

Relationship Between Different Anthropometric Measurements and Interleukin-1 β , Interleukin-17, Interleukin-27 and Interleukin-35 Levels For Iraqi Infertile Women with Polycystic Ovary Syndrome

- **Abstract**

Aims: the study aimed to study impact of type and amount of body fat distribution on interleukin-1 β , interleukin-17, interleukin-27, and interleukin-35 levels and on immunologic infertility.

Study design: the study was carried on infertile polycystic ovarian syndrome women.

Place and duration of study: the study was performed with study subjects attended consultant clinic of Higher Institute for Infertility Diagnosis and Assisted Reproductive Technologies at AL-Nahrain University in Baghdad/Iraq during the period from February 2016 to April 2016.

Materials and Methods: twenty-six infertile polycystic ovarian syndrome women were enrolled in this study. Body mass index (BMI), waist circumference (WC), and waist to hip ratio (WHR) measurements were calculated to all cases. Serum interleukin-1 β (IL-1 β), interleukin-17 (IL-17), interleukin-27 (IL-27), and interleukin-35 (IL-35) concentrations were measured on cycle day 2.

Results: Significant difference in distribution according to BMI, WC, and WHR ($P=0.0001$, $P=0.0001$, $P=0.04$, respectively). Significant difference in IL-1 β concentrations according to WHR ($P=0.04$). Significant difference in IL-17 concentrations according to BMI, WC, and WHR ($P=0.02$, $P=0.03$, $P=0.008$, respectively). Significant difference in IL-27 concentrations according to WC ($P=0.03$). Significant difference in IL-35 concentrations according to BMI and WC ($P=0.0001$, $P=0.0001$, respectively).

Conclusions: amount and type of body fat distribution considerably affected and altered IL-1 β , IL-17, IL-27, and IL-35 concentrations and consequently had a role in immunologic infertility.

Keywords: PCOS, anthropometric measurements, interleukin-1 β , interleukin-17, interleukin-27, interleukin-35, infertility.

- **Introduction**

Polycystic ovary syndrome (PCOS), a heterogenous condition correlated with elevated androgen and irregular menstrual cycle, is a common gynecological endocrine disease affecting 6%-12% of women at reproductive ages (1). Polycystic ovary disease (PCOD) is characterized by chronic insulin resistance, hyperandrogenism, and anovulation, disorders where obesity frequently accompanied them(2).

Body mass index (BMI) measures total body fat (3). Waist circumference (WC) has been proposed as a practical measure of intra-abdominal fat mass and total body fat (4). Waist to hip ratio (WHR) is a measurement of identifying patients with elevated abdominal fat accumulation (4).

Adipose tissue a dynamic organ, is releasing hormones, adipokines, and cytokines, and participating in the endocrine process that regulate glucose and fatty metabolism, immunity, inflammatory response, and reproduction, among other functions and activities (5). Adipose tissue dysfunction is included in the progress of metabolic and reproductive dysfunctions of polycystic ovarian syndrome women (5). Location of adipose tissue deposition significantly impact adipose tissue pathogenicity (6).

Cytokines, commonly named interleukins and crucial for cell signaling, are a broad and loose category of small proteins (~5-20KDa) (7). Adipose tissue secretes more than 50 interleukins (5). Immunity barrier and immunoregulatory mechanisms are necessary in the processes of follicle development, fertilization, and implantation of the embryo in the uterus (8). Interleukin activity in the ovary has been demonstrated as inducing processes of follicular growth, steroidogenesis, recruitment and stimulation of leukocytes necessary for ovulation and tissue remodeling during ovulation, luteinization, and luteolysis (9). The anomaly in the regulation of the immunity can lead to some pathological states and

diseases (10). Serum interleukin concentrations are altered in polycystic ovarian syndrome females (11).

