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CLINICAL RESEARCH

A Systematic Review of the Effect of N-Acetylcysteine on Serum Creatinine and Cystatin C Measurements

Johnny W. Huang[1,2], Brianna Lahey[2,3], Owen J. Clarkin[4], Jennifer Kong[3], Edward Clark[1,2,3], Salmaan Kanji[1,3], Christopher McCudden[1,2], Ayub Akbari[1,2,3], Benjamin J.W. Chow[4], Wael Shabana[1,2,3] and Swapnil Hiremath[1,2,3]

[1]The Ottawa Hospital, Ottawa, Ontario, Canada; [2]University of Ottawa, Ottawa, Ontario, Canada; [3]Division of Nephrology, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; and [4]University of Ottawa Heart Institute, Ottawa, Ontario, Canada

Introduction: N-acetylcysteine (NAC) is an antioxidant that can regenerate glutathione and is primarily used for acetaminophen overdose. NAC has been tested and used for preventing iatrogenic acute kidney injury or slowing the progression of chronic kidney disease, with mixed results. There are conflicting reports that NAC may artificially lower measured serum creatinine without improving kidney function, potentially by assay interference. Given these mixed results, we conducted a systematic review of the literature to determine whether there is an effect of NAC on kidney function as measured with serum creatinine and cystatin C.

Methods: A literature search was conducted to identify all study types reporting a change in serum creatinine after NAC administration. The primary outcome was change in serum creatinine after NAC administration. The secondary outcome was a change in cystatin C after NAC administration. Subgroup analyses were conducted to assess effect of creatinine assay (Jaffe vs. non-Jaffe and intravenous vs. oral).

Results: Six studies with a total of 199 participants were eligible for the systematic review and meta-analysis. There was a small but significant decrease in serum creatinine after NAC administration overall (weighted mean difference [WMD], −2.80 μmol/L [95% confidence interval {CI} −5.6 to 0.0]; $P = 0.05$). This was greater with non-Jaffe methods (WMD, −3.24 μmol/L [95% CI −6.29 to −0.28]; $P = 0.04$) than Jaffe (WMD, −0.51 μmol/L [95% CI −7.56 to 6.53]; $P = 0.89$) and in particular with intravenous (WMD, −31.10 μmol/L [95% CI −58.37 to −3.83]; $P = 0.03$) compared with oral NAC (WMD, −2.5 μmol/L [95% CI −5.32 to 0.32]; $P = 0.08$). There was no change in cystatin C after NAC administration.

Discussion: NAC causes a decrease in serum creatinine but not in cystatin C, suggesting analytic interference rather than an effect on kidney function. Supporting this, the effect was greater with non-Jaffe methods of creatinine estimation. Future studies of NAC should use the Jaffe method of creatinine estimation when kidney outcomes are being reported. Even in clinical settings, the use of an enzymatic assay when high doses of intravenous NAC are being used may result in underdiagnosis or delayed diagnosis of acute kidney injury.

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N-acetylcysteine (NAC) is an antioxidant that can regenerate glutathione and is primarily used for acetaminophen overdose.[1] It has also been tested in prevention of acute kidney injury (AKI) in different settings, such as postoperative AKI and contrast-induced AKI (CI-AKI) with mixed results, mainly using change in serum creatinine levels before and after NAC treatment as the outcome. The larger subsequent trials conducted with clinical outcomes have not shown any benefit, but the reason for the discrepancy between earlier trials that showed a benefit in serum creatinine levels and these subsequent trials has not been clearly established.[2–4] Given the low cost and lack of side effects, NAC has been recommended for use by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[5] Similarly, a systematic review from the Agency for Healthcare Research and Quality also supports its use for CI-AKI prophylaxis.[6] At

Correspondence: Swapnil Hiremath, The Ottawa Hospital, Riverside Campus, 1967 Riverside Dr, Ottawa, Ontario, Canada K1H 7W9. E-mail: shiremath@toh.ca
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present, there are still >20 ongoing trials testing the efficacy of NAC for prevention of AKI in various settings (e.g., contrast AKI, perioperative AKI, and drug-induced AKI) as well as in chronic kidney disease (CKD) for slowing progression or preserving residual kidney function.[7] As such, a significant body of research is in progress despite the evidence so far, and a biologic mechanism or rationale for a protective effect of NAC has not been satisfactorily reported.[8]

