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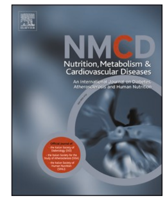

Sex differences of interferon-gamma levels according to burden of coronary atherosclerosis identified by CT coronary angiography

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ABSTRACT

Background and aims: The burden of coronary atherosclerosis differs between men and women. Beyond traditional cardiovascular risk factors, inflammatory biomarkers can influence plaque progression. We analyzed the influence of sex on coronary atherosclerosis and inflammatory cytokines.

Methods and results: Coronary CT angiography was performed in 301 patients and the extent of coronary atherosclerosis was assessed using semi-automated software. We analyzed total (TPV), non-calcified (NCPV), calcified (CPV) and low-density plaque volume in mm^3. Serum was analyzed for various cytokines. Out of 301 patients, 94 (31 %) were female and 207 (69 %) were male. Significant differences were seen between women and men respectively for age, BMI and smoking status (all $p < 0.05$). All plaque types showed significantly higher volumes in men as compared to women (all $p < 0.05$). In men, significantly lower serum levels for IL-2 (3.2vs.4.3; $p = 0.01$) and interferon-gamma (3.2vs.8.8; $p < 0.001$) but higher levels for MCP-1 (224vs.155; $p < 0.001$) were seen. In regression analysis, interferon-gamma - but not IL-2 or MCP-1 - showed significant inverse association with male sex (OR 0.32; 95 %CI: 0.16–0.67; $p = 0.002$). Of note, interferon-gamma levels significantly differed according to high and low TPV in men (16.8vs.9.9; $p < 0.001$) but not in women (14.5vs. 8.9; $p = 0.65$).

Conclusion: In our cohort of individuals with suspected CAD undergoing coronary CTA, serum levels of interferon-gamma were significantly higher in women, in spite of a lower coronary plaque burden. Higher interferon-gamma levels were associated with higher plaque burden among men, but not in women, which suggests an influence of sex on the role of interferon-gamma in atherogenesis and atherosclerosis progression.

1. Introduction

Coronary artery disease (CAD), characterized by the progressive development of coronary atherosclerosis, can manifest clinically as acute coronary syndrome (ACS) or chronic coronary syndrome (CCS). In the diagnostic evaluation of patients with CCS and in specific instances of ACS, coronary CT angiography (CTA) has emerged as a valuable diagnostic modality, demonstrating notable efficiency and efficacy, particularly attributable to its high negative predictive value [1]. Coronary CTA allows not only for non-invasive detection of obstructive CAD, but also for the evaluation of coronary plaque morphology in detail [2,3]. Beyond the quantitative evaluation of atherosclerotic plaque volume, identification of non-calcified plaque with particular features such as low CT attenuation is feasible. Such plaques with low CT attenuation are indicative of lipid-rich necrotic core thin-cap fibroatheromas, with increased risk for plaque rupture and subsequent major cardiovascular events, including myocardial infarction [4–6].

Atherosclerotic plaque formation and accumulation is a dynamic process influenced by various factors, including pro- and anti-inflammatory mediators [7,8]. Using serum analysis, unspecific biomarkers such as C-reactive protein (CRP) as well as more specific cytokines such as interleukins (IL) but also interferon-gamma and Moncyte Chemoattractant Protein-1 (MCP-1) can be identified [9–11]. Most of them have predominately either pro- or antiatherosclerotic effects, and very few seem to have both anti- and pro-atherogenic qualities [12,13]. The complex interaction of inflammatory biomarkers influence the

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developement from plaque initiation and plaque accumulation to transformation into high-risk plaques [14,15]. Innate and adaptive inflammatory response with its cytokine secretion and the magnitude of the inflammatory effect depends on multiple factors. Sex seems to be one of them [16]. For instance, higher levels of IL-1β, IL-6 and TNF-α were associated with higher levels of testosterone [17]. Sex specific differences also seem to exist for interferon-gamma, a centrally involved cytokine for atherosclerosis-related inflammation [18].

Whether there are differences in mechanisms of action in regard to pro- or anti-inflammatory effects in respect to sex is unclear. Thus, we sought to determine the association between serum cytokine profile and sex in the context of coronary plaque volume and plaque subcomponents identified by coronary CTA.

