Effect of a cooked meat meal on serum creatinine and estimated glomerular filtration rate in diabetes related kidney disease

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Abstract

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 estimate glomerular filtration rate (eGFR) following a standardised cooked meat meal in 80 subjects: healthy volunteers, diabetes patients with chronic kidney disease (CKD) stages 1 & 2, 3A, 3B and 4 (n=16/group).

RESEARCH DESIGN AND METHODS  The interventions were a standardised cooked meat and a non-meat meal, each providing approximately 54g protein, together with 250 mls of water, on separate days. Fasting and post-prandial blood samples at 1, 2, and 4 hours were drawn for creatinine measurement using kinetic alkaline picrate assay on an Olympus AU640 analyser. The modified 4-variable MDRD equation traceable to isotope dilution mass spectrometry creatinine was used to calculate eGFR.

RESULTS  Consumption of a standardised 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 hours 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.
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 and to guide dose adjustment of other medicines. Glomerular filtration rate (GFR) is recognised as the best measure of kidney function in health and disease, but measuring it by gold standard techniques such as inulin clearance, and radioisotopic methods is clinically impractical. Therefore estimation of GFR using serum creatinine and other variables like age, gender race and body size is recommended.

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. Most blood samples in the original modification of diet in renal disease (MDRD) study were drawn following an overnight fast. This is however overlooked in most clinical situations and eGFR is calculated by laboratories from all blood samples sent for renal function tests. The intra individual biological variation in creatinine measurement is significantly higher in people with CKD (CV= 5.3%) than in healthy people (CV=2.7%).

There have been several studies examining dietary protein and renal function. Glomerular filtration rate, renal plasma flow and creatinine clearance have been shown to increase protein consumption and amino acid infusion, particularly in pre-clinical studies. 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. 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. A large cooked meat meal (225gm) was shown to cause an average increase of 52% in
creatinine compared to the mean value on a control meal in 6 healthy individuals. The maximum concentration of serum creatinine was achieved 2 hours after the cooked meat meal. A study looking at the effect of protein load in renal transplant patients and healthy controls showed 30% increase in serum creatinine, with the rise in absolute terms being higher in the transplant group. 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 micromoles/L (0.91 to 1.14 mg/dL) and median eGFR fall from 84 to 59.5 mls/min/1.73m² one to two hours following intake of a normal helping of cooked meat. 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 hr & 4 hr postprandial values of creatinine was small, raising questions regarding persistence of the effects of cooked meal beyond 4 hours. 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 mellitus related CKD is lacking in the literature. The effect of a cooked meat meal on creatinine levels more than 4 hours postprandially is also uncertain.

The aim of the present study was to estimate the variation in creatinine caused by a standardised cooked meat meal in participants with various stages of diabetic chronic kidney disease. We hypothesised that a standardised cooked meat meal will cause a significant rise in serum creatinine and 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 4 subgroups: CKD stages 1 & 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 employed quota sampling, selecting consecutively to achieve equal numbers within the study groups; to allow progressional analyses through the stages. Inclusion criteria were Type 1 or 2 Diabetes mellitus, CKD stages 1 to 4 and Age above 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 (IQR 52.5 – 73), all were Caucasians, and 66 of them were males. All patients with eGFR<60 included in the study groups had increased albumin excretion as evidenced by urine ACR>2.5 in males and >3.5 in females on at least 2 occasions. 86% of the study group participants had type 2 diabetes.

Intervention

The intervention constituted of a standardised meal containing cooked meat in a quantity considered to be a normal helping. We provided patients with meat and non-meat meals each providing approximately 44g protein, which comprises no more than 65% of each patient’s daily protein allowance (1.0g protein/kg IBW per day). The meat meal consisted of 2 Aberdeen Angus quarter pounder beef burgers, and the non-meat meal comprised of 2 vegetarian burgers. The
Aberdeen Angus beef burgers, which contain 23 grams of protein, were grilled from frozen at moderate heat for 25 minutes. The meat free burgers containing 22 grams of protein were grilled at moderate heat for 15 minutes as per cooking instruction. These were served along with 2 buns and vegetable salad, followed by 250 mls of water.

On the first study visit participants attended after an overnight fast and a pre-prandial and 3 post-prandial blood samples 1, 2, and 4 hours after the meat meal were obtained. The evening before the second visit the participants had the standard meat meal with 250 ml of water and attended following an (12 hours) overnight fast. This was to estimate the effect of the standardised meat meal on serum creatinine following overnight fasting. A fasting and 3 post-prandial blood samples 1, 2, and 4 hours 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 analyser. The modified MDRD equation traceable to isotope dilution mass spectrometry (IDMS)-creatinine and adjusted for Olympus methodology (ml/min per 1.73m$^2$):

$$eGFR = 175 \times \left[ \frac{\text{Creatinine-intercept}}{\text{slope}} \times 0.011312 \right]^{-1.154} \times [\text{age}]^{-0.203} \times [1.212 \text{ if afro Caribbean race}] \times [0.742 \text{ if female}]$$

was used to calculate eGFR\textsuperscript{16}. For Olympus methodology the intercept is 16.14 and the slope is 0.955.

