**Original Research**

# Serum Nuclear Factor Erythroid-2 Related Factor-2 (NRF2) as an Indicator of Oxidative Stress is Related to Coronary in-Stent Restenosis

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**ABSTRACT**

**Objective:** In the treatment of coronary artery disease, stent implantation has become the standard treatment, but development of in-stent restenosis (ISR) limits the benefit of this treatment modality.

**Methods:** Based on the connection between oxidative stress and thiol/disulphate and NRF2, it was intended to measure NRF2 and thiol/disulphate levels.

**Results:** Coronary angiography images of 76 stable angina pectoris patients were evaluated. Of the 51 patients with a history drug eluting stent implantation, we determined 25 patients with ISR (Group 1) and 26 patients without ISR (Group 2). Twenty-five patients with normal coronary arteries were included in the study as control group (Group 3). NRF2 level was found to be significantly higher in patients who did not develop ISR (p=0.01). Total thiol was significantly higher in group 3 (738.76 micromole/L) compared to group 1 (626.11 micromole/L) and group 2 (630.27 micromole/L) (p=0.014). Native thiol was also significantly higher in group 3 (570.53 micromole/L) compared to group 1 (483.91 micromole/L) and group 2 (501 micromole/L)(p=0.006).

**Conclusion:** We think that total and native thiol levels might be useful as an indicator of oxidative stress in early diagnosis of coronary artery disease, and the NRF2 level can be used in predicting patients who might develop coronary ISR.

**Keywords:** NRF2, Thiol/Disulfate, Neointimal Hyperplasia, In-Stent Restenosis

## INTRODUCTION

The severity of remodeling and intimal proliferation in the damaged artery wall with elastic recoil and fibrotic contractions after angioplasty play a role in the pathophysiology of coronary in-stent restenosis (ISR). Neointimal hyperplasia after remodeling and intimal proliferation is a natural response of the endothelium for vascular healing after stent implantation. Some of the previous studies suggested that inflammation and proliferation together with oxidative stress also might play a role in the mechanism of ISR mechanism [1,2].

The disorder in the balance between the production of reactive oxygen species (ROS), free radicals and antioxidant defense mechanisms is called oxidative stress [3-5]. This situation arises as a result of the insufficiency of reactive oxygen species such as superoxide radical, hydrogen peroxide, hydroxyl radical and antioxidant agents that detoxify them.

After oxidative stress, the body's immune system, especially the cytokine cascade, is activated. Serum nuclear factor erythroid-2 related factor-2 (NRF2) is a central regulator of antioxidant response element-associated gene expression and immune response. NRF2 enhances the expression of many antioxidant enzymes [6-8].

Thiols are antioxidant compounds with a sulfhydryl group attached to a carbon atom that prevent any oxidative stress in the body. Free oxygen radicals created during any oxidative stress situation are neutralized via binding by thiols. With oxidative stress, this balance shifts in favor of disulfide and thiols are reduced. As a result of the reaction, free disulfide bonds are created. Thiol groups are accepted as antioxidants and disulfide bonds as oxidants. Thus, dynamic thiol/disulfide balance is provided in the body [9-12].

In this study, considering that the most common cause of coronary ISR is neointimal hyperplasia, we planned to measure serum nuclear factor erythroid-2 related factor 2 (NRF2), thiol and disuphate levels as potential antioxidants, which might play a role in inflammation. This study was planned with the anticipation that these molecules might potentially help in the early diagnosis and therefore possible early treatment of patients who would develop coronary ISR.

## METHODS

In this single-center cross-sectional study, patients who presented to our cardiology clinic with the complaint of stable angina pectoris (CCS II-IV) between January 2020 and December 2020 despite optimal anti-ischemic medications and also had a single drug eluting coronary stent implanted at least 12 months ago were included. Out of 484 patients whose coronary angiography images were investigated, 76 patients were included in the study after evaluation for exclusion criteria. The 76 patients included in the study were divided into 3 groups: patients with 50-100% restenosis in the implanted stent (Group 1, patients with ISR, n=25); patients without ISR (less than 50% stenosis) (Group 2, patients without ISR, n=26) and patients with similar age and atherosclerotic risk profile who have normal coronary arteries on coronary arteriography were included in the study as control group (Group 3, control group, n=25)..Hospital records, epicrisis and coronary angiography images of the patients were examined, and patients who had a single type of stent implanted (everolimus-eluting Promus stent, Boston Scientific, USA) were included in the study.

