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Ameliorating Effects Of Vitamin D On Cytokines As Markers Of Insulin Resistance And Glycemic Status In Polycystic Ovary Syndrome Patients Attending Mediheal Fertility Center And Moi Teaching And Referral Hospital In Western Part Of Kenya.

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Abstract
Introduction
Despite the growing evidence suggesting a link between Vitamin D and insulin resistance, there exists controversies and conflicting study findings on the efficacy of Vitamin D supplementation on improving insulin resistance and glycemic control in women living with polycystic ovary syndrome.
Objectives
The objective of the study was to determine the ameliorating effects of Vitamin D on Cytokines as markers of insulin resistance and glycemic status in PCOS patients attending Mediheal Fertility Center and Moi Teaching and Referral Hospital in Western part of Kenya.
Materials And Methods
The study adopted two phases; phase 1 was an observational study and phase 2 an interventional phase. A total of 100 participants were divided into 60 for observational comprising of PCOS (20) and controls (infertile-20 and fertile 20), while 40 PCOS served in the interventional study that were randomized into 60,000 IU/week of Vitamin D plus 500mg/day of Metformin (n=20) and Metformin 500mg/day only (n=20) for a period of 12 weeks. Quantification of HbA1c and Fasting blood sugars were done at AMPATH reference laboratories using fluorescence immunoassay and while Vitamin D and Insulin hormone levels were done at MTRH laboratories using Cobas automated Chemiluminescence Roche. Data was entered into a computer using excel sheets then analyzed using STATA version 15, Mann Whitney and Kruskal Wallis test and continuous variables are presented as median (interquartile range).
Results
The study established significant relationship on Interleukin 6, HbA1C, fasting blood sugar and HOMA-IR with one being a PCOS or non PCOS ($P<0.05$). The study further established that Vitamin D administered at 60,000 IU per week plus Metformin 500mg per day for 12 weeks led to statistical significant difference from pre intervention to post intervention on insulin, Vitamin D hormone, Interleukin 6, glycated hemoglobin (HbA1C), fasting blood sugar (FBS) and Homeostatic model assessment of insulin resistance (HOMA-IR) and QUICKI $p<0.05$ as compared to Metformin 500mg/day group for the same duration ($p>0.05$).However, the study failed to observe any statistical significant difference on HOMA-B in both arms of treatment ($p>0.05$).The study concludes that Vitamin D may augment Metformin in treatment of insulin resistance in women living with Polycystic ovary syndrome .
Key Words
Polycystic Ovary Syndrome, Vitamin D, Insulin Resistance

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I. Introduction

Polycystic ovary syndrome (PCOS), also commonly known as polycystic ovary disease, and often manifesting as bearded women, is a syndrome characterized by elevated androgen levels, anovulatory cycles and observable ovarian cysts when viewed under obstetric ultrasound (Azziz R, et al., 2016). Globally the WHO estimates the prevalence of PCOS among all women of reproductive age to be 3.4% translating to 116 million women with up to 70 % of affected women not being diagnosed (Alkhezi, F *et al*., 2024). However, this is dependent on the diagnostic criteria employed to study a particular population (Azziz et al. 2016). In Africa, the

prevalence of PCOS is approximately 8.6% in Nigeria (Makwe C, et al., 2023) while Pembe AB et al. (2009) found that 32% of Tanzanian infertile women had PCOS. In Kenya at least 131 women who attended the GOPC at Kenyatta National Hospital in 2018, 49 (37%) were diagnosed with PCOS as per Rotterdam criteria, while 26 (20%) as per the National Institute of health criteria (NIH), and 15 (12%) as per the Androgen Excess Society criteria (Odera et al., 2020). PCOS women present with metabolic derangements like obesity that affects 70%, insulin resistance, compensatory hyperinsulinemia and hyperglycemia, which, complicate to type 2 diabetes affecting 80% of franc PCOS and 40 % of phenotype D PCOS (Livadas S et al., 2022). PCOS also increases the risk of developing insulin resistance and hyperglycemia in lean PCOS women thus it is independent of increased BMI (Kakoly N.S et al., 2019).According to Ruchika Garg et al. (2017), 65–85% of PCOS women are vitamin D insufficient, and studies on vitamin D's potential benefits for PCOS have been largely inconclusive and inconsistent. The lack of vitamin D may be the missing connection between IR and PCOS (Hans et al., 2006).

