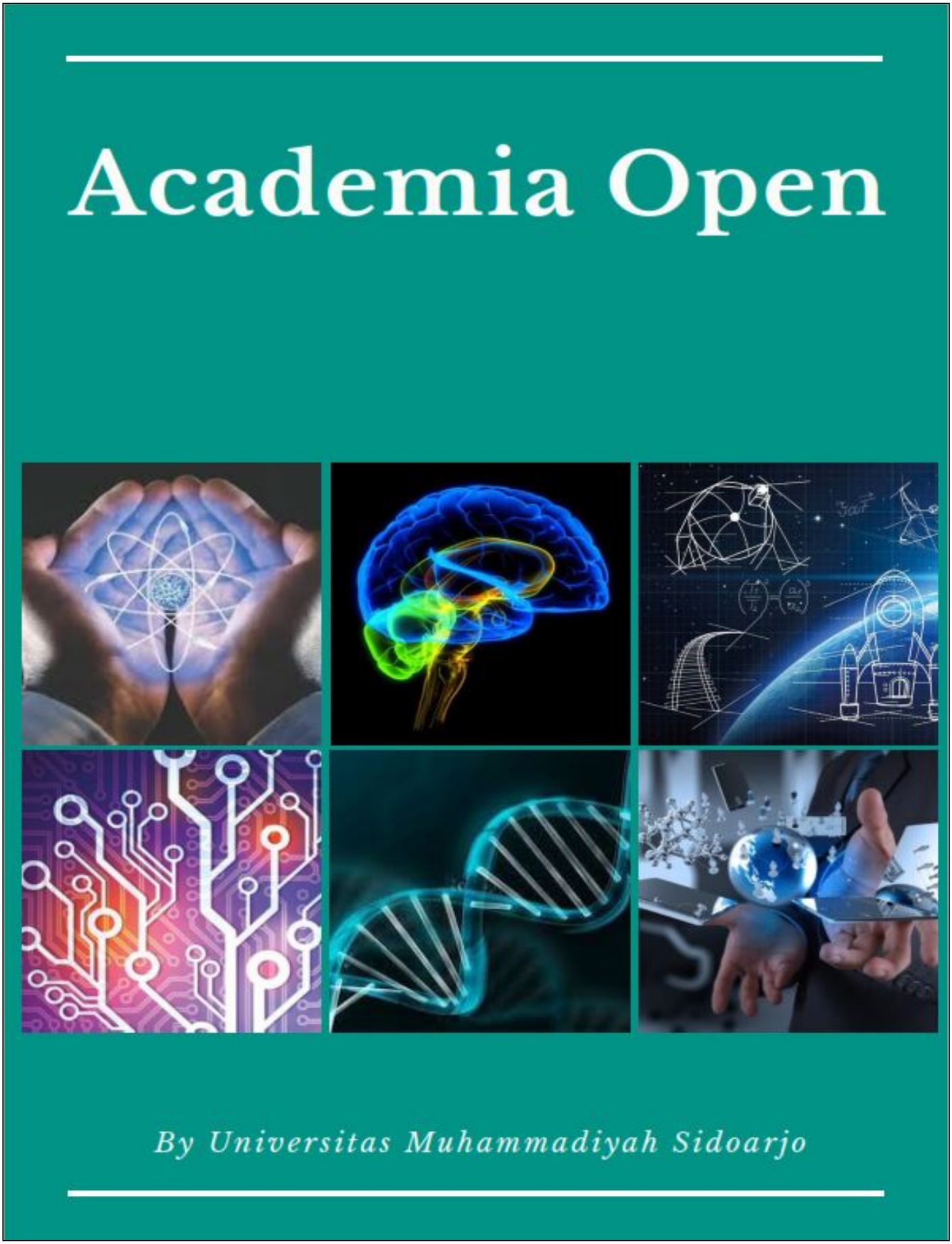
Academia Open
Vol 8 No 2 (2023): December
DOI: 10.21070/acopen.8.2023.7763 . Article type: (Clinical Research)

Table Of Content

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 8 No 2 (2023): December
DOI: 10.21070/acopen.8.2023.7763 . Article type: (Clinical Research)



ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 8 No 2 (2023): December
DOI: 10.21070/acopen.8.2023.7763 . Article type: (Clinical Research)

Originality Statement

The author[s] declare that this article is their own work and to the best of their knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the published of any other published materials, except where due acknowledgement is made in the article. Any contribution made to the research by others, with whom author[s] have work, is explicitly acknowledged in the article.