Interleukin-1 β (IL-1 β) and interleukin-17 (IL-17) are released from vascular endothelial cells, adipocytes, and macrophages (5). Interleukin-1 β (IL-1 β) is a crucial mediator of the pro-inflammatory immune response and is included in cell proliferation, differentiation, and apoptosis (12). Interleukin-1 β (IL-1 β) participates in a significant role in the regulation of the development and atresia of ovarian follicles (13). The principal source for interleukin-17 (IL-17) is T helper (Th)17 cells (14). Interleukin-17 (IL-17) mediate pro-inflammatory immunity (14). Interleukin-27 (IL-27) is majorly secreted from antigen-presenting cells (APCs) such as dendritic cells and macrophages (15)(16). Interleukin-27 (IL-27) can promote or restrict immune responses (15). Interleukin-35 (IL-35) is inhibitory interleukin that is specifically released by regulatory T (Treg) cells and is demanded for maximal suppressive functions (17).

This study aimed to:

- 1- Calculate different anthropometric measurements [body mass index (BMI), waist circumference (WC), and waist to hip ratio (WHR)].
- 2- Distribute interleukin-1 β (IL-1 β), interleukin-17 (IL-17), interleukin-27 (IL-27), and interleukin-35 (IL-35) concentrations according to different anthropometric measurements.
- 3- Impact of type and amount of body fat distribution on interleukin-1 β (IL-1 β), interleukin-17 (IL-17), interleukin-27 (IL-27), and interleukin-35 (IL-35) concentrations.
- 4- Role of type and amount of body fat distribution in incidence of infertility for polycystic ovarian syndrome infertile women by altering interleukin-1 β (IL-1 β), interleukin-17 (IL-17), interleukin-27 (IL-27), and interleukin-35 (IL-35) concentrations and consequently participating in immunologic pathogenicity for these women.

- **Materials and Methods**

- **Study Subjects**

This study was performed with study subjects attended consultant clinic of Higher Institute for Infertility Diagnosis and Assisted Reproductive Technologies at AL-Nahrain University in Baghdad/Iraq during

the period from February 2016 to April 2016. This study involved twenty-six infertile women with polycystic ovary syndrome (PCOS). All study cases were chosen randomly. Information concerning age and type and duration of infertility were obtained from their files.

Polycystic ovary syndrome (PCOS) was diagnosed according to Rotterdam criteria and was done by the specialist physician in the consultant clinic. 2003 European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (2003 ESHRE/ASRM or Rotterdam) diagnostic criteria included patient with polycystic ovary syndrome (PCOS) suffered at least from two of the three criteria: oligo-or chronic anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries. The conditions excluded before the diagnosis of polycystic ovary syndrome (PCOS) involved thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinaemia, Cushing's syndrome, and androgen-secreting tumors (18).

Women with uterine abnormalities, endometritis, endometriosis, sexually transmitted diseases (STDs), and tubal factor infertility (TFI) were departed from this study.

For the twenty-six polycystic ovarian syndrome women, their ages ranged from twenty-one years to thirty-five years. Twenty were primary infertile with duration ranged from one year to ten years (4.25 ± 0.58), and six were secondary infertile with duration ranged from one year to fourteen years (5.83 ± 2.60).

- **Body Mass Index**

Body mass index (BMI) was calculated by the weight in kilograms divided by the height in meters squared (Kg/m^2). Body mass index (BMI) was categorized as underweight ($<18.5 \text{ Kg/m}^2$), normal weight ($18.5\text{-}24.9 \text{ Kg/m}^2$), overweight ($25\text{-}29.9 \text{ Kg/m}^2$), and obesity as having a BMI $\geq 30.0 \text{ Kg/m}^2$ (19).

- **Waist Circumference**

Waist circumference (WC) was measured to the nearest 0.1 cm at the level of the iliac crest while the patient was at minimal respiration (19). Females with WC ≤ 88 cm were regarded to have a normal waist circumference (WC) while females with WC >88 cm were estimated to have a high waist circumference (WC) (19).

- **Waist-to-Hip Ratio**

Waist to hip ratio (WHR) was determined by using measuring tape to determine the circumference of hips at the widest part of the buttocks (20). Waist circumference (WC) was measured at the level midway between the lowest rib margin and the iliac crest (20). The ratio was calculated by dividing the waist measurement by hip measurement (20).

