Clin. Lab. 2019;65:XXX-XXX

ORIGINAL ARTICLE

Serum Amyloid A is a Novel Inflammatory Biomarker in Polycystic Ovary Syndrome

Yifan Sun [1, #], Xianhua Chen [1, #], Bohui Ouyang [2], Gangxi Pan [1], Lin Sun [1], Sufeng Li [1], Kun Chen [3]

[#] *Yifan Sun and Xianhua Chen contributed equally to this work, so they should be considered as co-first authors*
[1] *Department of Clinical Laboratory, Affiliated Liutie Central Hospital of Guangxi Medical University, LiuZhou, Guangxi, China*
[2] *Department of Clinical Laboratory, Third Affiliated Hospital of Guangxi University of Chinese Medicine, Liuzhou, Guangxi, China*
[3] *Department of Gynecology, Affiliated Liutie Central Hospital of Guangxi Medical University, LiuZhou, Guangxi, China*

SUMMARY

Background: **Serum amyloid A (SAA) is considered a biomarker of inflammation; however, the SAA levels in polycystic ovary syndrome (PCOS) are still uncertain.**
Methods: **In this study, SAA, glucose, insulin, C-reactive protein (CRP), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone concentrations were measured in 82 women with PCOS and 60 healthy controls.**
Results: **The median concentration of SAA was 5.000 mg/L (IQR: 2.825 - 5.400) in women with PCOS, which was significantly higher than that of controls (3.700 mg/L, IQR: 2.825 - 5.400, p = 0.025). SAA was only positively associated with the CRP (r = 0.303, p = 0.006). No significant association was observed between SAA and body mass index (BMI), total testosterone, or insulin resistance (IR).**
Conclusions: **SAA levels were increased in women with PCOS, and SAA may be a potential inflammatory biomarker for PCOS.**
(Clin. Lab. 2019;65:xx-xx. DOI: 10.7754/Clin.Lab.2018.181038)

Correspondence:
Kun Chen
Department of Gynecology
Affiliated Liutie Central Hospital of
Guangxi Medical University
Fei-e Road No. 14
LiuZhou
545007 Guangxi
China
Phone: +86 0772-8810442
Email: 20755375@qq.com

KEY WORDS

polycystic ovary syndrome, serum amyloid A, biomarker, inflammation

LIST OF ABBREVIATIONS

SAA - serum amyloid A
PCOS - polycystic ovary syndrome
CRP - C-reactive protein
FSH - follicle-stimulating hormone
LH - luteinizing hormone
IQR - interquartile range
BMI - body mass index
HOMA-IR - homeostasis model assessment of insulin resistance index
T2DM - type 2 diabetes
CVD - cardiovascular diseases
IR - insulin resistance

Manuscript accepted November 6, 2018

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine-metabolic disorder affecting women of reproductive age [1]. Approximately 40 - 70% of women with PCOS are overweight [2], and adipose tissue has shown significant changes in women with PCOS [3, 4], which contributes to various endocrine complications, including infertility, hirsutism, insulin resistance (IR), inflammation, and the risk of type-2 diabetes and cardiovascular disease [5]. The economic burden is great to screen for this disorder and treat its lifelong complications [6].

PCOS is a disease with low-grade chronic inflammation. In 1999, Gonzalez [7] first reported that serum tumor necrosis factor alpha (TNF-alpha) was elevated in normal-weight women with PCOS, which was further confirmed by Sayin in 2003 [8]. From then on, more and more serum markers of inflammation were found to have increased in PCOS. White blood cell (WBC) count is a known marker of inflammation and has been shown to be increased in 150 PCOS women, correlating with homeostasis model assessment values [9]. C-reactive protein (CRP), another typical inflammatory marker, has been shown to be elevated in PCOS women in many studies [10-12]; furthermore, CRP levels decreased after metformin treatment based on a meta-analysis [13]. In addition, pro-inflammatory cytokines and chemokines, such as interleukin (IL)-6, IL-18 and monocyte chemoattractant protein-1 (MCP-1), have also been demonstrated to increase in several studies [12,14,15]. Recently, we reported increased serum interferon gamma-inducible protein 10 in women with PCOS [16]. These studies have shown a significant association between low-grade chronic inflammation and PCOS.

