A Review on Pathophysiology, Pharmacokinetics and Treatment of Pcos Therapy for Pcos-Antidiabetic Agents

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***Abstract*—PCOS stands for polycystic ovary syndrome having another name also called as polycystic ovary disease, functional ovarian, hyperandrogenism, ovarian hyperthecosis, sclerocystic ovary syndrome. PCOS is an multi system disorder having symptoms such as insulin resistance, hyperandrogenism,etc also having long term metabolism risk atherosclerosis, cardiovascular complication, type 2 diabetes mellitus, etc.diagnostis study base on Rutherdam criteria. PCOS having etiology factor such as environment factor, diet, obesity, stress, hormonal changes, endocrine dysfunction,etc. pathophysiological factor mostly effect on insulin resistance, vitamin D deficiency, and heredity and genetic factor.Medication therapy involve drug such as Metformine, Thiazolidinedione and Vit D supliments**

I. INTRODUCTION

Pcos stands for polycystic ovary syndrome having another name also called as polycystic ovary disease, functional ovarian hyperandrogenism, ovarian hyperthecosis, sclerocystic ovary syndrome [Dr. P. Chaudhary and Dr. R. pingale pee vee 2022]. Pcos is an endocrine disorder which mostly affect women reproduction system which show common symptom such as insulin resistance, hyperandrogenism, ovulatory dysfunction [M.Palumbo et.al;2025]. Pcos is an multi system disorder which show multiple symptoms such as increased risk of long-term metabolism, atherosclerosis, cardiovascular complication, type diabetes mellitus(T2DM), oligo or annovulation, vit D deficiency cause hypovitamininosis [G.Morgante et.al;2022]. In 2003 on the basis of Rutherdam criteria diagnostic study done, according to this on the basis of 3 criteria diagnostic test perform. 1. Clinical and biochemical signs of hyperandrogenism. 2. Ovulatory dysfunction (oligo or annovulation). 3. Polycystic ovarian morphology (Defined as ≥12 follicles measuring 2- 9mm in diameter and ovarian volume >10ml on ultrasound [M.Palumbo et.al;2025].

On the basis of their calculating their score level range diagnostic study performance done in pcos disease such as • BMI: Body mass index • WHR: waist to hip ratio increase • HOMA-IR: Homeostasis model assessment of insulin resistance • Difference in endocrine and metabolic profile [M.Palumbo et.al;2025] Etiological

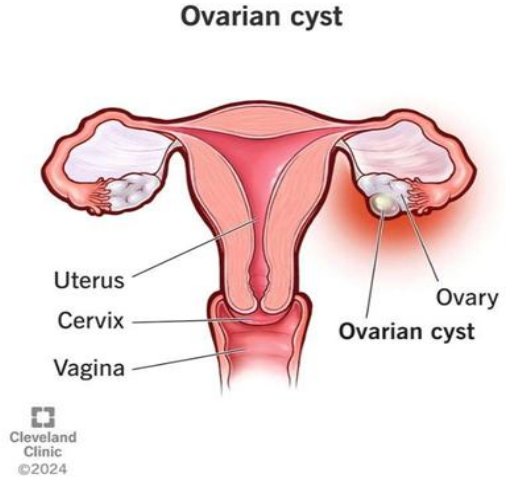

Fig 1. Normal ovary vs cyst formation in ovary

factor which cause pcos disease due to those factors such as environment factor, diet, lifestyle maintenance, dermatological abnormalities, obesity, stress, depression, hormonal changes, endocrine dysfunction, physical activity, genetic changes include hypermethylation, hypomethylation, steroidogenesis, less immune response which cause mostly inflammation (TNF alpha interferone), metabolic dysfunction, mood disturbance Hyperandrogenism, Hyperinsulinaemia, cardiovascular complication, psychological manifestation [R.Azziz et.al;2016]. Pathophysiology in which Insulin resistance/Hyperinsulinaemiawhich promotes increase level of insulin/glucose in blood, vit D difficiency promote increase oxidative stre ss, 9 | P a g e heredity and genetics promote excessive level of androgen leads to hyperandrogenism are most common causative agent seen in women with pcos disease [G.Morgante et.al;2022]. Women with pcos disease show clinical features include menstrual irregularities, infertility, acne, dermatological abnormalities, alopecia, obesity, annovulation, oligomenorrhea, anxiety, depression, disordered eating, low self-esteem, mood swings, hirutism, Hyperinsulinaemia, dislipidem Non pharmacological management : It maintain physical activity by doing exercise, continue meditation, manifestation and exercise reduce insulin secretion, reduce excessive androgen level secretion maintain ovarian function, maintain weight and health condition, quality of life. Other therapy involves assesment checklist such as patient report measurement, cardiovascular risk assessment and physical capacity [A.sabag et.al;2024]. Pharmacological management/ medication therapy: Drug like Metformin, Thiazolidiones, Acarbose, Naltrexone, Arlistat, Vit Suppliment, Stanins. [A.J.Duleba et.al;2015].

