Role of inositol in Reproductive Function

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HYPE OR HOPE ????
Inositol – an Introduction

Inositol has 10 types of isomers:

- Myo-inositol
- Muco-inositol
- D-Chiro-inositol
- L-Chiro-inositol
- D-Chiro Inositol and Myo-Inositol

D-Chiro Inositol and Myo-Inositol are known to have proven effects in PCOS by facilitating Insulin’s action.

Current Evidence - significant biological role.
INOSITOLS – Some basic facts

- Sugar alcohols belonging to Vitamin B family
- Highest concentration of Myo-Inositol in fruits, beans, corns, and nuts.
- Myoinositol – the most common isomer (90%) D-chiro inositol (10%)
- Myoinositol converted to DCI in some cells by epimerase
- Varying MI / DCI ratio in different tissues

Inositol - Functions

• Glucose metabolism
  – Insulin signal transduction

• Fat metabolism
  – Breakdown of fats and reducing blood cholesterol

• Intracellular functions
  – calcium (Ca^{2+}) concentration control
Myoinositol plays an important role as the structural basis for a number of secondary messengers in Human Cell.
Role of Inositol

Glucose metabolism

Secondary Messenger

MI/DCI role in glucose uptake

MI – Glucose uptake
DCI – Glycogen synthesis
Inositols
Secondary Messenger to
INSULIN, FSH and TSH
INOSITOLS – Cell level functions

• Inositols are secondary messengers for cell signaling pathways such as –
  • Insulin Signal transduction
  • Calcium trafficking
  • Lipid metabolism
  • Cytoskeletal protein assembly
  • Cell growth and differentiation
  • Oocyte maturation
MI/DCI – physiological role

- Pivotal role – as secondary messengers of insulin
- Tissue specific intra cellular levels and functions
- DCI
  - High levels in liver, muscle and fat cells
  - Mediates glycogen synthesis
  - Aids in glycogen storage
- MI
  - High in heart/brain cells which require increased glucose consumption
  - Mediates glucose uptake at cell level
  - Crucial in ovarian function
D-Chiroinositol – Myoinositol

D-Chiroinositol acts at Peripheral tissues

DCI-IPG (Inositol Phospho Glycans) reduces Insulin resistance and increases insulin sensitivity.

DCI reduces compensatory (excess) insulin production and hyperinsulinemia

DCI by reducing Hyper insulinemia, reduces conversion of MI to DCI at ovary (Epimerisation)

DCI spares MI for action at Ovary.

Myoinositol Acts at Ovary

MI normalises LH : FSH ratio

MI acts as a secondary messenger for hormonal response

MI (IP3) improves Ca 2+ ion oscillation

MI helps in Oocyte quality, Oocyte Maturation, Pro nucleus formation and conception
Myo-inositol

- Positive effect on reproductive axis
- Secondary messenger for FSH
- Facilitates ovarian function
- Improves oocyte quality
-Improves metabolic parameters

Myo-Inositol

- Myo-Inositol in follicular fluid
- Inositol phospholipids
- Inositol 1, 4, 5 tri phosphate
- Modulates intracellular calcium Ca$^{2+}$ release in oocytes
- Meiotic progression of Germinal vesicles
- Improve oocyte maturation & quality, fertilization, embryonic development

MI – Oocyte quality

Increases calcium levels intracellular fluid

Promotes **meiotic progression** of oocytes

Better quality oocyte
Myoinositol

Ensures larger follicle and higher E2 levels in follicular fluid in IVF treatment.
MI - oocyte quality

Specific role in follicular maturation

Enhances intracellular $\text{Ca}^{2+}$ oscillation

Facilitates meiotic division

Progress of germinal vesicle to mature oocyte

MI deficiency leads to poor oocyte quality

MI replacement improves ovulation

MI deficiency

Myo-Inositol (In Ovary)

Epimerase ↑↑

DCI formation ↑↑

Myo-Inositol deficiency

Oocytes maturation arrest

Oligo-ovulation/anovulation

Infertility

D-Chiroinositol is a crucial secondary messenger in insulin signal transduction as InositolPhosphoGlycans (DCI-IPG) leading to control of insulin resistance.

