The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Editorial

J Atheroscler Thromb, 2022; 29: 1138-1139. http://doi.org/10.5551/jat.ED197

IGF-1 and Cardiovascular and Non-Cardiovascular Mortality Risk in Patients with Chronic Kidney Disease: A Model of "Malnutrition-Inflammation-Atherosclerosis Syndrome"

Michio Shimabukuro

Department of Diabetes, Endocrinology and Metabolism, Fukushima Medical University, Fukushima, Japan

See article vol. 29: 1153-1165

Cardiovascular (CV) and Non-CV Mortality Risk in Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD)

CKD is an independent risk factor for CV diseases (CVDs)[1, 2]. Events in patients with CKD included are atherosclerotic CVD such as acute myocardial infarction or stroke, but also non-atherosclerotic events such as sudden cardiac death or fatal arrhythmia. Notably, patients with CKD have a higher risk not only for the incidence of CVD but also for death after CVD events[1, 2]. All-cause mortality and CVD mortality rates increase with progression of the stage of CKD and most dramatically when patients reach ESRD[1, 2].

Increased mortality in CKD/ESRD is considered to occur from traditional and emerging risk factors in this population[2]. Traditional CVD risk factors in CKD/ESRD include older age, male sex, hypertension, high low-density lipoprotein-cholesterol and low high-density lipoprotein-cholesterol, diabetes, smoking, physical inactivity, menopause, family history of CVD, and left ventricular hypertrophy. Emerging risk factors include albuminuria, anemia, abnormal calcium/phosphate metabolism, extracellular fluid volume overload, electrolyte imbalance, oxidative stress, inflammation (C-reactive protein), malnutrition, thrombogenic factors, and sleep disturbances[1, 2].

IGF-1 and CV and Non-CV Mortality Risk

In the current study, Nakaya *et al.*[3] showed that a lower insulin-like growth factor 1 (IGF-1) level is an independent predictor of all-cause mortality, and that it also predicts poor survival after new CVD events and infection in a Japanese cohort of hemodialysis patients. Divided into two steps, they suggested that a lower IGF-1 level can be linked not preferentially to the first step (occurrence of a CVD event), but to the second step (death after the CVD event). In addition, they suggested that a lower serum IGF-1 level serves as a biomarker of frailty in hemodialysis patients.

Sarcopenia is a progressive and generalized skeletal muscle disorder involving the enhanced loss of muscle mass and function, often associated with muscle weakness (dynapenia) and frailty. While primary sarcopenia develops with age, secondary sarcopenia develops independently of age in the milieu of chronic disease such as CKD/ESRD[4]. Sarcopenia, as well as its components, has been frequently shown to be associated with adverse outcomes, including multiple morbidity and all-cause mortality.

The development of sarcopenia in patients with CKD/ESRD[4] is common, and it may occur independently of weight loss, cachexia, or obese sarcopenia via multifactorial mechanisms. Hormonal imbalance is a cause of development of sarcopenia in CKD/ESRD and may be another emerging risk for all-cause and CVD mortality[4]. Hormones that may influence the development of sarcopenia include testosterone, growth hormone and IGF-1, insulin, thyroid hormones, vitamin D, ghrelin, estrogen, cortisol, and dehydroepiandrosterone[4, 5]. As mentioned above, the possible underlying mechanisms for the link between IGF-1 level and mortality in CKD/ESRD may be elucidated **(Fig. 1)**. Previous reports suggested that "malnutrition-inflammation-atherosclerosis syndrome"[6], "malnutrition-inflammation complex syndrome"[7], and protein-energy wasting[8] are the factors closely related to the

Address for correspondence: Michio Shimabukuro, Department of Diabetes, Endocrinology and Metabolism, Fukushima Medical University, 1 Hikarigaoka, Fukushima City, Fukushima 960-1295, Japan E-mail: mshimabukuro-ur@umin.ac.jp

