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Original Article

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

Abdel-Azeem M. El-Mazary[1]; Madiha Sayed[1]; Hazem Ali[2]; Waleed Abdel-Hameed[3]; Nancy Tawadros[*1]

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***Correspondence:** Department of Pediatrics, Faculty of Medicine, Minia university, Egypt
Email: nancytawadros@yahoo.com
Full list of author information is available at the end of the article.

Abstract

Background: Diabetes mellitus is one of the most common metabolic disorders that disturb the health of mothers during pregnancy and their babies. MCP-1 is a chemokine which accountable for the calling of inflammatory cell. It was linked to diminished cardiac function. HbA1c level is also considered a marker of follow-up and treatment in diabetes mellitus. **Objectives**: The study intended to measure the levels of cord blood Hemoglobin A1c and MCP-1 and correlate their levels with echocardiographic parameters in infants of diabetic mothers (IDMs). **Patients and methods**: it is a descriptive cross-sectional comparative one which comprised 110 term neonates separated into two groups, the first group included 70 neonates born to diabetic mothers (IDMs) and 40 healthy neonates born to healthy non-diabetic mothers as a control group. This study was conducted from April 2016 to April 2017 at the Maternal and Children Hospital of El Minia. During the first week of life, all babies were evaluated for medical history, thorough clinical examination with a focus on cardiac examination, and laboratory investigations which included CBC and neonatal blood sugar as routine investigations& HbA1c and MCP-1 as specific investigations in addition to echocardiographic assessment. **Results:** IDMs have increased cardiac dimensions, impaired diastolic function, and lower fractional shortening compared to the control group. Cord MCP-1and HbA1c was significantly high in IDMs and their levels significantly correlated with the echocardiographic parameters in IDMs the sensitivity and specificity of HbA1c in detecting cardiomyopathy was 83.3% and 95% with positive and negative predictive value 83.7 and 88.1 awhile for MCP-1 sensitivity and specificity93.3% and 97.5% positive and negative predictive values were93.1 %and 95.1%. **Conclusion:** MCP-1 and HbA1c were found to be excellent predictors for cardiomyopathy in infants of diabetic mothers with gestational diabetes.

Key words: Cardiac, diabetic, infant, macrosomia, complication, cardiovascular anomalies

Introduction

The incidence of hypertrophic cardiomyopathy (HCM), particularly interventricular septal hypertrophy (IVSH), has a prevalence of 10% to 71% [1]. Upregulation of Monocyte chemoattractant protein-1 (MCP-1) occurs under different inflammatory conditions .and considered the main signal for the monocytes/macrophages accumulation in various diseases, in patients with dilated cardiomyopathy (DCM), MCP-1 was detected in endomyocardial biopsy samples and the degree of cardiac function impairment was linked to MCP-1 expression levels in the myocardium. [2]

Glycated hemoglobin (HbA1c), which reflects glycemic state over the previous 1-2 months and used as an indicator for recent control of blood sugar and a treatment marker in diabetic patients [3], European Association for the Study of Diabetes and the International Diabetes Federation, and the American Diabetes Association defined levels of HbA1c at 7%, or more is found to be associated with increased risks of cardiovascular diseases and diabetic nephropathy, neuropathy and retinopathy and [4]. The chronic exposure of the fetus to maternal hyperglycemia is closely linked to fetal macrosomia and various cardiac anomalies and cardiomyopathy changes [1].

Methods

The present study was a descriptive cross-sectional comparative one that included 110 full-term neonates divided into two groups, the first group included70 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 the Maternal and Children Hospital, Minia University.

Term infants borne to diabetic mothers were eligible to be included in the study except those with evidence of sepsis based on clinical or laboratory findings,

babies with suspected or confirmed inborn error of metabolism, and those with major congenital malformation other than cardiac one. For all included neonates, complete history taking and which included the history of maternal illness with a focus on diabetes Mellitus of various types (type 1or type2 or gestational), maternal medication, parity mode of delivery, gestational age, APGAR score, and need for resuscitation. Detailed clinical examination was done and included birth weight, respiratory and cardiac assessment for respiratory distress, tachycardia, cardiac murmurs, cyanosis, abdominal and neurological examination, or presence of neonatal jaundice.

