

# Sensitivity or resistance to steroid therapy in children with idiopathic nephrotic syndrome is not associated with polymorphism of angiotensin converting enzyme (ACE)

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## ABSTRACT

It's about years that the relation between renin angiotensin aldosterone system (RAS) and involving enzymes such as angiotensin converting enzyme (ACE) with nephrotic syndrome is under the focus of researchers and also there are a lot of meta-analyses. However there were few studies investigated the relation of ACE polymorphism and sensitivity or resistance to steroid therapy in children. So we intend to do that. In the current study the sample size was 40 children. Among them, 22 patients were sensitive and 18 patients were resistant to steroid therapy. The samples were collected from Ali-Asghar pediatric hospital in Tehran, Iran. We used polymerase chain reaction (PCR) for the genotyping. After that, we used Chi-squared test for statistical analysis. The statistical analysis showed no significant correlation between ACE polymorphism and sensitivity or resistance to steroid therapy ( $P = 0.77$ ). Although the frequency of DD genotype was higher in the resistant group, but this difference was not statistically significant. Finally we found that although based on previous studies, D allele and DD genotype are more frequent in children with idiopathic nephrotic syndrome in comparison to healthy children, but the resistance or sensitivity to steroid therapy in children is not associated with ACE polymorphism. Further meta-analysis on the studies done on children is suggested.

## INTRODUCTION

It's about years that the relation between renin angiotensin aldosterone system (RAS) and involving enzymes such as angiotensin converting enzyme (ACE) with nephrotic syndrome is under the focus of researchers and also there are a lot of meta-analyses (Ai *et al.*, 2016; Cargin *et al.*, 2015). As an introduction, ACE is a renal-pulmonary enzyme which converts angiotensin-1 (the inactive form of the enzyme) to angiotensin-2 (the active form of the enzyme acts as a vasoactive peptide). Hence, over expression of ACE could result in higher levels of angiotensin-2 that in turn

leads to hemodynamic complications of kidneys (Bernstein *et al.*, 2016) such as glomerulosclerosis (Beer *et al.*, 2016). Other than playing the blood filtering role, kidneys are a part of the endocrine system that the RAS is the best example for this fact (Ahmadi, *et al.*, 2016; Nasri, 2015). In other words, RAS controls blood pressure, volume and electrolyte (Anderson *et al.*, 2016). Other than the items above, RAS plays a role in hematopoiesis and other physiological processes of human body (Kim *et al.*, 2016). In this endocrine system, in response to reduction of electrolyte level, blood volume and blood pressure, podocytes – the cells limiting plasma passing in glomerulus with help of their foot processes surrounding the capillaries and their penetrations to make the glomerular barrier (Hajhosieni *et al.*, 2014)-and juxtaglomerular apparatus release the hormone renin (Nasri, 2015). In blood, renin in turn converts the angiotensinogen produced by liver to angiotensin-1.

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In response to reduction of electrolyte, volume and pressure of blood, juxtaglomerular apparatus release renin in blood. Renin in turn impacts on angiotensinogen in liver and converts it to angiotensin I.

The angiotensin I converts to angiotensin II by the ACE presenting and acting in pulmonary circulation. Therefore, hypoxic injuries to lungs could results in imbalance of ACE. The angiotensin II in turn results in increase of feeling thirsty, intestinal salt absorption, aldosterone releasing from adrenal glands, maintaining salts and water by kidneys, increasing cardiac output, etc. (Gralinski *et al.*, 2016).

The most famous type of nephrotic syndrome are minimal changing, and focal and segmental glomerulosclerosis (FSGS) (Inaba *et al.*, 2016). This disease is the most commonplace kidney disease in children (Elie *et al.*, 2012; Yildiz *et al.*, 2013). The disease is usually primary and sometimes is secondary to metabolic, systemic (Lee *et al.*, 2016) or inflectional reasons (Chan *et al.*, 2016). Up to now, a lot of involving genes have been identified. Outbreak of nephrotic syndrome in Europe and the US gets to 16 out of 10000 children (Benoit *et al.*, 2010). This disease gets to end-stage in about 10-20% of the patients (Antignac, 2002). Relapse of the disease is commonplace and usually occurs 14 days after transplantation (Antignac, 2002). Patients with nephrotic syndrome are at risk of thrombo-emboli due to hemostatic disorders. It seems that crossing of heavy proteins triggers the coagulation cascade (Sagripanti and Barsotti, 1995).