II. Materials And Methods

This was both a cross sectional study and a randomized control trial that was conducted at Mediheal Fertility Center's and Moi Teaching and Referral Hospital in Western part of Kenya in the Reproductive, Endocrine and infertility clinic between July 2023 to December 2024. PCOS was diagnosed based on the Rotterdam criteria 2003, classifying participants into four phenotypes; A (full-blown syndrome PCOS: hyperandrogenism; HA + ovulatory dysfunction {OD} + PCO), Phenotype B (HA+OD), Phenotype C (ovulatory PCOS: HA+PCO), and Phenotype D (non-hyperandrogenic PCOS: OD+PCO). Diagnosis was confirmed if two out of three criteria were met. Sample size was determined using G* Power program 3.1.9.2 software, employing an exact statistical test correlation under a bivariate normal model. To achieve statistical significance, a sample size of 20 participants per group was calculated, later adjusted to 22 per group to account for a 10% drop out rate due to potential pre-analytic errors. In addition to evaluating the history and examination, demographic data were also collected.

Transvaginal ultrasound was performed on PCOS patients to assess ovarian morphology, with criteria including >20 follicles per ovary or ovarian volume >10ml.Fasting lipid profiles were assessed using photometric determination and plasma glucose were measured using a dehydrogenase method and HbA1C analysis was carried out using cation exchange high performance liquid chromatography (HPLC) within 8 hours of sampling at MTRH and Mediheal laboratories. Serum analysis for vitamin D and fasting insulin was performed using an automated Electro chemilumescent immune assay method (Roche Diagnostics; Basel, Switzerland e Cobas 311 series). HOMA-IR was calculated using the formula ;(fasting insulin fasting blood glucose/405) with a cut-off score >3.5 indicating insulin resistance. HOMA-B (20Xfasting insulin/fasting blood sugar-3.5), QUICKI (1/log FBS plus log of fasting insulin) (Pispraseert V et al, 2013). The BD CBA Human IL-6 Flex Set was used in conjunction with a BD CBA Human Soluble Protein Master Buffer Kit (Cat. No. 55876), a flow cytometer, and FCAP Array™ Software for the cytokine marker.

The study was approved by joint **MTRH/Moi university IREC (0004610)** and permission granted by the National Commission of Science and Technology (**NACOSTI/23/26592).** The trial was registered by Pan African trial registry in South Africa (**PACTR202401577278397**.) All participants provided written informed consent and the study adhered to the principles of Helsinki Declaration. Exclusion criteria included diabetes, hyperprolactinemia, hypothyroidism, androgen-secreting tumors, as well as Cushing syndrome.

Data analysis was conducted using SPSS version 25. Normality was assessed using Q-Q plots and the Shapiro-Wilks test. The Wilcoxon rank-sum test, Kruskal Wallis test and Spearman's rank correlation was applied with significance set at $P< 0.05$ and a 95% confidence interval. Data is presented as medians and interquartile ranges.

