Effect of a Cooked Meat Meal on Serum Creatinine and Estimated Glomerular Filtration Rate in Diabetes-Related Kidney Disease

Sunil Nair,[1,5] Sarah V. O'Brien,[5] Katharine Hayden,[2] Bhavna Pandya,[4] Paulo J.G. Lisboa,[3] Kevin J. Hardy,[5] and John P.H. Wilding[1]

OBJECTIVE

Fasting is not routinely recommended for renal function tests, despite the known effects of cooked meat on creatinine. We therefore studied variation in creatinine and estimated glomerular filtration rate (eGFR) after a standardized cooked meat meal in 80 subjects: healthy volunteers and diabetic patients with chronic kidney disease (CKD) stages 1 and 2, 3a, 3b, and 4 (*n* = 16/group).

RESEARCH DESIGN AND METHODS

The interventions were a standardized cooked meat and a nonmeat meal, each providing ~54 g protein, together with 250 mL water, on separate days. Fasting and postprandial blood samples at 1, 2, and 4 h were drawn for creatinine measurement using a kinetic alkaline picrate assay on an Olympus AU640 analyzer. The modified four-variable Modification of Diet in Renal Disease equation traceable to isotope dilution mass spectrometry creatinine was used to calculate eGFR.

RESULTS

Consumption of a standardized cooked meat meal significantly increased serum creatinine and resulted in significant fall in eGFR in all stages of CKD studied; 6 of 16 CKD 3a patients were misclassified as CKD 3b. This effect of cooked meat on serum creatinine disappears after 12 h of fasting in all study participants.

CONCLUSIONS

Creatine in meat is converted to creatinine on cooking, which is absorbed, causing significant increases in serum creatinine. This could impact management, as threshold for commencing and withdrawing certain medications and expensive investigations is defined by eGFR. eGFR calculated using fasting serum creatinine would be a better reflection of kidney function in these patients.

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Diabetic nephropathy is a leading cause of end-stage renal disease (ESRD) in the world. Accurate screening and staging of chronic kidney disease (CKD) is essential for timely intervention as recommended by national and international guidelines (1,2) and to guide dose adjustment of other medicines. Glomerular filtration rate (GFR) is recognized as the best measure of kidney function in health and disease, but measuring it by gold standard techniques such as inulin clearance and radioisotopic

[1]Obesity and Endocrinology Research Unit, Clinical Sciences Centre, University Hospital Aintree, University of Liverpool, Liverpool, U.K.
[2]Department of Biochemistry, Aintree University Hospitals National Health Service Foundation Trust, Liverpool, U.K.
[3]Department of Mathematics and Statistics, John Moores University, Liverpool, U.K.
[4]Department of Nephrology, Aintree University Hospitals National Health Service Foundation Trust, Liverpool, U.K.
[5]Diabetes and Endocrinology Department, St Helens and Knowsley Teaching Hospitals National Health Service Trust, Prescot, U.K.

Corresponding author: Sunil Nair, sunil.nair1@liv.ac.uk.

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methods is clinically impractical. Therefore, estimation of GFR using serum creatinine and other variables like age, sex, race, and body size is recommended (3,4).

Variations in serum creatinine could lead to misclassification of CKD stage with clinical implications for the patient and cost implications for services. Some of the factors responsible for variability in creatinine are ingestion of cooked meat, fluid status, diurnal variation, and delay in centrifugation of blood samples (5). Most blood samples in the original Modification of Diet in Renal Disease (MDRD) study were drawn after an overnight fast (6). This is, however, overlooked in most clinical situations, and estimated GFR (eGFR) is calculated by laboratories from all blood samples sent for renal function tests. The intraindividual biological variation in creatinine measurement is significantly higher in people with CKD (coefficient of variation 5.3%) than in healthy people (coefficient of variation 2.7%) (7,8).

There have been several studies examining dietary protein and renal function (9). GFR, renal plasma flow, and creatinine clearance have been shown to increase protein consumption and amino acid infusion, particularly in preclinical studies (8,10). Habitual increase in protein intake leads to increased total muscle mass and the total body pool of creatinine, but acute ingestion of cooked meat causes a transient increase in serum and urinary creatinine. Cooking meat converts creatine in skeletal muscle to creatinine. Studies looking at the effect of cooking on acid-extractable chemical constituents of beef have shown significant increase in creatinine levels (11,12). Ingestion of meals containing cooked meat caused a marked postprandial increase in serum creatinine concentration, whereas ingestion of raw meat had no effect on serum creatinine in normal human subjects (13). A large cooked meat meal (225 g) was shown to cause an average increase of 52% in creatinine compared with the mean value on a control meal in six healthy individuals (14). The maximum concentration of serum creatinine was achieved 2 h after the cooked meat meal. A study looking at the effect of protein load in renal transplant patients and healthy control subjects showed a 30% increase in serum creatinine, with the rise in absolute terms being higher in the transplant group (15). Hence, the effect of cooked meat on serum creatinine might be higher in more advanced CKD stages.