2. Methods

2.1. Study design and population

From a previously published cross-sectional cohort [19] of 455 patients undergoing cardiac computed tomography, we included all patients who additionally underwent coronary CTA (n = 306), except five patients, which were excluded due to poor CTA image quality, resulting in a final cohort of 301 patients. All patients underwent coronary CTA as part of a clinically indicated diagnostic workup, prompted by the presence of atypical chest pain and a low to intermediate pre-test probability of obstructive coronary artery disease. Blood was collected from all patients, independent of fasting status, immediately before the CTA. Patients with atrial fibrillation (AF), known CAD with previous coronary interventions such as stent implantation or bypass-grafts were excluded a priori. Similary, to avoid any influencing factors from concomitant inflammatory disease on cytokine levels, patients with a clinical or laboratory finding of any recent inflammation were excluded. All patients provided written informed consent and the local institutional review board approved the study.

2.2. Coronary plaque analysis

Coronary atherosclerosis was quantitatively and qualitatively assessed, using a semi-automated software (Autoplaque version 2.5, Cedars-Sinai Medical Center, Los Angeles, CA, USA) with scan-specific threshold level–based quantification of plaque volume and its subcomponents [2,20]. Excellent correlation between this software and intravascular ultrasound has been demonstrated previously. [20–22]. For plaque analysis, we included all vessels with a diameter of more than 2 mm. We evaluated total plaque volume (in cubic millimetres, mm^3), non-calcified plaque volume (NCP) and low density plaque volume (plaque volume <30 HU). The semi-automated evaluation followed a structured stepwise approach with 1) extraction of each coronary vessel 2) identification of proximal and distal plaque-boundaries 3) automated detection of the outer vessel wall and the contrast-filled lumen. The outer vessel wall and the thresholds for calcified and non-calcified plaque could be manually adjusted. 4) Finally, the software automatically analyzed and calculated the area between the outer vessel wall and the vessel lumen, reflecting atherosclerotic plaque (Fig. 1).

2.3. Serum inflammatory biomarker analysis

Serum inflammatory biomarkers were assessed using venous blood collected at the time of CT. Luminex-based biomarker analysis included IL-1a, IL-1b, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, interferon-gamma, TNFα, hsCRP, GM-CSF, G-CSF, MCP-1, MIP-1a and Eotaxin. Serum levels were measured in pg/ml [19].

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation or median and 25th and 75th percentiles. Categorical variables are presented as frequencies and percentages. We used Pearson's Chi-squared test for comparison of categorical variables and the Mann-Whitney *U* test for comparison of nonparametric data. For multivariable analysis, stepwise logistic regression according to backward Wald was used. As baseline covariates, we included age and sex as well as those CVRF, which were significantly correlated to plaque volumes in univariate analysis. These baseline covariates stayed in the models to account for potential effects. A two-sided p-value of less than 0.05 was considered to indicate statistical significance. All analyses were performed using SPSS (IBM SPSS Statistics, Version 24.0.0.2).

3. Results

Out of 301 patients, 94 (31 %) were female and 207 (69 %) were male. The mean age of the total cohort was 59 (±10) years.

