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N-acetylcysteine – passe-partout or much ado about nothing?

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In experimental studies, the old mucolytic agent N-acetylcysteine (NAC) has had beneficial effects in disorders supposedly linked to oxidative stress. Numerous, mainly small clinical trials with variable doses have yielded inconsistent results in a wide variety of diseases. NAC added to the conventional therapy of human immunodeficiency virus infection might be of benefit; in respect of chronic obstructive pulmonary disease, systematic reviews and meta-analyses suggested that prolonged treatment with NAC is efficacious, but a recent multicentre study has questioned this. In a large intervention trial on cancer recurrence, NAC was ineffective. NAC infusions have been widely used in acute hepatic failure but convincing evidence of its benefits is lacking. A preliminary study reported that NAC is effective in preventing radiocontrast-induced nephropathy but thereafter highly mixed results have been published, and even meta-analyses disagree on its efficacy. In intensive care NAC has mostly been a disappointment but recently it has 'given promises' in surgery with cardiopulmonary bypass. NAC therapy is routine only in paracetamol intoxication.

Beneficial beyond mucolytic action

N-acetylcysteine (NAC) was introduced as a mucolytic agent for chronic pulmonary diseases some 50 years ago. Its effect is based on breaking of the disulphide bridges of the high-molecular-weight glycoproteins of the mucus, resulting in reduced viscosity. In many European countries it is widely prescribed for this purpose but in the UK, for example, it is perceived to be ineffective [1]. The favourable effects of NAC might, however, extend much further than to chronic bronchitis; it has a plethora of properties that could be widely exploited in the clinical setting, at least in theory. At the moment, active research on NAC is on-going.

The magic word in the background of almost all the effects of NAC is oxidative stress. In animal cells, reactive oxygen species (ROS) are generated as a by-product of normal metabolism during the conversion of molecular oxygen to water. ROS have useful functions such as combating microorganisms by phagocytes and serving as mediators for signal transduction and gene expression, but they can also cause damage through oxidation and peroxidation of DNA, proteins and lipids. Oxidative stress arises when there is an imbalance

between oxidants and antioxidants, and this is assumed to play a key role in physiological conditions such as ageing and in the pathogenesis of miscellaneous diseases [2]. Among these are several cardiovascular, some liver, respiratory [chronic obstructive pulmonary disease (COPD), pulmonary fibrosis], renal (terminal kidney failure and its complications, chronic allograft nephropathy), articular and neurological diseases, cancer, multiple organ failure and critically ill conditions [2–8].

In ischaemia and reperfusion, the rapid change in the partial pressure of oxygen is a major adaptation stress for cells. Ischaemia-reperfusion injury is accompanied by remarkable morbidity and mortality, and it can lead to graft loss. Its mechanisms are complicated and poorly understood. In cells being damaged by hypoxia, ROS are generated, and they are supposed to be important also in the additional injury evolving during reperfusion. Inflammatory factors activated by ROS also contribute to the damage [9, 10].

Oxidative stress stimulates inflammatory response by activating particularly the redox sensitive nuclear factor (NF)-κB which leads to activation of tumour necrosis factor (TNF)-α and generation of various inflammatory cyto- and chemokines. ROS have a role in the pathogenesis of osteo- and other forms of arthritis, and they are generated also in acute pancreatitis [2, 11]. Intracellular glutathione (GSH) pool is reduced in chronic inflammation [12]. Lowered GSH levels have been observed also in T cells from patients with rheumatoid arthritis [2]. Even moderate changes in the intracellular GSH level have profound effects on lymphocyte functions which is supposed to play a key role in human immunodeficiency virus (HIV) infection [13].

In the endothelium, ROS can induce dysfunction and apoptosis, promote adhesion of inflammatory cells and play a role in angiogenesis [2, 7]. Tobacco smoke led to a loss of endothelial barrier function within minutes, while long-term exposure to tobacco smoke extracts induced endothelial necrosis; tobacco smoke oxidants (radicals) may mediate these phenomena [14]. Many functions of vascular smooth muscle cells also depend on ROS [2, 7].

