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Correlation of Homocysteine and Testosterone Levels with BMI in PCOS AND Non-PCOS Women Undergoing ICSI Procedure

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ABSTRACT

Background: Elevated serum homocysteine (Hcy) and testosterone levels are highly linked with polycystic ovary syndrome (PCOS). However, limited information exists regarding the correlation between body mass index (BMI) and these biomarkers in PCOS women undergoing intracytoplasmic sperm injection (ICSI). Serum Hcy measured in genetic and biochemical tests, is thought to influence reproductive function similarly to high testosterone and Hcy levels interact with BMI in women with PCOS is important for evaluation fertility potential compared to non-PCOS women.

Aim: This research investigated the connection between testosterone and Hcy with BMI in infertile women undergoing ICSI and to evaluate the impact of these markers on oocyte quality.

Methods: Forty infertile women undergoing IVF/ICSI were recruited, including 19 with PCOS and 21 with non-PCOS conditions, such as low AMH or unexplained infertility. Serum Hcy and testosterone levels were measured from cycle day 2 (CD2) to ovum pick-up (OPU) and their association with oocyte maturing were analyzed in both groups.

Results: PCOS patients were younger and more frequently under 35 years of age compared to non-PCOS women, with similar BMI across groups. PCOS women produced a higher number of total and mature oocytes. Hcy and testosterone levels increased during stimulation in both groups, the Hcy rise was more pronounced in non-PCOS women, whereas testosterone increased more in PCOS patients. Low BMI women with PCOS had a lower CD2 levels of both markers while the difference was less in higher BMI subgroups.

Conclusion: PCOS patients with lower BMI showed low Hcy at CD2 and testosterone levels but stronger response to hormonal stimulation. These findings reveal the physiological differences among PCOS subtypes that may call for individualized stimulation protocols according to phenotypes

KEYWORDS: BMI, Testosterone, Homocysteine, PCOS.

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INTRODUCTION

PCOS is one of the most common female fertility issues and disorders nowadays [1]. The term hyperandrogenism refers to the condition when women have elevated levels of male hormones (androgens), typically testosterone. Clinical and/or biochemical hyperandrogenism could appear in 70–80% of women diagnosed with PCOS [2].

Persistent hyperandrogenism is associated with disrupted hypothalamic-pituitary feedback, increased secretion of luteinizing hormone (LH), early luteinization of granulosa cells, abnormal maturation of oocytes, and premature cessation of activated primary follicles [3].

Androgen and estrogen levels get disrupted by the higher concentration of testosterone in PCOS [4]. Because of LH output rises suddenly, which shows the enhanced formation of testosterone from the theca cells of ovaries [5]. This event also promotes the formation of Anti mullerian hormone (AMH). Anti mullerian hormone was significantly up-regulated in PCOS [6]. Reproduction comprises a carefully coordinated sequence of events, with the immune system playing a crucial role in various reproductive functions. Any disruption in the properly regulated immune responses can result in infertility and various complications during pregnancy [7].

Androgen exposure may directly trigger apoptotic pathways in cumulus cell oocytes, exposing oocytes to metabolic aberrations [4].

Circulating androgen levels are enhanced in PCOS and in turn implicate aberrant humoral immune response, providing a unique basis of dysregulated immunity in PCOS [8]. Hyperandrogenemia and the ovarian-metabolic axis have a complicated interplay in which cause and effect are hard to disentangle in multiple feedback loops. Emerging evidence shows that metabolic disorders

can both cause and result from increased testosterone production [2].

Obesity is common among women with PCOS and insulin resistance is usually associated with obesity. Elevated insulin levels may contribute to follicular degradation by exposing the ovarian environment to excessive insulin leading to premature loss of developing follicles [9].

Body mass index (BMI) serves as a straightforward measure of the ratio of weight to height and is widely utilized for the classification of overweight and obesity in adults [10]. Adipose tissue produces two primary categories of molecules referred to as adipocytokines and adipose-derived hormones. These molecules are particularly noteworthy because they have linked to persistent state of inflammation and elevated insulin levels in individuals with obesity, both of which have been correlated with irregular reproductive function [11].

Additionally, obesity is associated with immune system abnormalities that likely arise from complex interactions between adipose tissue and the immune system [12,13].

A recent study found that women with PCOS have high levels of Hcy, a dietary amino acid associated with inflammation and cardiovascular disease [14].