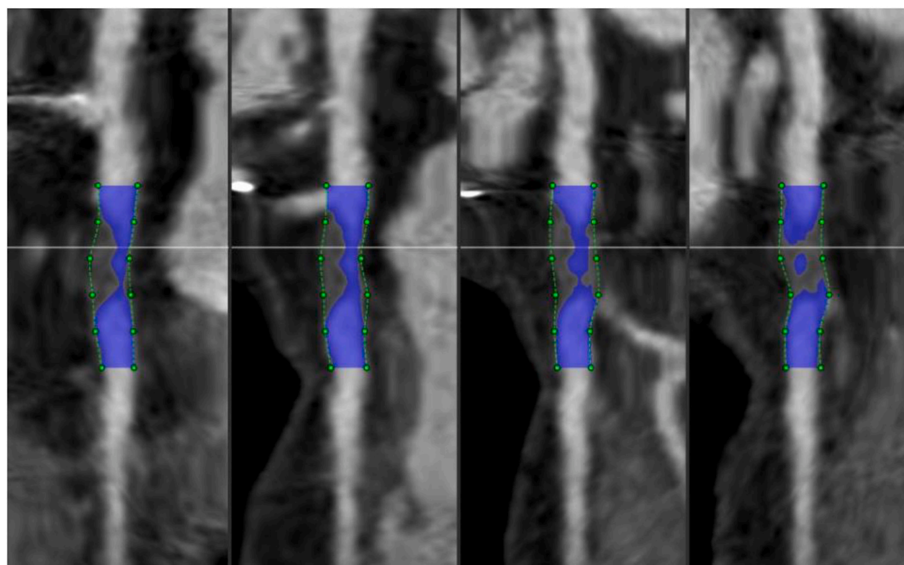

Fig. 1. Longitudinal multiplanar reconstruction demonstrating coronary atherosclerotic plaque using semi-automated software (vessel lumen depicted in blue, outer vessel wall delineated in green). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.1. Cardiovascular risk profiles

The patient's detailed cardiovascular risk profile according to sex is displayed in Table 1. Female patients were significantly older (62 vs. 57 years, $p < 0.001$) and less frequently reported former or current smoking (33 % vs. 51 %, $p = 0.003$). Also, female patients had lower BMI (26 vs. 28 kg/m2, $p = 0.005$). No differences were seen for hypertension, hyperlipidemia, diabetes, and family history of CAD.

3.2. Quantitative and qualitative coronary plaque results

Out of 301 patients, the presence of any atherosclerosis was ruled out in 54 (18 %) patients. The median plaque volumes were as follows: 418 mm^3 (IQR: 123; 836) for total plaque volume, 413 mm^3 (IQR: 122; 804) for non-calcified plaque volume, and 2.4 mm^3 (IQR: 0.0; 21) for calcified plaque volume. The median vulnerable plaque volume was 28 mm^3 (IQR: 2.6; 127).

All plaque volumes were significantly lower in women as compared to men. The median plaque volumes according to sex were (women vs. men respectively): 288 (0; 739) vs. 465 (178; 896) mm^3 ($p = 0.004$) for TPV; 285 (0; 735) vs. 440 (175; 835) mm^3 ($p = 0.005$) for NCPV; 0 (0; 5) vs. 4 (0; 31) mm^3 ($p < 0.001$) for CPV and 20 (0; 113) vs 30 (6; 137) mm^3 ($p = 0.029$) for vulnerable plaque volume.

3.3. Inflammatory biomarkers

In men, cytokine profiles showed significantly lower serum levels for IL-2 (3.2 [3.2; 7.0] vs. 4.3 [3.2; 9.7]; $p = 0.01$) and Interferon-gamma (3.2 [3.2; 14.7] vs. 8.8 [3.2; 26.3]; $p < 0.001$) and significantly higher levels for MCP-1 (224 [117; 327] vs. 155 [49; 260]; $p < 0.001$) as compared to women. All other cytokines showed no differences, as listed in Table 1.

In multivariable logistic regression analysis, interferon-gamma showed a significant inverse association to male sex (OR 0.32; 95 %CI: 0.16–0.67; $p = 0.002$), but IL-2 and MCP-1 did not. The association of interferon-gamma to sex was independent of age (OR 0.59; 95 %CI: 0.44–0.78; $p < 0.001$), BMI (OR 2.04; 95 %CI 1.19–3.50; $p = 0.01$) and smoking status (OR 1.96; 95 %CI: 1.13–3.39; $p = 0.02$).

Table 1
Conventional cardiovascular risk factors and cytokine levels according to sex.