GSH, the most abundant low-molecular-weight thiol in animal cells, plays a central role in the antioxidant defence against ROS. For tissue GSH synthesis, the availability of cysteine is generally the limiting factor, and one of the effective precursors of cysteine is its synthetic derivative, NAC [2]. NAC may also provide SH-groups and scavenge ROS itself. In addition to antioxidant function, NAC has some other mechanisms of action, such as inhibition of neutrophil activation, decreased microbial attachment and vasodilation.

Many drugs and poisons are detoxified through conjugation with GSH (e.g. paracetamol, among others) and additional GSH, provided by administering NAC, has been shown to be effective in intoxication by such drugs and poisons [2, 15].

NAC in the light of experimental research

In experimental research, NAC has largely been as effective as expected according to theory (see Table 1), and particularly so in various types of renal injury (Table 2). In theory, NAC has a variety of protective effects in cancer, particularly that related to smoking [2]. NAC has had an inhibitory effect on the generation of certain cancer-associated biomarkers in healthy smokers but it has also induced potentially deleterious structural changes affecting the fidelity of DNA synthesis [2, 48]. Antioxidants, among them NAC, may play a role in the functional restoration of the immune system in patients with advanced cancer [49].

Towards clinical use

The combination of low concentration and extreme reactivity of ROS makes their *in vivo* detection extremely difficult, thus stable endproducts of oxidation are used as surrogate biomarkers. No clinical trials, however, have been performed in which patient selection is based on biochemical evidence of oxidative stress, but in end-stage renal disease, for example, oxidative stress probably exists regularly [5, 50].

As a mucolytic agent, NAC is generally administered at 400–1200 mg daily but in clinical trials on other diseases the doses have varied widely, up to 18 g daily. NAC can also be administered intravenously or by inhalation. After oral dosing, NAC is resorbed rapidly but undergoes an extensive first-pass metabolism resulting in low plasma and tissue availability. This has been thought to be of minor importance because the effects of NAC are generated mainly through cysteine and glutathione, but it makes the function of NAC as a direct scavenger of ROS questionable [44]. The bioavailability of NAC seems to increase with the dose – after a single dose of 600 mg the serum peak of NAC is on average 16 μmol l^{-1} and after 1200 mg it is 35 μmol l^{-1}. *In vitro*, these two concentrations reduced in a concentration-dependent manner the activation of polymorphonuclear neutrophil oxidative burst but had no effects on phagocytosis and bacterial killing [51].

NAC in infectious diseases

HIV-infected patients may have exceptionally low levels of cysteine and glutathione, and they are thought to live under chronic oxidative stress. They have also been

Table 1
NAC in experimental research

Research subject	Results
Inflammation, infection, immunity	Attenuating, alleviating, adding resistance, healing and strengthening the immune response, including Leishmania infection and influenza [12, 16–20]
Endothelial cells	Protection against several hazardous factors, including urban air fine particles and tobacco smoke [2, 14, 21]
Vascular wall	Several protective effects [2, 22, 23]
Experimental models of cardiovascular diseases, cardiac surgery	Favourable effects in hypertension, in hypertensive cardiac injury, cardioprotection in ischaemia-reperfusion injury/myocardial infarct and cardiopulmonary bypass [24–27]
Lungs	Protective effect in injuries by different toxins (including tobacco smoke), in lung transplantation, in lung reperfusion injury, attenuation of pulmonary fibrosis [2, 28–30]
Nervous system	Neuroprotection in transient hypoxic injury (Alzheimer-type) to cortical neurones, prevention of primary sensory neuronal death, beneficial effects in deficits of learning and memory and in hearing loss [31–34]
Gastroenterology	Favourable effect in acute pancreatitis and liver injuries, inhibition of the growth of *Helicobacter pylori* [2, 11, 35, 36]
Endocrinology/pregnancy	Protection against complications of diabetes, insulin resistance, and oestrogen-deficiency bone loss, restores nitric oxide-mediated effects in the fetoplacental circulation in pre-eclampsia [37–40]
Articular structures	Protection against various injuries [2]
Miscellaneous	Protection against acute high-dose irradiation, photoageing of human skin, decreases plasma total homocysteine levels in healthy volunteers [41–43]

