Renalase in chronic kidney disease: the evolving story

To the editor I read with great interest the paper by Wiśniewska et al[1] published in *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*). The key finding was that serum renalase levels were higher in patients with CKD as compared with healthy controls, whereas these levels were lower in patients with CKD as compared with controls when measured in the erythrocyte lysates. Serum renalase correlated positively with plasma dopamine and noradrenaline. Plasma concentrations of all adrenergic mediators, that is, adrenalin, noradrenalin, and dopamine were significantly higher in patients with CKD as compared with controls. Serum renalase levels in patients at each stage of CKD were higher as compared with controls, but it peaked in those with CKD stage 3 and decreased in stages 4 and 5.

The paper adds important information to the body of knowledge on this interesting enzyme, its behavior and potential roles in CKD. It was quite surprising that patients with most advanced stages of CKD had renalase concentrations lower by roughly 25% as compared with those with stage 3 of the disease. As the authors mentioned, the reports on this topic differ: some show that renalase levels decrease along with the loss of glomerular filtration rate and reduction of renal mass (which might be expected given the fact that kidney tissue is the main source of this hormone), whereas others demonstrate their increase (such an increase may be secondary to enhanced synthesis upon increased adrenergic stimulation, impaired renal clearance or catabolism). In my opinion, it might also be worthy to analyze the relationship between proteinuria and serum renalase levels.

The interaction between adrenergic hormones and renalase is a "chicken or egg" dilemma: high levels of adrenergic hormones may be secondary to low levels of renalase, but on the other hand, adrenalin and noradrenalin are the most important triggers that upregulate renalase expression.[2]

Based on the results from the study by Wiśniewska et al,[1] it is tempting to speculate that just having CKD (of any cause and any stage) is enough to stimulate adrenergic system to upregulate renal synthesis of renalase (possibly, in advanced stages of CKD, the compensatory synthesis in other tissues can also take place).

Increased "low-grade" inflammation, oxidative stress, activation of renin-angiotensin-aldosteron axis, and adrenergic system are considered the key pathways to induce and accelerate cardiovascular disease in CKD. I would speculate that continuously increased release of adrenergic hormones in CKD (which is multifactorial) appears to be the primum movens that stimulates renal synthesis of renalase. Despite such an increase, the enzyme cannot sufficiently counterbalance adverse effects of enhanced adrenergic stimulation on target tissues (the rise is disproportionally high to be controlled by renalase).

Except for its catalytic function to degrade circulating adrenergic hormones, renalase has been recently demonstrated to interfere with intracellular pathways via the plasma membrane calcium-transporting ATPase 4 receptor and then cascade of kinases (including signal transducer and activator of transcription 3, extracellular signal-regulated kinase, p38 mitogen-activated protein kinases, and phosphatidylinositol 3-kinase/protein kinase B pathway).[3] This function of renalase is considered cytoprotective, antiapoptotic, and improving target cell viability. It is worth emphasizing that Wiśniewska et al[1] were the first to analyze renalase levels within red blood cells (RBC) and found that they were reduced. This finding may be of importance in explaining the reduced lifespan of RBC in the setting of CKD, although the significance of this finding remains elusive: kinase activation in turn activates or silences particular genes in the nucleus, but erythrocyte is a de-nucleated cell. Low RBC renalase levels may be the result of decreased enzyme activity in nucleated RBC precursors in bone marrow.

ARTICLE INFORMATION

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Authors' reply We would like to thank Prof. Stompór for his interest in our article[1] and for joining the discussion on the role of renalase in chronic kidney disease (CKD).

Renalase is a flavoprotein with enzymatic activity. The first studies suggested that renalase is mainly responsible for the metabolism of catecholamines and plays a significant role in the regulation of the adrenergic nervous system and blood pressure. Recent studies indicated that renalase has cytoprotective, renoprotective, antifibrotic, and antiapoptotic properties as well as may inhibit oxidative stress. The role of renalase in physiology and pathogenesis of diseases remains controversial. Early studies suggested that patients with CKD have reduced renalase levels and renalase deficiency is associated with increased levels of catecholamines and contributes to hypertension and cardiovascular diseases.[2,3] Recent studies indicated increased levels of renalase in patients with CKD that correlated negatively with kidney function.[4,5] We agree with Prof. Stompór that high levels of adrenergic hormones may stimulate renalase secretion or high levels of adrenergic hormones may be secondary to low levels of renalase.

In our study, serum concentrations of renalase in patients with CKD were increased, whereas the concentrations of renalase in erythrocytes of CKD patients were decreased. Urinary renalase concentrations did not differ between patients with CKD and the control group. Urinary and erythrocyte renalase concentrations were negatively correlated with estimated glomerular filtration rate.

The results of our study suggest that increased serum renalase levels may be caused by a compensatory secretion of renalase in patients with CKD induced by elevated levels of catecholamines. Unfortunately, this increase in renalase levels cannot sufficiently counterbalance the development of cardiovascular complications in patients with CKD.

Additionally, we observed decreased levels of renalase in erythrocytes. We concur with Prof. Stompór that there may be many hypotheses explaining this finding. Decreased renalase levels in erythrocytes of patients with CKD may be caused by the primarily decreased synthesis of renalase in CKD, the reduced lifespan of erythrocytes in CKD, or decreased renalase activity in red blood cell precursors in bone marrow. Despite numerous studies, the role of renalase in CKD remains ambiguous and requires further studies.

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