ABENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X

Online ISSN 2357-0016

Original article

Measurement of C-Peptide Level in the Umbilical Cord of Infants of Diabetic Mothers and its Relationship to the Risk of Hypoglycemia

Alrawhaa Abo Amer [a], Effat H. Asar [a], Maha T. Rashwan [b], Asmaa A. Ali [a]

[a] Department of Pediatrics, Faculty of Medicine Benha University, Egypt. [b] Department of Clinical and Chemical Pathology, Faculty of Medicine Benha University, Egypt.

Corresponding to: Asmaa A. Ali, Department of Pediatrics, Faculty of Medicine Benha University, Egypt.

Email: asmaaaidy22@gmail.com

Received: 6 December 2023

Accepted: 6 January 2024

Abstract

Background: Infants born to diabetic mothers face an increased risk of hypoglycemia, necessitating reliable predictive markers for early intervention. **This study aimed to** measure C-Peptide in umbilical cord blood, to determine whether it can be used as a predictor of hypoglycemia in infants of diabetic mothers. **Methods:** A total of 50 infants born to diabetic mothers were studied and they were divided according to blood glucose levels into 25 experiencing hypoglycemia and 25 remaining normoglycemic. Detailed histories, comprehensive examinations, and multi-level investigations were conducted, including C-peptide measurement from umbilical cord blood and monitoring of glucose levels postnatally. **Results**: In the hypoglycemic group, mean cord C-peptide levels were significantly higher (5.2 ± 0.55 ng/ml) compared to the normoglycemic group (1.71 ± 0.62 ng/ml). A significant negative correlation was found between cord C-peptide levels and the blood glucose levels in the early postnatal period. Additionally, a positive correlation existed between cord C-peptide levels and birth weight. The sensitivity of cord C-peptide in predicting hypoglycemia was 90%, with a specificity of 88% and a cut-off value of 4.2. **Conclusion:** Cord C-peptide levels in infants of diabetic mothers might be a predictive biomarker for hypoglycemia in infant of diabetic mother.

Keywords: Infants; Diabetic mothers; Cord C-peptide; Hypoglycemia; Predictive marker.

Introduction:

Infants born to diabetic mothers are still at high risk for morbidity and mortality despite advancements in specialized care units. Poor maternal blood sugar control exposes the fetus to maternal hyperglycemia, leading to a range of complications for these infants(1).Problems in infants of diabetic mothers include respiratory distress, growth abnormalities, premature birth, hyper viscosity due to polycythemia, and various metabolic complications such as hypoglycemia, hypocalcemia, hypomagnesemia, and hyperbilirubinemia. These infants also face an increased risk of congenital malformations like congenital heart disease, cardiomyopathy, and CNS malformations (2).

Neonatal hypoglycemia is a common metabolic issue in newborns, impacting their ability to maintain glucose levels necessary for brain function and overall physical development (3).

Blood glucose levels in these infants fluctuate significantly in the first hours of life. Accurate age determination is crucial for diagnosing hypoglycemia, which is defined as a blood glucose level below 46.8 mg/dL. Hypoglycemia in these infants is typically transient, often resolving within 24-48 hours with appropriate feeding and, when necessary, intravenous glucose therapy. Only a small percentage of infants continue to experience hypoglycemia at two days of age (4).

C-peptide is a valuable method for assessing pancreatic beta cell function. It connects alpha and beta chains of proinsulin, facilitating correct insulin folding and disulfide bridge formation. In a fasted state, healthy individuals have a plasma concentration of C-peptide ranging from 0.9 to 1.8 ng/ml, while postprandial levels range from 3 to 9 ng/ml (5).

The purpose of this study was to measure C-Peptide in umbilical cord blood, to determine whether it can be used as a predictor of hypoglycemia in infants of diabetic mothers.

