Ischemia Modified Albumin as a Marker of Oxidative Stress in Infants of Diabetic Mother: Relation to Lipid Peroxidation and Maternal Glycemic Control

Thesis

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Khaled Yousry Hassan

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Abb.	Full term

2, 3-DPG 2, 3-diphosphoglycerate
8-OHdG .....8-hydroxy-2'- deoxyguanosine
ACB .....Albumin cobalt binding
AGE .....Advanced glycation end-products
ALE .....Advanced lipoxidation end-products
AMP .....Adenosine monophosphate nucleoside
AMPK .....5' AMP-activated protein kinase
AOPP .....Advanced Oxidation Protein Products
Co .....Cobalt
CoA .....Coenzyme A
Cu .....Copper
DM .....Diabetes mellitus
DTT .....Dithiothreitol
Fe .....iron
GDM .....Gestational diabetes mellitus
GPX .....Glutathione peroxidases
GSH .....Glutathione
GSSG .....Glutathione disulphide
H2O2.....Hydrogen peroxide
HbA1c .....Hemoglobin A1c
Hgb .....Hemoglobin
HSA .....Human serum albumin
IDMs .....Infants of diabetic mothers
IL .....Interleukin
IMA .....Ischemia modified albumin
LGA .....Large for gestational age
MDA .....Malondialdehyde
NF-κB .....Kappa-light-chain-enhancer of activated B cells

List of Abbreviations (Cont...)

Abb.	Full term
Ni	*Nickel*
NO	*Nitric oxide*
NOX	*NADPH oxidase*
NTS	*N-terminal binding site*
OS	*Oxidatitve stress*
Pax 3	*Paired box 3 gene*
RNS	*Reactive Nitrogen Species*
ROS	*Reactive oxygen species*
SOD	*Superoxide dismutase*
TBA	*Thiobarbituric acid*
TBARS	*Thiobarbituric reactive substances*

Abstract

Background: Oxidative stress can play an important role in the pathogenesis of diabetes mellitus (DM), gestational DM and in the development of maternal and fetal complications of diabetic pregnancies. Ischemia modified albumin (IMA) is an altered type of serum albumin that forms under conditions of oxidative stress and is used as an early marker in several pathological conditions including diabetes. **Aim:** To determine the levels of IMA in infants of diabetic mothers as a marker of oxidative stress and to assess its relation to clinical and laboratory characteristics including lipid peroxidation, total anti-oxidant status, essential trace elements and maternal glycemic control. **Methods:** This study was conducted on 100 full term neonates delivered at Obstetrics and Gynecology hospital, Ain Shams University; 50 infants were born to diabetic mothers and another 50 age- and sex-matched healthy infants were enrolled as controls. Maternal laboratory investigations included random blood glucose (RBG) and HbA1c. Total antioxidant capacity (TAC), malondialdehyde (MDA), IMA and trace elements (copper, zinc and iron) were measured in cord blood. **Results:** TAC, copper and zinc were significantly lower while MDA, IMA and iron levels were higher among infants of diabetic mothers than control group. Low TAC levels were found among diabetic mothers on diet without insulin therapy compared with those on insulin therapy. Maternal HbA1c were negatively correlated to TAC while positively correlated with MDA and IMA. IMA was positively correlated to maternal RBG and HbA1c while there were negative correlations between IMA and each of TAC and copper. **Conclusions:** Oxidative stress is enhanced in infants of diabetic mothers as manifested by increased lipid peroxidation and IMA levels. IMA could be useful for detecting the potential oxidative stress among those infants. Increased oxidative stress is accompanied by alterations in the antioxidant defense status. Changes in oxidant-antioxidant balance in infants of diabetic mothers are related to maternal blood glucose and glycemic control. Proper metabolic control among diabetic mothers is mandatory to avoid oxidative stress and its potential harmful effects among their infants.

INTRODUCTION

Diabetes in pregnancy increases perinatal morbidity and mortality of both mother and her newborn. Although hyperglycemia is clearly recognized as the primary culprit in the pathogenesis of diabetic complications, even maximum glycemic control is associated with the development of complications ***(Rajdl et al., 2005)***.

Oxidative stress can play an important role in the pathogenesis of diabetes mellitus (DM), gestational diabetes mellitus (GDM) and in the development of maternal and fetal complications of diabetic pregnancies ***(Matteucci and Giampietro, 2000)***.