A routine investigation like complete blood count and, random blood sugar, were done in addition to assay of hemoglobin A1c (HbA1c) and monocyte chemotactic protein-1(MCP-1) . MCP-1 was measured in the hospital laboratory by enzyme-linked immunoassay (ELISA) method that allows for in vitro quantitative determination of Human Monocyte Chemotactic Protein 1 (MCP-1) concentration in serum .The concentration of MCP-1 in the samples was then determined by comparing the O.D of the samples to the standard curve. Assessment of HbA1c: by Nyco CardTM HbA1c is a boronate affinity assay.

Echocardiography Examination was performed by a pediatric cardiologist having experience in echocardiography according to the recommendations of The American Society of Echocardiography [5] and by the use of SonoSite, M-turbo system with P10x 8-MHZ transducer (multifrequency transducer) (SonoSite Fujifilm Inc., Bothell Wa, USA). The examination consisted of M-mode, 2-D, pulsed, continuous-wave, and color Doppler blood flow velocity measurements of the heart valves. Parameters like aortic valve diameter(AOV), fractional shortening(FS) , ejection fraction (EF) ,interventricular septal end-diastolic thickness (IVSd), interventricular septal

end-systolic thickness(IVSs), left ventricular end-diastolic dimension (LVDd), left ventricular end-systolic dimension (LVDs);, left ventricular posterior wall thickness (LVPW) and right ventricular end-diastolic dimension (RVDd) were taken.

Ethical considerations

The study was revised approved by the scientific committee of the pediatrics department, Minia University. Written and verbal consent was obtained from the parents of babies prior to inclusion in the study.

Statistical analysis

Analysis of data was done using Statistical Program for Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean ±standard deviation and range. Qualitative variables were described as a percent. In order to compare quantitative variables between two groups, Correlation studies were done using Spearman's rank correlation coefficient. P-value <0.05 was considered significant in all analyses.

Results

Table (1) showed that infants of diabetic mothers (IDMs) had a significant higher birth weight than the control group with p value< 0.001, and while. delivery by C.S in IDMs was significantly higher when compared to the control group with p value< 0.04. As regarding gestational age and sex distribution, there was an insignificant difference between the two groups.

Table (2) showed that there were a significant increase in levels of cord blood HbA1c,MCP-1, hemoglobin level and hematocrit in IDMs (P-0.024, 0.027, 0.041, and 0.001 respectively) when compared with healthy control neonates and there was significant hypoglycemia in IDMs when compared with the control group (P- 0.05), while there was insignificant difference in neonatal white blood cells and neonatal platelet count between the two studied group. Echocardiographic findings in

infants of diabetic mothers all were significantly different from normal healthy newborns.

Table (3) showed that Increase in IVSd, IVSs, LVPW, LVDd, LVDs and RVDd measures of patient IDMs when compared with the control group, also there were a decrease in EF% and FS % of IDMs when compared with the control group. Awhile insignificant difference was found in AVO (aortic valve diameter) between the two groups.

Table (4) showed that there was a significant positive correlation between birth weight and various echocardiographic findings LVDs ,IVSs, Lvpw , LVDd, LVDs , RVDd and AOV where r equals (0.768, 0.859, 0.412, 0.792, 0.781, 0.820, 0.784. respectively, p value (0.001) and negative correlation between birth weight and FS %and EF% r (-0.612 and-0.537) and p (0.004 and 0.063)