A potential reason for the discrepancy between the effect of NAC on serum creatinine and clinical outcomes may be assay interference from the effect of NAC on serum creatinine measurement. An initial report suggested that NAC lowers serum creatinine, without having any effect on cystatin C.[9] However, a subsequent larger study could not reproduce these findings.[10] A small *in vitro* analysis suggests that the assay interference from NAC on serum creatinine may only occur with the enzymatic assay, and not with the older colorimetric (Jaffe) method.[11,12]

Given these mixed results, we conducted a systematic review of the literature and determined the effect of NAC on serum creatinine. The objective of this study is to determine the effect of NAC on kidney function as measured by serum creatinine and cystatin C, in the absence of any confounders. Thus we excluded NAC use in the setting of AKI prophylaxis, such as contrast administration or perioperative setting. We also aimed to identify and potentially alleviate confounders regarding characteristics of the patient population including NAC dose and route of administration, and measurement of serum creatinine and cystatin C.

METHODS

Search Strategy

The protocol for this systematic review was registered in PROSPERO (registration no. CRD42017055984) and has been published.[13] This review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[14] A comprehensive literature search was conducted using electronic databases including MEDLINE, Embase, and the Cochrane Central Library. In consultation with an information scientist, databases were searched in all available time, from the oldest literature to the search date (i.e., 1947 to October 2018; Supplementary Table S1). Bibliographies and citations of published works were cross-referenced for additional potential studies. To minimize the potential for English-only language bias, manuscripts written in other languages encountered via cross-checking for relevance were also considered.

Inclusion and Exclusion Criteria

All studies that explored the potential effect of NAC on kidney function as quantified by baseline and follow-up serum creatinine, serum cystatin C, and/or glomerular filtration rate (GFR) measurements were considered for screening. There were no limitations by population, study design, date, or language. The study participants were ≥18 years of age and were receiving NAC with previous and subsequent serum measurement of creatinine, cystatin C, and/or GFR. Exclusion criteria included patients with minimal to no kidney function such as in end-stage kidney disease. Patient populations receiving contrast agents and those simultaneously undergoing surgery were excluded from the study to avoid potential for confounding because of CI-AKI or other causes of AKI. Existing systematic reviews and meta-analyses were excluded, but their bibliographies and more recently cited articles were cross-referenced to augment the literature search.

Study Selection

Pertinent articles identified by our search strategy were reviewed systematically in duplicate. Abstracts were screened independently by 2 authors (BL, OJC, or JWH), and studies that met exclusion criteria were excluded in the first-round of analysis. Articles that were not excluded outright via abstract analysis were reviewed as full-text documents and subject to full review (by BL, OJC, or JWH) for inclusion/exclusion criteria. All disagreement regarding article inclusion was resolved by an in-person meeting for consensus and forwarded to another reviewer (SH) for adjudication.

Data Collection Process

A data extraction template was developed by the principal investigator (SH) and modified by feedback from 2 independent reviewers (OJC and JWH) to ensure that complete data were obtained. OJC and JWH performed data extraction from selected manuscripts and compared for consistency. In cases with disagreement, consensus was attempted via further discussion, and input by a third reviewer (SH) if necessary. Reviewers were not blinded to the authors or journals during this process.

The following information was extracted from all included studies: research group, country of origin, year of publication, funding source, study design, patient population (i.e., healthy volunteers vs. patients with CKD, sample size, sex, age, presence of other comorbid conditions such as diabetes), NAC details (i.e., route of administration, dose, and frequency), and control group (placebo-controlled vs. no treatment).

Outcome and Data Synthesis

The primary outcomes of interest were biomarkers of kidney function. For randomized controlled trials, patients receiving NAC were compared with those receiving placebo. For single arm prospective cohort studies, data on change in creatinine from baseline (i.e., before and after NAC administration) were extracted.

The outcome data from included studies were pooled into a meta-analysis using Comprehensive Meta-Analysis software (version 3; Biostat Inc., Englewood, NJ). The weighted mean differences (WMDs) were calculated for change in creatinine and cystatin C with NAC using random-effects analysis as described by DerSimonian and Laird.[15] Statistical heterogeneity was assessed using Cochran Q and I^2 statistics.

