INTRODUCTION

Contrast-induced nephropathy (CIN) remains one of the most clinically important complications of the use of iodinated contrast medium (1-5). Generally, it is defined as an acute impairment of renal function manifested by an absolute increase in the serum creatinine concentration of at least 0.5 mg/dL (44.2 μmol/L) or by a relative increase of at least 25 percent from the baseline value after 24-48 hours from the administration of contrast media (6-10).

CIN extends hospitalization and increases the incidence of morbidity and mortality with increased medical care consumption (11). Renal function degrades due to increased glomerular sclerosis with age and intimal thickening in the renal arteries (12). Elderly adults administered contrast media are at higher risk of CIN. The reason for high risk is believed to be multifactorial, including an age-related reduction in tubular function, glomerular filtration rate, as well as more difficult vascular access requiring a greater amount of contrast, presence of multivessel disease, and comorbidities. A few studies showed that age older than 70 years is an independent predictor of CIN in multivariate analysis (13-15).

A novel oxidative stress marker in contrast-induced nephropathy; can dynamic thiol/disulfide homeostasis be a predictive marker for elderly patients?

Abstract

Aim: The aim of this study was to examine if dynamic thiol/disulfide homeostasis is a predictive marker for contrast-induced nephropathy for the first time in literature. Also, we aimed to investigate effecting factors for contrast-induced nephropathy in hospitalized elderly patients.

Materials and methods: A total of 39 patients who administered contrast media were included in the study; 9 developed contrast-induced nephropathy after the intervention, and the other 30 did not develop; matched for age, gender, and baseline-48 hour creatinine and native thiol, total thiol, disulfide values were recorded. Additionally, antioxidant parameters were compared with other clinical parameters within a comprehensive geriatric assessment.

Results: In the contrast-induced nephropathy (CIN) group, native and total thiol levels decreased, and disulfide levels increased at 48 hours, but it was not statistically significant. Patients with CIN had a significantly higher level of neutrophil-to-lymphocyte ratio (p=0.032) than non-CIN patients. Serum albumin, folic acid, Katz Activities of Daily Living (ADL) score, and Mini Nutritional Assessment (MNA) score levels correlated with serum native thiol values in all patients, and a significant inverse correlation was found between native thiol and C-reactive protein and ferritin. Total thiol levels correlated with lymphocyte count, albumin, Katz ADL score, and MNA score in all patients, and there was a significant inverse correlation between total thiol and CRP value.

Conclusions: This study demonstrated that antioxidant reserve is reduced by acute inflammation and induced by nutrition and functionality in elderly patients. In the light of this study relationship between antioxidant status and CIN can be examined in the elderly in further large, prospective, multicenter studies.

Keywords: Contrast-induced nephropathy, elderly, oxidative stress, antioxidants
The pathogenesis of CIN is not well known, but there is little evidence that it occurs as a combination of oxidative stress, direct toxicity to the renal tubular epithelium, ischemic injury, and renal tubular obstruction (16-18). Contrast media exposure causes oxidative stress as a result of renal medullary hypoxia and excessive reactive oxygen radicals production. Reactive oxygen radicals imbalance induces lipid peroxidation and changes antioxidant enzyme activities, so cytotoxic damage occurs (19).

Thiols are a class of organic compounds that contain a sulfhydryl group, which is composed of one hydrogen and one sulfur atom attached to a carbon atom. Plasma thiol pool is formed mainly by albumin and protein thiols and, to a lesser extent, by low-molecular-weight thiols such as cysteinyl glycine and cysteine (Cys), glutathione, homocysteine, and γ-glutamylcysteine (20). Thiols get oxidized by reactive oxygen radicals and form disulfide bonds. Also, the formed disulfide bonds can again be reduced to thiol groups by a number of antioxidants; therefore, thiol/disulfide homeostasis is maintained (21). Thiol-disulfide homeostasis has been measured since 1979 in only one direction, but with the novel method, the levels of both variables can be measured separately as well as individually and collectively (22).