	Female (n = 94)	**Male** (n = 207)	p-value
Cardiovascular Risk Faktors	*n (%) or mean (±SD)*	*n (%) or mean (±SD)*	
Age	62.0 ± *9.3*	57.1 ± *9.7*	**<0.001**
Diabetes	9 (9.6 %)	19 (9.2 %)	0.913
Hyperlipidemia	56 (59.6 %)	130 (62.8 %)	0.593
Hypertension	67 (71.3 %)	124 (59.9 %)	0.058
Smoker (current or prior)	31 (33.0 %)	106 (51.2 %)	**0.003**
Family histroy of CAD	36 (38.3 %)	80 (38.6 %)	0.954
BMI	26.3	27.7	**0.005**
Serum Cytokines	*median (IQR)*	*median (IQR)*	
IL-2	4.3 (3.2; 9.7)	3.2 (3.2; 7.0)	**0.010**
IL-12	5.1 (3.2; 9.5)	3.7 (3.2; 7.6)	0.366
IL-15	3.2 (3.2; 5.2)	3.2 (3.2; 4.9)	0.122
IFN-gamma	8.8 (3.2; 26.3)	3.2 (3.2; 14.7)	**<0.001**
IL-4	14.6 (3.2; 90.1)	9.9 (3.2; 78.2)	0.523
IL-10	13.1 (7.3; 35.3)	11.1 (3.2; 34.5)	0.175
IL-13	29.6 (3.6; 64.5)	12.1 (3.2; 63.9)	0.128
IL-1a	13.9 (3.2; 54.9)	11.9 (3.2; 51.0)	0.653
IL-1b	3.2 (3.2; 3.2)	3.2 (3.2; 3.2)	0.097
IL-6	7.3 (3.2; 24.5)	6.1 (3.2; 24.2)	0.904
IL-17	3.2 (3.2; 7.3)	3.2 (3.2; 6.8)	0.130
TNFa	5.0 (3.2; 8.1)	5.8 (3.2; 8.1)	0.381
CRP	1.7 (1.2; 2.1)	1.4 (1.1; 2.0)	0.146
IL-7	9.6 (4.3; 15.0)	9.1 (3.9; 16.2)	0.745
CSF	7.6 (4.7; 11.1)	8.0 (4.0; 13.1)	0.987
G-CSF	48.9 (7.0; 116.3)	50.9 (3.2; 102.9)	0.365
MCP-1	154.8 (49.1; 260.4)	224.4 (116.7; 327.2)	**<0.001**
MIP-1a	13.2 (3.2; 27.0)	13.7 (3.2; 31.4)	0.855
Eotax	76.3 (60.9; 103.2)	77.0 (59.7; 110.5)	0.752
IL-8	5.2 (3.2; 12.0)	5.7 (3.2; 12.1)	0.225

Pearson's Chi-squared test was used for comparison of categorical variables and the Mann-Whitney *U* test for comparison of nonparametric data.

3.4. Subgroup analysis

Divided by the median, total plaque volume of male patients below the median (n = 104) was 193 mm^3 (IQR: 0; 345) whereas it was 896 mm^3 (IQR: 680; 1379) in patients above the median (n = 103). Divided by the median, total plaque volume of female patients below the median (n = 47) was 0 mm^3 (IQR: 0; 123) whereas it was 739 mm^3 (IQR: 566; 999) above the median (n = 47).

Women with high TVP were significantly older and reported more frequently hypertension and hyperlipidemia as compared to women with low TPV. Similar results were observed among men with high as compared to low TPV as listed in Supplemental Table 1a and 1b No differences were seen for BMI, diabetes and family history of CAD.

Male patients above the median showed significant higher levels of interferon-gamma as compared to male patients with low TPV (9.9 vs. 16.8; $p < 0.001$), whereas no difference of interferon-gamma levels was detectable between women with high as compared to low TPV (14.5 vs. 18.9; $p = 0.65$).

In multivariable logistic regression analysis among men, high interferon-gamma levels showed a significant association to high TPV (OR 3.57; 95 %CI: 1.92–6.65; $p < 0.001$) independent of age (OR 1.35; 95 %CI: 0.99–1.84; $p = 0.06$), hypertension (OR 1.55; 95 %CI: 0.83–2.91; $p = 0.17$) and hyperlipidemia (OR 1.48; 95 %CI: 0.78–2.78; $p = 0.023$).

