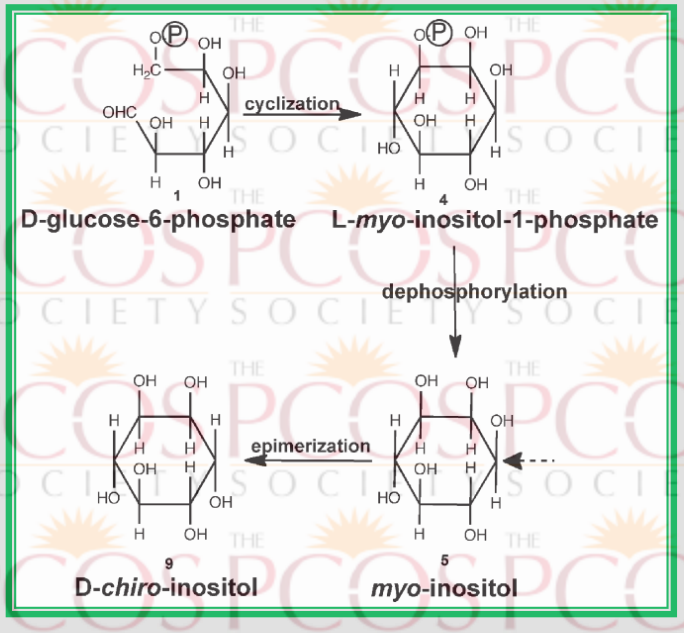
- As a consequence, DCI is present at high concentrations in glycogen storage tissue (liver, muscles and fat), while it is low in those tissue needing an elevated energy status (brain, ovary, heart).

(Eur.Rev.Med.Pharmacol.Sci., 2013)



Inositols

- Chemically derive by glucose-6-phosphate, and 9 possible stereoisomers exist.
- MYO- e D-chiro-inositol are the most relevant, with MYO being also the most abundant (99% of all Ins) and the precursor of DCI.
- MYO plays a role as the structural basis for a number of “second messengers” as important component of cellular membranes and as cytoskeleton modulator.
- Inside the cells it is present both in its free form and as a membrane component.



Inositol conversion

- Epimerase is an insulin-dependent enzyme that converts Myo-inositol (MYO) to D-chiro-inositol (DCI) through an oxido-reductive mechanism.
- Conversion rhythm is about 20-30% in normal insulin-sensitive tissues (liver, muscle and fat) and 5% only in diabetes *(Mol. Cells, 1998).*
- Gene search is on the way to identify mutations associated to insulin resistance *(Biochem. Genet. 2016)*

Insulin resistance

- DCI deficiency and imbalance with MYO are strictly related to insulin resistance, rather than to type II diabetes.
- DCI is reduced of about 50% in muscle and plasma of diabetic and PCOS patients, while DCI and MYO urinary excretion is increased *(Diabetes Care, 2006).*
- Excessive urinary MYO excretion, which is due to renal tubular competition between glucose and MYO, reduces its plasma levels and increases intracellular depletion.
- The consequent progressive decline in DCI epimerase-dependent production increases insulin resistance.

