DECREASED SEX HORMONE-BINDING GLOBULIN

by Muhammad Irsan Saleh

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DECREASED SEX HORMONE-BINDING GLOBULIN (SHBG) SERUM LEVEL IN POLYCYSTIC OVARIAN SYNDROME PATIENTS (PCOS)

Penurunan Kadar Sex Hormone-Binding Globulin Serum (SHBG) pada Pasien Polycystic Ovarian Syndrome Patients (PCOS)

Azalia Talitha Zahra[1], M. Irsan Saleh[2], Zen Hafy[3], Yusuf Effendi[4], Ziske Maritska[5], Iche Andriyani Liberty[6]

AFFILITIONS
1. Biomedical Science Master Program, Faculty of Medicine, Sriwijaya University
2. Department of Pharmacology, Faculty of Medicine, Sriwijaya University
3. Department of Histology, Faculty of Medicine, Sriwijaya University
4. Department of Obstetrics and Gynecology, Faculty of Medicine, Sriwijaya University
5. Department of Biology, Faculty of Medicine, Sriwijaya University
6. Department of Public Health, Faculty of Medicine, Sriwijaya University

ABSTRACT

Classic symptoms of PCOS including irregular menstruation, high serum androgen concentration, hirsutism, and infertility or subfertility. Low serum sex hormon binding globulin (SHBG) may cause increase of free serum androgen which in turn may cause ovarian dysfunction and clinical symptoms associated with hyperandrogenism. This study aims to look the difference of serum SHBG concentration in PCOS patients and healthy control in Palembang, South Sumatra. This was a case-control study involved 36 PCOS patients and 36 healthy controls. Patient serum was collected and SHBG concentration was conducted using ELISA according to manufacturer instruction. Median serum SHBG concentration in PCOS case group was 152.524 nmol/L (min. 5.756 nmol/L, max. 1539.383 nmol/L). meanwhile, median serum SHBG concentration in control group was 971.449 nmol/L (min. 114.479 nmol/L, max. 1944.036 nmol/L). The difference was found to be statistically significant, with $p < 0.001$ according to Mann-Whitney test. It is to be concluded that serum SHBG concentration is significantly lower in PCOS patient group compared to healthy control.

KEYWORDS:
PCOS, Serum SHBG Level

ABSTRAK

Gejala khas PCOS berupa berupa haid tidak teratur, kadar androgen serum yang tinggi, hirsutisme, dan infertilitas atau subfertilitas. Kadar sex hormon binding globulin serum yang rendah menyebabkan peningkatan kadar androgen bebas di serum yang dapat menyebabkan disfungsi ovarium dan gejala klinis yang terkait hiperandrogenisme. Penelitian ini bertujuan untuk melihat perbedaan kadar SHBG serum pada pasien PCOS dan kontrol sehat di Palembang, Sumatra Selatan. Penelitian ini menggunakan metode case control dengan sampel 36 pasien PCOS dan 36 kontrol sehat. Serum darah pasien diambil dan kadar SHBG diperiksa menggunakan ELISA sesuai instruksi pembuat. Kadar SHBG median pada kelompok kasus PCOS adalah 152,524 nmol/L (min. 5,756 nmol/L, maks. 1539,383 nmol/L). sementara itu, kadar SHBG median pada kelompok kontrol adalah 971,449 nmol/L (min. 114,479 nmol/L, maks. 1944,036 nmol/L). Perbedaan tersebut bermakna secara statistik dengan p< 0,001 dengan uji Mann-Whitney. Dapat disimpulkan bahwa kadar SHBG serum pada subjek dengan PCOS lebih rendah secara bermakna dibandingkan dengan kelompok kontrol.

KATA KUNCI:
PCOS, Kadar Serum SHBG

CORRESPONDING AUTHOR:
Azalia Talitha Zahra
azaliatz@gmail.com

INTRODUCTION

Polycystic ovarian syndrome (PCOS) symptoms include irregular menstruation, high serum androgen level, and polycystic ovaries. Although PCOS presentation is diverse, some common symptoms exist (Yang *et al.*, 2021). PCOS may manifest as oligo-amenorrhea, hirsutism, and/or infertility. PCOS risk factors include insulin resistance. Insulin resistance in PCOS create metabolic syndrome, hypertension, dyslipidemia, glucose intolerance, and diabetes. Depression, anxiety, bipolar disorder, and eating disorder are also common finding in PCOS patients (Sirmans and Pate, 2013).

