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Association of Bcl-2 Associated X Protein (Bax) with Immunopathogenesis of Poly Cystic Ovarian Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common chronic endocrinopathies affecting women in the reproductive age group. Hirsutism, acne, abnormal menstrual regularity, or obesity are common presenting features in the perimenarcheal stage, Granulosa cells play important role in oocyte maturation, fertilization, and subsequent implantation. Bax was the first Bcl-2 homologue gene to be identified acting as an apoptosis executer. Much research revealed a key role of Bax in the syndrome pathogenesis. Decreased levels of Bax, which is a pro-apoptotic protein, might be involved in the pathogenesis of PCOS. The study aimed to evaluate Bax in serum and estimate its correlation with demographic characteristics. 130 women, 66 patients with PCOS, and 64 regarded as control had estimated their serum levels of Bax, the mean levels were 17.27 in patients and 18.64 in control. The Bax showed a positive association with the immunopathogenesis of PCOS.

Keywords

PCOS, Bax, Granulsa cells, Apoptosis, Infertility

The most common gynecological disorder in women of reproductive age is polycystic ovary syndrome (PCOS), which is marked by endocrine and metabolic abnormalities and chronic inflammation [31, 43]. The incidence of polycystic ovary syndrome (PCOS) can vary greatly due to both genetic and environmental factors [35]. It ranged between 8 to13% of women of reproductive age and 6 to18% of adolescent girls [6]. The primary clinical signs of PCOS are oligo/anovulation, irregular menstruation, obesity, and hyperinsulinemia/insulin resistance [13]. Family history of PCOS, fast food, poor diet choices, inactivity, and body mass index are the most frequent risk factors for the progression of PCOS [5]. Many metabolic and reproductive health issues, such as gestational diabetes, dyslipidemia, insulin resistance, miscarriage, prediabetes, type 2 diabetes, obesity, breast cancer, endometrial cancer, and others are more common in women with PCOS [18].

The Rotterdam criteria (2003) are used to diagnose the syndrome when at least 2 of the 3 defining characteristics are present and all other possible explanations have been excluded [19]. Menstrual cycles that are irregular or nonexistent; high levels of free circulating testosterone (T) or hirsutism [22]; and the presence of 12 or more small follicles between 2 and 9 mm in diameter in both ovaries, as measured by ultrasonography [27]. Because of hereditary and environmental factors, the prevalence of PCOS can vary greatly. Having a lower socioeconomic status has been

linked to poorer health, which may be due to hormonal shifts or the activation of a genetic predisposition to the disease. Low rates of proper diagnosis and treatment are also associated with the inadequate healthcare conditions that exist today [35].

More than 80% of women with hyperandrogenism (hirsutism, acne, or alopecia) also have PCOS (Sanchez-Garrido and Tena-Sempere 2020). Clinically, hyperandrogenism in women with PCOS presents as hirsutism, acne, and androgenic alopecia, gaining weight, menstruation irregularities, acanthosis nigricans, and insulin resistance are also symptoms of androgen excess (Ashraf, Nabi, et al. 2019). Patients with PCOS have elevated insulin concentrations that lower SHBG levels in the serum, which increases the bioavailability of free testosterone. Additionally, these women have abnormal gonadotropin concentrations and high levels of androgen biosynthesis from the adrenal and ovaries, which is stimulated by elevated insulin levels (De Leo, Musacchio, et al. 2016).