In multivariable logistic regression analysis among women, age (OR 1.89; 95 %CI: 1.08–3.31; $p = 0.027$) and hyperlipidemia (OR 2.90; 95 % CI: 1.03–8.12; $p = 0.043$) showed significant association to high TPV, but interferon-gamma levels (OR 1.14; 95 %CI: 0.41–3.11; $p = 0.81$) and hypertension (OR 2.95; 95 %CI: 0.83–10.51; $p = 0.095$) did not.

4. Discussion

Beyond markers of coronary atherosclerosis including plaque burden and morphology, we identified a sex-based different cytokine profile in this cohort. In spite of a significantly lower coronary plaque burden in women, serum levels of interferon-gamma – a known pro-inflammatory cytokine - were significantly higher in women. Interestingly, interferon-gamma levels differed significantly according to high and low TPV in men (16.8 vs. 9.9; $p < 0.001$) but not in women (14.5 vs. 18.9; $p = 0.65$) as visualized in the graphical abstract.

Our data expands on previous work that studied the relationship between inflammatory mediators and coronary atherosclerosis and the influence of sex. One strength of our analysis is the sizable cohort of women included in our study, as women are commonly underrepresented in studies focusing on coronary atherosclerosis and inflammatory biomarkers. Interferon-gamma, a known pro-inflammatory and pro-atherogenic cytokine, was shown to be involved in multiple steps of atheroma formation [23]. In our analysis, interferon-gamma levels were significantly elevated in women as compared to men (8.8 (3.2; 26.3) vs. 3.2 (3.2; 14.7), $p < 0.001$).

Despite lower burden of coronary atherosclerosis in women in this cohort, higher levels of interferon-gamma primarily seem counterintuitive: However, multiple aspects should be noted.

First, in comparison with experimental animal studies, our findings seem to be in line with higher interferon-gamma expression and production in settings of inflammation in females as compared to male subjects. Interestingly, animal models indicate that interferon-gamma deficiency in female mice do not affect atherosclerotic lesion

formation, but it does in male mice [18].

Second, interferon-gamma is an important regulator of early atherosclerotic lesion formation and plaque progression. It is known, that women show later manifestation of significant coronary artery disease as compared to men. Thus, women in our cohort, might be at an earlier stage of plaque formation, potentially explaining the higher levels of interferon-gamma observed here [24].

Third, one important effect induced by interferon-gamma in the promotion of atherosclerosis is the upregulation of the expression of the chemokine MCP-1 (monocyte chemoattractant protein 1). This pro-atherogenic factor is chemotactic for monocytes and T-cells [25]. However, in our study MCP-1 levels were significantly lower in females, again potentially indicating, that the elevated interferon-gamma levels in women observed in our study may not inevitably trigger an increased proatherogenic milieu. Consequently, our data implicate that not only interferon-gamma expression but also the interferon-gamma effect seem to vary by sex. Elevated interferon-gamma levels in women as seen in the underlying analysis - might therefore not neccessarily translate into accelerated plaque formation. Consistent with this observation, we also observe no notable variance in interferon-gamma levels among female patients with elevated plaque burden compared to those with minimal plaque burden.

Furthermore, serum interferon-gamma levels were demonstrated to be not equivalent to interferon-gamma activity. This in turn might also partially explain, why higher levels of interferon-gamma do not inevitably correlate with premature plaque progression [26].

Of final note, a sex hormone-mediated anti-inflammatory environment in women might mitigate the detrimental vascular effects of interferon-gamma, thereby reducing plaque formation despite similar or elevated levels of this cytokine. Estrogen might play a pivotal role in this context, as it exerts its vascular protective effects through estrogen receptors, expressed on endothelial and vascular smooth muscle cells. Activation of these receptors were shown to lead to several atheroprotective effects, as a reduction in oxidative stress and inflammation, inhibition of vascular smooth muscle cell proliferation and migration, as well as enhancement of endothelial function and repair mechanisms [27]. These effects might collectively contribute to the maintenance of vascular integrity and the prevention of atherosclerotic lesion development.

In order to reliably identify inflammatory targets for immune therapy, it is important to first fully understand the complex nature of cytokines and their sex-specific differences. This emphasizes the need to meticulously analyze and interpret inflammatory cytokine profiles in respect to sex in future studies in order to provide more robust data for potential therapeutic anti-inflammatory agents.