- Corrects DCI Deficiency
  - (In Skeletal Muscles, Liver, Adipose Tissue)
  - Reduces insulin resistance
    - Corrects hyperinsulinemia
    - Corrects Hyperandrogenism
      - Controls T2DM
      - Controls HT
      - Controls MetS
      - Controls Hirsutism
      - Controls Acne
      - Controls Alopecia

*T2DM: Type 2 Diabetes mellitus, HT: Hypertension, MetS: Metabolic syndrome*
DCI deficiency

Myo-Inositol
(In skeletal Muscles, Liver, Adipose Tissue)

Epimerase

DCI deficiency

Insulin resistance

Hyperinsulinemia

Hyperandrogenism

T2DM

HT

MetS

Hirsutism

Acne

Alopecia

Metabolic Symptoms

Cosmetic Symptoms

T2DM: Type 2 Diabetes mellitus, HT: Hypertension, MetS: Metabolic syndrome

DeFronzo RA. Diabetes Care. 1991
Epimerase enzyme

• Epimerase is an insulin dependent enzyme
• Converts Myo-inositol into D-Chiro Inositol

Larner J et al. Mol Med. 2010 Nov-Dec;16(11-12):543-52
# Ovarian Paradox

Epimerase is an insulin dependent enzyme

Why is epimerase activity different in metabolic and reproductive organs?

<table>
<thead>
<tr>
<th>Skeletal muscles, liver and adipose tissue</th>
<th>Ovary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Become insulin resistant</strong></td>
<td>Does not become insulin resistant</td>
</tr>
<tr>
<td><strong>Reduced activity of Epimerase</strong></td>
<td>Increased activity of Epimerase</td>
</tr>
<tr>
<td><strong>Reduced conversion of MI to DCI leading to DCI deficiency</strong></td>
<td>Increased conversion of MI to MI deficiency</td>
</tr>
</tbody>
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Inositols and PCOS
PCOS - Pathophysiology

- Insulin Resistance (IR) and compensatory hyperinsulinemia
- Hyperandrogenism / Excess androgen
- Inositol deficiency
Pathway of Inositol deficiency & PCOS

1. Deficiency of inositol
2. Decrease level of PI 3 kinase
3. Decrease glucose uptake
4. Hyperglycemia
5. Hyperinsulinaemia/IR

Hormonal imbalance
Testosterone level

PCOS
Increased Insulin levels

- Ovary
- Adrenal
- Endometrium
- Liver
- Adipose tissue/Muscle
Hyperinsulinemia

- Stimulation of theca cells
- Increased production of androgens
- Hepatic effect
- Decreased SHBG

Hyperandrogenemia
In PCOD & Related Infertility

Root Cause is

Hormonal Imbalance Aggravated by Metabolic Impairment

- Altered LH:FSH Ratio
- Hyperinsulinemia
- Reduced SHBG
Hyperinsulinemia

Ovarian effect

IGF receptor activation
Increased LH

Ovarian androgen

Stromal cells
Leutinisation of theca cells

Disruption of follicular maturation
Hyperinsulinemia

Adrenal effects

Serine Phosphorilation

Androgens

DHS DAHS
Effects on Liver

Free testosterone
Free estradiol

SHBG
IGFBP
Role of androgens

PCOS - Follicular recruitment

Accelerated follicular development 2-5mm

ANDROGENS ++

Primordial
Pre-antral
Early antral

More early antral follicles

Excessive recruitment of early antral follicles
Paracrine control

Gonadotrophin Independent

AMH

FSH dependence

Endocrine control

Inhibin B

Gonadotrophin Dependent

Ovulatory
20 mm

Estradiol

Small antral
2-5 mm

Dominant
10 mm

Secondary

Primary

Primordial

I Recruitment

>120 days

II Recruitment

85 days

Selection

14 days

Dominance

Human Reproduction,
Morphology of polycystic ovary
Morphology of polycystic ovary

A excess $\rightarrow$ progression of primordial to small antral follicles

$\uparrow$ AMH & E2 $\uparrow$

$\downarrow$ FSH action $\downarrow$

$\rightarrow$ Arrest of follicular growth + apoptosis $\downarrow$

Multiple small follicles $\rightarrow$ A excess
MI/DCI – at ovarian level

**DCI paradox**

- Insulin dependent epimerase activity
- Increased conversion of MI -> DCI
- IN PCOS MI decreases, DCI Increases
- ↓MI – involved in FSH signaling
- ↑DCI – responsible for insulin mediated testosterone over production
- Poor oocyte quality

PCOS - ionisitols and changing Ovarian functions
MI:DCI in ovary

Follicular fluid

% MI-DCI

- myo
- D-chiro
PCOS – DCI Paradox

Dysovulation

- Hyperinsulinemia – M1/DCI imbalance
- Dysregulation of intra ovarian androgen metabolism
- Local hyper androgenism
- ↑ androgens promote excess follicle recruitment
- Excess antral follicles increase AMH levels
- AMH inhibits FSH induced aromatase activity
- Anovulation
MI – vital for fertility

