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- to 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, nondiabetic women who have 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[1]. Recent data from in vitro models outside of pregnancy suggest insulin signaling and angiogenesis are intimately related at a molecular level[2], but the single underlying factor linking these both pathways has not been found yet. In this view, insertion/deletion polymorphism of ACE gene seems very promising. Previously, it has been proven to serve as a predictive factor of PE/pregnancy-induced hypertension development[3, 4, 5], as well as to be associated with glucose intolerance and insulin resistance[6]. But the prognostic value of this gene polymorhic 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 diabetic controls without PE.

Methods:

Inclusion criteria for this case-control study were as follows: type 1 diabetes preceding pregnancy (Classes B to T according to the White classification); development of PE during the current pregnancy (in patients who were normoproteinuric at baseline PE was diagnosed in accordance with the ACOG and NICE criteria; in initially proteinuric patients PE was diagnosed in compliance with the criteria stated by the National Working Group on Hypertension in Pregnancy[7]); singleton pregnancy; completion of the informed consent to participate in the study. The exclusion criteria included the following: history of chronic hypertension; history of molar fetal hydrops; multiple pregnancies; smoking; the patient's desire to withdraw from the study in each stage. Neonatal hypoglycemia was defined as < 2.2 mmol/L blood[8]. Those pregnant women who met the above-mentioned eligibility criteria underwent standard examination and were divided into two groups depending on subsequently superimposed PE (Group I included 30 patients with PE; Group II - 30 patients without PE). Molecular genetic testing was used for detection of polymorphic variants in thd ACE (ID) gene. Genetic investigation included allele-specific polymerase chain reaction (PCR) with further visualization in agarose gel. The obtained results were analyzed with two-sample t-test and Chi-squared test, OR calculation using STATISTICA 10.0 software.

Results:

Figure 1. Levels of glycosylated hemoglobin (HbA1c) in the 1st trimester of pregnancy (%) in relation to II(1), ID(2) and DD(3) genotypes of ACE gene

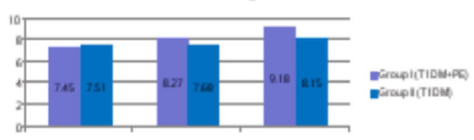


Figure 2

Mean total daily insulin doses in carriers of non-causative (1) and causative (2) alleles of ACE gene within Group 1 (IU/24h)

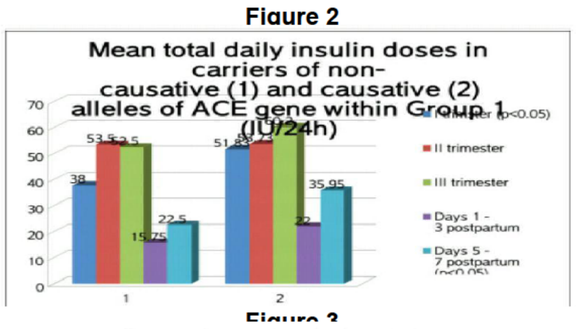


Figure 3

Serum glucose levels detected on Days 1(1), 3(2) and 7(3) in neonates born to mothers included into Group I and having corresponding ACE genotype (mean ± SD, mmol/L)

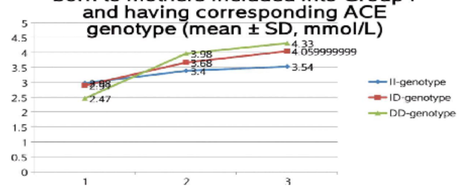


Figure 4 Serum glucose levels detected on Days 1, 3 and 7 in neonates born to mothers included into Group II and having corresponding ACE genotype (mean±SD,mmol/L)

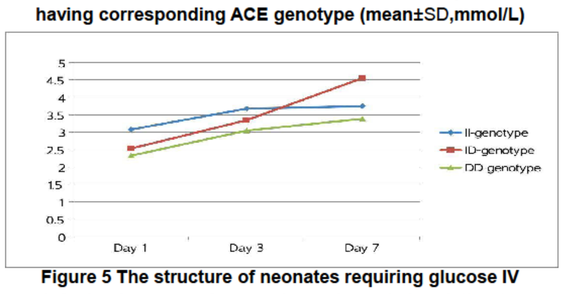
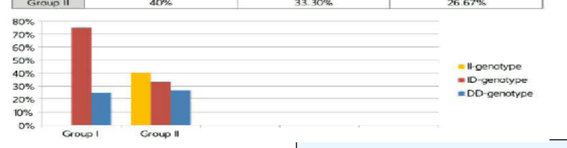


Figure 5 The structure of neonates requiring glucose IV infusion because of severe hypoglycemia in relation to maternal ACE genotype (%)

Study group	II-genotype	ID-genotype	DD-genotype
Group I	0%	75%	25%
Group II	40%	33.30%	26.67%



Risk of PE development

Patients of Group II had significantly higher prevalence of II genotype (χ^2=10.35; p<0.01) as compared to Group I (56.7% *vs* 16.7%, respectively) supporting the 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 I-alleles in 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 glycosylated hemoglobin were tested in the 1st trimester of pregnancy in all patients included. We found a tendency to correlation between levels glycosylated hemoglobin and ACE genotype. Within subgroups of carriers of causative alleles the values of this parameter were reported to be higher in preeclamptic patients as compared to women without PE (Figure 1). As the same alleles have been previously found 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[9] may be mediated through ACE genotype.

