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Suppressor of cytokine signaling-3 in pregnant females with or without hypertension

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Suppressor of cytokine signaling-3 in pregnant females with or without hypertension

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Abstract

Suppression of Cytokine Signalling-3 (SOCS-3) modulates the inflammatory pathways responsible for vascular stability. Therefore, we aimed to estimate SOCS-3 levels in 2nd trimester pregnant females and correlate it with blood pressure. A case control study recruiting (n=111) females was conducted at the Aga Khan University. They were classified as pregnancy induced hypertensives or normotensive as per American College of Obstetricians and Gynecologists Guidelines. Weight, Body mass index, lipid profile and blood glucose were recorded while SOCS-3 was measured by ELISA. Higher SOCS-3 levels were seen in hypertensive group (30 pg/ml) versus normotensive (16 pg/ml). Both Systolic & diastolic blood pressure ($r=0.520$; $p<0.001$) ($r=0.490$; $p<0.001$) showed an independent significant positive correlation with SOCS-3 level. It is safe to suggest that SOCS-3 has an association of causing high blood pressure. However, more research needs to be conducted to establish a mechanism and chronological order to these events in a pregnant female.

Keywords: Hypertension, Pregnancy, SOCS-3, Obesity.

Introduction

Pregnancy induced hypertension (PIH) is the development of new hypertension in a pregnant woman 20 weeks after gestation without the presence of protein in the urine or other signs of preeclampsia.PIH complicates around 6-10% of all pregnancies around the world.[1] These complications include pre-eclampsia, nervous system dysfunction, pulmonary oedema, elevated liver enzymes during pregnancy in the mother[2] and for the foetus, it may lead to intrauterine growth restriction (IUGR), premature birth or even death in extreme conditions.[1] In Pakistan itself, the morbidity and mortality are significantly higher — of 100 cases admitted for PIH, complications were seen in 98, one of them resulting in death due to inadequate antenatal management.[3,4]

The underlying cause of gestational hypertension in humans is commonly believed to be an improperly implanted placenta, or abnormal levels of inflammatory cytokines. The hypothesised mechanism by which PIH occurs is that the pro inflammatory state seen in pregnancy can lead to vascular damage and hypertension. This can be accounted by multiple possible factors, such as a low anti-oxidant/oxidant ratio, which would suggest that reactive oxygen species are able to cause more damage to the blood vessels in the pregnant females.[1] Some cases have been seen where there is increased natural killer cell function (due to increased production of stimulatory cytokines) which is the potential cause for the damage that leads to the development of high blood pressure.[5]

One such protein is called the Suppression of Cytokine Signaling (SOCS) which has a family of eight members (SOCS1-7 and CIS). These are modulators of the inflammatory pathway, that act by inhibiting the activation of Janus kinase-signal transducer and is activator of transcription (JAK-STAT) pathway to transmit their information into the cell nucleus. This is achieved by three potential routes (a) inhibiting JAK proteins that have been activated directly, (b) being a competitive antagonist for STAT proteins, and (c) up regulating the proteasome lists of the STAT complexes. In this way, SOCS is said to be involved in the regulation of the

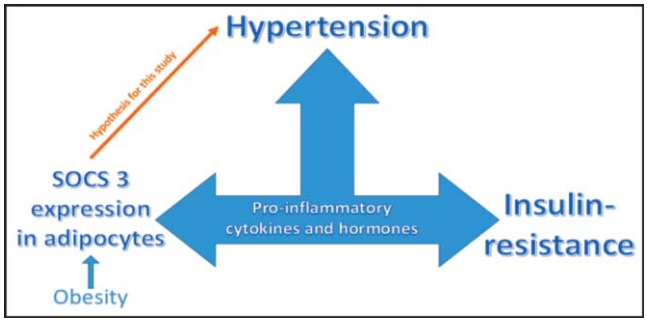

Figure-1A: Hypothetical diagram of SOCS 3 and its role in hypertension.

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inflammatory mediators, controlling the degree of the adverse effect.[6] Lately, additional roles are identified in suppressing the inflammatory pathways in the immune system and in cancer biology.[7] Yet, the functional importance of SOCS-3 in regulating vascular health is largely unknown but may be taken as an upcoming marker for metabolic diseases[8] (Figure-1A). Therefore, we aimed to estimate SOCS-3 levels in 2nd trimester pregnant females and correlate the levels with blood pressure.

