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Adiponectin and leptin in pregnancy induced hypertension, a matter of weight

La adiponectina y leptina en la hipertensión inducida por el embarazo, una cuestión de peso

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Resumen

Niveles bajos circulantes de adiponectina en conjunto con niveles altos de leptina han sido identificados como factores de riesgo noveles para diabetes y preeclampsia. Aun en presencia de embarazo normal, mujeres son sobrepeso embarazados tienen concentraciones bajas de adiponectina en comparación con aquellas normopeso. Más aún, niveles bajos de adiponectina en el primero trimestre es un factor de riesgo independiente para el desarrollo de diabetes mellitus gestacional (GDM). Concentraciones circulantes de leptina durante el embarazo, se elevan 2 o 3 veces por encima de lo observado en mujeres no gestantes, y se elevan aún más en preeclampsia. Desafortunadamente, no hay existen puntos de referencia reproducibles y validados para leptina mensuales en el embarazo. Es necesario estandarizar (si es necesario) los posibles valores de referencia de estas adipokinas como marcadores de desarrollo de preeclampsia.

Palabras Claves: adiponectina; diabetes gestacional; leptina; preeclampsia; diabetes tipo 2; peso.

Abstract

Low circulating levels of adiponectin and increased leptin have emerged as novel diabetic and preeclamptic risk factors. Even in the presence of a normal pregnancy, overweight pregnant women have a lower adiponectin concentration than those with a normal weight. Moreover, low concentrations of adiponectin in the first or early second trimester is an independent risk factor for the development of Gestational Diabetes Mellitus (GDM). Circulating leptin concentrations during pregnancy are elevated 2 to 3 fold above that observed in nonpregnant women, leptin concentrations are further elevated in preeclampsia. Unfortunately until now, there are not reproducible and widely accepted references for adiponectin and leptin for every month of pregnancy. So it is necesary to standardize the methodologies and propose posible values (if useful) of these adipokines as prognosis markers to develop preeclampsia.

Keywords: adiponectin; gestational diabetes; leptin; preeclampsia; type 2 diabetes mellitus; weight

Introduction

Maternal hormonal and metabolic factors related to the placenta, adipose tissue and the growth hormone axis are associated with the variation in insulin sensitivity seen during normal human pregnancy[1]. Obesity-mediated factors potentially may be relevant to the pathophysiologic relationship between weight gain and preeclampsia. Recently, low circulating levels of adiponectin and increased leptin and C-reactive protein (CRP) have emerged as novel diabetic risk factors; although their relevance to gestational diabetes mellitus (GDM) and subsequent diabetes has not been characterized. In the past decade, a growing body of evidence has identified two pathologic sequelae of obesity that may link adiposity to diabetic risk: increased serum leptin and low circulating levels of the insulin-sensitizing protein adiponectin[2,3].

Adiponectin

Adiponectin, an adipokine produced abundantly by adipocytes, is the most abundant gene (AMP1) product of adipose tissue[4], and circulates at high concentrations in the plasma[5]. This adipokine consists of three heterogeneous species of multimers that can exert differential biological effects: a) low-molecular-weight (LMW) trimers, b) medium-molecular-weight (MMW) hexamers and c) high-molecular weight (HMW) isoform[6-8]. Unlike other

adipokines, adiponectin concentrations are negatively correlated with adiposity[9], suggesting that adipose tissue exerts a negative feedback on adiponectin production and/or secretion. Adiponectin is postulated to play a role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues[10,11], besides antiinflammatory properties[12], thus providing a mechanistic molecular basis for the association between an excess fat depot and obesity-related complication including type 2 diabetes mellitus (2DM). Moreover, recent findings indicate that adiponectin has antiatherogenic, anti-diabetic and angiogenic properties[13].

Data regarding circulating maternal adiponectin multimers concentrations in human pregnancy are limited[14-16]. Normal pregnancy is associated with alterations in maternal circulating adiponectin[17-19] and with changes in the relative distribution of its isoforms[20,21]. In addition, even in the presence of a normal pregnancy, overweight pregnant women have a lower adiponectin concentration than those with a normal weight[22]. Moreover, low concentrations of adiponectin in the first or early second trimester is an independent risk factor for the development of GDM. Indeed, maternal adiponectin concentration < 6.4 µg/ml at 13 weeks of gestation is associated with a 4.6-fold increased risk to develop GDM later in pregnancy[23], suggesting a causal relationship between low circulating adiponectin and GDM[24-26]. Collectively, a growing body of evidence points to a key role of adiponectin in the pathophysiology of both 2DM and GDM.