- **Blood Sampling**

Informed and signed consent was obtained at the time of blood sampling from all females enrolled in this study. Venous blood samples were drawn on cycle day two (CD2). Serum levels of interleukin-1 β (IL-1 β), interleukin-17 (IL-17), Interleukin-27 (IL-27), and interleukin-35 (IL-35) were measured using enzyme linked immunosorbent assay (ELISA) kits (CUSABIO/China).

- **Statistical Analysis**

The Statistical Analysis System-SAS (2012) program was used to effect of different factors in study parameters. Chi-square test was used to significant compare between percentage and Least significant difference-LSD or T-test was used to significant compare between means in this study(21).

- **Results**

Twenty-six infertile women with polycystic ovary syndrome were enrolled in this study. Of twenty-six and according to body mass index (BMI), three (11.54%) were with normal body weight with mean levels $(22.75 \pm 0.45) \text{ kg/m}^2$, nine (34.62%) were overweight and with mean levels $(28.21 \pm 0.57) \text{ kg/m}^2$, and fourteen (53.84%) were obese with mean levels $(37.91 \pm 0.82) \text{ kg/m}^2$. According to waist circumference (WC), five (19.23%) were with normal weight with mean levels $(73.00 \pm 1.90) \text{ cm}$, four (15.38%) were overweight with mean levels $(83.00 \pm 0.00) \text{ cm}$, and seventeen (65.38%) were obese with mean levels $(100.23 \pm 2.94) \text{ cm}$. According to waist to hip ratio (WHR), seven (26.92%) were with normal weight with mean levels (0.72 ± 0.03) , nine (34.62%) were overweight with mean levels (0.82 ± 0.01) , and ten (38.46%) were obese with mean levels (0.92 ± 0.02) .

Table (1): Distribution of polycystic ovarian syndrome women according to body weight and different anthropometric measures.

| Body weight AM | Normal weight Number & (%) | Overweight Number & (%) | Obese Number & (%) | Total Number & (%) | Chi-square | P-value |
|-------------------------------------|---|--|---|---|-------------------|----------------|
| BMI | 3 (11.54%) | 9 (34.62%) | 14 (53.84%) | 26 (100%) | 11.56** | 0.0001 |
| WC | 5 (19.23%) | 4 (15.38%) | 17 (65.38%) | 26 (100%) | 10.04** | 0.0001 |
| WHR | 7 (26.92%) | 9 (34.62%) | 10 (38.46%) | 26 (100%) | 4.89** | 0.04 |
| Chi-square | 5.07* | 8.72** | 9.33** | - | - | - |
| P-value | 0.03 | 0.006 | 0.0002 | - | - | - |

AM: anthropometric measurements; (%): percentage; BMI: body mass index; WC: waist circumference; WHR: waist to hip ratio; *P*: probability; **(*P*<0.01); *(*P*<0.05); (*P*<0.05) considered significant

Table (2): distribution of interleukin-1 β mean levels according to different anthropometric measures

| IL-1 β Mean Levels AM | Number & (%) Mean \pm SE | Normal Weight Mean \pm SE | Number & (%) Mean \pm SE | Overweight Mean \pm SE | Number & (%) Mean \pm SE | Obesity Mean \pm SE | LSD value | P- value |
|--|--------------------------------------|---------------------------------------|--------------------------------------|---------------------------------|--------------------------------------|------------------------------|--------------|-------------|
| BMI | 3 (11.54%) | 72.29 \pm 13.06 | 9 (34.62%) | 77.18 \pm 9.00 | 14 (53.84%) | 72.46 \pm 5.22 | 12.79 NS | 0.25 |
| WC | 5 (19.23%) | 83.44 \pm 10.20 | 4 (15.38%) | 73.50 \pm 8.37 | 17 (65.38%) | 71.10 \pm 5.45 | 16.06 NS | 0.09 |
| WHR | 7 (26.92%) | 73.89 \pm 9.36 | 9 (34.62%) | 67.22 \pm 6.87 | 10 (38.46%) | 80.72 \pm 6.16 | 11.35* | 0.04 |

