RESEARCH ARTICLE

Inflammatory cytokines affecting cardiovascular function: a scoping review [version 1; peer review: awaiting peer review]

Risma Aprianda Kristanti¹, Taufan Bramantoro², Pratiwi Soesilawati³, Ninuk Hariyani², Arief Suryadinata⁴, Bambang Purwanto⁵, Alexander Patera Nugraha¹,⁶, Tengku Natasha Eleena binti Tengku Ahmad Noor⁷

¹Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
²Department of Dental Public Health, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
³Department of Oral Biology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
⁴Faculty of Medicine and Health Science, Universitas Islam Negeri Maulana Malik Ibrahim Malang, Malang, Indonesia
⁵Department of Physiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
⁶Department of Orthodontics, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
⁷Faculty of Dental Surgery, Royal College of Surgery, Edinburgh University, Edinburgh, UK

Abstract

Background: A chronic inflammatory process can cause disorders on the cardiovascular system. It is caused by an enhancement of inflammatory cytokines that can decrease the heart working-function. This article aims to review inflammatory cytokines that can cause the cardiovascular system disease.

Methods: The review process began by taking articles from two databases, namely PubMed and SpringerLink without using the publication year limit. The reviewed article was a research article using human samples, which analyzed the impact of inflammatory cytokines on cardiovascular disease or the risk level of cardiovascular disease.

Result: From a total of 3926 articles originating from two databases, 21 obtained articles have matched with the inclusion criteria for the review process. Of those 21 articles, 17 reported an increased effect of inflammatory cytokines on cardiovascular disease, while four articles showed no association between increased inflammatory cytokines and cardiovascular disease. There were six inflammatory cytokines that could affect cardiovascular disease, namely: TNF-α, IL-1β, IL-2, IL-6, IL-8, and IL-17 where cytokine IL-6 is confirmed by as many as 14 articles, TNF-α as many as six articles, and IL-1 β as many as three articles as inflammatory cytokines that could affect cardiovascular function.

Conclusion: The increased level of inflammatory cytokines can be a trigger for decreased function and cause the disease in the cardiovascular system.

Open Peer Review

Approval Status: AWAITING PEER REVIEW

Any reports and responses or comments on the article can be found at the end of the article.
Keywords
interleukin 6, tumor necrosis factor-α, medicine, cardiovascular disease, dentistry, non-communicable disease.

This article is included in the Cell & Molecular Biology gateway.
Introduction

One of the diseases that currently can cause health and socio-economic losses, both in developing and developed countries is cardiovascular disease. This is due to the increase in the number of cardiovascular diseases. Cardiovascular diseases that cause mortality and disability in the world include heart disease, vascular disease, and atherosclerosis.

The major risk factor for the development of cardiovascular disease is inflammation. The occurrence of the inflammatory response is regulated by cytokines. Several studies have shown that cardiovascular disease can be triggered by some inflammatory cytokines and their receptors at a time when the inflammatory process occurs on an ongoing basis. Cardiovascular diseases such as atherosclerotic heart disease, coronary heart disease, and congestive heart failure are associated with an increase in inflammatory cytokines such as Interleukin 1 Beta (IL-1β), Interferon-γ (IFN-γ), and Tumor Necrosis Factor - Alpha (TNF-α), these cytokines are known to induce atherosclerotic plaque formation. Additionally, higher quantities of the cytokines TNF-α, IL-1, and IL-6 have been demonstrated to induce the expression of proatherogenic genes in new findings.

Infection, nutritional imbalance, genetic factors, hypoxia, UV, allergic irritant, drugs, and physical stress can cause inflammation resulting in increased level of inflammatory cytokines. Enhancement of inflammatory cytokines induce cardiovascular diseases by triggering the expression of proatherogenic gen, induce the formation of atherosclerotic lesion, causing myocardial disfunction and cardiac hypertrophy.

This scoping review will map cytokines that have elevated in some inflammatory conditions and their effects on cardiovascular function. Exposure factor mapping will show various inflammatory conditions that can increase cytokines. The results of the outcome mapping will provide an overview of the effect of increasing cytokines on cardiovascular function while from the results of each study that we present will inform cytokine levels that can interfere with cardiovascular function.