Patients and methods:

Patients: In this interventional study, we compared C-peptide levels between hypoglycemic and normoglycemic infants born to diabetic mothers. Conducted at the pediatric department of Benha University hospitals over a year from October 2021 to September 2022, our study targeted infants born to diabetic mothers, purposively selected from pregnant women admitted for delivery in Benha University Hospital.

Informed written consent was obtained from the parents. Every parent received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University. **Approval code: Ms.46.10.2021**

Inclusion criteria were infants born to diabetic mothers of both sexes.

Exclusion criteria were infants with chromosomal abnormalities or severe birth defects, severe perinatal asphyxia, or erythroblastosis fetalis.

Our sampling method utilized non-randomized convenient sampling. The sample size of 50 (25 patients in each group) was determined based on C-peptide levels in hypoglycemic and normoglycemic neonates from a 2021 study (8), ensuring an adjusted alpha of 0.05 and a power of 0.8. the fifty infants of IDM were divided according to blood sugar into: The case group consisted of 25 infants who develop hypoglycemia after delivery, blood sugar less than 47mg/dl while the control group comprised 25 healthy infants who remain normoglycemic.

Methods:

Detailed History Taking:

A comprehensive history-taking process involved gathering personal details of the mother, encompassing age, gender, residence, and socio-economic status. Prenatal history including maternal risk

factors, diabetes onset and management, maternal glycated hemoglobin levels, fetal risk factors, and complications during pregnancy. Details regarding the natal phase covered mode of delivery, labor complications, gender, birth weight, gestational age, and Apgar score assessment. Postnatal scrutiny aimed to identify the symptoms of hypoglycemia inform of (Sweating, feeding difficulties, poor suckling, Weak or high-pitched cry, Tremors, Hypothermia, Irritability, Lethargy/stupor, Hypotonia, Seizures, Coma, Apnea, grunting or tachypnea, Cyanosis) and their occurrence timeline, while family history focused on consanguinity.

Examination:

The examination protocol began with a general assessment, including consciousness, vital signs, gestational age evaluation, and systemic examination. Systematic examination targeted the cardiovascular, respiratory, gastrointestinal, central nervous, and musculoskeletal systems to detect anomalies or irregularities.

Investigations:

Multiple investigations were conducted, involving blood sample collection (3 ml) from clamped umbilical cords for C-peptide measurement with MINIVIDAS APPARATUS by immune chemillucince technique. Random blood sugar levels were assessed using a glucose meter. Upon NICU admission, additional blood samples (2 ml) were obtained for a complete blood count and further investigations. Parameters from the complete blood count, such as hemoglobin, hematocrit, total leukocyte count, neutrophils, lymphocytes, and platelets, were compared between the groups for analysis.

Statistical analysis

The collected data underwent manual input into a computer for analysis using SPSS software version 26 (IBM Inc., Armonk, NY, USA). Quantitative data were presented as (Mean ±SD) and median (range), while qualitative data were expressed as events and percentages. Inferential statistics employed t-tests for quantitative data and chi-square tests for qualitative data, setting all coefficient intervals to 95%. The significance level was determined based on the p-value: a p-value greater than 0.05 indicated nonsignificance, while a p-value below 0.05 signified significance in the analyses conducted.

Results:

Table 1 illustrates that in the Hypoglycemic group, 17 (68%) infants were male, 8 (32%) were female, 18 (72%) were delivered via Cesarean section, and 7 (28%) through normal vaginal delivery (NVD). In the Normoglycemic group, 13 (52%) infants were male, 12 (48%) were female, 16 (64%) were delivered via Cesarean section, and 9 (36%) through NVD. No significant differences were observed between the groups.

