INSULIN RESISTANCE, POLYCYSTIC OVARIAN SYNDROME – An Overview

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What is Insulin Resistance?

- **Insulin Resistance**:
  - Tissues fail to respond to Insulin,
  - Ability of Insulin to dispose of blood glucose in Liver, Skeletal Muscle, Adipose tissue and other peripheral tissues is compromised;
- May be due to:
  - Reduced number Insulin Receptors on tissues,
  - Low affinity of Insulin Receptors,
  - Normal Insulin binding to receptors, but abnormal Post-Receptor responses, e.g., abnormal activation of Glucose Transport,
  - High expression of Tumor Necrosis Factor-α (TNF-α) in Adipocytes of Obese Individuals;

IMPORTANT TO NOTE

- The greater the quantity of body fat in susceptible individuals, the greater the resistance of normally Insulin-Sensitive cells to action of Insulin;
  - Skeletal muscle has the greatest impact on whole-body glucose disposal, and hence on Insulin Resistance,
- When Insulin Resistance, or Reduced Insulin Sensitivity exists, the body attempts to overcome this resistance by secreting more Insulin from Pancreas;
  - This **compensatory state of Hyperinsulinemia** (high insulin levels in blood) **is used as a marker for Insulin Resistance Syndrome**;

What causes Insulin Resistance?

- Exact mechanism for Insulin Resistance is not known,
- Some hypothesis have been proposed:
  - **Post-Receptor Defect in Adipose Tissue,**
  - **Abnormalities in Regulation of Expression of Insulin Gene is associated with Hyperinsulinemia;**
- Despite Insulin Resistance in Adipose Tissue and Skeletal Muscle:
  - **Ovary remains relatively sensitive to Insulin,**
  - **Insulin and Insulin-like Growth Factor-1 (IGF-1) have stimulatory effects on the production of Androgen by the Ovary;**

What are some of the characteristics of Insulin Resistance?

- Insulin resistance is characterized by:
  - High Fasting Blood Glucose,
  - High Post-glucose Loading Insulin levels (Oral Glucose Tolerance Test),
  - Decreased Responsiveness of Tissue to Insulin driven clearance of Glucose from blood;

What are some of the consequences of Insulin Resistance?

- Some consequences of Insulin Resistance includes:
  - Metabolic Syndrome “Syndrome X”,
  - Type 2-Diabetes Mellitus (NIDDM),
  - Obesity,
  - Polycystic Ovarian Disease,
  - Dyslipidemia (High Triglycerides & LDL, Low HDL);
  - Cardiovascular disease and Hypertension,
  - Sleep Apnoea,
  - High Plasminogen Activator Inhibitor (PAI-1);
- **NB:** PAI-1 reduces ability to dissolve blood clots;
  - High PAI-1 is risk factor for Heart Attack and Stroke;

What are some risk factors for developing Insulin Resistance?

- Overweight, (especially central obesity),
- Strong family history of Type II Diabetes Mellitus,
- History of Gestational Diabetes, Hypertension,
- Dyslipidemia, especially low HDL and High Triglycerides,
- Women with Polycystic Ovary Syndrome,
- Acanthosis Nigricans {Skin change: Velvety, Mossy, Flat Warty-like, Darkened Skin change occurring at Neck, Armpits (Axillae) and underneath breasts};
- Reduced Physical Activity, Aging, Tobacco Smoking,
- Regular use of diuretics,
- Some Anti-hypertensive drugs, or Steroids can worsen Insulin Resistance;

How is Insulin Resistance Diagnosed?

- Hyperinsulinemic Euglycemic Clamp Study is the "**Gold Standard**" for diagnosis of Insulin Resistance,
- Test MUST be done under Clinical supervision:
  - Patients is given Intravenous Infusions of Insulin and Glucose at different Doses to determine the amount of Insulin needed to control different blood glucose levels;

- **Simple diagnostic tests for Insulin Resistance**:
  - Fasting plasma Insulin Level of over 15uU/ml indicates Insulin Resistance,
  - This plasma level of fasting insulin highly correlates with Euglycemic clamp study;
  - Fasting Glucose to Insulin Ratio can also be use to diagnose Insulin Resistance,
  - Haemoglobin A1c (HbA_{1c}) can be use to determine if further testing is needed;

What is Polycystic Ovarian Syndrome (PCOS)?

- **PCOS**:
  - **Condition characterised by menstrual abnormalities and Biochemical features of Hyperandrogenism**;
- Features of PCOS may manifest at any age:
  - Childhood (Premature Puberty),
  - Teenage years (Hirsutism, Menstrual Abnormalities),
  - Early Adulthood and Middle life (Infertility, Glucose intolerance),
  - Later Life (Diabetes Mellitus, Cardiovascular Disease);

What is /are the biochemical basis for PCOS?