Methods

Scoping review was chosen because the review does not attempt to answer very specific study questions, but rather discusses a broader topic so that it is possible to apply more various study designs. We used guidance from Hilary Arksey & Lisa O’Malley framework in implementing the scoping review protocol which consisted of the following stages.

Stage 1: Identifying the research question

Discussions are carried out with the team to determine research questions by considering several key aspects such as study population, exposure, and outcomes. The research questions we will try to answer are: (1) What cytokines can affect cardiovascular function? (2) What inflammatory conditions can increase cytokine levels and interfere with cardiovascular function? (3) What types of disorders in cardiovascular function can appear due to increased cytokine levels? (4) What are the levels of cytokines that can cause impaired cardiovascular function?

Stage 2: Identifying relevant studies

The articles were taken from two database namely Pubmed (https://pubmed.ncbi.nlm.nih.gov) and SpringerLink(https://link.springer.com). Articles were searched using the terms related to cytokine, interleukin, inflammation, infection, cardiovascular. The search keywords for each database presented below: Search keywords for PUBMED:((cytokine OR interleukin[MeSH Terms] AND ((fft[Filter]) AND (english[Filter])))) AND (inflammation OR infection[MeSH Terms] AND ((fft[Filter]) AND (english[Filter]))) AND (cardiovascular AND coronary artery[MeSH Terms] AND ((fft[Filter]) AND (english[Filter])))) Search keywords for SPRINGER LINK:((cytokine OR interleukin) AND inflammation AND cardiovascular AND “coronary artery” AND human NOT extract NOT “a review” NOT “systematic review” Selected articles are restricted to English language and research articles only without using the publication year limit. The most recent search was executed on September 15, 2021 and duplicate articles will be filtered immediately.

Stage 3: Study selection

Two reviewers selected articles that were free from duplication. The selection of articles that suitable with the inclusion criteria is carried out based on reading the title and abstract. Studies that included in this step are: (1) Research articles both observational and experimental with human subjects that analyze changes in cytokines concentrations due to inflammatory condition and their effects on heart function, (2) The outcome of the research is the type of the cytokine that has increased and the type of disturbance in cardiovascular system, (3) no review articles. Furthermore, selection is carried out according to the eligibility criteria through full text reading to reselect articles that will be included in the scoping review process. The selected articles were articles that used the parameters of increasing cytokines in the population experiencing inflammatory conditions in their studies. Inflammatory conditions in the cardiovascular system that can elevate cytokines systemically and weaken cardiovascular function will be included. Any disagreement resolved through a third reviewer.
Stage 4: Charting the data
Two reviewer independently charted the data from final articles used MS Word 2019 form. The key data entered are: title, author, study design, subject, types of inflammatory conditions that cause an increase in cytokine levels and types of cytokines that have increased (cytokines exposure), outcomes on cardiovascular function, study results including cytokine levels that can interfere cardiovascular function, and research conclusion.

Results
Firstly, the researcher collected the articles from two databases and found 3,926 articles, 295 of those were taken from PubMed and 3,631 articles were taken from Springerlink. Those articles were selected first to find the duplicated articles from both databases. 24 duplicated articles were found and removed, so there were 3,901 remaining articles. Then, from the remaining articles, there were 75 selected articles that met the criteria based on abstract readings. Furthermore, the researcher selected articles by reading the entire content and obtained as many as 21 articles for review (Figure 1). More information about the final selected articles has been listed in Table 1.

Characteristics of the articles
The articles reviewed based on research from eight countries, include: five articles from China, five from Italy, three from America, two each from Poland and Germany, and one each from Korea, Johannesburg and Australia. One of the studies took the samples from 31 health centers in Europe. The number of the sample from each study varied from the smallest amount 55 to the largest amount 6,783 with the sample classification consisting of two articles using samples from children and 19 articles using samples from adults. A total of 16 studies used cross-sectional research design, three studies used cohort design, one study used case control, and one study used a combination of cross-sectional and cohort research designs. Article selection was conducted without limitation of the year of publication.