Table 2
NAC in experimental renal disease

In animals, protection of renal function in ischaemia-reperfusion injury, attenuation of proximal tubular necrosis, amelioration of microcirculation due to vasodilation, and improvement of medullary hypoperfusion in acute renal failure [44]
In haemodialysis patients, decrease of the increased rate of mononuclear leucocyte apoptosis, prevented apoptosis and oxidative stress, and restored intracellular pool of thiols [4]
In haemodialysis patients, inhibition of phagocyte oxidative responses induced by AOPP but not that induced by compounds mimicking pathogens: NAC could safely reduce oxidative stress-related inflammation [45]
Renoprotective effect in cisplatin, ciclosporin, mercuric chloride, cadmium, lithium, gentamicin and amphotericin-induced injury [46, 47]

AOPP, Advanced oxidation protein products.

found to experience a massive loss of sulphate equivalent to a net loss of approximately 4 g cysteine daily, and this increased excretion begins in the asymptomatic phase. In addition to immune deficiency, lack of glutathione can lead to muscular atrophy and cachexia [13]. In the USA, NAC was a popular alternative medicine for AIDS for years, although it was not until 1996 when the first study indicated that NAC treatment normalized at least some laboratory tests. There is a strong association between GSH deficiency and decreased survival in HIV disease: for those in whom the initial phase GSH levels in CD4 T cells were high, the 3-year survival was 60–80%, while for those with low GSH levels it was only 20%. NAC treatment for 8 weeks safely replenished whole blood and T-cell GSH, but it remained uncertain whether NAC increased life expectancy. In this modern highly active antiretroviral therapy (HAART) era, treatment with NAC as the only medicine is, of course, out of the question, but NAC could be tested as an adjunct to these therapies [3]. HAART does not prevent the loss of sulphate in progressing HIV and this may partially explain treatment failures [13]. It is, however, unlikely that NAC will be established as a treatment for HIV infection on the basis of randomized trials – such studies are too expensive for such an inexpensive drug as NAC [13].

Single studies have reported that administration of NAC (600 mg twice daily) in wintertime attenuated influenza and influenza-like episodes, particularly in elderly high-risk persons [52], and that NAC might be of help also in severe malaria as an adjunct to specific treatment [53].

Is NAC of any benefit in pulmonary disease?

In smokers with bronchitis, NAC treatment decreased the amount of bacteria recovered by pulmonary lavage [15], and in stable COPD it reduced exhaled hydrogen peroxide [54]. However, studies on real clinical efficacy of NAC have yielded inconclusive results. In acute exacerbations of COPD, addition of NAC to standard treatment did not modify the outcome [55]. Both a systematic quantitative review [56] and a meta-analysis [57] of the existing double-blind placebo-controlled studies on NAC in the treatment of chronic bronchitis arrived at the same conclusion: a prolonged course (3–6 months) of oral NAC with doses from 600 mg three times weekly to 400–1200 mg daily reduced acute exacerbations and improved symptoms without increasing the risk of adverse effects. A recent Cochrane review on NAC and other mucolytics arrived at a very similar conclusion [1]. In a large retrospective study, patients treated for COPD with NAC had a dose-dependent decrease in the rate of rehospitalization; the decrease achieved by different doses averaged 30% [58]. However, a recent extensive multicentre study (BRONCUS), where the patients were followed for 3 years, reported that at least the dose of NAC 600 mg daily is ineffective at prevention of deterioration in lung function and prevention of exacerbations in patients with COPD [59].