Quality Assessment

The quality of studies and potential for biases were assessed independently by 2 authors (OJC and JWH) using standard tools, the Cochrane Risk of Bias for randomized studies and Newcastle-Ottawa Scale for observational studies.[16–18] Stars were awarded on 3 domains: selection, comparability, and outcome. Good quality studies received 3 or 4 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome domain. Medium quality studies received 2 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome domain. Poor quality studies were awarded 0 or 1 star in the selection domain, 0 stars in the comparability domain, and 0 or 1 star in the outcome domain.

Subgroup Analysis and Metaregression

With regard to meta-bias assessment, univariate meta-regression analyses were conducted to assess the effects of clinical factors (e.g., dose of NAC) on the meta-analysis estimates, when applicable. Subgroup analyses were conducted based on route of NAC (oral vs. intravenous [i.v.]), method of creatinine measurement (Jaffe vs. non-Jaffe methods), and study population (CKD vs. healthy volunteers). Funnel plot methodology, using visualization of the asymmetry and the Egger statistic, were used to identify publication bias.[19]

RESULTS

Study Selection

The literature search identified 628 articles collectively from MEDLINE, Embase, and the Cochrane Central Library, citation tracking, and gray literature search. Five hundred seventy-eight articles were excluded after primary screening based on title and abstract. A full-text review of the remaining 50 articles resulted in the further exclusion of 43 articles, primarily because these studies examined the effects of NAC on kidney function in the context of CI-AKI or surgeries/procedures that involved contrast agents. During the data extraction phase, 1 article was excluded because the patient population of interest were individuals with end-stage kidney disease. A total of 6 studies involving 199 patients were included in the primary meta-analysis[9,10,20–23] (Figure 1). Four studies also reported changes in cystatin C change after NAC treatment, and these were analyzed for the secondary outcome.[9,10,20,21]

Study Characteristics

The clinical characteristics of the 6 studies are shown in Table 1. Overall, these studies are small, with a median sample size of 30 (range, 10–60). The proportion of men ranged from 48% to 83%. The mean patient age ranged from 33 to 71 years. Five studies included patients with stable CKD, while 1 study recruited healthy volunteers. In terms of study design, 4 studies were before/after single-arm prospective trials, and 2 were parallel randomized controlled trials, comparing NAC against placebo. The follow-up periods were mostly short (i.e., 48 hours after the last dose of NAC treatment), except 1 study with a 2-year study period.

In terms of NAC regimen, 600 mg of oral NAC was provided twice daily for 2 days in 1 study[9] while another study provided 1 dose.[20] Two studies used a shorter and higher dose of oral NAC at 120 0mg twice daily for 2 days,[10,21] while another study used a longer and lower protocol of dose once a day for a total of 8 weeks.[22] Lastly, one study used an i.v. NAC at a dose typically used for acetaminophen overdose at 100 mg/kg.[23]

Change in Serum Creatinine

Meta-analyses of the 6 studies are presented in Figure 2. All studies showed a varying degree (i.e., ranging from −0.35 to −31.1 μmol/l) of reduced serum creatinine change after NAC dosing with respect to the baseline measurement. The WMD was −2.80 μmol/l (95% confidence interval [CI], −5.6 to 0.0; $P = 0.05$), suggesting a small, statistically significant decrease in serum creatinine after NAC. The heterogeneity was not statistically significant, with a Cochran Q of 4.7 ($P = 0.45$).

