BODY MASS INDEX AND C-REACTIVE PROTEIN ARE POTENTIAL PREDICTORS OF ASTHMA DEVELOPMENT IN EGYPTIAN POLYCYSTIC OVARY SYNDROME PATIENTS

INDEKS TELESNE MASE I C-REAKTIVNI PROTEIN SU POTENCIJALNI PREDIKTORI RAZVOJA ASTME KOD PACIJENTKINJA SA SINDROMOM POLICISTIČNIH JAJNIKA U EGIPTU

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Summary

Background: Recent studies suggest asthma prevalence in polycystic ovary syndrome (PCOS) patients. This is the first study to explore asthma prevalence among Egyptian PCOS patients. It highlighted common findings in PCOS and asthma. It investigated whether these findings could serve as potential predictors of asthma.
Methods: A hundred PCOS patients, sixty asthmatic patients and thirty apparently healthy females of matched age were included. Body mass index (BMI), C-reactive protein (CRP), IL-6, IgE, 25 (OH) vitamin D, testosterone and lipid profile were measured.
Results: Both PCOS and asthmatics had significantly higher BMI, Total cholesterol (TC), LDL-C, IgE, CRP and IL-6 (P<0.001) and lower 25 (OH) vitamin D levels (P<0.001) compared to controls. Within the PCOS group, 47 patients developed asthma with a significant increase in BMI (P=0.003), CRP and IgE levels (P<0.001) compared to non-asthmatic PCOS. Both asthmatic PCOS and asthmatics expressed elevated BMI, IgE, IL-6 and CRP levels, but

Kratak sadržaj

Uvod: Nedavne studije ukazuju na prevalenciju astme kod pacijentkinja sa sindromom policističnih jajnika (PCOS). Ovo je prva studija koja je istraživala prevalenciju astme među egipatskim PCOS pacijentkinjama i dala je uobičajene nalaze u vezi sa PCOS i astmom. Osim toga, studija se bavi i istraživanjem da li ovi nalazi mogu poslužiti kao potencijalni prediktori astme.
Metode: Uključeno je 100 pacijentkinja sa PCOS, šezdeset pacijentkinja sa astmom i trideset očigledno zdravih žena odgovarajuće starosti. Izmereni su indeks telesne mase (BMI), C-reaktivni protein (CRP), IL-6, IgE, 25 (OH) vitamin D, testosteron i lipidni profil.
Rezultati: I pacijentkinje sa PCOS i one sa astmom su imale značajno veći BMI, ukupni holesterol (TC), LDL-C, IgE, CRP i IL-6 (P < 0,001) i niže nivoe vitamina D (P < 0,001) u odnosu na pacijentkinje u kontrolnoj grupi. U okviru PCOS grupe, 47 pacijentkinja je razvilo astmu sa značajnim porastom BMI (P = 0,003), CRP i IgE nivoa (P < 0,001) u poređenju sa ne-astmatičnim PCOS. I astmatične pacijen-

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with no significant difference between them. Asthmatic PCOS showed significantly higher testosterone and dyslipidemia profile. Multivariate regression revealed that BMI and CRP could predict asthma development within PCOS (OR=1.104, C.I 1.004–1.2 and OR=1, C.I. 1–1.02), respectively. Receiver operating characteristic (ROC) curve showed that BMI and CRP at a cutoff value 28.5 kg/m^2 and 117.6 nmol/L respectively could differentiate between asthmatic and non-asthmatic PCOS with sensitivity 63.8 % and specificity 62% for BMI, and sensitivity and specificity of 66% for CRP.

Conclusions: This study shows that BMI and CRP are predictors of asthma development in Egyptian PCOS.

Keywords: polycystic ovary syndrome, asthma, BMI, IgE, interleukin 6, CRP, dyslipidemia

tkinje sa PCOS i one bez PCOS su imale povišene nivoe BMI, IgE, IL-6 i CRP, ali bez značajne razlike između njih. Astmatične PCOS pacijentkinje su pokazale značajno veći testosteronski i dislipidemijski profil. Multivarijantna regresija je pokazala da BMI i CRP mogu predvideti razvoj astme unutar PCOS grupe (OR=1,104, C.I 1,004–1,2 i OR=1, C.I. 1–1,02), respektivno. ROC kriva je pokazala da se BMI i CRP kod graničnih vrednosti 28,5 kg/m^2 i 117,6 nmol/L mogu razlikovati između astmatičnih i neastmatičnih PCOS sa osetljivošću 63,8% i specifičnošću 62% za BMI, dok je osetljivost i specifičnost za CRP 66%.

