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Exploring Insulin Resistance and Glucose Dysregulation in PCOS: Current Diagnostics and Emerging Therapies.

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Abstract: ***The common endocrine disorder known as polycystic ovary syndrome (PCOS), which increases the risk of type 2 diabetes and cardiovascular disease, is characterized by insulin resistance and glucose intolerance. Accurate diagnosis is still challenging since gold standard procedures, such as the hyperinsulinemic-euglycemic clamp, are not practical for daily use. Surrogate markers such as HOMA-IR and oral glucose tolerance tests (OGTT) have limitations while being often used. The primary therapeutic options are lifestyle changes and insulin-sensitizing drugs, however treatment is hampered by patient variability and adherence issues. By describing current diagnostic techniques and underlining treatment challenges in managing metabolic dysfunction in PCOS, this review highlights the need for improved screening and tailored care.***
Keywords: Polycystic Ovary Syndrome (PCOS), Insulin Resistance, Glucose Intolerance, HOMA-IR, OGTT, Metformin, Personalized Therapy, Metabolic Dysfunction.

I. INTRODUCTION

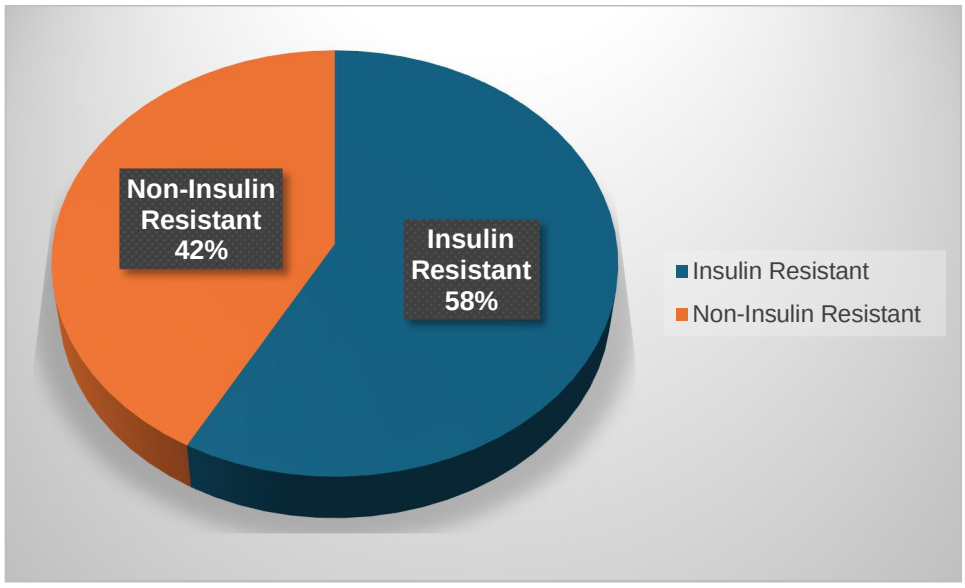
One of the most common endocrine disorders affecting women of reproductive age globally, polycystic ovarian syndrome (PCOS), has prevalence rates ranging from 6% to 18%, depending on the diagnostic criteria and populations studied. It is characterized by significant metabolic issues as well as reproductive abnormalities include hyperandrogenism, menstrual disruption, and polycystic ovarian morphology. These metabolic characteristics include insulin resistance (IR) and glucose intolerance, which significantly increase the risk of type 2 diabetes, heart disease, and other long-term effects. Insulin resistance is common in PCOS regardless of weight, albeit it is exacerbated by the accumulation of abdominal fat. This IR results in compensatory hyperinsulinemia, which worsens reproductive failure, by raising ovarian androgen production and lowering sex hormone-binding globulin levels. Many women have overt diabetes or impaired glucose tolerance, which is often undetectable by fasting glucose levels alone. Another common condition is glucose intolerance. The gold standard for diagnosing these aberrations is still the oral glucose tolerance test (OGTT). Although it is vital, precisely detecting insulin resistance and glucose intolerance in PCOS is still difficult because gold standard procedures like clamp studies are not practicable for everyday use. The limits of clinical testing and surrogate indicators differ. The syndrome's heterogeneity, a poor response to medications like metformin, and obstacles to lifestyle change are some of the therapeutic problems. In order to control metabolic risks and enhance PCOS health outcomes, it is imperative that these diagnostic and treatment issues be addressed.

A. Pathophysiology Overview

Reproductive and metabolic dysfunctions interact to form the complicated endocrine condition known as polycystic ovarian syndrome (PCOS). Up to 80% of women with PCOS have insulin resistance (IR), which is a key factor in the disease's etiology. The IR seen in PCOS is frequently selective, affecting glucose metabolism while maintaining insulin sensitivity in ovarian steroidogenic pathways. This selective insulin resistance leads to compensatory hyperinsulinemia, which exacerbates hyperandrogenism by promoting ovarian androgen synthesis and lowering hepatic production of sex hormone-binding globulin (SHBG), so raising free androgen levels.