The aim of this study was to investigate a novel, easily calculated, readily available, and relatively cheap oxidative stress marker, thiol/disulfide homeostasis, and geriatric assessment in patients with CIN and compare the results with non-CIN patients.

MATERIAL AND METHODS

Study Population

Patients hospitalized for elective reasons (elevated sedimentation rate, unexplained abdominal pain, suspicion of malignancy, suspicion of pulmonary embolism) and administered contrast media between January and October 2016 were selected. Patients with creatinine levels above 1.2 mg/dL, severe congestive heart failure, administered contrast medium less than one week before the procedure; allergy to iodinated contrast medium, with severe infection or sepsis were excluded from the study. Twenty-eight patients who administered contrast media were excluded from the study because of the insufficient match of study criteria. Additionally, some drugs like metformin, diuretic, nonsteroidal anti-inflammatory drugs, and angiotensin receptor blockers were discontinued two days before and after contrast administration. We used a preset diluted contrast solution containing 10 mL of iopamidol 300 mg/mL contrast medium for all patients. Laboratory and clinical parameters of all patients investigated within comprehensive geriatric assessment were included in the study. All patients were hydrated with normal intravenous saline at 1 mL/kg/h for 12 hours before and 12 hours after administration of contrast media, and all patients received N-acetyl cysteine 600mg effervescent tablet before administration. A 25% increase in the glomerular filtration rate after 48 hours of contrast administration was considered contrast-induced nephropathy.

Serum thiol/disulfide homeostasis

Blood samples were collected before contrast administration and after 48 hours of contrast administration to evaluate thiol/disulfide homeostasis. Collected samples were immediately centrifuged at 1500 rpm for 10 minutes to separate the plasma and serum, and the serum was stored at -80 °C until analysis. Thiol/disulfide homeostasis was determined as described previously (22). In the first step of the assay, reducible disulfide bonds were reduced to compose free functional thiol groups. Unused reductant sodium borohydride (NaBH4) was used up and extracted with formaldehyde, and all thiol groups containing native and reduced ones were determined after reaction with 5, 5′-dithiobis-(2-nitrobenzoic) acid (DTNB). Half of the difference between assay pairs gave disulfide amounts which were calculated automatically (23).

Comprehensive Geriatric Assessment

We performed mini nutritional assessment (MNA), and Katz Index of Independence in Activities of Daily Living (ADL) tests on all participants that we used routinely to evaluate nutrition and functionalities. Katz's ADL includes information about six activities; dressing, toileting, transferring, continence, bathing, and feeding. Participants scored yes/no for independence in each of the six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and two or less indicates severe functional impairment (24). Nutritional risk was assessed using the Short Form Mini Nutritional Assessment (MNA-SF), which comprises six items that assess decline in food intake, weight loss, mobility, psychological stress, neuropsychological problems, and the body mass index. According to the MNA-SF, elderly individuals were classified into three categories, adequate nutritional status (14 to 12 points), at risk for malnutrition (11 to 8 points), and malnutrition (7 to 0 points) (25).

Statistical analyses

Statistical analysis was performed using Statistical Package for Social Sciences Statistics for Windows version 22 (SPSS Inc. Chicago, IL). Quantitative data were given as mean ± SD or medians (interquartile ranges, IQR). Normal distribution and differences between variances were determined using the Kolmogorov–Smirnov and Levene tests, respectively. For comparisons between the two groups, Student's t-test and Mann–Whitney's U-test and Wilcoxon signed rank test were used as appropriate. Categorical variables were compared with χ2 and Fisher's exact χ2 tests. Spearman correlation test was performed between the variables. p-value <.05 was considered statistically significant.

