Impact of ACE gene polymorphism on preeclampsia (PE) development and insulin resistance aggravation in pregnant women with type I diabetes mellitus (T1DM)

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Background and Objectives

It’s a well established fact that PE risk is increased 2-4 fold among women with T1DM and T2DM. Moreover, strong correlations between these two conditions have been elucidated within last decades. On one hand, diabetes may have impact on PE development, as there is evidence that T1DM and GDM increase PE risk. On the other hand, women who had PE are more likely to develop T2DM later in life. Also, among women with T1DM, a history of PE is associated with an increased risk of further retinopathy and nephropathy.

Recent data from in vitro models outside of pregnancy suggest insulin signaling and angiogenesis are intimately related at a molecular level, but the single underlying factor linking these both pathways has not been found yet. However, the heterogeneity of polymorphism of ACE gene seems very promising. Previously, it has been proven to serve as a predictive factor of PE/pregnancy-induced hypertension development and progression, 1-4 as well as associated with glomerular filtration and insulin resistance. 5 But the predictive value of this gene polymorphic variant for PE prediction has not been evaluated in women with preexisting T1DM. Thus, the primary objective of our study was to establish the relevance of this prognostic marker in this specific population. And the secondary objective was to find out whether different genotypes of ACE gene correlate with the degree of insulin resistance and aggravate its level in diabetic women with PE as compared to diabetics without PE.

Results:

Risk of PE development

Patients of Group II had significantly higher prevalence of II genotype (p<0.05; p<0.01) as compared to Group I (66.7% vs 16.7%, respectively) supporting the role of protective effect of II genotype on PE development in the investigated population (OR=0.15,95% CI:0.05-0.51). Therefore, hereinafter patients with both type I diabetes and their genotype (II-genotype) are referred to as ‘carriers of non-causative alleles’, patients with both D-alleles or at least one D-allele within genotype (DD or ID-genotype) - as ‘carriers of causative alleles’.

Maternal glycemic status and insulin requirement

Levels of glycated hemoglobin were tested in the 1st trimester of pregnancy in all patients included. We found a tendency to correlation between levels glycated hemoglobin and ACE genotype. Within subgroups of carriers of causative alleles the values of this parameter were reported to be higher in pregnant PE patients as compared to women without PE (Figure 1). The same tendency was observed to be associated with PE development, this fact may be evident that existed correlations between increased HbA1c in the first trimester and further PE development may be mediated through ACE genotype.

Differences in total daily insulin dose were more pronounced within Group I with generally higher values in carriers of causative alleles as compared to patients with protective II genotype (Figure 2). Statistically significant differences were observed in the 1st trimester and in the late postpartum period, when the influence of pregnancy-related factors (in particular, production of contracoid hormones) is minimal. This means that the increase in insulin dose may predict higher insulin requirements in carriers of higher insulin resistance beyond pregnancy, even with better specificality.

Moreover, pregnancy-related environmental factors may modulate the gene-mediated level of insulin resistance.

Carriers of causative alleles of ACE gene of both study groups showed shorter periods of time from initiation of antenatal surveillance to the first episode of incursion in total insulin requirement as compared to patients with protective II genotype (Group I - 188.0±35.5 days vs. 200.3±35.5 days; Group II - 183.5±61.28 days vs. 198.0±45.06 days). Shorter periods of stable insulin dosing were reported in carriers of causative alleles (DD/DD) as compared to patients with II genotype with more pronounced differences detected in the control group (Group I - 120.0±67.07 days vs. 223.5±72.7 days; Group II - 116.3±32.72 days vs. 146.6±46.8 days).

It was speculated that the fraction of basal (background) insulin requirement within basal-bolus regimen might have more precisely reflected the degree of insulin resistance. Higher doses of basal insulin are associated with increased endogenous glucose levels because of accelerated insusceptibility of peripheral tissues to insulin effects towards glucose utilization. Furthermore, the values of basal insulin requirement are less dependent from food intake and, consequently, reflect the genuine glycemic status and level of insulin resistance. In our study we found higher proportions of basal insulin within basal-bolus regimen in carriers of causative alleles as compared to carriers of non-causative alleles.

Disadaptation of carbohydrate metabolism in neonates

We suggested that frequency of neonatal hypoglycemia might correlate with level of maternal hyperglycemia and insulin resistance and, subsequently, with maternal ACE genotype. Serum levels were obtained in newborns at predefined time points (Day 1, 3 and 7 of neonatal period) in relation to maternal genotype. DD-genotype which had been previously shown to be associated with more severe maternal insulin resistance naturally resulted in more pronounced propensity to neonatal hypoglycemia during early neonatal period (from birth to 6 completed days). In Group I (PE+DD) development of hypoglycemia was reported significantly more frequently in neonates born to mothers-carriers of causative ACE alleles (p=0.04, p=0.05) (Figure 3). Such differences were not observed in Group II (p=0.03, p=0.05) (Figure 4). This data shows that in type I diabetic women with pregestational PE the presence of causative ACE alleles within maternal genotype predisposes neonates to hypoglycemia more often as compared to women with diabetes without preeclampsia.

Within the group of diabetic patients with superimposed PE significantly more delayed terms of glycaemia normalization were observed born to carriers of causative ACE alleles in comparison to carriers of non-causative alleles (3.53 days vs. 0.50 days, p<0.05) In both study groups the majority of neonates requiring glucose IV infusion because of severe hypoglycemia were born to mothers-carriers of causative alleles (Figure 5).

Conclusions:

ACE gene polymorphism determines the risk of PE development in pregnant women with T1DM. DD- and ID-genotypes of ACE gene may modulate unfavourable course of the disease, particularly, through aggravation of insulin resistance beyond and during pregnancy. The presence of DD- and ID-genotypes may have negative impact on maternal glycemic status (being associated with higher values of HbA1c in the first trimester, higher total and basal insulin requirements, as well as shorter periods of time from initiation of antenatal surveillance to the first episode of incursion in total insulin requirement and shorter periods of stable insulin dosing). Changes in maternal glycemic status generally correlate with number of causative alleles present in the genotype. Neonates born to mothers with DD- and ID-genotypes are predisposed to deeper disadaptation of their carbohydrate metabolism with more severe neonatal hypoglycemia, significantly more delayed terms of glycaeoma normalization and they are at higher risk of glucose IV infusion because of severe hypoglycemia. More consistent associations between the abovementioned effects and genotypes of ACE gene were detected in women with type 1 diabetes and superimposed PE (Group I). The existed correlations between increased HbA1c in the first trimester and further PE development may be mediated through ACE genotype (corresponding genotypes may predispose to formation of deeper insulin resistance before pregnancy with subsequent alterations in angiogenesis.

References:

8. Summary of current knowledge and new evidence concerning the effects of maternal diabetes and obesity on pregnancy outcomes. World Health Organization. 2013