Editorial

Does twenty-four-hour biological variation of serum creatinine and cystatin C influence GFR estimation?

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In the evolution process, moving from the marine environment challenged organisms to adapt to terrestrial conditions. This increased the requirement of the kidney regarding urine concentration abilities and tubular reabsorption of solutes, while coping with day/night cycles (1). In this sense, glomerular filtration rate (GFR) and tubular function were proved to be strongly related to a circadian rhythm (2). This rhythm corresponds to a periodicity of 24 h, offering the organism the benefit to anticipate environmental modifications. The seminal study of Wesson in healthy subjects demonstrated that inulin clearance was 23% higher during the day as compared to the night (3), and this finding was later confirmed by Koopman *et al.*, that showed a 33% decrease in GFR at evening (4). Likewise, other authors endorse a circadian rhythm for inulin clearance, with a maximum during daytime, but simultaneously show that creatinine clearance rhythm was either absent or reduced. This later finding was associated to a higher rate of tubular creatinine secretion at night, while plasma creatinine concentration was constant during a 24-hour period (5). Further confirmation of GFR rhythmicity was obtained in patients with diabetes kidney disease, but with a substantially lower diurnal rise in GFR, of around 10% (6), perhaps reflecting impaired renal autoregulation in diabetes. Therefore, a well-established decrease in GFR has been overall documented during the night, possibly less pronouncedly in patients with kidney disease. Could creatinine and cystatin C based equations—considering their biological variation (BV)—accurately reflect real GFR and related specificities?

In May issue of Clinical Chemistry (7), Hilderink *et al.* have described the 24-h variability profile—hourly sampled—of plasma creatinine and cystatin C in 17 individuals without chronic kidney disease (CKD) and in 20 individuals with CKD. It was demonstrated that the within subject within-day biological variation (CV_I) of creatinine was higher in individuals without CKD, as compared to those with kidney disease (6.4% *vs.* 2.5%); in contrast, the CV_I of cystatin C was similar for those without *vs.* with CKD (4.1% *vs.* 3.2%). These findings have been attributed to a significant rise in creatinine levels provoked by meat ingestion, not observed for cystatin C. On the other hand, another phenomenon, the diurnal rhythmic variation was described only for cystatin C levels, with increasing concentrations during the evening and night, more evident in the group without kidney disease. The authors conclude that, regardless the differences in CV_I of creatinine between subjects with and without kidney disease, reference change values (RCV) of the CKD-EPI equations estimated GFR were similar between the groups. Perhaps these were not good news, and GFR should ideally have recognized the existing variation.

Regarding the putative circadian variability of both cystatin C and creatinine, a Swedish study in healthy individuals confirm higher cystatin C levels between 3 and 7 AM and lower levels between 9 AM and 14 PM, conjecturing an interaction with circadian rhythm of cortisol (8). However, it is tempting to speculate that only cystatin C was able to disclose the chronobiological fall of GFR at night, corroborating Hilderink findings. As for creatinine

levels, existing evidence seem to indicate that creatinine concentration is rather constant during a 24-hour period, except for the possible influence of food ingestion (5,8).

Hilderink demonstrated an increment in post dinner serum creatinine of up to 50% in patients without CKD. In patients with CKD, the increment was about 18%. In this study, the dishes individuals chose among the dinner options were not standardized, what made difficult to associate food sources or nutrients to the observed serum creatinine increase. The authors presumed that the creatinine increase might be associated to meat consumption, because most contained meat. Nonetheless, neither the preparation nor the quantities of meat during the dinner were specified. In some previous studies, the acute effect of meat meals intake on circulating creatinine has been specifically evaluated (9-13), both in healthy volunteers and in individuals with CKD. Increments of serum creatinine of up to 100% have been observed. The effect of meat intake on circulating creatinine increases depends on how meat was prepared, varying from no positive effect from raw meat to strong impact from boiled meat (9). This result could be associated to the increased conversion of creatine to creatinine in the meat with longer periods of boiling. Hilderink demonstrated that despite the effect of meat intake on serum creatinine, the resultant impact on estimated GFR was not relevant (7). In contrast, many previous pivotal studies have demonstrated a positive association between high dietary protein intake, especially from meat, and measured GFR (14). Furthermore, in short-term studies, the restriction of red meat intake has been associated with decreases in GFR in diabetic patients with or without glomerular hyperfiltration (15,16). In conclusion, this interference of meat intake on serum creatinine levels might misclassify the patients' renal function status, interfering with some clinical decisions. Therefore, considering these aspects, in clinical practice, it is better to avoid measuring serum creatinine after meat intake, or, if necessary in some situations, to confirm the obtained results. Moreover, eGFR once more was probably not able to reflect measured GFR.

