The effect of radiological contrast media on renal function and inflammatory markers in people with diabetes – a clinical study and review

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Abstract
Aim: To assess the association of inflammatory markers and the risk of developing contrast-induced nephropathy (CIN) in patients with diabetes undergoing lower limb angiography.

Methods: This was a retrospective study of 77 patients undergoing lower limb angiography. We measured renal function and markers of inflammation, in particular neutrophil and lymphocyte count and C-reactive protein (CRP) levels, before and at 24, 48 and 72 hours after administration of contrast medium.

Results: Those with pre-existing renal disease were at increased risk of CIN. We found no relationship between baseline renal function and CRP. There was a reduction in haemoglobin and lymphocyte count that is currently unexplained.

Conclusions: While several traditional risk factors for CIN have been identified, further work is needed to determine the significance of changes in other haematological parameters.


Key words: diabetes, angiography, contrast, contrast-induced nephropathy, inflammatory markers

Introduction
Contrast-induced nephropathy (CIN) is a form of acute kidney injury that occurs secondary to the administration of contrast medium (CM) and is not attributable to any other cause. CIN has been reported as the third most common cause of acute kidney injury occurring in hospital, after surgery and hypotension.

Until recently, CIN had been defined as a rise in serum creatinine of ≥50 µmol/L, or a 25% increase from baseline, assessed within 48–72 hours after administration of CM. In 2013 a new definition was accepted, based on the following findings after administration of CM: a rise of serum creatinine of >1.5 times the baseline value within seven days, an absolute increase of more than 26 µmol/L within two days, or urine output <0.5 mL/kg/hr for more than six hours following the procedure. Rising numbers of radiological procedures using CM have led to CIN becoming a significant source of morbidity and mortality, and it has been estimated that CIN accounts for 10% of all cases of iatrogenic acute kidney disease.

CIN is usually transient and reversible. Its pathogenesis is poorly understood, but is thought to be mediated in part by changes in renal haemodynamics and alterations in the balance of renal vascular vasodilators and vasoconstrictors, leading to reduced blood flow. Diabetes is one of a number of independent risk factors for developing CIN (along with hypotension, use of an intra-aortic balloon pump, heart failure, advanced age, high serum creatinine, anaemia, chronic kidney disease (CKD) and administration of a large volume of CM), and evidence is emerging for a role of the inflammatory marker C-reactive protein (CRP). CRP has been implicated in preventing vasodilation by increasing the activity of inhibitors of nitric oxide synthase and is widely recognised as a non-specific marker for systemic inflammation. Insulin resistance and diabetes are recognised as a generalised inflammatory states with raised CRP concentrations.

The aim of our study was to assess the effect of CM on renal function and inflammatory markers in patients with diabetes with and without pre-existing renal impairment. We also looked at the effect of pre-existing inflammation, as measured by CRP, on the risk of developing CIN.

Methods
Patients and study design
This was a single centre retrospective cohort study, which was conducted as a service improvement exercise so ethical approval was not required. We identified all patients at our institution who underwent a lower limb angiogram after receiving CM (iohexol, a
Non-ionic monomer containing 140–350 mg/mL of iodine between 1st January 2009 and 31st December 2010, using a database relating to our specialist diabetes vascular foot clinic. Procedures were conducted as an outpatient or inpatient, to assess peripheral vascular circulation for non-healing foot ulcers. The volume of CM given was determined according to the degree of arterial pathology within the usual care procedures of the radiologist undertaking the procedure.

We compared patients' baseline renal function (creatinine and estimated glomerular filtration rate [eGFR]) with available values 24, 48 and 72 hours after administration of CM. We also measured haemoglobin, white cell count and its white cell differential, and CRP. Patients without a blood test recorded within 1 week prior to the procedure or 72 hours after the procedure were excluded. Baseline eGFR levels were used to classify patients into relevant CKD sub-groups. Patients were also divided into two groups: "non-inflammatory" or "inflammatory" based on their CRP at baseline; a cut-off value for CRP of 1.6 mg/L was chosen for this purpose as inflammatory" or "inflammatory" based on their CRP at baseline;

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Results
Of 84 patients who were eligible for our study, seven did not have data available and were therefore excluded. Our analyses are based on the remaining 77 patients, of whom 52 had data at 24 hours, 23 had data at 48 hours and 31 had data at 72 hours; only seven patients had data available for all time points. Of the 77 eligible patients, 54 were male and 23 were female.