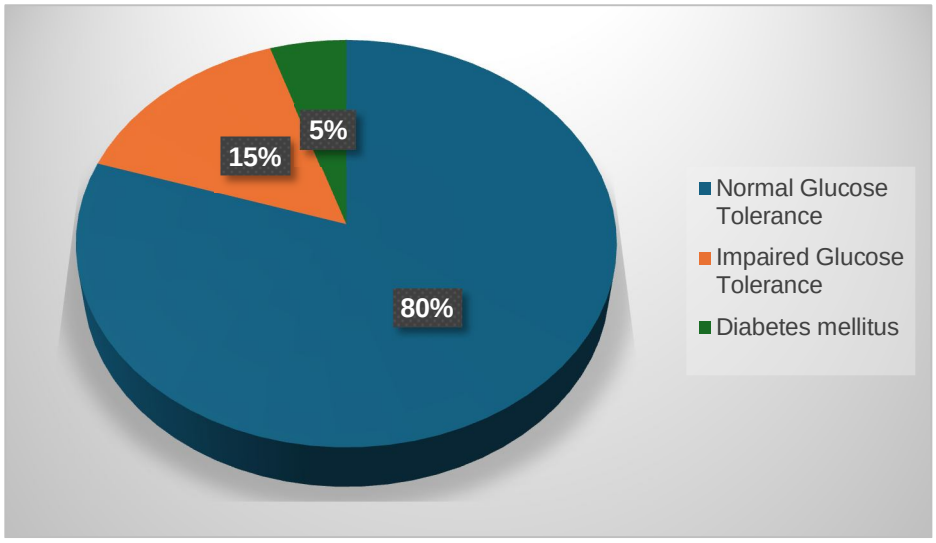
Variability in clinical presentation and metabolic risk is influenced by genetic predisposition and epigenetic variables in addition to insulin resistance. Although obesity frequently exacerbates insulin resistance, it is not a requirement because thin women with PCOS can still develop IR. Metabolic abnormalities are also caused by altered adipose tissue function and chronic low-grade inflammation. IR often coexists with glucose intolerance, which raises the risk of cardiovascular problems and type 2 diabetes. The complexity and variability of PCOS are caused by the interaction of various metabolic and endocrine disorders.

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Pie chart 1: Prevalences of Insulin Resistance in PCOS

(Based on average prevalence estimates of 35% - 80% insulin resistance in PCOS women)



Pie chart 2: Glucose Tolerance Status in PCOS

(Based on glucose tolerance abnormalities in PCOS reported in clinical studies)

Current Diagnostic Tool: Diagnostic tool for insulin resistance and glucose intolerance include several clinical tests and indices, widely used in both research and healthcare settings.

II. INSTRUMENTS FOR INSULIN RESISTANCE DIAGNOSTICS

1) Hyperinsulinemic-euglycemic clamp: Although this is the gold standard for assessing whole-body glucose elimination under controlled insulin infusion, it is too complicated and impractical for regular clinical use. A hyperinsulinemic euglycemic clamp is a diagnostic procedure that uses constant insulin and variable glucose infusions to measure the body's sensitivity to insulin. It involves infusing insulin at a steady rate while intravenously administering glucose to maintain a normal blood sugar level (euglycemia). The rate at which glucose must be infused indicates how sensitive the body is to insulin; a higher glucose infusion rate (GIR) signifies greater insulin sensitivity insulin sensitivity.

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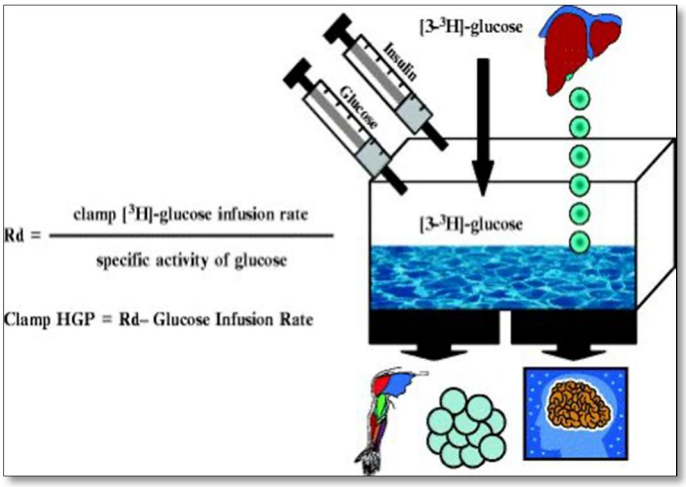


Fig.1 Hyper insulinemic-euglycemic clamp technique

2) Homeostatic Model Assessment for Insulin Resistance (HOMA-IR): This widely used surrogate marker is computed using fasting insulin and glucose levels. HOMO-IR, or Homeostatic Model Assessment of Insulin Resistance, is a calculation that uses your fasting blood glucose and fasting insulin levels to estimate your body's insulin resistance. It's a key tool for evaluating how well your body uses insulin and can help detect early signs of insulin resistance, a condition that may lead to type 2 diabetes and other metabolic issues. The formula for HOMA-IR is typically: HOMA-IR = [fasting insulin (µU/ml) × fasting plasma glucose (mg/dl)]/405