III. Results

After assessing the fasting blood sugars, the study established that fasting blood glucose was higher in PCOS with interquartile ranges from 5.6 mmol/l to 6.4mmol/l and a median of 5.9 mmol/l as compared to infertile controls that had FBS interquartile ranges of 4.55 mmol/l to 6.05 mmol with a median value of 4.55 mmol/l while the fertile controls had FBS interquartile ranges of 4.9mmol/l to 5.8 mmol/l with a median value of 5.2 mmol/l. The results also show that glycated hemoglobin (HbA1C) was higher in PCOS with interquartile ranges of 5.9% to 6.4 % with a median value of 6.2 % as compared to infertile controls that had HbA1C interquartile ranges of 5.3 % to 5.7 % with a median value of 5.6 % while the fertile controls had HbA1C interquartile ranges of 5.4% to 5.8% with a median value of 5.5 %. It was also established that the homeostatic model assessment of insulin resistance (HOMA-IR) was higher in PCOS with interquartile ranges from 2.5 to 3.3 with a median value of 3.2 as compared to infertile controls that had HOMA-IR intermediate ranges of 2.1 to 3.2 with a median value of 2.3 while the fertile controls had HOMA-IR ranges of 1.8 to 2.3 with a median value of 2.1.The quantitative insulin sensitivity check index (QUICKI) had a median and interquartile ranges of 0.548(0.522,0.594) for PCOS as compared with fertile controls which had 0.595(0.555,0.681) while infertile controls had 0.578(0.520,0.635).On

the homeostatic model assessment of the beta cells (HOMA-B). The median and interquartile ranges for PCOS were higher 44.342(33.896,58.187) than fertile controls 25.960(17.606,45.328) and infertile controls 28.758(18.245,40.236).

The difference among the groups on short term blood sugar control, long term blood sugar control, HOMA-IR, QUICKI and HOMA-B was statistically significant p<0.05 except on QUICKI p> 0.05 as shown in the table below.

Table 1; Show results findings of fasting blood sugars (FBS), glycated hemoglobin (HbA1C) and homeostatic model assessment of insulin resistance (HOMA-IR), HOMA-B and QUICKI in polycystic ovary syndrome, infertile controls and fertile controls

		PCOS (n=20)		FERTILE CONTROLS(n=20)		INFERTILE CONTROLS(n=20)		P VALUE =tested among the three groups
Glycemic status and insulin resistance markers		Median value	Interquartile range	Median value	Interquartile range	Media n value	Interquartile range	
	HbA1c	6.2	5.9-6.4	5.5	5.4-5.8	5.6	5.3-5.7	0.001*
	FBS	5.9	5.6-6.4	5.2	4.9-5.8	4.55	4.55-6.05	0.026*
	HOMA-IR	3.2	2.5-3.3	2.1	1.8-2.3	2.3	2.1-3.2	<0.001*
	QUICKI	0.548	0.522-0.594	0.595	0.555-0.681	0.578	0.520-0.635	0.098
	HOMA-B	44.342	33.896-58.187	25.960	17.606-45.328	28.758	18.245-40.236	0.005*