Aim of the study

The aim of this study was planned to evaluate associations of apoptotic markers Bcl-2 associated X protein (BAX) with Pathogenesis of Polycystic Ovarian Syndrome (PCOS) in a group of Iraqi women, the following objectives have been achieved in this work:

1. Determination of demographic data in patients and control.
2. Determination of Bax serum levels by ELISA test.

History of the disease

In 1935, Stein-Leventhal syndrome, Stein and Leventhal published their account of seven women with amenorrhea, hirsutism, obesity, and enlarged polycystic-looking ovaries, coining the term"polycystic ovary syndrome."There has been a lot of research on this complicated disease since then [30]. The panel members took into account the many consensus statements produced by different studies over time, including those issued at"the National Institutes of Health (NIH) consensus conference in 1990, the Rotterdam conference in 2003, and the Androgen Excess Society statement in 2006". They also concluded that the root of PCOS is unclear and likely complex [49]. The Androgen Excess Society's 2006 commission on PCOS phenotypes, for example, singled out HA as central to the condition but ignored the IM/PCO subgroup. According to the American Endocrine Society (AES), the presence of either anovulation or polycystic ovarian morphology is a necessary second condition for diagnosing PCOS [48].

Etiology of Polycystic Ovarian Syndrome

Insight into what causes polycystic ovary syndrome (PCOS) is still limited and so contested. The etiopathology of polycystic ovary syndrome (PCOS) is likely multifactorial, involving genetic, metabolic, environmental, and immunological variables. Although many genes have been identified as significant contributors to polycystic ovary syndrome (PCOS), no one gene or set of genes has been able to be directly linked to the development of the disorder [21, 29, 44]. To maintain follicular growth and oocyte maturation, granulosa cells (GCs) and oocytes rely on a coordinated metabolic mechanism to ensure a steady supply of glucose. Both FSH and LH promote glucose uptake by GCs and (oocyte-cumulus cell complexes) [9].

Inflammation

Chronic inflammation with high levels of leukocytes, pro-inflammatory cytokines, white blood cell count, and indicators such as C-reactive protein are characteristic of PCOS [39]. In addition, it's not just overweight women who have to worry about this syndrome; normal-weight (BMI) women can also suffer from this condition because of the effects of visceral adipose tissue [41]. Circulating adipose or intestinal monocytes produce pro and anti-inflammatory cytokines and lipopolysaccharide, which have direct effects on insulin resistance and steroidogenesis [20, 40].

Macrophages are"the most common immune cells in both the adipose tissue and the ovary"[25]. More recently, Fainaru et al. showed that dendritic cells (DCs) constitute an essential cellular component of the follicular fluid (FF) and that the maturation stage of these cells positively correlates with the ovarian response to gonadotropins [52]. Excessive inflammation has been associated with greater levels of androgen [37]. Presently, uterine NK cells are considered to be endometrial markers for PCOS [17]. T cells, of which the majority of lymphocytes are composed, have a variety of biological

tasks that are mostly related to the body's cellular immune response [33].

The Role of Bcl-2 associated X protein (BAX) in the Pathogenesis of PCOS

The Bcl-2 associated X protein (Bax) was the first Bcl-2 homologue gene to be identified acting as an"apoptosis executer"[16]. It is p53-dependently triggered by a variety of stimuli and plays important functions in cell survival by controlling the process of programmed cell death [23]. Immunohistochemistry has proven that granulosa cells in antral follicles are the primary location for Bcl-2 and BAX expression. Additionally, they hypothesized that these PCO follicles had higher BAX expression [11].

Patients and Methods

A case-control study included 130 Women, who attended an infertility center in Karbala gynecological and obstetric teaching hospital and a private gynecological clinic in karbala city, from September 2021 to June 2022 they were divided into two groups, the first group 66 patients with PCOS cause of infertility diagnosed"according to 2003 Rotterdam criteria, each patient had two or three of these criteria: (1. Oligo and/or anovulation, 2. Clinical and/or biochemical signs of hyperandrogenism, or 3. Polycystic ovaries presence of 12 or more follicles in each ovary measuring 2 ± 9 mm in diameter and/or increased ovarian volume in ultrasound)", Every female with autoimmune, inflammatory (such as inflammatory bowel disease) and infectious diseases were excluded from the study, the second group 64 women with no PCOS regarded as a control group.