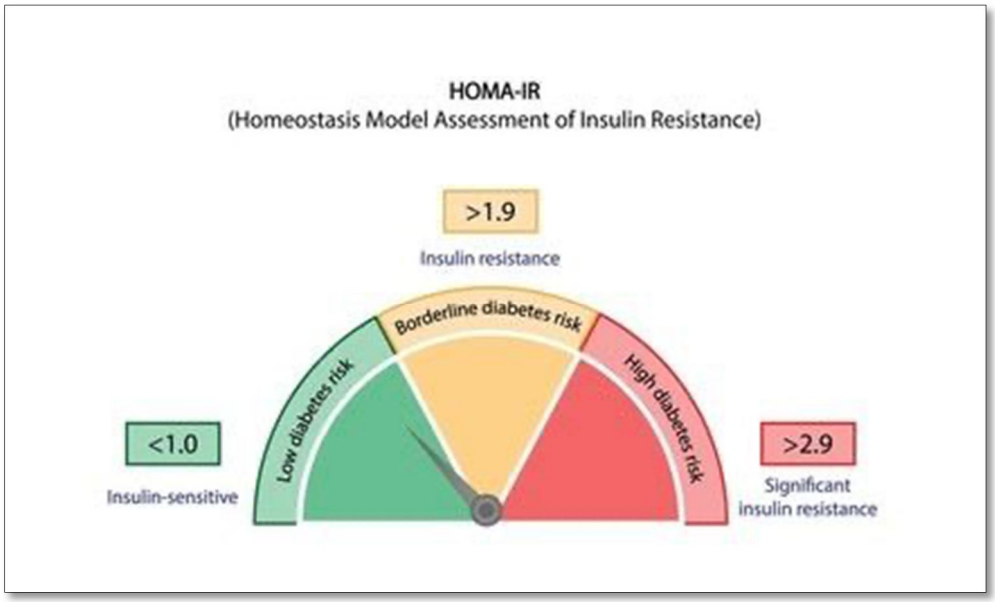


Fig.2 Homeostatic Model Assessment for Insulin Resistance

3) Another validated surrogate index based on insulin and fasting glucose is the Quantitative Insulin Sensitivity Check Index (QUICKI). QUICKI (Quantitative Insulin Sensitivity Check Index) is a formula that measures insulin sensitivity, with lower QUICKI values indicating higher insulin resistance. It is calculated using the inverse of the sum of the logarithms of fasting glucose and fasting insulin: QUICKI = 1 / (log(fasting glucose) + log(fasting insulin)). A QUICKI score below 0.339 often indicates insulin resistance, which can be associated with a higher risk of metabolic syndrome, obesity, and diabetes.

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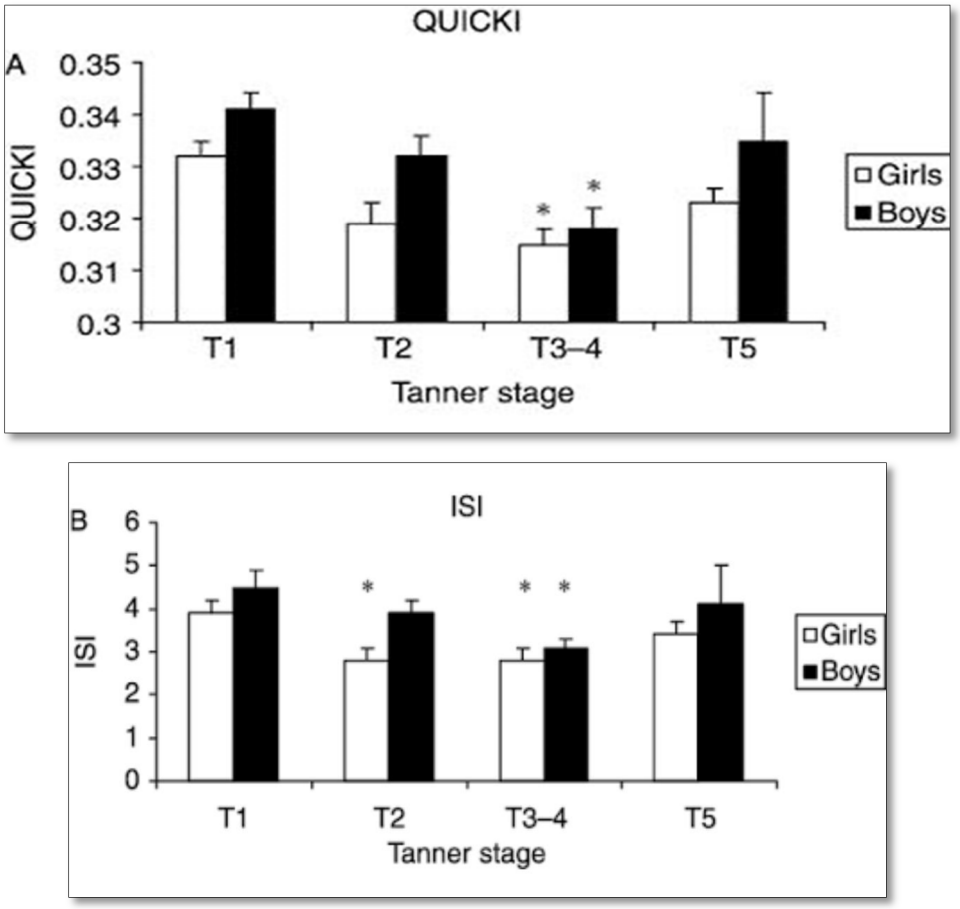


Fig.3 Quantitative Insulin Sensitivity Check Index (QUICKI).