Zaključak: Ova studija pokazuje da su BMI i CRP prediktori razvoja astme kod pacijentkinja sa sindromom policističnih jajnika u Egiptu

Ključne reči: sindrom policističnih jajnika, astma, BMI, IgE, interleukin 6, CRP, dislipidemija

Introduction

Polycystic Ovary Syndrome (PCOS) is the most abundant endocrine disorder in females of reproductive age and one of the main causes of infertility with a prevalence of 9–18 % worldwide (1). Reports state that PCOS constitutes a major health issue in Egyptian females (2, 3). According to the Rotterdam consensus in 2003, PCOS can be diagnosed by the occurrence of two of the following criteria: Oligo- and/or anovulation, clinical and/or biochemical features of hyperandrogenism, and polycystic ovaries on performing ultrasound investigations (4). In addition to infertility, PCOS is associated with several metabolic disorders such as obesity (5), insulin resistance (IR) (6), dyslipidemia (7), increased levels of inflammatory markers, with consequent increased risk of developing Type 2 diabetes and cardiovascular disorders among other serious disorders (7–9).

Meanwhile, asthma is a complex and chronic in ammatory disorder of the airways with local and systemic in ammation. It is characterized by a T helper cell 2 (Th2)-immune response, resulting in increased total immunoglobulin E (IgE), eosinophilia, elevated cytokines, interleukins (IL-4, -5, -13, -17–22), tumor necrosis factor-alpha (TNF-α) and elevated CRP levels (10, 11).

Multiple factors contribute to the pathology and severity of asthma attacks, including allergenic inhalation, environmental and immunological factors among others (12, 13). Treating asthma depends on both environmental control and strict medication that may be difficult to achieve. Consequently, asthma remains to be a chronic, recurrent health problem which requires better management and preventive protocols.

Recent studies are pointing out the higher prevalence of asthma in PCOS patients compared to normal females (14–16), which increases the need to study the common findings of both PCOS and asthma and explore the factors that contribute to such prevalence.

Obesity has been linked to both PCOS and asthma, whereas abnormal lipid profile is a well-known characteristic of PCOS patients (17). High levels of triacylglycerols (TAG), total cholesterol (TC) and LDL-cholesterol (LDL-C), lower HDL-cholesterol (HDL-C) together with elevated body mass index (BMI) are continuously reported in PCOS cases as compared to healthy matches (18, 19). Moreover, epidemiological studies have linked the presence of obesity and asthma (20–22). However, to date, no previous data was available about asthma in Egyptian PCOS patients and the effect of BMI and dyslipidemia on this relation.

In addition to obesity and dyslipidemia, nearly 67–85% of the PCOS patients are reported to suffer from 25 (OH) vitamin D deficiency, where Vitamin D is a crucial physiological player in follicular development, sensitivity to follicular stimulating hormone and Anti-Müllerian hormone (AMH) signalling (23). Furthermore, multiple studies have investigated the possible link between 25 (OH) vitamin D deficiency and asthma (24). However, no sufficient data is available whether 25 (OH) vitamin D level can play a role in asthma development within PCOS patients. In line with the documented inflammatory nature of asthma, PCOS is also reported to be accompanied by an inflammatory condition, where increased levels of cytokines, IL-18, CRP, IL-6 and its receptor gene have lately been linked to the pathogenesis of both disorders (8, 11). Yet again, limited data is available about the inflammatory markers in asthmatic PCOS patients.

To date and the best of our knowledge, there are very few community-based studies that explored the relationship between asthma and PCOS (14, 15). Furthermore, no previous study investigated the co-prevalence of asthma and PCOS in the Egyptian population, nor it studied the findings and biochemical parameters of both diseases.

Taking these facts into consideration, in this cross-sectional study, we aimed firstly to explore the

prevalence of asthma in Egyptian PCOS patients. Secondly, to investigate the common findings and biomarkers shared by both disorders. Finally, we aimed at detecting whether any of such common findings could serve as potential predictors of asthma development within PCOS patients.