Received: February 4, 2022 Accepted for publication: February 7, 2022

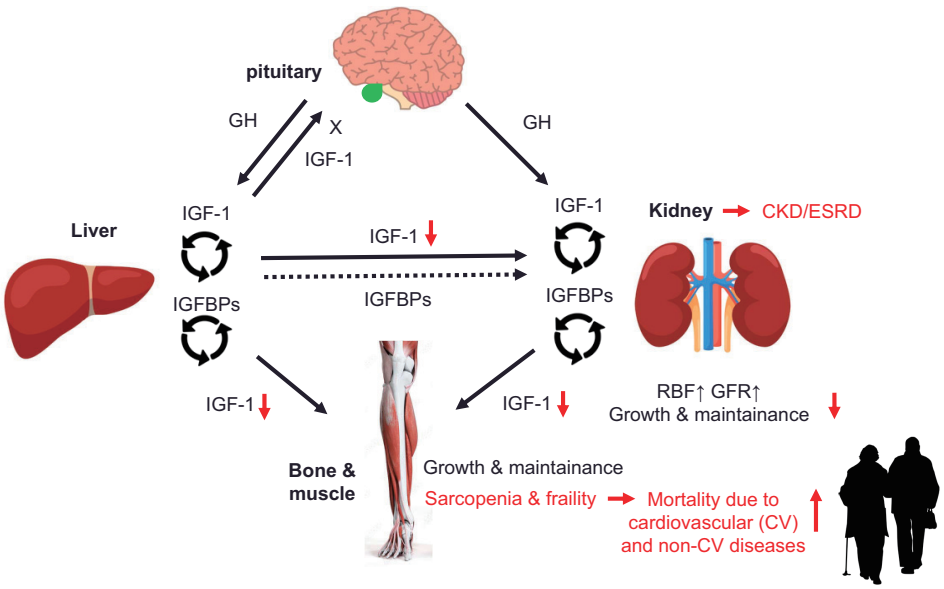

Fig. 1. Possible underlying mechanisms for the link between IGF-1 level and mortality in CKD/ESRD

The anterior pituitary gland secretes growth hormone (GH) that acts on the liver to synthesize insulin-like growth factor 1 (IGF-1) from where it has endocrine actions on the kidney and muscle/bone to mediate growth and maintainance[5]. Circulating IGF-1 suppresses GH secretion in a negative feedback loop. GH also acts on the kidney both directly and by increasing local IGF-1 production, which acts through autocrine or paracrine mechanisms. Circulating and locally synthesized IGF-binding proteins modulate IGF-1 actions, usually in an inhibitory manner, and may also have IGF-independent actions within the kidney. GH and IGF-1 result in kidney growth, increased renal blood flow, and increased glomerular filtration rate. When IGF-1 is depleted in the plasma of patients with CKD/ESRD via multifactorial mechanisms[4] (indicated by red arrows and characters), impairment of growth and maintenance of the muscle and bone trigger sarcopenia and frailty, finally causing an increased mortality due to CVD and non-CVD. These mechanisms may be called as "malnutrition-inflammation-atherosclerosis syndrome"[6], "malnutrition-inflammation complex syndrome"[7], or protein-energy wasting[8].

second step to CV death.

The paper prompted us to consider that IGF-1 and other related molecules can be a biomarker of frailty for all-cause and CVD mortality in patients with CKD/ESRD and also with other chronic diseases.

Conflict of Interest

None.

References

1) Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ and Wilson PW: Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation, 2003; 108: 2154-2169
2) Lai AC, Bienstock SW, Sharma R, Skorecki K, Beerkens F, Samtani R, Coyle A, Kim T, Baber U, Camaj A, Power D, Fuster V and Goldman ME: A personalized approach to chronic kidney disease and cardiovascular disease: JACC Review Topic of the Week. J Am Coll Cardiol, 2021; 77: 1470-1479
3) Nakaya R, Shoji T, Nagata Y, Nakatani S, Mori K, Morioka T, Tsujimoto Y, Emoto M: Associations of serum insulin-like growth factor-1 with new cardiovascular events and subsequent death in hemodialysis patients: The DREAM cohort. J Atheroscler Thromb, 2022; 29: 1153-1165
4) Gungor O, Ulu S, Hasbal NB, Anker SD and Kalantar-Zadeh K: Effects of hormonal changes on sarcopenia in chronic kidney disease: where are we now and what can we do? J Cachexia Sarcopenia Muscle, 2021; 12: 1380-1392
5) Bach LA and Hale LJ: Insulin-like growth factors and kidney disease. Am J Kidney Dis, 2015; 65: 327-336
6) Stenvinkel P, Heimbürger O, Lindholm B, Kaysen GA and Bergström J: Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant, 2000; 15: 953-960
7) Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM and Kopple JD: Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis, 2003; 42: 864-881
8) Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Treviño-Becerra A and Wanner C: A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int, 2008; 73: 391-398