In cystic fibrosis, NAC has been administered both orally and by inhalation. A systematic review indicated that NAC was of no distinct benefit, but scant adequate published data on this topic exist [60]. In fibrosing alveolitis, where activated inflammatory cells are believed to create oxidative stress in the lower respiratory tract, high-dose NAC (1.8 g daily for 12 weeks in addition to immunosuppressive therapy) improved pulmonary function tests and slightly reduced the oxidative activity, but did not clearly suppress the activity of inflammatory cells; later the initial enthusiasm of the authors for NAC seemed to fade [61]. In acute respiratory distress syndrome (ARDS), endothelial damage is associated with numerous inflammatory events, including formation of oxygen radicals. In a recent Cochrane evaluation, NAC was found to be of no clear benefit in ARDS therapy [62]. Recently, a Nordic multicentre controlled trial showed that a 6-day course of intravenous NAC during the first week of life does not prevent bronchopulmonary dysplasia or death, or improve lung function at term in infants with extremely low birth weight [63, 64].

NAC and liver diseases: need for large-scale studies

In the 1990s small open clinical trials indicated that intravenous NAC improved haemodynamics and oxygen transport in acute liver failure of various origins, and NAC came into widespread use in intensive care units for hepatic diseases. However, conclusive evidence of its efficacy is still lacking [65]. Small trials on NAC in liver transplantation have also yielded inconclusive results, and one study even suggests that the 'standard' high dose of NAC induces a net protein catabolism in the liver [66]. NAC is not included in a recent comprehensive review on protective strategies against ischaemic liver injury [10]. A small pilot study of chronic hepatitis C gave a promise that the addition of NAC to conventional therapy with interferon-α might make the treatment more effective, but a larger multicentre trial in Spain and Italy came to the opposite conclusion [67]. However, according to another Italian study combination therapy would be of benefit [68]. The dosage of NAC was 1.8 and 2.4 g daily, respectively, and treatment time was 6 months in both studies.

Point of dispute: NAC in the protection of the kidney

Many drugs have been tested with the aim of preventing radiocontrast-induced nephropathy, and in 2000, NAC was 'discovered' for this purpose [69]. This study has spawned numerous others, but they have yielded highly contrasting results, from dramatically positive to totally ineffective. The largest study until now was terminated early by the Monitoring Committee because of apparent futility of intravenous NAC treatment [70] and, in addition, one study suggests that NAC would not affect real renal function but only the serum creatinine value, because it had no simultaneous effect on cystatin C levels, a new marker of renal function [71].

NAC has, however, rapidly become widely used for kidney protection [44]. On this topic, several meta-analyses or systematic reviews have also been published; some concluded that NAC, when added to conventional hydration, decreases the risk of radiocontrast nephropathy in patients with chronic renal failure, the others that at present the results are too inconclusive for NAC to be recommended for routine use [69, 72–76]. Generally, contrast nephropathy is defined as a rise in serum creatinine of 44 μmol l^{-1} or 25% from baseline, clinically so modest that the value of avoiding this was recently questioned [77]. The preventive effect of NAC on clinically 'hard' end points (morbidity, mortality, need for chronic dialysis) has not been studied. In one study NAC decreased the duration of hospitalization, while another study showed that NAC therapy did not decrease the incidence of in-hospital adverse clinical events or the duration of hospital stay, and a recent study indicated that, although high-dose NAC prevented periprocedural nephropathy, this benefit did not translate into an overall decrease in adverse outcomes over 9 months [69, 77].

How to explain this puzzling controversy? The populations studied have been heterogeneous in respect of the risk of developing nephropathy, there have been differences in the dose and mode of administering NAC, and even the formulations of NAC have differed on different continents [44, 77]. At present, a common opinion is that ultimately only a randomized controlled trial with sufficient statistical power would settle the dispute. However, several authors, even on the basis of existing knowledge, have recommended the use of NAC for the prevention of contrast nephropathy (in addition of hydration) because 'there is no other effective treatment', NAC is inexpensive, safe and well tolerated [44]. However, NAC may cause adverse reactions and (very seldom) even fatal anaphylaxis [77]. The administration protocol in the initial NAC study [69], 600 mg orally twice daily on the day before and on the day of the procedure, might be reasonable, but recently other protocols have also been suggested (double dose, abbreviated higher dose and high-dose regimens) [44, 69, 77, 78].