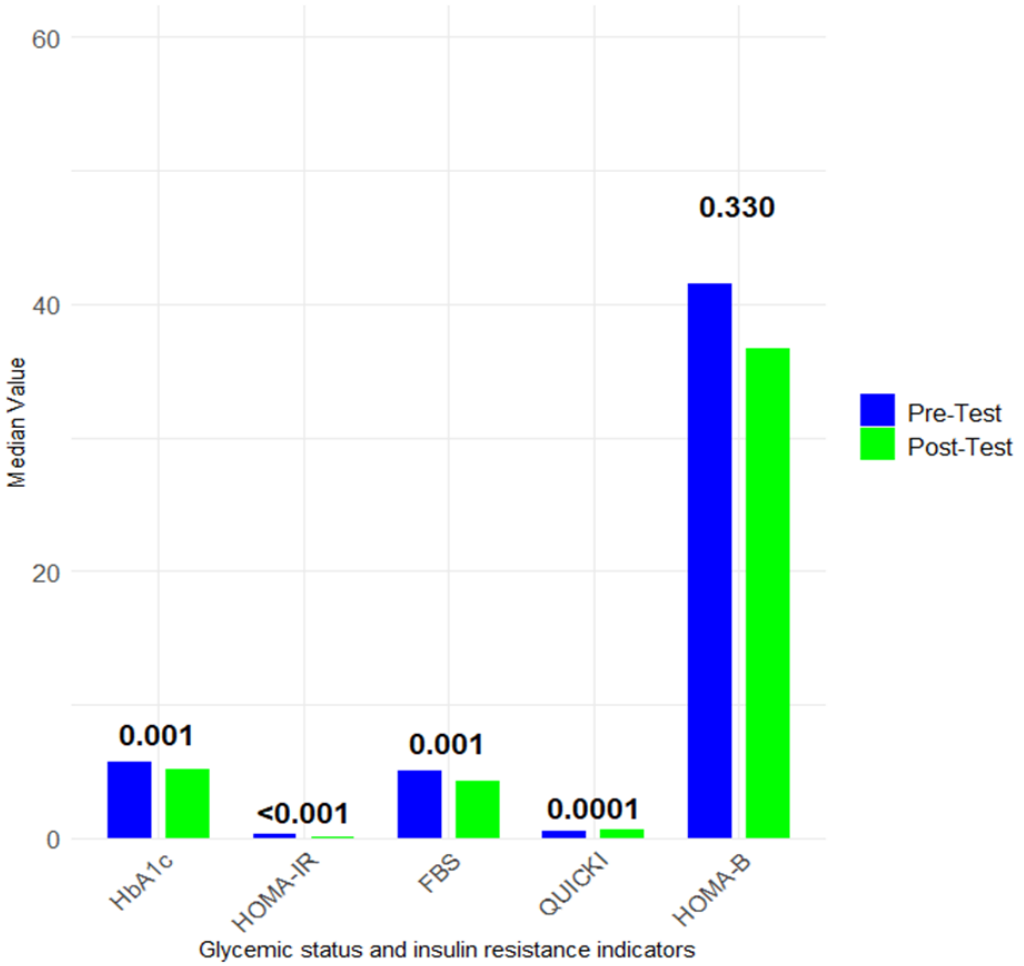
*****denotes statistically significant difference*

On correlation analysis, Vitamin D correlated negatively with glycated hemoglobin (rho = Rho= -0.2714, P= 0.247), homeostatic model assessment of insulin resistance (Rho= - 0.0045, P= 0.9873), HOMA-B (Rho= -0.0286, P= 0.9064) and QUICKI (Rho= -0.0294, P= 0.902) suggesting that increased HbA1C, HOMA-IR, HOMA-B and QUICKI are associated with lower Vitamin D levels and vice versa, though the correlation was not statistically significant p>0.05. Vitamin D correlated positively with fasting blood sugar (Rho= 0.3547, P= 0.1249), suggesting that low levels of Vitamin D are associated with low levels of fasting blood sugar and vice versa. However, the correlation was not statistically significant p> 0.05 as shown in the table below;

Table 2: Show how Vitamin D correlated with glycated hemoglobin (HbA1C), homeostatic model assessment of insulin resistance (HOMA-IR), fasting blood sugar (FBS), homeostatic model assessment of beta cell functions (HOMA-B) and quantitative sensitivity check index (QUICKI) as independent variables

	Vitamin D	P values	Significance
FBS	Rho= 0.3547	P= 0.1249	Not significant
HbA1c	Rho= -0.2714	P= 0.247	Not significant
HOMA-IR	Rho= - 0.0045	P= 0.9873	Not significant
HOMA-B	Rho= -0.0286	P= 0.9064	Not significant
QUICKI	Rho= -0.0294	P= 0.902	Not significant