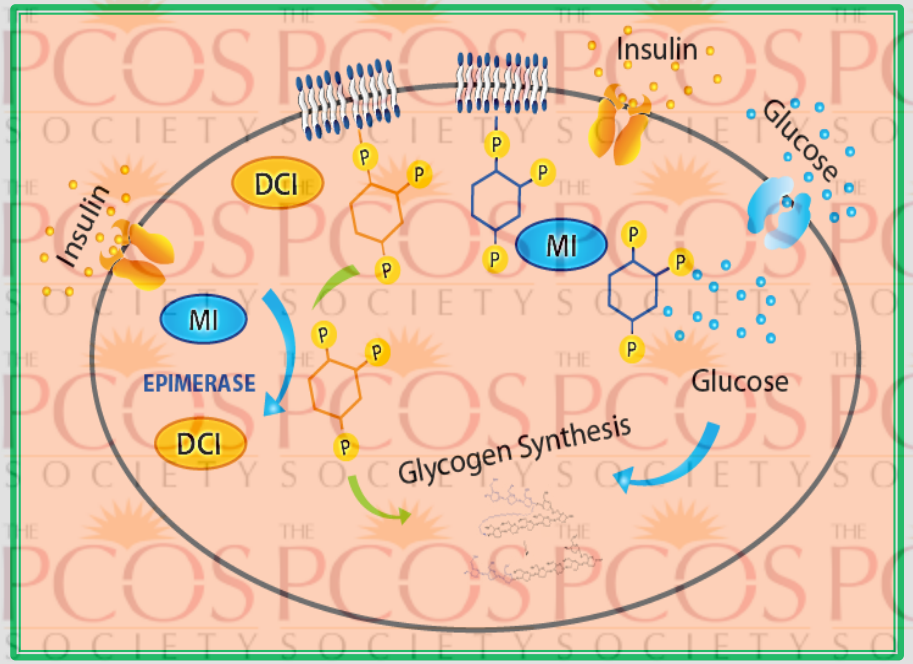
Inositols

MYO

- Increases glucose cell intake
- Increases oocytes quality
- Reduces the amount of FSH used during IVF cycles
- Improves metabolic and hormonal parameters in PCOS (reduces HOMA index, LH and Testosterone, increases SHBG, estrogens and progesterone)

DCI

- Stimulates glycogen synthesis
- It has a similar role to that of MYO on insulin resistance
- Limited effect at ovarian level (it may be detrimental at higher doses)



Inositols

- As “second messengers”, MYO and DCI are involved in signal transduction of insulin, FSH and TSH.
- In the ovary, MYO is involved in FSH signaling, while DCI is responsible for insulin-mediated testosterone production.

(Endocrine J., 2014)

Inositols and PCOS

The DCI "ovarian paradox"

Normally, epimerase MYO/DCI conversion activity induces a specific MYO to DCI ratio that is different in each tissue, but in accordance to the metabolic balance.

However, in insulin-resistant and PCOS patients this ratio is altered, due to a decreased epimerase conversion activity (1% vs. 8% in sensitive tissues) and a consequent increase in MYO to DCI ratio.

On the contrary, data show that in the ovary epimerase activity is increased, therefore inducing an increase in DCI concentrations and a decrease in MYO to DCI ratio.

(Consensus Conference, Florence, 2013; Endocrine J., 2014)

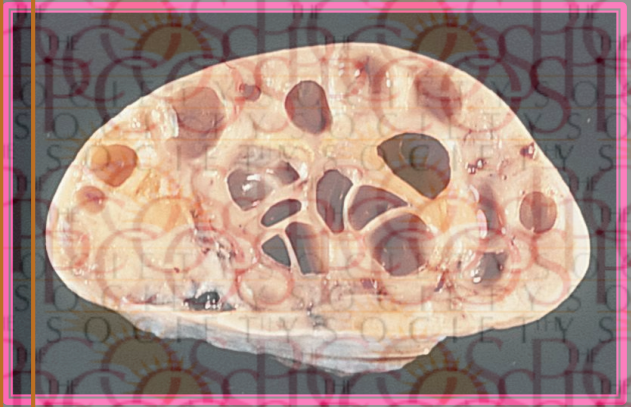
The DCI “ovarian paradox”

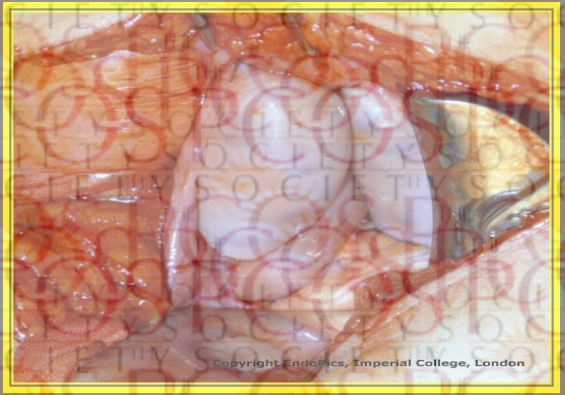
The increased ovarian DCI production would induce an insulin-mediated testosterone over production which will contribute to worsen peripheral insulin resistance.

In addition, the consequent reduction of MYO concentrations in the ovary may explain the reduction of follicles and oocytes quality.

(Consensus Conference, Florence, 2013; Best Pract.Res.Clin.Obstet.Gynaecol., 2016)

What to do ?

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2000 BC
2000 AD
EVOLUTION...