**Statistical considerations:**

To detect a mean shift of 10 micromoles/L (roughly equivalent to one standard deviation) between post minus pre-prandial values with a power of 90%, p=0.05 in a paired t-test required 13 participants in each group. However, for non-normal distributions, to use Wilcoxon signed rank test number of participants required for power of at least 90% was 15. Statistical analysis was carried out using SPSS (version 17.0 for Windows: SPSS, Chicago, IL) and Graph pad 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 non-normally distributed. Results are presented as median and interquartile ranges and p < 0.05 was taken to indicate statistical significance.

RESULTS

We obtained results from 80 participants following the standard cooked meat and non-meat meals. The mean glycated haemoglobin among the 64 participants with diabetic chronic kidney disease was 62.7± 16.1 mmol/mol (7.9 ± 1.6%).

Table 1 summarizes the fasting and post-prandial creatinine and eGFR values in the participants in all 5 groups. Postprandial values are 1 hour, 2 hours and 4 hours following the meat and non-meat meals.

Effect of cooked meat meal on serum creatinine over 4 hours:

Significant differences were found in serum creatinine and eGFR values following the standard meat meal in healthy volunteers and the participants with chronic kidney disease, but there were no significant differences following a non-meat meal. Figure 1 demonstrates the shift in serum creatinine and eGFR following the meat and non-meat meals. In healthy volunteers and CKD stage 1 & 2, the maximum rise in creatinine was noted at 2 hrs, while in CKD 3a and 3b the maximum rise was seen at 4 hours post-prandially. In CKD 4, the 4-hour creatinine was only 0.5 µmol/L (0.005mg/dL) lower than the 2-hour value (table 1).

Effect of cooked meat meal on serum creatinine after overnight fasting:

The median difference between fasting creatinine 12 hours following meat and non-meat meal was not statistically significant in any of the five groups studied as illustrated in figure 2.
CONCLUSIONS

Our study demonstrates significant increases in serum creatinine levels following a cooked meat meal in healthy volunteers and participants with diabetic chronic kidney disease stages 1 to 4. This is likely to be due 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. 6 out of the 16 patients in CKD 3a were misclassified as CKD 3b as a result of cooked meat consumption. This could have significant effects on 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 hours post-prandial in our study, as represented in the table. This could be related to the different rates of gastro-intestinal 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 in 12 hours 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.
Conflict of interest statement:

No conflict of interest declared by any of the authors.

No external funding was obtained for this study.

Author Contributions:

S.N. conceived and designed the study, researched data & wrote manuscript, S.O’B involved in study design and recruitment, reviewed/edited manuscript, K.H involved in study design, reviewed/edited manuscript, B.P involved in study design, reviewed/edited manuscript, P.L provided assistance with statistical analysis and reviewed/edited manuscript, K.J.H & J.P.H.W conceived and designed the study, contributed to discussion, reviewed/edited 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.
References:


### Table 1

Data are median and inter-quartile ranges of creatinine and eGFR before and after the standardised meat meal. Creatinine is expressed as µmole/L (1 µmole/L = 0.0113mg/dL) and eGFR as mls/min/1.73m². p values compare fasting vs. peak creatinine and nadir eGFR respectively.

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

Table 1: Data are median and inter-quartile ranges of creatinine and eGFR before and after the standardised meat meal. Creatinine is expressed as µmole/L (1 µmole/L = 0.0113mg/dL) and eGFR as mls/min/1.73m². p values compare fasting vs. peak creatinine and nadir eGFR respectively.
Legends to figures:

**Figure 1:** Panel A & B shows median and interquartile ranges of change in serum creatinine 2 hours after a meat and non-meat respectively. Panel C & D shows median and interquartile ranges of change in eGFR following meat and non-meat respectively. (** p < 0.01 and *** p <0.001 compare baseline and 2 hour values)

**Figure 2:** Median and inter quartile ranges of creatinine 12 hours following meat and non-meat meals in healthy volunteers and the 4 groups of participants with chronic kidney disease. No significant differences were noted in any group with all p values>0.05.
Figure 1: Panel A & B shows median and interquartile ranges of change in serum creatinine 2 hours after a meat and non-meat respectively. Panel C & D shows median and interquartile ranges of change in eGFR following meat and non-meat respectively. (** p < 0.01 and *** p < 0.001 compare baseline and 2 hour values)
Figure 2: Median and inter quartile ranges of creatinine 12 hours following meat and non-meat meals in healthy volunteers and the 4 groups of participants with chronic kidney disease. No significant differences were noted in any group with all p values > 0.05.