Factor's affecting pcos:

A) Insulin resistance and Hyperinsulinaemia:Generally insulin secrete from pancreatic Beta cell, it having mechanism insulin after binding to its receptor and start chemically functioning due to this it activates P13k (phosphatidylinositol-13 kinase) and MAPK (Mitogen activated protein kinase) pathway start signaling due to this insulin level get decreases. If any distribance arise in range of insulin secretion and use of glucose by peripheral tissue due to this body not secrete sufficient amount of insulin which result into insuline level in blood increase leads to Hyperinsulinaemia. Due to increase level of insulin level, it stimulates secretion of androgen in theca cell through addictive effect of cytochrome P40C17a which promotes excessive androgen level increase leads to hyperandrogenism, androgen production stimulates ovaries which stimulate luteinising hormone (LH), which secret by ovaries through theca cell and inhibit Sex hormone binding globuline(SHBG) and nsulin like growth factor binding protein (IGFBP) and also Follicle stimulating hormone (FSH) level increases due to this hyperandrogenism cause. [A.Rajabi et.al;2024].

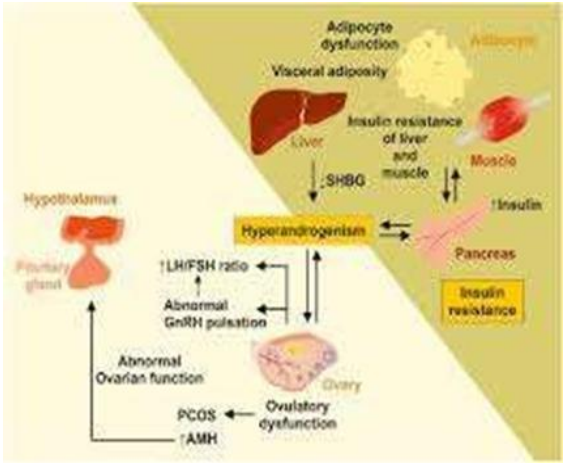

Fig 2. Insuline resistance leads to hyperinsulinaemia and hyperadronenism

B) Vitamin D difficiency: • Vitamin D formation:

1) vit D form from ergocalciferol (VitD2) and cholecalciferol (VitD3) which is originate from animal. 10 | P a g e 2) Ultraviolet radiation from sun ray is directly act on skin which convert into 7-dehydrocholesterol which form inform of previtamin , 7- dehydrocholesterol convert into activated vitamin form. 3) For formation of vit D 2 different hydroxylation required. 4) First hydroxylation process take place in liver with help of enzyme 25-hydroxylosemetabolize it converts into vitamin then Vit D convert into 25- Hydrovitamin D (25-OH-D). 5) Second

hydroxylation takes place in kidney to form 1,25-dihydrovitD(1,25-OHD)/calcitriol at last activated vitamin form.

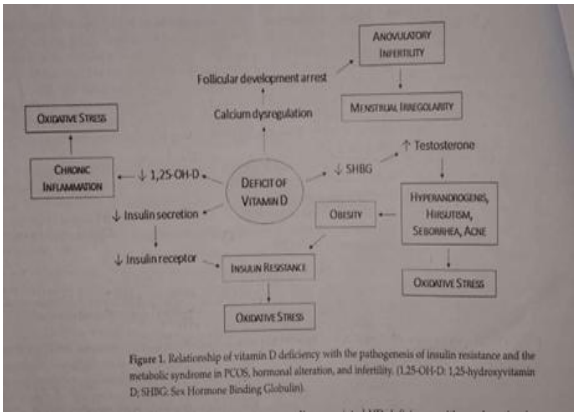

Figure 1. Relationship of vitamin D deficiency with the pathogenesis of insulin resistance and the metabolic syndrome in PCOS, hormonal alteration, and infertility. (1,25-OH-D: 1,25-hydroxyvitamin D; SHBG: Sex Hormone Binding Globulin).