One unanswered question of Hilderink's study is the possible age dependence of within-subject biological variation (BV) of creatinine, since mean ages of groups were around 70 years. Carobene *et al.* have updated data of BV of common clinical chemistry analytes, including creatinine, and showed that subjects with 78–96 years had significantly lower between days CV_I, around half the values of the 27–57 years individuals (17). Even though Hilderink evaluated within-day and not between-day CV_I values, some influence of aging might be anticipated. In the same line, the number of men was overrepresented in Hilderink sample, and since they have significantly higher creatinine levels than women despite gender-equivalent GFRs, the overall variability could have been underestimated (18,19). However, is has been recently demonstrated that there was no significant male/female BV differences in this regard (20). An elegant review of Delanaye *et al.*, suggestively entitled: "Serum creatinine: not so simple!" define several pitfalls and interferences with creatinine measurement, including biological variation analyses, and deserves a careful reading (21).

It is also noteworthy that about one third of patients in Hilderink's paper presented diabetes mellitus, and despite being equally distributed in the groups with *vs.* without CKD, it could have affected final results. It should be taken into account that creatinine levels could have been unpredictably influenced by the glycemic status in these patients (data not available in the paper), either by the induction of glomerular hyperfiltration by eventual hyperglycemia and/or by interference of glucose on creatinine measurement, fortunately less prominent with the use of enzymatic creatinine method, as was the case in the paper (22,23). Likewise, information about medications, either used by diabetic or non-diabetic patients would be of interest, especially for drugs with renal hemodynamic effects, such as angiotensin converting enzyme (ACE) inhibitors or sodium-glucose co-transporter-2 (SGLT2) inhibitors, that might affect GFR levels (24).

The importance of wisely using the concepts of BV has been recently highlighted by the European Biological Variation Study (EuBIVAS), designated to obtain and update BV parameters for several measurands, including creatinine, especially taking into account the present improvement of analytical procedures. Briefly, EuBIVAS involved 6 European laboratories that enrolled 91 healthy volunteers (38 males and 53 females; age range, 21–69 years). Specifically for creatinine, the between-day within-subject BV estimates [CV_I (95% CI)] were similar for enzymatic [4.4% (4.2–4.7)] and alkaline picrate [4.7% (4.4–4.9)] methods and lower than the value available online (CV_I 5.9%) (20). The analytical imprecision (CV_A) was 1.1% for enzymatic and 4.4% for alkaline picrate methods, indicating that the last method does not fulfill the analytical performance required. Hilderink's paper employed an enzymatic method to measure creatinine and described a higher CV_I of 6.4%, but as stated by the authors, a direct comparison is not suitable, since they evaluated within-day CV_I, which englobes greater variability due to

different periods of collection.

In conclusion, this paper followed the Biological Variation Data Critical Appraisal Checklist (BIVAC), ensuring the accuracy of BV estimates (25), and adds new original information to the research scenario.