Conflict of Interest Statement

The author[s] declare that this article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright Statement

Academia Open
Vol 8 No 2 (2023): December
DOI: 10.21070/acopen.8.2023.7763 . Article type: (Clinical Research)

EDITORIAL TEAM

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 8 No 2 (2023): December
DOI: 10.21070/acopen.8.2023.7763 . Article type: (Clinical Research)

Article information

Check this article update (crossmark)

Check this article impact (*)

Save this article to Mendeley

(*) Time for indexing process is various, depends on indexing database platform

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 8 No 2 (2023): December
DOI: 10.21070/acopen.8.2023.7763 . Article type: (Clinical Research)

Evaluation of Serum Fetuin-A as A Possible Marker for Polycystic Ovarian Syndrome Among Iraqi Women; Case-control Study

Ola Jamal Yasien, olaalyosef@gmail.com, (1)
Department of Obstetrics and Gynecology, AL-Yarmouk Teaching Hospital, Baghdad, Iraq

Fadia J. Al Izzi, fadiajalizzi@gmail.com, (0)
College of Medicine/Al-Mustansiriya University, Al-Yarmouk Teaching Hospital, Baghdad, Iraq

(1) Corresponding author

Abstract

Elevated levels of Fetuin-A, a protease inhibitor belonging to the cystatin family, have raised questions about its role in the pathogenesis of Polycystic Ovarian Syndrome (PCOS), the most prevalent endocrinopathy in reproductive-aged females. This case-control study, conducted in Iraq, aimed to assess changes in Fetuin-A levels among Iraqi women with PCOS. A convenient sample of 90 women, comprising 45 PCOS cases and 45 healthy controls, was enrolled. Fetuin-A levels were measured and found to be significantly higher in the PCOS group compared to controls. Additionally, significant positive correlations were observed between Fetuin-A levels and fasting plasma glucose, fasting serum insulin, insulin resistance, luteinizing hormone, and serum testosterone. Using a receiver operating characteristic curve, a cutoff point of 502.00 ng/mL was determined for predicting positive Fetuin-A levels, with a sensitivity and specificity of 84.4% and 73.3%, respectively. This study suggests that Fetuin-A could serve as a valuable marker for both screening and evaluating PCOS and its potential late consequences, including metabolic syndrome.

Highlights:

- **Elevated Fetuin-A Levels**: This study reveals significantly higher Fetuin-A levels in PCOS, shedding light on its potential role in the pathogenesis of the syndrome.
- **Correlations with Metabolic Factors**: Positive correlations between Fetuin-A and key metabolic markers like fasting glucose, insulin resistance, and luteinizing hormone highlight its relevance in the context of PCOS and metabolic health.
- **Screening Potential**: The identified cutoff point for predicting positive Fetuin-A levels offers a promising tool for screening and evaluating PCOS and associated late consequences, particularly metabolic syndrome.

Published date: 2023-08-31 00:00:00

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 8 No 2 (2023): December
DOI: 10.21070/acopen.8.2023.7763 . Article type: (Clinical Research)

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous collection of signs and symptoms that gathered together to form a spectrum of a disorder with a mild presentation in some, while in others a severe disturbance of reproductive, endocrine and metabolic function[1][2]

The exact cause of PCOS is unknown. However, it is understood to be a multifactorial condition with a genetic component[3]. Several environmental determinants of the prevalence and presentation of PCOS, including (e.g., socioeconomic, geographic, toxicologic, lifestyle, and dietary[4]. Other possible predisposing factors for PCOS include high maternal androgen, premature adrenarche, endocrinal factors (onset of type 1 diabetes mellitus before menarche, insulin resistance and obesity, and drugs such as anti-epileptic drugs (e.g., Valproate)[5]:

There has been no consensus on the absolute defining features of PCOS, Three scientific associations have published diagnostic criteria for PCOS including the National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD), European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM), and the Androgen Excess and PCOS Society (Table 1)[6].