- Biochemical basis of PCOS is not clearly understood;
- Several theories have been suggested:
  - Evidence of Autosomal Transmission related to strong Genetic Clustering,
    - **A Gene or Series of Genes causes the ovaries to become Sensitive to Insulin stimulation, causing the ovary to overproduce Androgens, while blocking Maturation of Follicles**;
- **Major underlying disorder in PCOS is Insulin Resistance, with resultant Hyperinsulinemia stimulating excess production of Androgens by the Ovaries**;

How does Hyperinsulinemia relate to Infertility in female?

- **Hyperinsulinemia** is Central Biochemical abnormality of PCOS;
- Hyperinsulinemia leads to **Hyper-Androgenism**:
  - Ovarian overproduction of Testosterone,
  - Adrenal overproduction of Androgens:
    - **Dehydroepiandrosterone Sulphate** (**DHEAS**),
    - **Androstenedione,**
- Increased Testosterone (or Androgens) affects HPO axis in the female, leading to abnormal production of **LH and FSH**;

- Consequences of abnormal LH and FSH production:
  - Ovarian underproduction of Estrogen, along with
  - Abnormal production of Progesterone,
- Overproduction of Testosterone that ultimately leads to Amenorrhea and Infertility;

How does defect in Insulin metabolism in females promotes Hyper-Androgenism in PCOS?

- Exact mechanism whereby defects in Insulin metabolism promote increased Androgen activity in PCOS is not fully understood;
- Several Hypotheses have been suggested:
  - **Insulin inhibits biosynthesis of SHBG in the liver, which leads to increase plasma level of Free Testosterone**,
  - **Insulin also inhibits biosynthesis of Insulin-like Growth Factor-1 (IGF-1) Binding Protein in liver,**

- Reduction in plasma levels of IGF-1 Binding Protein causes increase in plasma level of circulating Free Insulin-like Growth Factor –1 (IGF-1), which further enhances Ovarian Androgen production;
- In most cases of PCOS:
  - Ovary is major site of excess Androgen production,
  - Some women with PCOS may have an Adrenal contribution to increased Androgen production;

What are some consequence of Hyperinsulinemia in PCOS?

- Hyperinsulinemia produces **Hyperandrogenism** in via distinct and independent mechanisms:
  - By stimulating Ovarian Androgen Production,
  - By directly and Independently Reducing Plasma SHBG levels,
  - By reducing Plasma Level of IGF-1 Binging Protein,

- Net result is Increased levels of Circulating Free Testosterone;

IMPORTANT TO NOTE

- An inherent (genetically determined) ovarian defect in women with PCOS is one, which makes the ovary either susceptible to or more sensitive to insulin stimulation of Androgen production;
- **Hyperinsulinemia** adversely affect Folliculogenesis and Impede Ovulation by:
  - Increasing Intra-ovarian Androgen production,
  - Altering secretion of Gonadotrophins, and/or directly affecting Follicular development;

What endocrine Abnormalities are used as diagnostic tools in PCOS?

- Other disease conditions must be excluded before diagnosis of PCOS can be made with any credibility
- Disease conditions to be excluded include:
  - Thyroid disease,
  - Late Onset Congenital Adrenal Hyperplasia (CAH),
  - Hyperprolactinaemia,
  - Androgen secreting tumours;

- After excluding these conditions the following can then be used as diagnostic tool for PCOS:
  - **Elevated Free Testosterone activity, confirmed by High Free Androgen Index, is the currently acceptable Biochemical marker for Differential diagnosis of PCOS,**
  - **High LH and Normal FSH levels in Plasma,**
  - **Strong evidence of Insulin Resistance with Compensatory Hyperinsulinemia;**

Why is relationship of Hyperinsulinemia to PCOS important from a clinical standpoint?

- Women with PCOS should to be evaluated for disorders associated with Insulin Resistance, e.g:
  - Diabetes Mellitus,
  - Hypertension,
  - Dyslipidemia,
  - Atherosclerosis;

- Insulin reduction, whether achieved by Inhibition of Pancreatic Insulin Release or Improvement in Peripheral Insulin Sensitivity, is associated with a reduction in circulating Androgens in women with PCOS and Improvement in Ovarian function;

What are some of the consequences of PCOS?

- Some of the consequences include:
  - Infertility,
  - Irregular Menstruation,
  - Ovarian Cysts,
  - Darkening of the Skin Folds,
  - Acne,
  - Elevated Plasma Lipid Levels,
  - Hypertension,
  - Heart disease,
  - Gestational diabetes,
  - Uterine cancer;

- Elevation of Plasminogen Activator Inhibitor-1 (PAI-1),
  - PAI-1 is a potent inhibitor of Fibrinolysis and a predict of Myocardial Infarction,
- Eating disorders: May be due to link with Leptin that affects Hypothalamic release of GnRH, with important effects on reproduction,
- Obesity increases Risks of:
  - Stroke,
  - Gallbladder disease, Colon cancers,
  - Osteoarthritis,
  - Sleep Apnoea, and Respiratory problems
- **NB**: Not all women with PCOS have Insulin Resistance and Glucose Intolerance;

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