Regarding other parameters, in the Hypoglycemic group, the mean gestational age was 36.6 ± 1.71 weeks, mean birth weight was 3.41 ± 0.53 kg, mean Apgar score at 1 minute was 6.28 ± 0.98, mean Apgar score at 5 minutes was 9.16 ± 0.69, and mean temperature was 36.84 ± 0.14°C. In the Normoglycemic group, the mean gestational age was 35.6 ± 2.48 weeks,

mean birth weight was 2.6 ± 0.7 kg, mean Apgar score at 1 minute was 6.56 ± 1, mean Apgar score at 5 minutes was 9.04 ± 1.06, and mean temperature was 36.83 ± 0.15°C. A significant difference was noted between the groups concerning birth weight and Apgar score at 5 minutes.

Figure 2 indicates that in the Hypoglycemic group, the mean blood glucose levels at birth (mg/dl) were 33.56 ± 7.33, at 30 minutes 36.68 ± 7.86, at 1 hour 40.72 ± 8.29, at 3 hours 43.52 ± 8.74, at 6 hours 47.44 ± 7.88, at 12 hours 52.24 ± 8.88, at 18 hours 57.24 ± 11.48, and at 24 hours 66 ± 14.14. In contrast, in the Normoglycemic group, the mean blood glucose levels at birth (mg/dl) were 50.32 ± 4.18, at 30 minutes 52.24 ± 4.26, at 1 hour 56.68 ± 4.68, at 3 hours 59.68 ± 5.39, at 6 hours 63.2 ± 4.63, at 12 hours 68.88 ± 5.61, at 18 hours 76.12 ± 7.77, and at 24 hours 86.52 ± 8.98. A significant difference in blood glucose levels was observed between the two groups as blood glucose levels were lower in hypoglycemic group.

Table 2 shows that there was statistically significant difference between groups regarding poor feeding, breathing problem (transient tachypnea of newborn) and diarrhea as it was higher in hypoglycemic group. While there was no statistically significant difference between both groups regarding HB, lymphocyte, neutrophil, HCT, TLC, platelets, temperature instability, apnea, respiratory distress, lethargy, abdominal distension, seizures and vomiting.

Table 3 shows that there was highly statistically significant difference between groups regarding cord C peptide as it was higher in hypoglycemic group.

There was significant negative correlation between cord C peptide and blood glucose levels in the early postnatal period. There was significant positive correlation between cord C peptide and birth weight. **Table 4.**

The sensitivity of cord c peptide in predicting hypoglycemia was 90%. Specificity was 88%. Cut off value was 4.2. **Table 5.**

Table 1: Demographic data of the studied groups

		Hypogycemic group		Normoglycemic group		P-value
Sex of infant	**Male**	17	68%	13	52%	0.24
	Female	8	32%	12	48%	
Mode of delivery	**CS**	18	72%	16	64%	0.54
	NVD	7	28%	9	36%	
Gestational age (week)		36.6 ± 1.71		35.6 ± 2.48		0.07
Birth weight (Kg)		3.41 ± 1.53		2.6 ± 0.7		0.02
APGAR score 1 min		6.28 ± 0.98		6.56 ± 1		0.9
APGAR score at 5 min		9.16 ± 0.69		9.04 ± 1.06		0.04

CS: Cesarean Section, NVD: Normal Vaginal Delivery, APGAR: Appearance, Pulse, Grimace, Activity, Respiration

Table 2: Laboratory tests and signs suspect hypoglycemia

	Hypoglycemic group		Normoglycemic group		P value
Hgb g/dL	13.73 ± 2.19		14.24 ± 2.02		0.7
lymphocyte *1000	10.84 ± 2.21		10.56 ± 2.4		0.6
neutrophil	269.8 ± 8.31		269.24 ± 10.46		0.05
HCT (%)	57.03 ± 3.94		58.57 ± 4.27		0.07
TLC /mm3	7076.24 ± 961		7083.19 ± 1084.16		0.07
Platelet *1000/microliter	223.72 ± 66.09		255.68 ± 98.32		0.077
Temperature instability	1	4	2	8	0.55
Apnea	3	12	2	8	0.63
Respiratory distress	6	24	2	8	0.12
Lethargy	2	8	0	0	0.15
Poor feeding	10	40	2	8	0.008
Abdominal distension	4	16	1	4	0.157
Breathing problems (transient tachypnea of newborn)	8	32	0	0	0.002
Diarrhea	9	36	2	8	0.01
Seizures	3	12	0	0	0.07
Vomiting	6	24	3	12	0.27