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ORIGINAL ARTICLE

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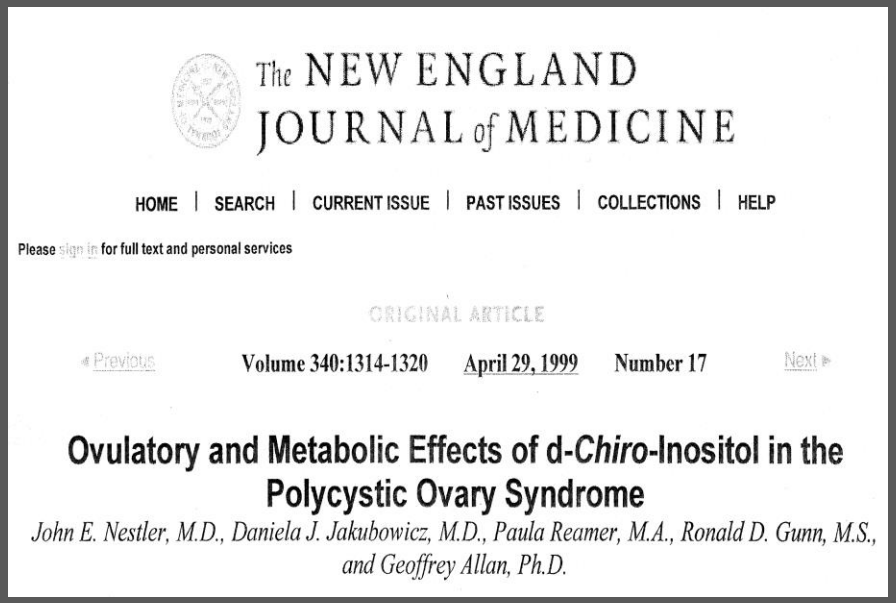
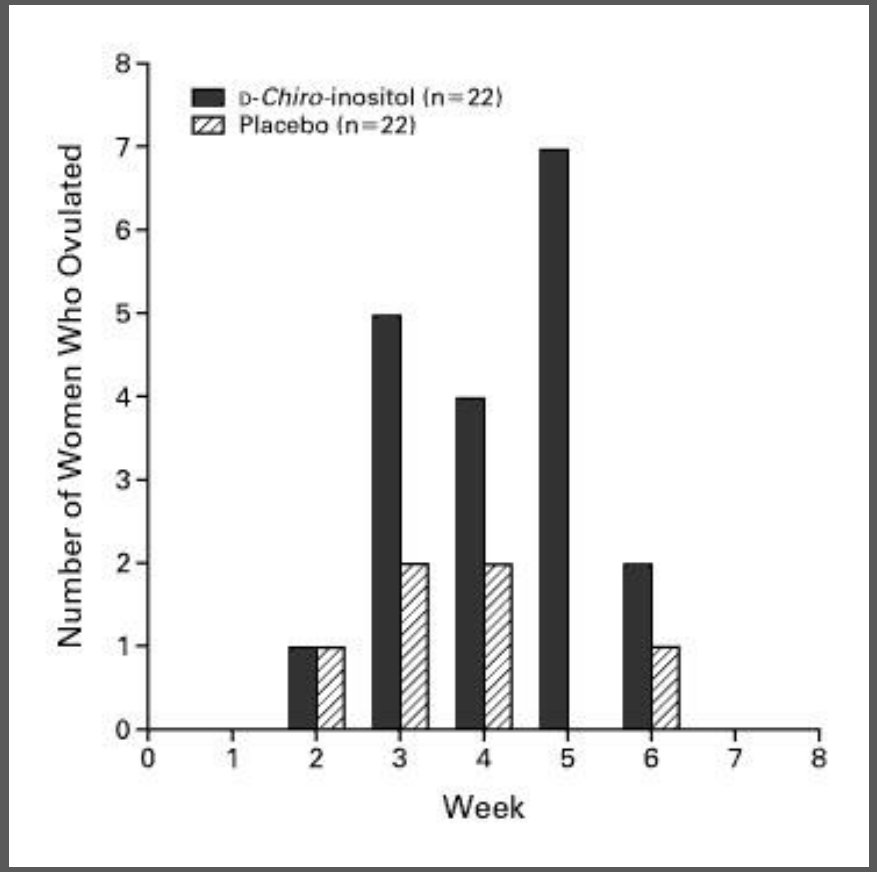
Ovulatory and Metabolic Effects of d-*Chiro*-Inositol in the Polycystic Ovary Syndrome

John E. Nestler, M.D., Daniela J. Jakubowicz, M.D., Paula Reamer, M.A., Ronald D. Gunn, M.S., and Geoffrey Allan, Ph.D.

