Cord Blood Hemoglobin A1c and MCP-1 as Predictors for Cardiomyopathy in Infants of Mothers with Gestational Diabetes

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Abstract

Introduction: Diabetes is one of the commonest and important metabolic disorder that affects the health of pregnant women and infants. MCP-1 in the myocardium was correlated with the degree of impairment of cardiac function and HbA1c concentration is also regarded as a treatment marker in patients with diabetes.

Objectives: The study aimed at measure the levels of cord blood Hemoglobin A1c and MCP-1 and correlate their levels with echocardiographic findings in infants of diabetic mothers (IDMs) in comparison to healthy neonates of healthy mothers.

Patients and methods: The current study was a descriptive cross-sectional comparative one included 110 full term neonates divided into two groups, the first group included 70 full term neonates born to diabetic mothers and the second group included 40 full term apparently healthy neonates born to healthy mothers as a control group. This study was conducted from April 2016 to April 2017 at Maternal and Children Hospital of El Minia. All Patients were assessed during the first week of life, this assessment included complete medical history, thorough clinical examination with stress on cardiac examination, and laboratory investigations included CBC and neonatal blood sugar as a routine investigations& HbA1c and MCP-1 as a specific investigations and echocardiographic assessment.

Results: IDMs have increased cardiac dimensions, impaired diastolic function and lower fractional shortening compared to control group. There was a strong positive correlation between levels of cord blood MCP-1 and echocardiographic measurements in IDMs. There was a strong positive correlation between levels of cord blood HbA1c and echocardiographic measurements in IDMs.

Conclusion: HbA1c and MCP-1 were good predictors for occurrence of cardiomyopathy in Infants of diabetic mothers with gestational diabetes.

Key words: Respiratory distress, Echocardiography; Neonates; NICU, Preterm
Background:
The incidence of hypertrophic cardiomyopathy (HCM), especially interventricular septal hypertrophy (IVSH), varies between 10% and 71% (Stuart et al., 2010). Monocyte chemoattractant protein-1 (MCP-1) is expressed under various inflammatory conditions and it is a major signal for the accumulation of monocytes/macrophages in several diseases, MCP-1 was expressed in endomyocardial biopsy samples obtained from patients with dilated cardiomyopathy (DCM) and that the expression level of MCP-1 in the myocardium was correlated with the degree of impairment of cardiac function (Dusi et al., 2016). Glycated hemoglobin (HbA1c), which reflects average plasma glucose concentrations over the preceding 1-2 months, is generally used as a marker of recent control of plasma glucose (Gillet, 2009). HbA1c concentration is also regarded as a treatment marker in patients with diabetes. Indeed, guidelines formulated by an international expert committee composed of members of the European Association for the Study of Diabetes and the International Diabetes Federation and the American Diabetes Association have set a target HbA1c as 7%, as higher levels are associated with increased risks of cardiovascular disease and diabetic nephropathy, neuropathy and retinopathy (Seino et al., 2010).

Patients and Methods:
The current study was a descriptive cross-sectional comparative one included 110 full term neonates divided in to two groups, the first group included 70 full term neonates born to diabetic mothers and the second group included 40 full term apparently healthy neonates born to healthy mothers as a control group. This study was conducted from April 2016 to April 2017 at Maternal and Children Hospital of El Minia. All Patients were assessed during the first week of life, this assessment included complete medical history, thorough clinical examination with stress on cardiac examination, laboratory investigations included CBC and neonatal blood sugar as a routine investigations& HbA1c and MCP-1 as a specific investigations and echocardiographic assessment.

Blood sampling:
1) Three mls of cord blood sample were taken and evacuated into a plain tube then divided into 2 tubes as following:
   - One ml on ethylenediaminetetraaetic acid (EDTA) containing tube for Hemoglobin A1c.
   - Two mls on a plain plastic tube left to be clotted in the incubator and was centrifuged approximately1000 x g and serum was stored at -20°C for MCP-1 level assay (pg/ml) by ELISA.
2) One ml of neonatal venous blood was taken into a plain plastic tube used to assay neonatal blood glucose.
3) One ml of neonatal venous blood was taken on ethylenediaminetetraaetic acid (EDTA) containing tube for complete blood count.

Echocardiographic measurements carried out during the first week of the neonatal life, The examination were performed by a pediatric cardiologist having experience in echocardiography. The examination was consisted of M-mode, 2-D, pulsed, continuous wave and color Doppler blood flow velocity measurements of the heart valves. The interventricular septum (IVS) was considered hypertrophied if its thickness was >4 mm at the end of diastole and the LVPW thickness was considered increased if >3.7mm (Skinner et al. 2000).
• AOV, aortic valve diameter; FS, fractional shortening ; EF, ejection fraction ; HbA1c, glycated hemoglobin A1c; IVSd, interventricular septal end-diastolic thickness; IVSs, interventricular septal end-systolic thickness; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVPW, left ventricular posterior wall thickness; p, probability value RVDd, right ventricular end-diastolic dimension. Monocyte chemotactic protein-1 (MCP-1).