Subjects and Methods

A case control study was conducted at the Aga Khan University, Karachi from January 2017 till February 2018. Inclusion criteria included pregnant females in their 2nd trimester (13 to 27 weeks) between the ages of 20-35 years. While females with any comorbid such as gestational diabetes, twin pregnancies, chronic cardio metabolic illness or infectious diseases such as HIV, HBV, HCV or females on anti-inflammatory medication, were excluded from the study. Furthermore, females with pre-existing hypertension, and complicated cases were excluded from this study. The sample size was calculated using the Open-Epi website,[9] with 1:1 distribution of cases and controls, where confidence level of 95%, power of 80%, least extreme odds ratio (OR) of 2 and a pregnancy hypertension prevalence of 8% was chosen as this was the result according to previously published data sources.[10] The minimum sample size calculated for this research was 106.More than 150 pregnant ladies were contacted from the outpatient clinics and community health centre waiting room areas, and a total of 111 females agreed to participate and were recruited for this study. All the study participants gave a written and informed consent to participate in the study. Weight, height, BMI at the time of admittance, gestational age, family history lipid, profile and blood glucose level were recorded for all subjects. A blood pressure measurement was performed on each subject and previous two blood pressure readings were recorded from the subject's file. The subjects were then classified for having pregnancy induced hypertension (PIH) following the ACOG Guideline which states that "A blood pressure of >140/90 mm Hg is considered as PIH (n=50),[11] and normotensive (n= 61) by the convienient randomn technique. Written informed consent was obtained from the participants and five milliliters blood sample was collected after an overnight fast. Serum was separated and stored for comparative analysis. ELISA assays were used to detect SOCS-3 levels (kit cat # H1415 by Glorybioscince, Belgium). The study was approved by the Ethics and Review Committee of Aga Khan University (ERC-4523-BBS-16).

Statistical Analysis

Data was analysed by using SPSS version 23. Quantitative variables were expressed as mean ± standard deviation. The Mann Whitney U test was used to compare the level of SOCS-3 between pregnant females, with and without hypertension and chi square or Fischer extact test is applied wherever applicable. The Spearman ranks correlation was applied to test the association of SOCS-3 with hypertension and obesity. In all instances, a p value of <0.05 was considered significant.

Results and Conclusion

The mean age and parity of the study subjects was on an average, matched between the two groups ($p>0.05$). Furthermore, obesity and lipid derangement are confounding factors for hypertension, SOCS-3 is associated with inhibiting insulin signaling which in turn inhibits the lipid reabsorption into the adipose tissue and liver.[12] Therefore, in this study, we wanted to assess if there was any lipid derangement along with the disruption of SOCs-3 in the study subjects. No difference in the lipid profile levels was observed, suggesting that SOCs-3 may act as an independent marker for blood pressure in pregnancy. However, hypertensive pregnant females were obese and had a higher BMI compared to normotensive females ($p<0.05$). Higher SOCS-3 levels were seen in hypertensive group (30 pg/ml) versus normotensive (16 pg/ml) (Table). When we stratified ours groups based on BMI in order to assess the difference in SOCS-3 levels; higher levels were observed in hypertensive group across all BMI categories (Table-1). Lastly, we plotted a relationship curve between the biomarker, BMI and blood pressure. Both Systolic blood pressure ($r=0.520$; $p<0.001$) and diastolic blood pressure ($r=0.490$; $p<0.001$) showed a significant positive correlation with SOCS-3 level, whereas a non-significant association was observed with BMI ($r=0.351$; $p=0.101$) (Figure). The results of this study indicate that there is a positive correlation between SOCS-3 and hypertension. This signifies that SOCS-3 may play a role in the pathogenesis of the disease, and hence opening a possible area of research and treatment route for PIH. Previous studies have shown that a low level of SOCS-3 was related to disease processes such as inhibition of differentiation of epithelial to mesenchymal cells and cellular proliferation in kidney proximal tubule cells.[13] However, our results show a higher SOCS-3 level in hypertensive individuals, suggests the possibility that SOCS-3 is being produced as a result of the inflammatory environment during pregnancy and obesity in an attempt to limit the inflammatory damage and maybe prevent the catastrophic effects of hypertension. We cannot comment

Table: Parameters of study subjects.

Variable		Normotensive (n= 61)	Hypertensive (n= 50)	p value
Age (year)		26.59 ± 5.26	27.21± 5.93	0.602
Weight (kg)		65.52 ± 13.40	72.37 ± 16.11	0.032
BMI (kg/m^2)		25.69 ± 4.94	27.95 ± 5.79*	0.050
Gestational Age (weeks)		26.22 ± 2.15	27.17 ± 1.24	0.848
Parity	Primi	40 (65.57)	33 (66.0)	0.648
	Multi	21 (34.42)	17 (34.0)	
Previous mode of delivery	LSCS	5 (8.19)	3 (6.00)	0.843
	SVD	56 (91.80)	47 (94.0)	
FBG (mg/dl)		93.32 ± 26.02	91.53 ± 19.56	0.733
TAG (mg/dl)		144.32 ± 58.25	147.62 ± 60.04	0.798
HDL (mg/dl)		50.96 ± 8.613	51.65 ± 6.98	0.698
SBP (mmHg)		110.98 ± 10.44	148.75 ±16.60*	<0.001
DBP (mmHg)		70.00 ± 8.63	101.25 ±10.99*	<0.001
SOCs3 (pg/ml)		16.75 ± 7.402	30.43 ± 13.505*	<0.001

Stratification of subjects based on Hypertension and BMI category

Variable	Normal Weight HTN (n=20)	Overweight HTN (n=12)	Obese HTN (n=18)	Normal Weight Normotensive (n=21)	Overweight Normotensive (n=10)	Obese Normotensive (n=30)
SOCS-3 (pg/ml)	24.46 ±3.48	37.34 ± 2.39	26.50 ±2.91	12.61± 6.53	14.25 ±4.65	20.49 ±6.93

Where: BMI (Body mass index), FBG (fasting blood glucose), TAG (triglyceride), HDL (high density lipoprotein), SBP (systolic blood pressure) DBP (diastolic blood pressure). Values expressed as Mean ± SD or absolute number with percentage in parenthesis. Groups compared by.