Associations	Definition
NIH/NICHD, 1992	Includes all of the following:Clinical and/or biochemical hyperandrogenism.Menstrual dysfunction
ESHRE/ASRM, 2004(Rotterdam Criteria)	Includes two of the followingClinical and/or biochemical hyperandrogenismOligo- and/or anovulationPolycystic ovaries
Androgen Excess Society, 2006	Includes two of the followingClinical and/or biochemical hyperandrogenismOvarian dysfunction.Polycystic ovaries

Table 1. *Criteria for the diagnosis of polycystic ovary syndrome[6]*

The hallmark of PCOS is the presence of increased circulating luteinizing hormone (LH) levels compared to increased follicular stimulating hormone (FSH) (increased LH: FSH ratios), elevated LH pulse frequency and/or amplitude, as well as relatively decreased FSH levels[7].

The main clinical features of PCOS include hyperandrogenism (hirsutism, acne alopecia – not virilization), menstrual disturbance, infertility, and obesity, with Possible late sequelae including diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease[2]

The approach to the evaluation of the patient with signs and symptoms suggestive of PCOS begins with a thorough history, including detailed family history and a complete physical examination, and laboratory investigations[8]. All diagnostic criteria specify that diagnosis of PCOS should only be made after the exclusion of other endocrine disorders including congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, thyroid dysfunction, and hyperprolactinemia[9].

Fetuin derived its name from 'fetus' to reflect the observation that fetal serum contained the highest concentration of this protein. Fetuin was renamed 'fetuin-A' upon the discovery of a fetuin-like molecule termed 'fetuin-B'. Human Fetuin A is also known as α2-Heremans-Schmid glycoprotein[10]. Fetuin-A is a member of the protease inhibitors cystatin superfamily, which refers to a major serum glycoprotein mainly secreted by liver tissue[11][12]. After secretion from the liver, it reversibly binds the insulin receptor tyrosine kinase in peripheral tissues, thereby inhibiting the insulin-induced intracellular signal cascade and producing peripheral insulin resistance[13]. Considering this, elevated levels of fetuin-A and subsequently insulin resistance may play important roles in the development of PCOS[14].

Aim of the study

To evaluate the changes in Fetuin-A levels in polycystic ovarian syndrome among a sample of Iraqi women.

Method

An analytic case-control study was conducted in Iraq, Baghdad, Al-Yarmouk Teaching Hospital, Department of Gynecology and Obstetrics during the period from 1st of January to 1st of October 2021. A convenient sample of 90 women was enrolled in the current study and consisted of two groups:

Group A (cases group): Consist of 45 women with PCOS. The diagnosis of PCOS was done depending on Rotterdam criteria[15]. All PCOS patients were newly diagnosed without lifestyle intervention or any medication.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 8 No 2 (2023): December
DOI: 10.21070/acopen.8.2023.7763 . Article type: (Clinical Research)

Group B (control group): This consisted of 45 normal women without PCOS who attend the gynaecological outpatient Clinics and obstetric Department for medical treatment or just for routine checking.

Exclusion criteria included diabetes mellitus, chronic liver disease, thyroid disease, hypertension or coronary artery disease, chronic kidney disease, endocrine diseases (Cushing syndrome, androgen-secreting adrenal tumor and pituitary tumour, late-onset congenital adrenal hyperplasia, and hyperprolactinemia), and patient who present in acute infection condition.

Measurements of serum Fetuin-a, sex hormone, and biochemical parameters (LH. FSH, serum testosterone, prolactin, Fasting serum insulin (FSI), and fasting plasma glucose (FPG) were measured

Insulin resistance using the homeostasis model (HOMA-IR) to measure insulin resistance, it is calculated using the formula with a normal value < 2.77[16]:

[FSI (μU/mL) × FPG (mmol/L)]/22.5.