Serum amyloid A is also considered to be a biomarker of infection and inflammation. SAA is released predominantly in the liver [17], and human adipose tissue is a major SAA expression site [18]. Moreover, SAA levels were associated with the size of adipocytes [19]. Previous studies have investigated SAA levels in women with PCOS [20-23]; however, the results have been inconsistent and, in addition, the relationships between SAA and PCOS's biochemical characteristics - such as elevated androgen and CRP levels and IR - have also not been fully clarified. Therefore, we investigated whether SAA is increased in women with PCOS using a case-control study, and we aimed to establish a potential association between SAA levels and IR, androgen status, and CRP of PCOS patients to assess the potential clinical values of SAA in PCOS.

MATERIALS AND METHODS

Study Population

The study was conducted at the affiliated Liutie Central Hospital of Guangxi Medical University. A total of 82 women with PCOS (mean age: 25.44 ± 0.55 years old) were recruited from the department of gynecology in accordance with the inclusion/exclusion criteria. The diagnosis of PCOS was based on the 2003 Rotterdam ESHRE/ASRM consensus criteria [24] and at least two of the following three criteria: clinical and/or biochemical signs of hyperandrogenism, oligomenorrhea or amenorrhea, and polycystic ovaries as determined by ultrasonography. In the current analysis, control women were recruited from a medical examination center, and the group consisted of 60 BMI-matched healthy women (mean age: 31.12 ± 0.72 years old) with regular menstrual cycles.

Women were excluded if they were human papillomavirus (+), hepatitis B virus (+), human immunodeficiency virus (+), tuberculosis (+), had a recent illness or any chronic illness likely to influence SAA results, including thyroid disease or Cushing's syndrome, tobacco use, pregnancy, malignancy, anemia, or other inflammatory diseases (e.g., rheumatism, nephritis, or systemic lupus erythematosus). In addition, subjects who were under any treatment or receiving medication were also excluded.

All study participants gave their written consent to participate, and this study was approved by the Ethics Committee of the affiliated Liutie Central Hospital of Guangxi Medical University.

Laboratory methods and anthropometric measurements

Blood samples were taken following a 12-h fast, and then centrifuged at 3,000 rpm for 10 minutes to obtain the serum. Serum total testosterone, progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and estradiol concentrations were measured on the Abbott Architect i2000 analyzer (Abbott Diagnostics, Santa Clara, CA, USA). Serum glucose was measured on the Abbott Architect C16000 analyzer (Abbott Diagnostics, Santa Clara, CA, USA) and serum insulin concentrations were measured on the Roche Cobas e601 analyzer (Roche Diagnostics, Basel, Switzerland), then the homeostasis model assessment of the insulin resistance index (HOMA2-IR) was calculated on the basis of the glucose and insulin levels, using the Oxford Diabetes Trials Unit calculator (www.dtu.ox.ac.uk). C-reactive protein (hs-CRP) was measured on the Abbott Architect C16000 analyzer. The levels of SAA were measured on the Hitachi 7600 automatic analyzer (Hitachi Co., Tokyo, Japan), using the immunoturbidimetric method with reagents (Iprocom Biotechnology Co., Ltd Anhui, China), and the intra-assay and inter-assay coefficients of variations (CVs) were less than 5.0%.

Data Analysis

BMI was calculated as the weight/(height)^2 (kg/m^2). Results were expressed as mean (standard deviation, SD) or medians (interquartile ranges, IQR). Between-group comparisons were analyzed by an independent Student's *t*-test when the continuous variables were consid-

Table 1. Clinical characteristics of PCOS patients and healthy controls.