Inositols





However, when administered at higher doses (2.4g/daily) to non-IR women, DCI seems to exert negative effects on ovarian tissues (testosterone biosynthesis promotion from theca cells) ***(Endocr.Pract., 2002)***

Inositols

Since MYO and DCI regulate different biological processes, a balance between them is required to normal tissues and cells functions.

Therefore, a therapy based upon the combined use of MYO plus DCI in a physiological plasma ratio seems to be a highly rational and effective approach to PCOS treatment.

In fact, their concomitant administration may be more beneficial than MYO alone in the treatment of overweight, insulin-resistant PCOS patients.

Endocrine J., 2014; Eur.Rev.Med.Pharmacol.Sci., 2014

Inositols

- Previous laboratory works identified the physiological plasma ratio of the two isomers to be as of 40:1 (MYO/DCI).
- At the beginning, when only the powder was available, at that time the therapeutic window ranged around 2g daily. That means 2g of MYO and 50mg of DCI (powder).
- Recently, additional pharmaceutical forms have been developed, which guarantee a more efficacious GI absorption at lower doses (550mg MYO and 13.8mg of DCI, tablets).
- MYO supplementation is well tolerated and safe. In humans, a daily dose of up to 18 grams per os, for 3 months, did not induce any significant adverse effect.

(Eur.Rev.Med.Pharmacol.Sci, 2011)

European Review for Medical and Pharmacological Sciences 2012; 16: 575-581

The Combined therapy with myo-inositol and D-Chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone

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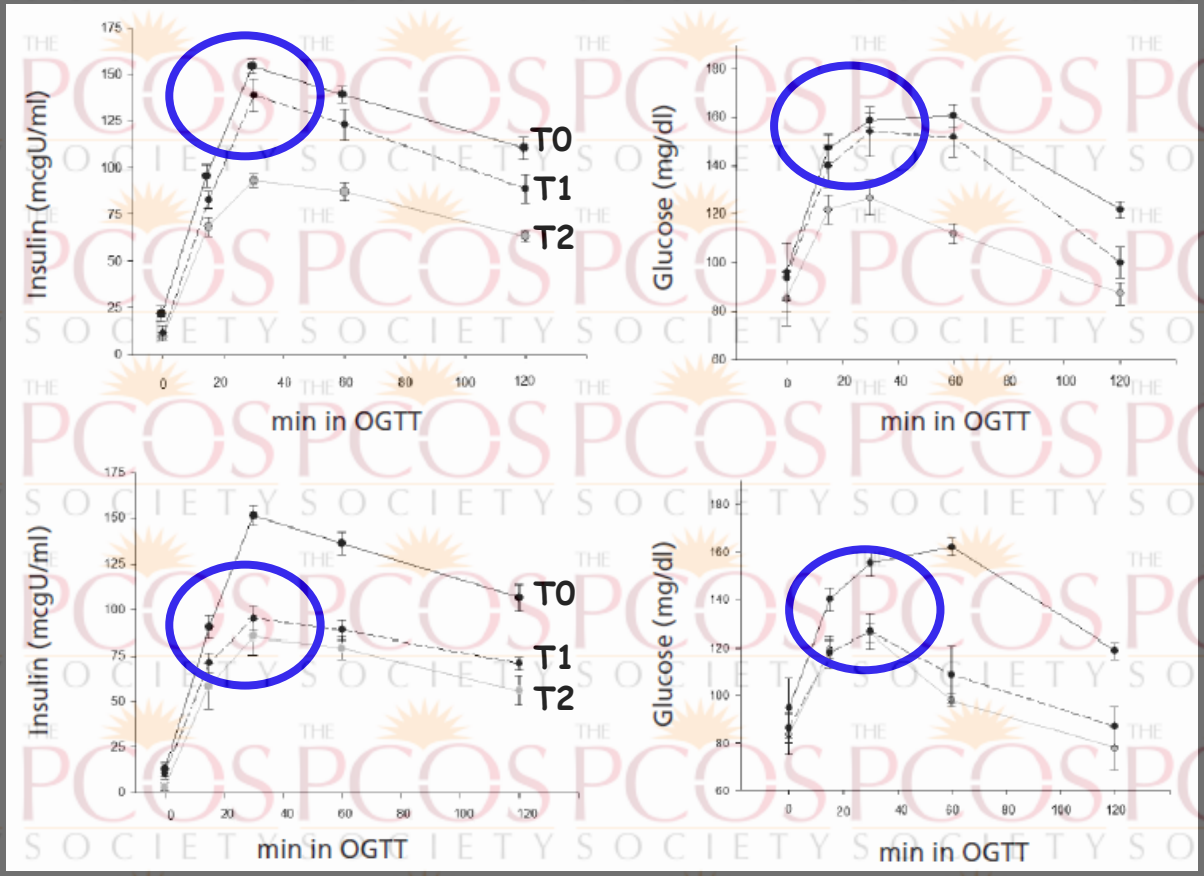
50 overweight PCOS patients