Patients who had pregnancy, active infection, cancer, rheumatologic and autoimmune diseases were excluded from the study. Patients presenting with acute coronary syndrome, having high troponin values, having more than one coronary stent or drug eluting stents containing different types of antiproliferative drugs, and patients who have implanted bare metal stents were excluded from the study. If the patient was a woman during the menstrual period, she is also excluded from the study. The patients were informed with our written consent form approved by the ethics committee of the institution, and patient consent was obtained.

Two-dimensional coronary angiographies of the patients were evaluated by performing selective left and right coronary arteriography using the Judkins technique. Angiography procedures were performed and evaluated by interventional cardiologists who have coronary angiography and percutaneous coronary intervention experience (>250 cases/year). Coronary arteries were visualized using cranial, caudal, and antero-posterior angulation in right and left anterior oblique positions [13,14].

Stenosis degrees were determined by angiographic images and calibration techniques for the vessels. The stenosis of the detected lesion was measured with the Quantitative Coronary Angiography (QCA) software (Siemens, Erlangen, Germany) with reference to the healthy segment in the proximal and distal part of the lesion (Figure 1). For optimal evaluation of the previously implanted stent, operators paid attention to take images from at least two orthogonal planes. Measurements were taken as the diameter of the artery in such a way that it cuts the vessel cross sectionally through the lumen and the stenosis severity was calculated over the vessel luminal diameter. ISR was defined as greater than 50% diameter of narrowing in the stent or within 5 mm of stent proximal or distal margins. In a study, it was determined that quantitative methods are better than visual calculation in detecting in stent restenosis [15]. Both intra and interobserver variability for in stent restenosis was less than%1. It's If there is diffuse neointimal hyperplasia along the stent, the healthy segment distal to the stent was taken as reference [16-18].
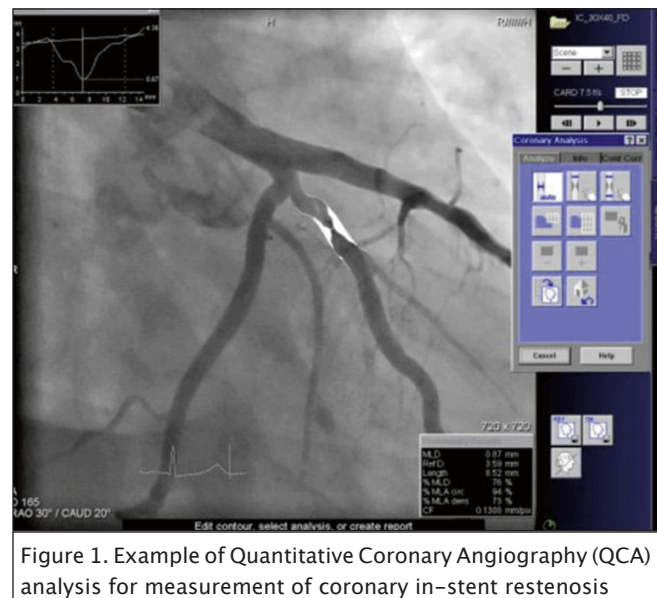


Figure 1. Example of Quantitative Coronary Angiography (QCA) analysis for measurement of coronary in–stent restenosis

Venous blood samples were taken immediately after the angiography procedure from the patients and serum was obtained by centrifugation at 5000 rpm for 10 minutes. It was kept at -80°C until the day of calculation. When the samples were completed, they were taken out of the freezer and kept at room temperature until they melted, and the measurements were made with the same kit. NRF-2, Total Thiol, Native Thiol, Disulfide levels, Total Thiol/Disulfide, Native Thiol/Disulfide and Native Thiol/Total Thiol ratios were measured in the blood samples.

Serum nuclear factor erythroid-2 related factor 2 (NRF2) measurement was made with the human NRF2 ELISA kit coded REF: CK-bio-12691 LOT: 202008 (Shanghai Coon Koon Biotech Co. Ltd). Total thiol measurement was made with the Rel Assay Diagnostics brand kit with the code REF: RL0178 LOT: AS2001T. Native thiol measurement was performed with the Rel Assay Diagnostics brand kit with the code REF: RL0185 LOT: AS2001N. After measuring native and total thiol, disulfide content, disulfide/total thiol ratio (SS/SH + SS), native thiol/total thiol ratio (SH/SH + SS), disulfide/native thiol ratios (SS/SH) were calculated.

### Statistical Analysis

The compatibility of numerical variables to normal distribution was tested by Shaphiro Wilk test. For the comparison of variables

in three groups, ANOVA and LSD tests were used in normal distribution, and Kruskal Wallis and Dunn multiple comparison tests were used in other parameters. Mann-Whitney-U test was used to compare variables that were not normally distributed in two groups. Relationships between categorical variables were tested with Chi-square and Bonferroni tests. SPSS 25.0 (IBM, USA) program was used for the analyzes. p value of <0.05 was accepted significant.

## RESULTS

The demographic characteristics of all patients included in the study are shown in Table 1. As can be appreciated, age, gender characteristics, atherosclerotic risk factors and statin drug use are similar. Coronary artery stents of the patients were selected as the everolimus eluting (Promus, Boston Scientific, USA) drug type. In Table 1, it has been demonstrated that there is no statistically significant difference regarding stent diameter or length between groups 1 and 2 (p>0.05).

Total thiol was significantly higher in group 3 (738.76 micromole/L) compared to group 1 (626.11 micromole/L) and group 2 (630.27 micromole/L)(p=0.01). Native thiol was significantly higher in group 3 (570.53 micromole/L) compared to group 1 (483.91 micromole/L) and group 2 (501 micromole/L)(p= 0.006). There was no significant difference between the groups in terms of Native thiol/Total thiol ratio (p = 0.428)(Table 2).

For disulfide, no significant difference was found between group 1 (71.1 micromole/L), group 2 (64.64 micromole/L) and group

3 (84.11 micromole/L)(p=0.10). Also, there was no significant difference in Native thiol/Disulfide ratio in all three groups (p=0.42). Additionally, there was no significant difference between the three groups in the ratio of Total thiol/Disulfide (p=0.428)(Table. 2).

Total thiol levels were significantly higher in the control group than in group 1 and group 2 (p=0.009 and p=0.013, respectively). No difference was found between group 1 and group 2 in terms of total thiol (p=0.92). Native thiol levels were significantly higher in the control group than group 1 and group 2 (p=0.003 and p=0.015, respectively). No difference was also found between group 1 and group 2 in terms of native thiol (p=0.54)(Table 3). Thiol levels were found to be higher in patients with normal coronary arteries (group 3), as expected.

NRF2 levels were found as 105.97 pg/mL in group 1, 131.53 pg/mL in group 2 and 116.54 pg/ mL in group 3, and a statistically significant difference was also observed (p=0.029)(Table 4). When the groups are compared with each other in terms of NRF2 levels there was a significant difference between the group 1 and 2 (p=0.01)(Table 5).

In our study, the low level of NRF2 in group 1 patients who developed ISR suggests that NRF2 did not prevent neointimal hyperplasia and remodeling sufficiently, but NRF2 was significantly higher in group 2, that NRF2 protects coronary vessels from ISR and neointimal hyperplasia.

**Table 1.** Comparison of the demographic characteristics of all three groups and the sizes of implanted stents for Groups 1 and 2

| | Group 1 (ISR +) | Group 2 (ISR -) | Group 3 (Control) | p |
|---|---|---|---|---|
| | n=25 | n=26 | n=25 | |
| Age (year) | 62.8±7.6 | 64.5±9.9 | 62.5±9.7 | 0.42 |
| Gender (M/F) | 18/7 | 18/8 | 16/9 | 0.82 |
| Diabetes mellitus n(%) | 10 (40) | 8 (30) | 9 (36) | 0.78 |
| Hypertension n(%) | 16 (64) | 15 (57) | 10 (40) | 0.12 |
| Hyperlipidemia n(%) | 20 (80) | 20 (76) | 14 (56) | 0.18 |
| Smoker n(%) | 8 (32) | 10 (38) | 6 (24) | 0.53 |
| Family history n(%) | 10 (40) | 10 (38) | 8 (32) | 0.82 |
| Stent diameter (mm) | 3.15±0.57 | 3.11±0.59 | - | 0.84 |
| Stent length (mm) | 30.9±5.1 | 29.3±4.2 | - | 0.07 |
| Use of statin n(%) | 12 (48) | 13 (50) | 11 (44) | 0.11 |

ISR: in-stent restenosis; M: male; F: female, mm: milimeter

**Table 2.** Comparison of thiol, disulfide levels and their ratios between study groups

|  | Group1 ( ISR+)<br>n=25 | Group2 (ISR-)<br>n=26 | Group3<br>(Control)<br>n=25 | p |
|---|---|---|---|---|
| Total thiol (micromole/L) | 626.11±173.47 | 630.27±111.42 | 738.76±150.16 | 0.01 |
| Native thiol (micromole/L) | 483.91±105.69 | 501.00±87.79 | 570.53±96.49 | 0.006 |
| Disulfide (micromole/L) | 71.10±36.70 | 64.64±22.85 | 84.11±33.21 | 0.10 |
| Native thiol/Disulfide | 10.26±10.08 | 8.57±2.93 | 8.04±4.11 | 0.42 |
| Total thiol/Disulfide | 12.26±10.08 | 10.57±2.93 | 10.04±4.11 | 0.42 |
| Nativ thiol/Total thiol | 0.79±0.07 | 0.8±0.05 | 0.78±0.06 | 0.42 |

ISR: in-stent restenosis

**Table 3.** Comparison of Total Thiol and Native Thiol levels between groups of two

|  |  |  |  |
|---|---|---|---|
| Total thiol (micromole/L) | Group1 | Group2 | 0.922 |
|  |  | Group3 | 0.009 |
|  | Group2 | Group1 | 0.922 |
|  |  | Group3 | 0.013 |
|  | Group3 | Group1 | 0.009 |
|  |  | Group2 | 0.013 |
| Native thiol (micromole/L) | Group1 | Group2 | 0.540 |
|  |  | Group3 | 0.003 |
|  | Group2 | Group1 | 0.540 |
|  |  | Group3 | 0.015 |
|  | Group3 | Group1 | 0.003 |
|  |  | Group2 | 0.015 |

**Table 4.** Comparison of NRF2 value between study groups

|  | Group 1 (ISR +)<br>n=25 | | | Group 2 (ISR -)<br>n=26 | | | Group 3 (Control)<br>n=25 | | | p |
|---|---|---|---|---|---|---|---|---|---|---|
|  | Median | % 25 | % 75 | Median | % 25 | % 75 | Median | % 25 | % 75 | |
| NRF2<br>(pg/mL) | 105.97 | 100.68 | 133.58 | 131.53 | 111.84 | 140.63 | 116.54 | 106.56 | 128.88 | 0.029 |

ISR: in-stent restenosis

**Table 5.** Multiple comparisons between study groups for NRF2 value

| Groups | p |
|---|---|
| Group 1 – Group 3 | 0.48 |
| Group 1 – Group 2 | 0.01 |
| Group 3 – Group 2 | 0.06 |

## DISCUSSION

Coronary stents used in the percutaneous treatment of coronary artery disease are thin strut metal skeletons that are implanted in the stenotic part of the vessel lumen and apply radial force to the intima layer of the vessel and provide luminal opening. Trauma to the vascular wall causes an increase in neointimal hyperplasia and restenosis that develops within the first 6-12 months [19,20]. Since rapamycin analogues (sirolimus, zotarolimus, everolimus, biolimus A9, novolimus and amphilimus) and paclitaxel, which show anti-inflammatory and antiproliferative properties, these drug eluting coronary stents prevent neointimal hyperplasia. Consequently ISR is less common in these patients. In this way, ISR rates have been reduced to 5-10% [21]. However, ISR development still continues to be an issue for daily clinical practice. Inflammation and neointimal proliferation play a role in the ISR mechanism, and it is thought that oxidative stress might also have possible effects for ISR [22].

It is predicted that oxidative stress could be responsible for the pathogenesis of many diseases, especially cancer, diabetes mellitus, cardiovascular and neurological diseases, atherosclerosis and inflammatory disorders [23,24]. Free oxygen radicals occurring in any oxidative stress situation are neutralized via binding by thiols. Thiol groups are considered to be effective as antioxidants, while disulfide bonds are considered to be effective as oxidants.

Abnormal thiol hemostasis has been associated with a variety of diseases, while exogenous thiol administration increased tolerance to oxidative stresses and, in some cases, the prevention or treatment of diseases in humans [25]. The compounds used include "protiol" compounds such as GSH and its derivatives, thiols such as cysteine and N-acetyl-L-cysteine, dithiols such as lipoic acid, and OTC that are converted intracellularly into free thiols [12]. In our study, we measured thiol and disulfide levels in coronary artery disease patients with and without ISR, and also in cases who have normal coronary arteries. Statins have antioxidant and pleiotropic effects. But in our study all the groups used statins with similar ratio.