4) The Matsuda Index and Insulin Sensitivity Index (ISI) are calculated using measurements of insulin and glucose obtained from an oral glucose tolerance test (OGTT). An oral glucose tolerance test (OGTT) is a medical test that measures how the body processes sugar. It is used to diagnose prediabetes, diabetes, and gestational diabetes. The test involves drinking a sugary liquid after fasting, and then having blood samples taken at intervals to see how your blood sugar levels change.

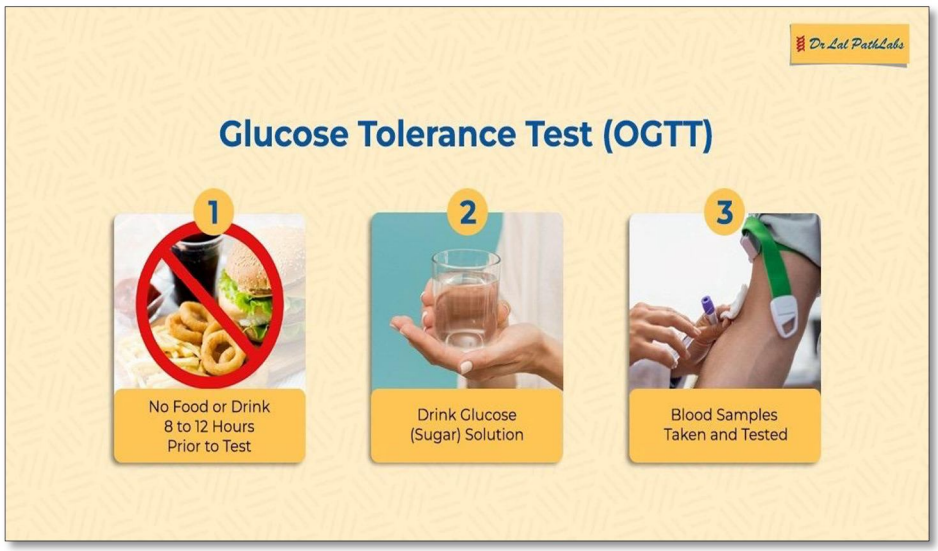


Fig.4 oral glucose tolerance test (OGTT).

5) Other indicators including fasting insulin and triglycerides include the McAuley Index and the Glucose to Insulin Ratio (GIR). Research has shown that a lower McAuley Index is associated with an increased risk of cardiovascular disease and mortality, including in individuals who are not diabetic. It is considered a reliable indicator of insulin resistance, often showing a stronger correlation with insulin resistnce than other indices.

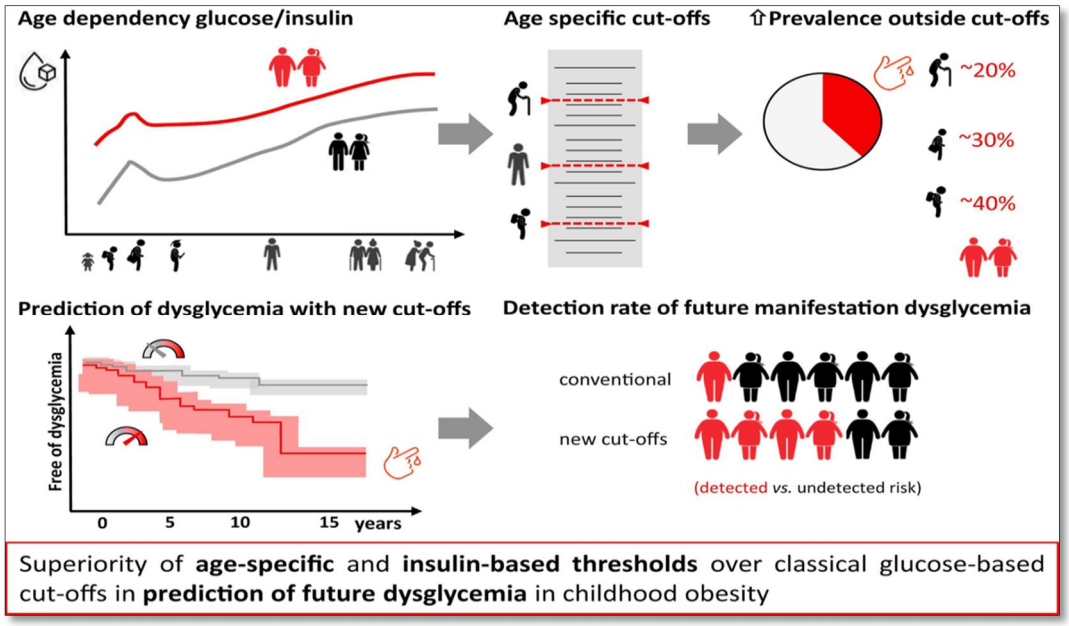


Fig.5 Glucose to Insulin Ratio (GIR).

