Relation of insulin like growth factor and glycocylated hemoglobin at different gestational periods of pregnancy in diabetic pregnant women

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ABSTRACT

Background: Diabetes mellitus complicating pregnancy is one of the most common antenatal complications that are associated with significant perinatal mortality and morbidity. Insulin like growth factor-1 (IGF-1) has been implicated with micro-vascular complications during pregnancy. Glycosylated hemoglobin (HbA1c) is a reliable index, used to evaluate the glycemic control at the last 8 weeks.

Aim: To find the relation between the level of insulin like growth factor and HbA1c at different gestational periods of pregnancy in diabetic pregnant women.

Methods: The study was carried out on 190 pregnant women. They were 134 pregnant women with abnormal carbohydrate metabolism and 56 healthy pregnant women. Those of abnormal carbohydrate metabolism were also classified into two groups, those with gestational diabetes mellitus (70) and those with pregestational diabetes mellitus (64). IGF-1 and HbA1c levels were measured in the studied pregnant women at the second and third trimesters of pregnancy.

Results: IGF-1 concentrations was found to be higher in patients with GDM when compared with those of PGDM and the control groups, in both 2nd and 3rd trimesters with a significant ($P < 0.001$) difference among subgroups. HbA1c concentrations were found to be significantly ($P < 0.001$) higher in pregnant women with GDM and PGDM than in the control group. There was a significant ($r=0.27$, $P<0.001$) weak correlation between IGF-1 and HbA1c in both 2nd and 3rd trimesters.

Conclusion: Both, IGF-1 and HbA1c levels elevate in pregnant women with GDM and PGDM, such rise is manifested by a weak positive correlation between the concentrations of the two parameters.

Recommendation: It is useful to study the role of IGF-1 therapy in pregnant with diabetes mellitus especially those with vasculopathy.

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Introduction

Diabetes mellitus complicating pregnancy is one of the most common antenatal complications that are associated with significant preinatal mortality and morbidity [1, 2]. Diabetic pregnancies can be divided into two categories: those with pre-gestational or pre-existing diabetes mellitus in which the diagnosis is made in the pre-pregnancy state (PGDM), and those with gestational diabetes mellitus (GDM). Pre-existing diabetes consists of type 1 diabetes mellitus with an incidence of around 0.5%, and type 2 diabetes with an incidence of 2-3% [4]. The incidence of gestational diabetes mellitus differs in different populations and ethnic groups, and was shown to be as high as 13% in Chinese populations [4, 5]. Effective treatment of pre-existing as well as gestational diabetes mellitus was shown to improve outcome and reduce perinatal mortality, as compared to untreated patients [6].

An atherogenic factor that promotes vascular endothelial growth, IGF-1 has been implicated with micro-vascular complications during pregnancy. To date, short-term beneficial metabolic effects of recombinant human IGF therapy have been demonstrated in numerous diabetic conditions, including type 1 DM and type 2 DM. Until recently, IGF-1, based upon its enothilial growth promotion, was considered a mediator of vascular disease. Conversely, increasing evidences indicate the protective mechanism of IGF-1against vascular derangements, relating to its ability of NO production [7]. IGF-1, also called somatomedin C, is a protein that in human is encoded by the IGF1 gene [8].

IGF-1 is a hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults. A synthetic analog of IGF-1, mecasermin is used for the treatment of growth failure [9]. It is a 70-amino acid peptide in a single chain protein having a molecular mass of 7649 Dalton, with a structure similar to insulin, particularly proinsulin, and an ability to bind with its receptor although with lesser affinity. The IGF-1 receptor is also composed, like the insulin receptor, of 2 chains, α and β, and is related to tyrosine kinase activity, hence there is a possibility of exerting similar clinical effects by both hormones [10]. IGF-1 is produced primarily by the liver as an endocrine hormone as well as in target tissues in a paracrine/autocrine fashion. Production is stimulated by growth hormone (GH) and can be retarded by under nutrition, growth hormone insensitivity, lack of growth

hormone receptors, or failures of the downstream signaling pathway. Approximately 98% of IGF-1 is always bound to one of 6 binding proteins (IGF-BP). IGFBP-3, the most abundant protein, accounts for 80% of all IGF binding. IGF-1 binds to IGFBP-3 in a 1:1 molar ratio. In rat experiments, the amount of IGF-1 messenger ribonucleic acid in the liver was positively associated with dietary casein and negatively associated with a protein-free diet [11].

IGF-1 is a primary mediator of the effects of GH, it stimulates the liver to produce IGF-1. IGF-1 which enhances the systemic body growth. It has growth promoting effects on almost every cell in the body, especially skeletal muscle, cartilage, bone, liver, kidney, nerves, skin, hematopoietic cell, and lungs. In addition to the insulin-like effects, IGF-1 can also regulate cell growth and development, especially in nerve cells, as well as cellular DNA [12]. A normal range of IGF-1 in non-pregnant women in different ages has been shown to be varied [13].