Materials and Methods

Study population

The present cross-sectional study included 3 main groups. First, Group 1 comprised 100 PCOS patients aged from 21 to 29 years old with primary or secondary infertility, it was called PCOS group. The PCOS group was further divided into 2 subgroups. Subgroup 1 included 47 patients diagnosed with both PCOS & asthma, called asthmatic PCOS. Subgroup 2 included 53 patients diagnosed with PCOS only, called non-asthmatic PCOS. The diagnosis of PCOS was made according to Rotterdam consensus. Thereby, two out of the three following conditions were required to confirm the diagnosis of PCOS: Oligo- and/or anovulation (defined by the presence of oligomenorrhea or amenorrhea), clinical and/or biochemical features of hyperandrogenism (defined by having clinical hirsutism (Ferriman-Gallaway score 6), acne or alopecia and/or elevated androgens) and polycystic ovaries on ultrasound examination (3). Asthma diagnosis was based on both clinical examination and spirometry together with eosinophilia and increased IgE level (25).

Second, Group 2 comprised 30 apparently healthy females aged from 21 to 29 set as the control group. All control females were healthy and had regular cycles ranging from 25 to 35 days and had neither ovarian gynecological disorders nor endocrinal abnormalities. In addition, they were not suffering from bronchial asthma or allergic rhinitis. Third, Group 3 included 60 female asthmatic patients of matched age (22–28) were set as asthmatics group. Group 2 and 3 were collectively called non-PCOS group (N=90). All subjects were recruited from the outpatient clinics of Al-Azhar University Teaching Hospitals all over Egypt. Subjects having Cushing's syndrome, androgen-secreting tumors, congenital adrenal hyperplasia, diabetes, immunological diseases, any form of malignancy and hyperprolactinemia were excluded from the study. No cases included in the study were smokers nor received oral contraceptive drugs. All subjects had stable body weight for at least 3 months. The study was performed after obtaining informed consent from all subjects and the approval of the ethics committee and the Review Board at Al-Azhar University, Cairo, Egypt in accordance with The Code of Ethics of the Declaration of Helsinki.

Laboratory Procedure

In the present investigation, all blood samples were taken at a specified day of the menstrual cycle. Weight and height were measured on the same day of blood sampling and used to calculate BMI. Sera were separated, and samples were stored at -80 °C until the time of analysis. Serum total testosterone was measured by immunoassay (Architect 2nd Generation, Abbott Diagnostics, and USA). 25 (OH) vitamin D was measured using DRG 25 (OH) vitamin D (total) ELISA (DRG Instruments GmbH, Germany). Serum IL-6 was measured using Human Interleukin 6 (IL-6) ELISA Kit (My BioSource, USA). Total IgE was measured using The Elecsys IgE II immunoassay (Roche Diagnostics, USA). CRP levels were measured using Tina-quant C-reactive protein Gen.3 (Roche Diagnostics, USA). TAG, TC and HDL-C were determined using enzymatic spectrophotometric assay (Diamond Diagnostics, D-P international, Egypt). LDL-C was calculated from TAG and HDL-C values using the Friedewald's formula (26):

$$\text{LDL-C} = \text{Total C} - [(\text{TAG}/5) + \text{HDL-C}] \ (1)$$

Statistical analysis

In the current investigation, differences in variables between different groups of the study population were assessed using the Mann-Whitney test. Continuous data were presented as a median and interquartile range. Categorical data were presented as percentages. Multivariable regression analysis was done to detect the presence of possible predictors of asthma within the PCOS group. Factors included in the model were selected based on identifying the measured clinical variables of possible prognostic importance for the outcome in question (Asthma). To explore the ability of the selected markers measured to differentiate between asthmatic and non-asthmatic patients in the PCOS group, Receiver operating characteristic (ROC) curve was used. The area under the curve (AUC) was calculated. The yield values were from 0.5 (no predictive power) to 1.0 (perfect prediction). The optimal cut-off was determined using Yoden's Index: maximum [sensitivity – (1-specificity)] (27). For all data, a P value of <0.05 (two-tailed) was considered significant. All statistical analyses were performed using the SPSS package (version 23 for Windows; SPSS Inc., Chicago, IL, USA).