AM: anthropometric measurements; IL-1 β : interleukin-1 β ; (%): percentage; *P*: probability; *(*P*<0.05) considered significant; NS: non-significant; BMI: body mass index; WC: waist circumference; WHR: waist to hip ratio

Table (3): distribution of interleukin-17 mean levels according to different anthropometric measures

| IL-17 Mean Levels AM | Number & (%) | Normal Weight Mean±SE | Number & (%) | Overweight Mean±SE | Number & (%) | Obesity Mean±SE | LSD value | P- value |
|-------------------------|-----------------|---------------------------------|-----------------|---------------------------|-----------------|------------------------|--------------|-------------|
| BMI | 3 (11.54%) | 26.08±10.12 | 9 (34.62%) | 15.66±5.36 | 14 (53.84%) | 7.15±3.11 | 13.50* | 0.02 |
| WC | 5 (19.23%) | 18.36±7.30 | 4 (15.38%) | 23.89±10.74 | 17 (65.38%) | 7.76±2.69 | 11.86* | 0.03 |
| WHR | 7 (26.92%) | 20.35±7.09 | 9 (34.62%) | 5.61±2.05 | 10 (38.46%) | 12.63±4.98 | 8.43** | 0.008 |

AM: anthropometric measurements; IL-17: interleukin-17; (%): percentage; *P*: probability; **(*P*<0.01); *(*P*<0.05) considered significant; BMI: body mass index; WC: waist circumference; WHR: waist to hip ratio

Table (4): distribution of interleukin-27 mean levels according to different anthropometric measures

| IL-27 Mean Levels AM | Number & (%) | Normal Weight Mean±SE | Number & (%) | Overweight Mean±SE | Number & (%) | Obesity Mean±SE | LSD value | P- value |
|-----------------------------------|-----------------|---------------------------------|-----------------|---------------------------|-----------------|------------------------|--------------|-------------|
| | | | | | | | | |
| BMI | 3 (11.54%) | 9.48±1.60 | 9 (34.62%) | 9.61±2.74 | 14 (53.84%) | 8.91±1.59 | 4.27 NS | 0.25 |
| WC | 5 (19.23%) | 11.03±3.58 | 4 (15.38%) | 6.05±0.49 | 17 (65.38%) | 9.43±1.61 | 3.75* | 0.03 |
| WHR | 7 (26.92%) | 9.93±2.60 | 9 (34.62%) | 8.39±1.97 | 10 (38.46%) | 9.47±2.23 | 3.18 NS | 0.14 |

AM: anthropometric measurements; IL-27: interleukin-27; (%): percentage; P: probability; *($P<0.05$) considered significant; NS: non-significant; BMI: body mass index; WC: waist circumference; WHR: waist to hip ratio

Table (5): distribution of interleukin-35 mean levels according to different anthropometric measures

| IL-35 Mean Levels AM | Number & (%) | Normal Weight Mean±SE | Number & (%) | Overweight Mean±SE | Number & (%) | Obesity Mean±SE | LSD value | P- value |
|-------------------------|-----------------|---------------------------------|-----------------|---------------------------|-----------------|------------------------|--------------|-------------|
| BMI | 3 (11.54%) | 105.12±4.96 | 9 (34.62%) | 28.10±6.75 | 14 (53.84%) | 43.33±8.31 | 22.79** | 0.0001 |
| WC | 5 (19.23%) | 83.22±14.39 | 4 (15.38%) | 24.23±0.00 | 17 (65.38%) | 38.48±7.30 | 16.34** | 0.0001 |
| WHR | 7 (26.92%) | 61.08±17.42 | 9 (34.62%) | 40.45±8.47 | 10 (38.46%) | 40.80±10.37 | 24.06 NS | 0.09 |

AM: anthropometric measurements; IL-35: interleukin-35; (%): percentage; *P*: probability; **(*P*<0.01) considered significant; NS: non-significant; BMI: body mass index; WC: waist circumference; WHR: waist to hip ratio.

