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Original Article

Evaluation Of Novel Hormone Asprosin And Its Role In Insulin Resistance In Neonatal Cord Blood Of Preeclamptic And Healthy Pregnant Mothers

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ABSTRACT

Asprosin, a novel glucogenic adipokine, plays a complex role in central nervous tissue, peripheral tissues and other organs. It is involved in glucose metabolism, appetite, insulin resistance, cell apoptosis etc. This study aimed to find relationship between asprosin and other insulin resistance related-hormones in neonates of preeclamptic mothers. A comparative cross-sectional study was conducted on 42 neonates of preeclamptic pregnant mothers and 42 neonates of healthy pregnant mothers. Samples were taken from placentas at the time of delivery and were processed for estimation of asprosin, insulin, C-peptide and glucose hormones. Data was analysed using SPSS 21. Normality of the data was checked and independent t-test was applied. A p-value of ≤0.05 was considered significant. P-values of asprosin, insulin, C-peptide, glucose and HOMA-IR index were 0.020, 0.550, 0.360, 0.310 and 0.740, respectively when compared between neonates of preeclamptic pregnant mothers and healthy pregnant mothers.

INTRODUCTION

Preeclampsia is a complex hypertensive disorder. Its definition and classification have remained confusing for many years. It is seen globally in 5-7% of all pregnancies. In developing countries like Pakistan prevalence rate of preeclampsia is higher and one out of 89 women dies due to PE and eclampsia . Preeclampsia is defined as start of hypertension after the five month pregnancy along with dysfunction of female organ.To ascertain continuous nutrient supply to developing fetus in pregnant woman, multiple changes such as increased reallocation of adipose tissue in mothers occurs causing a state of dysmetabolism and increasing the risk of adverse pregnancy outcome. Exposure of fetus to suboptimal conditions that is gestational diabetes mellitus, PE and obesity has been identified as risk factor for future diseases in infants and impaired ability to respond to metabolic changes. Diabetic pregnancies are associated with elevated fetal insulin and C-peptide levels because increase maternal glucose is reaching in the fetal circulation . Similarly, a study suggests that higher maternal basal metabolic index and gestational weight gain is associated with increased C-peptide levels in cord blood of neonates. Accumulating evidences suggests that many factors such as genetics, maternal co-morbidities and hormonal secretion may affect and determine growth of fetus and long term complications such as development of endocrine

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morbidities. A theory called "Fetal Origins of Adult Diseases" proposed that in utero environment during pregnancy have considerable impact on future health of babies. Blood samples from umbilical cord of preeclamptic children show deranged lipid profiles and elevated tumor necrosis factor α levels when measured for inflammatory and metabolic parameters. PE is an independent risk factor for long term endocrine morbidity of children specifically obesity. The QUICKI acts as a predictive marker for onset of diabetes and its measurement is based on fasting levels of glucose and insulin. Low values of QUICKI correspond to increased IR. Children which were exposed to PE during pregnancy had independently low values of QUICKI showing increased IR in them. One study proposed that during peripubertal time, children born to preeclamptic mothers have increased BMI and waist circumference as compared to children of normotensive mothers. Multiple studies reported lower intelligence quotient scores, reduced verbal abilities, deficit in working memory, failure in visuospatial processing, higher rates of depressive episodes, risk of stroke, enlarged brain regional volumes in right and left amygdala, temporal lobe, brainstem and cerebellum in offspring of preeclamptic mothers in their later life . Insulin resistance, high blood glucose levels and disturbance in endocrine system lead to disturbance in infant's energy metabolism. Asprosin is a fasting glucogenic hormone with molecular weight about 3kDa. It is synthesized and release from white adipose tissue in very low concentration. Encoded by two exons of FBN1(fibrillin-1), both exone65 and exon 66 coded for 11 and 129 amino acids respectively. Asprosin have ability to cross the brain barrier regulate appetite behaviour by effecting on CNS Agouti-related peptide neurons. Genetic defect in synthesis of asprpsin may develop neonatal progeroid syndrome which lead to developed complication such as intrauterine growth restriction (IUGR) marked by abnormal fetus growth in pregnancy. Plasma asprosin level increase during starvation and promote glucose synthesis by hepatocytes .Increase glucose concentration in turn stimulate release of insulin from pancreatic cells .Wen et al demonstrated that injection of asprosin in animal and human increased food intake, body weight , blood glucose and insulin concentration and opposite effect were observed in low asprosin level. Now a days HOMA-IR test is frequently use to measure insulin resistance and its also help to find out how much insulin should be synthesized to maintained blood glucose level. Connecting peptide (C-peptide) is a protein that unites α and β chains of insulin in the proinsulin molecule. During production of insulin, C-peptide is enzymatically separated from proinsulin and is released in equal amounts of insulin. Levels of peripheral insulin. may not properly reflect the amount of portal insulin secretion because it is extensively metabolized by the liver. Therefore, C-peptide is best in calculating secretion of insulin in clinical practise when assessing β-cell function as compared to peripheral insulin levels. Numerous studies demonstrated that there is relationship between the blood asprosin level and insulin resistance. High concentration of asprosin were observed in insulin resistance disease such as in TDM-2 and over weight individuals. However, the effects of novel hormone asprosin and other insulin resistance-related hormones in newborns of preeclamptic mothers are not studied till date.