The disrupted function of insulin action in follicles and HOMA-IR is positively related to Hcy in patients with PCOS. Patients with PCOS experience insulin resistance and high insulin concentrations. It is essential to address the fact that hyperinsulinemia is an underlying metabolic factor of PCOS. The association between hyperhomocysteniemia, insulin resistance, overweight, and PCOS might suggest that the biological disruption associated with PCOS leads to elevated Hcy [15].

Several previous studies have demonstrated the association of hyperhomocysteinemia and hyperandrogenemia in PCOS and non-PCOS women [16], however the relation of BMI with high levels of testosterone and Hcy and their effect on oocyte quality in PCOS that undergone ICSI procedure need more search , therefore the aim of this study is to evaluate the correlation of BMI with testosterone and Hcy levels and their potential effects on oocyte maturity and quality in PCOS women that undergone ICSI procedure.

STUDY POPULATION AND METHODS

This research was conducted as a cross-sectional study involving a total of 40 women, both infertile PCOS and non-PCOS, who were randomly selected to ensure unbiased representation between December 2024 and March 2025. The participants, aged 25 to 45, underwent the ICSI procedure. The diagnosis of PCOS in women was established following the Rotterdam ESHRE ASRM-sponsored PCOS consensus workshop group criteria to differentiate the PCOS individuals from non-PCOS [17]. Patients with conditions such as hypogonadism, endometriosis, and autoimmune disorders, including hypo- or hyperthyroidism, were excluded from the study.

Infertile women were grouped according to standard range of BMI at CD2 as the following: 20-24.99 kg/m^2 was classified as normal, 25-30 kg/m^2 as overweight and more than 30 kg/m^2 as obese [18]. BMI was calculated for each infertile women according the following equation: BMI=Kg/M^2.

SAMPLE COLLECTION

Blood samples were collected from all participants on CD2 and on OPU. After collection, the samples were allowed to close for approximately 10 minutes then Center refused for 20 minutes at 3000 RPM separate the serum That was obtained as adequate rapidly frozen and stored at – 20 C until analysis [3]. Both, Hcy and Testosterone were tested using enzyme-linked immunosorbent assay (ELISA) following the instructions in the kit (Reed Biotech Ltd/China).

STATISTICAL ANALYSES

Analyses were done using R programming language and its statistical analysis-related packages. Continuous variables following a normal disruption were summarized as ± mean standard deviation while non normally distributed data were reported as median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages. Comparisons between PCOS and non-PCOS groups were carried on using independent samples t-test for normally distributed data, Mann-Whitney U test for non-normally distributed data, and Fisher's exact test for categorical variables. Paired comparisons of biomarker levels between CD2 and OPU were evaluated using paired t-test for normally distributed differences or Wilcoxon signed-rank test for non-normally distributed differences. Age and BMI subgroup analyses were performed to examine biomarker patterns across different demographic subgroups. Partial correlation analyses, controlling for age and BMI, were conducted to assess relationships between reproductive parameters and biomarkers within the overall population and separately for PCOS and non-PCOS groups. A significance level of $p < 0.05$ was considered statistically significant, with additional levels indicated as *$p<0.05$, **$p<0.01$, and ***$p<0.001$.

RESULTS

The research involved a total of 40 infertile women, 19 were diagnosed with PCOS and 21 served as non-PCOS controls (**Table 1**). Participants with PCOS were noticeably younger than non-PCOS group (29.58 ± 4.61 vs 36.33±6.92 years, $p<0.05$), with nearly 84% of PCOS women being under 35 years compared to only 38% in the control group. Both groups had similar BMI distributions, with no significant difference in median BMI between PCOS [25.59 (23.66-28.27) kg/m²] and non-PCOS patients

[25.39 (23.59-29.67) kg/m²] (p>0.05). PCOS patients gave significantly more oocytes [20 (17.5-24)] compared to non-PCOS patients [6 (4-9)] (p<0.05), including more mature M2 oocytes [15 (7-17.5) vs 4 (2-7), p<0.05].(Table 2). Table 3, shows that the baseline homocysteine levels on cycle day 2 were lower in PCOS patients [1146.83 (938.68-1537.4) µmol/L] compared to non-PCOS patients [1825.62 (1662.59-1902.57) µmol/L] (p<0.05), Interestingly, CD2 testosterone levels were also lower in PCOS group [1.3 (1.25-1.74) ng/ml] compared to non-PCOS group [2.04 (1.95-2.14) ng/ml] (p<0.05).