Subgroup Analyses and Metaregression

Subgroup analyses was performed to compare the 6 included studies that used different serum creatinine determination methodology, study population, and route of NAC administration (Table 2). The decrease in serum creatinine was statistically significant with the non-Jaffe method (−3.24 μmol/l [95% CI, −6.29 to −0.18]; $P = 0.04$) compared with the Jaffe method (−0.51 μmol/l [95% CI, −7.56 to 6.53]; $P = 0.89$). There

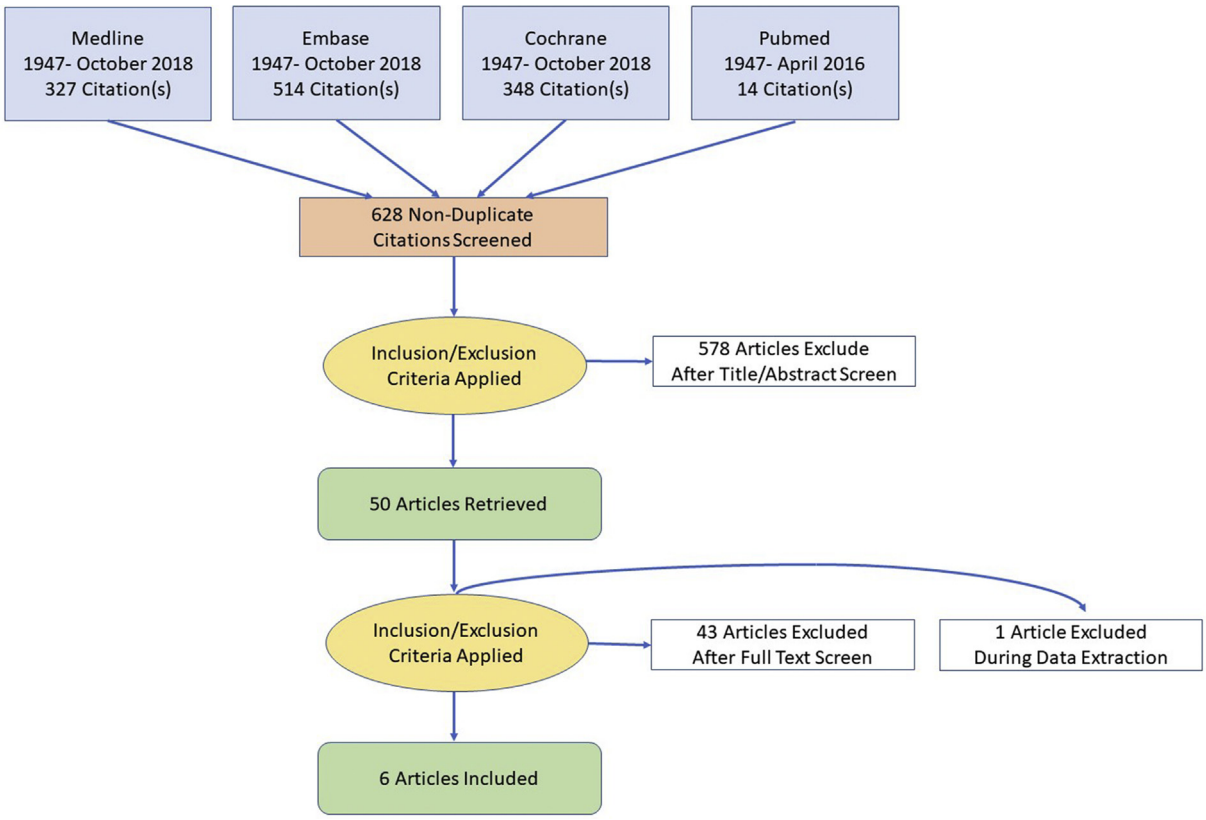

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram of literature search and study selection.

also was a greater decrease in serum creatinine with the route of i.v. NAC (−31.10 μmol/l [95% CI, −58.37 to −3.83]; $P = 0.03$) compared with oral NAC (−2.5 μmol/l [95% CI, −5.32 to 0.32] $P = 0.08$). The univariable metaregression analysis did not show a significant effect of NAC dose, baseline creatinine, or other demographic characteristics studied on mean serum creatinine.

Change in Cystatin C

Meta-analyses of the 4 studies that reported pre- and post-NAC serum cystatin C are presented in Figure 3. No changes were demonstrated in cystatin C change post–NAC dosing with respect to the baseline measurement, with a WMD of −0.84 μmol/l (95% CI, −3.14 to 1.47]; $P = 0.48$). Heterogeneity for NAC and cystatin C was not significant (Cochran $Q = 0.13$, $I2 = 0$; $P = 0.99$).