Ankara University Faculty of Medicine’s Local Ethics Committee approved the study protocol, and all participants provided their written informed consent.
RESULTS

Two groups, CIN, and non-CIN groups included 9 (23%) and 30 (77%) patients, respectively. The demographic and clinical characteristics of the groups are shown in Table 1. Gender (p = 0.711), age (p = 0.583), number of disease (p = 0.235), diabetes mellitus (p = 0.266) (DM), hypertension (p = 0.266), number of drugs (p = 0.313) of the CIN and non-CIN groups were not different statistically significant.

The comparison of antioxidant levels and laboratory and clinical parameters of the two groups at baseline are shown in Table 2. Native thiol, total thiol and disulfide levels, median age, hemoglobin, median lymphocyte, total protein level, albumin level, sedimentation rate, 25-Hydroxy D vitamin level, CRP level, cobalamin level, folic acid level, ferritin level, and MNA score were not different significantly. The median neutrophil/lymphocyte ratio was higher in patients with CIN when compared with non-CIN patients (4.15 vs. 1.81, p=0.032).

Furthermore, we correlated that total thiol levels of the CIN group at 0-hour decreased with increasing creatinine levels (r=-0.682, p=0.043). Native thiol levels of all patients at 0-hour, increased with increasing albumin (r=0.660, p<0.001), folic acid (r=0.326, p=0.043), Katz ADL score (r=0.363, p=0.025) MNA score (r=0.461, p=0.004), and native thiol levels decrease with increasing CRP (r=-0.497, p<0.001) and ferritin level (r=-0.459, p=0.003). Total thiol levels of all patients at 0-hour, increased with increasing lymphocyte count (r=0.387, p=0.015), albumin (r=0.706, p<0.001), Katz ADL score (r=0.361, p=0.026), MNA score (r=0.508, p=0.001) and total thiol levels decreased with increasing neutrophil count (r=-0.359, p=0.025), CRP level (r=-0.438, p=0.006). Disulfide levels of all patients at 0-hour increased with increasing ferritin levels (r=0.385, p=0.015) and decreased with increasing cobalamin levels (r=-0.436, p=0.006). Thiol/disulfide parameters and their correlation with laboratory parameters and clinical findings are shown in Table 3.

Patients called for laboratory control to the outpatient clinic after 1-3 months from contrast administration. All patients developed late acute renal failure diagnosed with diabetes mellitus. Clinical and laboratory characteristics of patients who developed late acute renal failure are shown in Table 4.

In the CIN group, native and total thiol levels decreased, and disulfide levels increased at 48 hours, but it was not statistically significant. 0 and 48 hours Thiol/disulfide levels of CIN group patients were shown in Table 5.

| Table 1. Demographic characteristics and laboratory findings of the study population |
|------------------------------------------|------------------------------------------|------------------------------------------|
| Gender                                   | CIN n (%)                                | Non-CIN n (%)                            |
| Female, n (%)                            | 5 (20.8%)                                | 19 (79.2%)                               |
| Male, n (%)                              | 4 (26.6%)                                | 11 (73.4%)                               |
| Age, mean±SD (minimum-maximum)           | 76.96±6.74 (62-90)                       | 75.55±6.54 (68-88)                       |
| Number of disease, n (%)                 | ≤2, 3 (18.7%)                            | 13 (81.3%)                               |
|                                         | >2, 6 (26%)                              | 17 (74%)                                 |
| Diabetes mellitus                        | 5 (33.3%)                                | 10 (66.7%)                               |
| Hypertension, n (%)                      | +, 4 (16.6%)                             | 20 (83.4%)                               |
|                                         | -, 5 (33.3%)                             | 10 (66.7%)                               |
| Number of drugs, n (%)                   | 0, 2 (66.6%)                             | 1 (33.4%)                                |
|                                         | ≤4, 3 (17.6%)                            | 14 (82.4%)                               |
|                                         | >4, 4 (21%)                              | 15 (79%)                                 |
| Prophylaxis, n (%)                       | +, 8 (22.8%)                             | 27 (77.2%)                               |
|                                         | -, 1 (33.3%)                             | 3 (66.7%)                                |
| SD: Standart deviation                   |                                         |                                         |
Table 2. The comparison of antioxidant levels, laboratory and clinical parameters of two groups at baseline