MYO

T0 = 0
T1 = +3 months
T2 = +6 months

MYO+DCI



European Review for Medical and Pharmacological Sciences 2013; 17: 537-540

The combined therapy myo-inositol plus D-Chiro-inositol, in a physiological ratio, reduces the cardiovascular risk by improving the lipid profile in PCOS patients

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Table I. Metabolic profile of the enrolled subjects at baseline and after 6 months treatment (means ± SD).

	Baseline	After 6 months treatment with myo-inositol plus D-chiro-inositol	*p* value
Age (years)	26.8 ± 5.1		
BMI	33.71 ± 6.1	33.1 ± 5.3	
Waist-hip ratio (cm)	0.92 ± 0.05	0.91 ± 0.09	
Tanita (% fat)	47.8 ± 4.4	47.1 ± 4.4	
BP systolic (mmHg)	121 ± 9.6	119 ± 8	
BP diastolic (mmHg)	71 ± 3.9	69 ± 8.5	
F. insulin (μU/ml)	18.2 ± 8.1	15 ± 8.7	= 0.05
F. glucose (mmol/L)	5.6 ± 0.5	4.7 ± 0.5	= 0.05
HOMA	5.8 ± 1.7	3.5 ± 1.1	= 0.05
T. cholesterol (mmol/L)	6.0 ± 1.8	5.01 ± 0.9	= 0.10
LDL (mmol/L)	3.5 ± 0.8	3.0 ± 0.8	= 0.03
TG (mmol/L)	2.0 ± 1.2	1.75 ± 1	= 0.24
HDL (mmol/L)	1.2 ± 0.2	1.3 ± 0.2	= 0.05

BMI: body mass index, BP: blood pressure, T. cholesterol: total cholesterol, LDL: low density lipoprotein, TG: triglycerides, HDL: high density lipoprotein, F. Insulin: fasting insulin, F. Glucose: fasting glucose.

Conclusions

- Of course, the best therapy should include a 360° approach to the problem, taking into consideration the complexity of the syndrome.

- Therefore, besides the need to change their own lifestyle (that is considered the first-line intervention), a nutraceutical and/or pharmacological treatment should be initiated as soon as the correct diagnosis is made, to avoid comorbidities progression.

- Today we have additional and potent tools that help us to answer to patients needs (as to infertility, weight, “cycle”, cosmetic and metabolic concerns).

Conclusions

- In this view, the use of inositol may be of great efficacy, either if the target is primarily “metabolic” (i.e. obesity, dyslipidemia, hyperinsulinemia, CV risk, hyperandrogenism signs), or fertility-oriented (anovulation, oligoovulation, IVF techniques).

- In addition, it is safe even with long term therapies.

- Data of the literature confirm that the combination therapy has a higher degree of efficacy, in terms of shorter time to obtain the results. Recent Consensus Conference guidelines stated that inositols may be succesfully used in most PCOS patients.

- All the above besides the fact that Pharmaceutical Companies should guarantee the highest purity and quality of their products to maintain constantly high results.

Take-home message

Finally, I do believe that administration of compounds that already belong to our organisms (as inositols) could be a modern and elegant approach to the therapy of PCOS, giving the body the chance to react by itself.

Thank you…