University of Papua New Guinea
School of Medicine and Health Sciences
Division of Basic Medical Sciences
Discipline of Biochemistry and Molecular Biology
PBL SEMINAR

INSULIN RESISTANCE, POLYCYSTIC OVARIAN SYNDROME – An Overview

What is Insulin Resistance?

- Insulin resistance: Tissues fail to respond to Insulin
- Insulin resistance: The ability of Insulin to dispose of Glucose in the Liver, Skeletal Muscle, and other peripheral tissues is compromised
- May be due to:
  - Reduced number of Insulin Receptors
  - 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 Tumour Necrosis Factor-α (TNF-α) in Fat cells of Obese individuals

TAKE NOTE:

- In general, the greater the quantity of body fat in a susceptible individual, the greater the resistance of normally Insulin-sensitive cells to action of Insulin
- From a quantitative standpoint, skeletal muscle is presumed to have 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 the Pancreas
  - **This compensatory state of Hyper-insulinemia (high insulin levels in the blood) is used as a marker for Insulin Resistance Syndrome**

What causes Insulin Resistance?

- Exact mechanism for Insulin Resistance is not known
- Following ideas put forward:
  - Post-receptor Defect in Adipose Tissue has been identified
  - Abnormalities in Regulation of Expression of Insulin Gene has been shown to be associated with Hyper-insulinemia

- Despite Insulin Resistance in Adipose Tissue and Skeletal Muscle:
  - Ovary remains relatively sensitive to Insulin
  - Insulin and Insulin-like Growth Factor-1 have stimulatory effects on the production of Androgens by the Ovary

What are some of the characteristics and consequences 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

- Insulin resistance is a common feature and contributing factor to several frequent health problems, including the following:
    - Metabolic Syndrome "Syndrome X"
    - Type 2-Diabetes Mellitus (NIDDM),
    - Polycystic Ovarian Disease,
    - Dyslipidemia (High Triglycerides and LDL, but Low HDL in plasma)
    - Cardiovascular disease and Hypertension,
    - Sleep Apnea,
    - Obesity
    - High Plasminogen Activator Inhibitor (PAI-1)
        - **Note**: PAI-1 reduces the ability to dissolve blood clots (Thrombi), thus, High PAI-1 is an independent risk factor for Heart Attack and Stroke

What are some of the risk factors for developing Insulin Resistance?

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

How is Insulin Resistance Diagnosed?

- Hyper-insulinemic Euglycemic Clamp Study is the "**Gold Standard**" for diagnosis
    - 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 levels of glucose

- **Simple diagnostic tests**:
    - Fasting Insulin Levels of over 15uU/ml indicates Insulin Resistance
        - This 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

Polycystic Ovarian Syndrome (PCOS):

What is PCOS?

- Polycystic Ovary Syndrome (PCOS) is a condition characterised by Menstrual Abnormalities and Clinical or Biochemical features of Hyperandrogenism
- Features of PCOS may manifest at any age ranging from:
    - Childhood (Premature Puberty),
    - Teenage years (Hirsutism, Menstrual Abnormalities),
    - Early Adulthood and Middle life (Infertility, Glucose intolerance) to
    - Later Life (Diabetes Mellitus and Cardiovascular Disease)

- Hyperinsulinemia is the central biochemical abnormality of Polycystic Ovary Syndrome (PCOS)
- Hyperinsulinemia leads to:
  - Ovarian Overproduction of Testosterone
  - Hyper-Androgenism: that is:
    - Adrenal Overproduction of DHEAS and Androstenedione {two Androgenic sex hormones}

- Increased Testosterone affects the HPO-axis, leading to low LH and FSH
- Low LH and FSH leads to:
  - Ovarian underproduction of Estrogens
  - Abnormal production of Progesterone,
  - Overproduction of Testosterone, which consequently results in Amenorrhea and Infertility

What is/are the Biochemical basis (aetiology) for PCOS?

- Biochemical basis of PCOS is not clearly understood
- Several Theories have been suggested:
  - Some 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 starts Overproducing Androgen, while blocking Maturation of Follicles

- **Major underlying disorder in PCOS is Insulin Resistance, with Resultant Hyper-insulinemia Stimulating Excess Ovarian Androgen production**

Why does defect in Insulin metabolism leads to increase Androgen in PCOS?

- Exact mechanism whereby a defect in Insulin Metabolism Promote Increased Androgen activity in PCOS is not fully understood
- Several Hypothesis have been suggested:
  - Insulin inhibits biosynthesis of Sex Hormone Binging Globulin (SHBG), resulting in Increase in Plasma Level of Free Testosterone
  - Insulin also inhibits biosynthesis of Insulin-like Growth Factor-1 (IGF-1) Binding Protein in the Liver
    - Reduction in plasma levels of IGF-1 binding protein causes an increase in plasma concentration of circulating Free Insulin-like Growth Factor –1 (IGF-1), which further enhances Ovarian Androgen production

<u>TAKE NOTE</u>:

- In most cases of PCOS the Ovary is the major site of excess Androgen production, but some women with PCOS may have an Adrenal contribution to the increased Adrogen production

What are some of the consequence of Hyperinsulinemia in PCOS?

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

- Net result is Increase concentrations of Circulating Free Testosterone
- **An inherent (genetically determined) ovarian defect that is likely present in women with PCOS is one, which makes the ovary either susceptible to or more sensitive to insulin's stimulation of androgen production**

- Hyperinsulinemia adversely affect Folliculogenesis and Impede Ovulation by:
  - Increasing Intra-ovarian Androgen production,
  - Altering Gonadotropin secretion, and/or directly affecting Follicular development

What endocrine Abnormalities are used as diagnostic tool 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 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 concentrations in Plasma**
  - **Strong evidence of Insulin Resistance with Compensatory Hyper-insulinemia**

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

- Women with PCOS need to be evaluated for other disorders associated with Insulin Resistance: disorder, such as

  - 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 an Improvement in Ovulatory function

What are some of the consequences of PCOS?

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

- Elevated concentrations of Plasminogen Activator Inhibitor-1 (PAI-1)
  - PAI-1 is a potent inhibitor of Fibrinolysis and a predict of Myocardial Infarction

- Women with PCOS are prone to eating disorders
  - May be due to a link with Leptin, which affects Hypothalamic Pulsatility of GnRH, with important effects on reproduction

- Most women suffering from PCOS are usually Obese,
  - Obesity increases Risks of Stroke, Gallbladder disease, Osteoarthritis, Sleep Apnea, Respiratory problems and Colon Cancers

- Not all women with PCOS have Insulin Resistance and Glucose Intolerance