MIDPREGNANCY HYPOADIPONECTINAEMIA MAY BE AN INDICATOR FOR HIGHER RISK OF GESTATIONAL DIABETES

THESIS

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Abstract

The demographic characteristics of the women in the 2 studied groups were shown in Table (10).There were no statistically significant differences ($p<0.05$) between the 2 groups concerning the mean age, gestational age, parity and BMI.

The mean adiponectin levels of the pregnant women in the study group were significantly lower than the controls (5.92 ±2.68 versus 15 ±3.61, respectively) ($p<0.0001$). This shows and confirms that midpregnancy hypoadiponectinemia is associated with GDM. Further studies is needed to elucidate the potential role of adiponectin in regulating insulin resistance and development of GDM.

Kyword;

MIDPREGNANCY HYPOADIPONECTINAEMIA MAY BE AN

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List of abbreviations

ACC	: Acetyl-CoA Carboxylase
ACOG	: American college of obstetrics and gynecology
ACRP30	: Adipocyte complement-related protein of 30 Kda
ADA	: American diabetes association
AdipoR1	: Adiponectin receptor 1
AdipoR2	: Adiponectin receptor 2
AMPK	: AMP-activated protein kinase
APM1	: Adipose most abundant gene transcript 1
APN	: Adiponectin
APPL1	: Pleckstrin homology-domain-containing adaptor protein
BMI	: Body mass index
CAD	: Coronary artery disease
CB1	: Cannabinoid-1
CVD	: Cardiovascular disease
Ecs	: Endothelial cells
ELISA	: Enzyme-linked immunosorbent assay
FAD	: Fatty acid diet
FBS	: Fasting blood sugar
FEBRASGO	: Brazilian federation of gynecology and obstetrics
Fetal NST	: Fetal non stress test
FFA	: Free fatty acid
GAD	: Glutamic acid decarboxylase
GBP28	: Glutamic-binding protein of 28 Kda
GDM	: Gestational diabetes mellitus
GWAS	: Genome-wide association studies
HAPO	: Hyperglycemia and adverse pregnancy outcomes study group
HDL	: High density lipoprotein
HLA-G	: Human leucocyte antigen-G
HMW	: High molecular weight
IAA	: Insulin antibodies
IADPSG	: International association of diabetes and pregnancy study group
IDF	: International diabetes federation
IFG	: Impaired fasting glucose
IFN	: Interferon
IGF-1	: Insulin growth factor 1
IGT	: Impaired glucose tolerance
IL	: Interleukin

IR	: Insulin resistance
LDL	: Low density lipoprotein
LGA	: Large for gestational age
LMW	: Low molecular weight
MiG	: Metformin in GDM
MMPs	: Matrix metalloproteinases
MMW	: Middle molecular weight
MODY	: Maturity-onset diabetes of the young
NF-kB	: Nuclear factor-kB
NGT	: Normal glucose tolerance
n-3 PUFA	: n-3 polyunsaturated fatty acids
OGTT	: Oral glucose tolerance test
OxLDL	: oxidized low density lipoprotein
PI	: Phosphatidyl inositol
PPAR$_\alpha$	: peroxisome-proliferator-activated receptor α
PPBS	: Postprandial blood sugar
RCT	: Reverse cholesterol transport
ROS	: Reactive-oxygen species
SA	: Adiponectin sensitivity index
SBD	: Brazilian diabetes society
SR-A	: Scavenger receptor type A
T1D	: Type 1 diabetes
T2D	: Type 2 diabetes
TC	: Triglycerid
TNFα	: Tumor necrosis factor α
TZD	: Thiazolidinedione
USPSTF	: United states preventive services task force
VCAM-1	: Vascular cell adhesion molecule -1
WHO	: World health organization

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INTRODUCTION

Gestational diabetes mellitus (GDM)

Gestational diabetes mellitus (GDM) is a common metabolic abnormality during pregnancy. It usually manifests in the second half of pregnancy and is characterized by carbohydrate intolerance of variable severity (1). Generally, the prevalence of GDM is proportional to the frequency of type 2 diabetes within a given population (2) .

Risk factors for GDM include obesity, increased maternal age, family history of type 2 diabetes, past history of GDM, previous adverse pregnancy outcome and belonging to a high-risk ethnic group (3).

The presence of GDM has implications for both the mother and the baby. Perinatal morbidity includes macrosomia, hypoglycaemia, hyperbilirubinaemia and respiratory distress syndrome, which in turn may generate subsequent complications (4). Longer term consequences for the offspring may include obesity and diabetes independent of genetic factors (5). For the mother, there is an increased risk of overt type 2 diabetes later in life (6).

The progressive increase of insulin resistance during pregnancy may play a role in the pathogenesis of GDM. The development of pregnancy-induced insulin resistance is associated with maternal obesity (7), increased maternal diabetogenic hormones (progesterone, cortisol and others) (8) and increased plasma free fatty acid (FFA) concentration (9).

Adiponectin hormone

Adiponectin is a physiologically active polypeptide hormone derived from adipose tissue and exhibits insulin-sensitizing, anti-atherogenic and anti-inflammatory properties (10).

Adiponectin was first identified in the mid- 1990s and named as AdipoQ, apM1 (adipose most abundant gene transcript 1), GBP28 (gelatin-binding protein), or Acrp30 (adipocyte complement-related protein 30) (11,12,13) .