All had diabetes. Their mean age was 73.8 ± 9.4 years. No patients with end-stage renal failure (eGFR <15 mL/min/1.73m²) underwent an angiographic procedure.

Renal function (eGFR) across the entire cohort was significantly (p<0.01) lower 72 hours after receiving CM (Table 1), and was also reduced between 24 hours and 48 hours after administration of CM (p=0.0377, data not shown). Marked changes in serum creatinine were uncommon: 25/77 patients had baseline creatinine >120 µmol/L and, of these, one patient went from serum creatinine concentration of 221 µmol/L (baseline) to 240 µmol/L (72 hours), and another went from 163 µmol/L (baseline), to 164 µmol/L (24 hours), 237 µmol/L (48 hours) and 273 µmol/L (72 hours). There were no marked changes in serum creatinine in the remaining patients.

The overall incidence of CIN (defined as 25% rise in creatinine within 72 hours) was 5/77 (6.5%). All had pre-existing renal impairment (one with stage 2 CKD [CKD2], three with stage 3 CKD [CKD3] and one with stage 4 CKD [CKD4]).

Haemoglobin was significantly lower at both 48 hours and at 72 hours (Table 2). When assessed according to baseline renal function, only those classified as CKD3 demonstrated a significant difference at 48 and 72 hours (p=0.042 and p=0.03 respectively, data not shown). There was no significant difference in baseline haemoglobin according to renal function at baseline. About half of our patients (44/77; 54.5%) were classified as anaemic prior to the administration of CM, but this was not associated with an increased risk of CIN (data not shown).

Table 2 also shows data for inflammatory markers. There were no significant changes over time in white cell count, CRP or neutrophil count, although the lymphocyte count was reduced significantly at 48 hours (p=0.003) and at 72 hours (p=0.008). Changes in the neutrophil:lymphocyte ratio at 48–72 hours did not correlate with changes in creatinine at these times (correlation coefficient 0.0071), suggesting that there was no relationship between changes in this ratio and changes in renal function.

Ten patients had “non-inflammatory” levels of CRP and 14 patients had “inflammatory” levels of CRP (mean baseline CRP levels were 3.8 ± 4.4 and 95.1 ± 52.3 mg/L respectively, p<0.0001). Changes in eGFR in the non-inflammatory and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Change in renal function (estimated glomerular filtration rate [eGFR]) after administration of contrast medium, shown for the cohort as a whole and for patients stratified for categories of severity of chronic kidney disease (CKD) at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>CKD1 (n=15)</td>
</tr>
<tr>
<td>Mean change (±SD) in eGFR from baseline to 72 hours (mL/min/1.73m²)</td>
<td>−5.1 ± 27.5</td>
</tr>
<tr>
<td>Mean % change (±SD) from baseline</td>
<td>−8.4 ± 10.1</td>
</tr>
<tr>
<td>p (baseline vs. 72hours)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>n (at 72 hours)</td>
<td>31</td>
</tr>
</tbody>
</table>

Data are mean ± SD, where applicable. CKD1: eGFR >90 mL/min/1.73m²; CKD2: eGFR 60–90 mL/min/1.73m²; CKD3: eGFR of 30–60 mL/min/1.73m²; CKD4: eGFR <30 mL/min/1.73m².
inflammatory groups were similar 72 hours following administration of CM (6.9 ± 7.0 vs. −5.21 ±13.8 ml/min/1.73m², p=0.658).

Renal function declined (any decrease in eGFR or increase in creatinine) in 20 patients between 48–72 hours following administration of CM and did not decline in a further 14 patients. There was no difference in CRP between these groups (47.7 ± 48.3 vs. 65.9 ± 74.7 mg/L, p=0.559). Changes in CRP did not correlate with changes in eGFR at 72 hours (correlation coefficient 0.035), suggesting no relationship between these variables.