• Discussion

Obesity, characterized by an accumulation of excess body fat, is a disorder of body weight regulatory systems (3). Obesity is caused by an increase in the number and in the size of adipocytes (6). There are three anthropometric measures of obesity [body mass index (BMI), waist circumference (WC), and waist to hip ratio (WHR)] involved in the study (4) (22). Body mass index (BMI) measures the relative weight, adjusted for height (3). Very high considerable correlation between the incidence of polycystic ovary syndrome (PCOS) and body mass index (BMI) and the prevalence of overweight and obesity were significantly higher in polycystic ovarian syndrome women. Elevated body mass index (BMI) directly and significantly impacts the occurrence of polycystic ovary syndrome (PCOS) (22). A study conducted by Chitme et al. (2017) found that the prevalence of overweight, obesity, and central obesity were significantly higher in polycystic ovarian syndrome females (22). Even in the lack of frank obesity, increased abdominal adiposity is disseminated in all weight classes for women with polycystic ovary syndrome (PCOS) (23). Persons with a similar body mass index (BMI) can vary significantly in their abdominal-fat mass (4). A study revealed that women with polycystic ovary syndrome (PCOS) showed significantly higher concentrations of body mass index (BMI), waist circumference (WC), and total free testosterone (24). Elevated body mass index (BMI) is linked to an increase in serum and follicular fluid leptin concentrations and decrease in serum adiponectin concentrations (25) (26). Leptin working through the receptors on the theca and granulosa cells obstacles steroidogenesis in the

ovaries (26). less adiponectin concentrations are correlated with increased serum insulin which can result in hyperandrogenaemia in part by blocking the sex hormone binding globulin (SHBG) synthesis and secretion (25). Moreover, insulin functioning through insulin like growth factor 1 (IGF1) promotes luteinizing hormone (LH) mediated steroidogenesis in the theca cell compartment of the ovary and thus increases ovarian androgens, especially testosterone (26). Hyperandrogenaemia leads to granulosa cell apoptosis while peripheral conversion of androgens to estrogen in adipose tissue blocks gonadotrophin release(25).

Measurement of waist circumference (WC) is an easy method to estimate body fat distribution (5). Polycystic ovary syndrome (PCOS) are diagnosed with increased waist circumference (WC) (22). Highly considerable relationship was between the occurrence of polycystic ovary syndrome (PCOS) and high waist and hip circumferences (22). Waist circumference (WC) alone is proposed as being a more practical measuring procedure of intra-abdominal fat mass and total body fat (4). Some studies demonstrated that waist circumference (WC) was more closely linked to the level of abdominal visceral adipose tissue than to waist to hip ratio (WHR) (4).

Waist to hip ratio (WHR) is an acceptable feature of identifying patients with excess abdominal fat accumulation (4). Anatomic distribution of body fat has a main effect on associated health hazards. Excess fat accumulated in the central abdominal region is called android "apple shaped", or upper body obesity, and is attributed to greater risk of insulin resistance (3). On the contrary, fat distributed in the lower extremities around the hips or gluteal region is identified as gynoid, pear-shaped, or lower body obesity (3). The pear shape is somewhat benign health-wise, and is ordinarily present in females (3). Of the three measurements [body mass index (BMI), waist circumference (WC), and waist to hip ratio (WHR)], only waist to hip ratio (WHR) is combined to the differences in body structure (27). Fat cells in the abdomen are much larger and have a higher rate of fat turnover than lower body adipose cells. The abdominal adipocytes are hormonally more responding than adipose cells in the buttocks and legs. Substances secreted from abdominal adipose tissue are absorbed via the portal vein and, thus, directly accessed to the liver. Fatty acids (FAs) taken up by the liver can result in insulin resistance. On the contrary, free fatty acids (FFAs) from gluteal adipose tissue enter general blood circulation, and do not have preferable work on hepatic metabolism (3). Increased waist size i.e., apple shaped adiposity resulted from accumulated fat in the abdomen leads to more metabolic disruption than the hips or thighs fat accumulation i.e., pear shape adiposity (28). Therefore, patients