Results

Comparing different variables in PCOS and asthmatic groups vs control

In the present investigation, both PCOS (Group 1) and asthmatic (Group 3) groups showed significantly higher BMI, TC, LDL-C and higher inflammato-

Table I Comparison between different variables in PCOS vs. controls, and Asthmatic patients vs. controls respectively. Data are presented as median and interquartile range. *indicates significant difference at P<0.05.

Parameters	PCOS (N=100)	P value	Controls (N=30)	Asthmatic (N=60)	P value
IgE (µg/L)	342 (177.6–1110)*	<0.001*	54 (40.8–62.4)	1162.4 (1083–1281)*	<0.001*
Age (years)	26 (21–29)	0.67	25 (23–29)	25 (22–28)	0.28
BMI (kg/m²)	28.53 (27.2– 34.1)*	<0.001*	23.34 (21.6–26.9)	31.6 (28.3–33.46)*	<0.001*
25 (OH) vitamin D (nmol/L)	36.5 (19.4–44.22)*	<0.001*	81.5 (66.4–100)	31.9 (28.3–33.46)*	<0.001*
Total Testosterone (nmol/L)	4.7 (4.3–5)*	<0.001*	0.7 (0.45–1.1)	0.76(0.35–1.1)	0.9
TC (mmol/L)	6.47 (6.1–6.88)*	<0.001*	4.6 (4.35–5.3)	5.1 (4.6–5.8)*	<0.001*
LDL-C (mmol/L)	4.68 (4.4 –5.2)*	<0.001*	2.9 (2.5–3.4)	3.2 (2.9–4.2)*	<0.001*
HDL-C (mmol/L)	0.99 (0.85–1.1)*	<0.001*	1.1 (1.1–1.8)	1.03 (0.88–1.11)	0.2
TAG (mmol/L)	1.42 (1.07–1.86)	0.2	1.17 (1.13–1.8)	1.4 (1.26–1.8)	0.1
IL-6 (nmol/L)	0.0015 (0.0013–0.0017)*	<0.001*	0.00021 (0.0002–0.00025)	0.0017 (0.0014–0.0018)*	<0.001*
CRP (nmol/L)	114.28 (102.85–180.95)*	<0.001*	57.1 (38–76.19)	146.4 (130–180.95)*	<0.001*

Table II Comparison between different parameters in PCOS vs non-PCOS cohort. (Collectively healthy controls and asthmatic non-PCOS). Data are presented as a median and interquartile range. *indicates a significant difference at P<0.05.

Parameters	PCOS (Group 1) (N=100) (Asthmatic PCO =47, Non Asthmatic PCOS=53)	Non PCOS cohort (N=90) Controls=30 (Group 2), Asthmatics=60 (Group 3)	P value
IgE µg/L	342 (177.6–1110)	1086 (61.8–1190)	0.26
Age (years)	26 (21–29)	25 (23–28)	0.81
BMI (kg/m²)	28.53 (27.2–34.1)	28.8 (24.7–32.9)	0.32
25 (OH) vitamin D (nmol/L)	36.5 (19.4–44.22)	37.44 (29.44–68.5)	0.01*
Total Testosterone(nmol/L)	4.7 (4.3–5)	0.72 (0.35–1.1)	<0.001*
TC (mmol/L)	6.47 (6.1–6.88)	4.85 (4.61–5.8)	<0.001*
LDL-C (mmol/L)	4.68 (4.4–5.2)	3.2 (2.8–4.12)	<0.001*
HDL-C (mmol/L)	0.99 (0.85–1.1)	1.08 (0.93–1.11)	0.12
TAG (mmol/L)	1.42 (1.07–1.86)	1.55 (1.2–1.8)	0.3
IL-6 (nmol/L)	0.0015 (0.0013–0.0017)	0.0014 (0.0002–0.0018)	0.016*
CRP (nmol/L)	114.28 (102.85–180.95)	130 (76.19–160)	0.6

Table III Comparison between different variables between non-asthmatic PCOS and asthmatic PCOS (Columns 1 & 3) and comparing different variables between asthmatic PCOS and asthmatic patients (Columns 3 & 4). Data are presented as a median and interquartile range. *indicates a significant difference at P<0.05.

