Sex and Age Differences Related to Renal *OCT2* Gene Expression in Cisplatin-induced Nephrotoxicity

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Dear Editor,

Cisplatin is one of the most remarkable successes in "the war on cancer." Since the accidental discovery over 4 decades ago, cisplatin has been widely used for chemotherapy.[1,2] The main dose-limiting side effect of cisplatin is nephrotoxicity.[3] Yet, in spite of intense efforts over the ensuing decades to find less toxic but equally effective alternatives, cisplatin continues to be widely prescribed.[4]

Rat organic cation transport proteins are present in the kidney and are responsible for the transport of a number of organic cations.[5] Three isoforms of organic cation transport proteins are expressed in renal proximal tubules, mainly at the basolateral side.[6] Organic cation transporter 2 (OCT2) mediates cisplatin-induced nephrotoxicity and act as target for protective interventions.[7] Studies indicated that OCT2 is present in high levels in the kidney, with very low expression in the other organs.[8] Less nephrotoxic analogues of cisplatin such as carboplatin and oxaliplatin did not interact with OCT2.[9] Cisplatin uptake was increased by *OCT2* overexpression in human embryonic kidney 293 cells, which was associated with increased cellular sensitivity to cisplatin toxicity.[9]

Cisplatin nephrotoxicity is sex related.[10] A recent study demonstrated greater intensity of damage due to cisplatin in male rats than females.[11] The reason for these differences is not related to the female sex hormone, because estrogen itself promotes cisplatin-induced nephrotoxicity.[12] I suggest these differences may be related to cisplatin uptake by OCT2 due to the markedly higher renal expression of *OCT2* in male than female rats.[13] Therefore, cisplatin uptake was increased by *OCT2* overexpression in male rats and associated with increased cellular sensitivity to cisplatin toxicity. Another study demonstrated that OCT2 level was significantly reduced in mice after castration.[14] I suggest the main determinant for sex differences in *OCT2* gene expression is testosterone and this suggestion is consistent with a recent study that concludes that cisplatin therapy should be avoided when serum testosterone level is high because testosterone in high concentrations promotes cisplatin-induced nephrotoxicity.[15]

On the other hand, there is age-related differences in susceptibility to cisplatin-induced renal toxicity.[16] I suggest these differences may also be related to cisplatin uptake by OCT2 and the main determinant for that also is testosterone. This suggestion is in agreement with a study that showed renal OCT2 levels dramatically increased after day 25 in male rats and that due to an increase in testosterone levels before day 25 and renal OCT2 levels in gonadectomized adult male rats were substantially lower than that present in the kidneys from intact males.[8] Moreover, another study demonstrated that cisplatin was less likely to induce nephrotoxicity and had lower renal platinum concentrations in younger rats (age, 10 to 15 days) than that found in adult rats following cisplatin exposure.[17]

The predominant expression of OCT2 in rat kidneys is analogous to human expression of *OCT2* mRNA, which is also primarily expressed in the kidney.[18] Moreover, proximal tubular cells isolated from a human diabetic kidney showed reduced cisplatin uptake, which was attributed to the well-documented lower expression of OCT2 in diabetes mellitus.[9] Thus, the human OCT2 acts as the critical transporter for cisplatin-induced nephrotoxicity in isolated human proximal tubules and offers a potential mechanism for reducing nephrotoxicity in clinical practice. Finally, I suggest research is needed to evaluate potential sex and age differences in regulation, expression, and activity of OCT2 involved in the uptake of cisplatin in human to represent ideal renal protective compounds through the interference of cisplatin uptake by OCT2 to improve the therapeutic index of cisplatin.

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Re: Prognostic Factors in Crescentic Glomerulonephritis: a Single-Center Experience

Dear Editor,

I read the article "Prognostic Factors in Crescentic Glomerulonephritis A Single-Center Experience" by Ozturk and coworkers with great interest.[1] In this retrospective study, a group of patients with crescentic glomerulonephritis because of different kidney diseases were evaluated for poor prognostic factors that led them to end-stage renal disease. They determined that renal survival was poor in those with serum creatinine levels greater than 4.2 mg/dL on admission and those with more than 63% crescentic glomeruli of the total glomeruli.[1] The article is interesting and directs our consideration towards an important area in which early diagnosis and proper treatment could save the kidney. Crescentic glomerulonephritis is an important area of new discoveries and ideas.

The value of pathology examination of the kidney is double in glomerular disease, first, to establish the diagnosis, and the second, to provide prognostic information. It is actually a snapshot of prior and ongoing events. The morphologic classification of glomerular disease and prognostic pathological features is not static, but it is rather undergoing modification to increase the prognostic precision in response to generation of new knowledge. Studies investigating the tubulointerstitial involvement in lupus nephritis (LN) and in antinuclear antibody glomerulonephritis have shown that the predictive value of tubulointerstitial inflammatory cell infiltration, fibrosis, and tubular atrophy is even greater than that of glomerular changes, and it is