HOMOCYSTEINE LEVELS

Looking at the biomarker analysis results, homocysteine levels showed a significant increase from CD2 to ovum pick-up OPU for all populations (Figure 1). Overall, homocysteine increased from 1663.24 (1139.32-1873.58) µmol/L to 1916.24 (1085.06-3263.20) µmol/L with a median difference of 375.57 (-0.33-1406.21) µmol/L (p<0.05). This increase was particularly pronounced in non-PCOS women, rising from 1825.62 (1662.59-1902.57) µmol/L to 2658.53 (1912.84-3353.46) µmol/L with a median difference of 775.19 (110.94-1541.26) µmol/L (p<0.05), while PCOS patients showed a more modest increase from 1146.83 (938.68-1537.40) µmol/L to 1078.57 (1000.86-1941.04) µmol/L with a median difference of 146.72 (-17.69-628.46) µmol/L (p<0.005). In similar context, testosterone levels increased significantly during the same period (Figure 2), rising from 1.96 (1.30-2.10) ng/mL to 2.32 (2.10-2.55) ng/mL overall with a median difference of 0.41 (0.09-0.85) ng/mL (p<0.001). Non-PCOS women showed an increase from 2.04 (1.95-2.14) ng/mL to 2.33 (2.25-2.50) ng/mL with a median difference of 0.40 (0.28-0.62) ng/mL (p<0.001), while PCOS patients demonstrated a larger relative increase from 1.30 (1.25-1.74) ng/mL to 2.20 (1.65-3.82) ng/mL with a median difference of 0.66 (-0.03-2.10) ng/mL (p=0.002).

BMI-stratified analysis showed marked differences between PCOS and non-PCOS patients, particularly in the lower BMI category (Figure 3). Among patients with BMI <30 kg/m², baseline testosterone on CD2 was significantly lower in PCOS individuals [1.29 (1.25-1.43) ng/ml] compared to non-PCOS women [2.01 (1.92-2.14) ng/ml] (p<0.05), while no significant difference was observed in the higher BMI group (≥30 kg/m²) between PCOS [2.20 (1.73-2.43) ng/ml] and non-PCOS patients [2.09 (2.04-2.12) ng/ml] (p>0.05). At OPU, testosterone levels showed no statical differences between PCOS and the control non-PCOS counter partners in either BMI category, though PCOS patients with lower BMI demonstrated a wider interquartile range [2.14 (1.24-4.40) ng/ml] compared to non-PCOS women [2.33 (2.20-2.48) ng/ml] (p>0.05).

Homocysteine patterns followed a similar manner, with distinct differences observed primarily in the lower BMI category (Figure 4). Patients with BMI <30 kg/m² showed substantially lower baseline homocysteine levels in PCOS patients [1105.69 (911.87-1236.45) µmol/L] compared to non-PCOS women [1825.80 (1662.58-1901.25) µmol/L] (p<0.05), while those with BMI ≥30 kg/m² showed no significant difference between groups [1958.29 (1735.97-1964.86) vs 1804.49 (1663.90-1982.80) µmol/L, p>0.05].
This pattern remained at OPU, where PCOS patients lower BMI continued to show significantly lower Hcy levels [1068.811 (997.02-1853.00) µmol/L] compared to non-PCOS women [2503.42(1900.08-3306.65) µmol/L] (p<0.05), while no significant difference was observed in the higher BMI group between PCOS [194.04(1701.58-2350.14) µoml/L] and non-PCOS patients [2658.58(1915.43-3635.06) µmol/L] (p<0.05).

DISCUSSION

This research gives a comprehensive analysis of the correlation between Hcy and testosterone levels with BMI in infertile women diagnosed with or without PCOS undergone ICSI. The investigation highlights distinct profiles in response to ovarian stimulation and focusing on how BMI serves as a critical modulator of hormonal shifts and reproductive biomarker expression.

The results also confirm several demographic and clinical recorded characteristics about PCOS women. The patients with this disorder were younger than the non-PCOS controls and their number of retrieved oocytes were higher yet it came with a higher number of immature germinal vesicle and metaphase I oocytes (GV and MI).

While it clearly shows good ovarian reserve and responsiveness, it also demonstrates the well known reported concern about oocytes competence and developmental potential [19]. The high numerical yield doesn't necessarily mean an improved fertility outcomes because of the weak maturity yield [20].

The hormonal biomarker complex trends at CD2 There was a significant low level of HCY and in PCOS patients when compared to non PCOS ones This surprisingly counters the usual classical model that is expected in PCOS with hyperhomocysteinemia and hyperandrogenism [14].