	PCOS (n = 82)	Control (n = 60)	p-value
Age (years)	25.27 ± 5.04	31.12 ± 5.57	< 0.001
BMI (kg/m^2)	21.59 ± 3.62	22.37 ± 2.69	0.162
Progesterone (ng/mL)	0.28 (0.17 - 0.39)	0.30 (0.20 - 6.56)	0.035
Estradiol (pg/mL)	44.0 (29.8 - 71.8)	104.0 (58.0 - 183.0)	< 0.001
Prolactin (ng/mL)	15.60 (9.41 - 23.57)	15.44 (11.80 - 19.32)	0.918
FSH (mIU/mL)	4.77 ± 0.16	6.35 ± 1.03	0.082
LH (mIU/mL)	8.90 (5.69 - 12.73)	5.45 (3.07 - 11.55)	0.012
Testosterone (ng/mL)	0.470 (0.360 - 0.603)	0.365 (0.310 - 0.448)	< 0.001
Glucose (mmol/L)	4.74 ± 0.19	4.62 ± 0.05	0.551
Insulin (uIU/mL)	13.68 ± 2.58	6.51 ± 0.77	0.023
HOMA-IR	2.90 ± 0.52	1.35 ± 0.15	0.014
SAA (mg/L)	5.000 (3.375 - 6.600)	3.700 (2.825 - 5.400)	0.025
CRP (mg/L)	5.20 ± 0.75	3.12 ± 0.27	0.038

FSH - follicle-stimulating hormone, LH - luteinizing hormone.

ered to have normal distribution; otherwise, the Mann-Whitney *U* test was used. Correlations between variables were conducted by Spearman's two-tailed bivariate analysis. If there were parameters with values significantly associated with SAA levels, a multivariate linear regression analysis was performed. The SAA levels were entered as the dependent variables, with the other parameters being the independent variables. The statistical analysis was carried out using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA). Significance was set as $p < 0.05$ for all analyses.

RESULTS

Baseline characteristics

Baseline characteristics for PCOS and control women are shown in Table 1. PCOS women were significantly younger compared with control women ($p < 0.001$). As expected, total testosterone, insulin, and CRP were significantly higher in women with PCOS compared with control women, while progesterone and estradiol were lower in women with PCOS ($p < 0.05$ for all comparisons). The level of BMI, PRL, FSH, and glucose did not differ between the two groups ($p > 0.05$).

The median concentration of SAA was 3.700 mg/L (IQR: 2.825 - 5.400) in the healthy controls (Table 1); however, the SAA levels (median: 5.000 mg/L, IQR: 3.375 - 6.600) were significantly increased in the women with PCOS ($p = 0.025$), even after removing the extreme values in PCOS women (Figure 1A, $p = 0.044$). The concentration of CRP was 5.20 ± 0.75 mg/L in the PCOS patients, which was significantly higher than that of the healthy controls (3.12 ± 0.27mg/L; $p = 0.038$). In the univariate analysis (Table 2), the levels of SAA were found to only be positively associated with CRP ($r = 0.303$, $p = 0.006$, Figure 1B). No significant association was observed between SAA and BMI, glucose, insulin, LH, FSH, progesterone, estradiol, PRL, total testosterone, and HOMA-IR.

The associations between various SAA levels and the risk of PCOS were analyzed (Table 3). According to the SAA concentrations in control women, the quartile intervals for SAA levels were < 2.825 mg/L, 2.825 - 3.699 mg/L, 3.700 - 5.400 mg/L, and > 5.400 mg/L. The frequency of SAA levels > 5.400 mg/L in PCOS women was higher than that of control women (43.8% vs. 25.0%); however, there were no remarkable differences among the four groups ($p = 0.092$). When compared with women with SAA values below 2.825 mg/L, women with SAA > 5.400 mg/L had an approximate 1.65-fold increase in PCOS odds, but the association was not statistically significant ($p = 0.529$).

DISCUSSION

In this study, we investigated whether SAA levels were increased in women with PCOS, and whether they played a role in the associated baseline characteristics of PCOS. The results showed that the levels of SAA were significantly increased in women with PCOS. In addition, SAA was only positively correlated with the hs-CRP. These results indicate that SAA is a potential inflammatory biomarker for PCOS.

Table 2. Correlation of SAA with clinical characteristics in PCOS.

	SAA level	
Variables	**Spearman's correlation**	**p**
Age	**0.099**	**0.376**
BMI	**0.015**	**0.891**
ProG	**-0.057**	**0.612**
E2	**0.207**	**0.061**
PRL	**-0.112**	**0.314**
FSH	**0.012**	**0.916**
LH	**0.047**	**0.673**
Total testosterone	**-0.017**	**0.880**
Glucose (mmol/L)	**0.002**	**0.987**
Insulin	**0.193**	**0.082**
HOMA-IR	**0.172**	**0.123**
CRP	**0.303**	**0.006**

Table 3. Association between SAA levels and PCOS risk.