Regarding therapeutic approaches, previous studies have used biological therapy to target inflammation e.g. in patients with psoriasis. Biological therapy could significantly reduce total coronary plaque burden by 5 % and also interferon-gamma levels after one-year [median (IQR), 10.7 (5.6–28.0) vs. 10.2 (5.2–20.3); P = 0.02] [28]. Of note, it remains unknown whether the magnitude of the underlying effect is similar in men and women. Although higher levels of interferon-gamma exist in women as compared to men, interferon-gamma levels among women seem not to differ regardless of high or low burden of coronary atheroclersosis, as shown in our analysis. Thus, demonstrated effects on atherosclerosis after interferon-gamma therapy may be mostly driven by effects seen in male patients, as men are on one hand frequently over-represented in trials and on the other hand have in general a higher burden of atherosclerotic disease. Whether targeting interferon-gamma could significantly, but more importantly meaningful, reduce the burden of atherosclerosis in women needs to be explored in future studies.

To justify the use of specific anti-inflammatory agents in respect to side-effects, but also from an economic perspective, it remains essential to correctly identify patients at high risk for events. Since publication of the PROSPECT-Trial, we clearly appreciate that major cardiovascular events can result from non-obstructive coronary lesions [29]. As demonstrated in our analysis, coronary CTA will provide detailed information about coronary atherosclerosis and non-obstructive CAD cannot be accurately identified noninvasively by other imaging modalities. Most women presenting with chest pain will have low pretest-probability for obstructive coronary artery disease, a subgroup with high diagnostic yield for imaging with coronary CTA. Similar to LDL cholesterol, for which patients with very high LDL-C levels benefit the most in terms of lipid lowering therapy, certain cohorts, e.g. patients with high burden of atherosclerotic disease and high inflammatory status, might benefit from a tailored antiinflammatory therapeutic approach. Thus, the combination of coronary CTA and serum analysis of inflammatory cytokine profile, seems a promising concept to help further reduce residual risk in patients with coronary atherosclerosis.

4.1. Limitations

A number of limitations of the underlying analysis should be acknowledged. First, this is a cross sectional analysis at a single time point rather than a longitudinal analysis. Thus, progression or regression of coronary artery plaque and changes in plaque morphology in respect to cytokine levels are unknown. Second, testing of multiple variables resulted in significant results in univariate analysis for some of them. Although the cohort is of reasonable size, for multivariable analysis conservative statistical methods were used to reduce the risk of false positives and clinically irrelevant findings. Due to the retrospective design of our analysis, data on baseline medication is not complete. Hence, some effects of medication on the analyzed associations cannot be completely ruled out. However, to avoid interaction on cytokine levels, patients with concomitant inflammatory disease were excluded a priori. Menopausal status was not recorded, therefore no conclusion can be drawn in regard to menopausal status and interferon-gamma levels.

5. Conclusion

We demonstrate in this cohort beyond coronary plaque volume and morphology a significant sex-based difference in inflammatory cytokine profile. In spite of a significantly lower coronary plaque burden in women, serum levels of interferon-gamma were significantly higher as compared to men. However, higher interferon-gamma levels were associated with high plaque burden only among male patients, which suggests different roles of interferon-gamma in men and women or the presence of sex-specific protective mechanisms in females against interferon-gamma mediated atherogenesis.

Declaration of competing interest

The authors declare that there is no conflict of interest related to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2025.104123.

References

[1] Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: the Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J 2019;41:407–77.
[2] Dey D, Schepis T, Marwan M, Slomka PJ, Berman DS, Achenbach S. Automated three-dimensional quantification of noncalcified coronary plaque from coronary CT angiography: comparison with intravascular US. Radiology 2010;257:516–22.
[3] Liu T, Maurovich-Horvat P, Mayrhofer T, et al. Quantitative coronary plaque analysis predicts high-risk plaque morphology on coronary computed tomography angiography: results from the ROMICAT II trial. Int J Cardiovasc Imag 2018;34:311–9.