Publication Bias

There was evidence of publication bias by visual examination of the funnel plot for the outcome of serum creatinine (Figure 4). One study was imputed which changes the pooled WMD estimate to −2.50 μmol/l (95% CI, −5.29 to 0.29; Figure 4). The Egger regression intercept was not significant ($P = 0.32$). There was no

Table 1. Study characteristics of the included studies and route, dose, and regimen of NAC

Study	Country	Year	Study design	Setting/ population	Dose and regimen	Sample size, n	Men, %	Mean age, yrs	Patients with diabetes, %	Follow-up
Hoffmann *et al.*[9]	Germany	2004	Before/after single arm	Healthy volunteers	4 doses of oral NAC (each 600 mg) at 12-hr intervals for 2 days	50	48	32.8	N/A	48 hrs after last NAC
Mainra *et al.*[20]	Canada	2007	Before/after single arm	Patients with CKD	1 dose of oral NAC (600 mg) for 1 day	30	83.3	66	N/A	48 hrs after last NAC
Moist *et al.*[10]	Canada	2010	Double blind, randomized controlled trial	Patients with CKD	4 doses of oral NAC (each 1200 mg) at 12-hr intervals for 2 days	60	76.7	68.6	50	48 hrs after last NAC
Rehman *et al.*[21]	US	2008	Before/after single arm	Patients with CKD	4 doses of oral NAC (each 1200 mg) at 12-hr intervals for 2 days	30	60	65.3	38	48 hrs after last NAC
Renke *et al.*[22]	Poland	2010	Placebo and randomized controlled	Patients with CKD	2 doses of oral NAC (each 1200 mg) per day for 8 weeks	20	60	39.4	0	N/A
Sochman and Krizova[23]	Czech Republic	2006	Before/after single arm	Patients with CKD	1 dose of i.v. NAC (100 mg) for 1 day	10	70	71	10	24 hrs after last NAC

CKD, chronic kidney disease; i.v., intravenous; N/A, not available; NAC, N-acetylcysteine; US, United States.

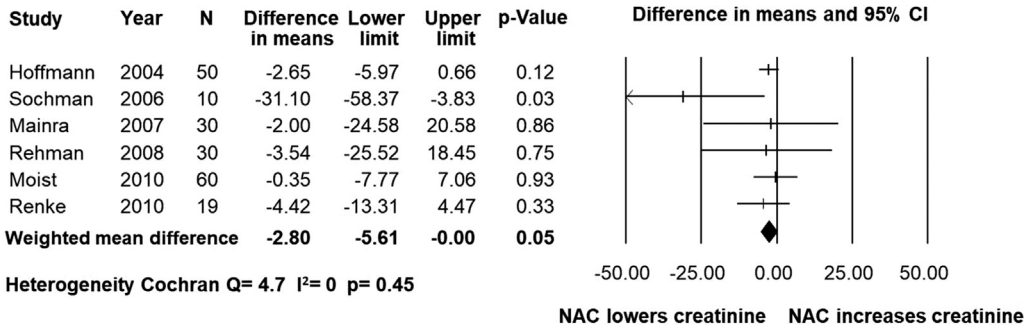

Figure 2. Forest plot of randomized trials meeting inclusion criteria for change in serum creatinine. CI, confidence interval; NAC, N-acetylcysteine.

evidence of publication bias both by visual examination or the Egger test for the analysis of NAC and cystatin C.

Quality Assessment

Table 3 presents the Newcastle-Ottawa Scale quality assessment scores of the 6 included studies. Overall, 1 study achieved a total score of 8 (out of 9), 4 studies scored 5 points, and 1 study scored 4. In terms of selection, all but 1 study incorporated the before/after single-arm design, and therefore did not include a matched control group for comparison. All studies used secure medical records for ascertainment of exposure. In terms of comparability, 5 studies did not report adjustment for potential confounding variables in their respective methodologies. The lone study with a matched control group showed statistical comparisons of baseline characteristics. In terms of outcome, 4 studies received a score of 2 for appropriate assessment of outcome and an adequate proportion of patients with follow-up. Finally, 5 studies lost a point for short duration of follow-up (e.g., 48 hours after last dose of NAC).