The entry and analysis of data were done by Statistical Package of social science, version 22. The descriptive analysis focused on frequencies and percentages. Continuous variables were presented as mean ± Standard Deviation (SD) and were compared using the Mann–Whitney U test, Pearson's correlation coefficient test was used to calculate the correlation between the continuous variables. The chi-square test was used for the difference in the proportions between the study groups. A P-value of ≤ 0.05 was considered statistically significant.

Results and Discussion

Results

The mean age was 28.07 (±4.390) years. The mean age in the PCOS group was 27.18 (±3.8) years, while it was 28.96 (±4.7) years in the control group. There was no significant difference in age and The mean body mass index (BMI) between the study groups with a P-value of 0.057 and 0.071, respectively, as shown in table 2.

Variables	Groups		P-value
	PCOS groupMean (±SD)	Control groupMean (±SD)	
Age (years)	27.18 (±3.8)	28.96 (±4.7)	0.057
BMI (kg/m2)	26.82 (±3.7)	25.46 (±3.2)	0.071

Table 2. *Distribution of the age and BMI according to age group*

**Mann-Whitney U Test significant at P-value<0.05*

The level of Fetuin-A was significantly higher in the PCOS groups than in the control group. There was a significant difference between the study groups regarding LH and serum testosterone levels, while the FSH was insignificantly different between the two groups. A significant difference was obtained between the study groups regarding FPG, FSI, and insulin resistance, as shown in table 3.

Variables	Groups		P-value
	PCOS groupMean (±SD)	Control groupMean (±SD)	
Fetuin-A (ng/mL)	571.57 (68.2)	479.84 (27.2)	<0.001*
LH (IU/L)	14.73 (±2.2)	3.02 (±0.8)	<0.001*
FSH (IU/L)	6.90 (±0.5)	7.09 (±1.4)	0.412
Serum testosterone (ng/ml)	0.97 (±0.2)	0.31 (±0.1)	<0.001*
FPG (mmole/L)	5.18 (1.35)	4.28 (0.12)	<0.001*
FSI (mIU/mL)	24.71 (3.25)	9.82 (1.36)	<0.001*
Insulin resistance	5.69 (1.67)	1.87 (0.27)	<0.001*

Table 3. *Distribution of LH, FSH and serum testosterone according to the study groups*

**Mann-Whitney U Test significant at P-value<0.05*

There was a significant positive correlation between the fetuin-A level and LH, serum testosterone, FPG, FSI, and insulin resistance while there was an insignificant negative correlation between the fetuin-A level and FSH. The correlation between fetuin-A and BMI was not significant, as shown in table 4.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 8 No 2 (2023): December
DOI: 10.21070/acopen.8.2023.7763 . Article type: (Clinical Research)

Variables	N	Fetuin-A	
		Pearson Correlation	P-value
BMI (kg/m2)	90	0.019	0.862
LH (IU/L)	90	0.638*	<0.001
FSH (IU/L)	90	-0.022	0.838
Serum testesteron (ng/ml)	90	0.569*	<0.001
FPG (mmole/L)	90	0.750*	<0.001
FSI (mIU/mL)	90	0.701*	<0.001
Insulin resistance	90	0.865*	<0.001

Table 4. *Correlation between fetuin-A level and FPG, FSI, insulin resistance*

** Correlation is significant at the 0.01 level*

According to the receiver operating characteristic (ROC) curve, the cutoff point of 502.000 ng/mL was selected, as shown in figure 1.