Cytokines that affect cardiovascular function
There are 6 cytokines that can affect cardiovascular function, namely:

IL-6

A total of 14 studies reported that an increased in IL-6 can lead the cardiovascular function disorders, in which two studies used samples of children suffering from Kawasaki Disease. A research found that IL-6 concentration were higher in patient with Kawasaki Disease with coronary artery lesion compared to people Kawasaki Disease without coronary artery lesion (p=0.016). The study Si, et al., 2017, showed serum IL-6 concentration, higher in the group of Kawasaki Disease patients accompanied by coroner artery lesions than the Kawasaki Disease patient group without coroner artery lesions (p<0.05).
| NO | Heading                                                                 | Writer                                                                                       | Study design    | Subject                                                                 | Exposure/cytokine parameters                                                                 | Outcome on cardiovascular function                                                                 | Result                                                                                                                                                                                                                           | Conclusion                                                                                           |
|----|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1  | Coronary artery ectasia is related to coronary slow flow and inflammatory activation | Natale Daniele Brunetti, Giuseppe Salvemini, Andrea Cuculo, Antonio Ruggiero, Luisa De Gennaro, Antonio Gaglione, Matteo Di Biase | Cross sectional | 14 Coronary artery ectasia (CAE) patients                              | Coronary artery ectasia, coronary atherosclerosis                                              | Coronary flow                                                                                           | CAE patients had higher TNF-α, IL-1β, IL-10 levels compared to coronary atherosclerosis and the control (p < 0.05)                                                                 | In patients with CAE, the disease progression was associated with inflammatory activation and impaired coronary circulation. |
|    |                                                                         |                                                                                            |                | 17 coronary atherosclerosis patients                                    | IL-1β, IL-10, IL-8, IL-2                                                                      | Inflammatory activity                                                                                     | Coronary segments experiencing CAE correlated with levels of IL-10 (p < 0.01), IL-1β (p < 0.01)                                                                 | Inflammatory responses were also associated with impaired coronary circulation. |
|    |                                                                         |                                                                                            |                | 15 people as controlled patients                                        |                                                                               | Coroner flow in the left anterior descending artery coronary (p<0.05), at right coronary artery (p<0.001), IL-1β (p<0.01), IL-8 (p<0.05), IL-10 (p<0.01) in CAE sufferers increased, compared to control and subject with atherosclerosis without CAE |                                                                                                                                                                       |                                                                                                                                                                      |
|    |                                                                         |                                                                                            |                |                                                                        |                                                                               | Coroner flow in the left anterior descending segment is associated with TNF-α (r=0.92, p<0.05) and IL-8 (r=0.88, p<0.05) in CAE sufferers                       | Subjects with above-average IL-1β showed higher coroner flow values at left anterior descending (p<0.01)                                                                 |                                                                                                                                                                       |
| NO | Heading                                                                 | Writer                                                                 | Study design     | Subject                                                                                             | Exposure/cytokine parameters | Outcome on cardiovascular function | Result                                                                                                           | Conclusion                                                                                                    |