with metabolic syndrome and infertility have increased waist to hip ratio (WHR) (28). A study showed both lean and obese polycystic ovarian syndrome females were characterized with increased waist to hip ratio (WHR) and decreased insulin sensitivity in comparison with their non-hyperandrogenic counterparts (2). Obesity is recognized in about 60% of polycystic ovarian syndrome women, mainly visceral or abdominal adiposity are noted, with an increase of the waist to hip ratio (WHR) (20). Females with polycystic ovary syndrome (PCOS) frequently have central obesity (visceral adiposity), and therefore are characterized by having increased waist to hip ratio (WHR) (20). Android obesity is prevalent in about 52%-64% of polycystic ovarian syndrome females and is correlated with metabolic abnormalities such as insulin resistance (23). About 30% of normal weight polycystic ovarian syndrome women suffer from abdominal adiposity(23). Android obesity is present in around 52% to 64% of polycystic ovary syndrome (PCOS) women and is independently associated with metabolic abnormalities such as insulin resistance which have a strong association with chronic inflammation (8).

Insulin resistance induces the differentiation of pre-adipocytes to adipocytes, especially in the abdominal region, facilitating the development of visceral-type obesity in polycystic ovarian syndrome females(5). Abdominal adiposity frequently found in non-obese polycystic ovary syndrome (PCOS) females is an indicating feature of insulin resistance (5). Obesity, and especially visceral or abdominal obesity, is very common among polycystic ovary syndrome (PCOS) women, with the prevalence percentages ranging from 38% to 88%. It has been supposed that androgen, particularly testosterone, stimulate the differentiation of pre-adipocyte to adipocytes, majorly in the abdominal state, facilitating the development of central adiposity (12). Fat tissue is a dynamic organ, releasing hormones, adipokines, and interleukins, and taking part in endocrine processes that regulate inflammatory response, immunity, and reproduction among other important functions (5). High body weight considerably influences blood concentrations of total testosterone and sex hormone binding globulin (SHBG) (1). Hyperandrogenaemia is able to cause obesity (29). Hyperandrogenism favors a central/abdominal distribution type of body fat and principal contributor to the progress of systemic insulin resistance (29). Adipose tissue secretes more than 50 interleukins and exhibit effect on pro-inflammatory or anti-inflammatory functions (5). Obesity is known as a hallmark reason for high risk of infertility, almost through ovulatory dysfunction(30).

Excess body fat can lead to inflammatory response (31). Abdominal fat is more probably result in inflammation (31). Visceral or abdominal obesity is linked to a low-grade inflammatory condition, propagated by metabolic surplus where specialized metabolic cells such as adipocytes stimulate cellular stress initiating and boosting the inflammatory situation (6). Adipose tissue dysfunction is regarded as a specific component of obesity-related inflammatory response and the principal instigator of the pathological consequences of obesity, frequently via insulin resistance correlation (6). Abdominal or central obesity is the major component of the metabolic syndrome, which involves insulin resistance (6). High fat mass is accompanied by less insulin sensitivity and pro-inflammatory marker become increased (6). A study demonstrated that like obese women, lean ones with polycystic ovary syndrome (PCOS) exhibit increased reactive oxygen species (ROS) generation compared with lean controls (5). Reactive oxygen species-induced (ROS-induced) oxidative stress (OS) is a known activator of nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B), inducing inflammatory responses (5). Polycystic ovary syndrome (PCOS) is associated with chronic low-grade inflammation as demonstrated by elevated circulating inflammatory agents (32). Obesity and hyperandrogenism stimulate chronic low-grade inflammation in polycystic ovarian syndrome women (32). It is acceptable to propose that monocytes (MNC) recruited into the polycystic ovaries lead to a local inflammatory response that stimulates cytochrome P450 family 17 (CYP17), the ovarian steroidogenic enzyme, responsible for androgen synthesis (5). Inflammatory response and oxidative stress (OS) look to contribute to hyperandrogenemia in polycystic ovary disease (PCOD) (29). Inflammatory reaction can be able to directly stimulate hyperandrogenism in polycystic ovary disease (PCOD) (8). It is found that the adipose tissue of polycystic ovarian syndrome women has an aberrant morphology and action (33). Adipocytes, particularly from polycystic ovarian syndrome women are hypertrophic and there is an impaired function of the sympathetic nervous system in their abdominal fat (33). Change in morphology and function of the adipose tissue leads to reduced adipose tissue vascularization and a consequent hypoxia that stimulates a local low grade inflammation with an elevated secretion of interleukins, chemokines, adipokines, free fatty acid (FFA), leptin, resistin, and visfatin, and a decreased synthesis of adiponectin (33). This chronic low-grade inflammatory condition is correlated with the development of local and systemic insulin resistance (33). Androgens, especially testosterone, induce the hypertrophy of adipocytes, by affecting the expression of proteins and enzymes included in carbohydrate and lipid metabolism, in oxidative stress (OS) and in the conversion