| Variables                        | Non-CIN, n=30 median (q1-q3) | CIN, n=9 median (q1-q3) | P     |
|----------------------------------|------------------------------|-------------------------|-------|
| Native thiol, μmol/L             | 248.20 (194.45-296.70)       | 274.90 (221.15-344.50)  | 0.205 |
| Total thiol, μmol/L              | 289.70 (239.05-333.07)       | 302.60 (258.25-372.40)  | 0.334 |
| Disulphide, μmol/L               | 20.35 (13.36-25.38)          | 13.85 (12.27-24.02)     | 0.463 |
| Creatinine, mg/dL                | 0.88 (0.70-1.15)             | 0.82 (0.54-0.96)        | 0.193 |
| 0-hour                           | 70 (58-85.5)                 | 86 (65.5-90)            | 0.174 |
| GFR, mL/min                      | 11 (9.77-12.32)              | 11.90 (10.40-13.90)     | 0.166 |
| Hemoglobin, g/dL                 | 3.75 (1.81-5.77)             | 5.45 (4.15-9.67)        | 0.250 |
| Neutrophyl, x10⁹/ L              | 1.10 (0.90-1.70)             | 0.97 (0.80-1.10)        | 0.095 |
| Lymphocyte, x10⁹/ L              | 3.75 (1.81-5.76)             | 5.45 (4.15-9.67)        | 0.032*|
| Neutrophile/lymphocyte           | 6.50 (6.20-7.109)            | 6.90 (6.40-7.60)        | 0.210 |
| Total protein, g/dL              | 3.80 (3.25-4.0)              | 3.70 (3.45-4.15)        | 0.628 |
| Albumin, g/dL                    | 40 (14-68)                   | 26 (13-33)              | 0.173 |
| Sedimentation, mm/h              | 17.50 (10.9-33.8)            | 7.6 (6.10-36.75)        | 0.257 |
| 25-hydroxy D vitamin, μG/L       | 14.60 (2.65-54.50)           | 30 (7.50-53)            | 0.718 |
| CRP, mg/L                        | 416 (279.5-643)              | 300 (176.50-429.50)     | 0.131 |
| Cobalamin, pg/mL                 | 5.95 (4.87-8.77)             | 7.90 (4.55-12.20)       | 0.243 |
| Folic asid, ng/mL                | 61 (29.20-282.50)            | 27.90 (12-89.50)        | 0.172 |
| Ferritin, ng/mL                  | 11 (10-12.50)                | 9 (8.25-11.50)          | 0.060 |
| MNA                              | 1 (33.3%)                    | 3 (66.7%)               |       |

GFR: Glomerular filtration rate, CRP: C-reactive protein, MNA: Mini nutritional assessment
Parameters were expressed median (Q1-Q3)
*p<0.05 was considered significant for statistical analyses

Table 3. Thiol/disulphide parameters and their correlation with laboratory parameters and clinical findings

| rs     | RRC   | GFR   | Neutrophile | Lymphocyte | Albumin | CRP    | Ferritin | Cobalamin | Folic asid | Katz ADL | MNA     |
|--------|-------|-------|-------------|------------|---------|--------|----------|-----------|-----------|----------|---------|
|        | P     |       |             |            |         |        |          |           |           |          |         |
| Native thiol | -0.600 | 0.117 | -0.281      | 0.315      | 0.660   | -0.497 | -0.459   | 0.191     | 0.326     | 0.363    | 0.461   |
|        | 0.088 | 0.477 | 0.083       | 0.051      | p<0.001*| 0.001* | 0.003*   | 0.251     | 0.043*    | 0.025*   | 0.004*   |
|        | 9     | 39    | 39          | 39         | 38      | 39     | 38       | 39         | 39        | 38       | 38      |
| Total thiol | -0.700 | 0.183 | -0.359      | 0.387      | 0.706   | -0.438 | -0.315   | 0.077     | 0.258     | 0.361    | 0.508   |
|        | 0.036*| 0.266 | 0.025*      | 0.015*     | p<0.01* | 0.006* | 0.051    | 0.646     | 0.113     | 0.026*   | 0.001*  |
|        | 9     | 39    | 39          | 39         | 38      | 39     | 39       | 39         | 39        | 38       | 38      |
| Disulphide | -0.283 | 0.254 | -0.160      | 0.228      | 0.144   | 0.172  | 0.385    | -0.436    | -0.160    | -0.159   | 0.056   |
|        | 0.460 | 0.118 | 0.331       | 0.162      | 0.381   | 0.301  | 0.015*   | 0.006*    | 0.330     | 0.341    | 0.739   |
|        | 9     | 39    | 39          | 39         | 38      | 39     | 39       | 39         | 38        | 38       | 38      |