Parameters	Non-asthmatic PCOS (N=53)	P value	Asthmatic PCOS (N=47)	Asthmatic (N=60)	P value
IgE (µg/L)	183.6 (92.4– 269.04)	<0.001*	1176 (816–1276)	1162.4 (1083–1281)	0.23
Age (years)	26 (22–29)	0.39	26 (21–28)	25 (22–28)	0.95
BMI (kg/m^2)	28 (24.6–30.16)	0.003*	29.7 (28.3–35.6)	31.6 (28.3–33.46)	0.84
25 (OH) vitamin D (nmol/L)	36.5 (17.09–41.17)	0.08	37.44 (22.46–51.417)	31.9 (28.3–33.46)	0.067
Total Testosterone (nmol/L)	4.7 (4.5–5.1)	0.052	4.67 (3.9–5.1)	0.76 (0.35–1.1)	<0.001*
TC (mmol/L)	6.34 (6.07–6.9)	0.43	6.47 (6.14–7)	5.1 (4.6–5.8)	<0.001*
LDL-C (mmol/L)	4.66 (4.44–5.21)	0.8	4.8 (4.4–5.23)	3.2 (2.9–4.2)	<0.001*
HDL-C (mmol/L)	1.03 (0.87–1.13)	0.17	0.95 (0.82–1.1)	1.03 (0.88–1.11)	0.2
TAG (mmol/L)	1.35 (1.01–1.8)	0.2	1.53 (1.2–1.88)	1.4 (1.26–1.8)	0.3
IL-6 (nmol/L	0.0015 (0.0014–0.002)	0.15	0.0015 (0.0012–0.0017)	0.0017 (0.0014–0.0018)	0.12
CRP (nmol/L)	109.5 (72.38–128.6)	<0.001*	142.86 (104.76–200)	146.4 (130–180.95)	0.6

Table IV Multivariable regression analysis model, to detect the predictors of asthma within PCOS patients. All factors that previously exhibited P<0.1 within the two subgroups of PCOS patients were included in the model. Regression analysis confirmed that only BMI and CRP levels maintained their significance as predictors of asthma at P<0.05. (Denoted by *).

Parameters	OR	P-value	95% C. I.	
			Lower	Upper
BMI	1.104	0.041*	1.004	1.213
CRP	1.010	0.014*	1.002	1.07
25 (OH) vitamin D	1.031	0.61	0.999	1.064
Total Testosterone	0.68	0.23	0.36	1.3

ry markers as IgE, IL-6 and CRP levels (P <0.001) and lower 25 (OH) vitamin D levels (P<0.001) compared to controls (Group 2). On the other hand, only the PCOS group (Group 1) showed significantly higher total testosterone levels (P<0.001) and lower HDL-C (P<0.001) compared to controls (Group 2). In contrast, there was no significant difference in age, and TAG levels compared to controls (Group 2) as shown in (*Table I*).

Comparing different variables in the PCOS group vs non-PCOS cohort

We investigated the difference in the detected physical and biochemical parameters between PCOS patients and the non-PCOS cohort which included both healthy controls and asthmatic patients (Groups 2 & 3 collectively) (N=90). PCOS patients (Group 1) showed significantly higher total testosterone, TC and LDL-C levels (P<0.001) and lower 25 (OH) vitamin D levels as compared to the non-PCOS cohort. On the other hand, there was no significant difference in age, BMI and TAG levels between both cohorts as shown in (*Table II*).

Comparing different variables in asthmatic PCOS vs non-asthmatic PCOS

Within the PCOS group, asthmatic PCOS patients showed significantly higher IgE level (P<0.001), BMI (P=0.003) and CRP level (P<0.001) compared to the non-asthmatic PCOS patients. Meanwhile, there was no significant difference between both groups concerning total testosterone, 25 (OH) vitamin D levels and lipid profile parameters. Detailed data are shown in (*Table III*).

Comparing different variables in asthmatic PCOS vs asthmatic patients

In the present investigation, asthmatic PCOS patients (Subgroup 1) showed significantly higher total testosterone level (P<0.001), TC and LDL-C levels (P<0.001) as compared to asthmatic patients (Group 3). On the other hand, there was no significant difference between the two groups concerning BMI, vitamin D, HDL-C and TAG levels. Both asthmatic PCOS and asthmatic patients shared a common increase in BMI, IgE, IL-6 and CRP levels with no

significant difference between the two groups as shown in (*Table III*).

