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Is there a role for resistin in the pathogenesis of polycystic ovary syndrome in Sudanese women?

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Resistin is a polypeptide hormone firstly identified in mice adipocytes. The role of resistin in the pathogenesis of polycystic ovary syndrome (PCOS) is controversial. This cross-sectional case–control study was conducted to evaluate the possible involvement of resistin in the pathogenesis of PCOS in Sudanese women with PCOS, in relation to insulin levels, insulin resistance (IR), and body mass index (BMI).Three hundred women were enlisted in this study. Two hundred were cases with PCOS; and 100 healthy women without PCOS as controls. The mean BMI of the PCOS group was (27.8 ± 6 kg/m^2) versus (24.5±4.9 kg/m^2) in controls (P =0.000). The mean age in PCOS patients was (27.2 ± 4.9 years), versus (27.5±3.9 years) in controls. The mean serum resistin among women with PCOS was (3549.4±1571.2 pg/mL) versus (2012.1±1501.3 pg/mL) in controls; (P = 0.000).The mean serum resistin within obese/overweight women with PCOS was (3610.7±1574.2 pg/ml) versus (2163.4±1664.1 pg/ml) in obese/overweight controls (P = 0.000). The mean serum resistin through normal weight women with PCOS was (3457.5±1572.1 pg/ml) versus (1860.7±1318.3 pg/ml) in normal weight controls (P = 0.000). The mean serum insulin in women with PCOS was (16.4±13.2 mU/L) versus (10.1±4.2 mU/L) in controls (P = 0.000). The mean IR among women with PCOS was (3.9±3.5) versus (2.2±1.1) in controls (P = 0.000). Resistin was significantly positively correlated with BMI (P=0.003), fasting insulin (P=0.000) and the degree of IR (P= 0.001). In Sudanese women with PCOS; resistin significantly increases and positively correlates with insulin levels, insulin resistance and body mass index. Resistin may play an important role in the pathogenesis of PCOS.

Keywords:resistin, polycystic ovary syndrome, insulin, insulin resistance, body mass index, Sudan.

INTRODUCTION

Resistin is a 12.5 kDa polypeptide adipokine (Sartori et al., 2016). Adipokines are proteins and bioactive peptides molecules which are secreted by adipose tissue and have paracrine or endocrine actions [Andrade-Oliveira et al., (2015)]. Adipokines are involved in many processes in the body; such as glucose metabolism and modulation of insulin resistance (Michalakis and Segars 2010). Change in adipokines can lead to a metabolic disturbance that plays a major role in the development of metabolic disorders (Pereira and Alvarez-Leite 2014). The name of resistin has come from its ability to interfere with the action of insulin leading to insulin resistance (Sartori et al., 2016);

(Codoñer-Franch and Alonso-Iglesias 2015). In human; resistin mainly expressed by peripheral blood mononuclear cells and macrophages(Park et al., 2017)].Resistin is expressed by the RETN gene, located at position 19 of chromosome 19p 13.3 (Codoñer-Franch and Alonso-Iglesias2015); it has two isoforms low molecular weight (LMW) and high molecular weight (HMW) (Park et al., 2017); Cao (2014). Resistin was firstly identified in mice adipocytes in 2001, in a screen for adipocyte genes that are inhibited by insulin-sensitizing drugs (Steppan et al., 2001); (Park et al., 2017). Resistin mediates its action through binding to the receptor in the target cells [Pereira and Alvarez-Leite (2014)]. It has been suggested that in human the resistin acts through Toll-like receptor 4 (TLR4) (Sartori et al., 2016); (Park et al., 2017)]. Binding of resistin to its receptor activates two signaling pathways; nuclear factor kappa (NFκB) and mitogen-activated protein kinase (MAPK), that most likely changes in insulin signaling (Codoñer-Franch and Alonso-Iglesias 2015). Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in the women of reproductive age [Bednarska and Siejka (2017); Sharma (2015)]. The diagnostic criteria of PCOS have been the subject of debate for many years [Dewailly (2016)]. The exact cause of PCOS is unknown [Andrade et al., (2016)], but both genetic and environmental factors are implicated [Franks S (2013)]. The prevalence of PCOS varies by geographic region; the prevalence is ranging from 1 to 19% according to the population and the sample size (Bellver et al., 2017); Merkin et al., (2016); (Dargham et al., 2017)]. The role of resistin in the pathogenesis of PCOS is controversial; several studies demonstrated that resistin was significantly increased in women with PCOS (Wang et al., 2010); Nambiar et al., (2016)]; other studies showed no significant correlation between resistin and PCOS (Spanos et al., 2012); (Dikmen et al., 2011); Pangaribuan et al., (2011)].

The present study aimed to assess the serum levels of resistin in Sudanese women with PCOS, in relation to insulin levels, insulin resistance, and body mass index compared to apparently healthy control women.