• High concentration of MYO-INOSITOL in the follicular fluid is a marker of good quality oocyte – Human Reproduction vol 17 : 2002
Myo-inositol – improves oocyte quality & maturation

Myo-inositol plays a key role in nuclear and cytoplasmic oocyte development

Higher concentration of myo-inositol in follicular fluid is a marker of good quality oocytes

Gynecological Endocrinology, 2012; 28(7): 509–515
MI role in oocyte maturation

- MI normalizes the LH/FSH ratio
- Triggers calcium ion oscillation in endoplasmic reticulum
- Helps in oocyte maturation
MI role in Male Fertility

Spermatogenesis
Capacitation
Chemotaxis
Acrosomal Reaction

Calcium ion oscillation

Depends on Myoinositol
MI – vital for fertility

The concentration of MYOINOSITOL in the Seminiferous tubules fluid is higher than the levels found in the seminal plasma.

European Review for Medical and Pharmacological Sciences 2011; 15: 129-134
Capacitation

- Mature spermatozoa - held immotile within the epididymis.
- Spermatozoa are motile after ejaculation, but unable to fertilize an oocyte.
- Spermatozoa gain fertilization ability only after shedding glycoprotein in the female reproductive tract with Ca\(^{2+}\) ion oscillation.
Chemotaxis – Travel guide

• With calcium ion oscillation, sperm is directed towards ovum by chemoattractant.
Acrosomal reaction
Myo & Ca²⁺
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Myoinositol improves sperm parameters and serum reproductive hormones in patients with idiopathic infertility: a prospective double-blind randomized placebo-controlled study

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MI role in fertilization
Improves embryo to grade 1 in IVF treatment

Improves fertilizing ability and IVF outcome

Human reproduction 2002, 17(6) 1591-1596
Myoinositol overcomes insulin resistance

65% reduction in high insulin levels
Myo-inositol reduces androgen level

73% reduction in free androgen level

92% increase in SHBG

Gynecological Endocrinology 2007, Vol. 23, No. 12, Pages 700-703
Myo inositol- menstrual cycle

- 88% restoration of spontaneous menstruation
- 72% patients maintained normal ovulatory activity (6 months follow up)
- 30% patients maintained normal ovarian rhythm
Metformin

- Has been first line of treatment for insulin resistance in PCOS
  - Normalizes I.R at Systemic level
  - Non I.R. PCOS – use of metformin debatable
  - Improves I.R in only 50% of PCOS
MI / DCI

- MI - Safer at ovarian and non-ovarian level
- DCI - Beneficial effect mainly limited to non-ovarian tissue
- MI / DCI – safer than metformin; less side effects; effective in PCOS with or without IR
Remarkably, in all the studies analyzed, no side effects were reported.
Thank you
Hyperinsulinemia & macro vessels

- Endothelial dysfunction
- Impaired vasodilatation
- Increased macro vascular disease

- Circ: 2001 March, University of Indiana
Long term Cardiovascular effects

- Direct atherogenic action of insulin
- Direct relationship between insulin level & BP
- Adverse lipoprotein changes
- Impaired fibrinolysis – Increased PAI - I
Long term Cardiovascular effects

• Increased risk of MI
  – Age 40 – 49 4.2 fold increase
  – Age 50 – 60 11 fold increase
PCOS-Diabetes Mellitus

- Increased risk of NIDDM
  - 15% in post menopausal PCOS
  - 5% in control population

- Increased diabetes in pregnancy
  - Abnormal GTT 32%
  - Gestational Diabetes 13%

Dahlgren et al 1992
Urman et al 1997
Hyper insulinemia

- ↑ Obesity
- ↑ Android obesity (Central body fat)
- Abdominal wall and mesenteric location
- Waist - hip ratio > 0.85
- Waist circumference
  - > 100 cm in men
  - > 90 cm in women
Anovulation of PCOS: generated by androgen excess
Insulin resistance / hyperandrogenemia

PCOS – systemic manifestations

- hyperinsulinemia directly stimulates
  - Testosterone production by ovarian thecal cells
  - Promotes hyperandrogenic states
  - Leading to
    - Hirsutism
    - Acne
    - Alopecia
    - Higher waist to hip ratio
    - Detrimental effects on follicular growth (anovulation)
    - Menstrual disturbances

Hyperandrogenemia

PCOS - Long term sequelae

Androgen excess

↓

Visceral fat

↑

Lipolysis

↓

Insulin sensitivity

↓

HDL

↓

LDL

↑

?Direct vascular action

?Renal hypertension

↓

↑Atherosclerosis – CV morbidity
Hyperinsulinemia

Adipose tissue/Muscle effects

Triglycerides
Cholesterol
↑ LDH
HDL