A more recent study on 17 healthy volunteers and 15 patients from a care-of-the-elderly day unit showed a significant median serum creatinine rise from 80.5 to 101.0 μmol/L (0.91 to 1.14 mg/dL) and median eGFR fall from 84 to 59.5 mL/min/1.73 m^2 at 1–2 h after intake of a normal helping of cooked meat (6). The study also showed that the rise in creatinine measured by three different methods was similar after a cooked meat meal. The difference between 2 and 4 h postprandial values of creatinine was small, raising questions regarding persistence of the effects of a cooked meal beyond 4 h. This is clinically relevant, as patients attending a morning clinic may well have consumed a large cooked meat meal the previous evening.

Evidence for the effect of cooked meat on creatinine in a well-defined patient population with different stages of diabetes-related CKD is lacking in the literature. The effect of a cooked meat meal on creatinine levels >4 h postprandially is also uncertain.

The aim of the current study was to estimate the variation in creatinine caused by a standardized cooked meat meal in participants with various stages of diabetic CKD. We hypothesized that a standardized cooked meat meal will cause a significant rise in serum creatinine and that overnight fasting will eliminate this effect.

RESEARCH DESIGN AND METHODS

This was a prospective experimental study that involved participants with different stages of diabetic CKD and healthy volunteers. The patients with CKD were recruited into four subgroups: CKD stages 1 and 2, 3a, 3b, and 4. We recruited 16 participants in each of the five groups (total *n* = 80). The study was reviewed and approved by the Liverpool Research Ethics Committee, and all study participants gave written informed consent.

Study Subjects and Sampling

Study participants were recruited from diabetes clinics, and healthy volunteers were drawn from staff and the general public, recruited via advertisements. As our sampling strategy, we used quota sampling, selecting consecutively to achieve equal numbers within the study groups and to allow progression analyses through the stages. Inclusion criteria were type 1 or 2 diabetes, CKD stages 1–4, and age >18 years. Patients known to have nondiabetic renal disease, anyone who could not eat meat, and patients on renal replacement therapy were excluded from this study. The median age of the participants was 67 years (interquartile range [IQR] 52.5 – 73), all were Caucasians, and 66 were male. All patients with eGFR <60 mL/min/1.73 m^2 included in the study groups had increased albumin excretion as evidenced by urine albumin-to-creatinine ratio >2.5 in males and >3.5 in females on at least two occasions. 86% of the study group participants had type 2 diabetes.

Intervention

The intervention constituted of a standardized meal containing cooked meat in a quantity considered to be a normal helping. We provided patients with meat and nonmeat meals, with each providing ~44 g protein, which comprises no more than 65% of each patient's daily protein allowance [1.0 g protein/kg ideal body weight/day]. The meat meal consisted of two Aberdeen Angus quarter-pounder beef burgers, and the nonmeat meal comprised of two vegetarian burgers. The Aberdeen Angus beef burgers, which contain 23 g protein, were grilled from a frozen state at moderate heat for 25 min. The meat-free burgers, containing 22 g protein, were grilled at moderate heat for 15 min as per the cooking instructions. These were served along with two buns and a vegetable salad, followed by 250 mL water.

On the first study visit, participants attended after an overnight fast and a preprandial and three postprandial blood samples 1, 2, and 4 h after the meat meal were obtained. The evening before the second visit, the participants had the standard meat meal with 250 mL

Table 1—Median (IQR) of creatinine and eGFR before and after the standardized meat meal