6) Indirect information on insulin resistance can also be obtained from clinical blood tests like fasting plasma glucose (FPG) and lipid panels (triglycerides and cholesterol)

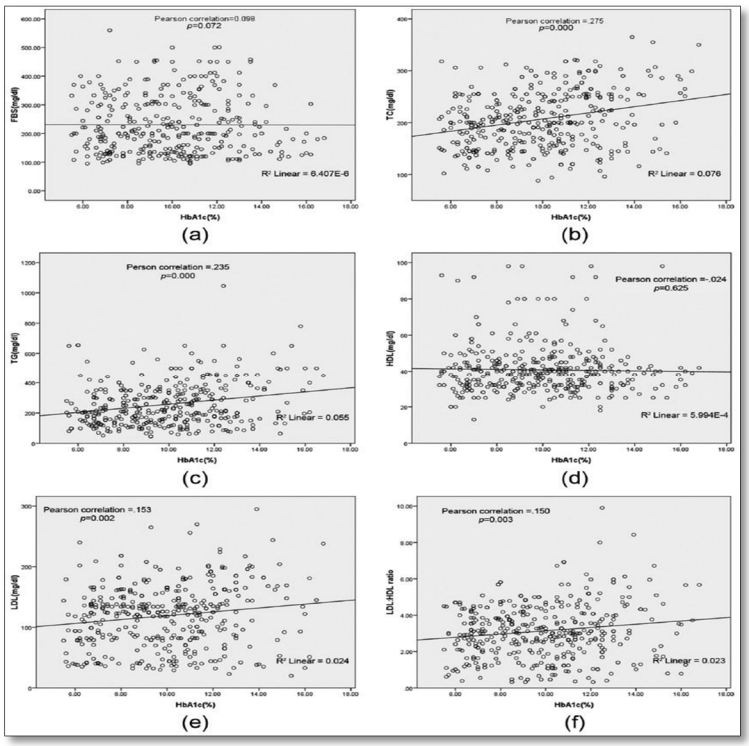


Fig.6 FPG and Lipid panel

HbA1c showed weak but significant positive correlations with total cholesterol ($r = 0.275$, $p < 0.001$), triglycerides ($r = 0.235$, $p < 0.001$), and LDL ($r = 0.153$, $p = 0.002$). Its correlations with FBS ($r = 0.098$, $p = 0.072$) and HDL ($r = –0.024$, $p = 0.625$) were very weak and not significant.

A. Instruments for Diagnosing Glucose Intolerance:

1) Fasting Plasma Glucose Test (FPG): This test gauges blood sugar levels following an overnight fast. those between 100 and 125 mg/dL are indicative of prediabetes, whereas those above 126 mg/dL are indicative of diabetes.

2) Oral Glucose Tolerance Test (OGTT): This dynamic test measures blood glucose levels both during fasting and periodically following a 75-g glucose load. When diagnosing diabetes and impaired glucose tolerance, also known as glucose intolerance, it is highly instructive.

3) Glycated hemoglobin (HbA1c): This test measures the average blood glucose over a period of two to three months; results between 5.7% and 6.4% indicate prediabetes, and 6.5% or higher indicate diabetes. For a thorough evaluation, these instruments are combined in clinical and research contexts.