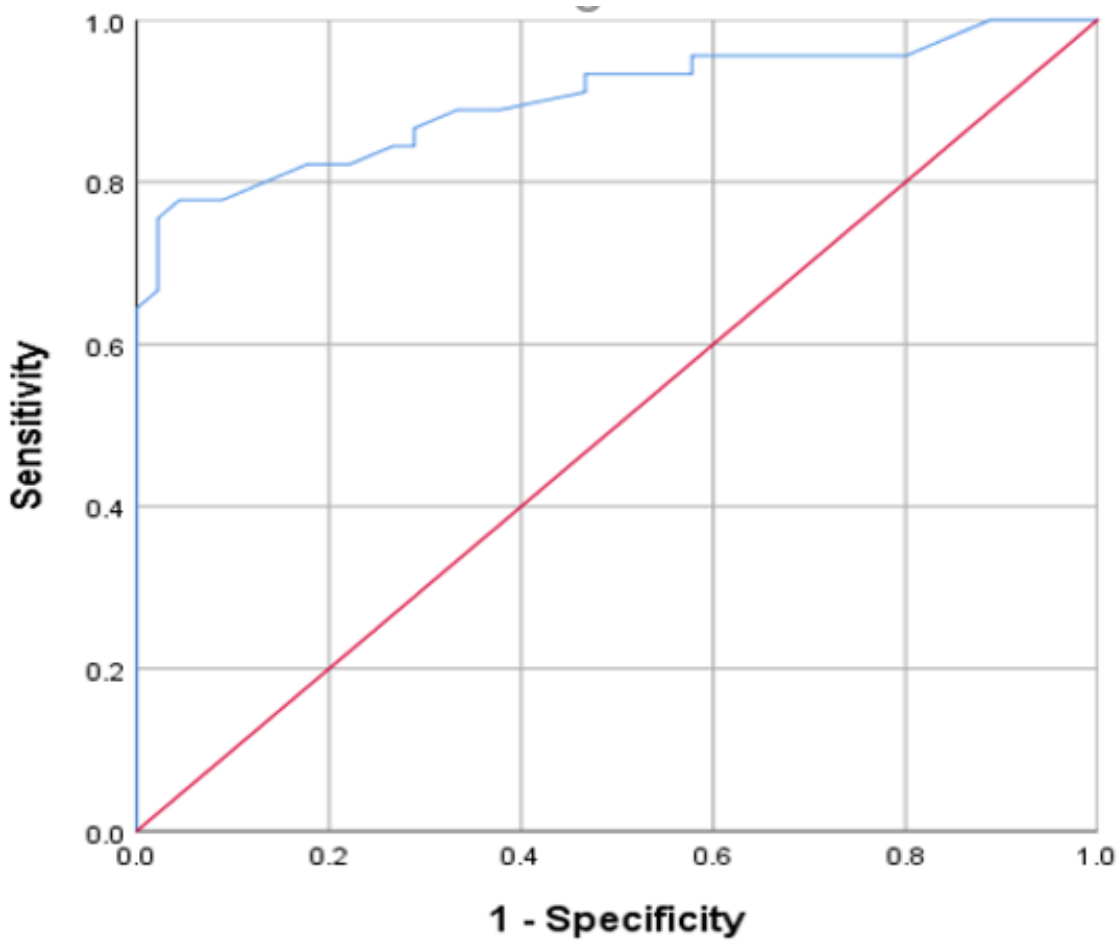


Figure 1. *Cut-off point of Fetuin-A level according to ROC curve*

According to the cut-off point of 502.00 ng/mL, 55.5% of the participants had positive Fetuin-A results, as shown in figure 2.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 8 No 2 (2023): December
DOI: 10.21070/acopen.8.2023.7763 . Article type: (Clinical Research)