The effects of Vitamin D 60,000 IU per week plus Metformin 500mg per day for a period of twelve weeks, the acute phase of glycemic status control (fasting blood sugar) declined from pre intervention phase with interquartile ranges of 4.1 mmol/l to 5.9 mmol/l and a median value of 5.1 mmol/l to post intervention phase with interquartile ranges of 3.8 mmol/l to 4.6 mmol/l and a median value of 4.3 mmol/l. The long term phase of glycemic status control (HbA1C) declined from pre intervention phase with interquartile ranges of 5.4 % to 6.0 % with a median value of 5.7 % to post intervention phase with interquartile ranges of 5.0 % to 5.4 % with a median value of 5.2 %. The homeostatic model assessment of insulin resistance declined from interquartile ranges of 0.230 to 0.345 with median values of 0.318 to post intervention phase with ranges of 0.139 to 0.168 and a median of 0.155. The quantitative insulin sensitivity check index median and interquartile ranges varied from 0.561(0.537,0.597) during pre-intervention to0.642(0.625,0.661) on post intervention. The Homeostatic assessment of the beta cells median and interquartile ranges varied from 41.591(36.933,49.50) to 36.738(33.710,46.346). The results demonstrate that the difference in decline was statistically significant p <0.05 except for HOMA-B p> 0.05 as shown in the figure below:



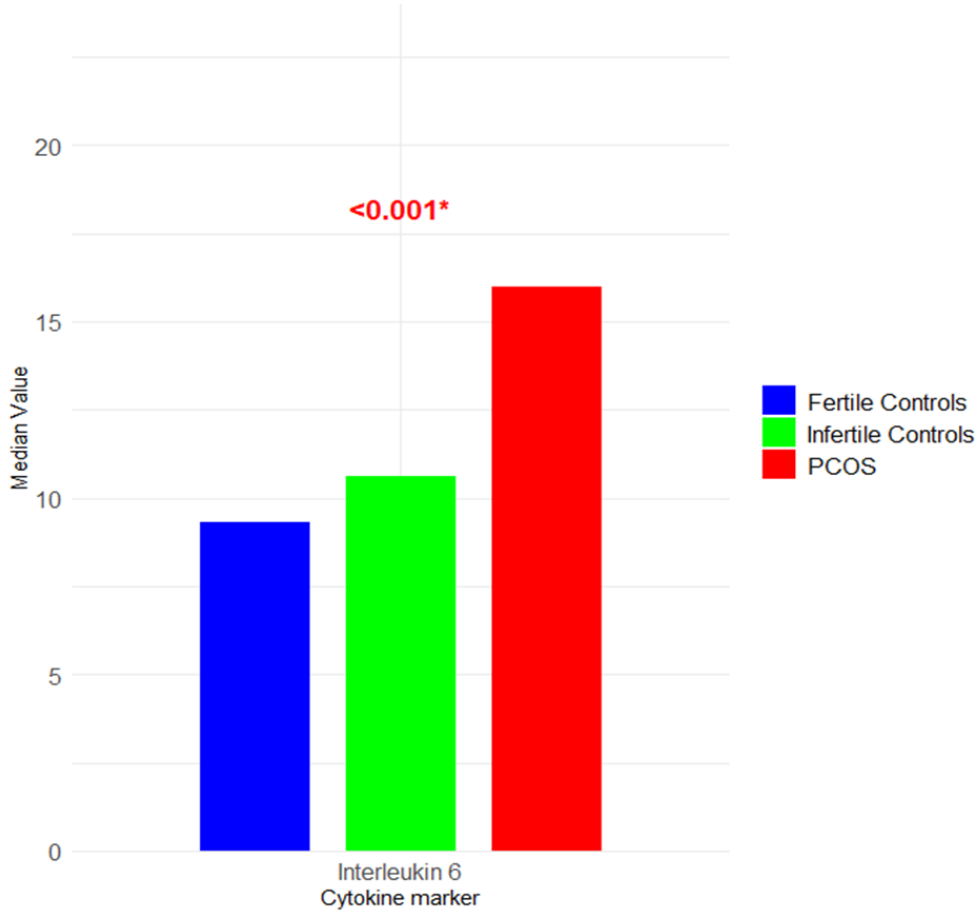
On the analysis of the effects of Metformin 500mg only per day for a period of twelve weeks, the acute phase of glycemic status control (fasting blood sugar) declined from pre intervention phase with interquartile ranges of 4.8 mmol/l to 6.0 mmol/l and a median value of 5.8 mmol/l to post intervention phase with interquartile ranges of 3.9 mmol/l to 4.8 mmol/l and a median value of 4.1mmol/l, the difference was statistically significant $p<0.05$. The long-term phase of glycemic status control (HbA1C) declined from pre intervention phase with interquartile ranges of 5.53 % to 6.2 % with a median value of 5.9 % to post intervention phase with ranges of 5.43 % to 6.0 % with a median value of 5.8 % but the decline was not statistically significant $p>0.05$. The homeostatic model assessment of insulin resistance declined from interquartile ranges of 0.2 to 0.4 with median values of 0.3 to post intervention phase with interquartile ranges of 0.15 to 0.35 with a median value of 0.2 while homeostatic model assessment of beta cells (HOMA-B) varied from 43.810(31.517,61.527) during preinterevntion to 43.846(34.736,64.221) on post intervention and QUICKI median and interquartile ranges changed from 0.548(0.503, 0.5923) on pre interevntion to 0.5897(0.5514,0.6469) on post intervention.The results shows that metformin only intervention had significant difference on FBS,HOMA-IR and QUICKI $p<0.05$ while did not have significant effect on HbA1C and HOMA-B $p> 0.05$ as shown in the table below