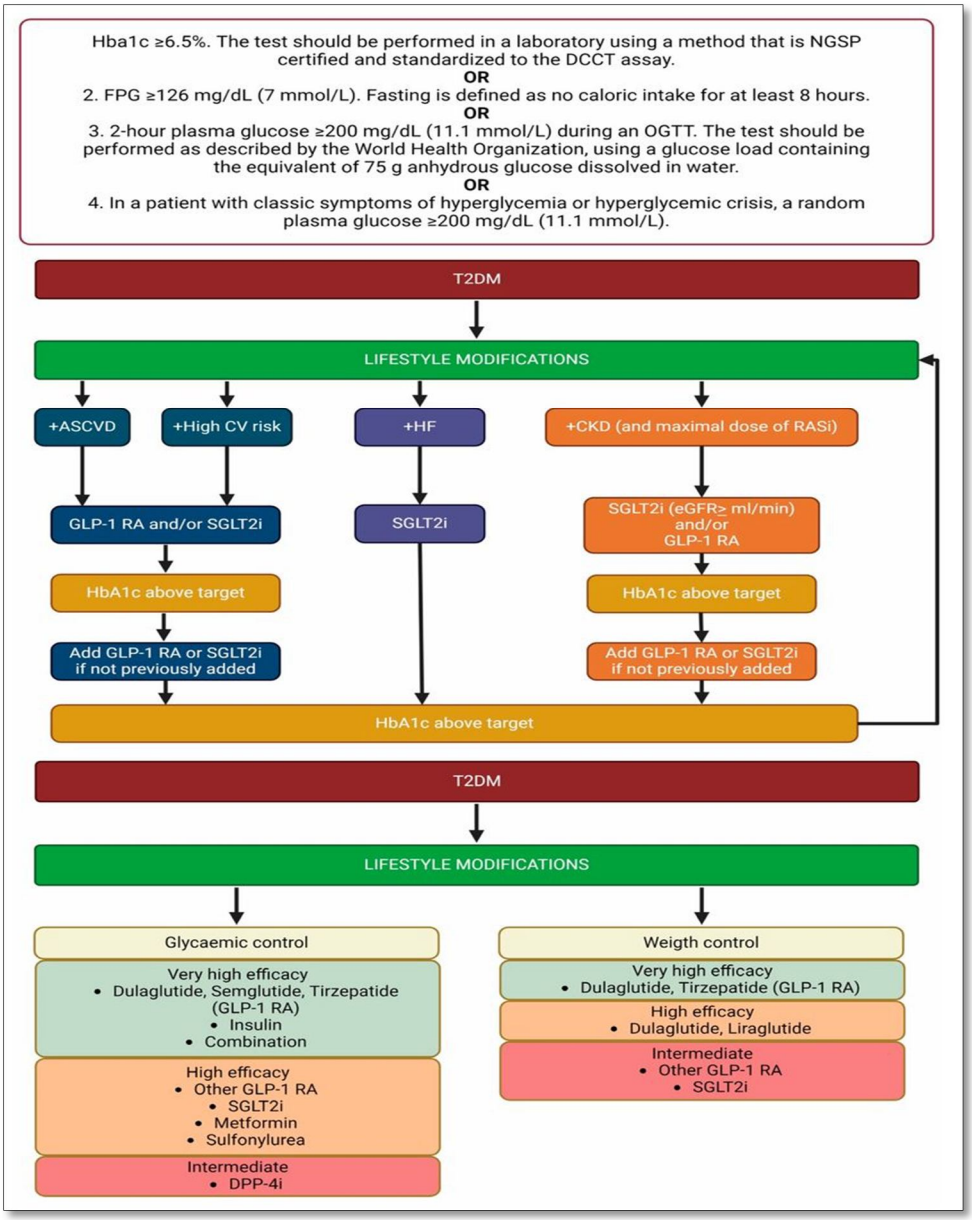


Fig.7 T2DM Therapeutic Algorithm

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III. THERAPEUTIC CHALLENGES

1) Variability in PCOS Presentation: PCOS appears differently in every woman — some show more metabolic symptoms, while others have reproductive or hormonal imbalances. Because of this wide variation, it's difficult to create one standard treatment plan that works for everyone.
2) Inconsistent Drug Response: Common insulin-sensitizing drugs such as metformin and thiazolidinediones don't work equally well for all patients. For example, non-obese women with PCOS often show minimal improvement in their insulin sensitivity even after medication