HbA1c was introduced into a clinical use in the 1980s and subsequently has become a cornerstone of clinical practice. It reflects average plasma glucose over the previous 8-12 weeks [14]. It is the preferred test for assessing glycaemic control in people with diabetes. Moreover, there has been substantial interest in using it as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes [15]. Before pregnancy, the target for metabolic control in women with diabetes is HbA1c [16]. Increased third-trimester HbA1c levels are associated with an increased risk of preeclampsia, macrosomia [17], and still birth [18], leading to speculations that the target for HbA1c in pregnancy should be even lower than outside pregnancy to prevent adverse events.

Methods

The studied 190 pregnant women were of a single viable fetus and cephalic. They were divided into groups, of these, 70 women were having gestational diabetes mellitus (GDM) (group 1a) and 64 women were having pregestational diabetes mellitus (PGDM) (group 1b). The remaining 56 pregnant women (group 2) were having normal pregnancy free from DM and hypertension and served as a control group. The study was carried between October, 2012 and August, 2014

Fasting blood samples for at least 12 h were collected according to a standardized protocol from each participant, 5 ml of blood was drawn and transferred to the laboratory for the measurements of IGF-1 concentration. It is performed by means of an ELISA

method with the use of a ready-made kit in accordance with the manufacturer's instructions (Demeditec IGF-1 600 ELISA DE 4140, Germany). HbA1c estimation was carried out with the use of 2 ml of the whole blood mixed with EDTA and HbA1c is measured directly by auto analyzer (Selectra E).

Ultrasound examination was performed in semi recumbent position .It was done for estimation of gestational age, for checking of fetal congenital anomalies, head circumference, femur length, amniotic fluid index and placental position.

Analysis of data was done by using SPSS program. The analysis of variance (ANOVA) with LSD have been used to compare more than two groups with measured data. Pearson Correlation coefficient was calculated to rank variables against each other.

Results

One hundred and ninety pregnant were included in the final analysis, participants were divided into groups, group 1a (GDM= 70), group1b (PGDM= 64) and group 2 as (Control= 56). The maternal characteristics of the studied pregnant women were illustrated in table 1. IGF-1 concentrations was found to be higher in patients with GDM when compared with those of PGDM and the control groups, in both 2nd and 3rd trimesters with a significant (P <0.001) difference among subgroups. There was significant differences between the 2nd and 3rd trimesters concentrations in all groups, in the 3rd trimester, concentrations were evident to be higher than in the 2nd trimester with a significant (P<0.001)difference. HbA1c concentrations were found to be higher in GDM, PGDM than in the control groups with a significant (P< 0.001) difference. In the 3rd trimester the mean values were lower than in the 2nd trimester with a significant (P< 0.001) difference (Tables 2&3).

There were significant (r=0.27, P<0.001) weak correlations between IGF-1 and HbA1c in both 2nd and 3rd trimesters (Fig 1 & 2).