This hormone has been implicated in both the physiological adaptation to normal pregnancy and in obstetrical complications[27]. Circulating adiponectin concentrations decrease in insulin-resistant states, including 2DM[11,28]. Hypoadiponectinemia in pregnancy predicts postpartum insulin resistance, beta-cell dysfunction, and fasting glycaemia[29]. Low adiponectin levels in intra uterine growth restriction (IUGR) infants may actually predict the subsequent development of visceral fat and insulin resistance[30].

Previous studies have demonstrated that, in pregnancy, women with GDM exhibit evidence of sub-clinical inflammation and dysregulation of adipokines, including low circulating levels of both adiponectin and its HMW multimeric form[21,23]. In fact, both sub-clinical inflammation and hypoadiponectinemia may be chronic defects in this patient population, as increased CRP and low adiponectin in the first trimester have each been shown to independently predict the subsequent development of GDM later in pregnanc[23]. The significance of the current findings rests in the potential implications that a relationship between antepartum adiponectin and future 2DM could hold for diabetic risk stratification and modification. Specifically, it follows from these data that antepartum adiponectin concentration may provide a means of stratifying women with GDM with respect to their future risk of 2DM. Ideally, this information could help to target postpartum surveillance efforts to those women at the highest risk of developing diabetes. The availability of this predictor at the time of diagnosis in pregnancy may be particularly important, in light of the well-recognized sub-optimal rates of postpartum metabolic follow-up in women with GDM[31]. Secondly, the current data also suggest that chronic hypoadiponectinemia could provide a therapeutic target for risk modification in this patient population. In this respect, it is of interest to note that thiazolidinedione therapy, which has been shown to preserve beta-cell function and significantly reduce the risk of developing 2DM in women with a history of GDM[32] is also known to increase adiponectin levels. It thus emerges that a pathophysiologic relationship between hypoadiponectinemia and diabetic risk following GDM could hold important clinical implications.

Leptin

The central source of leptin is the adipose tissue, although it can also be produced in other sites, including the placenta[33,34], in fact, microarray experiments have demonstrated a higher expression profile of placental leptin gene in preeclamptic women than in normal pregnancies[35].

Leptin mainly acts by binding to specific central and peripheral receptors in the hypothalamus, adipose tissue, liver, and pancreatic beta-cells[36]. Leptin stimulates a negative energy balance by increasing energy expenditure and reducing food intake[37]. Rodents and humans lacking leptin or functional leptin receptors develop severe obesity and hyperphagia[38]. However, endogenous hyperleptinemia fails to stimulate body weight loss in obese individuals, suggesting that a state of leptin resistance is linked to the development of obesity[39].

Leptin receptor is a possible new candidate for the endocrine control of human pregnancy[40]. To maintain the increased energy intake in the face of increased adiposity and rising leptin levels, pregnant females become resistant to the central anorectic actions of leptin. In rats, pregnancy-induced leptin resistance is characterised by elevated neuropeptide Y (NPY) and reduced pro-opiomelanocortin (POMC) expression in the arcuate nucleus (Arc), reduced leptin receptor mRNA levels and suppression of leptin-induced phosphorylated signal transducer and activator of transcription-3 protein (STAT-3) in the ventromedial hypothalamic nucleus, as well as a loss of anorectic responses to both leptin and alpha-melantocyte-stimulating hormone (a-MSH). This leptin-resistance may also cause central insulin resistance and an altered peripheral glucose homeostasis[41]. Even more, findings from a Chinese group suggest that the Lys656Asn polymorphism, a functional variant in the LEPR, and high leptin levels are risk factors for preeclampsia[42].

Leptin is produced in both maternal and fetal adipose tissues and the placenta[43,44], while its receptors are abundant in the uterine endometrium, trophoblast, and the fetus[45]. Fetal adipose tissue is an important source of leptin and fetal leptin levels are strongly related to birth weight and fetal adiposity[46-48]. The role of leptin in placental function

has not been fully elucidated but it is supposed to play a role in the regulation of placental amino acid transport by activation of the JAK-STAT pathway[49].