RRC: Rise ratio of creatinine, GFR: Glomeruler filtration rate, CRP: C-reactive protein, MNA: Mini nutritional assessment, Katz ADL: Katz activities of daily living *p<0.05 was considered significant for statistical analyses
DISCUSSION

To the best of our knowledge, this is the first study that investigated thiol/disulfide homeostasis as a novel marker of oxidative stress in patients with CIN and compared the results with non-CIN patients. Our results demonstrated that measurable antioxidant reserve (native thiol, total thiol levels) is reduced by acute inflammation and induced by nutrition and functionality in elderly patients.

We found that 23% of patients developed CIN in our study. Although the incidence of CIN varies between 0.6% and 2.3% in the general population (26), the incidence of CIN was found at 38.46% in elderly patients with critical illnesses, and stable renal function after contrast-enhanced CT scans in another study (27). Furthermore, in a meta-analysis with 49 randomized controlled trials, the incidence of CIN was 12.16%, and the incidence interval varied from 4.9% to 27.7% (28). The reason for high CIN incidence in our study should be that older hospitalized patients have several risk factors like decreased baseline renal function, heart failure, diabetes, dehydration, hypotension, and older age.

We investigated that the neutrophil-to-lymphocyte ratio (NLR) was significantly higher in the CIN group than in the non-CIN group. In a study, increased NLR was observed to be an independent predictor of CIN in patients with ST-elevation myocardial infarction who underwent coronary intervention (29). It is shown that ischemia-reperfusion, sepsis-endotoxemia, and nephrotoxic models act in acute kidney injury pathogenesis. When there are morphological and/or functional changes in vascular endothelial cells, leukocytes, including neutrophils, macrophages, natural killer cells, and lymphocytes, infiltrate into the injured kidneys (30). First, neutrophils adhere to the vascular endothelium in the extravasation of these cells into injured tissue. After adherence and chemotaxis, infiltrating neutrophils can release reactive oxygen species that damage the tubular cells (31). Activation of neutrophils increases cytokine release, reactive oxygen species, proteases, elastases, and many enzymes, which degrade endothelial function by increasing vascular permeability (32, 33). As a result of cell damage, oxygen free radicals occurs, and inflammatory reactions are activated; then leukocytes, including neutrophils, macrophages, and natural killer cells, infiltrate the injured kidneys. Because of this intense

| Table 4. Clinical and laboratory characteristics of patients developed late ARF |
|-----------------------------|-----------------------------|
| 84 y,F (DM, HT, HF, MM)     | 0.98-0.87                  |
| 64, M (DM, migraine, hypothyroidism) | 1.2-1.1               |
| 76, M (DM, PTE, HF, COPD)   | 1.03-1.31                  |
| DM: Diabetes mellitus, HT: Hypertension, HF: Heart failure, MM: Multiple myelome, PTE: Pulmonary tromboembolism, COPD: Chronic obstructive pulmonary disease |

| Table 5. 0 and 48 hours Thiol/disulphide levels of CIN group patients |
|-----------------------------|-----------------------------|
| CIN + (n:9)                 | 0.hour (n:9)                |
| Native thiol,               | 48.hour (n:9)              |
| Median                      | 274.90                      |
| (Min.-max.)                 | (209.20-365.30)             |
| Total thiol,                | 302.60                      |
| (Min.-max.)                 | (235.80-392.50)             |
| Disulphide,                 | 13.85                       |
| (Min.-max.)                 | (10.15-26.95)               |
| CIN: Contrast induced nephropathy |

