Myoinositol
Pharmacology and Mode of action

Glucose 6-P → MIPs

Ins(1,4,5)P₃
Myo-inositol 1-phosphate → IMP

PtdIns ← Myo-inositol → D-Glucuronic acid

GPI
IAA:Inositol
Ononitol
Galactitol
Pinitol
Raffinose

InsP₆
(Phytate)

D-Chiro Inositol

Cell Wall Polysaccharides
Inositol

- Inositol is a 6-carbon ring compound with a hydroxyl group attached to each carbon of the ring.
- Inositols & their derivatives are sugar alcohols- belong to Vitamin B family, chemically stable molecules.
- There are 9 possible stereo-isomeric forms of inositol (constitutionally similar), related to epimerization of the six hydroxyl groups.
- Myo-inositol (MI) & D-chiro-inositol (DCI) are the 2 of 9 important existing stereoisomers.
- MI is abundant form in nature & mammalian cells, comprising up to 99% of inositol amount.
- DCI - represents balance 1%
Inositols

- Average daily intake of myo-inositol from diet varies between 225 and 1500mg/day per 1800kcal diet.
- Dietary products containing inositol include:
  - Fruits- mainly cantaloupe and oranges,
  - High bran content cereals, nuts, and beans.
- Fresh fruits & vegetable contain more inositol compared to frozen, salted, or canned products.
- Inositols are not considered an essential nutrient since they can be formed endogenously from glucose.
The activity of this insulin-dependent enzyme strongly influences the intracellular ratio between these two molecules in adipose, hepatic, or muscle cells.
**Inositol conversion**

- Epimerase is an insulin-dependent enzyme that converts Myo-inositol to D-chiro-inositol 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).
- Ratio of MI;DCI 40:1
Myo inositol

- Precursors for the synthesis of phosphatidyl-inositol polyphosphates (PIPs). PIPs are key biomolecules belonging to the signal transduction system.
- Biological actions of Myo occur via PIPs or via inositol polyphosphates (InsPs)
- PIPs are crucial factors in regulating several cellular processes (membrane lipids)
- InsPs - important role in calcium signaling through its receptors (InsP3Rs).
Role of Myo-inositol

• Important role in cellular morphogenesis and cytogenesis
  – synthesis of lipids
  – creation of cell membranes &
  – cell growth.

• Regulates, secretion of some exocrine glands such as pancreas & ovaries via signal transduction pathways.
Myo-inositol & the ovary / oocyte

Regulates calcium metabolism

- Involved in the release of cortical granules,
- Inhibition of polyspermy,
- Completion of meiosis and
- Activation of the cell cycle - results in embryonic development (Papaleo 2009).
Role of Inositol in calcium metabolism

Oogenesis

Intracellular fluid

Myo-inositol

Inositol tri phosphate IP3

IP3R

Release Intracellular Ca\textsuperscript{+2}
Inositol - second messenger

MI & DCI are intracellularly incorporated into inositol phosphoglycans (IPGs), which are second messengers of Insulin, FSH & TSH.

Some actions of insulin are mediated by these IPG's.

Two IPG's have been identified:

(ii) the MYO-IPG which inhibits cyclic AMP-dependent protein kinase - involved in Cellular Glucose uptake.

(i) the D-chiro-IPG mediator, which activates pyruvate dehydrogenase phosphatase, and involved in Glycogen synthesis.
Actions in the ovary

- At ovarian level it has been shown that MI based second messenger is involved in both glucose uptake and FSH signaling.
- DCI-based second messenger is devoted to the insulin-mediated androgen production.
Rationale for use in PCOS

Derives from their activities as insulin mimetic (or “insulin sensitizing”) agents and their beneficial effects on metabolism.
In women with PCOS, a deficiency of IPGs in tissues, or
- An altered metabolism of inositols to IPG mediators, could play a role in inducing IR

(Baillergion et al 2010)
Pathway of Inositol deficiency & PCOS

1. Deficiency of inositol
2. Decrease level of PI3 kinase
3. Decrease glucose uptake
4. Hyperglycemia
5. Hyperinsulinaemia/IR
6. PCOS
7. Hormonal imbalance
   - Testosterone level
Inositol & PCOS

• The epimerase activity is increased in the theca cells of PCOS women, causing a deficit of MI. MI:DCI ratio altered. (Heimark et al 2014)

• Intraovarian MI may adversely affect glucose uptake and metabolism of both oocytes and follicular cells.

