

Newly discovered myokines in chronic kidney disease

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Chronic kidney disease (CKD) is a heterogeneous group of disorders affecting both the structure and function of the kidney.¹ Its long-term consequences including uremic complications, cardiovascular diseases, infections, cognitive impairment, impaired physical function, and, finally, end-stage renal disease (ESRD) are major contributors of the increased mortality seen in patients with CKD.^{1,2}

Interestingly, sarcopenia, or reduced muscle mass, is common in patients with CKD³ and is clearly associated with mortality in different cohorts (eg, the Framingham Heart Study).⁴ In the last few years, the role of several cytokines potentially influencing body composition has been established, including adipokines (eg, adipocyte fatty acid-binding protein)⁵ and myokines (eg, irisin).⁶

The current issue of the *Polish Archive of Internal Medicine (Pol Arch Med Wewn)* features a paper by Kałużna et al⁷ who determined circulating levels of the myocyte-secreted cytokines adropin and irisin in patients with ESRD on chronic renal replacement therapy including hemodialysis and peritoneal dialysis. In their single-center study, they evaluated 48 patients with ESRD, aged 26 to 84 years, as compared with 36 healthy and age- and sex-matched controls. Both myokines were further studied in relation to nutrition, body composition, and insulin resistance. The authors demonstrated that, in this setting, adropin could serve as a new marker of nutritional status in patients with ESRD. Irisin levels were significantly lower in patients with ESRD as compared with controls. Furthermore, irisin levels were adversely correlated with markers of glucose tolerance in patients with ESRD, whereas irisin was associated with a beneficial profile of markers of insulin resistance in healthy controls.

Data on myocyte-secreted proteins, especially in ESRD, are of clinical importance since sarcopenia is a major predictor of mortality.⁴ A few

additional issues that may potentially affect the results by Kałużna et al⁷ should be mentioned. The (myo-)cytokine adropin has recently been described as a nutrition-dependent and secreted factor that significantly influences adiposity.⁸ Human data on the association of adropin with renal function, as well as with markers of body composition, are lacking. Therefore, the present study adds valuable information on adropin regulation. Adropin is not differentially regulated in patients with ESRD as compared with control patients; however, the already known negative associations with markers of body composition seem to be transferable to human ESRD. These findings greatly support the data of Ganesh-Kumar et al⁹ in adropin knockout mice. They showed that adropin knockout mice exhibit increased adiposity at 9 weeks of age as assessed by body weight and body fat percentage.⁸ Further studies in larger cohorts, including the analysis of body composition, are therefore needed to evaluate adropin as a potential marker of sarcopenia in patients with ESRD. In contrast to the mouse data,⁸ Kałużna et al⁷ did not find an association of adropin with markers of insulin resistance and dyslipidemia in ESRD. Thus, the impact of adropin on the development of insulin resistance is still to be confirmed.⁹

The myokine irisin was recently introduced as a secreted and circulating protein that reverses visceral obesity and improves glucose tolerance in rodents.⁶ Irisin levels are reduced in patients with ESRD as compared with controls. This is in accordance with several other reports investigating irisin, as well as serum¹⁰ and urinary¹¹ markers of renal function. Interestingly, Kałużna et al⁷ could not detect an association between irisin levels and nutritional status as assessed by a bioelectrical impedance analysis. This is in contrast to other reports, for example, to that by Lee et al.¹² Different patient characteristics might explain the differences between the study cohorts. Here, Kałużna et al⁷ used specific exclusion criteria and,

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in contrast to other studies,¹² might have recruited patients with ESRD only due to hypertension.

The authors of the present study elegantly described the associations of adropin and irisin levels with anthropometric markers, as well as markers of body composition, glucose tolerance, and dyslipidemia. Interestingly, irisin was differently associated with markers of glucose tolerance in patients with ESRD as compared with controls. Here, further studies are needed to investigate whether the already known associations of irisin with glucose metabolism during an oral glucose tolerance test¹³ are also valid in ESRD.

One further open question is whether the two myokines are differentially regulated in patients on hemodialysis as compared with those on peritoneal dialysis. There is some evidence that hemodialysis is reducing serum irisin levels¹⁰ but no study has compared the levels of both myokines in hemodialysis and peritoneal dialysis.