However, both markers during extermination increased with testosterone showing more Avias rise in PCOS patients this dynamic shift May propose I'm in haste sensitivity in the ovaries of PCOS women to gonadotropin stimulation, Triggering a rise in the production of testosterone, a known disruptor of granulosa cell function and oocyte maturation [21].

HCY levels followed a similar trajectory in the increase across all groups from CD2 to OPU however the amount of increase varied A sharper rise, While it was modest and pure assuming the difference was more obvious in lean PCOS individuals possibly Mediated by differences in hepatic methylation pathways or folate metabolism [22]. Such individuals may not much the typical resistant phenotype of PCOS Which make necessary for a tailored clinical approach.

When comparing women based on BMI the differences in HCY and testosterone were mainly seen induced with BMI < 30KG/m^2 among these lean women PCOS patients had notably lower baseline and OPU testosterone levels when compared to non PCOS

women. In contrast obese women BMI ≥ 30 KGM showed no significant differences in these biomarkers supporting the idea that metabolic load plays an important role in shaping PCOS related abnormalities

Elevated HCY is known to be linked with oxidative stress, endothelial dysfunction and poor productive outcomes. Interestingly in this study lean PCOS women should lower at HCY levels despite an increased oocyte yield and sensitivity to stimulation. This may indicate a compensatory metabolic mechanism or a different hormonal pathway. Variation in testosterone especially the sharp rise during stimulation might reflect increase all edge sensitivity or downstream enzyme activity in ovarian cells these findings are consistent with earlier research connecting hyperandrogenism with disturbed follicular growth and reduce oocyte quality [4].

The observed pattern of lower CD2 testosterone and HCY and PCOS followed by a strong cost stimulation increase suggesting that single time measurements are not enough for accurate diagnosis or prognosis. The link between changing biomarker levels and oocyte development Further supports this. As HCY rose, especially in non PCOS women, oocyte maturation seemed reduced, hinting a Possible toxic ore inhibitory effect of elevated at HCY during stimulation.

Although this study offers valuable insights into the variability of PCUS responses especially when considering BMI differences several limitations must be taken into account. The small sample size low number of obese participants and lack of outcome data, such as fertilization rate, embryo quality or pregnancy results, limit the ability to make to make a firm conclusion. Moreover some hormonal and metabolic markers like insulin, SHBG, estradiol and AMH were not included which could have enhanced understanding of the results.

Although, this study contributes valuable insights into the heterogeneity of PCOS, particularly in the context of BMI-stratified responses to controlled ovarian stimulation however, the limitations of current study including relatively small sample size with low number of obese women and absence of outcome data such as fertilization rates, embryo quality, or pregnancy outcomes. These limitations restrict the ability to draw direct correlations between biomarker dynamics and treatment success. Additionally, some hormonal and metabolic markers such as insulin, SHBG, estradiol, and AMH weren't included in the analysis, which could have strengthened the understanding of the observed trends.

The data supposes that lean PSOS women shouldn't be treated using the generalized protocols as their hormonal and metabolic patterns differ from those of obese PCOS patients, implying that individualized treatment approaches are essential for them and recognizing these distinct responses may help make a better open stimulation strategy strategies and improve reproductive outcomes for women with PCOS.

CONCLUSION

Our results show that PCOS can appear differently among women especially those with lower BMI lean PCO assuming had lower starting levels of testosterone and HCY but showed a strong rise in these hormones and higher egg yield during stimulation this shift over time rather than single baseline values may describe better how the ovaries respond in different PCOS types.

We recommend clinicians should pay attention to how BMI, testosterone and HCY interact during stimulation in PCOS women. These patterns can affect oocyte yield and quality, so focusing on hormonal changes not just baseline levels may help improve ART outcomes.

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Tables

Table 1. Descriptive statistics and group comparisons between PCOS and non-PCOS patients

Variable	PCOS (n=19)	Non-PCOS (n=21)	p-value
Demographics			
Age (years)	29.58 ± 4.61	36.33 ± 6.92	<0.001[a]
Age group, n (%)			
<35 years old	16 (84.2)	8 (38.1)	0.004c
≥35 years old	3 (15.8)	13 (61.9)	
BMI (kg/m2)	25.59 (23.66-28.27)	25.39 (23.59-29.67)	0.786[b]
BMI category, n (%)			
<30 kg/m2	15 (78.9)	16 (76.2)	1.000
≥30 kg/m2	4 (21.1)	5 (23.8)	
Infertility type, n (%)			
Primary	11 (47.8)	10 (58.8)	0.538[c]
Secondary	12 (52.2)	7 (41.2)	