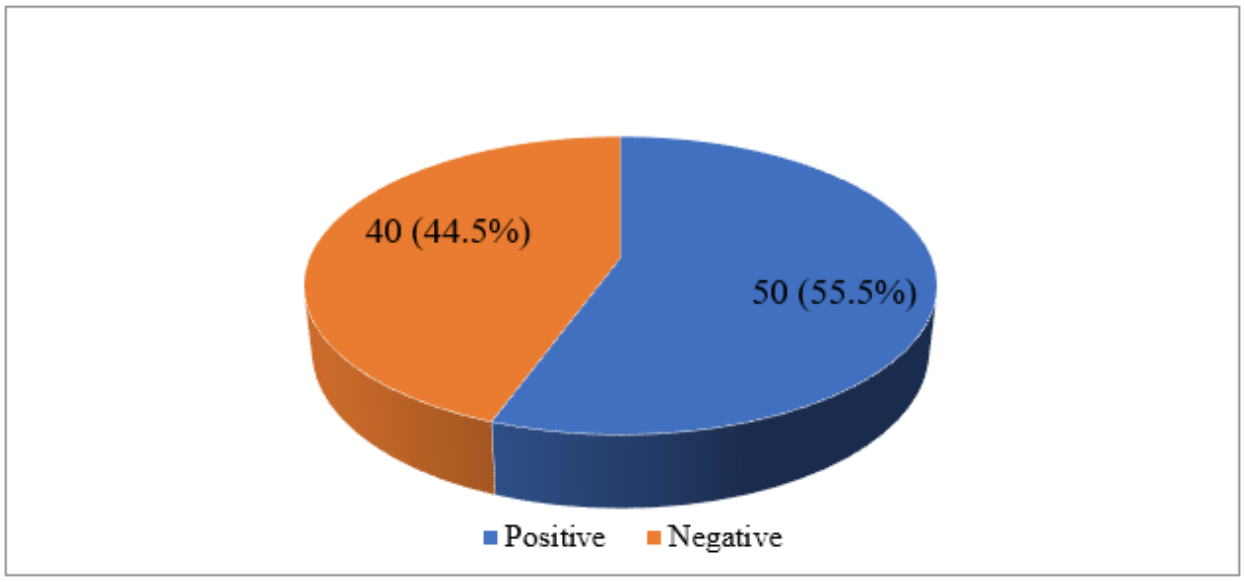


Figure 2. *Results of fetuin-A*

There was a significant difference in the Fetuin-A results between the study groups. The sensitivity (SN), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) were 84.4%, 73.3%, 76%, and 82.5% respectively, as shown in table 5.

Fetuin-A	Control group	PCOS group	Total	P-value
Positive(≥502. 000 ng/mL)	12 (24.0)	38 (76.0)	50 (100.0)	<0.001
Negative (<502. 000 ng/mL)	33 (82.5)	7 (17.5)	40 (100.0)	
Total	45 (50.0)	45 (50.0)	90 (100.0)	

Table 5. *Distribution of Fetuin-A according to the study groups*

SN=84.4%, specificity=73.3%, PPV=76%, NPV=82.5%

Discussion

In the past decade, several population-based studies reported the relationship between circulating fetuin-A concentrations and PCOS. However, the conclusions of these studies were contradictory. In these studies, circulating Fetuin-A levels were increased or unchanged in PCOS patients compared with healthy women[17]. Best to our knowledge, this was the first study in Iraq to evaluate the association between fetuin-A and PCOS.

In the current study, there was a significant difference between the study groups regarding the mean BMI as the mean was higher in the PCOS group than the control group, the same finding was obtained by another study that was done by Bayramoğlu et al in Turkey[18].

The LH and serum testosterone were significantly higher in the PCOS, while the FSH was significantly lower in the PCOS group. This result agreed with the results of another study that was done in Egypt by Elsirgany et al and revealed that the LH and serum testosterone were significantly increased in the PCOS group, while the FSH was significantly decreased in the PCOS group[19]. In another study that was done in India, Malini et al agreed with the results of the current study as they revealed a significant increase of LH, and serum testosterone among PCOS women compared to healthy women and disagreed regarding the FSH as they revealed a significant increase of FSH among PCOS women compared to healthy women[20].

The fasting plasma glucose, fasting insulin, and HOMA-IR were significantly higher in the PCOS group than in the control group. The same findings were obtained by other studies, in Suadi Arabia by Kensara et al[21], In Iran by Rashidi et al[22], and in Egypt, by Halawa et al revealed that the fasting insulin and HOMA-IR were significantly higher in the PCOS group than in the control group[23].

The main finding of the current study was a significant increase in the fetuin-A level among women with PCOS compared to normal women. In comparison, other studies revealed a similar result. In Finland, by Sha Liu et al[17].

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

In Turkey by Bayramoğlu et al[18] and Libya by Aghilla et al[24], all revealed that Fetuin-A levels were significantly higher in PCOS patients than in the control group.

In contrast, other studies disagreed with the current study, a study was done in Turkey, in 2012 by Gulhan et al revealed that there was no difference between women with PCOS and normal women concerning Fetuin-A[25], this corresponding to the results of another study that was also in Turkey by Gurbuz, 2021[26].