SAA (mg/L)	PCOS (n = 82)	Control (n = 60)	OR (95% CI)	OR (95% CI) [a]
< 2.825	**16**	**15**	**1 Ref**	**1 Ref**
2.825 - 3.699	**11**	**14**	**0.737 (0.256 - 2.122)**	**0.760 (0.117 - 4.938)**
3.700 - 5.400	**20**	**16**	**1.055 (0.398 - 2.795)**	**0.682 (0.136 - 3.418)**
> 5.400	**35**	**15**	**2.312 (0.917 - 5.833)**	**1.653 (0.346 - 7.895)**

[a] **- Adjusted for age, BMI, IR, and hormones.**

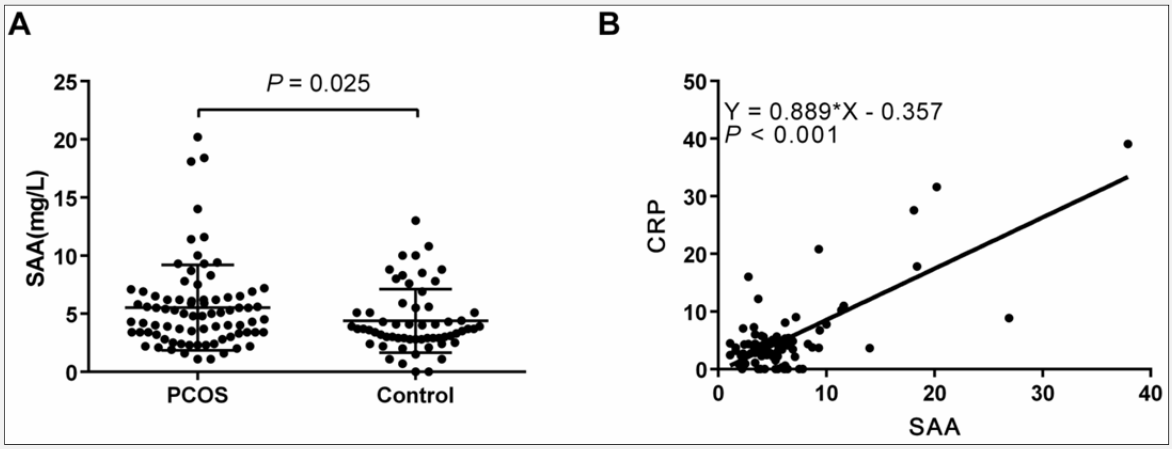

Figure 1. The SAA levels in women with PCOS. A: Compared with controls; B: Correlation between SAA and hs-CRP. Horizontal lines represent the median values and data were analyzed by Mann-Whitney *U* test (A) and Spearman's analysis (B).

PCOS is associated with low-grade systemic inflammation. SAA is also considered an inflammatory marker, and elevated SAA levels have been found in several inflammatory diseases, including pulmonary tuberculosis [25] and hepatitis [26], and play an important role in chronic inflammatory disease [27]. Cancer is a typical chronic inflammatory disease, and significantly increased SAA levels have been observed in several types of cancer [28-30]. These studies have suggested that SAA is an inflammation-related biomarker. As expected, our results showed significantly increased SAA levels in women with PCOS compared with healthy controls. Only four studies to date have reported the relationship between SAA and PCOS, and three of these studies have found elevated SAA in PCOS women compared with BMI, percentage body fat, and IR matched controls [20-22], which was consistent with our results. Contrary to our results, Manneras-Holmet et al. [23] found that SAA did not differ between 31 PCOS women when compared with the same number of controls. These inconsistent results may be caused by the different study populations, sample sizes, and methods of SAA detection in these studies.