DISCUSSION

This systematic review was conducted to determine the effect on kidney function, namely serum creatinine and cystatin C, while excluding studies in the setting of contrast administration and patients undergoing surgeries/procedures to avoid confounding caused by concomitant AKI. This study identified 6 prospective studies, with the pooled estimate of a small but statistically significant effect of NAC on lowering serum creatinine of −2.8 μmol/l. Moreover, on subgroup analysis, the effect was greater when pooling the studies that did not use the Jaffe method of creatinine estimation. In addition, i.v. NAC also resulted in a greater lowering of serum creatinine then oral NAC. In contrast, there was no effect of NAC on cystatin C measurement. This implies that the effect of NAC on serum creatinine is a result of analytic interference and was greater with the enzymatic assay compared with the Jaffe method.

These findings support the initial report from Hoffman *et al.*,[9] which suggested that NAC causes a change in serum creatinine without truly having an effect on kidney function. *In vitro* analysis does suggest that at extremely high concentration, NAC may interfere with the enzymatic assay, causing a falsely lower serum creatinine.[24] The concentration of NAC achieved in the serum with oral administration of NAC, as is done in clinical trials, rarely achieves these high concentrations. However, this concentration will be achieved with i.v. NAC administration, which is coherent with the analysis from the present study showing a greater effect (−31 μmol/l) with i.v. NAV compared with oral (−2.5 μmol/l). In addition, though the decrease in serum creatinine with oral NAC does not seem clinically significant, it may still result in a difference in CI-AKI events with NAC compared with placebo if these are only measured in terms of change in creatinine. This may explain the discrepancy between the beneficial effect of NAC as reported in some trials but not others.[4] More specifically, this finding—that the effect of NAC is an artifact of assay interference—explains the null finding of more recent large clinical trials of NAC.[25,26]

Table 2. Subgroup analysis of Jaffe vs. non-Jaffe, oral vs. i.v., and CKD vs. non-CKD

Study subgroups	Weighted mean difference (95% CI)	*P* value
Method of creatinine measurement		
Jaffe	−0.51(−7.56 to 6.53)	0.89
Non-Jaffe	−3.24(−6.29 to −0.18)	0.04
NAC route		
Oral	−2.50(−5.32 to 0.32)	0.82
i.v.	−31.10(−58.37 to −3.83)	0.03
Study population		
CKD	−3.19(−8.44 to 2.07)	0.24
Non-CKD	−2.65(−5.97 to 0.66)	0.12

CKD, chronic kidney disease; i.v., intravenous; NAC, N-acetylcysteine.

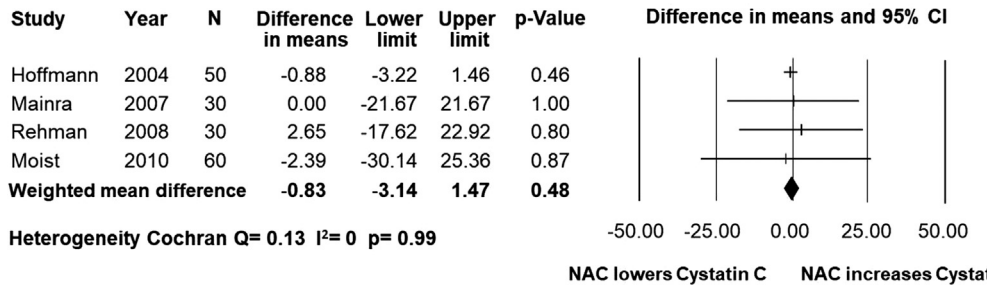

Figure 3. Forest plot of randomized trials meeting the inclusion criteria for change in cystatin C. CI, confidence interval; NAC, N-acetylcysteine.