Table 3: Distribution of Cord C peptide among the studied groups

	Hypoglycemic group	Normoglycemic group	P value
Cord C peptide ng/ml	5.2 ± 0.55	1.71 ± 0.62	<0.0001

Table 4: Correlations between cord c peptide and another parameter

		Cord C peptide
Blood glucose levels	r	-0.495**
	P	**<0.0001**
birth weight	r	0.498**
	P	**<0.0001**
APGAR 1 min	r	0.160
	P	**0.1**
APGAR 5 min	r	0.20
	P	**0.1**

APGAR: Appearance, Pulse, Grimace, Activity, Respiration.

Table 5: ROC curve for C peptide to predict hypoglycemia

Test Result Variable(s): C peptide							
Area	Std. Error[a]	Asymptotic Sig.[b]	Cut off value	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
0.889	0.051	0.000	4.2%	90%	88%	0.788	0.989

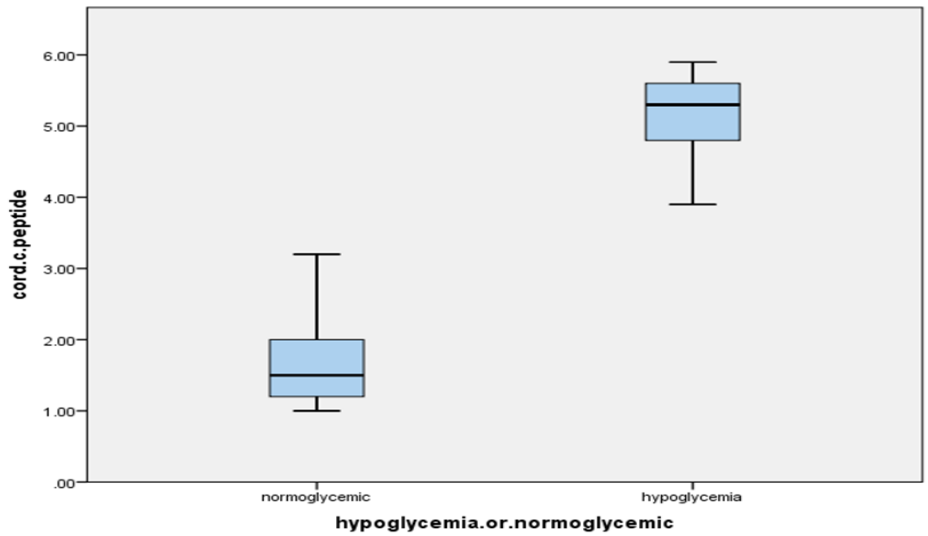

Fig. (1): Blot Box of Cord C peptide.