Fig 3. Vitamin D difficiency

• Vitamin D, Hypothalamic – pituitary – Gonadal axis and androgen level : 1) Vit D on Hypothalamic pituitary Gonadal (HPG) come from mini-puberty and period of time for 1 month of life during activation of Hypothalamic pituitary Gonadal it produce Gonadal hormone which important for Gonadal function. 2) According to kilinc.et.al; relationship between 25-OHD (vitD) level and Gonadal hormone at mini puberty. Total testosterone level gets High (it shows moderate effect on 25-OHD (vit D) and inhibiting 25-OH-D(vit D) if level get low (it shows moderate effect due to both the reason vit D effect on Gonadal function in early stage seen.due to this androgen level in imbalance that's why vit D level decrease, testosterone level increases, SHGH level decrease.

3) Also, vit D and calcium both level decreases it show symptoms like endocrine dysfunction,IR (Insulin resistance), type 2 DM, Anovulatory (complete menstrual period stop) all those symptoms promote oxidative stress. 4) vitD activate Sex hormone but if difficiency in SHBG arrise result comple menstrual cycle stop. ▪ Vit D suppliment: High dose of vit and calcium daily for 3 months: decrease testosterone level and androstenedione level [G.Morgante et.al.2022].

C) Heredity and genetic factor: According to genetical changes in family history, heredity mostly effect on alleles, women with pcos show impaired gene sequencing such as DNA methylation, Histone status and micro(RNA) which promote androgen level increament also normally affect ovary , follicular growth. GnRH (Gonadotropins releasing hormone), LH(luteinising hormone), steroidogenesis which regulate protein level get increases and p450 side chain clevage, 3B- hydroxysteroid dehydrogenase and cytochrome p450c17produce androstenedione which convert into 11 | P a g e estrogen then it undergoes to influence Follicle stimulating hormone in granulosa cell. If deficiency in FSH secretion seen follicular growth reduces due to this excess amount of androgen secrete leads to hyperandrogenism which is responsibleto cause pcos(A.Rajabi et.al; 2024).

Treatment :

A) Metformine

Fig 4. Metformine Drug 500 Mg Tablet

Sr No	Specification	Details
1	General Information	Metformin is the oldest insulin sensitizer used in treatment of Type 2 Diabetes Mellitus (T2DM).
2	Effects on Metabolic Parameters	Lowers serum lipid, androgen, and insulin levels. • Improves glucose tolerance and reduces basal & post-prandial glucose.
3	Reproductive Effects	Induces ovulation. • Promotes regular menstrual cycles.• Increases pregnancy rate (Dumitrescu R et al., 2015).
4	Major Actions on Glucose Metabolism	Decreases hepatic gluconeogenesis. • Increases peripheral glucose uptake. • Indirectly reduces insulin levels.

5	Classification	Antihyperglycemic agent
6	Pharmacokinetics	Absorption 50%–60% Distribution Highest in intestine, liver, kidney; transported by organic cation transporter proteins (OCT). Plasma Protein Binding 90% Time to Reach Max Level 24–48 hours, approx. 5 mcg/mL at max dose. Metabolism Not metabolized (or minimal liver metabolism). Elimination Excreted unchanged in urine by active tubular secretion. Half-life ~5 hours. Dosage Forms 500 mg, 850 mg, 1000 mg tablets. Route ofAdministration Oral.
7	Pharmacodynamics	Mechanism of Action • Improves glucose uptake. • Reduces hepatic gluconeogenesis. • Lowers fatty acids.• Improves insulin sensitivity. • Reduces androgen production. • Improves 13 | P a g e serum lipid profile (↑ HDL, ↓ LDL, triglycerides, cholesterol).•Reduces BMI and waist-to-hip ratio
8	Side Effects	•Reduced appetite• Metallic taste• Nausea, vomiting• Flatulence• Diarrhea• Lactic acidosis (rare but serious)
9	Drug–Drug Interactions	ACE inhibitors + Metformin → increased risk of lactic acidosis, may cause acute kidney injury (AKI) (A.J. Duleba, 2011).