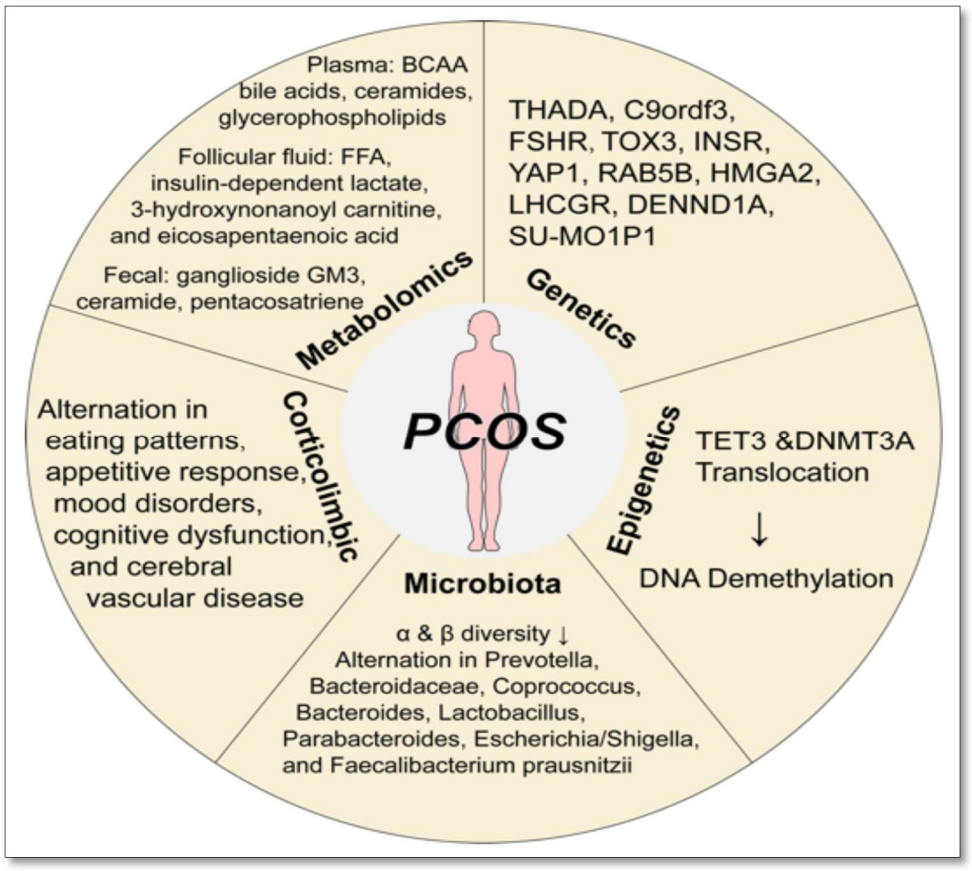


Fig.8 Pathophysiological factors involved in PCOS

3) Challenges in Maintaining Lifestyle Changes: Lifestyle management through diet control and exercise is the first-line therapy, but sticking to these changes over the long term is tough. Many women face emotional and physical challenges that affect consistency and reduce overall benefits.
4) Difficulty in Early Detection and Monitoring: Basic tests like fasting glucose and insulin levels often miss early signs of insulin resistance. More sensitive methods such as oral glucose tolerance tests (OGTT) or insulin indices are needed for timely and accurate diagnosis.
5) Separation of Metabolic and Reproductive Care: In many cases, doctors focus mainly on restoring menstrual cycles and fertility, while the underlying metabolic issues are overlooked. Ignoring these increases the risk of type 2 diabetes and heart diseases in the long term.
6) Limited Research on Alternative Therapies: Herbal medicines, dietary supplements, and gut microbiome-based therapies show potential in improving PCOS symptoms, but there's still not enough research on their long-term safety and effectiveness.
7) Risk of Long-Term Metabolic Disorders: Without proper management, insulin resistance can lead to chronic metabolic problems such as type 2 diabetes, abnormal lipid levels, and fatty liver disease, further complicating PCOS outcomes.

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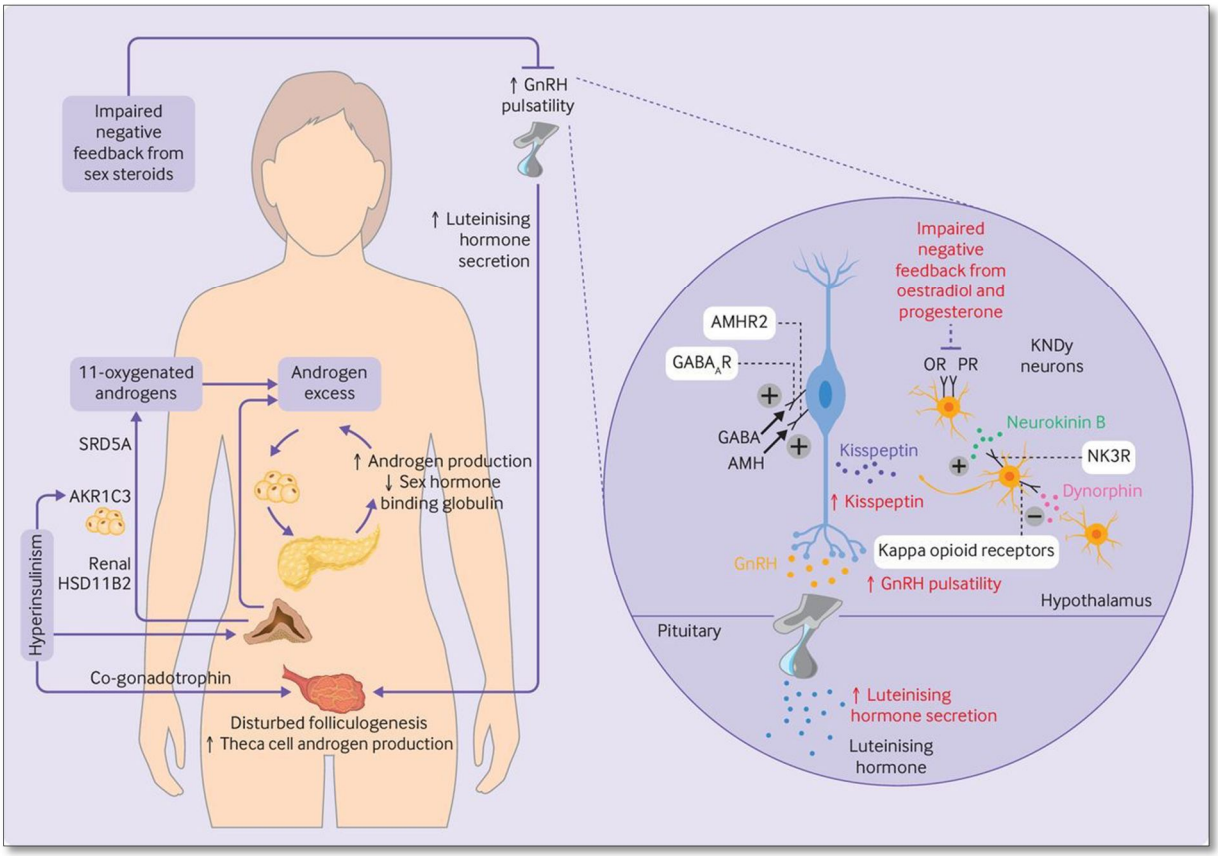


Fig. 9 Mechanistic overview of insulin resistance and hyperandrogenism in PCOS.