Previous research in Europe shows BMI (body mass index) of the subjects with PCOS were higher than controls. Anisya (2019) states that 38-88% of women with PCOS are estimated to be overweight or obese (Anisya, 2019). This is also supported by complaints of oligomenorrhea which are generally complained of after excessive weight gain. Obesity in PCOS is associated with lower SHBG levels, as can be seen in this study where SHBG levels were lower in the PCOS group compared to the control group. Elevated insulin levels, as seen in PCOS, can inhibit SHBG synthesis and secretion because insulin suppresses SHBG synthesis. Suppression of SHBG synthesis causes an increase in free testosterone levels, which in turn exacerbates insulin resistance and increases insulin secretion as a release mechanism, creating a vicious circle. Obesity increases insulin resistance, which in turn increases insulin secretion as a form of insulin resistance, which suppresses SHBG production.

Hyperinsulinemia may disrupt theca cells of endometrium and increase androgen level. Increased serum androgen in turn reduces hepatic synthesis of sex hormone-binding globulin (SHBG), major plasma transporter for sex steroid (Ajmal *et al.,* 2019). SHBG in circulation has high affinity and selectivity for free testosterone and estradiol. SHBG also regulates free sex steroids in circulation. Meanwhile, serum SHBG is dependent on hormonal, metabolic, and nutritional status (Hogeveen *et al.,* 2001). Low serum SHBG is common in PCOS patients. Decreased SHBG concentration is also commonly used as indicator for hyperandrogenism in PCOS. Low SHBG concentration is also considered to be an important biomarker for abnormal metabolism and related to insulin resistance and other metabolic disorders in PCOS (Zhu *et al.,* 2019).

Although SHBG concentration is commonly decreased in PCOS, the main cause of decreased SHBG synthesis is unknown, but hypothesized to be related with genetic variation (McAllister *et al.,* 2015), such as repeat (TAAAA)n polymorphism in SHBG promoter region (Fan *et al*., 2013).

In this study, we explore difference between serum SHBG PCOS patients and normal population in Palembang, South Sumatra. As far as our knowledge, this is the first study exploring difference of serum SHBG concentration in PCOS and control group in Palembang population.

METHODS

Our study is case-control study involving 36 clinically-diagnosed PCOS patient and 36 healthy controls. Our study was conducted in July to August, 2022 in Palembang. After obtaining informed consent from all participants, we collected serum from all subjects involved. After sufficient samples were obtained, we conducted ELISA measurement using Invitrogen® Human SHBG ELISA kit (Cat. No. EH421RB) according to manufacturer instruction in Biomedical Laboratory, Faculty of Medicine,

Sriwijaya University. Data obtained was analyzed using SPSS® version 25 (IBM™) to measure significant difference between two groups with Mann-Whitney test. This study has been granted ethical approval from KEPKK FK UNSRI (Protocol No. 180-2022)

RESULTS AND DISCUSSIONS

Table 1. Subjects Characteristics

	PCOS (n = 36) Median (min-max)	Control (n = 36) Median (min-max)	*p-value*	Spearman's correlation
Age (years)	27.00 (22-33)	26.50 (22-33)	0.558	-
BMI	24.28 (18.03-35.00)	20.94 (15.24-30.82)	0.009*	0.312
Menarche (years)	13.0 (11-17)	12.0 (11-15)	0.045*	0.238
Serum SHBG (nmol/L)	152.254 (5.756-1539.383)	971.449 (114.478-1944.036)	<0.001*	-0.654

*significant

Our result showed significantly lower serum SHBG in PCOS group compared to healthy control (p< 0,001) with moderate negative correlation (-0.654), although median age of menarche was older in PCOS group, the correlation was weak (0.238) therefore we did not pursue investigation for relationship of menarche and PCOS. *Sex hormone-binding globulin* (SHBG) plays role in regulating bioavailability and sex steroid action on its target receptor (Guadarrama-García *et al.*, 2020). In human, SHBG regulates availability and effect of both testosterone and estrogen on its target organ.(Zhu *et al.*, 2019) SHBG is also produced in placenta, testes, brain, and endometrium. Placental SHBG is suspected to regulate fetal exposure to androgen (Xita and Tsatsoulis, 2010).

