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Identification of D-serine as a dual biomarker for the estimation of kidney function and for the early diagnosis of kidney diseases

➢ Abstract

Currently, early diagnosis of chronic kidney disease (CKD) is ineffective because there is no precise and reliable method to estimate kidney function. Tomonori Kimura, director of Center for Rare Disease Research and project leader of KAGAMI Project in National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN), found that D-serine, one of D-amino acids※1, which present only trace in human, is a useful biomarker for both the estimation of kidney function and the early diagnosis of kidney diseases. The present discovery would facilitate more accurate estimation of kidney function and earlier diagnosis of CKD treatment. Once applied in the clinics, this discovery would improve the prognosis of CKD and reduce the number of patients with end-stage kidney disease requiring kidney replacement therapy. Furthermore, D-serine may also be applicable for the discovery of novel therapy. The potential application is not limited to the kidney diseases: the disease context ranges to life style-related diseases such as diabetes mellitus and hypertension, as well as lethal diseases including cardiovascular diseases.

➢ Main text

Chronic kidney disease (CKD) is a highly prevalent, global health problem; 850 million people are estimated to have CKD in the world. The number of end-stage kidney disease (ESKD) patients requiring costly kidney replacement therapy is increasing year by year (over 330,000 patients in Japan, Figure 1). Additionally, the risk of life-threatening cardiovascular diseases increases in the presence of CKD. Early detection of CKD is therefore critical, but unfortunately current methods to detect CKD at early stage is insufficient and ineffective.

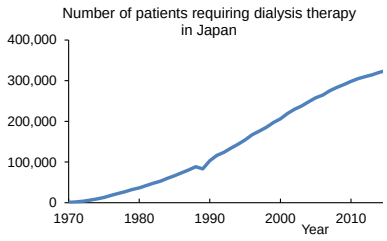

Figure 1. The increasing number of ESKD patients is a big social, medical, and financial problem.

On the other hand, D-amino acids, the enantiomers※2 of L-amino acids (Figure 2), are increasingly recognized as potential biomarkers in several diseases, especially kidney diseases. Although the amounts of D-amino acids are usually very trace in human and their existence have been overlooked, recent technological advancement enables us to measure D-amino acids accurately. In the previous study, we saw the association between D-amino acids with the prognosis of CKD. In the current study, we further examined if D-amino acids are useful for early detection of CKD.

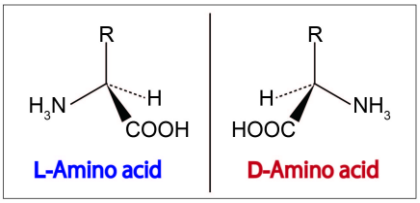

Figure 2. Chiral amino acids. L- and D-amino acids have different properties. It has long been thought that living organisms contain only L-amino acids.

The research group measured D-amino acids in blood from CKD patients by applying micro-two-dimensional HPLC (2D-HPLC) system※3. The research group found blood level of D-serine, one of D-amino acids, strongly correlated with the function of the kidney (glomerular filtration rate, GFR※4; Figure 3A). This correlation was equal to or better than conventional markers of kidney disease. On the other hand, urinary level of D-serine reflected kidney function other than GFR, and the diagnostic accuracy improved by combining D-serine in blood and urine (Figure 3B).

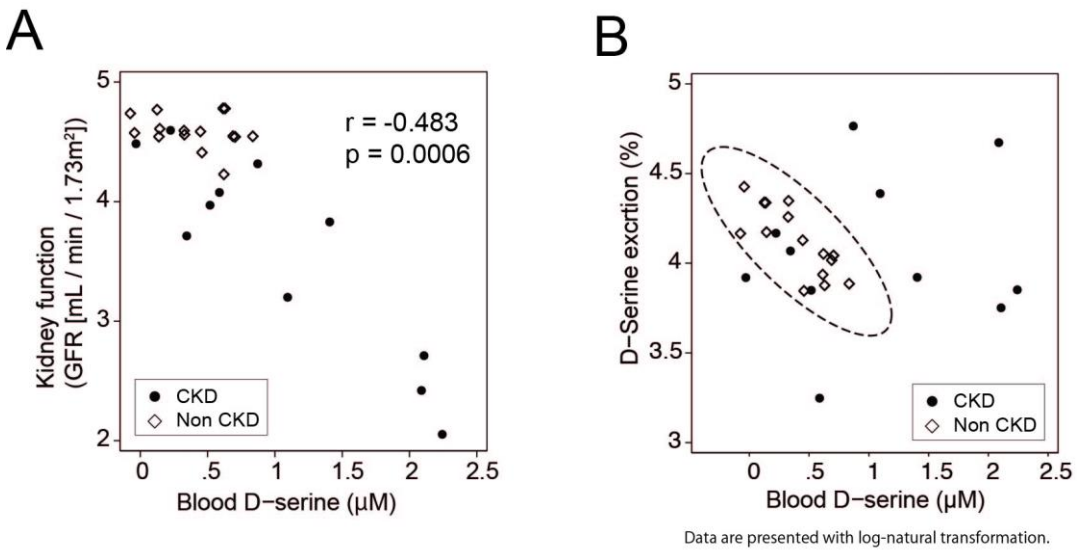

Figure 3. Assessment of kidney diseases by D-serine. (A) Blood D-serine level well correlates with actual kidney function, GFR. (B) The combination of blood and urine D-serine well detects the presence of CKD. Most CKD patients are located outside the non-CKD ranges (dotted eclipse).

The present study discovered a useful method to estimate GFR that could not be estimated sufficiently thus far. This method is useful for early diagnosis of kidney disease and provides important information in medical practice. On the other hand, urinary D-serine has information other than major kidney function, GFR, and the combination of blood and urine D-serine is useful for the detection of CKD. D-serine serves as a dual biomarker, both for the estimation of kidney function and the detection of CKD. Because D-serine also has prognostic information, measuring D-serine would facilitate comprehensive management of CKD. CKD is also prevalent in patients with lifestyle-related diseases, such as diabetes and hypertension, or cardiovascular diseases. Measuring D-serine is likely to improve the prognosis of these diseases.

Reference:

Hesaka A, Sakai S, Hamase K, Ikeda T, Matsui R, Mita M, Horio M, Isaka Y, Kimura T: D-Serine reflects kidney function and diseases. *Sci Reports* 9: 5104, 2019.

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Terminology:

※1 D-Amino acid

Most amino acids, the component of proteins, have two chiral bodies (stereoisomers): L-amino acids and D-amino acids. The amino acids present in living organisms are the L-forms almost exclusively, however, current technological advancement has just revealed the presence of D-amino acids in higher animals including humans, and the D-amino acids are gradually recognized as physiologically active molecules.

※2 Enantiomer (chiral body)

An enantiomer (also known as optical isomer or chiral body) is one of two stereoisomers that are mirror images of each other, just like one's left and right hands. L-amino acids cannot be superimposed to their chiral bodies, D-amino acids.

※3 2D-HPLC system

HPLC (high performance liquid chromatography) is a technique to separate, identify and quantify each component in a mixture. Single HPLC system is not sufficient to detect amino acids with chiral selectivity. The 2D-HPLC system, composed of tandemly-connected two HPLC systems, has enabled the detection of amino acids with chiral selectivity.

※4 Glomerular filtration rate (GFR)

GFR is the volume of blood filtered by the kidney. GFR roughly represents remnant kidney function. GFR is measured by inulin clearance, but this method is laborious and is rarely used. Instead, GFR is estimated from creatinine or cystatin C, conventional kidney markers, but these estimations are variable, and therefore, better kidney markers are required.