The discrepancy may be related to individual factors that affect the level of fetuin-A, sampling method, sample size, the accuracy of laboratory tests and ethnicity.

According to the ROC curve analysis, the fetuin-A value of 502.00 ng/mL was selected as a cut-off point for positive results. According to this cut-off point, the Sensitivity and specificity were 84.4% and 73.3%, respectively.

Liu et al study in china find that the cut-off point was 366.3 µg/L with sensitivity and specificity of 69.7% and 83.5% respectively[17]. In another study that was done by ElSirgany et al in Egypt, The fetuin-A cut-off point was 515 ng/ml, with a sensitivity of 100% and specificity of 45 %, respectively[19].

The current study revealed an insignificant correlation between fetuin-A and BMI in contrast to another study that was done by Sha Liu et al which revealed that the serum fetuin-A was positively correlated with BMI[17].

The last finding of the current study revealed a significant positive correlation between serum Fetuin-A and LH, serum testosterone, FPG, FSI, and insulin resistance. These results agreed with Liu et al results which found that serum fetuin-A was positively correlated with LH, serum testosterone, and HOMA-IR and concluded that circulating fetuin-A levels were associated with insulin resistance and hyperandrogenism[17]. Enali et al concluded that serum fetuin-A level was related to insulin resistance and ovarian hyperandrogenism in women with PCOS and these results suggest that fetuin-A might have a role in triggering the processes leading to insulin resistance and androgen excess in PCOS[27].

Conclusions

Fetuin-A was significantly higher in the PCOS group than in the control group. With a cut-off point of 502.00 ng/mL. There was a positive correlation between fetuin-A and LH, serum testosterone, FPG, FSI, and IR.

References

1. S. Arentz, J. A. Abbott, C. A. Smith, dan A. Bensoussan, "Herbal medicine for the management of polycystic ovary syndrome (PCOS) and associated oligo/amenorrhoea and hyperandrogenism; a review of the laboratory evidence for effects with corroborative clinical findings," BMC complementary and alternative medicine, vol. 14, no. 1, pp. 1-19, 2014.
2. K. Edmonds, C. Lees, dan T. Bourne, Dewhurst's Textbook of Obstetrics & Gynaecology, 9th ed., Wiley, 2018.
3. C. C. Dennett dan J. Simon, "The role of polycystic ovary syndrome in reproductive and metabolic health: overview and approaches for treatment," Diabetes Spectrum, vol. 28, no. 2, pp. 116-120, 2015.
4. R. Azziz, "Introduction: Determinants of polycystic ovary syndrome," Fertility and Sterility, vol. 106, no. 1, pp. 4-5, 2016.
5. M. T. Dattani dan C. G. D. Brook, Brook's Clinical Pediatric Endocrinology, 7th ed., John Wiley & Sons, 2019.
6. R. D. Nadaraja, M. Pavai Sthaneshwar, dan M. B. Nuguelis Razali, "Establishing the cut off values of androgen markers in the assessment of polycystic ovarian syndrome," The Malaysian journal of pathology, vol. 40, no. 1, pp. 33-39, 2018.
7. L. Ibáñez et al., "An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence," Hormone Research in Paediatrics, pp. 371-395, 2017.
8. S. F. Witchel, S. E. Oberfield, dan A. S. Peña, "Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls," Journal of the Endocrine Society, vol. 3, no. 8, pp. 1545-1573, 2019.
9. R. C. Fernandez et al., "Sleep disturbances in women with polycystic ovary syndrome: prevalence, pathophysiology, impact and management strategies," Nat Sci Sleep, vol. 10, pp. 45-64, 2018.
10. J. F. Trepanowski, J. Mey, dan K. A. Varady, "Fetuin-A: a novel link between obesity and related complications," International Journal of Obesity, vol. 39, no. 5, pp. 734-741, 2015.
11. J. Ochieng et al., "Impact of Fetuin-A (AHSG) on Tumor Progression and Type 2 Diabetes," International Journal of Molecular Sciences, vol. 19, no. 8, p. 2211, 2018.
12. L. Bourebaba dan K. Marycz, "Pathophysiological Implication of Fetuin-A Glycoprotein in the Development of Metabolic Disorders: A Concise Review," Journal of Clinical Medicine, vol. 8, no. 12, p. 2033, 2019.
13. M. K. Jensen et al., "Genetically Elevated Fetuin-A Levels, Fasting Glucose Levels, and Risk of Type 2