Table (5) significant correlation was noticed between HbA1c and various echocardiographic findings where HbA1c correlated significantly with LVPW r=, 0.298. (p=0.012.). Another high significant correlation between HbAIc and each of IVSd ,IVSs , LVDs ,LVDd, RVDd and AOV were noticed where(r = 0.724,0.544,0.544 0.433and0.673) respectively p-value(<0.000).A significant negative correlation was noticed between HbA1c and ES and EF where r = -0.551- and -0.688 respectively p (<0.000).MCP-1 was strongly associated with each of IVSd. IVSs, LVPW , LVDs and RVDd and AOV where (r= o.793,0.687 ,0.465, 0.557, o.548 and 0.437) (p<0.000). Also, negative highly significant correlations were noticed between MCP-1 and each of FS AND EF where r=-0.-663 and -0.664) p (< 0.000).

The sensitivity and specificity of HbA1c in the prediction of cardiomyopathy at cutoff point > 4.7% were 83.3%, 95%. AUC was 0.93 while that of MCP-1 in detecting cardiomyopathy in IDM babies was Sensitivity 93.3%, specificity was

97.5% at cutoff point >390 pg/ml , AUC was 0.96 (figure 1&2).

Discussion

Fetuses and newborns of mothers with GDM are vulnerable to Cardiac complications due to congenital heart malformation and ventricular hypertrophy which represent the major causes of morbidity and mortality [6]. The incidence of hypertrophic cardiomyopathy (HCM), particularly interventricular septal hypertrophy (IVSH), ranges from 10%to 71% [1]. Regarding the demographic data, birth weight was significantly high in IDMs in comparison to controls in the present study. These results can be explained by the fact that maternal diabetes and/or obesity affects this pathway through exaggeration of the physiological insulin resistance which develops during pregnancy, which in turn contributes to maternal high blood sugar and dyslipidemia then leads to increased nutrient delivery to the fetus, subsequently resulting in fetal hyperinsulinemia and macrosomia as per the modified Pedersen hypothesis [6]

In our study cesarean section was the predominant mode of delivery in macrosomic babies. This was inconsistent with Mahy-Eldin et al who reported similar results [7]. Similarly, Mathew et al described an increased incidence of cesarean section in macroscopic neonates [8].A significant increase in levels of neonatal hemoglobin and neonatal hematocrit in IDMs when compared with healthy controls was noticed in our study. These results were near to that done by Cetin et al., 2011 [9] who found that hemoglobin, HbF levels, and venous neonatal hematocrit values in IDMs were significantly high when compared to controls and Metzger et al., 2010 who reported that IDMs have higher levels of RBCs and consequently hemoglobin and hematocrit levels and this could be due to the positive effect of fetal insulin on erythropoiesis [10].

There was significant hypoglycemia in IDMs when compared with the control

group, and this is in agreement 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 [11]. This metabolic risk is supposed to be a result of relative fetal hyperinsulinism, manifested as a feedback mechanism counterattack the high glucose levels induced by maternal diabetes [12]. In our study, we found that there were insignificant 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 was insignificant difference in WBCs and platelet numbers between IDM and control group [13], however another study reported that WBCs and platelet values were high in IDM which can be explained by chronic acidosis and hypercapnia in diabetic pregnancies and different sample size and criteria of patients [14] Cord blood HbA1c was significantly higher in IDMs than healthy normal neonates which is significantly associated with early postnatal hypoglycemia. These results were in agreement with several previous reports Davison et al showed that glycated hemoglobin levels were significantly higher in IDMs compared to infants of nondiabetic mothers [15], similarly Koja et al., 2011 reported that the levels of glycated hemoglobin collected from infant borne to diabetic mothers were higher than that of healthy neonates [16]. It was postulated that glycated hemoglobin levels were significantly elevated in the diabetic mothers and their babies in comparison to controls. These data strongly suggest that neonatal hypoglycemia is a result of high maternal blood glucose in pregnancy and consequent fetal hyperglycemia and hyperinsulinemia [17].