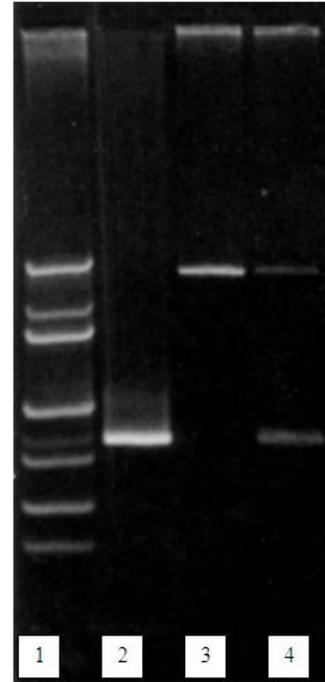
Because of anti-inflammatory effects of the steroids, they are used for treatment of nephrotic syndrome in children. Individuals with nephrotic syndrome divided into two groups of sensitive and resistant to steroid therapy (Braun *et al.*, 2016). Among them about 90% are sensitive to steroid therapy (Benoit *et al.*, 2010).

ACE has two allelic forms of insertion (I) and deletion (D). It has been proved in a lot of meta-analyses that severity of nephrotic syndrome is associated with the genotype DD followed by ID (El-Gayar *et al.*, 2015). So we intend to find that whether sensitivity or resistance to steroid therapy is associated with ACE polymorphism or not.

## METHODS

In the current study we used randomized sampling. The sample size was 40 children (20 boys and 20 girls). Among them, 22 patients were sensitive and 18 patients were resistant to steroid therapy. The samples were collected from Ali-Asghar pediatric hospital in Tehran, Iran. This study had been approved by ethic committee of Iran University of Medical Sciences.

After getting the written consents from the parents of the children, we collected blood samples from them. Then we used polymerase chain reaction (PCR) for the genotyping. After collection of the results from electrophoresis on 1% agarose gel (figure 1), we used Chi-squared test for statistical analysis with considering  $P = 0.05$  as the significance level.



**Fig. 1:** The results on the 1% agarose gel. 1) DNA indicator ( $\phi$ X174 HaeIII cleaved M<sub>r</sub>); 2) DD genotype; 3) II genotype; 4) ID genotype.

## RESULTS AND DISCUSSION

The statistical analysis showed no significant correlation between ACE polymorphism and sensitivity or resistance to steroid therapy (figure 2) ( $P = 0.77$ ). Although the frequency of DD genotype was higher in the resistant group, but this difference was not statistically significant. The results of our study in Iran, shows no significant relation. Ahmed El-Gayar *et al.* in Egypt found that the frequency of DD genotype was higher in steroid resistant patients, of course in adults (El-Gayar *et al.*, 2015). In the study of Öktem *et al.* done on children, DD genotype was more frequent in patients group; but there was no assessment between resistant and sensitive patients (Öktem *et al.*, 2004). There were just few studies compared ACE polymorphism with resistance or sensitivity to steroid therapy that most of them were reanalyzed in a meta-analysis done by Zhou *et al.* (2011). They found that ACE polymorphism cannot predict the sensitivity or resistance to steroid therapy in children with idiopathic nephrotic syndrome.

Kidney injuries are serious conditions with serious consequences if failed to diagnose on time. Hence, finding diagnostic tests for prevention of kidney injuries is necessary (Poorshahbaz *et al.*, 2015). As a strategic prevention program for low-income countries, governments are supposed to give insight and awareness to their people about screening tests (Perico and Remuzzi, 2016). However based on the findings of ours and previous researchers' the PCR cannot be used for prediction of the sensitivity or resistance to steroid therapy, but the PCR test for prediction of nephrotic syndrome in children with familial history is necessary to take prophylactic measures.

	Relation of sensitivity to steroid therapy with ACE genotype.			
	II	ID	DD	
<b>Sensitive</b>	12 11.55 ( 0.02)	8 7.70 ( 0.01)	2 2.75 ( 0.20)	<b>22</b>
<b>Resistant</b>	9 9.45 ( 0.02)	6 6.30 ( 0.01)	3 2.25 ( 0.25)	<b>18</b>
	<b>21</b>	<b>14</b>	<b>5</b>	<b>40</b>

$\chi^2 = 0.519$ ,  $df = 2$ ,  $\chi^2/df = 0.26$ ,  $P(\chi^2 > 0.519) = 0.7713$

**Fig. 2:** The statistical results.

## CONCLUSION

Finally we found that although based on previous studies, D allele and DD genotype are more frequent in children with idiopathic nephrotic syndrome in comparison to healthy children, but the resistance or sensitivity to steroid therapy in children is not associated with ACE polymorphism. Further meta-analysis on the studies done on children is suggested.

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