		POSITIVE CONTROL GROUP				**p-value= tested between pretest and post test**
		The median values and interquartile ranges before Metformin 500mg per day intervention for a period of 12 weeks (PRE TEST)		**The median values and interquartile ranges after Metformin 500mg per day intervention for a period of 12 weeks (POST TEST)**		
		Median value	Interquartile range	Median value	Interquartile range	
Glycemic status	HbA1c	5.9	5.53-6.2	5.7	5.26-5.9	0.157
	HOMA-IR	0.3	0.2-0.4	0.2	0.15-0.35	0.029*

	FBS	5.8	4.8-6.0	4.1	3.9-4.8	<0.001*
	QUICKI	0.548	0.503-0.5923	0.5897	0.5514-0.6469	0.0292*
	HOMA-B	43.810	31.517-61.527	43.846	34.736-64.221	0.7146

**denotes statistically significant difference*

It was established that median values and interquartile ranges of interleukin 6 in PCOS was significantly higher 16.5 (15.2-22.2) as compared to infertile controls 10.6 (9.4-11.7) and fertile controls 9.3 (7.7-11.2) respectively p<0.001 as shown in the table 18 and figure below.



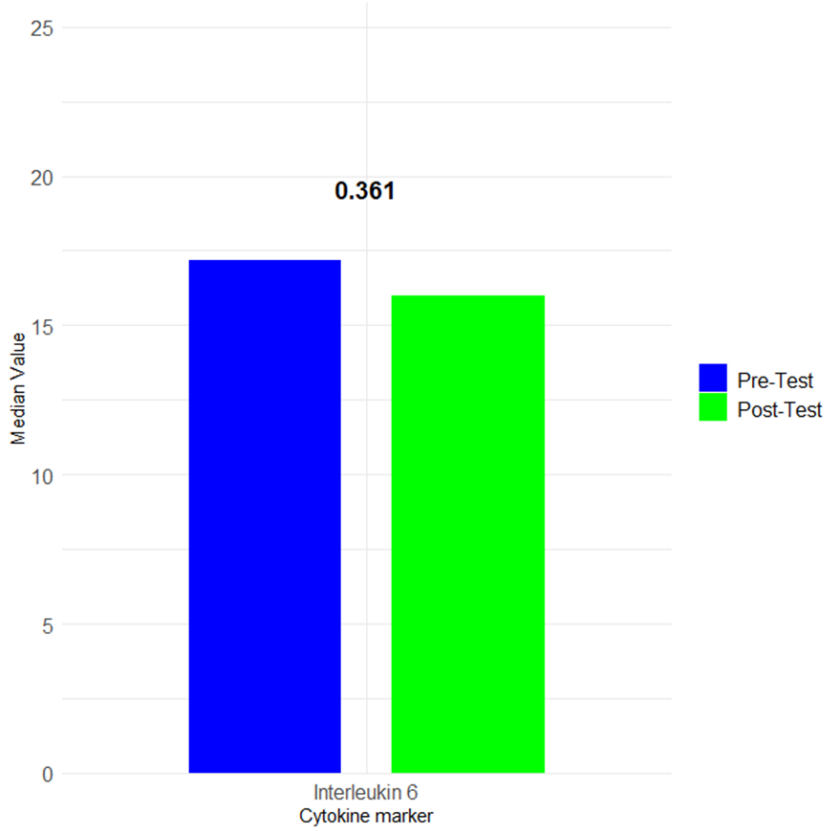
The effects of Vitamin D in combination with Metformin led to significant decline from pre intervention phase with a median and interquartile ranges of 17.9 (14.8-23.2) to a post intervention median and interquartile ranges of 9.8 (8.9-12.7) with a p<0.001 as shown in the table below

Table: Shows how the cytokine marker (Interleukin 6) median values and interquartile ranges varied before intervention and after intervention with Vitamin D 60,000 IU per week plus Metformin 500mg per day over a period of 12 weeks in PCOS

		INTERVENTIONAL GROUP				**p-value= tested between pretest and post test**
		The median values and interquartile ranges before Vitamin D 60,000 IU per week and Metformin 500mg per day intervention for a period of 12 weeks (PRE TEST)		**The median values and interquartile ranges after Vitamin D 60,000 IU per week and Metformin 500mg per day intervention for a period of 12 weeks (POST TEST)**		
		Median value	Interquartile range	Median value	Interquartile range	