In the present study there was a significant rise in levels of cord blood MCP-1 in IDMs when compared to healthy controls, and this was similar to the study of Vuguin et al. who mentioned that MCP-1 levels in IDMs

were high when compared to control and which can be a result of hyperglycemic state reflected by higher HbA1c levels in diabetic patient and the presence of the acetoacetate ketone which may be a factor in the increased MCP-1 levels in IDMs cord blood [18]. Another t study found that MCP-1 is elevated during pregnancy and also augmented in GDM compared to non-GDM, this increased MCP-1 levels may lead to adverse pregnancy outcomes [19]. In contrast with our study, Kurepa et al 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) [20].

In the present study, there was a significant correlation between neonatal birth weight cord blood HbA1c. This matches with a previous study which reported that elevated HbA1c was a reliable predictor for poor pregnancy outcomes, especially macrosomia; they attributed this to hyperinsulinemia which has a strong anabolic effect [21]. Our study showed that there was a significant positive relationship between birth weight and cord blood MCP-1, and this was in agreement with Lappas, et al who reported MCP-1 is a pro-inflammatory cytokine that is expected to play a key role in the development of insulin resistance, and so may play a part in the fetal overgrowth and maybe enhanced fat deposition seen in infants whose mothers have GDM [19].

Kurepa et al, on the other hand, observed MCP-1 levels in the blood and fetal has no relation to birth weight, suggesting that MCP-1 levels and birth weight are unrelated and MCP-1 was considered one of the pro-inflammatory cytokines [20]. However, Kurepa et al, 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[20].

As regarding echocardiographic measures in this study, there was 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 a lower value of FS% and this matches with El-Ganzoury et al who reported a 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 [21, 22]. Similarly, Korraa et al found a significant abnormality in the left atrial thickness and inter-ventricular septal dimension in IDMs in comparison to control [23].

In contrast with our study, Katheria etal reported that the thickness of the interventricular septum between the controls and IDMs were similar(24), also Demirorem et al reported no differences 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 [25].

Our findings revealed that HbA1c has high sensitivity and specificity for detecting cardiomyopathy and that there was a highly significant correlation between cord blood HbA1c and all echocardiographic measurements. We noticed that cord blood HbA1c in IDMs was inversely correlated with EF percent and FS percent. El-Ganzoury observed that 26 of the 30 newborns with HCM had a Hb A1c of less than 8% (8–9.1), while the remaining four had a HbA1c of less than 6.5 percent. Ullmo et al also identified the association between poor maternal glycemic management and hypertrophic cardiomyopathy [22, 26]. In contrast with our study Pradhan et al

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 [27].

Our findings showed that MCP-1 has high sensitivity and specificity for detecting cardiomyopathy and there was a highly significant correlation between cord blood MCP-1 and all echocardiographic measurements. We also discovered that cord blood MCP-1 in IDMs was inversely correlated with EF percent and FS percent, which agrees with the findings of Kobayashi et al where the serum levels of MCP-1 in patients with dilated cardiomyopathy were significantly elevated compared with those of healthy control subjects and the expression level was inversely correlated with left ventricular ejection fraction (LVEF) [28]. Also, Iwasaki et al reported that in HCM patients' levels of MCP-1 are negatively correlated with left ventricular fractional shortening which was determined by echocardiography [29].

The results of this study showed that there was a highly significant positive relationship between birth weight and all echocardiographic measurements except AOV and EF%, this agrees with El-Ganzoury et a similar results [23]. In this field, Tugertimur et al. found that IVS thickness and fraction shortening values of Large for the gestational group were higher than those of appropriate for gestational age [30].

Our study should that echocardiographic changes is significantly high in infants of diabetic mothers also HbA1c and MCP-1 were up-regulated in those infants and their levels are strongly correlated with echocardiographic changes MCP-1and HbA1c were found to have high sensitivity and specificity in detecting cardiomyopathy in those groups of babies making them sensitive and good predictors of cardiomyopathy.

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

Conclusions

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

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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

Conflict of interest

The authors have no conflict of interests to declare.