One of the major issues in studies on newly-discovered proteins is the performance of the respective enzyme-linked immunosorbent assay (ELISA) kits used for measuring the candidate. This is especially important for irisin. Here, the irisin kit used in the study revealed relatively higher absolute values when compared with other kits.¹⁴ This needs to be considered when interpreting data from clinical studies, and it may partially explain the controversial observations on the relation of circulating irisin levels. Clearly, further validation of the available ELISA kits is needed. Nevertheless, other explanations for the variability include different sample additives, storing conditions and times, and other preanalytical conditions.¹⁵

The strengths of the present study clearly include the availability of bioelectrical impedance analysis, as well as different dialysis procedures, in patients with ESRD. If validated in larger and more heterogeneous trials, these findings could lead to improved diagnosis of sarcopenia in ESRD.

However, some limitations of the study by Kałużna et al,⁷ which reduce comparability with different trials, have to be taken into consideration. First, the number of enrolled subjects was rather low. Second, the regulation of both cytokines was only demonstrated in patients with ESRD as compared with healthy controls and not in a cohort comprehensively covering the whole spectrum of renal dysfunction ranging from stages G1 to G5. Third, specific exclusion criteria limit the findings to nondiabetic subjects with ESRD and with no history of an active malignant neoplasm, autoimmune disease, active inflammatory disease, and advanced hepatic disease. Therefore, the significance of the current work would be strongly improved if a future trial with a higher number of subjects with different stages of disease and with different underlying pathologies would obtain similar results.

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REFERENCES

- 1 Levey AS, Coresh J. Chronic kidney disease. *Lancet*. 2012; 379: 165-180.
- 2 Coresh J, Turin T, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA*. 2014; 311: 2518-2531.
- 3 Foley RN, Wang C, Ishani A, et al. Kidney function and sarcopenia in the united states general population: NHANES III. *Am J Nephrol*. 2007; 27: 279-286.
- 4 Roubenoff R, Parise H, Payette HA, et al. Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: the Framingham Heart Study. *Am J Med*. 2003; 115: 429-435.
- 5 Tönjes A, Kralisch S, Lössner U, et al. Metabolic and genetic predictors of circulating adipocyte fatty acid-binding protein. *Int J Obes*. 2012; 36: 766-773.
- 6 Boström P, Wu J, Jedrychowski MP, et al. A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012; 481: 463-468.
- 7 Kałużna M, Hoppe K, Schwermer K, et al. Adropin and irisin levels in relation to nutrition, body composition, and insulin resistance in patients with end-stage renal disease on chronic hemodialysis and peritoneal dialysis. *Pol Arch Med Wewn*. 2016; 126: 474-482.
- 8 Ganesh-Kumar K, Zhang J, Gao S, et al. Adropin deficiency is associated with increased adiposity and insulin resistance. *Obesity*. 2012; 20: 1394-1402.
- 9 Li L, Xie W, Zheng X-L, et al. A novel peptide adropin in cardiovascular diseases. *Clin Chim Acta*. 2016; 453: 107-113.
- 10 Ebert T, Focke D, Petroff D, et al. Serum levels of the myokine irisin in relation to metabolic and renal function. *Eur J Endocrinol*. 2014; 170: 501-506.
- 11 Wang H, Zhang X, Chen W, et al. Relationship between serum irisin levels and urinary albumin excretion in patients with type 2 diabetes. *J Diabetes Complications*. 2015; 29: 384-389.
- 12 Lee MJ, Lee SA, Nam BY, et al. Irisin, a novel myokine is an independent predictor for sarcopenia and carotid atherosclerosis in dialysis patients. *Atherosclerosis*. 2015; 242: 476-482.
- 13 Ebert T, Kralisch S, Wurst U, et al. Association of metabolic parameters and rs726344 in FNDC5 with serum irisin concentrations. *Int J Obes*. 2016; 40: 260-265.
- 14 Hee Park K, Zaichenko L, Brinkoetter M, et al. Circulating irisin in relation to insulin resistance and the metabolic syndrome. *J Clin Endocrinol Metab*. 2013; 98: 4899-4907.
- 15 Nüsken K-D, Nüsken E, Petrasch M, et al. Preanalytical influences on the measurement of visfatin by enzyme immuno assay. *Clin Chim Acta*. 2007; 382: 154-156.