MATERIALS AND METHODS

This cross-sectional case-control study was conducted in Reproductive Health Care Center in Khartoum, Sudan, which is a specialized center for the diagnosis and treatment of infertility. The research was done in the period from May 2017 to December 2018. Three hundred Sudanese women were included in this study. Two hundred were women with confirmed PCOS; who were sub grouped as: (120) obese or overweight group with (BMI ≥ 25), and (80) normal weight group with (BMI < 25), according to Rotterdam criteria (The Rotterdam 2004); these were included as patients' group. Besides 100 apparently healthy Sudanese women with regular menstrual cycles involved as a control group; which in turn sub grouped to (50) obese or overweight group with (BMI ≥ 25) and (50) normal weight group with (BMI < 25).

The diagnosis of all PCOS was done by an expert gynecologist, who runs the management as well as operating the ultrasound.

After signing informed consent; the socio-demographic characteristics, medical and gynecological history were taken from each patient using a questionnaire. The body weight and height of all participants were measured. Body mass index (BMI) was calculated by dividing the weight in (kg) by the squared height (m2). About 5 ml of venous blood were collected from each participant after overnight fasting in the morning (between 0800 and 1100 am). Samples were collected under standard procedure under aseptic conditions and placed in plain containers; samples were allowed to clot for half an hour and then centrifuged for 5 minutes at 2000 RPM to obtain the serum. The serum was separated in new plain containers. Resistin was measured by using a sandwich ELISA kit for quantitative detection for human resistin (EK0581) from Boster Biological Technology Co., Ltd.USA; the concentration of resistin in the samples was obtained automatically by a microplate reader [Linear GEA] at 450nm. The quantitative measurement of insulin was carried out using the TOSOH Automated Immunoassay Analyzer AIA-600II (Japan) instrument by using commercial insulin ELISA kits provided by TOSOH. Glucose levels were measured immediately via an enzymatic colorimetric method using BA-88A chemistry analyzer. The IR was calculated using the homeostatic model assessment (HOMA) equation (HOMA-IR= (Glucose (mg/dl) x insulin (mU/L))/ 405) (Condorelli et al., 2017)

Data were analyzed by a computer program IBM (SPSS) version 20.

RESULTS

The mean age in all PCOS patients was (27.2 ± 4.9 years), versus (27.5±3.9 years) in controls

Table 1.A comparison study of the serum resistin between polycystic ovary syndrome groups and their control groups.

	All PCOS Cases (n=200)	All non PCOS Control (n=100)	Overweight & obese PCOS (n=120)	Overweight & obese Control (n=50)	Normal-Weight PCOS (n=80)	Normal-Weight control (n=50)
BMI (kg/m$^{2)}$	27.8±6*	24.5+4.9	31.5±4.7**	28.2±4.1	22.2±2.2***	20.8±1.9
Resistin (pg/ml)	3549.4±1571.2 *	2012.1±1501.3	3610.7±1574.2**	2163.4±1664.1	3457.5±1572.1***	1860.7±1318.3
Fasting Insulin (mU/L)	16.4±13.2*	10.1±4.3	17.8±11.8**	10.5±3.9	14.3±14.8***	9.5±4.5
Insulin resistant (IR)	3.9+3.5*	2.2±1.1	4.1±3.2**	2.3±1.1	3.7± 3.9***	2.1±1.1

Data are presented as mean ± SD.
* P < 0.05 for difference between respective all PCOS cases and their control groups.
**P < 0.05 for difference between respective overweight with PCOS and the overweight with non-PCO control groups.
*** P < 0.05 for difference between respective normal-weight with PCOS and normal-weight with non-PCOS control groups.

Table 2.Pearson correlation (P.value and r) of serum resistin with body mass index, fasting insulin, and insulin resistance in Sudanese women with polycystic ovary syndrome.

	BMI	INSULIN	HOMA-IR
r	.170	.210	.191
p	.003*	.000*	.001*

*. Correlation is significant P < 0.05.

This study revealed that the mean BMI of all PCOS group was (27.8 ± 6 kg/m^2) versus (24.5±4.9 kg/m^2) in controls (P = 0.000).

The mean serum levels of resistin among women with PCOS was (3549.4±1571.2 pg/mL), and (2012.1±1501.3 pg/mL) in controls women (P = 0.000) (Table 1). The mean serum levels of resistin among obese/overweight women with PCOS was (3610.7±1574.2 pg/ml) versus (2163.4±1664.1 pg/ml) in their controls (P = 0.000) (Table 1). Mean serum levels of resistin in normal weight women with PCOS was (3457.5±1572.2 pg/ml); while in the normal weight controls was (1860.7±1318.3 pg/ml) (P = 0.000) (Table 1).