Human adiponectin is encoded by the ADIPOQ gene (previously named APM1 or ACDC), which spans 17 kb on chromosome locus 3q27 . Interestingly, human chromosome 3q27 has been identified as a region carrying susceptibility genes for type 2 diabetes and metabolic syndrome . The gene for human adiponectin contains three exons, with the start codon in exon 2 and stop codon in exon 3 (14). Plasma concentration of adiponectin is reduced in the setting of obesity , in patients with non-insulin dependent diabetes mellitus, acute myocardial infarction, essential hypertension , inflammation and atherosclerosis (15). Adiponectin has an important role in glucose metabolism (16). In addition, increased adiponectin levels lead to nephrotic syndrome (17).

Adiponectin acts as a systemic insulin sensitizer by targeting mainly liver and muscles (18,19). The regulation of adiponectin is complex.

The adiponectin level may be affected by nutritional status such as feeding, fasting, or weight loss (20). Plasma adiponectin level is negatively correlated with body mass index (BMI), insulin resistance index and triacylglycerol and positively correlated with high-density lipoprotein cholesterol (HDL-C) in adults (20).

Aim of the work

The aim of this study is to investigate plasma adiponectin level in a group of patients of gestational diabetes comparing it with its level in non diabetics trying to answer the question is mid pregnancy hypoadiponectinemia associated with GDM or not?

GESTATIONAL DIABETES MELLITUS

DEFINITION :-

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (21). Although most cases resolve with delivery, the definition applies whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. Even though GDM is a common disorder in pregnancy, it has been difficult to compare its frequency among various populations and estimate its global incidence, due to the lack of uniform diagnostic criteria (22).

According to the American Diabetes Association (ADA), it complicates approximately 7% of all pregnancies (23), whereas its total incidence is estimated to be up to 17.8% (21).

CLASSIFICATION:-

There are 2 different methods of classifying diabetes in pregnancy:-.

1. The Modified White classification (Table 1) (24).
2. The American Diabetes Association (ADA) classification (Table 2) (25).

Table (1):-

Modified White Classification
A: Abnormal glucose tolerance test at any age or of any duration treated only by diet therapy
B: Onset at age 20 years or older and duration of less than 10 years
C: Onset at age 10 to 19 years or duration of 10 to 19 years
D: Onset before 10 years of age, duration over 20 years, benign retinopathy, or hypertension (not preeclampsia)
– D1: Onset before age 10 years
– D2: Duration over 20 years
– D3: Calcification of vessels of the leg (macrovascular disease)
– D4: Benign retinopathy (microvascular disease)
– D4: Hypertension (not preeclampsia)
R: Proliferative retinopathy or vitreous hemorrhage
F: Renal nephropathy with over 500 mg/d proteinuria
RF: Criteria for both classes R and F
G: Many pregnancy failures
H: Evidence of arteriosclerotic heart disease
T: Prior renal transplant
Gestational diabetes
– A1: Controlled by diet and exercise
– A2: Requires insulin

Table (2):-

American Diabetes Association Classification
1.Type 1 diabetes a. immunologically mediated. b. idiopathic. 2.Type 2 diabetes 3.Other specific types -Genetic disorder of B-cell function (MODY, mitochondrial DNA) -Genetic disorder in insulin action (lipoatrophic diabetes) -Exocrine pancreas diseases (pancreatitis, hemochromatosis) -Endocrinopathies (acromegaly, cushing syndrome) -Drug-induced (glucocorticoids, tiazidics) -Infections (cytomegalovirus, congenital rubeola) -Uncommon immunological forms (insulin receptor antibodies) -Other genetic syndrome (Down, Turner, Prader-willi syndrome) 4.Gestational diabetes: A glucose intolerance that had not previously been present prior to pregnancy.

AETIOLOGY & PATHOLOGY:-

*Insulin resistance and relative pancreatic β-cell dysfunction:-

Insulin requirements are high during normal late pregnancy and differ only slightly between normal and gestational diabetic women. However, in contrast to healthy women, GDM women consistently show reduced insulin responses to nutrients (8). When insulin levels and responses are expressed relative to each individual's degree of insulin resistance, a large defect in pancreatic β-cell function is consistently found in women with prior GDM (26). The majority of women with GDM appear to have β-cell dysfunction that occurs on a background of chronic insulin resistance already present before pregnancy (27). Both lean and obese women developing GDM show distinct resistance to the ability of insulin to

stimulate glucose disposal and to suppress both glucose production and fatty acid levels (28).

Defects in the binding of insulin to its receptor in skeletal muscles do not appear to be involved in the state of insulin resistance in GDM women (29). Many other defects, such as alterations in the insulin signaling pathway, reduced expression of PPARγ and reduced insulin-mediated glucose transport have been found in skeletal muscles or fat cells of women with GDM (30). Whether any of these defects are primary or the result of more fundamental defects in insulin action is currently unknown. It has been suggested that post-receptor defects are present in the insulin signaling pathway in the placenta of women with pregnancies complicated by diabetes and obesity. In addition, expression studies demonstrate that post-receptor alterations in insulin signaling may be under selective maternal regulation and are not regulated by the fetus (31).

On the other hand, it has also been proposed that events leading to the development of GDM are triggered by an antigenic load which is the fetus itself. Human leukocyte antigen-G (HLA-G) expression, which functions to protect the fetus from immune attack by down-regulating cytotoxic T cell responses to fetal trophoblast antigens, is postulated to protect pancreatic islet cells as well. The interaction between HLA-G and nuclear factor-κB (NF-κB) is suggested to be central in the events leading to GDM development. It has been postulated that the development of DM in patients who have undergone organ transplantation is analogous to GDM development in a proportion of pregnancies. In both cases, an antigenic load triggers the diabetogenic process. If future studies further support this hypothesis then it may be possible to use recombinant HLA-G for the prevention of GDM in high risk patients (32).