Hyperhomocysteinaemia, a controversial risk factor of cardiovascular disease, occurs in dialysis patients almost without exception, and it resists conventional vitamin B therapy. NAC treatment did not work either, and a 1200-mg oral dose of NAC taken before dialysis session did not accentuate the homocysteine level reduction that normally occurs during dialysis, but NAC administered intravenously during dialysis normalized the homocysteine level, which was accompanied by improved pulse pressure and endothelial function [69]. This same research group has shown that treatment with NAC reduced cardiovascular events in haemodialysis patients, but it had no effect on total or cardiovascular mortality [69]. NAC might be of benefit also in the treatment of hepatorenal syndrome, but the evidence is based only on case reports [79].

NAC and cancer: a big disappointment

EUROSCAN, a large randomized intervention trial, was designed to determine whether vitamin A and NAC could prevent tumour recurrence or the occurrence of second primary tumours in patients with head and neck or lung cancer. NAC was administered at 600 mg daily for 2 years. In contrast to expectations, neither of the antioxidants was of any benefit, at least not during the first 2-year follow-up period [80]. The group of Mantovani from Italy has performed studies on maintenance treatment of cancer with a combination of drugs including NAC 1800 mg daily. The treatment has had positive effects on oxidative stress and on the elevated concentrations of inflammatory markers in patients with advanced cancer [49]. A small study suggested that in allogeneic stem cell transplantation, NAC might protect against busulfan-induced liver damage, possibly potentiated by the following high doses of cyclophosphamide. It was safe and did not have interactions with busulfan [81].

NAC in cardiovascular diseases: flagging enthusiasm

NAC has interested cardiologists for 10 years or even longer (Table 3) and it has shown some efficacy, mainly in small trials [82]. As a disulphide bond-reducing agent NAC was thought to have some effect on lipoprotein(a) formation [83]. Horowitz's group's interest in NAC seems to have weakened, and Sochman's zest has apparently met with little response (Table 3) [82]. NAC potentiated, perhaps by a nitric oxide-dependent mechanism, the antihypertensive effect of ACE inhibitors (capto- or enalapril) in smokers (who probably have endothelial dysfunction) with a dose of 1800 mg daily [69].

Cardiovascular surgery and intensive care: new interest

Recently, small studies with positive results have been published on NAC in surgery with cardiopulmonary bypass (Table 4).

Studies on NAC therapy in critically ill patients have yielded conflicting results. Some authors have suggested that the effects of NAC might be favourable for certain mechanisms of disease (e.g. ischaemia-reperfusion, endothelial cell activation), for others (infection) these might be detrimental (Table 5) [87]. It has also been suggested that the beneficial effect of NAC is limited to prophylactic administration. However, in a study in which extensive abdominal surgery was used as a model for imminent multiple organ failure, even prophylactic NAC proved to be rather ineffective [6]. Two recent studies totally reject the benefits of NAC in severe sepsis (Table 5) [89, 90].

Intoxications and miscellanous diseases

NAC therapy in paracetamol intoxications is standard clinical practice [15]. NAC has been of benefit also in the prevention of liver injury caused by the mushroom *Amanita phalloides*, and it might be useful in many other intoxications and adverse effects of drugs, caused by electrophilic intermediates, but no adequate studies are available to support such uses of NAC [91]. Many small trials have been performed on NAC in the treatment of diseases that have no conventional therapy (Table 6). *In vitro*, the anti-inflammatory actions of methotrexate are critically dependent upon the production of ROS; thus, although NAC therapy has been