Differences in total daily insulin dose were more pronounced within Group 1 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 contrainsular hormones) is minimal. This fact means that ACE genotype may predict higher insulin requirements in carriers of causative alleles beyond pregnancy (even with better specificity!). Moreover, pregnancy-related environmental factors may modify 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 increment in total insulin requirement as compared to patients with protective II genotype (Group I – 188.00±35.94 days *vs.* 200.33±35.94 days; Group II – 183.57±61.28 days *vs.* 198.08±45.06 days). Shorter periods of stable insulin dosing were reported in carriers of causative alleles (ID+DD) as compared to patients with II genotype with more pronounced differences detected in the control group (Group I – 126.00±106.07 days *vs.*123.23±64.03 days; Group II – 119.33±87.42 days *vs.* 68.00±46.01 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 severity of neonatal hypoglycemia might correlate with level of maternal hyperglycemia and insulin resistance and, subsequently, with maternal ACE genotype. Serum glucose levels were studied 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+T1DM) development of hypoglycemia was reported significantly more frequently in neonates born to mothers-carriers of causative ACE alleles (χ2=4.44, p<0.05) (Figure 3). Such differences were not observed in Group II (χ^2=3.23, p>0.05) (Figure 4). This data shows that in type 1 diabetic women with preeclampsia the presence of causative alleles within maternal genotype predisposes neonates to hypoglycemia more frequently as compared to women with diabetes and without preeclampsia.

Within the group of diabetic patients with superimposed PE significantly more delayed terms of glycemia normalization were observed in neonates 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 prpegnancy. 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 increment 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 ID- and DD-genotypes are predisposed to deeper disadaptation of their carbohydrate metabolism with more severe neonatal hypoglycemia, significantly more delayed terms of glycemia 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:

1) Weissgerber TL, Mudd LM. Preeclampsia and diabetes. Curr Diab Rep. Mar 2015; 15(3):9. doi: 10.1007/s11892-015-0579-4
2) Thadhani R, Ecker JE, Mutter WP et al. Insulin resistance and alterations in angiogenesis: additive insults that may lead to preeclampsia. Hypertension. 2004;43:988-992; originally published online March 15, 2004; doi: 10.1161/01.HYP.0000124460.67539.1d
3) Bereketoğlu C., Kasap M., Pazarbaşı A. Studies on angiotensin-converting enzyme insertion/deletion polymorphism and genotype distributions in Turkish preeclampsia patients. Journal of Pregnancy. Volume 2012 (2012), Article ID 108206.
4) Rahimi Zohreh, Rahimi Ziba, Mozafari H et al. Preeclampsia and angiotensin converting enzyme (ACE) I/D and angiotensin II type-1 receptor (AT1R) A1166C polymorphisms: association with ACE I/D polymorphism. Journal of Renin-Angiotensin-Aldosterone System. June 2013 vol. 14 no. 2 174-180; doi: 10.1177/1470320312448950.
5) Yang J, Shang J, Zhang S et al. The role of the renin–angiotensin–aldosterone system in preeclampsia: genetic polymorphisms and microRNA. J Mol Endocrinol. April 1, 2013;50;R53-R66.
6) Bonnet F, Patel S, Laville M et al. Influence of the ACE gene insertion/deletion polymorphism on insulin sensitivity and impaired glucose tolerance in healthy subjects. Diabetes Care. 2008 Apr;31(4);789-94.
7) McCane D, Maresh M, Sacks D. A practical Manual of Diabetes in Pregnancy. Oxford, UK: Wiley-Blackwell, 2010, 280 p.
8) Rozance PJ, Hay WW. Describing hypoglycemia -definition or operational threshold? Early Hum Dev. 2010 May; 86(5): 275–280; doi: 10.1016/j.earlhumdev.2010.05.002
9) Cohen AL, Wenger JB, James-Todd T et al. The association of circulating angiogenic factors and HbA1c with the risk of preeclampsia in women with preexisting diabetes. Hypertens Pregnancy. 2014 Feb;33(1):81-92.

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Diabetes (to include obesity, pathophysiology & epidemiology)

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