Table 2. Oocyte characteristics comparisons between PCOS and non-PCOS patients

Oocyte characteristics	PCOS	Non PCOS	p-value
Retrieved oocytes (n)	20 (17.5-24)	6 (4-9)	<0.001[b]
GV oocytes	3 (1.5-6.5)	1 (0-1)	0.001[b]
M1 oocytes	2 (1-4)	0 (0-2)	0.004[b]
M2 oocytes	15 (7-17.5)	4 (2-7)	<0.001[b]

Table 3. Hormonal parameters comparisons between PCOS and non-PCOS patients

Hormonal parameters	PCOS	Non-PCOS	p-value
Hcy CD2 (µmol/L)	1146.83 (938.68-1537.4)	1825.62 (1662.59-1902.57)	0.002[b]
Hcy OPU (µmol/L)	1078.57 (1000.86-1941.04)	2658.53 (1912.84-3353.46)	0.001[b]
Testosterone CD2 (ng/ml)	1.3 (1.25-1.74)	2.04 (1.95-2.14)	0.004[b]
Testosterone OPU (ng/ml)	2.2 (1.65-3.82)	2.33 (2.25-2.5)	0.533[b]

Data are presented as median (interquartile range) for continuous variables and frequency (%) for categorical variables. [a]Independent samples t-test (for normally distributed data), [b]Mann-Whitney U test (for non-normally distributed data), and cFisher's exact test. p<0.05 indicates statistically significant difference between groups. Abbreviations: GV: germinal vesicle; M1: metaphase I; M2: metaphase II; CD2: cycle day 2; OPU: ovum pick-up; E2: estradiol; BMI: body mass index.

Figures

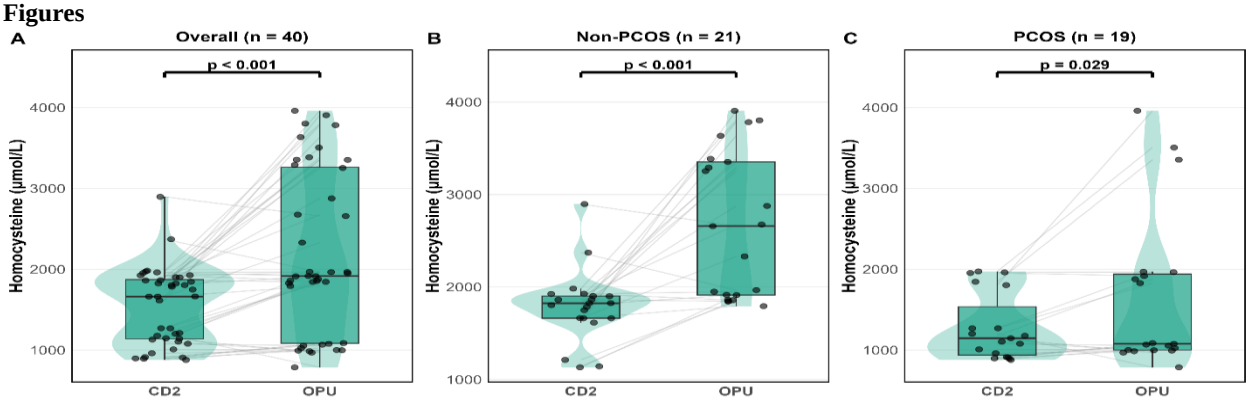

Figure 1. Comparison HCY levels Measured on CD2 and on OPU among three groups: (A) All infertile women included in the study (B) Non PCOS participants only and (C) PCOS participants only. Each gray line represents the trajectory of an individual participant connecting paired measurements statical significance between CD2 and OPU values were determined using either the paired t-test or Wilcoxon signed-rank test according to the data distribution box plots depict the media and quarters with all individual data points displayed.

