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Commentary

Impaired Citric Acid Cycle in Nondiabetic Chronic Kidney Disease

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Chronic kidney disease (CKD) influences more than 10% of adult population worldwide (Hill et al., 2016). Among this population, many of them could progress into the end stage renal disease and finally require the therapies of kidney transplantation or dialysis. Thus, it is of vital importance in retarding the progression of CKDs during the early stage (stages 1–2) via an effective intervention. Unfortunately, by now, the nephrologists still lack satisfactory tools in dealing with this issue because of the elusive understanding on the common mechanisms mediating the CKD progression. Recently, metabolomics study revealed a new aspect of CKD. In diabetic kidney disease, Sharma et al. reported a marked alteration of 12 metabolites in mitochondrial metabolic pathways, which was not seen in the diabetic patients without CKD, suggesting that such an abnormality is more relevant with the kidney injury but not hyperglycemia (Sharma et al., 2013). Moreover, this study further raised the question that whether such a phenomenon also exists in the nondiabetic CKD population. Importantly, Hallan et al. performed a study in nondiabetic CKD patients and found an abnormality of citric acid cycle using the urine and blood samples along with the partial confirmation in renal biopsy specimens (Hallan et al., 2017). The similar findings from two reports highly suggested a common phenomenon of the impairment of mitochondrial metabolism in CKDs. In agreement with above findings, recent studies from CKD animals also confirmed the existence of mitochondrial dysfunction in kidneys undergoing the chronic injury, and targeting the mitochondria could ameliorate CKD (Sun et al., 2014; Zhao et al., 2017).

Hyperparathyroidism and mixed uremic osteodystrophy are common manifestations in advanced CKD patients (Behets et al., 2015). Thus, the major purpose of the therapy with vitamin D analogues is to treat the uremia-associated calcium disorder and osteodystrophy. However, accumulating evidence demonstrated a beneficial role of vitamin D and its signaling pathway in AKI and CKD. For example, loss of vitamin D receptor (VDR) aggravated the peritubular inflammation and fibrotic response, while the VDR ligand calcitriol attenuated the fibrogenesis in UUO CKD model (Xiong et al., 2012). Under the acute kidney injury, vitamin D deficiency impaired renal repair responses to I/R injury and promoted fibrosis and inflammation possibly due to the exacerbation of renal capillary loss, which could further contribute to the AKI transition to CKD (de Braganca et al., 2016). The evidence of vitamin D in CKD and AKI demonstrated a renoprotective role of vitamin D and vitamin D signaling beyond its contribution to the homeostasis of mineral metabolism. In agreement with this notion, Stein Hallan, et al. found that 8-week treatment of paricalcitol, a VDR agonist, improved the blood and urine metabolite profile to some extent, suggesting a possible improvement of basic cellular functions of kidney (Hallan et al., 2017). However, a mild decrease of GFR estimated from serum creatinine is somewhat against expectation. Consistent with this finding, Agarwal et al. reported that use of VDR activators enhanced the blood creatinine generation and urinary creatinine excretion without affecting the GFR (Agarwal et al., 2011). For this phenomenon, we could not exclude a possibility that the systemic application of vitamin D analogues might improve the mitochondrial metabolism of skeletal muscle in CKD patients (Ryan et al., 2016), leading to the increment of creatinine in blood and urine. Due to the wide use of vitamin D analogues in treating CKD-associated mineral disorders and bone disease, these data along with previous similar findings definitely raised a serious question in figuring out the exact effects of the vitamin D analogues on GFR under different stages of CKD, as well as the mechanisms.

Overall, Hallan and colleagues' research work importantly provided some insights into the understanding of CKD. First, the abnormality of citric acid cycle could be a common renal phenomenon in CKDs, which could serve as a new direction of basic and clinical research. Second, targeting mitochondrial metabolism might be promising in developing more effective therapeutic strategies of CKD. Third, the profiles of mitochondria-associated metabolites in urine and blood could be important markers for the evaluation of CKD status, disease prognosis, and efficacy of therapies. Fourth, vitamin D analogues have a potential in protecting the renal mitochondria against various CKD insults, though its effect on

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GFR is suspicious. However, this research still has some weaknesses. First, this study did not observe and compare the metabolic profiles between CKD stage 1–2 patients and healthy controls. It is worth to study whether the abnormalities of mitochondrial metabolism occurred during the early stage of nondiabetic CKD, which would suggest us the time window for the intervention on mitochondrial metabolism in CKD patients. Second, as mentioned by the authors, the sample number in this study is relatively small, which makes it hard to analyze the impact of various etiologies of CKD on the metabolites profiles. For example, whether IgA nephropathy has a difference in urinary metabolite profile as compared with hypertensive nephropathy and others.