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Diabetes," The Cardiovascular Health Study, vol. 36, no. 10, pp. 3121-3127, 2013.
14. S. Sak et al., "Associations of serum fetuin-A and oxidative stress parameters with polycystic ovary syndrome," Clin Exp Reprod Med, vol. 45, no. 3, pp. 116-121, 2018.
15. M. E. Smet dan A. McLennan, "Rotterdam criteria, the end," Australas J Ultrasound Med, vol. 21, no. 2, p. 59, 2018.
16. R. A. Lobo, D. M. Gershenson, G. M. Lentz, dan F. A. Valea, Comprehensive Gynecology, Elsevier, 2016.
17. S. Liu et al., "Serum Fetuin-A levels are increased and associated with insulin resistance in women with polycystic ovary syndrome," BMC Endocr Disord, vol. 20, no. 1, p. 67, 2020.
18. E. Bayramoğlu et al., "Evaluation of the pathophysiological role of Fetuin A levels in adolescents with polycystic ovary syndrome," Journal of Pediatric Endocrinology and Metabolism, vol. 34, no. 7, pp. 911-916, 2021.
19. S. ElSirgany et al., "Serum Fetuin a Level: A New Possible Marker for Polycystic Ovarian Syndrome in Women with Infertility," Obstetrics and Gynecology Research, vol. 2, no. 4, pp. 100-107, 2019.
20. N. Malini dan K. R. George, "Evaluation of different ranges of LH: FSH ratios in polycystic ovarian syndrome (PCOS)–Clinical based case control study," General and comparative endocrinology, vol. 260, pp. 51-57, 2018.
21. O. A. Kensara, "Prevalence of hypovitaminosis D, and its association with hypoadiponectinemia and hyperfollistatinemia, in Saudi women with naïve polycystic ovary syndrome," Journal of Clinical & Translational Endocrinology, vol. 12, pp. 20-25, 2018.
22. H. Rashidi, S. B. Ghaderian, dan L. Moradi, "The effect of vitamin D3 on improving lipid profile, fasting glucose and insulin resistance in polycystic ovary syndrome women with vitamin D deficiency," Middle East Fertility Society Journal, vol. 23, no. 3, pp. 178-183, 2018.
23. M. R. Halawa et al., "Chemerin level in a sample of Egyptian females with PCOS and its relation to insulin resistance," The Egyptian Journal of Internal Medicine, vol. 32, no. 1, p. 18, 2020.
24. M. Aghilla, R. Adya, B. Tan, H. Lehnert, K. Ashawesh, dan H. Randeva, "The Hepatokine Fetuin-A is increased in PCOS women. Association with metabolic syndrome and regulation by metformin," dalam Endocrine Abstracts, 2012: BioScientifica.
25. I. Gulhan, G. Bozkaya, D. Oztekin, I. Uyar, A.G. Kebapcilar, dan B. Pamuk, "Serum Fetuin-A levels in women with polycystic ovary syndrome," Arch Gynecol Obstet, vol. 286, no. 6, hal. 1473-1476, 2012.
26. T. Gurbuz, S.A. Tosun, A. Cebi, O. Gokmen, dan M. Usta, "Investigating Fetuin-A and Paraoxonase-1 Activity as Markers in Polycystic Ovary Syndrome Based on Body Mass Index: A Prospective Case-Control Study," Cureus, vol. 13, no. 10.
27. Y. Enli, S.M. Fenkci, V. Fenkci, dan O. Oztekin, "Serum Fetuin-A levels, insulin resistance and oxidative stress in women with polycystic ovary syndrome," Gynecol Endocrinol, vol. 29, no. 12, hal. 1036-1039, 2013.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo