Iron levels and vulnerable coronary atherosclerotic plaques

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ABSTRACT

Background: Preliminary research indicates that higher iron levels are associated with worse outcomes in patients with coronary artery disease.

Aims: The study aimed to investigate the relationship between iron levels and the type and composition of coronary plaques.

Methods: In patients with ≥1 coronary stenosis ≥50% on computed tomography angiography, iron levels, presence of high-risk plaque features, such as low-attenuation plaque (LAP), napkin-ring sign, positive remodeling, and spotty calcium, as well as type and plaque composition (calcified/fibrous/fibro-fatty/necrotic core) were evaluated. Fibro-fatty and necrotic core components were analyzed together as vulnerable component.

Results: The study included 300 patients (191 men, 62.2 [23.0] years). Two thousand one hundred and eighty-four plaques were found (1201 calcified, 584 non-calcified, and 397 mixed). High-risk plaque was observed in 208 patients (107 LAP, 54 napkin-ring signs, 354 positive remodeling, and 281 spotty calcium). Patients with LAP had higher iron levels (P <0.0001). In univariable regression, LAP predictors were high iron levels (odds ratio [OR], 1.02; 95% CI, 1.00–1.03; P <0.0001), male sex (OR, 2.50, 95% CI, 1.40–4.46; P = 0.002), and hemoglobin (OR, 1.23; 95% CI, 1.01–1.49; P = 0.04). In multivariable regression, only iron and male sex were LAP predictors (OR, 1.02; 95% CI, 1.01–1.03; P = 0.0002, and OR, 2.41; 95% CI, 1.24–4.70; P = 0.009, respectively). The iron threshold for LAP prediction was >98 µg/dl (AUC 0.665; P <0.001), which corresponds with an OR of 3.2 (95% CI, 1.80–5.80; P = 0.0001) for LAP prediction.

Higher iron correlated with more fibro-fatty (P = 0.01) and necrotic core (P = 0.02) components, with no relation to calcified and fibrous components. Higher iron was positively correlated with the percentage of vulnerable plaque component (P = 0.004).

Conclusions: Higher iron levels were associated with LAP presence and more vulnerable component of coronary atherosclerotic plaques.

Key words: atherosclerosis, coronary artery disease, iron, low attenuation plaque, vulnerable plaque

INTRODUCTION

In 1981, Sullivan proposed high iron levels as a cardiovascular risk factor, hypothesizing that lower body iron stores were associated with a lower incidence of cardiovascular disease (CVD) in premenopausal women compared to men and postmenopausal women [1]. The "iron hypothesis" was based on observations of myocardial failure in iron storage diseases, with iron accumulating with age in men and post-menopausal women, who achieve levels comparable to men [1]. Further research indicated higher iron levels to be associated with enhanced oxidative stress, higher SYNTAX (SYNergy between PCI with TAXUS™ and Cardiac Surgery) score, more severe atherosclerosis, and aggravated atherosclerosis progression in the aorta in the mouse model [2–4]. Moreover, Salonen et al. [5] showed that men with high serum ferritin levels had a 2.2-fold higher risk of myocardial infarction (MI). However, the results from studies on the role of iron in CVD differ [6].

Reactive oxygen species (ROS) mediated changes to lipoproteins have a crucial role in

WHAT'S NEW

This study aimed to examine the pathophysiological link between the "iron hypothesis" and coronary artery disease. We showed that a higher iron level was associated with the presence of low attenuation plaque. Patients with higher iron levels had more fibro-fatty and necrotic core plaque components; therefore, higher iron was associated with coronary plaque vulnerability.

atherogenesis. Preliminary research indicated that iron participates in a redox reaction (Fenton's reaction) through the transfer of electrons between the Fe^{3+} and Fe^{2+} and catalyzes the formation of ROS, which play a crucial role in the oxidation of low-density lipoproteins (LDLs) [7, 8]. Hypothetically, the above mechanism may contribute to the development of atherosclerosis, including the formation of its vulnerable components, plausibly linking the increased iron levels with adverse cardiovascular outcomes. However, the potential association between iron and coronary plaque morphology is unknown.

Therefore, our study aimed to investigate the relationship between free blood iron levels and the type and composition of atherosclerotic plaques in coronary arteries as evaluated on computed tomography coronary angiography (CTCA).

MATERIAL AND METHODS

Study population

This was a prospective single-center study with enrolled 300 consecutive patients with newly diagnosed coronary artery disease (CAD) on CTCA (Figure 1). The analysis was carried out as part of a grant funded by the National Science Centre (grant number 2016/21/N/NZ5/01450, awarded to AO). A detailed study design has been published previously [9]. In the examined patients in the National Institute of Cardiology, active screening was conducted in the CT lab between March 2017 and October 2019, and then consecutive patients meeting the inclusion criteria were offered the opportunity to participate in the study. Patients were referred to the CTCA following the ESC recommendations in force at the time of recruitment [10, 11]. The inclusion criteria were signed informed consent, age over 18 years, ≥1 plaque with ≥50% narrowing of the coronary artery lumen with a reference diameter >2.0 mm on CTCA. The exclusion criteria were poor quality of CTCA, presence of artificial heart valves or pacemakers, previous coronary revascularization, previous MI, and being a recipient of red blood cell concentrate or iron supplementation during the previous four months before CTCA. The study did not include patients with advanced renal impairment (estimated glomerular filtration ratio <30 ml/min/1.73 m^2) and heart failure with reduced ejection fraction (HFrEF). All patients provided informed consent, and the study received ethical approval.

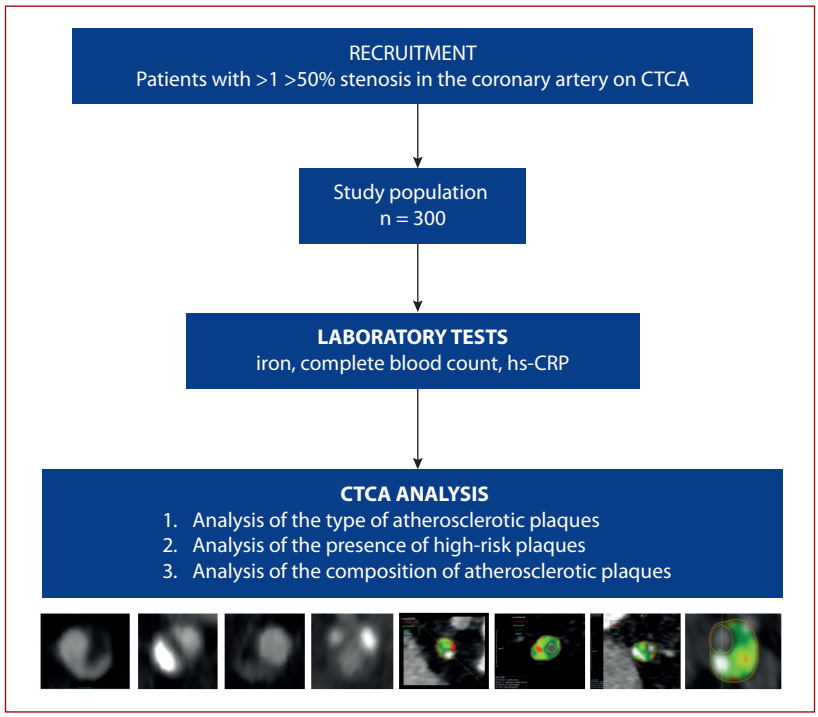

Figure 1. Study flowchart

Abbreviations: CTCA computed tomography coronary angiography; hs-CRP, high-sensitivity C-reactive protein

Laboratory tests

All patients underwent laboratory tests directly after CTCA, including complete blood count, iron level, and high sensitive C-reactive protein (hs-CRP). The reference iron values were 33–193 µg/dl, and the reference hemoglobin (Hb) levels were 11.2–15.7 mg/dl in women and 13.7–17.5 mg/dl in men. The reference hs-CRP value was <0.5 mg/dl.

CTCA performance and analysis

Computed tomography coronary angiography was performed with a dedicated CT scanner (Somatom Force; Siemens, Germany). Sublingual nitrates (0.8 mg) were administered. If the heart rate was ≥70 beats/min, an intravenous bolus of metoprolol (increasing doses at 2.5 mg intervals, up to a maximum dose of 20 mg) was given if necessary. From 60 to 70 ml of contrast agent (iohexol) was injected intravenously at 6 ml/s. An electrocardiogram-gated retrospective or prospective acquisition protocol was used in all patients when possible. Scan data were reconstructed routinely in mid to end-diastole (60%–70% of R–R interval). Data sets that contained motion artifacts were individually optimized by changing the reconstruction window. CTCA analyses were performed in our core lab by an experienced reader (at least 10 years of experience with CTCA) fully blinded to clinical and laboratory data, who evaluated all arteries with a reference diameter of above 2 mm for the presence of coronary stenoses. QAngioCT analysis was performed by a blinded reader professionally trained in QAngioCT analysis.

In the study population, we assessed the presence of high-risk plaque (HRP) features: low-attenuation plaque (LAP), napkin-ring sign, positive remodeling and spotty calcium (Syngo, Siemens), type of plaque (calcified, mixed, non-calcified) (Syngo, Siemens) and their composition provided as a percentage value of each plaque component per patient (calcified, fibrous, fibro-fatty, or necrotic core) (QAngioCT, Medis) (Figure 2) [12–14].

In noncalcified plaques, the readers placed 3 random region-of-interest measurements in the noncalcified low CT attenuation area of the plaque. LAP was defined as the mean CT number within these 3 regions of interest <30 Hounsfield units (HU). The napkin ring sign was defined as a ring-like peripheral higher attenuation of the non-calcified portion of the coronary plaque. Spotty calcification was defined as the presence of calcification <3 mm

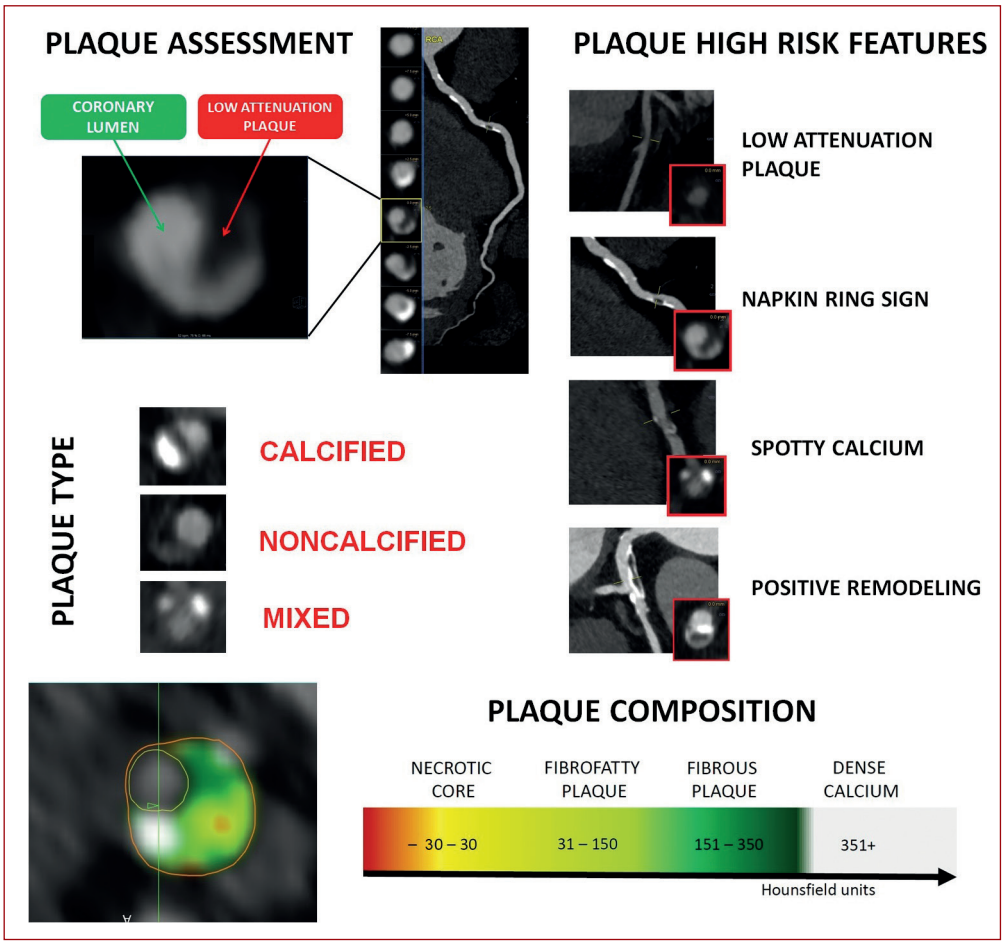

Figure 2. Advanced coronary plaque analysis by computed tomography coronary angiography, including coronary plaque type (calcified, non-calcified, mixed), presence of high-risk plaque features (low-attenuation plaque, napkin ring sign, spotty calcium, positive remodeling), and plaque composition (fibro-fatty, necrotic core, fibrous and dense calcium)

in any direction within a plaque. The threshold of 1.1 was used to define positive remodeling [15, 16].

The atheroma composition was distinguished based on tissue attenuation ranges in HU: dense calcium (>351 HU), fibrous plaque (151 to 350 HU), fibro-fatty plaque (31 to 150 HU), and necrotic core (–30 HU to 30 HU) (Figure 2) [15, 17]. The combination of fibro-fatty and necrotic core components was analyzed together as vulnerable plaque component, and the combination of fibrous and dense calcium as stable plaque component. All coronary stenoses were categorized as minimal <25%, mild 25%–49%, moderate 50%–69%, and severe 70%–100%.

Statistical analysis

Continuous data with normal distribution were presented as means (standard deviation). Non-normally distributed variables were presented as medians with interquartile ranges. The categorical variables were presented as frequencies and percentages. The differences between patients were determined with Student's t-test (normal distribution) or the Mann–Whitney U test (non-normal distribution), as appropriate. The differences between the qualitative variables were determined using the χ^2 test or Fisher's exact test, as appropriate. Correlation analysis, univariate logistic regression, multivariable regression analyses, and receiver operating characteristic analysis were used as appropriate. In multivariable regression, we included all factors that presented at least a trend association in univariate regression (P <0.10). Additionally, the normalized parameter of iron/Hb was used for subanalysis to exclude the influence of anemia on the results. P <0.05 was considered statistically significant. All analyses were performed using MedCalc Software (version 13.2.2, Ostend, Belgium).

RESULTS

The study included 300 patients (191 men [63.7%], 62.2 [23.0] years). The baseline study group characteristics are provided in Table 1. CASC was 565.2 (454.4–633.7). Dose length product for CTCA was 431.8 (413.7–458.9) mGy × cm.

The median iron level was 87.5 (80.8–100.0) µg/dl for women and 100.9 (96.7–106.0) µg/dl for men (P = 0.01). According to the reference values, 5 (1.7%) patients had iron levels under the reference values (3 men [60%]), and 4 (1.3%) patients had iron levels above the reference values (4 men [100%]). The median Hb level was 13.5 (13.2–13.7) g/dl in women and 14.7 (14.5–15.0) g/dl in men (P <0.0001). According to the reference values, 34 (11.3%) patients had anemia (30 men [88.2%]). The median hs-CRP level was 0.14 (0.13–0.16) mg/dl, with no differences between men and women (P = 0.2).

On CTCA, 2184 coronary plaques were found, from which 1201 (55%) were calcified, 584 (27%) were non-calcified, and 397 (18%) were mixed. In all analyzed plaques, 864 (39.6%) plaques caused minimal stenosis, 613 (28.0%) caused mild stenosis, 500 (22.9%) caused moderate stenosis, and 207 (9.5%) caused severe stenosis. HRP features were found in 208 (69.3%) patients, including 107 low-attenuation plaques in 85 (28.3%) patients, 54 plaques with napkin-ring sign in 50 (16.7%) patients, 354 plaques with a positive remodeling in 168 (56.0%) patients, and 281 plaques with spotty calcium in 151 (50.3%) patients. Fifty-two (17.3%) patients had only 1 HRP feature, and 156 (52.0%) patients had ≥2 HRP features.

Table 1. Baseline patient characteristics

Parameter	Value (n = 300)
Clinical characteristics:	
Age, years	62 (23)
Sex (male)	191 (64%)
BMI, kg/m^2	27.6 (27.0–28.5)
CAD risk factors:	
Hypertension	257 (86%)
Dyslipidemia[a]	203 (68%)
Diabetes	74 (25%)
Family history of CAD	51 (17%)
Smoking — current	46 (15%)
Smoking — in the past	42 (14%)
Medications:	
Beta-blocker	207 (69%)
Statin	180 (60%)
Other lipid lowering drugs	23 (8%)
ACEi	99 (33%)
ARB	89 (30%)
Calcium antagonist	106 (35%)
Diuretic — any	98 (33%)
Metformin	55 (18%)
Acetylsalicylic acid	143 (48%)

Values are mean (SD), n (%), or median [IQR]
[a]Dyslipidemia diagnosis in the medical records on the day of CTCA

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CASC, coronary artery calcium score; CTCA, computed tomography coronary angiography; IQR, interquartile range; SD, standard deviation

Iron levels correlated with LAP presence (P <0.0001) and with the increasing number of LAPs per patient (P = 0.005). Patients with LAPs had higher iron levels (111.0 vs. 91.7 µg/dl; P <0.0001). There were no associations between iron levels and napkin-ring sign, positive remodeling, or spotty calcium (P = 0.6; P = 0.5; P = 0.9, respectively).

In univariable regression analysis, the predictors of LAP were iron level (odds ratio [OR], 1.02; 95% confidence interval [CI], 1.00–1.03; P <0.0001), male sex (OR, 2.50; 95% CI, 1.40–4.46; P = 0.002), and Hb level (OR, 1.23; 95% CI, 1.01–1.49; P = 0.04) (Supplementary material, *Table S1*). The inflammation parameters (hs-CRP and white blood cell) were not LAP predictors (P = 0.4; P = 0.9, respectively). In multivariable regression analysis, only iron levels and male sex were predictors of LAP (OR, 1.02; 95% CI, 1.01–1.03; P = 0.0002, and OR, 2.41; 95% CI, 1.24–4.70; P = 0.009, respectively) (Supplementary material, *Table S1*). In additional multivariable regression analysis, normalized parameter iron/Hb level and male sex were predictors of LAP (OR, 1.28; 95% CI, 1.12–1.46; P = 0.0003, and OR, 2.48; 95% CI, 1.36–4.49; P = 0.003, respectively). Multivariable regression

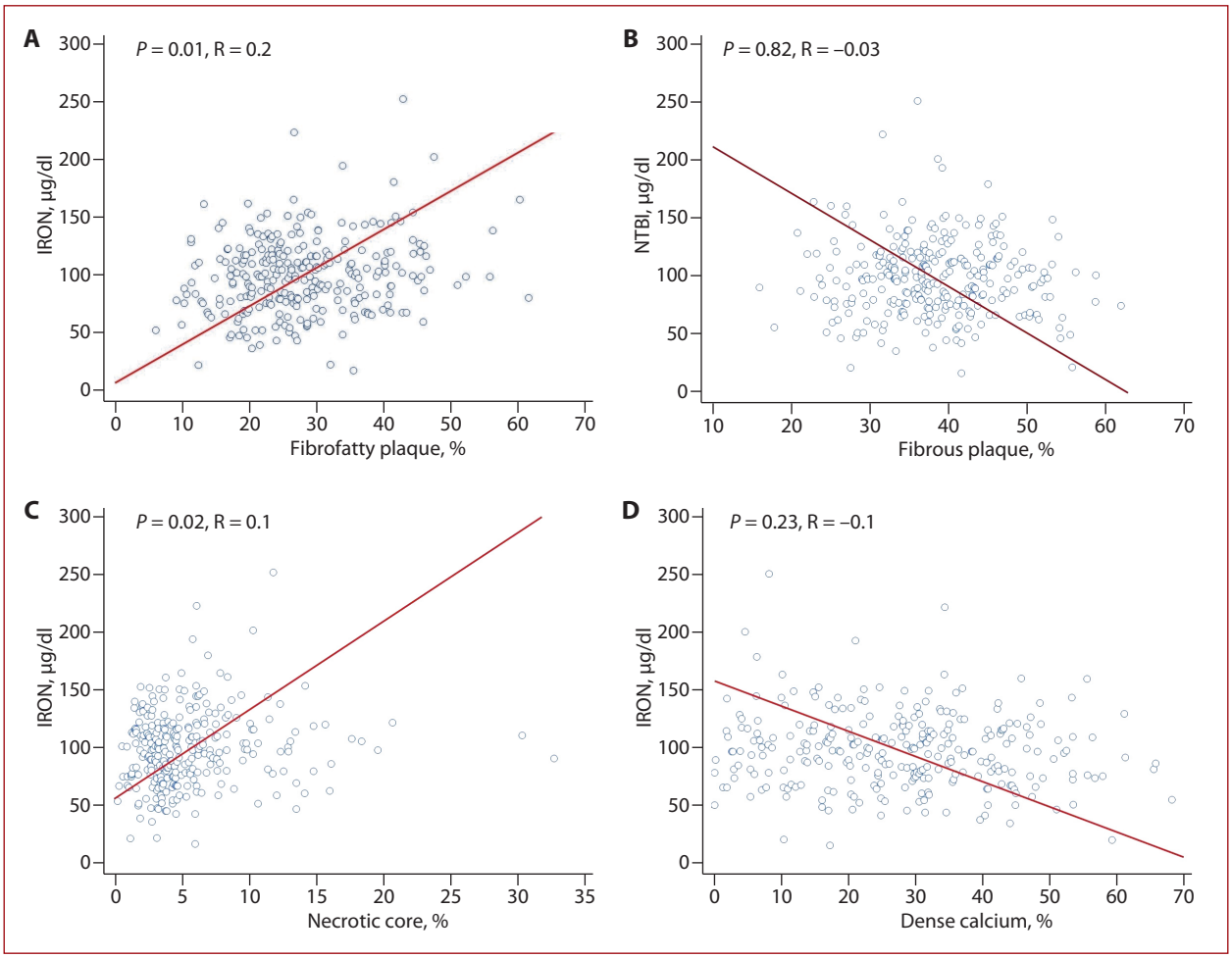

Figure 3. A–D. Association between iron level and main plaque components in quantitative plaque analysis (fibro-fatty, necrotic core, fibrous and dense calcium)

analysis performed separately for both sexes showed that iron level was independently associated with LAP in both men ($P = 0.003$) and women ($P = 0.03$).

Additionally, performed receiver operating characteristic curve analysis showed the iron threshold for LAP prediction >98 µg/dl (area under the curve 0.665; $P < 0.001$). In univariable regression analysis, iron >98 µg/dl was a LAP predictor (OR, 3.2; 95% CI, 1.87–5.56; $P < 0.0001$). In the multivariable regression analysis model, iron >98 µg/dl and male sex were predictors of LAP (OR, 3.2; 95% CI, 1.80–5.80; $P = 0.0001$, and OR, 2.41; 95% CI, 1.25–4.74; $P = 0.009$, respectively).

Higher iron levels correlated with more fibro-fatty (r = 0.2; $P = 0.01$) and necrotic core (r=0.1; $P = 0.02$) components, but not with calcified (r = –0.1; $P = 0.23$) or fibrous (r = –0.03; $P = 0.82$) plaque components (Figure 3). Higher iron levels were positively correlated with the percentage of vulnerable plaque component ($P = 0.004$) and inversely correlated with stable plaque component ($P = 0.004$).

DISCUSSION

Our study, for the first time, showed a significant association between higher iron levels, the presence of LAP, and an increased quantity of vulnerable coronary plaque, including fibro-fatty component and necrotic core [18].

The role of iron in the pathogenesis of atherosclerosis has been investigated for more than 40 years since Sullivan proposed high iron levels as a cardiovascular risk factor, suggesting that it might explain the lower incidence of CVD in premenopausal women [1]. Salonen et al. [5] showed that men with high serum ferritin levels had a 2.2-fold higher risk of MI. Later, Bagheri et al. [3] showed that patients with increased serum iron levels had more severe atherosclerosis. Also, Gustaffson et al. [19] demonstrated that higher iron concentrations in carotid plaques positively correlated with plaque vulnerability to rupture. A more recent study by Vinchi et al. [4] investigated the susceptibility to atherosclerosis in the mouse model (ApoE–/– FPNwt/C326S), where the disease developed in the context of elevated iron levels. The authors showed that iron overload aggravated atherosclerosis in the aorta, suggesting that elevated iron levels lead to atherosclerosis progression [4]. However, none of the studies investigated the relationships between circulating iron and coronary atherosclerosis structure, including coronary plaque type, the presence of HRP features, and plaque composition. The role of iron stores

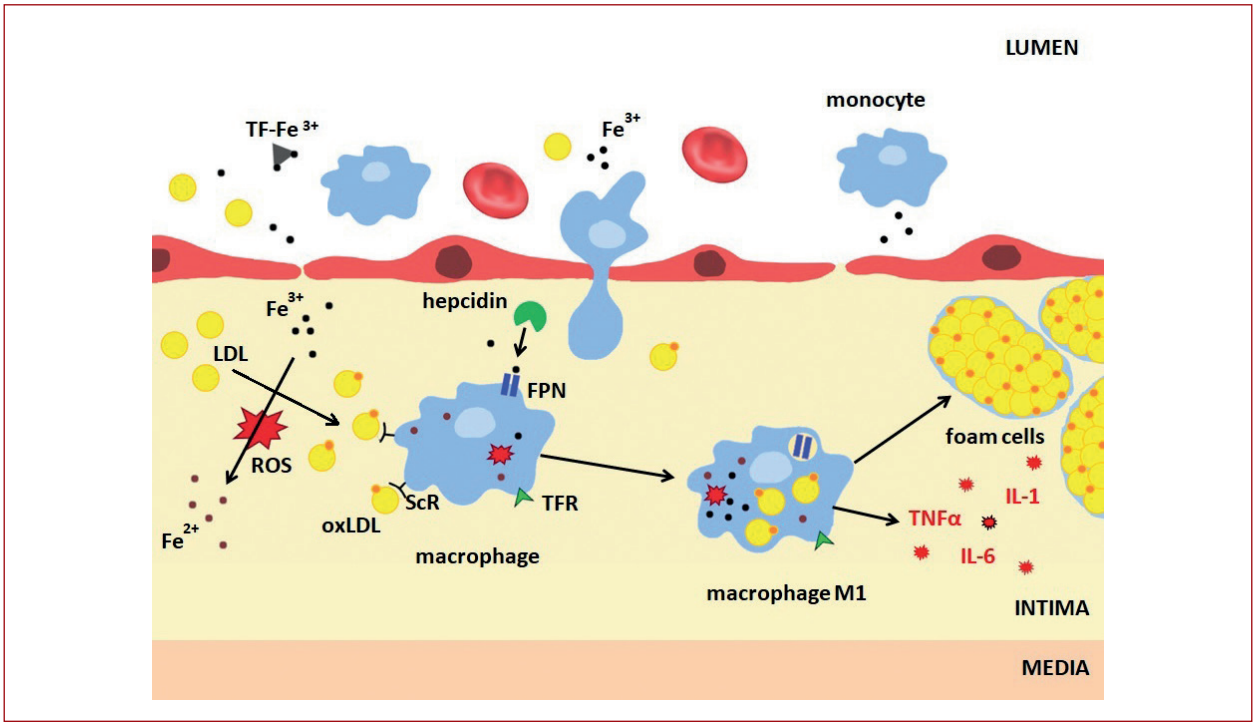

Figure 4. Possible explanation of the role of iron (presented as Fe^{3+}) in the pathogenesis of low-attenuation plaque (LAP) formation

Abbreviations: Fe, iron; FPN, ferroportin; IL-1, interleukin 1; IL-6, interleukin 6; LDL, low density lipoprotein; oxLDL, oxidized low density lipoprotein; ROS, reactive oxygen species; ScR, scavenger receptor; TF-Fe, transferrin-iron complex; TFR, transferrin receptor; TNF-*α*, tumor necrosis factor α

and iron deficiency in CAD patients cannot be described with certainty because published reports presented contradictory results [6, 18]. A recent study that investigated the association between iron levels and all-cause mortality in patients with acute coronary syndromes showed that patients with lower iron levels had worse prognosis [20]. However, study participants were mostly male (75%) with a great proportion of ST-segment elevation MI; therefore, the results may have been influenced by heart failure development after MI. Moreover, the influence of anemia on the outcomes was not excluded [20]. CVD patients may be negatively affected by both iron deficiency and higher iron levels through different metabolic pathways and mechanisms.