	Healthy volunteers	CKD 1 and 2	CKD 3a	CKD 3b	CKD 4
n	16	16	16	16	16
Creatinine					
Fasting	74 (68.2–84.25)	98 (84–107)	128.5 (113–139)	152.5 (133–166)	238 (191–303)
1 h	75 (73.2–89.5)	102 (88–110.5)	135 (127–143)	158 (142–169)	246.5 (191–327)
2 h	79 (73.5–89.5)†	105.5 (93.5–109)*	146.5 (132–158)	162.5 (155–173)	256 (193–325)‡
4 h	75.5 (69.5–84.5)	104.5 (91–108.7)	150.5 (131–163)*	165 (147–169)§	255.5 (194–334)
eGFR					
Fasting	102.8 (85.3–130.4)	80.4 (68.6–97.2)	52 (47.1–63.6)	41.9 (38.2–48.5)	23.1 (17.8–29.4)
1 h	93.5 (76.9–132.9)¶	71.8 (65.2–85.4)	49.8 (45.4–53.8)	40.8 (36.9–45.7)	22.8 (15.8–29.8)
2 h	95 (76.1–107.9)	71.6 (67.5–83.3)†	45.2 (40.5–50.2)	38.8 (36.4–41.4)*	21.8 (15.6–30.8
4 h	97.3 (77.6–133.9)	72.5 (66.6–87.6)	42.8 (38.6–51.5)*	39 (35.5–43.8)	21.55 (14.5–27.5)‖

Creatinine is expressed as μmol/L (1 μmol/L = 0.0113 mg/dL) and eGFR as mL/min/1.73 m^2. *P = 0.001, †P = 0.002, ‡P = 0.007, §P = 0.009, ‖P = 0.038, and ¶P = 0.125. All P values compare fasting vs. peak creatinine and nadir eGFR, respectively.

water and attended after an overnight (12 h) fast. This was to estimate the effect of the standardized meat meal on serum creatinine after overnight fasting. A fasting and three postprandial blood samples 1, 2, and 4 h after the standard meat free meal were obtained.

Measured Variables

The principal variable in the study was serum creatinine, which was measured using the kinetic alkaline picrate assay on an Olympus AU640 analyzer. The modified MDRD equation traceable to isotope dilution mass spectrometry–creatinine and adjusted for Olympus methodology (mL/min/1.73 m^2) is as follows: eGFR = 175 × {[(creatinine − intercept)/slope] × 0.011312}$^{-1.154}$ × (age)$^{-0.203}$ × (1.212 if Afro-Caribbean race) × (0.742 if female) (16). For Olympus methodology, the intercept is 16.14 and the slope is 0.955.

Statistical Considerations

To detect a mean shift of 10 μmol/L (roughly equivalent to 1 SD) between postprandial minus preprandial values with a power of 90%, P = 0.05 in a paired t test required 13 participants in each group. However, for nonnormal distributions, use of Wilcoxon signed rank test required 15 participants for power of at least 90%. Statistical analysis was carried out using SPSS (version 17.0 for Windows; SPSS, Chicago, IL) and Graphpad Prism 5 for Windows. The shifts in creatinine and eGFR values in all groups were compared using Wilcoxon signed rank test, as most data were nonnormally distributed. Results are presented as median (IQR), and $P < 0.05$ was taken to indicate statistical significance.