Oxidative stress results from a disparity between the generation of reactive oxygen species (ROS) and the antioxidant ability of the organism. The alteration of the oxidant–antioxidant system brings an effective state of imbalance, which may influence the pathogenesis of many diseases ***(Chiavaroli et al., 2011).***

The current understanding of the complex role of ROS in the organism and pathological sequelae of oxidative stress points to the necessity of comprehensive studies of antioxidant reactivities and interactions with cellular constituents ***(Augustyniak et al., 2010).***

Lipid peroxidation is a well-established mechanism of cellular injury in both plants and animals, and is used as an indicator of oxidative stress in cells and tissues ***(El-Beltagi and Mohamed, 2013)***. Malondialdehyde (MDA) has been widely used as a convenient biomarker for lipid peroxidation of omega-3 and omega-6 fatty acids because of its facile reaction with thiobarbituric acid (TBA) ***(Ayala et al., 2014).***

Ischemia modified albumin (IMA) is an altered type of serum albumin that forms under conditions of oxidative stress ***(Awadallah et al., 2012)***. It has been suggested that elevated levels of IMA may reflect a generalized rather than organ- or tissue-specific state of oxidative stress ***(Borderie et al., 2004).*** IMA is currently used as an early marker for myocardial ischemia and cardiac damage ***(Aslan and Apple, 2015; Açıkgöz et al., 2014; Pan and Li, 2016).*** It is also increased in diabetes mellitus, hyperlipidemia, chronic renal disease, obesity, and others ***(Borderie et al., 2004; Kaefer et al., 2010; Topaloğlu et al., 2014)*** and β-thalassemia major patients ***(Awadallah et al., 2012)***.

Human serum contains several antioxidants. Total antioxidant capacity (TAC) assessment is an established methodology of simultaneous measurement of different elements of antioxidant defense system ***(Gawron-Skarbek et al., 2015)***. TAC is composed of antioxidant capacity of total protein (85%; mainly albumin), uric acid, bilirubin,

carotenoids, tocopherol, and ascorbic acid ***(Akbayram et al., 2010).***

Essential trace elements such as copper (Cu), zinc (Zn), iron (Fe) and others are antioxidant trace elements that are crucial for growth, carbohydrate and protein metabolism, gene transcription, endocrine function and nutrient transport in humans. The altered concentration of essential trace elements could have deleterious influences on the health of diabetic mother as well as the fetus and newborns ***(Keen et al., 2003; Al- Saleh et al., 2005)***.

Although pregestational and gestational diabetes mellitus represent increased oxidative stress for both mother and her infant, few studies ***(Topaloğlu et al., 2014; Mohsen et al., 2017)*** investigated the role of IMA as a marker of maternal-fetal oxidative stress in diabetic mothers and their infants and its possible relation to lipid peroxidation and antioxidant status including essential trace elements among those infants remains to be elucidated.

Aim of the Work

The aim of this study was to determine the levels of IMA in infants of diabetic mothers as a marker of oxidative stress and to assess its relation to clinical and laboratory characteristics including lipid peroxidation, anti-oxidant status, essential trace elements and maternal glycemic control.

INFANT OF DIABETIC MOTHER

Despite advances in perinatal care, infants of diabetic mothers (IDMs) remain at risk for a multitude of physiologic, metabolic, and congenital complications ***(Hay, 2012a).***

Overt type 1 diabetes around conception produces marked risk of congenital anomalies (neural tube defects, cardiac defects, caudal regression syndrome), whereas later in gestation, severe and unstable type 1 maternal diabetes carries a higher risk of intrauterine growth restriction, asphyxia, and fetal death. IDMs born to mothers with type 2 diabetes are more commonly obese (macrosomic) with milder conditions of the common problems found in IDMs ***(Hay, 2012a).***

I- Incidence:

Congenital malformations are frequent in diabetic pregnancies, almost exclusive from mothers with unstable hyperglycemia prior to and around the time of conception and have been related to poor control of maternal diabetes during the periconceptional period and the embryonic period that encompasses organogenesis. The incidence of all congenital malformations may be in excess of 10% in poorly controlled diabetic pregnancies. Most major congenital malformations occur very early in gestation and, therefore, cannot be attributed to fetal hyperinsulinemia. The fetal pancreas does not make