One may wonder about the clinical significance of these findings, given that the most recent large RCTs have shown clearly that NAC has no benefit in the setting of CI-AKI. However, NAC is still being studied in other settings, with 30 ongoing trials to prevent AKI and the progression of CKD.[27] It is important that serum creatinine measurement be performed in these trials with an assay (such as the Jaffe method) that does not interfere with NAC administration. Alternately, the investigators could validate the creatinine measurements using both enzymatic and Jaffe methods in a subset of participants both before and after NAC administration. This consideration is especially valid with i.v. NAC administration. The effect reported in the present study was strongest with high doses of NAC administered. Oral NAC has poor oral bioavailability, so the higher effect seen with i.v. NAC may reflect greater serum NAC concentrations and subsequent interference. High doses of i.v. NAC are used in the setting of acetaminophen overdose and in patients with alcoholic hepatitis.[1] A falsely low serum creatinine, when measured with the enzymatic assay, may mask the development of AKI in this clinical setting. The change in serum creatinine with i.v. NAC was −31 μmol/l, which is certain to result in a significant difference in AKI count in any trial if using the Kidney Disease: Improving Global Outcomes staging (stage 1 being 26.5 μmol/l). This will also likely result in the underdiagnosis or delayed of clinically significant AKI occurrence in these settings of i.v. NAC use, which is typically used as an antidote.

This systematic review has certain limitations. The sample size of the individual studies was small, but that is typical for mechanistic studies of this nature. The change in creatinine was small but statistically significant and contrasts with the lack of change in cystatin C. There is publication bias, with the imputation of a study shifting the pooled estimate to the null. Lastly, the overall quality of the studies included was not high.

In conclusion, the systematic review reports a small but significant decrease in serum creatinine with NAC administration but not in cystatin C. This effect seems to be higher when creatinine is measured with the enzymatic assay and with i.v. NAC administration.

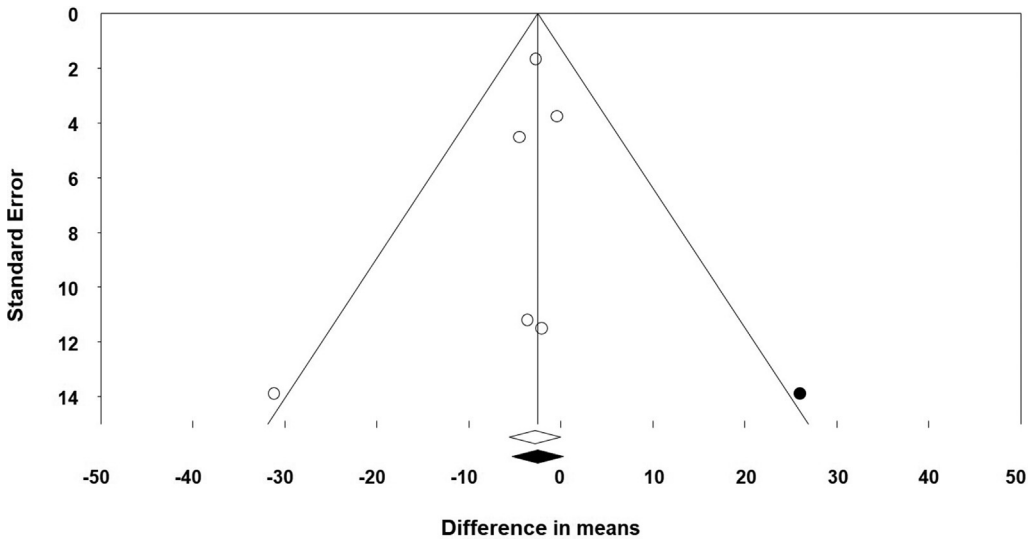

Figure 4. Funnel plot displaying the difference in means on the x axis and the standard error on the y axis.

Table 3. Newcastle-Ottawa quality assessment score of the 6 studies

Study	Year	Selection	Comparability	Outcome	Total score
Hoffmann *et al.*[9]	2004	***		**	*****
Mainra *et al.*[20]	2007	***		**	*****
Moist *et al.*[10]	2010	****	*	***	********
Rehman *et al.*[21]	2008	***		**	*****
Renke *et al.*[22]	2010	***		*	****
Sochman and Krizova[23]	2006	***		**	*****

The * represent the quality of the study by each domain mentioned in the column. More * refers to higher quality and absence of * or less * denote a lower quality. See "quality assessment" section in methods for details.

DISCLOSURE

BC has a potential competing interest with CV Diagnostix, AusculSciences, and Toronto-Dominion Bank. The other authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

SH, AA, and CM did the initial design. SH, JWH, OJC, BL, and JK wrote the manuscript. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Details of literature search strategy.

PRISMA Checklist.

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