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IGFBP-2 – an old and yet new factor in gestational diabetes mellitus

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SUMMARY

IGFBP-2 as part of theinsulin-like growth factor system has so far generatedsubstantial interest among researchers due to its participation in the process of carcinogenesis. At present,its vital role in maintaining proper carbohydrate management is frequently emphasized. The most common metabolic complication in pregnancy is *gestational diabetes* mellitus,during which carbohydrate tolerance is disturbed. Changes in IGFBP-2 concentration in GDM areobserved as early as in the first trimester of pregnancy, which proves the significant role of this protein in the pathogenesis of GDM.

Key words: gestational diabetes mellitus, insulin-like growth factor binding protein, insulin-like growth factor–1

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INTRODUCTION

Gestational diabetes mellitus (GDM), defined as carbohydrate intolerance of a variable degree occurring forthe first time in pregnancy or diagnosed at that time, reflects the inability to maintain proper tolerance of carbohydrates during metabolic stress in pregnancy. [1]

Not only do women with prior GDM run a risk of developing type 2 diabetes[2], but also their neonates are vulnerable to severe metabolic complications at a later stage of their lives. [2,3]

Consequently, acquiring comprehensive knowledge of GDM pathophysiology may bring health benefits for two generation groups:mothers and their children. [4] Research conducted in the recent years highlights the participation of theIGF axis in the regulation of carbohydrate management. [5] This axis includes, among others, insulin-like growth factors (IGF),which are present in the bloodstream in two forms: protein-bound or free. IGF-binding proteins that have been identified include proteins from IGFBP-1 to IGFBP-6. IGF-binding proteins inhibit IGF actions, extending their half-life and modulating their IGF-binding to their specific receptors. [6]

Recently, researchers have been demonstrating a growing interest in IGFBP-2 due to its pleiotropic activities. [7] Specific mechanisms responsible for the participation of IGFBP-2 in the metabolism of carbohydrates still remain to be discovered, but it is already a common fact that proteins may function both dependently and independently of IGFs. As for the former type of function, by competing with IGF-binding receptors,a proteinhas an inhibitive effect on IGFs. As for the latter, IGFBP-2 binds toá5â1-integrin receptors and initiates a "downstream" signalling cascade,including the phosphatidylinositol 3-kinase, and protein kinase pathway mediates glucose uptake and contributes to a decrease in insulin resistance. [8]

THE COMPOSITION OF IGFBP-2

As in the case of other IGF-binding proteins, three structural regionscan be distinguished also in IGFBP-2: N-terminal cysteine-rich region, middle region and C-terminal cysteine-rich region. IGFBP-2 contains 18 cysteine residues, 12 of which are located in the N-terminal region and the other 6 in carboxyl-terminal ends. [9,10] In N- and C-terminal cysteine-rich regions, there are IGF-binding domains. The middle region presents a heparin binding domain (HBD-1). The second heparin binding domain (HBD-2) is identified in the C-terminal region which binds with integrinthrough the integrin-binding domain (RGD). [7] HBD-1 mediates IGFBP-2 binding to RPTP b leading to the inhibition of RPTPb phosphatase. [11] The middle region of IGFBP-2 also contains a classic NLS sequence which gains access to the cell nucleus by binding importin.

The human IGFBP-2 gene is located on chromosome 2 in the region q33–q34. It consists of four exons with sizes of ~ 568, 220, 141 and 496 nucleotides, respectively, and 3 introns with the length of2700, 1000 and 1900base pairs, respectively. [12]

The recently published report by Zhu et al. offers a prospective analysis of the insulin-like growth factor system in relation to the development of GDM. Blood was collected from 107 pregnant women with GDM and from 214 pregnant women assigned to the control group (without GDM) at various stages of pregnancy. Next, IGF-1 and IGFBP concentrations were examined. As a result, it was observed that higher IGFBP-2 concentrations identified between 10–14 and 15–26 weeks of gestation were related to a substantially lower risk of GDM. The results of this study also point to an essential role of IGFBP-2 in GDM pathogenesis. The quoted researchers also noted a negative correlation between IGFBP-2 and a fasting blood glucose level in 100 g OGTTand between IGFBP-2 and HOMA-IR as early as at 10–14 weeks of gestation. Based on this and other studies, we can conclude that IGFBP-2 may play a key role in GDM development. [13]

Interesting results were produced in the analysis of IGF-1, IGF-2, IGFBP-1 and IFGBP-2 concentrations in patients with prior GDM twelve weeks after delivery. After 10 years, these women were subject to subsequent examination concerning the development of type 2 diabetes. Based on the obtained results, the scientists formulated a conclusion that a low IGFBP-2 concentration and a high IGF-1level in serum of GDM mothers are related to a higher risk of developing type 2 diabetes. [14] IGFBP-2 is also listed as a potential metabolic system marker and a sensitive parameter reflecting an early stage of insulin resistance. [15]

In the opinion of Liu et al., IGFBP-2 is the main IGF-binding protein during fetal life. [16] In the investigationof Kanai and et al., an average IGFBP-2 concentration in cord blood in the group of respondents without glucose intolerance amounted to 926 +/- 364 ng/mL and was comparable to the concentration of this protein in the group with GDM respondents - 965 +/- 467 ng/mL. [17]

Lappas, on the other hand, has observed statistically lower concentrations of IGFBP-2 in cord blood ofneonates born to patients with GDM in comparison to those who were born to mothers without GDM. [18]According to the researcher quoted above,adecrease in IGFBP-2 concentration leads to anincrease in biologically active insulin-like growth factors, which may accelerate fetal growth in the case of GDM whereas a negative correlation of IGFBP-2 concentration in cord blood serum in relation to a fasting blood glucose level in OGTT may suggest the influence of the mother's blood glucose level on IGFBP-2 concentration in the fetus. [18]

CONCLUSIONS

The identification of the substance enablingpregnant women to be tested for GDM as early asin the first trimester of gestation would result in a possibility of introducing early therapeutic management aimed at the minimization of early andlateGDM complications for both the mother and fetus.Based on the presented data we may draw a conclusion regarding a potential role of IGFBP-2 as a marker/ predictor of GDM development. Studies taking into account postnatal changes in IGFBP-2 concentration and its participation in the development of type 2 diabetes can provide us with important data.

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