Multivariable regression analysis

Within the PCOS group (Group 1), it was found that asthmatic patients (Subgroup 1) had significantly higher BMI, IgE and CRP levels (P<0.05) as compared to non-asthmatic PCOS patients (Subgroup 2). For further exploration for these variables as possible predictors of asthma in PCOS patients, multivariable regression analysis was done. Moreover, factors exhibiting P<0.1 were also included in the model (25 (OH) vitamin D and total testosterone). As IgE was already used as a diagnostic factor for asthma in combination with clinical symptoms, it was not included in the multivariable regression analysis.

Results showed that the significant relationship between BMI, CRP levels and asthma was maintained in the multivariable regression analysis. Both BMI and CRP were significant predictors of asthma within the PCOS group (OR=1.104, C.I 1.004–1.2 and OR=1, C.I. 1–1.02), respectively as shown in (*Table III*).
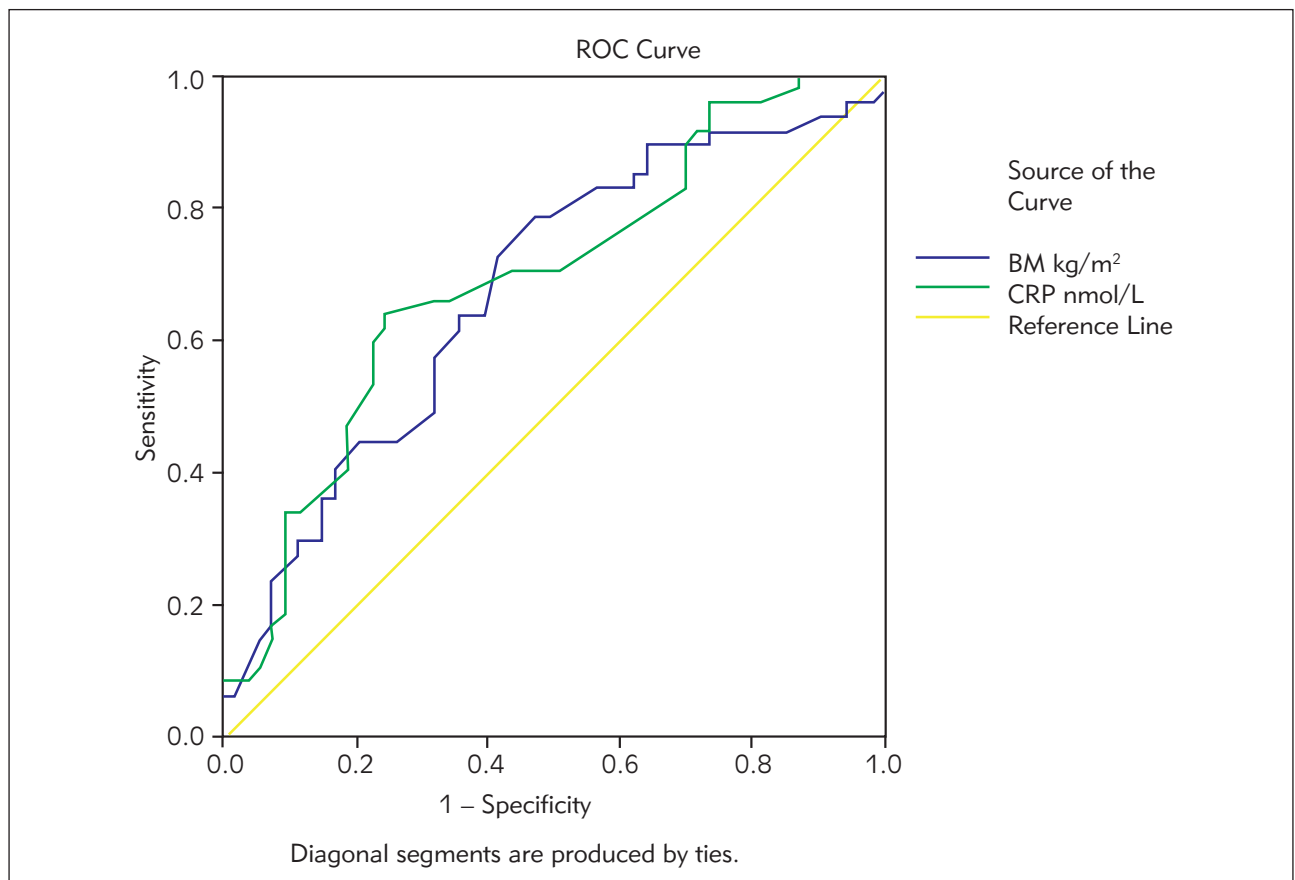

Figure 1 ROC curve illustrating the potential of BMI and CRP to differentiate between asthmatic and non-asthmatic PCOS patients. At area under the curve (AUC=0.67, P=0.003), the optimal cutoff value for BMI is 28.5 kg/m2 with sensitivity 63.8 % and specificity 62%, whereas the optimal cutoff value of CRP level is 117.6 nmol/L with sensitivity and specificity 66% at (AUC= 0.69, P=0.001.)