METHODS

Study design: Study was approved by Ethical Review Committee, UHS, Lahore, Pakistan. It was a cross-sectional study.

Study population: This study comprised 42 neonates of Preeclamptic females and 42 neonates of healthy pregnant females. The mothers having severe blood deficiency, liver and kidney diseases, diabetes, hypertensive condition, persistent inflammatory infection was excluded from this research study. The pregnancy between 20-40 years with 36 weeks of gestational were selected for this study.

Group 1 include normal pregnant women with their neonates. Group 2 include preeclamptic pregnant according to ACOG (2013) guidelines and their neonates were included in group 2. (Rana et al., 2019).

Collection of Sample: Informed consent of all the participants were taken. 5ml of blood was drawn from fetal side of umbilical cord of placenta of the neonates of the respective mothers immediately following delivery of placenta.

Serum Preparation: The whole blood sample were collected in tubes. Leave the blood sample at room temperature for 30 mint and then centrifuged for 15 minutes. The serum was transferred to eppendorf tube and stored at -80 °C for biochemical estimation.

Biochemical investigation: Asprosin hormone, insulin, C-peptide levels in serum estimated by their respective kit on ELISA machine. While glucose estimation was done by chemistry analyzer

Formal for HOMA-IR

HOMA –IR = fasting glucose x Fasting insuline /22.5

Glucose in mmol/l Insulin in mIU/L

Statistical Analysis: SPSS 21 version use for statistical study. Shapiro-Wilks's analysis was carried out checking the normality of data. To compare the means of two groups Independent-t test was used. Pearson correlation test was applied. A p-value ≤ 0.05 was considered as statistically significant.

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RESULTS

Serum asprosin was elevated by 15.8% in newborns of preeclamptic mothers as compared to newborns of healthy mothers (fig 1). The levels of insulin, C-peptide, glucose and HOMA-IR in newborns of Preeclamptic females were increased by 6.7%, 11.7%, 7.5% and 4.3% respectively but showing no significant difference between the two groups (fig 2,3,4 &5).

Biochemical estimation.

Asprosin level in newborns of preeclamptic and healthy pregnant females: The increased level of asprosin hormone was observed in newborns of preeclamptic mothers in contrast to newborns of healthy mothers (p=0.020)(figure 1).

Insulin level in newborns of preeclamptic and healthy pregnant females: There was no significant difference between two groups. (p=0.550)(figure 2).

C-peptide level in newborns of preeclamptic and healthy pregnant females: No significant difference was found between the newborns of two groups (p=0.360)(figure 3).

Glucose level in newborns of preeclamptic and healthy pregnant females: No significant difference was found between the newborns of two groups (p=0.310)(figure 4).

HOMA-IR index in newborns of preeclamptic and healthy pregnant females: No significant difference was found between the newborns of two groups (p=0.740)(figure 5).

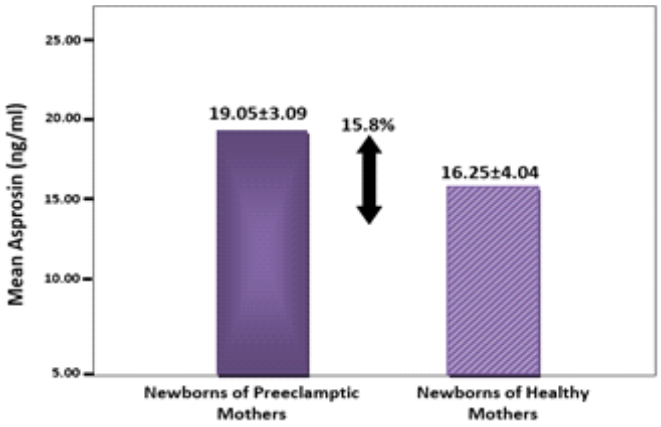

Figure 1: Asprosin level in newborns of preeclamptic and healthy pregnant females (p=0.020).