In this study, we found that SAA was positively related with hs-CRP in women with PCOS, which is consistent with the study by Blair et al. [20]. Several studies have previously assessed the potential interplay between hs-CRP and SAA. SAA was positively correlated with hs-CRP in periodontitis [31], antiphospholipid syndrome [32], and bacterial infection in febrile and chronic obstructive pulmonary disease patients [33,34]. PCOS is also considered one of the endocrine-metabolic disorders, as hs-CRP and SAA were shown to increase simultaneously in 94 patients with metabolic syndrome [35]. These studies suggest that higher SAA may be implicated in enhanced low-grade systemic inflammation in PCOS women.

IR is also frequently observed in women with PCOS, with IR being seen in 95% of obese and 65% of lean women with PCOS [36]. Hatanaka et al. [37] have demonstrated that SAA was triggered in diabetes, and they further showed that SAA enhanced proliferation and inhibited differentiation in 3T3-L1 preadipocytes and altered insulin sensitivity. In mice, SAA links endotoxemia to weight gain and IR [38], and may be a biomarker of IR [39]. However, in this study, we did not find a significant relationship between SAA and HOMA-IR in PCOS women. The possible reason is that all the participants we randomly selected had a BMI ≤ 25 kg/m^2 because it is now known that human adipose tissue is a major SAA expression site during the non-acute-phase reaction condition [18,40]. In addition, previous studies have shown that SAA genetic polymorphisms in China were significantly associated with plasma glucose levels [41,42]; therefore, differences across racial and ethnic groups should be noted.

We analyzed the associations between various SAA levels and the risk of PCOS, and the results showed that there were no remarkable differences among various SAA levels ($p = 0.092$). Although the frequency of high SAA levels in PCOS women was higher than that of control women, but the association was not statistically significant ($p = 0.529$). In addition, we also did not find a significant association between SAA and androgen in correlation analyses ($p = 0.880$). These associations are still needed to continue this research.

This study has several limitations, for example the age between the patients and controls was not matched, and we only evaluated SAA concentrations in PCOS women with a BMI ≤ 25 kg/m^2; therefore, the levels of SAA in overweight women with PCOS compared with BMI-matched controls are still unclear. In addition, the lack of clinical and therapeutic information should be regarded as another limitation. Moreover, we did not evaluate the impact of the treatment of PCOS on SAA levels, which could help to better clarify the role of SAA in PCOS. Nevertheless, our sample size ($n = 82$) is larger than the previous studies and, moreover, we used an automatic biochemical analyzer to measure the value of SAA. The results are more stable and reliable than the ELISA method used in previous studies [20,23].

CONCLUSION

Overall, this study found that SAA levels were increased in normal-weight women with PCOS and were positively correlated with hs-CRP, but not IR status. This suggests that SAA may be a potential inflammatory biomarker for PCOS.

Acknowledgment:

This study was supported by National Natural Science Foundation of China (grant No. 81760501); Natural Science Foundation of Guangxi (grant No. 2017GXNSFAA198041); the Self-funded research project of Guangxi Zhuang Autonomous Region Health and Family Planning Commission (Grant No. Z20180177).

Declaration of Interest:

The authors have declared that no competing interests exist.

References:

1. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89:2745-9 (PMID: 15181052).

2. Glueck CJ, Dharashivkar S, Wang P, et al. Obesity and extreme obesity, manifest by ages 20-24 years, continuing through 32 - 41 years in women, should alert physicians to the diagnostic likelihood of polycystic ovary syndrome as a reversible underlying endocrinopathy. Eur J Obstet Gynecol Reprod Biol 2005;122:206-12 (PMID: 16219521).

3. Sun Y, Wu Z, Wei L, Liu C, Zhu S, Tang S. High-visfatin levels in women with polycystic ovary syndrome: evidence from a meta-analysis. Gynecol Endocrinol 2015;31:808-14 (PMID: 26422683).

4. Toulis KA, Goulis DG, Farmakiotis D, et al. Adiponectin levels in women with polycystic ovary syndrome: a systematic review and a meta-analysis. Hum Reprod Update 2009;15:297-307 (PMID: 19261627).

5. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 2013;6:1-13 (PMID: 24379699).

6. Azziz R, Marin C, Hoq L, Badamgarav E, Song P. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J Clin Endocrinol Metab 2005;90:4650-8 (PMID: 15944216).