• Pearson’s correlations were performed to assess unadjusted association between the echocardiographic measurements with birth weight, maternal HbA1c and cord blood MCP-1.

• *: significant difference at p value < 0.05.

Discussion:
Cardiac complications due to congenital heart malformation and ventricular hypertrophy are the major causes of morbidity and mortality in fetuses and newborns of mothers with GDM (Demiroren et al., 2005). The incidence of hypertrophic cardiomyopathy (HCM), especially interventricular septal hypertrophy (IVSH), varies between 10% and 71% (Stuart et al., 2010).

A significant increase in levels of neonatal hemoglobin and neonatal hematocrit in IDMs when compared with healthy controls were noticed in our study. These results were similar to the study done by Cetin et al., 2011 who found that hemoglobin, HbF levels and venous neonatal hematocrit values were significantly higher in IDMs compared with control infants and Metzger et al., 2010 who reported that IDMs have higher levels of RBCs and consequently hemoglobin and hematocrit levels and this could be explained by the positive effect of fetal insulin on erythropoiesis.

There was significant hypoglycemia in IDMs when compared with control group, and this agrees with Mimouni et al., 2013 who showed that the prevalence of hypoglycemic episodes in IDMs is as high as 40% when compared with the control group. This metabolic risk is believed to be due to the relative fetal hyperinsulinism, manifested as a feedback mechanism for the balance of the high glucose levels induced by the maternal diabetes (Nold and Georgieff, 2004).

In our study, we found that there were no significant differences in WBCs count and platelet count between IDMs and control groups, which was in agreement with Pilgaard et al., 2010 who reported that there were no significant difference in WBCs count and platelet count between IDM and control group, and in contrast with us Jahromi et al., 2011 who reported that WBCs and platelet count were significantly higher in IDM than control group explaining that by chronic acidosis and hypercapnea in diabetic pregnancies this difference compared to healthy controls, and this agrees with Raj, 2016 may be attributed to sample size and criteria of patients.

Cord blood HbA1c was found to be significantly higher in IDMs when who showed high cord blood HbA1c in IDMs which is significantly associated with early postnatal hypoglycemia and Davison et al., 2011 who showed that glycated hemoglobin levels were significantly higher in IDMs compared to infants of non diabetic mothers. Koja et al., 2011 reported that the levels of glycated hemoglobin in umbilical cord
blood samples collected from diabetic mothers were higher than those from mothers without diabetes mellitus and Sosenk et al., 1982 showed that glycated hemoglobin levels were significantly elevated in the diabetic mothers and their offspring as compared with controls and maternal and cord blood levels were highly correlated in the diabetic group. These data strongly suggest that neonatal hypoglycemia is the result of maternal hyperglycemia in pregnancy and consequent fetal hyperglycemia and hyperinsulinemia.

In the present study there were a significant increase in levels of cord blood MCP-1 in IDMs when compared to healthy controls, and this was similar to the study done by Piemonti et al., 2003 who found that MCP-1 levels are increased in infants of diabetic mothers. Also Vuguin et al., 2013 observed that levels of cord blood MCP-1 in IDMs were higher in relation to the control and this could be explained by hyperglycemic environment reflected by higher HbA1c levels in diabetic mothers and the presence of the acetoacetate ketone which may be a factor in the increased MCP-1 levels in the cord blood of IDMs. Klein et al., 2008 found that MCP-1 is elevated during pregnancy and also augmented in GDM compared to non-GDM, and also two separate studies from Poland reported that women with gestational diabetes showed increased levels of the chemokine MCP-1 possibly leading to adverse pregnancy outcomes (Lappas et al., 2011).

In contrast with our study, Kurepa et al., 2012 showed that MCP-1 levels in cord-blood of mothers with gestational diabetes was similar to healthy mothers, this may be related to small sample size as they studied all types of diabetes (gestational, type 1 diabetes and type 2 diabetes).

In the present study, there was significant correlation between birth weight and cord blood HbA1c. This matches with Al-Biltagi et al., 2015 who showed significant positive correlation between neonatal birth weight and HbA1c value in IDMs and Damm et al., 2014 who found that elevated HbA1c was a significant predictor for poor pregnancy outcomes especially macrosomia; they attributed this to hyperinsulinemia which has a strong anabolic effect.

Our study showed that there were significant positive relationship between birth weight and cord blood MCP-1, and this was in agreement with Lappas M, 2014 who reported that inflammation play a central role in mediating insulin resistance and thus may contribute to the fetal overgrowth and or increased fat deposition observed in infants of women with GDM and MCP-1 was considered one of pro-inflammatory cytokines. However, Kurepa et al., 2012 reported that there was no relationship between blood MCP-1 levels and fetal birth weight, thus, differences in gestational age or fetal birth weight are unlikely to have any effect on changes in MCP-1.