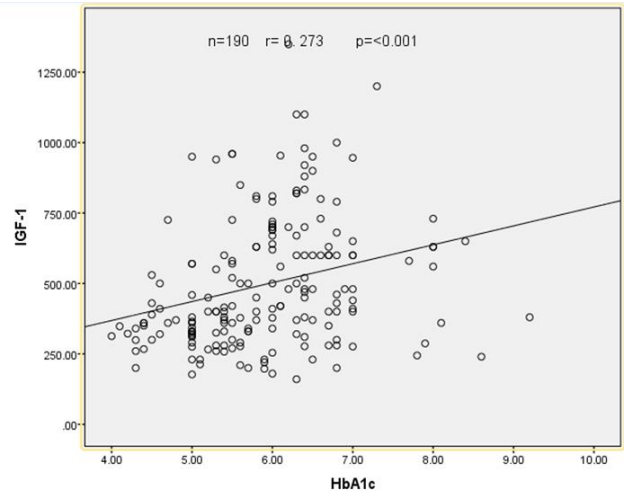

Figure 1: Scattered of IGF-1 with HbA1c levels in the third trimester

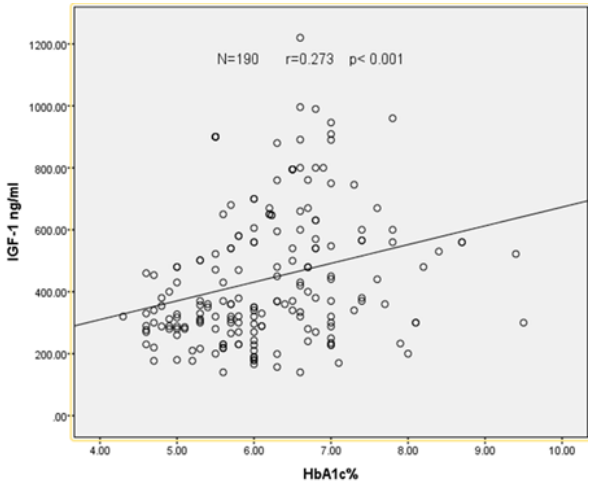

Figure 2: Scattered plot of IGF-1 with HbA1c levels in the second trimester

Discussion

On the basis of the performed examinations, IGF-1concentrations in the 2nd trimester were obtained to be raised in pregnancy complicated with GDM and PGDM. There was significant differences between 2nd and 3rd trimesters values in all groups ($p<0.001$), which remained consistent with results of other authors [19-21]. An increase in IGF-1 concentration observed in physiological pregnancy in the healthy pregnant women, in comparison with post-delivery values, may result from increased production of growth hormone by the placenta, and other gestational hormones, ensure well-being of the fetus. The explanation of increased concentrations of IGF-1 observed in the studied group of women with GDM in comparison with the healthy pregnant women is probably directly related to pronounced metabolic disturbances characterized by insulin resistance and secondary hyperinsulinemia [22].

Our results are partially consistent with the findings of Biase et al., regarding the increment of IGF-1 concentrations throughout pregnancy, but differed in values of diabetic and non-diabetic pregnant women, in their study, the IGF-1 was found to be more in non-diabetic than diabetic pregnancies [23]. However, the current results are consistent with those of Matuszek et al. who have shown that the concentrations of IGF-1 was significantly higher in women with GDM than in the control group[24].

In the current study the mean ± SD of HbA1c in GDM, PGDM in the 3rd trimester were 6.29±0.78% and 6.27±0.87% respectively compared to the control group (5.08±0.57%), these were lower than the corresponding values in the 2nd trimester with significant difference ($p<0.001$). HbA1c values in the control group were less than that in diabetic groups and were less than the normal values of non-pregnant women. This decline in the HbA1c in pregnancy could be due to several reasons.

Table 1

Maternal characteristics of the studied groups

Variable	GDM (1a)n=70	PGDM (1b)n=64	Control (2)n=56	P value		
	Mean ±SD	Mean± SD	l Mean± SD	1a vs 1b	1a vs 2	1b vs 2
Age/years	29.25±5.76	28.75±6.17	26.91±5.33	0.613	0.025	0.084
Fetal age 2nd	25.42±1.56	25.35±1.65	25.30±0.98	0.784	0.632	0.834
Fetal age 3rd	35.25±4.53	35.38±1.45	35.85±1.78	0.815	0.274	0.396
Parity	2.14±1.90	2.09±1.98	1.37±1.40	0.875	0.018	0.031
Gravidity	3.98±2.06	4.54±2.40	2.76±1.73	0.125	0.001	<0.001

Table 2

HbA1c and IGF-1 concentrations in second trimester of pregnant women with GDM, PGDM and control groups

Variable	GDM (G1a)	PGDM (G1b)	Control (G2)	P-value		
	Mean ±SD	Mean ±SD	Mean ±SD	G1a vs G1b	G1a vs G2	G1b vs G2
HbA1c%	6.59±0.89	6.42±0.90	5.35±0.56	0.225	<0.001	<0.001
IGF-1 (ng/ml)	582.61±183.7	429.5±231.3	278.6±60.8	<0.001	<0.001	<0.001

Table 3

HbA1c and IGF-1 concentrations in third trimester of pregnant women with GDM, PGDM and control groups

Variable	GDM(G1a)	PGDM(G1b)	Control(G2)	P-value		
	Mean ±SD	Mean ±SD	Mean ±SD	G1a vs G1b	G1a vs G2	G1b vs G2
HbA1c%	6.29±0.78	6.27±0.87	5.08±0.57	0.843	<0.001	<0.001
IGF-1 (ng/ml)	653.69±197.6	487.5±242.4	316.6±60.9	<0.001	<0.001	<0.001

First, a decrease in the fasting blood glucose occurs in early pregnancy, mainly between weeks 6 and 10, and is sustained during the remaining part of pregnancy [25-26]. Second, new erythrocytes formed will therefore be exposed to a lower time-averaged glucose concentration than those of non-pregnant women, and the degree of glycosylation might therefore be less [27]. Third, the erythrocyte lifespan is likely to be decreased in pregnancy, hence reducing the HbA1c value [28]. Our values were in agreement with previous findings [25].

Compared to other studies, the present study results of the control group were consistent with those reported by Redder & Roosmalen [29]. Moreover, the mean values of HbA1c in PGDM were close to finding of Marek Pietryga et al. [30]; who found no significant difference between mean values of HbA1c in pregnant women with and without vascular complications. On the other hand, our results were higher than those obtained by Usama et al. [31]. Similarly, our results of GDM were higher than those obtained by Capula et al. [32]. Differences may be due to variations in management protocols.

In conclusion, both, IGF-1 and HbA1c levels elevate in pregnant women with GDM and PGDM, such rise is manifested by a weak positive correlation between the concentrations of the two parameters. It is recommended to study the role of IGF-1 therapy in pregnant with diabetes mellitus especially those with vasculopathy.

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