Ethically all consents had been taken from the ethical committee of karbala college of medicine, the ethical Committee of karbala Health Department, and the director of Karbala gynecological and obstetric teaching hospital. In addition, verbal approval had been taken from patients and controls before sample collection. A 5ml blood sample had been collected to measure the serum level for the ELISA test to determine the concentration of Bax. Bax level measured according to manufacturer's instructions (BT LAB Bax ELISA kit). Data collected were statistically analyzed by SPSS statistical package for Social Sciences" (version 20.0 for windows, SPSS, Chicago, IL, USA)". P-value >0.05 is regarded as significant.

Results

The (mean±SD) age was (32.4±8.5) for patients with PCOS and (25.8±6.4) for control, The p=0.005 significance level indicates a substantial distinction between the patient and control groups. Married patients were 54 (81.8%) and unmarried patients were 12 (18.2%) while in the control group, married women was 60 (93.8%) while the unmarried women were 4 (6.2%) Patients with PCOS were significantly more likely to be unmarried than controls (P=0.038). Infertile patients 30 (45.5%) and fertile women with one child18 (27.3%), a fertile woman with two children was 10 (15.2%) and fertile women with more than two children reached 8 (12.1%), while the control group showed that infertile women 7 (10.9%) and the fertile women with one child was 6 (9.4%), the number of fertile women with two children reached 7 (10.9%) and the fertile women with more than two children were 44 (68.8%) A statistically significant difference (P=0.005) was found between PCOS patients and controls. Patients with PCOS with regular Menstruation was 11 (16.7%) and the patients with irregular menstruation were 55 (83.3%), Women with regular menstruation totaled 36 (56.2%) in the control group, while the number of women with irregular menstruation peaked at 28 (43.8%) Patient with PCOS differed significantly from controls (P=0.005). 37 patients had hirsutism (56.1%), while 29 did not (43.9%). In the control group, 0 women had hirsutism (0.00%), while 64 did not (100%). A statistically significant distinction (P=0.005) was found between PCOS patients and controls. 7 patients (10.6%) had a family history of PCOS, while 59 patients (89.5%) reported no such connection. Only four (6.2%) of the control group women had a family history of polycystic ovary syndrome, while sixty (93.8% of the group) did not. PCOS patients and controls did not differ significantly from one another (P= 0.531).

There was a significant relation between the groups studied and age, marital status, fertility, menstruation, and hirsutism, but the family history was not significant as shown in table (1).

Table 1 Demographic characteristics of the studied subjects

		Group				P value
		Patients		Control		
		Mean±SD		Mean±SD		
Age		32.4±8.5		25.8±6.4		0.005*
		Count	%	Count	%	
Marital status	Yes	54	81.8%	60	93.8%	0.038*
	No	12	18.2%	4	6.2%	
Fertility	None	30	45.5%	7	10.9%	0.005*
	One child	18	27.3%	6	9.4%	
	Two children	10	15.2%	7	10.9%	
	>2 children	8	12.1%	44	68.8%	
Menstruation	Regular	11	16.7%	36	56.2%	0.005*
	Irregular	55	83.3%	28	43.8%	
Hirsutism	Yes	37	56.1%	0	0.0%	0.005*
	No	29	43.9%	64	100.0%	
Family history	Yes	7	10.6%	4	6.2%	0.531
	No	59	89.4%	60	93.8%	

The (mean±SD) of Bax was found with a (mean±SD) value (17.27 ± 14.02), median (14.4), and IQR (8.7) in patients with PCOS. The control group was found with a (mean±SD) (18.64 ± 14.96) and the median was (17.6) while IQR was (8.2). there was a significant difference between patients and the control group (p=0.049*) as demonstrated in the table (2).

Table (2): Serum level of Bax comparison according to patients with PCOS and control subjects

	Group						P valve
	Patients			Control			
	Mean ± SD	Med	IQR	Mean ± SD	Med	IQR	
Bax ng/ml	17.27 ± 14.02	14.4	8.7	18.64 ± 14.96	17.6	8.2	0.049*

All of the characteristics had no significant difference on Bax (P>0.05). Means, SD, Median, and IQR were summarized in table (3).