As regarding echocardiographic measures in this study there were significant increase in cardiac dimensions (except aortic valve diameter) in IDMs than control group, and impaired systolic and diastolic function in IDMs than control group in the form of lower value of FS% and there was thirty cases of cardiomyopathies (42.8%), and this agrees with El-Ganzoury et al., 2012 where their was highly significant progressive increase in IVSd, IVSs, LVPW, LVDd,
LVDs, and RVDd with the increase in birth weight ratio from SGA to AGA to LGA neonates, whereas, aortic valve diameter (AOV) and ejection fraction showed insignificant differences between the three studied groups and there was an important number of cases of cardiomyopathies (43.5%).

Ullmo et al., 2007 found that the percentage of neonates suffering with HCM upon the pregnancies of women with the type I and II diabetes accounts 33%, which is much higher than the rate of CHD among the same group of diabetic women (12%), also Korraa et al., 2012 found a significant increase in left atrial thickness and interventricular septal dimension in IDMs in comparison to control and these results matched with our study.

Abu-Sulaiman and Subaih, 2004 showed that the risk of cardiomyopathy among offspring of mothers with insulin dependant diabetes mellitus (IDDM) was 18 times the risk among offspring of mothers not affected and 38% of neonates had HCM, mainly hypertrophy of the interventricular septum which is matched with our study.

In contrast with our study, Katheria and Leone, 2012 reported that the thickness of the interventricular septum between the controls and IDMs were similar and Demirorem et al., 2005 reported absence of any statistical difference in the echocardiographic measurements of macrosomic and non macrosomic IDMs, they suggested that cardiac changes are not only due to presence of macrosomia or glucose-insulin metabolism, but rather to the combination of macrosomia, glucose-insulin metabolism, genetic and maternal anthropometric factors.

Our study showed high sensitivity with comparable high specificity of HbA1c to cardiomyopathy and there was highly significant correlation between cord blood HbA1c and all echocardiographic measurements, also we found that cord blood HbA1c in IDMs were inversely correlated with EF% and FS%. This was similar to the study done by El-Ganzoury et al., 2012 where they found that 26 of the 30 neonates with HCM had their Hb A1c ≥ 8% (8–9.1) and the remaining 4 had their HbA1c ≥ 6.5%. Several investigators addressed this issue and somehow conflicting reports were presented. In concordance with our findings, Narchi and Kulaylat, 2000, Czeszyńska et al., 2004, and Ullmo et al., 2007 reported an association between poor maternal glycemic control and hypertrophic cardiomyopathy.

In contrast with our study, early report Sheehan et al., 1986 showed that there was no correlation between HbA1c and IDMs cardiomyopathy and Pradhan et al., 2007 who reported that HbA1c remained a strong predictor of diabetes but was no longer significantly associated with incident cardiovascular disease, this difference may be attributed to the difference in gestational ages and weights of patients in this study.

Our study showed high sensitivity with comparable high specificity of MCP-1 to cardiomyopathy and there was highly significant correlation between cord blood MCP-1 and all echocardiographic measurements, also we found that cord blood MCP-1 in IDMs were inversely correlated with EF% and FS%, and this
agrees with the study done by Kobayashi et al., 2008 where the serum levels of MCP-1 in patients with dilated cardiomyopathy were significantly elevated compared with those in healthy control subjects and the expression level was inversely correlated with left ventricular ejection fraction (LVEF), and also the study done by Iwasaki et al., 2009 where HCM patients had significantly elevated levels of MCP-1, and the serum levels of MCP-1 in patients with HCM were inversely correlated with left ventricular fractional shortening which determined by echocardiography.

The results of this study showed that there was highly significant positive relationship between birth weight and all echocardiographic measurement except AOV and EF% . And this agrees with El-Ganzoury et al 2012 study, as the assessment of cardiac morphological and functional parameters of the three studied groups of IDM, a highly significant progressive increase in all echocardiographic measurements (except FS% and AOV) with the increase in birth weight ratio from SGA to AGA to LGA neonates was found. Moreover, FS values were significantly lower among AGA followed by SGA then LGA neonates, whereas the AOV showed insignificant differences between the three studied groups. In this field, Tugertimur et al., 2000 found that IVS thickness and fraction shortening values of LGA group were higher than those of AGA. Moreover, Narchi and Kulaylat, 2000 reported the presence of cardiac septum hypertrophy in LGA. This could be explained by anabolic, hyperinsulinemic fetal state triggered by maternal hyperglycemia during the third trimester.

In contrast with our study, Sheehan et al., 1986 showed that there was no correlation between birth weight and IDM with cardiomyopathy.

Limitations for this study were following up of those IDM as regard their echocardiographic measures as well as serial measurement of neonatal glucose and maternal HbA1c during the third trimester. Also, examination of IDM with significant congenital heart diseases and its relation to HbA1c and MCP-1 was not studied enough.

**Conclusions:**
HbA1c and MCP-1 were good predictors for occurrence of cardiomyopathy in Infants of diabetic mothers with gestational diabetes.

**Conflict of interest:** The authors declared no conflict of interest.

**Author's contributions:** SS and EA conceived the study. ME revised the patients' medical reports and the final manuscript. All authors revised the final draft of the manuscript.

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