7. Gonzalez F, Thusu K, Abdel-Rahman E, Prabhala A, Tomani M, Dandona P. Elevated serum levels of tumor necrosis factor alpha in normal-weight women with polycystic ovary syndrome. Metabolism 1999;48:437-41 (PMID: 10206434).

8. Sayin NC, Gucer F, Balkanli-Kaplan P, et al. Elevated serum TNF-alpha levels in normal-weight women with polycystic ovaries or the polycystic ovary syndrome. J Reprod Med 2003;48:165-70 (PMID: 12698773).

9. Orio F Jr, Palomba S, Cascella T, et al. The increase of leukocytes as a new putative marker of low-grade chronic inflammation and early cardiovascular risk in polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90:2-5 (PMID: 15483098).

10. Hu W, Qiao J, Yang Y, Wang L, Li R. Elevated C-reactive protein and monocyte chemoattractant protein-1 in patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2011;157:53-6 (PMID: 21530057).

11. Makedos A, Goulis DG, Arvanitidou M, et al. Increased serum C-reactive protein levels in normal weight women with polycystic ovary syndrome. Hippokratia 2011;15:323-6 (PMID: 24391413).

12. Phelan N, O'Connor A, Kyaw Tun T, et al. Leucocytosis in women with polycystic ovary syndrome (PCOS) is incompletely explained by obesity and insulin resistance. Clin Endocrinol (Oxf) 2013;78:107-13 (PMID: 22712547).

13. Chen Y, Li M, Deng H, et al. Impact of metformin on C-reactive protein levels in women with polycystic ovary syndrome: a meta-analysis. Oncotarget 2017;8:35425-34 (PMID: 28404960).

14. Yang Y, Qiao J, Li R, Li MZ. Is interleukin-18 associated with polycystic ovary syndrome? Reprod Biol Endocrinol 2011;9:7 (PMID: 21244650).

15. Glintborg D, Andersen M, Richelsen B, Bruun JM. Plasma monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1alpha are increased in patients with polycystic ovary syndrome (PCOS) and associated with adiposity, but unaffected by pioglitazone treatment. Clin Endocrinol (Oxf) 2009;71:652-8 (PMID: 19170716).

16. Deng H, Li Z, Liu G, et al. Elevated serum interferon gamma-inducible protein-10 in women with polycystic ovary syndrome. Gynecol Endocrinol 2017;33:363-7 (PMID: 28051885).

17. Urieli-Shoval S, Linke RP, Matzner Y. Expression and function of serum amyloid A, a major acute-phase protein, in normal and disease states. Curr Opin Hematol 2000;7:64-9 (PMID: 10608507).

18. Poitou C, Viguerie N, Cancello R, et al. Serum amyloid A: production by human white adipocyte and regulation by obesity and nutrition. Diabetologia 2005;48:519-28 (PMID: 15729583).

19. Sjoholm K, Lundgren M, Olsson M, Eriksson JW. Association of serum amyloid A levels with adipocyte size and serum levels of adipokines: differences between men and women. Cytokine 2009;48:260-6 (PMID: 19758820).

20. Blair SA, Kyaw-Tun T, Young IS, Phelan NA, Gibney J, McEneny J. Oxidative stress and inflammation in lean and obese subjects with polycystic ovary syndrome. J Reprod Med 2013;58:107-14 (PMID: 23539878).

21. Gidwani S, Phelan N, McGill J, et al. Polycystic ovary syndrome influences the level of serum amyloid A and activity of phospholipid transfer protein in HDL(2) and HDL(3). Hum Reprod 2014;29:1518-25 (PMID: 24842896).

22. Tan BK, Adya R, Shan X, et al. The anti-atherogenic aspect of metformin treatment in insulin resistant women with the polycystic ovary syndrome: role of the newly established pro-inflammatory adipokine acute-phase serum amyloid A; evidence of an adipose tissue-monocyte axis. Atherosclerosis 2011;216:402-8 (PMID: 20869715).

23. Manneras-Holm L, Leonhardt H, Kullberg J, et al. Adipose tissue has aberrant morphology and function in PCOS: enlarged adipocytes and low serum adiponectin, but not circulating sex steroids, are strongly associated with insulin resistance. J Clin Endocrinol Metab 2011;96:E304-11 (PMID: 21084397).

24. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19-25 (PMID: 14711538).