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Author's details

[1]Pediatric Department, Faculty of Medicine, Minia University, Egypt

[2]Cardiology Department, Faculty of Medicine, Minia University, Egypt.

[3]Clinical-Pathology Department, Faculty of Medicine, Minia University, Egypt

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Table 1: Neonatal demographic data for Infants of diabetic mothers (IDMs) and control groups.

Item	Group I IDMs (n=70)	Group II Control (n=40)	P value
Gestational age(Weeks) Mean ± SD Range	38.88 ± 0.843 (40 - 38)	38.1 ± 0.901 (40 – 38)	0.186
Birth weight (Kg) Mean ± SD Range	 3.45 ± 0.535 (2.6 - 4.2)	 2.9 4 ± 0.228 (2.35 - 3.4)	 0.001**
Mode of delivery NVD CS	 13 (19 %) 57 (81 %)	 15 (38 %) 25 (62%)	 0.041*
Sex **Male Female**	 32 (45.7 %) 38 (54.3 %)	 20 (50 %) 20 (50 %)	 0.527

Cs, caesarean section; NVD, spontaneous vaginal delivery; SD, standard deviation.
*: significant difference at p value < 0.05

Table 2 : Studied laboratory data of IDMs and control groups.

Item	Group I IDMs (n=70)	Group II Control (n=40)	P value
Neonatal HB (gm %) Mean ± SD Range	15.5 ± 0.96 (14 – 17)	13.9 ± 0.65 (12 – 15)	0.041*
Neonatal Hematocrit (%) Mean ± SD Range	47.9 ± 2.68 (40.5 – 57)	43.7 ± 2.20 (35 – 46)	0.001**
Neonatal WBCs (cu.mm× 10^9 / L) Mean ± SD Range	11 ± 3.26 (5.5 – 13)	10.7± 2.98 (5 – 12.4)	0.082
Neonatal Platelets (1000's /cu.mm) Mean ± SD Range	270 ± 1.43 (225 – 310)	268 ± 1.63 (216 – 304)	0.164
Neonatal blood glucose (mg/dl) Mean ± SD	34.6±11.3	77.2±19.8	0.05*
Cord blood HbA1c (%) Mean ± SD Range	7.49 ± 0.95 (5.7 – 8.9)	4.218±0.165 (4.0 – 4.4)	0.027*
Cord blood MCP-1 Mean ± SD Range	389.4 ± 97.5 (243 – 590)	200.85 ± 37.94 (104 – 280)	0.024*

Student' test to compare between mean of two groups of numerical (Parametric) data.
Chi square test for qualitative data between groups
*: significant difference at p value < 0.05
HB, hemoglobin ; WBCs, White blood cells; HbA1c, glycated hemoglobin A1c; Monocyte chemotactic protein-1 (MCP-1).

Table 3: echocardiographic data in IDMs and controls

Item	Group I IDMs (n=70) Mean ± SD	Group II Control (n=40) Mean ± SD	P value
IVSd(mm)	4.157 ± 0.63	3.140 ± 0.11	0.007**
IVSs(mm)	4.906 ± 0.54	4.22 ± 0.91	0.001**
LVPW(mm)	3.85 ± 1.27	3.20 ± 0.37	0.002**
LVDd(mm)	16.2 ± 1.3	15.1± 0.97	0.0035**
LVDs(mm)	11.4 ± 1.04	9.120 ± 0.53	0.001**
RVDd(mm)	41.62± 2.47	37.3 ± 2.24	0.007**
AOV(mm)	9.54 ± 1.15	9.13 ± 0.854	0.418
FS (%)	36.11 ± 5.31	41.2 ± 0.992	0.041*
EF (%)	69.12 ±3.98	73.53 ± 4.71	0.049*

AOV, aortic valve diameter; FS, fractional shortening ; EF, ejection fraction; 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; RVDd, right ventricular end-diastolic dimension; SD, standard deviation.