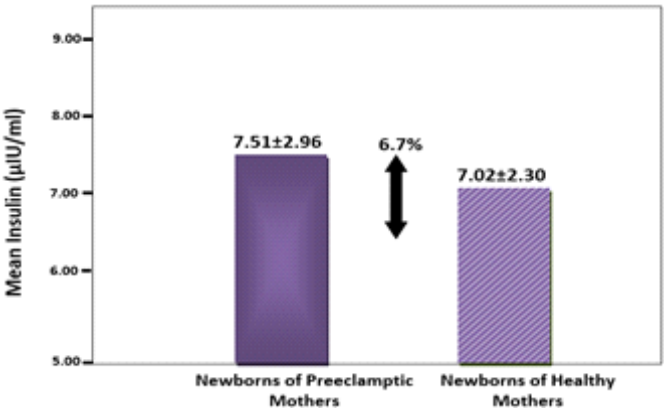

Figure 2: Insulin level in newborns of preeclamptic and healthy pregnant females (p=0.550).

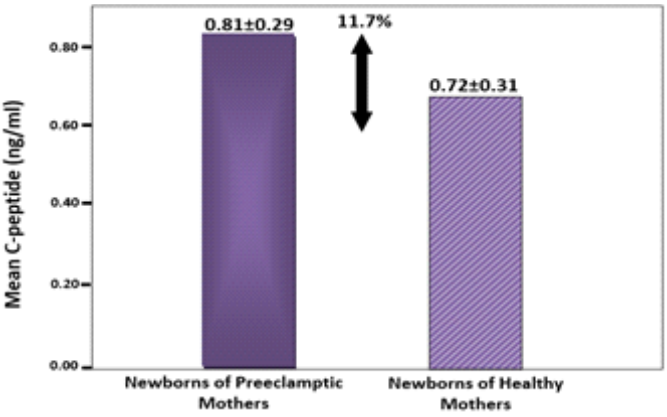

Figure 3: C-peptide level in newborns of preeclamptic and healthy pregnant females (p=0.360).

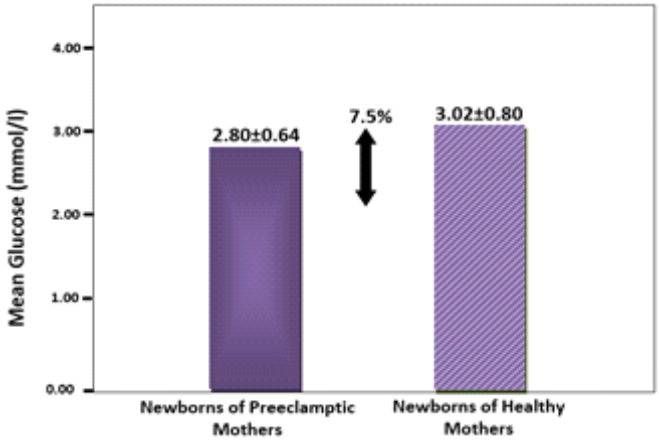

Figure 4: Glucose level in newborns of preeclamptic and healthy pregnant females (p=0.310)

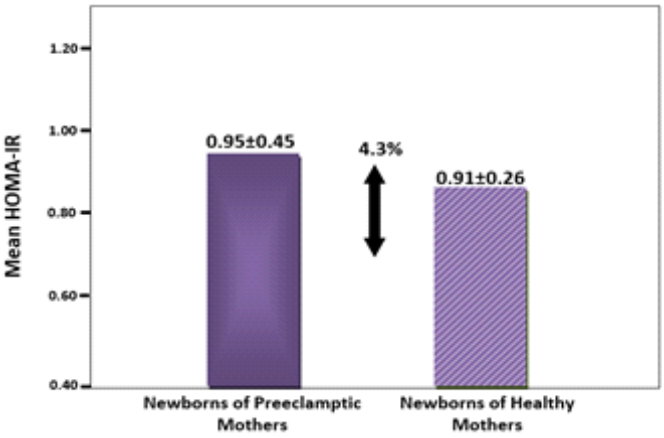

Figure 5: HOMA-IR index in newborns of preeclamptic and healthy pregnant females (p=0.740)

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	Newborns Healthy mothers n=21		Newborns Preeclamptic mothers n=21	
	Pearson Correlation rho (ρ)	p-value	Pearson Correlation rho(ρ)	p-value
INSULIN (µIU/ml)	.107*	.645	.153*	.507
C-PEPTIDE(ng/ml)	.185*	.423	-.115	.619
GLUCOSE (mmol/l	-.105	.650	.533*	.013
HOMA IR	.021*	.929	.393*	.078

Correlation is significant at ≥ 0.01 level.