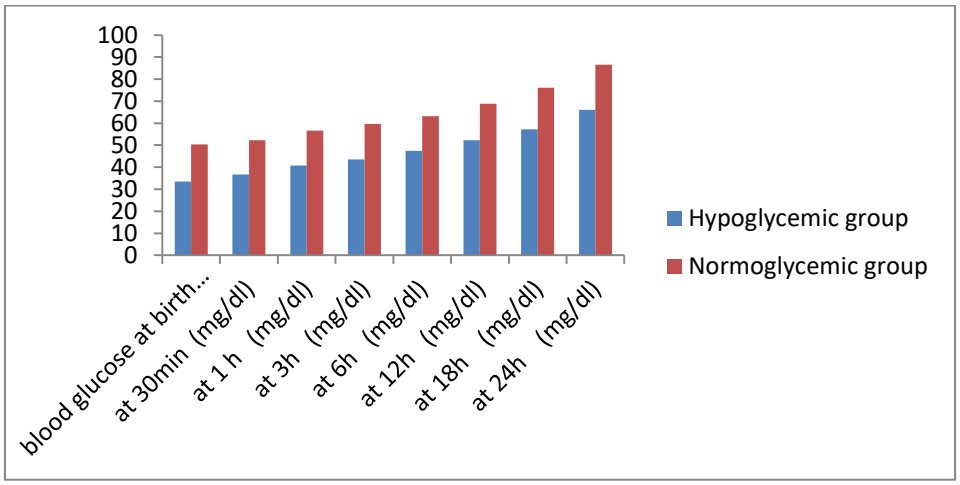

Fig. 2: Neonatal blood glucose level.

Discussion:

Regarding the demographic data, three studies examined hypoglycemic versus normoglycemic groups in infants of diabetic mothers. They showed no significant differences in maternal age or weight between these groups, aligning with our findings demonstrated similar results in cases and controls (6-8). Our findings indicated that the hypoglycemic and normoglycemic groups showed no significant differences in gestational age at birth or 1-minute Apgar scores. However, significant differences emerged regarding birth weight and 5-minute Apgar scores between the two groups. Similarly, a comparable finding in gestational age and 1-minute Apgar scores between the hypoglycemic and normoglycemic groups but highlighted no significant distinctions in neonatal

weight or 5-minute Apgar scores, was noted (6). Additionally, a study (8) reported no significant differences in newborn characteristics between case and control groups, while another (7) found no significant disparities in gestational age and Apgar scores at 1 and 5 minutes between hypoglycemic and normoglycemic groups.

Our study revealed differences in admission reasons between hypoglycemic and normoglycemic groups, these results run in accordance with other previous study (6) as it showed similar results regarding preeclampsia and PROM rates in hypoglycemic and normoglycemic groups.

In our study, we observed notable differences in blood glucose levels between the hypoglycemic and normoglycemic groups at various time points within the first 24 hours post-birth, with significant disparities persisting throughout. The study done in 2021(6) corroborated these findings, highlighting that hypoglycemia peaked within the first 3 hours of life and was significantly lower in the hypoglycemic group compared to the normoglycemic group. Additionally, another study (8) noted a rapid decrease in blood glucose after birth in both groups, with consistently lower levels in cases compared to controls, showing significant differences at multiple time points up to 24 hours post-birth and reporting varying percentages of hypoglycemia occurrences across the first 12 hours of life in the case group.

This can be explained by that hypoglycemia can be caused by conditions such as: Fetal growth restriction (slow growth prior to birth) or small size for gestational age at birth. Low blood glucose levels (hypoglycemia) at birth have been associated with brain injury and intellectual and developmental disabilities.

Also, this can be explained by that low blood glucose levels in neonates have been found to be directly associated with apnea, irritability, lethargy, seizures, and brain damage.

In our study, no significant differences in various blood parameters were observed between the hypoglycemic and normoglycemic groups, including hemoglobin, hematocrit, total leukocyte count (TLC), platelet count except cord C-peptide levels which show significant difference. A study by Begum et al (8) supported our findings by noting significant disparities in cord C-peptide levels between these groups, indicating an association between higher C-peptide and hypoglycemia risk in infants of diabetic mothers (IDMs). Additionally, significant differences in hematocrit and cord C-peptide levels was reported, indicating higher levels in the hypoglycemic group, further supporting the association between these parameters and the risk of hypoglycemia in IDMs (7).

Two studies (9,10) highlighted similar trends, with hypoglycemic IDMs exhibiting significantly higher cord C-peptide levels than normoglycemic ones, suggesting a potential link between

elevated C-peptide and hypoglycemia risk.

This can be explained by that C-peptide is secreted in equimolar concentrations with insulin from the beta cells. It is a valid measure of insulin secretion especially following challenges with glucagon or a mixed meal. C-peptide is extremely useful in the differential diagnosis of hyperinsulinemic-hypoglycemia

Also, this can be explained by the fact that the C-peptide, which indicates insulin production, is directly connected to the degree of maternal diabetes and is highly correlated with newborn problems such as hypoglycemia.

