A Narrative Review on Nephrotic Syndrome Emphasizing its Correlation With Polymorphism of Angiotensin Converting Enzyme and Renin-Angiotensin System

Parisadat Ahmadi1, Hassan Ahmadvand2, Seyyed Amir Yasin Ahmadi3, Rozita Hoseini4, Parvaneh Rahimi-Moghaddam5

Abstract
Numerous meta-analyses have been shown that the nephrotic syndrome is one of the most important reasons of renal failure in children that is monies-taking for health organizations around the world. Because of the global and strategic importance of this issue we intend to investigate the different aspects of nephrotic syndrome to propose our suggestions with a multi-dimensional perspective. Present narrative review is based on scrutinizing the contents of relevant papers searched in PudMed search engine. The correlation of nephrotic syndrome with renin-angiotensin system (RAS) and involving enzymes, in particular angiotensin converting enzyme (ACE), has been investigated in different populations. Nephrotic syndrome in children is usually in two types of minimal change and focal and segmental glomerulosclerosis (FSGS), but more of minimal change. ACE gene has 2 polymorphic alleles of deletion (D) and insertion (I). DD genotype is associated with higher production of angiotensin-II. So it seems that persons with DD genotype are more at risk of renal diseases. Through identifying and screening the involving genetic diversities we can take the prophylactic actions. It seems that early starting of steroid therapy can prevent symptoms of the disease. As well, early starting of supplement administration of vitamin A and E could be a less harmful preemptive measure. Further researches on gene therapy methods is recommended.

Keywords: Nephrotic syndrome, Genetic polymorphisms, Angiotensin converting enzyme, Renin angiotensin system

Introduction
Numerous meta-analyses have been shown that the nephrotic syndrome is one of the most important reasons of renal failure in children that is monies-taking for health organizations around the world. Knowledge of involving pathways in renal injuries like renin angiotensin system (RAS) enables us to progress in treatment of both diabetic and non-diabetic nephropathies (1). Numerous factors are associated with progression of glomerulonephropathy and tubulointerstitial injuries that can lead to early development of end-stage renal diseases (2), such as the diabetes mellitus (3) and non-diabetic causes of nephrotic syndrome (4) which are now the major cause of end-stage renal failure around the world even in developed countries (3). Because of the global and strategic importance of this issue we intend to investigate the different aspects of nephrotic syndrome to propose our suggestions with a multi-dimensional perspective.

Methods
This paper is a narrative review, based on scrutinizing contents of the relevant papers searched in PudMed search engine with a historical approach. Our literature review method was Matrix.

Results and Discussion
The correlation of nephrotic syndrome with RAS and involving enzymes, in particular angiotensin converting enzyme (ACE), has been investigated in different populations in the recent decades and there are numerous meta-analyses from the findings of such populations. Numerous genes have been recognized in pediatric nephrotic syndrome so far. ACE gene has two polymorphic alleles of deletion (D) and insertion (I). DD genotype is associated with higher production of angiotensin-II. So it seems that persons with DD genotype are more at risk of renal diseases. Nephrotic syndrome is in 5 types that in children is usually in 2 types of minimal change and focal and segmental glomerulosclerosis (FSGS), but more of minimal change (4). In addition, it seems that resistance to steroid therapy is associated with FSGS and the procedure of the disease toward the end-stage is more rapid (5).
About Renin-Angiotensin System
This system is of the controlling systems of blood pressure, volume and electrolyte that plays important role (and even a vital role with regard to aldosterone). In addition to above information, RAS performs a function in hematopoiesis and other physiologic processes (11). In response to blood pressure, volume and electrolyte, juxtaglomerular apparatus makes signal of releasing renin protein. Renin goes in blood stream and through affecting on liver-released angiotensinogen convert it to angiotensin-I. Angiotensin-I under effect of the ACE – which is aggregated in endothelium of vessels and in particular pulmonary circulation (12) – converts to angiotensin-II. Thus mechanic and hypoxic traumas to lung could lead to imbalance in the level of ACE (12). ACE circulates in plasma and expresses on the surface of endothelial cells (13). Angiotensin-II intern results in some phenomena such as, increasing thirsty feeling, increasing intestine uptake of salts, increasing production and secretion of aldosterone from adrenal glands, saving further water and salt by kidneys, increasing cardiac output, vasoconstrictor effect on smooth muscle layer of vessels and so forth (14).

Physiopathology of RAS and Involving Genetic Issues
ACE is a zinc dependent peptidase (15) that plays a key role in RAS (16). In addition to affecting on RAS, ACE is a nonspecific enzyme that plays a role in physiologic phenomena such as blood pressure control, hematopoiesis, reproduction, development and function of kidneys and other inflammatory and immune reactions (8,15). ACE has 2 domains (C and N); C is related to angiotensin converting and N is related to hydrolysis of other peptides (17). ACE gene locates on 17q23 (18) and like most of the other genes has polymorphism. This gene has 2 recognized allele; insertion (I) and deletion (D); D allele makes more danger for kidney disease (18) and DD has reported as the most dangerous genotype (19).

Figure 1. Difference Between Aneurysm and Restenosis. Both of them are hypertrophy of vessel wall, but aneurysm is toward the external side (with dilation) and restenosis is toward the internal side.
order to limit the permeability of glomerulus with its foot processes (pedicel). The basal lamina of capillary and basal lamina of podocytes are integrated each other and make basal glomerular membrane. The spaces between the pedicels and relating diaphragms are called filtration slit. The most important protein of this diaphragm is nephron. All of the above items make a barrier that impedes losing macromolecules such as proteins and cells such as red blood cells. This barrier is called filtration barrier that the layers from blood side to urine side are respectively fenestrated endothelium, basal glomerular membrane and diaphragm of filtration slit. Hence, impaired in diaphragm and nephron results in the protein losing which is called nephrotic syndrome (Figure 2) (7,28,29).