of pre-adipocytes to mature adipocytes, i.e. fat cells (34). Besides, androgens increase lipolysis leading to an increased secretion of free fatty acids (FFA) (35). Oxidative stress (OS) in polycystic ovarian syndrome women may take part in systemic inflammation and together with insulin resistance and consequent hyperinsulinaemia stimulate ovarian thecal system dysregulation and dysfunction of endothelial cells, causing hyperandrogenism and anovulation (33). Hypertrophy of adipose cells can lead to compression phenomena in the stromal blood vessels, thus causing adipose tissue hypoperfusion and, as a result, hypoxia incident. In addition, the hypertension which is repeatedly linked to the polycystic ovary disease results in peripheral vasoconstriction attributed to increased release of angiotensin II, which further adversely impact perfusion of the adipose tissue. Hypoxia of adipose tissue induces the activation of intracellular nuclear factor-kappa B (NF- κ B), which migrates into the nucleus. Nuclear factor-kappa B (NF- κ B) is a transcription factor that plays a primary role in regulating immunity stimulating the synthesis and secretion of factors which are included in the process of inflammation, such as tumor necrosis factor-alpha (TNF- α), transforming growth factor-beta (TGF- β) and interferon gamma (IFN- γ), interleukins [such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and interleukin-10 (IL-10)], factors of the complement cascade and monocyte chemoattractant protein-1 (MCP-1). This leads to the recruitment of macrophages into the adipose tissue, which keeps the inflammatory condition, deteriorates adipocyte function and finally causes cellular necrosis, more deteriorating the inflammation and resulting the setting up of a vicious cycle (12). Interleukin-1 β (IL-1 β) is an important mediator of the inflammatory response and is included in cell proliferation, differentiation and apoptosis (12). Systemic inflammation is frequent to polycystic ovarian syndrome women and, thus, a rise in the levels of pro-inflammatory mediators in follicular fluid can be expected (36). Respective imbalance might result in folliculogenesis defects commonly seen in women with polycystic ovary disease (PCOD) (36). There were significant overproduction in inflammatory mediators in polycystic ovarian syndrome women (30).

The pro-inflammatory state of obesity contributes to the stimulation of insulin resistance and atherogenesis when found in polycystic ovary disease (PCOD) (23). Hypoxia-related adipocyte death in response to adipose tissue expansion induces an influx of monocytes (MNC) into the stromal-vascular system. Monocytes (MNC) change morphologically to become resident macrophages. Monocyte-derived macrophages induce interleukin synthesis in adipocytes through paracrine mechanics (23). There is inflammatory cell recruitment to adipose tissue of obese patients where