Cytokine marker	Interleukin 6	17.9	14.8-23.2	9.8	8.9-12.7	<0.001*

*Denotes statistically significant difference

On the analysis of the effect of Metformin 500mg only group that served as positive control group established that the median and interquartile ranges did not vary significantly from the pre intervention phase 17.2 (15.4-23.4) to post intervention phase 14.4-4.22) with a p>0.361 as shown in the figure below



IV. Conclusion And Recommendation

There were significantly higher levels of HbA1C, fasting blood sugar and HOMA-IR and HOMA-B in PCOS as compared to infertile controls and fertile controls p<0.05 and lower levels of QUICKI in PCOS versus the controls and the difference was not statistically significant p>0.05.On the intervention phase; Vitamin D plus Metformin led to decline in HbA1C, HOMA-IR, FBS and increase in QUICKI and the difference was statistically significant p<0.05 while Metformin only group had a significant decline on HOMA-IR and FBS <0.05 but on HbA1C and HOMA-B the decline was not significant p>0.05 and also increase on QUCIKI was also not significant p>0.05.On correlation analysis, Vitamin D correlated negatively with HbA1C, HOMA-IR, HOMA-B and QUICKI suggesting that higher levels of glycemic status are associated with insulin resistance and lower Vitamin D levels.

The study established statistically significant difference on interleukin 6 among the PCOS and the controls p<0.001 in the observation phase. The intervention study established significant decline from pre intervention phase to post intervention when 60,000 IU of Vitamin D once per week was combined with 500mg of Metformin once per day for a period of 12 weeks p< 0.05 as compared to positive controls which received only Metformin 500mg per day for same duration of 12 weeks p> 0.05. The study recommends that Vitamin D may be used as an adjuvant drug to Metformin in regulating glycemic status and cytokines in women living with PCOS.

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