In SCOT-HEART, a large multicenter study, an increased burden of low-attenuation plaque was the principal predictor of an increased number of coronary events, above and beyond other established classic markers of cardiovascular risk, including the severity of coronary artery stenosis and calcium score [21]. Also, a review by Nerlekar et al. [14] showed that the presence of HRP features is an independent predictor of major adverse cardiac events [16]. It has been shown that 88% of ruptured coronary plaques in patients with acute coronary syndrome had a low attenuation (P <0.0001) [22]. Until recently, reliable differentiation between lipid-rich and fibrotic lesions solely based on CT attenuation was not possible [12]. New automated plaque quantification software tools, with scan-specific adaptive attenuation threshold settings, can potentially overcome some of these limitations and improve CT-based plaque component quantification [23, 24]. Factors causing vulnerable atherosclerotic plaque growth and LAP formation may comprise potential targets for new anti-atherosclerotic therapies.

The results of our study may be plausibly explained within the context of known pathophysiological and biochemical processes contributing to atherogenesis, as presented in Figure 4. Iron is a redox-active metal. Increased serum iron levels catalyze the formation of ROS and promote LDL oxidation. Oxidized LDLs trigger endothelial activation and induce macrophage recruitment [7]. Moreover, oxidized LDLs are taken up by the LDL receptor (ScR, scavenger receptor) on pro-inflammatory M1 macrophages leading to their development into foam cells [7, 8, 25–27]. Foam cell infiltration and necrotic core expansion are key events in atherogenesis and vulnerable plaque formation [7]. Necrosis of foam cells leads to further plaque growth and, finally, to the formation of a necrotic core. Moreover, foam cells may upregulate proteolytic enzymes, leading to plaque rupture [28]. Multiple macrophage phenotypes have been detected in atherosclerotic lesions, including macrophages with M1, M2, or M(Hb) phenotypes [29]. Classically activated M1 macrophages promote inflammation and are characterized by high expression of pro-atherogenic cytokines, including tumor necrosis factor-alpha, interleukin (IL)-6, and IL-1 [30]. M1 macrophages are the predominant phenotype found in advanced, unstable, atherosclerotic plaques, which have a large lipid-rich ne-

crotic core [31]. Moreover, the role of the local intraplaque hemorrhage with local iron deposition and oxidation contributing to individual plaque development has not been established yet.

Taking into account the abovementioned data, our study provides a mechanistic link between the current knowledge of iron homeostasis, clinical manifestation of CAD, and higher iron levels. More studies investigating this issue are needed to fully explain the influence of the observed phenomenon.

Limitations

The limitations of our study include single center analysis, lack of full iron metabolism assessment (including the levels of hepcidin, ferritin, and transferrin, etc.), and a wider spectrum of inflammatory parameters. Further studies with a wider range of investigated iron homeostasis parameters are needed. However, iron measurement is low cost and easily accessible, even for primary care physicians, which may be of practical importance in the context of new biomarkers for increased risk of vulnerable plaque.

Depending on the duration of lipid-lowering therapy and the degree of a sustained level of LDL cholesterol, some patients may have already remodeled plaque, including the plaque components. However, the presented association between iron and LAP is significant nonetheless. Our study population reflects a "real-life" population of patients who underwent CTCA in one of the leading cardiology centers in Poland.

Although there were 2 women aged under 50 and 7 women aged between 50 and 55, a subanalysis including pre- and post-menopausal subgroups was impossible.

This article did not analyze the association between iron levels and cardiovascular outcomes during long-term follow-up. Therefore, the association between increased iron levels and LAP does not allow us to conclude that higher iron levels are associated with cardiovascular events in CAD patients.

CONCLUSIONS

Higher iron levels are associated with the presence of low-attenuation plaque and a greater proportion of vulnerable (fibrofatty and necrotic core) component of atherosclerotic plaques in CAD patients.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

Conflict of interest: None declared.

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