DOES INSULIN RESISTANCE CAUSE HYPERANDROGENEMIA OR HYPERANDROGENEMIA CAUSES INSULIN RESISTANCE IN PCOS

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INTRODUCTION

- In 18th century, signs of androgen excess was coupled with metabolic abnormalities such as increased visceral fat.
- 1921, Achard and Thiers reported the coexistence of diabetes mellitus with clinical signs of androgen excess in a postmenopausal woman—“Achard-Thiers syndrome” or “diabetes of the bearded women”.
- Jean Vague introduced the term “android obesity” to define the abdominal fat accumulation.
Knobil’s experiments—more rapid GnRH pulse frequencies favor luteinizing hormone (LH) secretion.
PCOS
Characterized by –
disordered gonadotropin secretion,
Hyperandrogenemia,
insulin resistance and hyperinsulinemia,
follicular arrest.
DOES INSULIN RESISTANCE CAUSE HYPERANDROGENEMIA?
INSULIN RESISTANCE

CAUSES

1. Increase in GnRH release
2. Increase in Adrenal production of androgens
3. Reduction in SHBG production
4. Increase in Ovarian production of androgens
Insulin increases GnRH gene transcription through the MAPK pathway.

As a result, increased GnRH synthesis and secretion lead to a subsequent elevation of LH levels.

LH stimulates ovarian theca cell androgen production.
Insulin regulation of GnRH gene expression through MAP kinase signaling pathways, Molecular and Cellular Endocrinology, 2005
INSULIN AND SEX HORMONE BINDING GLOBULIN

- Not per se by direct insulin action
- Via indirect mediators - glucose and fructose
- Monosaccharides down regulates hepatocyte nuclear factor 4-alpha (HNF-4alpha) activity
- Insulin represses insulin-like growth factor-1 binding protein (IGFBP-1) synthesis in a direct, rapid, and complete way in both the liver and the ovaries

- This allows for greater IGF-1 availability at ovaries and liver
Insulin and dysregulation of hypothalamus-hypophysis-adrenal signalling

- Insulin inhibits hippocampal activity
- Indirectly enhances hypothalamic CRH secretion
- It has a possible direct role in both the hypothalamus and the hypophysis
- Insulin appears to augment adrenal cortex sensitivity to ACTH stimulation, with increased androgen secretion
SELECTIVE INSULIN RESISTANCE
The differential effects of tyrosine (Tyr) vs. serine (Ser) phosphorylation of the IR. Tyrosine phosphorylation of IRβ after the binding of insulin to IRα leads to tyrosine phosphorylation of IRS-1 and the activation of downstream effector molecules. However, serine phosphorylation of IRβ inhibits IRS-1 activation.

The serine phosphorylation hypothesis. The serine phosphorylation hypothesis proposes that a dominantly inherited kinase (or kinases) serine phosphorylates both IR$_{\beta}$ and P450c17, leading to insulin resistance and increased androgen production, respectively. Both positive and negative regulatory factors may modulate kinase activity.

![Diagram](image)

INSULIN SIGNALING IN OVARIAN TISSUE AND SELECTIVE INSULIN RESISTANCE
Decrease in insulin levels by metformin/TZD, or diazoxide or somatostatin—significantly reduce androgen levels in PCOS women.

There was improvement in 17-20 lyase activity.

Decrease in DHEAS levels.
DOES HYPERANDROGENEMIA LEAD TO HYPERINSULINEMIA?

- Testosterone or DHEAS signaling - upregulation of beta 3 adrenergic receptors and hormone-sensitive lipase expression in visceral adipose tissue (VAT)
- Increases lipolytic activity and release of FFA into circulation
- FFAs activate PKC, a serine/threonine kinase
- This leads to serine threonine kinase activation - inhibition of insulin signalling
Hyperandrogenemia decreases the amount of type I muscle fibers, which are highly oxidative and insulin-sensitive.

Increases type II fibers, which are glycolytic and less sensitive, as well as decreasing expression of glycogen synthase.
Androgen-driven pro inflammatory cytokine secretion from VAT and androgen-induced interference of insulin signalling.

HA – associated with abdominal fat accumulation in women and lower levels of circulating SHBG and also lower adiponectin levels.
GnRH pulses

Rapid

LH / FSH ratio increased

Ovarian theca cell androgen production
Decreased granulosa cell aromatisation

Hyperinsulinemia (insulin receptor defect/binding defect/post receptor defect)

Selectivity insulin resistance

Adrenal androgen production

Reduced SHBG production

Decrease adiponectin, increase NEFA, increase type 2 muscle fibres

Hyperandrogenism
MINIMAL MODEL OF PCOS PATHOPHYSIOLOGY

**Theca Cell**

**Functional Ovarian Hyperandrogenism**

1. Sex steroid excess
2. Anovulation
3. PCOM

**Luteinized Granulosa Cell**

**Pilosebaceous Unit**

**Hirsutism**

**Adipocyte Obesity**

**Insulin-Resistant Hyperinsulinism**

**Pituitary**

**LH excess**

**FSH**
Insulin resistance

Hyperinsulinemia → Chronic inflammation

Hypophys: ↑ LH pulse frequency and amplitude

Liver: ↓ SHBG + ↑ IGFBP-1 → ↑ free testosterone + ↑ free IGF-1

Arterial hypertension-dyslipidemia-type 2 diabetes mellitus-metabolic syndrome-cardiovascular disease

Ovary

Ovarian cysts-menstrual disturbances-hirsutism

↑ FFA

↓ TIMF

↑ TIIMF