### Discussion

#### Pathophysiology of CIN

It is believed that CIN arises due to a combination of factors and three main concepts have been described: medullary hypoxia secondary to increased plasma viscosity resulting in renal tubular necrosis; direct tubular cytotoxicity of CM; stimulation by CM of adenosine release with a predominant vasoconstrictor effect on the renal vasculature. Elevated CRP prior to exposure to CM is a significant and independent predictor of CIN, inflammation is a pro-thrombotic state and elevated levels of inflammatory markers may contribute to increased plasma viscosity and subsequent tubular damage.

#### Consequences of administration of contrast medium

Our study supports previous findings that people with co-existing diabetes and renal dysfunction are at increased risk of CIN; all five of our patients who developed CIN had pre-existing CKD. The risk of CIN has been shown to be related to the severity of pre-existing CKD, but the exact relationship and the point at which damage is most likely to occur has yet to be determined. Our study did not address this issue due to its relatively small sample size and missing data for some patients. The incidence of CIN of 6.5% in our cohort is consistent with previous reports in people with diabetes (5-29%).

#### Inflammatory markers

Elevated levels of inflammatory markers, in particular CRP, prior to administration of CM may play a role in CIN following coronary angiography. A recent study involving 423 patients found that 13.5% of patients with CRP >5 mg/dL developed CIN, compared with 6.25% of patients with a lower level of CRP. We found no significant difference in renal function when patients were divided into groups depending on their CRP level at baseline. In addition, there did not appear to be an association between CRP and the severity of renal impairment following administration of CM. This is also likely to be due to our relatively small sample size.

It has also recently been reported that the neutrophil:lymphocyte ratio may be an independent risk factor for CIN, although we found no such correlation. Overall, we did not find a significant difference in the white cell count, neutrophil count or CRP. Our data relating to CRP may be skewed because the average baseline CRP was significantly elevated at 53.4 mg/L, suggesting that a pro-inflammatory state already existed in a proportion of our patients, probably due to the presence of a foot ulcer. Although CRP levels tended to decline after administration of CM, the difference did not achieve statistical significance, once again probably due to the small sample size of our study. We did, however, observe a significant decrease in lymphocyte count at 48 and 72 hours after administration of CM. The reason for this is unclear, particularly as the other markers of infection and inflammation remained unchanged. It is possible that the CM may have an effect on lymphocyte production or stimulation, in line with previous data that suggested a role for T-lymphocytes in delayed hypersensitivity to CM.
Contrast-induced nephropathy (CIN) is a commonly encountered phenomenon in patients with diabetes. The risk is increased in those with pre-existing renal impairment undergoing angiography. There are several factors that determine the development of CIN. Little work has been done to assess the impact of contrast on markers of inflammation.

Haemoglobin
In our study, we found that haemoglobin was significantly reduced at both 48 and 72 hours. This was probably due to haemodilution secondary to routine intravenous and oral rehydration following the procedure, although our study design did not permit follow-up beyond 72 hours. Previous work has shown that low haemoglobin before treatment is a risk factor for the development of CIN. Prior anaemia was not associated with an increased risk of CIN in our population and we did not observe a reduction in haemoglobin when patients were stratified according to eGFR at baseline.

Limitations
Our study has several limitations in addition to its small size, as described above. We did not record the prior use of angiotensin converting enzyme inhibitors or whether intravenous fluids were given prior to the administration of CM. Fluid administration may have been limited to those with pre-existing renal disease in an attempt to prevent any further deterioration. In addition, we did not collect the presence of contemporaneous infection in individual patients. It has previously been shown that the volume of CM administered is related to the risk of developing CIN, however, these data were not collected. Finally, given the retrospective nature of the study, we were unable to collect all of the data and were limited to those collected in ‘real life’ clinical practice.

Conclusions
In daily practice, CIN is an important clinical issue to consider when ordering any radiographic imaging involving the administration of CM. Patients with diabetes and, in particular, those with pre-existing renal disease are at particular risk of CIN. Further research is needed to define the role of inflammatory markers in the pathophysiology of CIN.

Conflict of interest
The authors declare that they have no conflicts of interest.

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- all contributors will be listed in publications arising from data submission