[4] Nerlekar N, Ha FJ, Cheshire C, et al. Computed tomographic coronary angiography-derived plaque characteristics predict major adverse cardiovascular events: a systematic review and meta-analysis. Circulation Cardiovascular imaging 2018;11:e006973.
[5] Williams MC, Kwiecinski J, Doris M, et al. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction, 141; 2020. p. 1452–62.
[6] Williams MC, Moss AJ, Dweck M, et al. Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-. HEART Study 2019;73:291–301.
[7] Libby P. Inflammation in atherosclerosis. Nature 2002;420:868–74.
[8] Ross R. Atherosclerosis — An Inflammatory Disease 1999;340:115–26.
[9] Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways, 86; 2006. p. 515–81.
[10] Dimitris T, Evangelos KE, Evangelos O, et al. The role and predictive value of cytokines in atherosclerosis and coronary artery disease. Curr Med Chem 2015;22: 2636–50.
[11] Ditiatkovski M, Toh B-H, Bobik A. GM-CSF deficiency reduces macrophage PPAR-γ expression and aggravates atherosclerosis in ApoE-deficient mice. 2006. 26:2337-44.
[12] Taleb S, Tedgui A, Mallat Z. IL-17 and Th17 cells in atherosclerosis, 35; 2015. p. 258–64.
[13] Gong F, Liu Z, Liu J, Zhou P, Liu Y, Lu X. The paradoxical role of IL-17 in atherosclerosis. Cell Immunol 2015;297:33–9.
[14] Fatkhullina AR, Peshkova IO, Koltsova EK. The role of cytokines in the development of atherosclerosis. Biochemistry 2016;81:1358–70.
[15] Hansson GK, Libby P, Tabas I. Inflammation and plaque vulnerability. J Intern Med 2015;278:483–93.
[16] Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 2016;16:626–38.
[17] Bernardi S, Toffoli B, Tonon F, et al. Sex differences in proatherogenic cytokine levels. Int J Mol Sci 2020;21.
[18] Kantarci OH, Goris A, Hebrink DD, et al. IFNG polymorphisms are associated with gender differences in susceptibility to multiple sclerosis. Gene Immun 2005;6: 153–61.
[19] Raaz-Schrauder D, Klinghammer L, Baum C, et al. Association of systemic inflammation markers with the presence and extent of coronary artery calcification. Cytokine 2012;57:251–7.
[20] Matsumoto H, Watanabe S, Kyo E, et al. Standardized volumetric plaque quantification and characterization from coronary CT angiography: a head-to-head comparison with invasive intravascular ultrasound. Eur Radiol 2019;29:6129–39.
[21] Dey D, Cheng VY, Slomka PJ. Automated 3-dimensional quantification of noncalcified and calcified coronary plaque from coronary CT angiography. Journal of cardiovascular computed tomography 2009;3:372.
[22] Tzolos E., McElhinney P., Williams M.C., et al. Repeatability of quantitative pericoronary adipose tissue attenuation and coronary plaque burden from coronary CT angiography. J Cardiovasc Comput Tomogr 2021 Jan-Feb;15(1):81-84. doi: 10.1016/j.jcct.2020.03.007. Epub 2020 Apr 14. PMID: 32312662; PMCID: PMC7554067.
[23] Tousoulis D, Economou EK, Oikonomou E, et al. The role and predictive value of cytokines in atherosclerosis and coronary artery disease. Curr Med Chem 2015;22: 2636–50.
[24] Moss JW, Ramji DP. Interferon-gamma: promising therapeutic target in atherosclerosis. World J Exp Med 2015;5:154–9.
[25] Harvey EJ, Ramji DP. Interferon-gamma and atherosclerosis: pro- or anti-atherogenic? Cardiovasc Res 2005;67:11–20.
[26] Pedersen ER, Midttun O, Ueland PM, et al. Systemic markers of interferon-gamma-mediated immune activation and long-term prognosis in patients with stable coronary artery disease. Arterioscler Thromb Vasc Biol 2011;31:698–704.
[27] Fairweather D. Sex differences in inflammation during atherosclerosis. Clin Med Insights Cardiol 2014;8:49–59.
[28] Elnabawi YA, Dey AK, Goyal A, et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. Cardiovasc Res 2019;115:721–8.
[29] Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.