We investigated that the neutrophil-to-lymphocyte ratio (NLR) was significantly higher in the CIN group than in the non-CIN group. In a study, increased NLR was observed to be an independent predictor of CIN in patients with ST-elevation myocardial infarction who underwent coronary intervention (29). It is shown that ischemia-reperfusion, sepsis-endotoxemia, and nephrotoxic models act in acute kidney injury pathogenesis. When there are morphological and/or functional changes in vascular endothelial cells, leukocytes, including neutrophils, macrophages, natural killer cells, and lymphocytes, infiltrate into the injured kidneys (30). First, neutrophils adhere to the vascular endothelium in the extravasation of these cells into injured tissue. After adherence and chemotaxis, infiltrating neutrophils can release reactive oxygen species that damage the tubular cells (31). Activation of neutrophils increases cytokine release, reactive oxygen species, proteases, elastases, and many enzymes, which degrade endothelial function by increasing vascular permeability (32, 33). As a result of cell damage, oxygen free radicals occurs, and inflammatory reactions are activated; then leukocytes, including neutrophils, macrophages, and natural killer cells, infiltrate the injured kidneys. Because of this intense
inflammation answer; the neutrophil-lymphocyte ratio increases. The plasma thiol pool is formed mainly by albumin and protein thiols (20). In a study, it was shown that response to oxidative stress of human albumin is closely related to its antioxidant capacity, decreases with a reduction in the filtration rate and advancing stages of diabetic nephropathy as a consequence of the oxidation of thiol groups (34). Also, in our study, there was a stronger correlation between albumin and thiols. In this context, the reduction of albumin production due to nutritional deficiency and acute inflammation also reduces the level of available antioxidant levels.

Our results indicated a positive correlation between native thiol and albumin, folic acid, and MNA score; a negative correlation between native thiol and CRP level, and ferritin level. Also, there is a positive correlation between total thiol and albumin, lymphocyte, MNA score, and a negative correlation between total thiol and neutrophil, CRP level. According to these results, it seems that antioxidant reserve decreases with acute inflammation and increases with nutrition in elderly patients. Also, the significant positive correlation between Katz ADL score and both native and total thiol; suggests that the antioxidant reserve is related to functionality and requires further study.

The limitation of our study is that it is a prospective, observational study and relatively had a small sample size, and is based on patients who were enrolled from a single center. Additionally, because ethics committee approval was for six months, the sample size could not be increased. Although the small sample size of patients, it is substantially important that the neutrophile/lymphocyte ratio may be a cut-off value for CIN in older patients, and also this study demonstrated that antioxidant reserve induces by nutrition and functionality in elderly patients for the first time in the literature.

Developing acute renal failure in 3 patients after weeks from contrast administration suggests that patients, especially those with diabetes mellitus, should be followed up for a long time than two days.

CONCLUSION

We hypothesized that CIN would be associated with the antioxidant reserve in hospitalized older patients. As a result, in the present study, we could not find an association between thiol/disulfide level and CIN, but we found a significant association between NLR levels and the development of CIN. Also, this study demonstrated that antioxidant reserve is reduced by acute inflammation and induced by nutrition (MNA) and functionality (Katz ADL) in elderly patients. In the light of this study relationship between antioxidant status and CIN can be examined in the elderly in further large, prospective, multicenter studies.

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The authors declare that they have received no financial support for the study.

Ethical approval
Ankara University Faculty of Medicine’s Local Ethics Comittee approved the study protocol and all participants provided their written informed consents.

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