Table (3): Serum level of Bax comparison according to different patients' characteristics

Bax ng/ml		Mean±SD	Median	IQR	P value
Marital	Yes	17.94±7.79	17.94	7.79	0.606
	No	16.40±7.42	16.40	7.42	
Fertility	None	15.96±7.53	15.96	7.53	0.147
	One child	21.11±14.01	21.11	14.01	
	Two children	17.59±4.86	17.59	4.86	
	>2 children	19.81±3.73	19.81	3.73	
Menstruation	Regular	16.36±9.28	16.36	9.28	0.612
	Irregular	17.72±8.54	17.72	8.54	
Hirsutism	Yes	17.42±8.54	17.42	8.54	0.993
	No	17.74±6.64	17.74	6.64	
Family history	Yes	19.95±10.17	19.95	10.17	0.239
	No	17.53±9.92	17.53	9.92	

Discussion

The study estimated whether serum level of Bax was affected in women with PCOS, and whether this biomarker plays an important role in relation with demographic characteristics. The results obtained in the present study found that there was a significant difference in age between patients with PCOS and control, these finding consistent with Curtis and Karki [12], who concluded that there was a highly significant difference (P<0.001) in mean age between healthy individuals and patients with PCOS. Also, the results of a study by Hong [24], women with PCOS and control, the women with PCOS were younger than the control group. In the study of Tabassum [47], as in the present study, there was a significant difference between PCOS group and control group according to marital status. Moreover, similar results were found in the study by Shahrokhi and Naeini [45], PCOS cases and healthy control, results showed a significant difference between the two groups in terms of marital status.

PCOS women are at increased risk for infertility owing primarily to anovulation [32]. The prevalence of infertility in PCOS women varies between 70 and 80% [34]. In this community-based cohort of women, infertility and the use of fertility hormone treatment were significantly higher in women reporting PCOS [26]. According to the current study's findings, PCOS patients have higher levels of primary

infertility than the control group, which is consistent with other observation performed previously [1]. Moreover, in PCOS group, only few women were fertile (⩾ 1 children), while in the control group, more women were fertile (⩾ 1 children) [4].

A study by Nazeer and Lone [38], agreed with present study, ovaries with multiple cysts and irregular menstrual cycle were significantly higher in PCOS women than in non-PCOS women (P-value <0.05). Another study showed that the women with PCOS had significantly higher irregular menstruation ratio in comparison with the control group [7]. Women with PCOS had increased hirsutism scores compared to controls [28]. A study by Asdaq and Yasmin [2], showed Significantly high proportion of PCOS cases were found with hirsutism when compared to control group. Moreover, Chatterjee and Bandyopadhyay [10], showed that participants diagnosed with PCOS had hirsutism, whereas the occurrence of the same was much lower in the non-PCOS group. The present study showed no significant difference between PCOS patients and control according to family history. Another study showed that There was no significant difference in family history of PCOS among cases and controls [36].

The study showed that significantly increased in the level of Bax in women with PCOS, to our knowledge, no studies have been performed recently on the effects of Bax on apoptosis of ovarian cells in women with PCOS. Level of BAX proteins in goat ovaries showed that the relative expression of BAX was greater in atretic than in healthy follicles (p <0.05) [51]. The expressions of pro-apoptotic genes: including Bax were significantly reduced in PCOS women [14], which supports the current study results. The present study has found that Bax was not significantly different between all the studied characteristics of the patients with PCOS.

Conclusion

The study demonstrated Bax had a significant association with PCOS; All the characteristics had no significant difference in Bax (P>0.05).

Recommendations are Studying Bax in a larger sample size of patients with PCOS and studying the gene polymorphisms of Bax in women with PCOS.

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