IV. FUTURE DIRECTIONS

Future research should focus on developing personalized treatment strategies based on genetic, metabolic, and microbiome profiles of PCOS patients. Early diagnostic biomarkers for insulin resistance and glucose intolerance need validation for routine use. Combination therapies integrating lifestyle, pharmacological, and nutraceutical interventions should be explored through long-term clinical trials. Additionally, artificial intelligence and omics-based approaches may enhance prediction, monitoring, and individualized care in PCOS management.

V. CONCLUSION

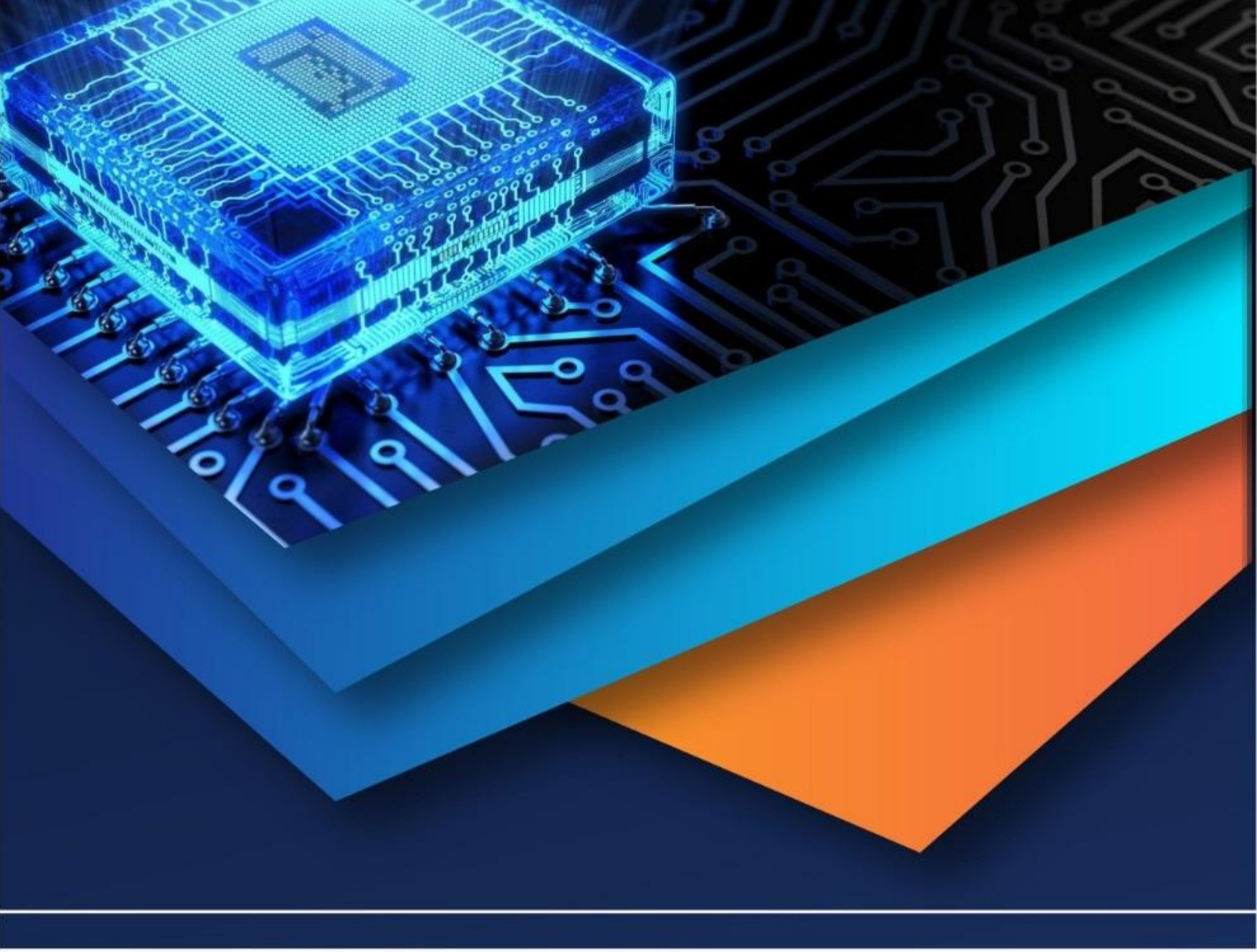
Polycystic ovary syndrome is a complex condition that affects many aspects of women's health, form metabolism to reproduction. While we have made significant progress in understanding its causes and finding ways to diagnose it, treating PCOS remains a challenge. Insulin resistance and glucose intolerance are key problem that complicate the condition and increase the risk of diabetes and heart disease. Treatments like lifestyle changes and medications such as metformin help many women but don't work equally well for everyone. Newer therapies show promise, but more research is needed to confirm their safety and effectiveness over time. Moving Forword, a personalized approach that considers each women's unique symptoms and risks, along with continued scientific advancement, will be essential to improve care and quality of life for those living with PCOS.

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