RESULTS

We obtained results from 80 participants after the standard cooked

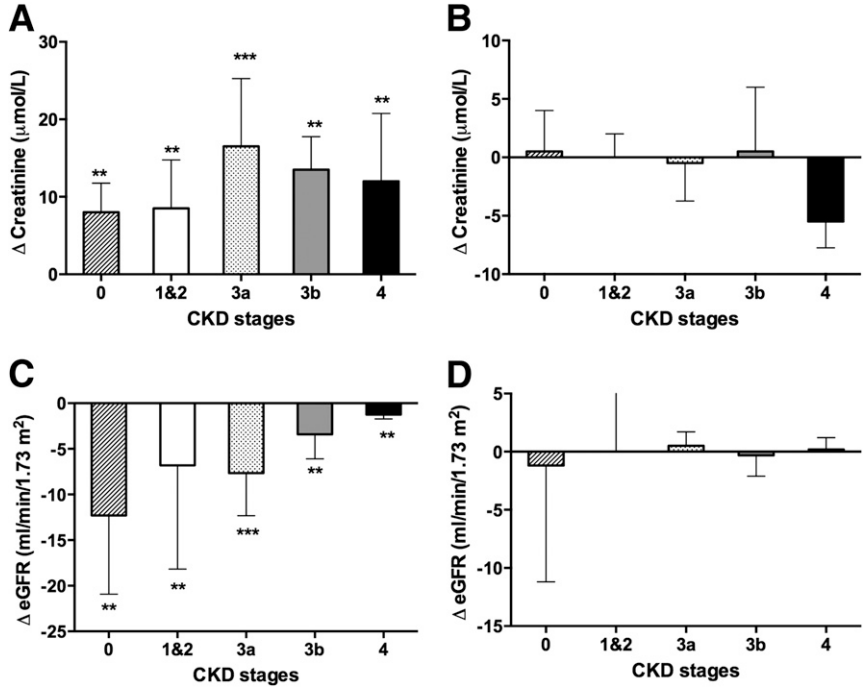

Figure 1—Median and IQRs of change in serum creatinine 2 h after a meat (*A*) and nonmeat (*B*) meal. Median and IQRs of change in eGFR after meat (*C*) and nonmeat (*D*) meals. **$P < 0.01$ and ***$P < 0.001$ compare baseline and 2-h values.

meat and nonmeat meals. The mean glycated hemoglobin among the 64 participants with diabetic CKD was 62.7 ± 16.1 mmol/mol (7.9 ± 1.6%).

Table 1 summarizes the fasting and postprandial creatinine and eGFR values in the participants in all five groups. Postprandial values are 1 h, 2 h, and 4 h after the meat and nonmeat meals.

Effect of Cooked Meat Meal on Serum Creatinine Over 4 h

Significant differences were found in serum creatinine and eGFR values after the standard meat meal in healthy volunteers and the participants with CKD, but there were no significant differences after a nonmeat meal. Figure 1 demonstrates the shift in serum creatinine and eGFR after the meat and nonmeat meals. In healthy volunteers and CKD stages 1 and 2, the maximum rise in creatinine was noted at 2 h, while in CKD 3a and 3b the maximum rise was seen at 4 h postprandially. In CKD 4, the 4-h creatinine was only 0.5 μmol/L (0.005 mg/dL) lower than the 2-h value (Table 1).

Effect of Cooked Meat Meal on Serum Creatinine After Overnight Fasting

The median difference between fasting creatinine 12 h after the meat and nonmeat meals was not statistically significant in any of the five groups studied, as illustrated in Fig. 2.

CONCLUSIONS

Our study demonstrates significant increases in serum creatinine levels after a cooked meat meal in healthy volunteers and participants with diabetic CKD stages 1–4. This is likely to be due to the effect of absorbed creatinine present in the cooked meat. This resulted in a fall in estimated GFR in all the groups studied. The relative fall in eGFR is proportionately less in patients with more advanced CKD stages, but the percentage fall remains significant in all groups. A proportion of patients with CKD could be misclassified to more severe stages depending on their baseline eGFR. Six of the 16 patients in CKD 3a were misclassified as CKD 3b as a result of cooked meat consumption. This could have had significant effects on the management of these patients, particularly as the threshold for commencing and withdrawing certain medications and the need for expensive investigations are defined by eGFR.

The peak creatinine and nadir eGFR were not consistently at 2 h postprandial in our study, as represented in the table. This could be related to the different rates of gastrointestinal absorption in different patients. So, from our data we are unable to conclude when the rise in serum creatinine reaches the maximum in different groups. We can only propose that there is no significant difference 12 h after meat meal consumption.

The effect of cooked meat on serum creatinine has been shown to be consistent irrespective of the methodology used for serum creatinine measurement in previously published studies (6,13–15).

We also demonstrate that after an overnight fast, the effect of cooked meat on serum creatinine does not remain statistically or clinically significant. We suggest that GFR be estimated using fasting rather than random serum samples.

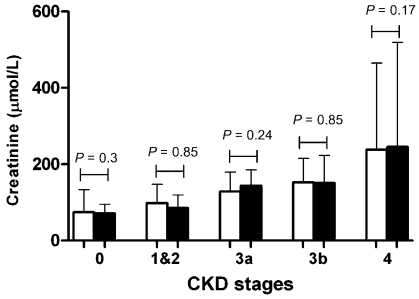

Figure 2—Median and IQRs of creatinine 12 h after meat (□) and nonmeat (■) meals in healthy volunteers and the four groups of participants with CKD. No significant differences were noted in any group, with all *P* values >0.05.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.N. conceived and designed the study, researched data, and wrote the manuscript. S.V.O. was involved in the study design and recruitment and reviewed and edited the manuscript. K.H. and B.P. were involved in the study design and reviewed and edited the manuscript. P.J.G.L. provided assistance with statistical analysis and reviewed and edited manuscript. K.J.H. and J.P.H.W. conceived and designed the study, contributed to discussion, and reviewed and edited the manuscript. S.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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