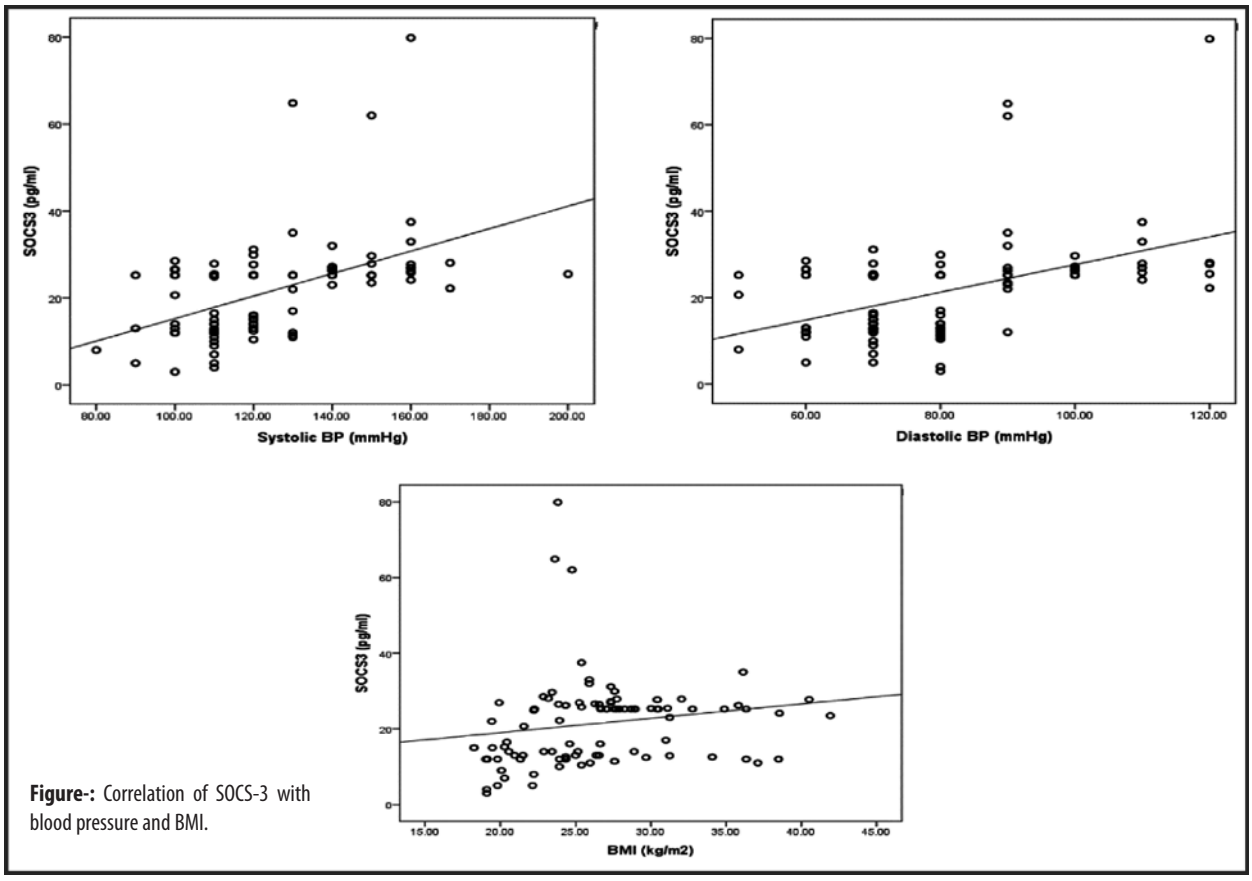

Figure-: Correlation of SOCS-3 with blood pressure and BMI.

on the role of SOC-3 an anti inflammtory marker as we were limited to measuring cytokine levels in the study subjects due to budget constraints. Yet more observations and information about SOCS-3 as a chemical (as to the exact effects in the body, the production and the potential side effects it's administration may have) would be required before considering this route. It is important to note that only a few studies were available on SOCS-3, obesity,[14] diabetes and inflammatory cytokines.[15] However, no articles were available that established associated levels of SOCS-3 with obesity or hypertension in pregnant females. Once a relationship between the two is established, levels of SOCS-3 can be monitored and changed through intervention to avoid comorbids like hypertension and other associated complications.

Disclaimer: None to declare.

Conflict of Interest: The authors declare that they have no conflict of interest.

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