Receiver operating characteristic curve

To further explore the potential of BMI and CRP to differentiate between asthmatic (Subgroup 1) and non-asthmatic PCOS (Subgroup 2) patients, the ROC curve was done on all 100 patients in Group 1. ROC curve showed that both BMI and CRP has a diagnostic ability to detect asthma in PCOS patients with an area under the curve (AUC=0.67 and 0.69, P value=0.003, 0.001) respectively. A cutoff value of BMI 28.5 kg/m^2 can detect asthma with a sensitivity of 63.8 % and specificity 62%, whereas a cutoff value of CRP 117.6 nmol/L can detect asthma within PCOS group with sensitivity and specificity 66% as illustrated in *Figure* (1).

Discussion

Up to date, there have been no community-based studies that investigated the association between PCOS and asthma, especially in relation to the common findings of both disorders. Hence, in this study, we aimed to explore the common biomarkers of PCOS and asthma in Egyptian PCOS patients, and we investigated the possible potential of these factors as predictors for asthma development.

We examined the BMI and a panel of metabolic, hormonal and inflammatory markers in PCOS patients versus age-matched healthy controls and asthmatic female patients.

Upon comparing PCOS patients to non-PCOS cases, we found that PCOS patients had significantly higher total testosterone, higher TC, and LDL-C together with significantly low levels of 25 (OH) vitamin D. The same profile was maintained upon comparing asthmatic PCOS patients to asthmatic patients with no PCOS. Such results are in accordance with previous studies (3, 17, 28) and they confirm the main findings of PCOS, where dyslipidemia is highly prevalent in PCOS even in lean females mostly due to insulin resistance (29). Whereas vitamin D deficiency has also been reported in PCOS patients (30), contributing to their disturbed metabolic profile.

On examining the findings of both disorders, we found that both PCOS and asthmatic patients had significantly higher BMI, TC, and LDL-C as compared to healthy controls. This goes in agreement with previous studies that link PCOS and asthma to obesity and associated dyslipidemia, where both PCOS and asthma are reported to worsen by obesity and improve by weight loss (17, 31, 32).

Our findings also showed that both PCOS and asthmatic patients suffered from significantly low levels of 25 (OH) vitamin D as compared to controls. Decreased levels of 25 (OH) vitamin D have been linked to increased risk of asthma attacks in asthmatic patients (23, 24, 28). Additionally, Vitamin D deficiency is known to be highly prevalent in PCOS patients (67–85%), where the deficiency is especially reported to worsen the symptoms of PCOS (29), including menstrual irregularities, cardiac disorders (33), obesity (34, 35) and deteriorating metabolic phenotype (36).

Concerning the inflammatory markers, asthmatic patients showed significantly higher inflammatory markers levels against healthy controls. Similarly, PCOS patients had significantly higher IL-6, CRP and IgE levels as compared to controls. However, the asthmatic group expectedly showed higher inflammatory marker levels in comparison with the PCOS group. PCOS is associated with low-grade systemic inflammation which elevates biomarkers such as CRP, IL-18, monocyte chemoattractant protein-1, and leucocytes (37), especially when accompanied by obesity (38–40). Moreover, the increased levels of IL-6 and its receptor gene have lately been linked to the pathogenesis of PCOS and asthma, with recommendations for further investigations to explore the clinical significance of IL-6 in both disorders (40, 41).