Table 3
NAC in cardiology

Disease	Dose of NAC	Results
High plasma lipoprotein(a) concentration	(1) Orally 2 g day^{-1} 4 weeks→ 4 g day^{-1} 4 weeks (2) Orally 4 g day^{-1} 2 weeks	(1) Concentration reduction of 70% [83] (2) No effect on lipoprotein(a), reduction of homocysteine levels [82]
Unstable angina pectoris, conventional therapy	(1) i.v.i. 5 g 6 hourly + i.v.i. NG (2) Orally 600 mg three times daily + transdermal NG, 4 months	(1) Fewer infarcts, but severe hypotension [82] (2) Fewer cardiac events, but intolerable headache [82]
Acute myocardial infarction	i.v.i. 15 g per 24 h	Decreased level of oxidative stress, more rapid reperfusion, better left ventricular preservation [82]
Acute myocardial infarction	i.v.i. 100 mg kg^{-1}	Reduced infarct size, better preservation of global and regional left ventricular function, rudimentary R wave or R wave recovery in left precordial leads [82]
Angina pectoris, normal left ventricular function	i.v.i. bolus 2 g, then 5 mg kg^{-1} h^{-1}	NAC attenuated tolerance development to continuous NG infusion [12]
Chronic heart failure	(1) Orally 200 mg kg^{-1} + i.v.i. NG (2) i.v.i. 100 mg kg^{-1} per 30 min + ISDNi	(1) NG tolerance partly disappeared [82] (2) Haemodynamic effects of ISDNi potentiated [82]
Viral myocarditis, case report	i.v.i. 150 mg kg^{-1} per 15 min, 6.25 mg kg^{-1} h^{-1}	Positive inotropic effect [82]
Cardiac catheterization in patients with or without atherosclerosis	i.a. 48 mg min^{-1}	Coronary and peripheral endothelium-dependent vasodilation improved [82]

NG, Nitroglycerine; ISDNi, isosorbidedinitrate.

Table 4
NAC in cardiac surgery

Operation with CPB	Dose of NAC	Results
Elective CABG	i.v.i. 100 mg kg^{-1} 1 h before, 40 mg kg^{-1} day^{-1} after CPB	Improvement of systemic oxygenation [84]
Cardiac surgery	Combination of antioxidants including NAC	Protection of pulmonary endothelial function [85]
Coronary artery surgery	100 mg kg^{-1} into cardiopulmonary bypass prime, then infusion at 20 mg kg^{-1} h^{-1}	Attenuation of myocardial oxidative stress [27]
Cardiac surgery	As above	Myocardial apoptosis signal cascade induced by cardioplegic arrest effectively prevented [27]
CABG	i.v.i. 50 mg kg^{-1} 3 days	Decrease of pump-induced oxidoinflammatory response during CPB [86]

CPB, Cardiopulmonary bypass; CABG, coronary artery bypass grafting.

suggested for rheumatoid arthritis, it should not be prescribed to patients taking methotrexate [3, 103].

After this: what is the answer?

In animal studies NAC works 'as it should', and it has been 'promising' also in numerous small clinical trials for a variety of indications, but often, when the studies have been repeated, the results have been conflicting. The dosage of NAC used has been extremely variable, e.g. in 'EUROSCAN' the dose was quite small compared with many other, more recent studies. The large-scale study 'BRONCUS' gave a disappointing negative result, but it does not exclude better efficacy at higher doses. An equivalent study would be needed to provide