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Footnote

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References

1. Wuerzner G, Firsov D, Bonny O. Circadian glomerular function: from physiology to molecular and therapeutical aspects. Nephrol Dial Transplant 2014;29:1475-8.
2. Firsov D, Bonny O. Circadian regulation of renal function. Kidney Int 2010;78:640-5.
3. Wesson LG Jr. Electrolyte excretion in relation to diurnal cycles of renal function. Medicine (Baltimore) 1964;43:547-92.
4. Koopman MG, Koomen GC, Krediet RT, et al. Circadian rhythm of glomerular filtration rate in normal individuals. Clin Sci (Lond) 1989;77:105-11.
5. Van Acker BA, Koomen GC, Koopman MG, et al. Discrepancy between circadian rhythms of inulin and creatinine macromolecules. J Lab Clin Med 1992;120:400-10.
6. Hansen HP, Hovind P, Jensen BR, et al. Diurnal variations of glomerular filtration rate and albuminuria in diabetic nephropathy. Kidney Int 2002;61:163-8.
7. Hilderink JM, van der Linden N, Kimenai DM, et al. Biological variation of creatinine, Cystatin C, and eGFR over 24 Hours. Clin Chem 2018;64:851-60.
8. Larsson A, Akerstedt T, Hansson LO, et al. Circadian variability of cystatin C, creatinine, and glomerular filtration rate (GFR) in healthy men during normal sleep and after an acute shift of sleep. Chronobiol Int 2008;25:1047-61.
9. Mayersohn M, Conrad KA, Achari R. The influence of a cooked meat meal on creatinine plasma concentration and creatinine clearance. Br J Clin Pharmacol 1983;15:227-30.
10. Jacobsen FK, Christensen CK, Mogensen CE. Pronounced increase in serum creatinine concentration after eating cooked meat. Brit Med J 1979;1:1049-50.
11. Preiss DJ, Godber IM, Lamb EJ, et al. The influence of a cooked-meat meal on estimated glomerular filtration rate. Ann Clin Biochem 2007;44:35-42.
12. Nair S, O'Brien SV, Hayden K, et al. Effect of a cooked meat meal on serum creatinine and estimated glomerular filtration rate in diabetes- related kidney disease. Diabetes Care 2014;37:483-7.
13. Toffaletti JG, Hammett-Stabler C, Handel EA. Effect of beef ingestion by humans on plasma concentrations of creatinine, urea, and Cystatin C. Clin Biochem 2018;58:26-31.
14. King AJ, Levey AS. Dietary protein and renal function. J Am Soc Nephrol 1993;3:1723-37.
15. Pecis M, Azevedo MJ, Gross JL. Chicken and fish diet reduces glomerular hyperfiltration in IDDM patients. Diabetes Care 1994;17:665-72.
16. Gross JL, Zelmanovitz T, Moulin CC, et al. Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: a randomized crossover trial. Diabetes Care 2002;25:645-51.
17. Carobene A, Graziani MS, Lo Cascio C, et al. Age dependence of within-subject biological variation of nine common clinical chemistry analytes. Clin Chem Lab Med 2012;50:841-4.
18. Weinert LS, Prates AB, do Amaral FB, et al. Gender

does not influence cystatin C concentrations in healthy volunteers. Clin Chem Lab Med 2010;48:405-8.
19. Soares AA, Prates AB, Weinert LS, et al. Reference values for glomerular filtration rate in healthy Brazilian adults. BMC Nephrol 2013;14:54.
20. Carobene A, Marino I, Coşkun A, et al. European Biological Variation Study of the EFLM Working Group on Biological Variation. The EuBIVAS Project: within- and between-subject biological variation data for serum creatinine using enzymatic and alkaline picrate methods and implications for monitoring. Clin Chem 2017;63:1527-36.
21. Delanaye P, Cavalier E, Pottel H. Serum Creatinine: Not So Simple! Nephron 2017;136:302-8.
22. Cheuiche AV, Soares AA, Camargo EG, et al. Comparison between IDMS-traceable Jaffe and enzymatic creatinine assays for estimation of glomerular filtration rate by the CKD-EPI equation in healthy and diabetic subjects. Clin Biochem 2013;46:1423-9.
23. Silveiro SP, Araújo GN, Ferreira MN, et al. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation pronouncedly underestimates glomerular filtration rate in type 2 diabetes. Diabetes Care 2011;34:2353-5.
24. Nespoux J, Vallon V. SGLT2 inhibition and kidney protection. Clin Sci (Lond) 2018;132:1329-39.
25. Aarsand AK, Røraas T, Fernandez-Calle P, et al. The Biological Variation Data Critical Appraisal Checklist: A standard for evaluating studies on biological variation. European Federation of Clinical Chemistry and Laboratory Medicine Working Group on Biological Variation and Task and Finish Group for the Biological Variation Database. Clin Chem 2018;64:501-14.

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