Anisya (2019) stated that 38-88% PCOS patients are overweight or obese (Anisya, 2019). Obesity on PCOS is related with low SHBG concentration (Luo *et al.*, 2020; Zhu *et al.,* 2019). In this study, we found that serum SHBG concentration is significantly lower on PCOS compared to control. Hyperinsulinemia, as is common on PCOS, may reduce SHBG synthesis and secretion. Reduced SHBG synthesis also increases free testosterone level, further stimulating compensatory hyperinsulinemia (Zhu *et al.,* 2019). Obesity also creates insulin resistance, further worsening hyperinsulinemia and PCOS (Xing *et al.,* 2022).

In short, obesity in PCOS patients are co-related via mechanism of increased free testosterone, hyperinsulinemia, insulin resistance, and compensatory hyperinsulinemia, creating endless loop conducive for obesity commonly found in PCOS patients(Xing *et al.*, 2022; Zhu *et al.*, 2019).**Table 2. Symptoms of PCOS**

Symptoms		Median (min-max) serum SHBG, nmol/L	*p-value*	Spearman's correlation
Oligo-amenorrhea	Oligo-amenorrhea (n = 45)	947.538 (21.981-1944.036)	<0.001*	-0.494
	Normal cycle (n = 27)	142.491 (5.756-1539.383)		
Hirsutism	Hirsutism found (n = 21)	182.721 (5.756-1539.383)	0.002*	-0.371
	No hirsutism (n = 51)	771.842 (21.981-1944.036)		

*significan

Further, our study shows low correlation between oligo-amenorrhea and hirsutism with serum SHBG concentration (-0.494 and -0.371, respectively), although the difference is significant in both groups ($p < 0.001$ and $p = 0.002$, respectively). Considering that reduced serum SHBG concentration increases free testosterone activity (Ajmal *et al.,* 2019; Hogeveen *et al.,* 2001; Zhu *et al.,* 2019), we suspect that high testosterone activity causing hirsutism and suppression of ovaries seen as oligo-amenorrhea is caused in part by low SHBG concentration as seen in our study.

Our study is in accordance with meta-analysis by Deswal *et al.* showing significantly lower serum SHBG concentration in PCOS (SMD: -1.11; 95%CI -1.63 to -0.60) (Deswal *et al.,* 2018). Our result is also in accordance with another study showing significantly lower serum SHBG in PCOS (37.9 ± 26.4 nmol/L vs 60.5 ± 26.7 nmol/L, $p < 0.001$) (Xita *et al.,* 2008). Further proof of SHBG role in PCOS came from another review showing increased serum SHBG concentration measured after successful treatment of PCOS (Xing *et al*., 2022).

Due to increased free testosterone in PCOS, hepatic SHBG synthesis is reduced. Reduced SHBG synthesis decreased available SHBG to bind free testosterone, creating worsening spiral and also worsening ovarian dysfunction (Xing *et al.,* 2022). Further, decreased SHBG concentration also affect free testosterone, creating and worsening hyperandrogenemia and subsequent ovarian dysfunction with related clinical symptoms seen in PCOS (Qu and Donnelly, 2020; Xing *et al.,* 2022).

Serum SHBG concentration is significantly affected by different factors, including free testosterone, insulin, and adiponectin(Crawford *et al.,* 2015). Further, SHBG concentration can be affected by genetic variation, including TAAAA(n) polymorphism. Length of TAAAA(n) repetition on promoter region of *SHBG* affects transcription activity, with six or more repetition of TAAAA sequence silenced *SHBG* transcription (Cousin *et al.,* 2004). Some studies has also found that rs1799941, rs6257, rs6259, rs727428 SNPs is able to influence serum SHBG concentration in PCOS patients(Martínez-García *et al.,* 2012). It is possible that genetic variations in our study population affects our serum SHBG concentration.

Our study is limited by the fact that serum SHBG concentration is affected by many different factors, thus we are unable to pinpoint the exact reason of lower serum SHBG in our study, although we believe that insulin resistance and genetic variation may play some role.

CONCLUSION

Our result showed significantly lower serum SHBG concentration on PCOS patients compared to healthy control.

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REFERENCES

Ajmal, N., Khan, S. Z., and Shaikh, R. 2019. Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article. *Eur J Obstet Gynecol Reprod Biol X.* 3. P: 100060.