Our results found that there was significant negative correlation between cord C peptide and blood glucose levels in the early postnatal period. There was significant positive correlation between cord C peptide and birth weight.

This finding is comparable with other studies reporting that cord C-peptide levels were inversely related to BG concentrations in the early postnatal period. Furthermore, the increased UC C-peptide level may be associated with infant macrosomia (9,10).

Correlation between umbilical cord C-Peptide level and neonatal hypoglycaemiain infants of diabetic mother, was studied. The study revealed that increased cord blood C-peptide levels in infants of diabetic mother was significantly associated with hypoglycaemia and increased birth weight. Therefore, timely estimation of cord blood C-peptide values can predict and prevent neonatal hypoglycaemia prior to the onset of symptoms (11).

Conclusion:

Elevated umbilical cord C-Peptide levels could serve as an early indicator of the risk of neonatal hypoglycemia, offering potential implications for predictive measures and early intervention strategies.

limitations

Our study had several limitations, including that they are generally of short duration and often use definitions of acceptable glycaemia that are far less stringent than those in use today. A large number of commercially available C-peptide assays are in use worldwide and have significant variations in comparability of results and precision. Finally, the study needs longer period follow-up.

References:

1. Kheir AE, Berair R, Gulfan IG, Karrar MZ, Mohammed ZA. Morbidity and mortality amongst infants of diabetic mothers admitted into Soba university hospital, Khartoum, Sudan. Sudan J Paediatr. 2012;12:49-55.

2. Mitanchez D, Yzydorczyk C, Simeoni U. What neonatal complications should the pediatrician be aware of in case of maternal gestational diabetes? World J Diabetes. 2015;6:734-43.

3. De Angelis LC, Brigati G, Polleri G, Malova M, Parodi A, Minghetti D, et al. Neonatal Hypoglycemia and Brain Vulnerability. Front Endocrinol (Lausanne). 2021;12:634305.

4. Gandhi K. Approach to hypoglycemia in infants and children. Transl Pediatr. 2017;6:408-20.

5. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. Diabetes Ther. 2017;8:475-87.

6. Saber AM, Mohamed MA, Sadek AA, Mahmoud RA. Role of umbilical cord C-peptide levels in early prediction of hypoglycemia in infants of diabetic mothers. BMC Pediatr. 2021;21:85.

7. Assar EH, Rachwan MMT, Khalifa OAE, Ahmed ME. Role of Umbilical Cord C-Peptide Level in Early Detection of Hypoglycemia in Infant of Diabetic Mother. The Egyptian Journal of Hospital Medicine. 2023;90:2695-700.

8. Begum M, Hassan MQ, Azad K. Relationship between Umbilical Cord C-peptide and Risk of Hypoglycemia in Infants of Diabetic Mothers. Bangladesh Journal of Child Health. 2012;36.

9. Metzger BE, Persson B, Lowe LP, Dyer AR, Cruickshank JK, Deerochanawong C, et al. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. Pediatrics. 2010;126:e1545-52.

10. ANNABESTANI, Z., et al. Amniotic fluid, maternal, and neonatal serum C-peptide as predictors of macrosomia: A pilot study. Journal of Diabetes and Metabolic Disorders, 2009, 8: 15.

11. Shankar H. Study of Correlation of Umbilical Cord C-Peptide Levels with Hypoglycemia in Infants of Diabetic Mother: Rajiv Gandhi University of Health Sciences (India); 2019.

To cite this article: Alrawhaa Abo Amer, Effat H. Asar, Maha T. Rashwan, Asmaa A. Ali. Measurement of C-Peptide Level in the Umbilical Cord of Infants of Diabetic Mothers and its Relationship to the Risk of Hypoglycemia. BMFJ 2024;41(1):34-42.