Chi square test for qualitative data between groups

*: significant difference at p value < 0.05

Table 4: Correlation between cord blood HbA1c, cord blood MCP – 1, and echocardiographic measures and birth weight in IDMs group .

Item	Cord blood HbA1c		Cord blood MCP - 1	
	r	p	r	p
IVSd	0.724	0.000*	0.793	0.000*
IVSs	0.605	0.000*	0.687	0.000*
LVPW	0.298	0.012*	0.465	0.000*
LVDd	0.433	0.000*	0.252	0.035*
LVDs	0.544	0.000*	0.557	0.000*
RVDd	0.604	0.000*	0.548	0.000*
AOV	0.673	0.000*	0.000*	0.000*
FS (%)	-0.551-	0.000*	-0.666-	0.000*
EF (%)	-0.688-	0.000*	-0.666-	0.000*
Birth weight	0.706	0.000	0.734	0.000

*: significant difference at p value < 0.05

Table 5: correlation between birth weight and echocardiographic measurements.

Item	Birth weight	
	r	p
IVSd	0.768	0.001**
IVSs	0.859	0.001**
LVPW	0.412	0.001**
LVDd	0.792	0.001**
LVDs	0.781	0.001**
RVDd	0.820	0.001**
AOV	0.784	0.001**
FS (%)	- 0.612	0.004**
EF (%)	- 0.537	0.063

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 asses unadjusted association between the Echocardiographic measurements with birth weight, maternal HbA1c and cord blood MCP- 1.
*: significant difference at p value < 0.05

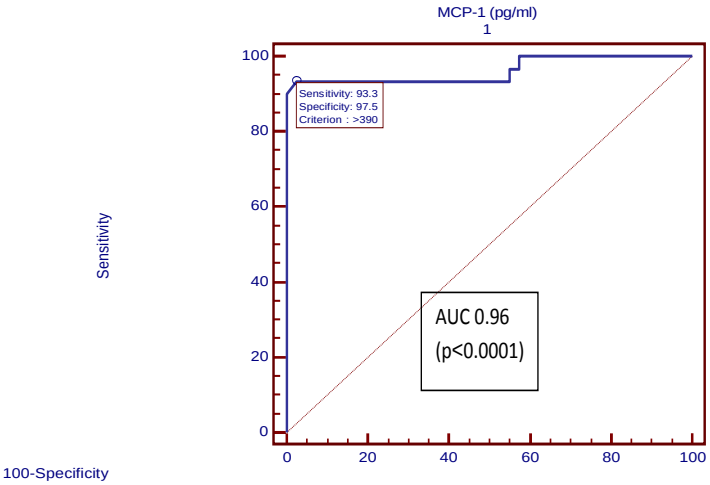

Figure 1: Receiver operating characteristic (ROC) curve of the MCP-1 for prediction of cardiomyopathy

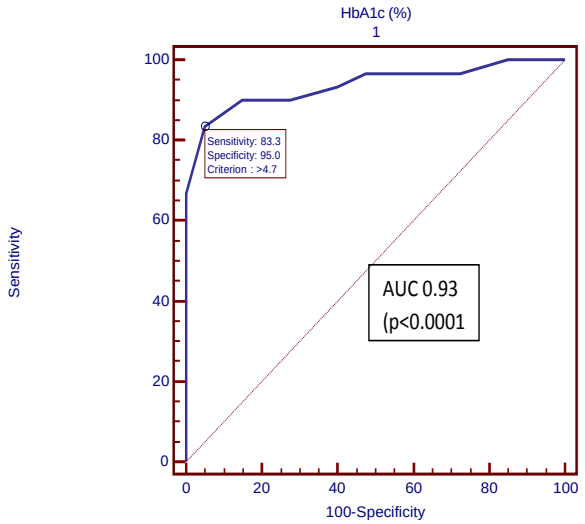

Figure 2: Receiver operating characteristic (ROC) curve of the HbA1c% for prediction of cardiomyopathy

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