25. Jiang TT, Shi LY, Wei LL, et al. Serum amyloid A, protein Z, and C4b-binding protein beta chain as new potential biomarkers for pulmonary tuberculosis. PloS One 2017;12:e0173304 (PMID: 28278182).

26. Gschwantler M, Dulic M, Dulic-Lakovic E, et al. Increased levels of serum amyloid A during the early phase of hepatitis C treatment with interferon are associated with sustained virologic response-a pilot study. J Gastrointestin Liver Dis 2014;23:101-2 (PMID: 24689108).

27. Nishida E, Aino M, Kobayashi SI, et al. Serum Amyloid A Promotes E-Selectin Expression via Toll-Like Receptor 2 in Human Aortic Endothelial Cells. Mediators Inflamm 2016;2016:7150509 (PMID: 27799725).

28. Agilli M, Aydin FN, Cayci T. Serum amyloid-A increases with disease stage in squamous cell cervical cancer patients. Int J Gynecol Cancer 2015;25:344 (PMID: 25695540).

29. Ren Y, Wang H, Lu D, et al. Expression of serum amyloid A in uterine cervical cancer. Diagn Pathol 2014;9:16 (PMID: 24447576).

30. Yang M, Liu F, Higuchi K, et al. Serum amyloid A expression in the breast cancer tissue is associated with poor prognosis. Oncotarget 2016;7:35843-52 (PMID: 27058895).

31. Ardila CM, Guzman IC. Comparison of serum amyloid A protein and C-reactive protein levels as inflammatory markers in periodontitis. J Periodontal Implant Sci 2015;45:14-22 (PMID: 25722922).

32. Sciascia S, Roccatello D, Bertero MT, et al. 8-isoprostane, prostaglandin E2, C-reactive protein and serum amyloid A as markers of inflammation and oxidative stress in antiphospholipid syndrome: a pilot study. Inflamm Res 2012;61:809-16 (PMID: 22638905).

33. Lopez-Campos JL, Calero C, Rojano B, et al. C-reactive protein and serum amyloid a overexpression in lung tissues of chronic obstructive pulmonary disease patients: a case-control study. Int J Med Sci 2013;10:938-47 (PMID: 23801879).

34. Qu J, L X, Liu Y, et al. Evaluation of procalcitonin, C-reactive protein, interleukin-6 & serum amyloid A as diagnostic biomarkers of bacterial infection in febrile patients. Indian J Med Res 2015;141:315-21 (PMID: 25963492).

35. Deetman PE, Bakker SJ, Dullaart RP. High sensitive C-reactive protein and serum amyloid A are inversely related to serum bilirubin: effect-modification by metabolic syndrome. Cardiovasc Diabetol 2013;12:166 (PMID: 24209691).

36. Stepto NK, Cassar S, Joham AE, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp. Hum Reprod 2013;28:777-84 (PMID: 23315061).

37. Hatanaka E, Monteagudo PT, Marrocos MS, et al. Interaction between serum amyloid A and leukocytes - a possible role in the progression of vascular complications in diabetes. Immunol Lett 2007;108:160-6 (PMID: 17267050).

38. de Oliveira EM, Ascar TP, Silva JC, et al. Serum amyloid A links endotoxaemia to weight gain and insulin resistance in mice. Diabetologia 2016;59:1760-8 (PMID: 27126803).

39. Scheja L, Heese B, Zitzer H, et al. Acute-phase serum amyloid A as a marker of insulin resistance in mice. Exp Diabetes Res 2008;2008:230837 (PMID: 18584041).

40. Poitou C, Coussieu C, Rouault C, et al. Serum amyloid A: a marker of adiposity-induced low-grade inflammation but not of metabolic status. Obesity (Silver Spring) 2006;14:309-18 (PMID: 16571858).

41. Xie X, Ma YT, Yang YN, et al. SAA1 genetic polymorphisms are associated with plasma glucose concentration in non-diabetic subjects. Clin Chem Lab Med 2013;51:2331-4 (PMID: 23940069).

42. Zhang X, Tang QZ, Wan AY, et al. SAA1 gene variants and childhood obesity in China. Lipids Health Dis 2013;12:161 (PMID: 24171731).