3.6. Reasons of Nephrotic Syndrome

Nephrotic syndrome is in 5 types of minimal change, FSGS, diabetic nephropathy, membranous disease and immune-based like amyloidosis. The point is that FSGS is not a disease but it is a tissue damage in kidney with impaired function of podocytes (36). Mutation in alpha-actinin-4 (ACTN4) gene – locating on 19q13 and responsive for encoding the cross proteins with actinin filaments – counts as a reason of FSGS; also the genes nephrosis-1 congenital finnish type (NPHS1) and nephrosis-2 idiopathic steroid-resistant (NPHS2) are respectively responsive for encoding of nephrin and podocin that podocin gene is involved with resistance to steroid therapy (7,37). It seems that mutations in the genes involving with podocytes play important roles in nephrotic syndrome (35). For example, it seems that genetic factors involving with alpha-glucocorticoid receptors, glycoprotein P and cytochrome P450 are relevant to steroid resistance (30).

Table 1. Genes Which Are Responsible for Encoding Involving Filtration Macroproteins That Might Be Mutated In Nephrotic Syndrome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPHS1</td>
<td>nephrosis-1, congenital, finnish type</td>
</tr>
<tr>
<td>NPHS2</td>
<td>nephrosis-2, idiopathic, steroid-resistant</td>
</tr>
<tr>
<td>CD2AP</td>
<td>CD2 associated protein</td>
</tr>
<tr>
<td>PLCE1</td>
<td>Phospholipase C, epsilon 1</td>
</tr>
<tr>
<td>ACTN4</td>
<td>alpha-actinin-4</td>
</tr>
<tr>
<td>TRPC6</td>
<td>Transient receptor potential action channel, subfamily C, member 6</td>
</tr>
<tr>
<td>INF2</td>
<td>Inverted formin, FH2 and WH2 domain containing</td>
</tr>
</tbody>
</table>

Two-thirds of steroid resistant individuals has mutation on below seven genes (Table 1) (29,31,37) which are responsible for encoding the involving filtration macro-proteins.

Because of anti-inflammatory effect of steroids, steroid therapy is used for nephrotic syndrome in children (30). Individuals with this syndrome fall into two categories of sensitive and resistant to steroid therapy (35). About 90% of them are sensitive and 10% are resistant to steroid therapy, and the resistant ones are at risk of reaching to end-stage that unfortunately end-stage occurs in 30%-40% of them by the age of 10 (31).

Figure 2. Barriers of Filtration From Blood Side to Urine Formation Side.
How to Diagnose and Treat
In our literature review generally 2 invasive and non-invasive methods are represented. Invasive methods include biopsy (41) and non-invasive methods include assessment of circulatory immune biomarkers (42), amount of protein in 24 hours urine (proteinuria more than 3.5 g/24 h) and of course infectious assessment (10,41). In addition to protein losing, edema is of the clinical expressions and hypoalbuminemia and hyperlipidemia are of the circulatory markers of nephrotic syndrome. If this proteinuria reaches to 20-30 g/d, it is called nephrosis (37). Evaluation of blood creatinine level is not a marker for diagnosis of nephrotic syndrome, but is a good marker for evaluation of the progression of the disease. It should be regarded in future researches to screen diabetic patients; why diabetes leads to increasing of the level of serum creatinine (43) that this creatinine upcoming could be a reason of mistake with the creatinine upcoming secondary to up-grading of idiopathic nephrotic syndrome.

Generally the therapeutic protocol is based on below items (44):

- Reduction of glomerular permeability factors;
- Inhibition of the above factors’ receptors on podocytes;
- Protecting glomerular endothelium with inhibition of glycoprotein digestion through improving the level of VEGF and anti-oxidants;
- Protecting kidney with lipid control and using anti-inflammatory and anti-fibrinotic drugs. This protection is based on RAS inhibition, anti TNFs, anti TGFs and reducer factors of fibrates and lipids.

In addition to the above items, there are some co-treatment suggestions to improvement of histologic complications such as the nephrotoxicity modeled by gentamicin in animal studies, and the other nephropathies has been proven in previous researches that some of them needs to be investigated in human samples:

- Vitamin E with the amount of 400-800 unit/day can have saving effect on kidney as supplement (45).
- Erythropoietin therapy; because erythropoietin may attenuate renal fibrosis via macrophage adjustment and endothelial cell protection (46).
- Co-enzyme Q10 because of its antioxidant effects (43,47).
- Herbal medicines like olive leaf extract because of its antioxidant and anti-inflammatory effects and reduction of creatinine (48,49).

Conclusion
Through identifying and screening the involving genetic diversities in patients with family history – from the most recognized gene ACE to genes encoding involving proteins in glomerular barrier formation – we can take the prophylactic actions. It seems that the early starting of steroid therapy can prevents the symptoms of disease. As well, early starting of supplement administration of vitamin E and A (50) could be a less harmful preemptive measure rather than other pharmaceutical prophylaxises. Further researches on gene therapy methods is recommended.

Ethical Issues
Not applicable.

Conflict of Interests
The authors declare that there are no conflicts of interest.

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References


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