NRF2 provides gene regulation by taking part in intracellular signal transduction, thus it is effective in the development of transcription, anabolic metabolism, cell proliferation and extracellular matrix remodeling [26]. As a result, NRF2 manages the resistance and repair of tissue against damage [27]. We expected the NRF2 level to be high in group 2 patients who did not develop restenosis by suppressing the in-stent inflammatory response caused by oxidative stress and keeping remodeling in balance. Thus, NRF2 level was found to be significantly higher in this group compared to other groups in our study.

A study has been conducted to suggest that there might be a relationship between atherosclerosis resistance and NRF2 activation in human endothelial cells [12] Exposure to oxidized LDL in the endothelium causes an increase in NRF2 protein in macrophages and protects cells from oxidative injury. NRF2 deficiency in macrophages leads to increased proatherogenic foam cell formation and aggravation towards atherosclerosis [28].

Considering the protective effect of NRF2, it can be considered that a drug that induces NRF2 is promising for possible protection from atherosclerosis and its clinical results.

In a study conducted by Serruys PW et al, it was observed that everolimus significantly reduced late lumen loss in angiographies at 6 and 12 months in the comparison of cobalt chromium bare metal stent and everolimus-releasing stent in coronary artery patients during 5-year follow-up [29]. In our study, all patients were selected among the patients with new generation everolimus eluting coronary stents, and thus, the effect of possible antiproliferative drug diversity or the use of bare metal stents between the groups was eliminated.

In a study conducted with coronary artery patients, the relationship between total antioxidant status, oxidative stress and coronary artery disease was investigated [30]. 87 patients who were hospitalized for coronary angiography were included in the study group. Plasma total oxidative status (TOD) and total antioxidant capacity (TAC) levels were measured and the oxidative stress index (OSI) was calculated. Plasma total antioxidant capacity levels were found to be high in people with coronary artery disease and the severity of coronary atherosclerosis was found to be associated with TAC. In our study, total and native thiol levels were studied, and antioxidant thiols in group 1 and group 2 with coronary artery disease were significantly lower than in group 3 without coronary artery disease. However, the number of patients in our study was not sufficient to determine a cut-off thiol level to exclude the presence or absence of coronary artery disease.

Recently in a study it's determined that some oxidative and antioxidative markers showed the potential in the prediction of ISR risk.31 Also in our study we found that NRF2 protects coronary vessels from ISR and neointimal hyperplasia

In a study done by Chen QM et al, it was found that high NRF2 levels suppressed the development of inflammation and atherosclerosis in the vascular endothelium. Considering the possible protective effect of NRF2, it was thought that a drug that induces NRF2 level could be promising for myocardial protection [7].

In order to evaluate the importance of thiol/disulfide balance for antioxidant defense mechanisms in protecting against oxidative stress, Kundi et al. investigated the role of thiol/disulfide balance in patients with acute myocardial infarction [32,33]. As a result of the study, it was determined that native thiol and total thiol levels were lower, and disulfide/native thiol and disulfide/total thiol ratios were higher in the acute myocardial infarction group compared to healthy adults. They reported that high disulfide levels and disulfide/total thiol levels are risk indicators for acute myocardial infarction. In our study, unlike this study group, patients with stable angina pectoris predicted to have stable atherosclerotic plaques were selected instead of acute coronary syndrome. In this way, we eliminated the expected inflammatory response in patients with acute coronary syndrome possibly affecting oxidative stress test results.

**Study Limitations**

The relatively small number of patients is the most important limitation of the study. However, even with this number of patients, statistically significant results were obtained. In addition, making a single measurement from each patient and not checking repetitive values in the time interval might be another limitation of the study.

**CONCLUSION**

In conclusion, it is thought that thiol/disulphate balance could be used as an indicator of oxidative stress in the early diagnosis of coronary artery disease, and the NRF2 level might allow early diagnosis and treatment of patients who develop coronary ISR. Further studies which could be done with larger number of patients would clarify this situation.

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**Author's Contributions:** Conception: FC; Design: FC, EV; Supervision: EV; Fundings: FC, EV; Materials: FC, MK; Data Collection and/or Processing: TGK, ST; Analysis and/or Interpretation: FC, GA, TGK, ST; Literature: FC, MK; Review: FC, IVD, GA, MAB, MS; Writing: FC, IVD, GA, MAB, MS; Critical Review: FC, IVD, MAB, MS.

**Ethics Committee Approval:** Ethics committee approval was obtained from the Gaziantep University Clinical Research Ethics Committee on January 15, 2020, with Decision No. 2019/466.

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