To get more understanding of asthma development and prevalence in PCOS patients, we classified PCOS patients in our study to asthmatic and non-asthmatic PCOS subgroups and analyzed their BMI, metabolic, hormonal and inflammatory profiles. Within the PCOS group, 47 out of 100 PCOS patients (47%) developed asthma. This finding confirms our hypothesis and agrees with previous reports that show a high prevalence of asthma within PCOS patients in different populations (22). Glintborg and colleagues (14) reported the elevated prevalence of asthma and higher use of asthma drugs (19.2% vs 14.1%; p<0.001) in PCOS females against non-PCOS females in the Danish population. Similarly, a retrospective study in Australian women with and without PCOS showed that PCOS women were more frequently hospitalized for asthma as compared to non-PCOS females (10.6% vs 4.5%, p<0.001) (15). Both the Danish and Australian studies did not report detailed data on the BMI or metabolic profiles of the recruited cases. Here, it is worth mentioning that to the best of our knowledge, our study is the first report to assess asthmatic and non-asthmatic PCOS patients concerning their metabolic, hormonal and inflammatory markers.

Within the PCOS group, we found that asthmatic PCOS patients had significantly higher BMI, IgE and CRP levels as compared to the non-asthmatic PCOS patients whereas no significant difference appeared between the two subgroups in terms of the measured hormonal or lipid profile. This correlates with the fact that IgE is one of the characteristic biological markers of asthma (42) and sheds more light on the probable role of CRP in the pathogenesis of asthma.

Furthermore, upon comparing asthmatic PCOS patients to asthmatic patients with no PCOS, we

found that both populations shared high BMI, inflammatory markers levels and low 25 (OH) vitamin D level with no significant difference between them, which support the assumption that some or all of these factors contribute to asthma development. In accordance, it is documented that asthmatic women have a trend of higher BMI in PCOS and non-PCOS cases (20, 21). Thaw et al. (22) showed that asthmatic PCOS patients had a trend for a higher BMI compared with non-asthmatic PCOS patients (29.9 ± 0.9 versus 27.7 ± 0.4 kg/m^2). Moreover, recent studies relate obesity to a higher incidence of asthma even after exclusion of smoking and chronic obstructive pulmonary disease (COPD) cases (11, 22, 43).

Whereas the mechanism linking obesity and asthma is still unclear, it can be attributed to the enhanced inflammation present in cases of obesity that may trigger airway inflammation (20, 21, 44). Taking this into consideration, and since PCOS is widely characterized by obesity, we suggest that the elevated BMI and the accompanying inflammation (represented here in high CRP, IgE and IL-6) in PCOS cases may contribute further to airway inflammation and consequent high incidence of asthma in PCOS females.

To explore how far these factors can actually affect asthma development within the PCOS population, multivariable regression was performed, and it confirmed the ability of both elevated BMI and CRP levels to act as predictors of asthma development within PCOS patients (OR=1.104, C.I 1.004–1.2 and OR=1, C.I. 1–1.02), respectively. Contrarily, none of the other parameters as testosterone level, vitamin D or IL-6 showed a prognostic ability to predict asthma among PCOS patients. These results are in agreement with our hypothesis that obesity in PCOS might provoke mild inflammation that can furtherly increase air passage inflammation and asthma incidence. Meanwhile, the inability of disturbed vitamin D and IL-6 levels to predict asthma among PCOS patients needs to be confirmed with studies on different populations.

In order to determine the optimal cutoff values, ROC curve for both BMI and CRP level within PCOS patients showed that BMI higher than 28.5 kg/m^2 can differentiate between asthmatic and non-asthmatic PCOS patients with a sensitivity and specificity of 63.8% and 62%, while CRP of higher than 117.6 nmol/L can differentiate asthmatic and non-asthmatic PCOS with both sensitivity and specificity of 66%. Even though poor accuracy of these parameters remains to be a limitation, yet the proved prognostic ability of BMI and CRP level can present an aiding tool for better management of asthma within PCOS patients, and can be further confirmed or improved with more studies on larger populations.

There is an increasing demand for precision medicine and management of heavy burden diseases as asthma. Consequently, studies for strategic prevention or earlier control of asthma are highly required, especially in complicated cases like PCOS. This study presents a better understanding of the prevalence and common findings of asthma within Egyptian PCOS where elevated BMI and CRP levels showed their ability to predict asthma development among PCOS patients.

The limitations in this study were the relatively small population and the inability to monitor the patients on the long term to examine the effect of controlling BMI and CRP changes. Further larger population studies, with trials to control these two parameters among other characteristics are encouraged, in the hope of better management of asthma occurrence or severity of attacks within PCOS patients.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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