• Since oocytes are characterized by high glucose consumption this would compromise oocyte quality.

• PCOS women have lower serum DCI levels & > urinary loss of DCI-IPG. (Baillergion et al 2008)
Decreased myo-inositol to chiro-inositol (M/C) ratios and increased M/C epimerase activity in PCOS theca cells demonstrate increased insulin sensitivity compared to controls.

Douglas Heimark 1), Jan McAllister 2) and Joseph Larner 1)
How supplementation may help

• **MI** reduces insulin levels, probably
  – by conversion to D-chiro-Ins (via the epimerase enzyme) restoring MI:DCI ratio.
  – or by serving as substrate for formation of MI & DCI-IPGs,
  – which would in turn amplify insulin signaling.

• DCI supplementation replenished stores of the mediator & improved insulin sensitivity in both lean and obese women with PCOS (Unfer et al 2017)

• **MI** deficiency responsible for oligo ovulation & poor oocyte quality in PCOS. Supplementation restores N ovarian function. (Carlomagno et al.)
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, in the ovary data show that epimerase activity is increased, therefore inducing an increase in DCI concentrations and a decrease in MYO.

(Consensus Conference, Florence, 2013; Endocrine J., 2014)
The "DCI paradox" in the ovary

Unfer, Carlomagno and Roseff

- In PCOS HI stimulated epimerase activity in the ovary - an overproduction of DCI & a concomitant depletion of MI.
- DCI supplementation would be ineffective in such women as they already have > levels in ovary.
- > dose DCI - negative effects.
- It was anticipated that the synergetic activity of the two stereoisomers would result in a
  - (1) DCI-mediated enhancement of insulin sensitivity in liver and muscle resulting in a decrease in circulating insulin, and
  - (2) repletion of MI in the ovary, resulting in restored FSH sensitivity & improved oocyte quality.
Rationale of combining DCI and MI

- DCI in Periphery leads to Improved glucose metabolism
- MI in Ovary improves Ovulatory function
- Insulin resistance is reduced by both DCI and MI
- Reduced hyperinsulinemia
- Improved lipid profile
- Reduced cardiovascular risk

Myoinositol – Is there enough evidence?

**Review Article**

Inositol Treatment and ART Outcomes in Women with PCOS

Deepika Garg¹ and Reshef Tal²

J.I Endocrinol 2016

- Admin. of inositol in PCOS improves metabolic & hormonal parameters ovarian function & ovarian response.
- Vascular permeability, VEGF and COX-2 expressions were < in animals treated with MI and/or metformin. Turan et al 2015
### Table 1

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Authors</th>
<th>Population Characteristics</th>
<th>Type of Treatment</th>
<th>Study Size</th>
<th>Outcome Measures</th>
</tr>
</thead>
</table>
| Randomized controlled trial | (Chen et al., 2011) | 60 women with PCOS | Oral contraceptive pills | 60 | Significantly lower number of ovulatory cycles, clinical pregnancy rate, and miscarriage rate.

**Analysis of studies**

- **Reduced dose of FSH (P = 0.016), peak E2 level at hCG admin (P = 0.002), and peak E2 level at hCG admin (P = 0.002)**
- **No. of germinal vesicles (1 versus 3, P = 0.003)**
- **No. of cancelled cycles (1 versus 3, P = 0.003)**
- **No. of embryos (1 versus 3, P = 0.003)**
- **No. of embryos (1 versus 3, P = 0.003)**

Significantly lower number of ovulatory cycles, clinical pregnancy rate, and miscarriage rate in group A. No significant difference in number of embryos between group A and group B. Other parameters provided.
Conclusion

• Inositols are IS agents.
• They act at an intra-cellular level via the second messenger system.
• They have an important role to play in oogenesis and embryogenesis (Ca metabolism).
• Deficiency can increase IR & its subsequent effects.
• Supplementation appears to improve IS & metabolic parameters.
• Further studies required.