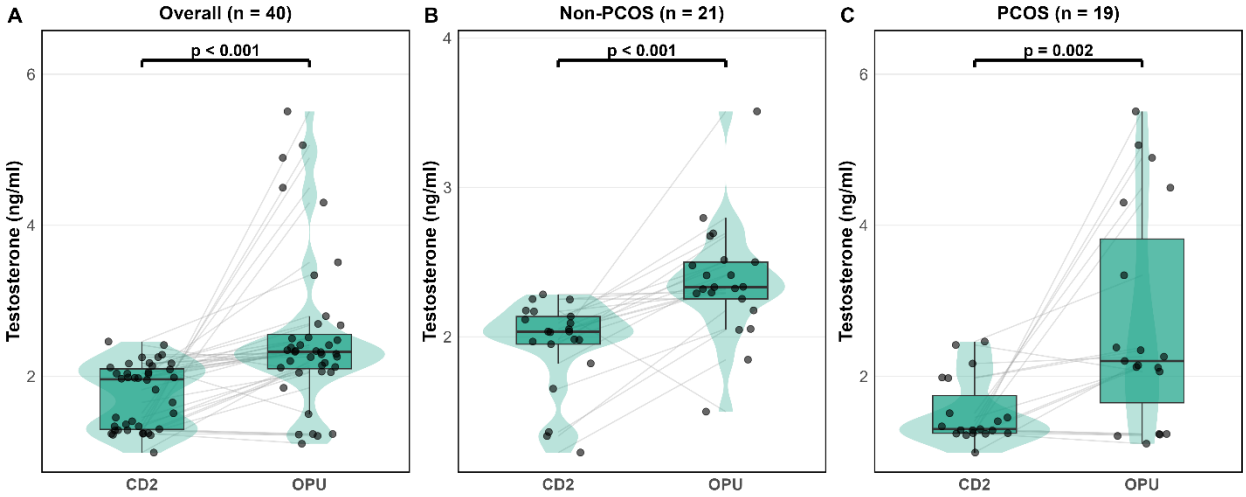

Figure 2. Comparison of testosterone levels measured on CD2 and on OPU among three groups (A) All infertile women included in the study (B) Non PCOS participants only and (C) PCOS participants only. Each Gray line represents an individual participant's trajectory connecting paired CD2 and OPU measurements. Statical differences between paired values were evaluated using either the paired t-test or Wilcoxon signed-rank test, depending on data distribution displayed medians and quartiles with all individual data points shown.

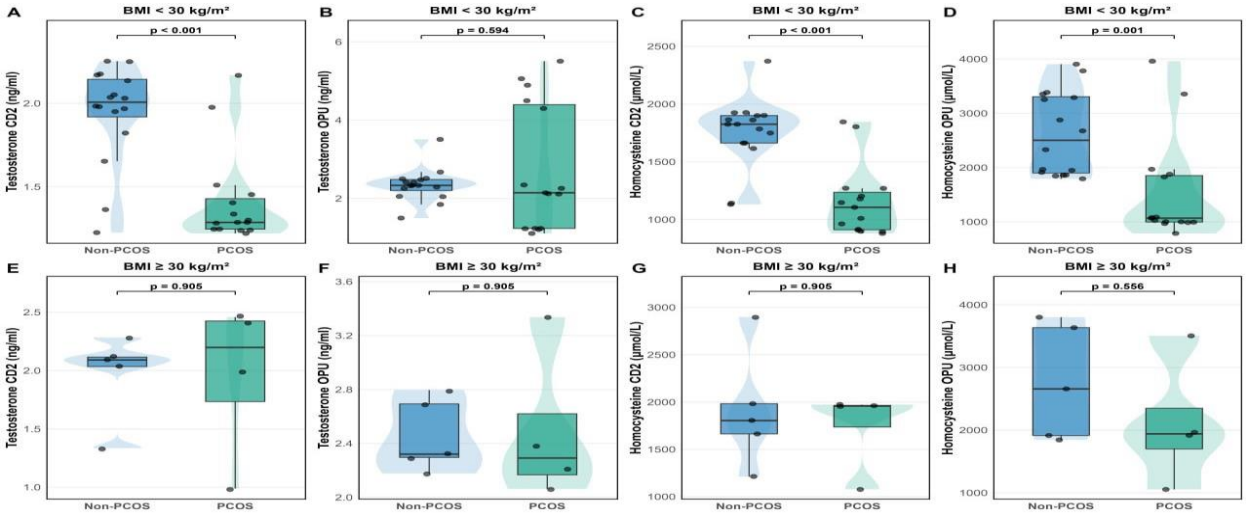

Figure 3. Comparison of biomarker levels (Testosterone and HCY) measured on CD2 and on OPU between POS and non PCOS further categorized by (BMI < 30 and 30 Kg/m$^{2)}$ data are presented as median values with interquartile ranges (IQR). Violin plots illustrate the data distribution including media and quartile with all individual data points shown. Statistical differences were evaluated using Mann-Whitney U test