Disclosure

The author declared no conflicts of interest.

References

Agarwal, R., Hynson, J.E., Hecht, T.J., Light, R.P., Sinha, A.D., 2011. Short-term vitamin D receptor activation increases serum creatinine due to increased production with no effect on the glomerular filtration rate. Kidney Int. 80:1073–1079. https://doi.org/10.1038/ki.2011.207.

Behets, G.J., Spasovski, G., Sterling, L.R., Goodman, W.G., Spiegel, D.M., De Broe, M.E., D'Haese, P.C., 2015. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. Kidney Int. 87:846–856. https://doi.org/10.1038/ki.2014.349.

de Braganca, A.C., Volpini, R.A., Mehrotra, P., Andrade, L., Basile, D.P., 2016. Vitamin D deficiency contributes to vascular damage in sustained ischemic acute kidney injury. Phys. Rep. 4. https://doi.org/10.14814/phy2.12829.

Hallan, S., Afkarian, M., Zelnick, L.R., Kestenbaum, B., Sharma, S., Saito, R., Darshi, M., Barding, G., Raftery, D., Ju, W., Kretzler, M., Sharma, K., Boer, I.H.d., 2017. Metabolomics and gene expression analysis reveal down-regulation of the citric acid (TCA) cycle in non-diabetic CKD patients. EBioMedicine https://doi.org/10.1016/j.ebiom.2017.10.027.

Hill, N.R., Fatoba, S.T., Oke, J.L., Hirst, J.A., O'Callaghan, C.A., Lasserson, D.S., Hobbs, F.D., 2016. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. PLoS One 11, e0158765. https://doi.org/10.1371/journal.pone.0158765.

Ryan, Z.C., Craig, T.A., Folmes, C.D., Wang, X., Lanza, I.R., Schaible, N.S., Salisbury, J.L., Nair, K.S., Terzic, A., Sieck, G.C., Kumar, R., 2016. 1alpha,25-dihydroxyvitamin D3 regulates mitochondrial oxygen consumption and dynamics in human skeletal muscle cells. J. Biol. Chem. 291:1514–1528. https://doi.org/10.1074/jbc.M115.684399.

Sharma, K., Karl, B., Mathew, A.V., Gangoiti, J.A., Wassel, C.L., Saito, R., Pu, M., Sharma, S., You, Y.H., Wang, L., Diamond-Stanic, M., Lindenmeyer, M.T., Forsblom, C., Wu, W., Ix, J.H., Ideker, T., Kopp, J.B., Nigam, S.K., Cohen, C.D., Groop, P.H., Barshop, B.A., Natarajan, L., Nyhan, W.L., Naviaux, R.K., 2013. Metabolomics reveals signature of mitochondrial dysfunction in diabetic kidney disease. J. Am. Soc. Nephrol. 24:1901–1912. https://doi.org/10.1681/ASN.2013020126.

Sun, Y., Zhang, Y., Zhao, D., Ding, G., Huang, S., Zhang, A., Jia, Z., 2014. Rotenone remarkably attenuates oxidative stress, inflammation, and fibrosis in chronic obstructive uropathy. Mediat. Inflamm. 2014:670106. https://doi.org/10.1155/2014/670106.

Xiong, M., Gong, J., Liu, Y., Xiang, R., Tan, X., 2012. Loss of vitamin D receptor in chronic kidney disease: a potential mechanism linking inflammation to epithelial-to-mesenchymal transition. Am. J. Physiol. Ren. Physiol. 303:F1107–1115. https://doi.org/10.1152/ajprenal.00151.2012.

Zhao, H., Liu, Y.J., Liu, Z.R., Tang, D.D., Chen, X.W., Chen, Y.H., Zhou, R.N., Chen, S.Q., Niu, H.X., 2017. Role of mitochondrial dysfunction in renal fibrosis promoted by hypochlorite-modified albumin in a remnant kidney model and protective effects of antioxidant peptide SS-31. Eur. J. Pharmacol. 804:57–67. https://doi.org/10.1016/j.ejphar.2017.03.037.