Anisya, V., Puspitasari, R.D., Hanriko, R., dan Graharti, R. 2019. Policystic Ovary Syndrom: Resiko Infertilitas yang dapat Dicegah melalui Penurunan Berat BadanPada Wanita Obesitas. *Medula.* 9 (2). Pp: 257-65

Cousin, P., Calemard-Michel, L., Lejeune, H., Raverot, G., Yessaad, N., Emptoz-Bonneton, A., Morel, Y., and Pugeat, M. 2004. Influence of SHBG Gene Pentanucleotide TAAAA Repeat and D327N Polymorphism on Serum Sex Hormone-Binding Globulin Concentration in Hirsute Women. *J Clin Endocrinol Metab.* 89(2). Pp: 917–24.

Crawford, T. N., Arikawa, A. Y., Kurzer, M. S., Schmitz, K. H., and Phipps, W. R. 2015. Cross-sectional study of factors influencing sex hormone-binding globulin concentrations in normally cycling premenopausal women. *Fertil Steril.*104(6). Pp: 1544–51.

Deswal, R., Yadav, A., and Dang, A. S. 2018. Sex hormone binding globulin - an important biomarker for predicting PCOS risk: A systematic review and meta-analysis. *Syst Biol Reprod Med.* 64(1). Pp: 12–24.

Fan, W., Li, S., Chen, Q., and Huang, Z. 2013. Association between the (TAAAA)n SHBG polymorphism and PCOS: A systematic review and meta-analysis. *Gynecol Endocrinol.* 29(7). Pp: 645–50.

Guadarrama-García, C., Bello, M., and Soriano-Ursúa, M. 2020. Molecular insights into how SHBG dimerization exerts changes on ligand molecular recognition. *J Steroid Biochem Mol Biol.* 197. 105502.

Hogeveen, K. N., Talikka, M., and Hammond, G. L. 2001. Human Sex Hormone-binding Globulin Promoter Activity Is Influenced by a (TAAAA) n Repeat Element within an Alu Sequence. *J Biol Chem.* 276(39). Pp: 36383–90.

Luo, X., Yang, X. M., Cai, W. Y., Chang, H., Ma, H. L., Peng, Y., and Wu, X. K. 2020. Decreased Sex Hormone-Binding Globulin Indicated Worse Biometric, Lipid, Liver, and Renal Function Parameters in Women with Polycystic Ovary Syndrome. *Int J Endocrinol.* 2020:7580218

Martínez-García, M. Á., Gambineri, A., Alpañés, M., Sanchón, R., Pasquali, R., and Escobar-Morreale, H. F. 2012. Common variants in the sex hormone-binding globulin gene (SHBG) and polycystic ovary syndrome (PCOS) in Mediterranean women. *Hum Reprod.* 27(12). Pp: 3569–76.

McAllister, J. M., Legro, R. S., Modi, B. P., and Strauss, J. F. 2015. Functional genomics of PCOS: from GWAS to molecular mechanisms. *Trends Endocrinol Metab.* 26(3). Pp:118-124.

Qu, X., and Donnelly, R. 2020. Sex hormone-binding globulin (SHBG) as an early biomarker and therapeutic target in polycystic ovary syndrome. *Int J Mol Sci.* 21 (21). Pp: 1–17.

Sirmans, S.M. and Pate, K.A. 2013. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clin Epidemiol.* 6. Pp:1-13.

Xing, C., Zhang, J., Zhao, H., and He, B. 2022. Effect of Sex Hormone-Binding Globulin on Polycystic Ovary Syndrome: Mechanisms, Manifestations, Genetics, and Treatment. *Int J Womens Health.* 14. Pp: 91–105

Xita, N., Georgiou, I., Lazaros, L., Psofaki, V., Kolios, G., and Tsatsoulis, A. 2008. The synergistic effect of sex hormone-binding globulin and aromatase genes on polycystic ovary syndrome phenotype. *Eur J Endocrinol.* 158(6). Pp: 861–5.

Xita, N., and Tsatsoulis, A. 2010. Molecular and Cellular Endocrinology Genetic variants of sex hormone-binding globulin and their biological consequences. *Mol Cell Endocrinol.* 316. Pp: 60–5.

Yang, Y., Xia, J., Yang, Z., Wu, G., and Yang, J. 2021. The abnormal level of HSP70 is related to Treg/Th17 imbalance in PCOS patients. *J Ovarian Res.* 14(1). Pp: 1–9.

Zhu, J. ling, Chen, Z., Feng, W. jie, Long, S. lian, and Mo, Z. C. 2019. Sex hormone-binding globulin and polycystic ovary syndrome. *Clin Chim Acta.* 499. Pp: 142–8.

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