Table 1: Correlation of asprosin with other variables among newborns of preeclamptic and healthy pregnant females.

DISCUSSION

Preeclampsia poses great harm to the mother and the fetus. There are many pathological features in the development of the disease but the specific regulatory mechanism is still unclear. Asprosine belonged to cytokine family , mainly synthesize and secreted from adipose tissue .Concentration of asprosin in blood increase with insulin resistance individual .(Yuan et al., 2020) .It was reported that asprosin level in newborns cord blood of preeclamptic pregnant mothers are elevated as compared to newborns cord blood of healthy pregnant women(Baykus et al., 2019). But the role of asprosin is still unclear.In our study, asprosin in umbilical cord blood of newborns of preeclamptic pregnant female was increased by 15.8% as compared to newborns of healthy mothers. The result was significant difference among the two groups (p=0.02)(figure 1). Similar results were observed in a previous research(Baykus et al., 2019). According to Zhon and co-worker, insuline resistance in body can affect the asprosin hormone level in blood. Asprosin expressed specially on cytotrophoblast and syncytiotrophoblast cells of placenta in pregnancy.(Zhong et al., 2020). The reason for increased asprosin in newborns of preeclamptic mothers may perhaps be due to the increased production of asprosin in ischemic placentas of preeclamptic mothers. Evidence suggests that PE has implications for the mothers beyond pregnancy as well as long term effects on offspring health –(Yates et al., 2018). More research required to understand the mechanism of regulation of asprosin in placenta and their role in insulin resistance. Environmental and genetic factors , life style, medication and hormonal disbalance contribute to develop childhood obesity. Elevated asprosin hormone may result in resistance to insulin hormone insulin resistance, high concentration of blood glucose levels and other endocrine disturbances provoking the disturbance of infant's energy regulation and increasing the prevalence for childhood overweight and obesity. Its produce their effect through direct action on Agouti-related protein (*AgRP*) neurons in CNS through a adenylyl cyclase , protein kinase dependent cycle and stimulate food intake and increase body mass (Duerrschmid et al., 2017). The results of our study showed that no significant difference is present between mean levels of serum insulin, C-peptide, glucose and HOMA-IR between newborns of healthy and preeclamptic pregnant mothers (p=0.550, p=0.360, p=0.310 and p=0.740, respectively)(figures 2,3,4 & 5). Our result was in agreement with Zhong et al, who found no difference in serum insulin, C-peptide and glucose levels between neonates of healthy and gestational diabetic mothers (Zhong et al., 2020). In contrast to this study, Faupel at el. reported decreased cord blood levels of C-peptide in newborns of preeclamptic mothers than healthy mothers, at birth (Faupel-Badger et al., 2012). The current study found a positive association among asprosin and HOMA-IR in newborns of Preeclamptic females (ρ=.393) (table 1). This positive association among asprosin and HOMA-IR could be because asprosin is responsible for malfunctioning and inflammation of β-cells of pancreas through toll like receptor-4 mediated signalling and leads resistance to insulin (Lee et al., 2019). Asprosin being a novel hormone, is not reported much in newborns of preeclamptic mothers till date. Our study found positive association between asprosin and insulin as well as between asprosin and glucose. previous research demonstrate the role of asprosin in glucose level, its promote glucose synthesis from hepatic tissues. (Romere et al., 2016). Increased glucose level in blood give signal to pancreatic β cell to release insulin (Yuan et al., 2020). This might be possible the reason for positive correlation between asprosin, glucose and insulin in newborns of preeclamptic females in our research study

CONCLUSSION

In conclusion we believe that future studies especially in vivo at different intervals during pregnancy can clarify the mechanism by which asprosin is produced or is transported across the placenta of preeclamptic women and thereby contribute to a better understanding of newborns status about insulin resistance and IR-related hormones.

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