B) Thiazolidinediones (TZDs) Drug

Fig 5. Rosiglitazon 4 mg Tablet

Fig 6. Pioglitazone 15 mg Tablet

Sr No	Specification	Details
1	Name of drug	Thiazolidinediones (short form: TZDs)
2	Class	Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists
3	Also Known As	Glitazones
4	Drugs Included	Rosiglitazone, Pioglitazone

A) Rosiglitazone

Sr No	Specification	Details
1	Pharmacokinetics	1. Absorption Well absorbed from the gastrointestinal tract (GIT)Distribution Distributed through biological systems; similar to nutrients (e.g.,thiamine) mixing with food and transported throughout body tissues. Metabolism In liver via CYP2C8 and CYP3A4 enzymes.Excretion Mainlythrough bile.
2	Dose	4 mg/day; may increase up to 8 mg/day after 8–12 weeks.
3	Half Life	3 – 4 hrs
4	Adverse Effects	Myocardial infarction risk
5	Routeof Administration	oral

B) Pioglitazone

Sr No.	Specification	Details
1	Dose	15 mg/day; may increase up to 30–45 mg/day
2	Route of Administration	oral
3	Half Life	3–7 hours (parent drug), 16–24 hours (active metabolites).
4	Adverse Effects	Weight gain, fatigue, edema, diarrhea, anemia, congestive heart failure
5	Pharmacodynamics	Mechanism of Action Improves insulin resistance Improves systolic blood pressure Reduces systemic inflammation Improves dyslipidemia.

Combinational Drug Interaction with Thiazolidinediones (TZDs) – Comparison Table

Sr No	Specifications	Drugs That Increase the Effect of TZDs	Drugs That Reduce the Effect of TZDs:
1	Interacting Drug class	NSAIDs	Enzyme-inducing Antiepileptics.
2	Example	Ibuprofen, Diclofenac, etc	Phenytoin, Carbamazepine.
3	Interaction type	Induce/ Increase TZDs effect	Reduce TDZ effect.
4	Mechanism	NSAIDs inhibit COX-2 reduce prostaglandins reduce inflammation; TZDs activate PPAR- improve insulinsensitivity	Induce CYP enzymes increase TZD metabolism
5	Result/ Effect	Enhanced anti-inflammatory activity and improved glycemic control.	Reduced plasma levels and reduced therapeutic effect.

D). Reason why Thiazolidinedione drug show addictive effect than that of Metformin drug 1. Thiazolidinedione in which drug such as Rosiglitazone and Pioglitazone are newer drug which is oral Antidiabetic agent drug with insulin sensitivity activity show which treat type 2 DM. 2. Rosiglitazone and Pioglitazone show antihyperglycemic effect which reduce insulin circulation and free fatty acid level such as reduce level of triglyceride, Low density lipoprotein, high density lipoprotein increase, reduce cholesterol level means lowering effect of blood glucose level in body. 16 | P a g e 3. Thiazolidinedione act as nuclear peroxisome proliferator activated receptor gamma (PPARy), which mediate transcription of certain gene that responsive to insulin agent to improve insulin action (C.J.Bailey et.al;2001).

E) Vitamin D suppliment:

SrNo	Specification	Details
1	Vitamin D Receptor (VDR)	Present in most body tissues; functions include: • Inhibition of cell proliferation • Induction of cell differentiation • Immunomodulation
2	Effects of Vitamin D Administration	Improves insulin sensitivity • Decreases insulin levels • Reduces triglycerides • Increases HDL levels • Improves blood pressure • Reduces systemic inflammation.
3	Dose	• Daily: 1000–2000 IU/day • Weekly: 50,000 IU/week (depending on deficiency severity) • Goal: Serum 25(OH)D > 30 mg/mL for at least 3 months.
4	Route of Administration	Oral (Vitamin D2 or Vitamin D3).
5	Contraindications	• Hyperparathyroidism • Hypercalcemia • Malabsorption syndrome • Renal failure
6	Adverse Effects	Headache • Nausea & vomiting • Dizziness • Loss of appetite • Dry mouth.

II. CONCLUSION:

Review of the literature may suggest on the Study of medical treatment to correct the metabolic dysfunction associate with PCOS. However closer inspection of the study conclude that Metformin appears as metabolic dysfunction, but improvement is modest while side effect is very common.further metformin mostly treat insulin resistance. Thiazolidinediones show some adverse effect such as congestive heart failure , weight gain.furthermore vit D show adverse effect such as Headache, nausea, vomiting,dry mouth and long term patient compliance in using medication is likely to be poor. However, their effects on insulin sensitivity in women with PCOS are still not well understood.

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