Table 5
NAC in critically ill patients

Disease	Dose of NAC	Results
Intensive care	i.v.i.bolus 150 mg kg^{-1}, then 12 mg kg^{-1} h^{-1}	Initiation of treatment >24 h after hospital admission may potentially be harmful, earlier application may be beneficial, but insignificant difference in mortality [6]
Major abdominal tumour surgery	i.v.i.bolus 150 mg kg^{-1}, then 12 mg kg^{-1} h^{-1} before and during operation	CRP levels decreased, no attenuation of other inflammatory response; no effect on organ dysfunction parameters, length of intensive care stay, days of mechanical ventilation or mortality [6, 88]
Sepsis/systemic inflammatory response syndrome or multiple trauma	i.v.i., increase of dose daily from 6 to 18 g, 4 days, controls 900 mg day^{-1}	Significantly improved phagocytosis activity, significantly reduced morphonuclear burst activity [87]
Septic shock	i.v.i.150 mg kg^{-1} 15 min, then 12.5 mg kg^{-1} h^{-1}	Transient improvement in tissue oxygenation in about half of patients, in whom higher survival rate, in whole population no benefit; hepatosplanchnic flow and liver function improved [69, 89]
Sepsis	i.v.i.150 mg kg^{-1} 15 min, then 50 mg kg^{-1} 4 h, then 50 mg kg^{-1} 24 h	NF-κB and IL-8 decreased, no effect on IL-6 and ICAM-1 [89]
Severe sepsis	i.v.i. bolus 150 mg kg^{-1} 5 min, then 12.5 mg kg^{-1} h^{-1} 6 h	No effect on cytokine levels, patient outcome, or gastric intramucosal pH [89]
Severe sepsis	i.v.i. 50 mg kg^{-1} 4 h, then 100 mg kg^{-1} per 24 h for 44 h	No effect on microalbuminuria, even aggravation of sepsis-induced organ (particularly cardiovascular) failure [90]

CRP, C-reactive protein; NF, nuclear factor; ICAM, intercellular adhesion molecule; IL, interleukin.

Table 6
NAC in miscellaneous diseases

Disease	Dose of NAC	Results
Amyotrophic lateral sclerosis	Subcutaneously 50 mg kg^{-1} day^{-1}, 12 months	No benefit [92]
Probable Alzheimer's disease	50 mg kg^{-1} day^{-1}, 6 months	Seemed to be useful, but significant difference only for subset of cognitive tasks [93]
Complex regional pain syndrome (reflex dystrophy)	600 mg three times daily, 17 weeks	NAC about as good as dimethylsulfoxide ointment [94]
Recurrent otitis media with effusion	Topical NAC instillation	Of benefit in many parameters [95]
Type 2 diabetes without obesity	1200 mg day^{-1}	Elevated adhesion molecule levels decreased [2]
Polycystic ovary syndrome	1.8 g, in some very obese 3 g day^{-1}, 5–6 weeks	Improvement of insulin sensitivity in hyperinsulinaemic patients [96]
Dense cell formation in sickle cell disease	2.4 g day^{-1}	Favourable effects [97]
Lamellar ichtyosis, case report	Topical	Outstanding improvement [98]
Sjögren's syndrome	200 mg three times daily, 4 weeks	Particularly ocular symptoms improved [99]
Raynaud's phenomenon (RP) secondary to systemic sclerosis	i.v.i. bolus, then 15 mg kg^{-1} h^{-1}, 5 days	RP attacks decreased significantly, safe [100]
Chronic blepharitis	100 mg three times daily	Beneficial [101]
Frail geriatric patients	1.8 g day^{-1}, 6 weeks	Muscular strength increased, plasma TNF-α level decreased [93]
Nevirapine-induced toxic epidermal necrolysis and hepatitis; case report	NAC + i.v.i. immunoglobulin	Exceptionally fast recovery [102]

TNF, Ttumour necrosis factor.

a conclusive assessment of the benefits of NAC in the prevention of radiocontrast nephropathy. If NAC is to be used on a large scale for this purpose on the basis of present knowledge it may remain an eternal enigma whether it is really effective – the same thing that is in danger of happening to NAC therapy in liver failure and HIV infections. Accordingly, the authors of a recent systematic review and meta-analysis consider as premature the recommendation of using NAC for the prevention of contrast nephropathy [72, 76]. The small trials of Tepel's group (that originally discovered NAC in contrast nephropathy) raise hopes about NAC being of benefit also in other types of renal failure but, of course, a large-scale 'UREMICUS' study would be needed for convincing evidence. Taking all the evidence together, it seems that in the clinical setting, NAC has so far not fulfilled the impressive promises that theory and experimental research have put forward, thus it seems to share the destiny of other antioxidants.

Competing interests: None to declare.

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