The mean fasting insulin levels among women with PCOS was (16.4 ± 13.2 mU/L) while in their control group was (10.1 ± 4.3 mU/L) (P = 0.000) (Table 1).Serum levels of insulin in obese/overweight women with PCOS was (17.8±11.8 mU/L) comparing to (10.5±3.9 mU/L) in women without PCOS (P = 0.000) (Table 1).Serum levels of insulin among normal weight women with PCOS was (14.3±14.8 mU/L) while in the controls group was (9.5±4.5mU/L) (P = 0.015) (Table 1).

The mean insulin resistance among women with all PCOS group was (3.9±3.5) while in women without PCOS was (2.2±1.1) (P = 0.000) (Table 1). The mean insulin resistance in obese/overweight women with PCOS was (4.1±3.2) versus (2.3±1.1) in their controls group (P = 0.000) (Table 1). The mean insulin resistance among normal weight women with PCOS was (3.7± 3.9) while in normal weight control group was (2.1±1.1) (P = 0.003) (Table 1).

Resistin was significantly positively correlated with BMI (P = 0.003), fasting insulin (P = 0.000) and the degree of insulin resistance (P = 0.001) (Table 2).

DISCUSSION

The role of resistin in the pathogenesis of PCOS is controversial. In the present study, the serum resistin levels in obese/ overweight and normal weight Sudanese women with PCOS groups were significantly higher than their control groups (P=0.000); these results are consistent with results of a previous study in three Chinese studies conducted by (Wang et al., 2010) and (Chu et al., 2009) (Wang and Zhu 2012). this study also in agreement with Indian study reported by Nambiar et al., (2016) who concluded that polymorphisms of the resistin gene play a role in increasing the risk of PCOS. Another study by

(Yilmaz et al., 2009) reported significantly increased resistin levels in PCOS patients Yilmaz et al., (2009). Munir et al., found in their study, there was a 40% increase in resistin concentrations in the serum of women with PCOS compared with control women (Munir et al. 2005). (Wang and Zhu 2012) reported that resistin level was significantly higher in obese PCOS than in non-obese PCOS patients, which indicated that a relationship probably exists between adipokines and PCOS with body fat mass Wang and Zhu (2012). In an Iranian study done by Farshchian et al., (2014); they found that serum levels of resistin were higher among both obese and normal-weight women with PCOS, and this increase is due to the upregulation expression of resistin in the women with PCOS. This study is in disagreement, with a study of Spanos et al., (2012) in Greek women who found that serum level of resistin did not differ in women with PCOS and resistin do not appear to play major pathogenic roles in overweight/obese patients with polycystic ovary syndrome. This study also in contrary with Taiwanese study conducted by(Shen et al., 2015) who found that there was no difference in the serum resistin levels between the PCOS cases and the controls, and the serum resistin level is not a good marker for PCOS. Alshammari et al., (2017) reported that there were no differences between obese patients and obese controls in levels of adipocytokines including resistin; they concluded that there were no effects of PCOS on the expression of any of the adipocytokines genes measured in subcutaneous adipose tissue. In this study; serum insulin levels in obese/ overweight and normal weight PCOS groups were significantly higher than those in the control groups (P = 0.000) these results are inconsistent with results of several previous studies reported by (Wang et al., 2010); (Wang and Zhu 2012); (Munir et al., 2005) and(Chu et al., 2009). In the present study; insulin resistance levels in obese/ overweight and normal weight PCOS groups are significantly higher than those in the control groups (P = 0.000) these results are in agreement with findings of many previous studies like; (Wang et al., 2010); Munir et al., (2005) (Chu et al., 2009). In this research; serum resistin levels in PCOS women positively correlate with insulin levels and insulin resistance (HOMA-IR), indicating that resistin is one of the adipocytokinesthat regulating IR in PCOS; this result was also concluded by a group of previous studies done by (Wang et al., 2010); Munir et al., 2005) (Chu et al. 2009). In the same line; Kawashima et al., (2003) cultured 3T3-Ll adipose cells with insulin, and found that resistin participated in the development of IR. In the present study; serum resistin level in PCOS patients is significantly correlated with BMI; this result is consistent with a Turkish study reported by Dikmen et al., (2011).

CONCLUSION

Serum resistin in Sudanese women with polycystic ovary syndrome was found to be significantly increased; we suggest that resistin may play an important role in the pathogenesis of PCOS through the development and progression of insulin resistance.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

Ahmed M. Asmali**:** was responsible for designing the research project,data collection, specimen's analysis, laboratory work, and writing of the paper and communication with the authorities, he is the corresponding author.

EltayebTayrab:was responsible fordata analysis and writing the manuscript.

Samia Mahdi Ahmed:was responsible fordesigning the research project, data collection and communication for the approval.

Abdelatif Ashmaig Khalifa: diagnosis of PCOS cases by the aid three-dimensional ultrasound imaging in the Reproductive Health Care Center.

Zuhier Ahmed Awan:was responsible forthe logistic support of the research project.

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