macrophages surround dead adipocytes, for each dead adipocyte, several macrophages are recruited, implying a large amplification of the inflammatory immune response, since macrophages are thought to locally synthesize and secrete inflammatory agents. In addition, it is supposed that abdominal adipose tissue growth is mainly due to hypertrophy, while in other locations there may be majorly growth through hyperplasia (6). Most of the inflammatory interleukin synthesis from the adipose tissue of obese subjects is related to inflammatory cells rather than to adipocytes (6). Polycystic ovarian syndrome women experience a low-grade chronic inflammation reflected by minor but significant increase in circulating levels of pro-inflammatory and anti-inflammatory factors (5). Inflammatory interleukins act through paracrine and autocrine mechanisms to stimulate insulin resistance (2). Hyperandrogenism in polycystic ovary syndrome (PCOS) exhibits an anti-inflammatory influence when obesity is found, but does not stimulate inflammation in the disease (23). Androgens have a pleiotropic impact on inflammation dependent on the combination of polycystic ovary disease (PCOD) and weight status found in a given subject (23). Systemic inflammation is common to polycystic ovarian syndrome females (36). Depending on this, a rise in the concentrations of pro-inflammatory agents in follicular fluid can be supposed (37). Pro-inflammatory state is correlated with obesity (6). Regarding pro-inflammatory interleukins, abdominal adipose tissue is related with higher while producing lower amounts of the anti-inflammatory which relates more effectively with subcutaneous fat(6). Circulating interleukins levels are altered in females with polycystic ovary disease (PCOD) (11).

Adipose tissue releases inflammatory interleukins (2). Interleukin-1 β (IL-1 β) and interleukin-17 (IL-17) are produced by adipocytes and macrophages or vascular endothelial cells (5). Interleukin-1 β (IL-1 β) and interleukin-17 (IL-17) have an important role in immunity and lead to insulin signaling (5). A study recognized that interleukin-1 β (IL-1 β) concentrations were high in obese polycystic ovarian syndrome women compared to obese control group (38). Interleukin-1 β (IL-1 β) stimulates T helper 17 (Th17) cell differentiation (39). Interleukin-17 (IL-17) stimulates the synthesis of interleukin-1 β (IL-1 β) (30). Interleukin-17 (IL-17) promotes pro-inflammatory immunity (14). Dysregulated interleukin-17 (IL-17) synthesis can lead to excessive pro-inflammatory interleukin expression and chronic inflammatory immunity (14). Interleukin-27 (IL-27) is synthesized and secreted by antigen presenting cells (APCs) such as macrophages and dendritic cells. Interleukin-27 (IL-27) directly blocks T helper 17 (Th17) cells by hindering interleukin-6 (IL-6) signaling. Interleukin-27 (IL-27) stimulates interleukin-10 (IL-10)

producing type 1 regulatory T cells which in turn suppresses T helper 17 (Th17) cells (my dissert). Interleukin-27 (IL-27) signaling stimulates immunosuppressive dendritic cells to express high concentrations of CD39, which in turn stimulates the differentiation of T regulatory (Treg) cells (40). Interleukin-27 (IL-27) stimulates interleukin-35 (IL-35) synthesis and release (30). Interleukin-35 (IL-35) suppresses the differentiation of T helper 17 (Th17) cells (39).

In a study significant aberration were found in mean concentrations of interleukin-1 β (IL-1 β), interleukin-17 (IL-17), interleukin-27 (IL-27), and interleukin-35 (IL-35) and so led to infertility in polycystic ovarian syndrome patients (30). Altered interleukin profile concentration measurements might impact negatively ovulation, and endometrial preferable microenvironment during endometrial receptivity and thereby, hostile intrauterine environment obtained and thereby, negatively affected implantation (30)(41). Low and high levels are detrimental but an intermediate optimal levels of interleukins are required for successful embryo implantation (42). In polycystic ovary syndrome (PCOS) where low-grade chronic inflammation was documented some studies reported increased concentrations of circulating interleukins such as interleukin-1 β (IL-1 β) and interleukin-17 (IL-17) (38). A study documented that impaired interleukin-1 β (IL-1 β), interleukin-17 (IL-17), interleukin-27 (IL-27), and interleukin-35 (IL-35) played a principal role in the immunopathogenesis of polycystic ovary syndrome (PCOS) (8)(30).

• **Conclusions**

Type and amount of fat distribution significantly correlated with interleukins levels. Abdominal or visceral adiposity negatively impact interleukins concentrations. Abdominal adiposity altered viciously interleukins levels and consequently negatively influenced ovulation resulting in anovulation, deteriorating intrauterine environment and therefore adversely affected endometrial receptivity and embryo implantation, leading to infertility in polycystic ovarian syndrome women.

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