A possible leptin's involvement in pathophysiological adaptations that define the foetal growth potential can be supported[50], because this adipokine seems to be a critical factor for overall fetal development[42,51]. For example, maternal first trimester serum leptin demonstrates a significant negative association with neonatal weight in preeclamptic pregnancies and to a lesser extent in normotensive pregnancies.

Furthermore, a strong association between neonatal leptin levels, bone mineral content and estimated bone density has been confirmed, supporting a role for leptin in the process of fetal bone remodelling[52]. Leptin may play a role in the control of substrate utilization and in the maintenance and functional characteristics of fat mass before birth, producing permanent changes concerning adiposity and body composition in adult life.

Circulating leptin concentrations during pregnancy are elevated 2 to 3 fold above that observed in nonpregnant women, leptin concentrations are further elevated in the pregnancy complication preeclampsia and are lower in pregnancies complicated by IUGR[53,54]. However, clinical and experimental trials have not yet clarified the definite role of leptin in the pathophysiologic mechanisms of high-risk pregnancies[55,56]. Previous studies have demonstrated that plasma leptin concentrations are increased significantly during the third trimester of preeclamptic pregnancies in contrast to normal pregnancies[57,58]. Other studies have documented that plasma leptin levels are elevated even before preeclampsia had become clinically evident[59-61]. Amongst the groups involved in the study of leptin and preeclampsia our team has showed that a value above 40 ng/ml in the third trimester of pregnancy seems to be a good predictor for preeclampsia[62]. However, the exact mechanism underlying the increased plasma leptin levels in preeclampsia and the functional role of leptin in the development of hypertension need to be further clarified[63]. How the knowledge that leptin is associated to hypertension could be applied in clinical practice is still a matter of debate.

Impaired Glucose Tolerance (IGT) during pregnancy is associated with leptin gene DNA methylation adaptations with potential functional impacts. These epigenetic changes provide novel mechanisms that could contribute to explaining the detrimental health effects associated with fetal programming, such as long-term increased risk of developing obesity and 2DM[64].

Until now, there are several papers relating to leptin and adiponectin in pregnancy but we have found heteregenous results (Table 1). So it is necesary to standardize the methodologies and propose posibles values (if useful) as prognosis markers to develop preeclampsia.

Summary

Maternal adipokines are related to several diseases. Being more specific, adiponectin has antiatherogenic, antidiabetic and angiogenic properties but in pregnancy overweight women have a lower adiponectin concentration than those with a normal weight. In relation to leptin, its concentrations during pregnancy are elevated 2 to 3 fold above the values observed in nonpregnant women, and are further elevated in preeclampsia. Our group has reported that in Mexican morbid obese women, a value higher than 40 ng/ml in the second trimester, is highly predictive of preeclampsia. To our best knowledge there isn't any drug targeting at leptin receptor to explore new antihypertensive options.

Table 1. Comparative values reported for leptin and adiponectin in pregnancy*

	Month																		
	3			4			7			8			9						
	Normal	IGT	Overweight	Normal	IGT	GDM	Normal	IGT	GDM	Normal	Obesity	Severe preeclampsia	Normal	IGT	GDM	Overweight	Obesity	Mild preeclampsia	Severe preeclampsia
Adiponectin (µg/ml)																			
Retnakaran R[29]							8	7	7										
Mazaki-Tovi S[18]													6.019		3.022		5.207		
Nien JK[27;65]										8.48	6.946	9.632							
Nakatsukasa H[66]													13						30
Gao XL[67]				9.18	6.88	5.06	5.7	4.5	3										
Kyriakakou M[68]													11.8						
Leptin (ng/ml)																			
Retnakaran R[29]							32.9	35.7	35.8										
Bouchard L[64]	28.9	25.8											44.1	25.7					
Nakatsukasa H[66]													20				21		
Sucak A[63]													16.3					30.6	31.7
Kim KH[69]	9.87		17.8										15.73			20.93			
Gao XL[67]				4.89	9.61	12.79	8.88	15.11	22.64										
Kyriakakou M[68]													20.4						

IGT: impaired glucose test, GDM: gestational diabetes mellitus.

* If necesary,values have been transformed into the same units, µg/ml for adiponectin and ng/ml for leptin.

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