|----|--------------------------------------------------------------------------|------------------------------------------------------------------------|------------------|------------------------------------------------------------------------------------------------------|-----------------------------|------------------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| 2  | Association between Adipokines and Coronary Artery Lesions in Children with Kawasaki Disease | Hyun Jung Kim, Eun Hye Choi, Hong Ryang Kil | Cross-sectional | 15 afebrile controls patients<br>32 febrile controls patients<br>40 Kawasaki disease patients         | Kawasaki disease (KD), resistin<br>IL-6, TNF-α | Coronary artery lesions            | Serum resistin levels in subjects with KD were higher than in the control group (KD had a level of 177.56 ng/mL, whereas febrile controls had a level of 76.48 ng/mL and afebrile controls had a level of 17.95 ng/mL)<br>Kawasaki disease patients experienced an increase in IL-6 (p = 0.014)<br>Levels of serum IL-6 were statistically higher, while BMI was statistically lower in the KD group with coronary artery lesions than in the KD group without coronary artery lesions (p = 0.016)<br>Levels of serum IL-6 in KD with coronary artery lesions = (228.26 ± 303.97) pg/ml and in KD without coronary artery lesions group = (39.18 ± 107.20) pg/ml<br>Levels of serum TNF-α in KD with coronary artery lesions = (9.21 ± 31.1) pg/ml and in KD without coronary artery lesions group = (0.21 ± 0.22) pg/ml | Resistin levels are higher in Kawasaki disease patients, although this hasn't been used as a predictor of coronary artery lesions in the acute phase. |
| NO | Heading | Writer | Study design | Subject | Exposure/cytokine parameters | Outcome on cardiovascular function | Result | Conclusion |
|----|---------|--------|--------------|---------|----------------------------|----------------------------------|--------|------------|
| 3  | Myocardial Microvascular Dysfunction in Rheumatoid Arthritis (Quantitation by (13)N-Ammonia Positron Emission Tomography/Computed Tomography) | Isabelle Amigues, Cesare Russo, Jon T Giles, Aylin Tugcu, Richard Weinberg, Sabahat Bokhari, Joan M. Bathon | Cohort | • 76 rheumatoid arthritis (RA) patients  
• 34 Non RA asymptomatic controls patients  
• 14 people for Non RA asymptomatic controls | • Rheumatoid arthritis  
• IL-6 | • Myocardial flow reserve (MFR),  
• Myocardial blood flow | • RA patients experienced a 29% decrease in MFR (<2.5) and an increase in IL-6.  
• High IL-6 levels associated with lower MFR values (p=0.024) | One-third of RA patients without cardiovascular illness had lower MFR, which is related with inflammation and increased mass and volume of the left ventricle. |
| 4  | Systemic inflammation is related to coronary microvascular dysfunction in obese patients without obstructive coronary disease | F. Tona, R. Serra, L. Di Ascenzo, E. Osto, A. Scarda, R. Fabris, R. Montisci, G. Famoso, S. Tellatin, M. Foletto, A. Giovagnoni, S. Iliceto, R. Vettor | Cross sectional | • 86 obese patients  
• 48 healthy people as controls | • Obesity without obstructive coronary disease  
• IL-6, TNF-α, adiponectin | • Coronary Flow Reserve (CFR)  
• Coronary microvascular dysfunction | • CFR was higher in non-obese patients (p=0.02), compared to obese patients  
• Abnormal CFR occurs in 27 (31%) obese patients and in 1 (2%) control subjects (p=0.0001)  
• Multivariate analysis results show TNF-α and IL-6 are determinants of CFR (p<0.02)  
• The results of a multivariable logistic regression analysis show IL-6 (p=0.03) and TNF-α (p=0.03) are determinants of CFR ≤ 2.5  
• IL-6 levels were higher in the group with decreased CFR (4.6 [3.6-6.1] ng/l) than the group with normal CFR (3 [2.3-3.8]) ng/l  
• TNF-α levels were higher in the group with decreased CFR (12 [10.5-15.0]) ng/l than the group with normal CFR (10 [8.8-11.5]) ng/l | Obese people with no clinical indications of cardiac disease had lower CFR.  
• Microvascular dysfunction is associated with chronic inflammation mediated by adipocytokines. |
| NO | Heading                                                                 | Writer                                           | Study design         | Subject                                                                 | Exposure/cytokine parameters                                                                 | Outcome on cardiovascular function                                                                 | Result                                                                 | Conclusion                                                                                      |
|----|-------------------------------------------------------------------------|--------------------------------------------------|----------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| 5  | Role of interleukin-17 and interleukin-17-induced cytokines interleukin-6 and interleukin-8 in unstable coronary artery disease | Satwat Hashmi and Qiu Tang Zeng                  | Cross-sectional     | 58 patients consisting of: 14 stable angina patients, 24 unstable angina patients, 20 acute myocardial infarction subjects, 20 healthy people as a control | • Culprit lesion, IL-17, IL-10, IL-8, IL-6, and hs-CRP                                                                 | • Acute Myocardial Infarction (AMI) • Unstable angina • Stable angina                         | • Increased concentrations of proinflammatory cytokines IL-6 (p<0.05), IL-17 (p<0.05), IL-8 (p=0.07 for unstable angina and p<0.05 for AMI), hs-CRP (p<0.05 for unstable angina) and decreased IL-10 concentration (p<0.01) in acute myocardial infarction and unstable angina compared with the control group. • Plasma IL-17 concentrations were positively correlated with hs-CRP (r=0.655, p<0.001) and plasma IL-6 concentrations (r=0.65, p<0.01) • IL-17 levels were greater (326.47±126.10 pg/ml) in patients with more lesions, but no significant difference were compared to the group with a simple picture of lesions (299.47±123.14 pg/ml) • IL-6 levels in the group with complex lesions = (53.24±33.30 pg/ml) and in the group with simple lesions = (46.62±16.33 pg/ml) | Inflammation appears to play a role in boosting the activity of IL-6, IL-17, and IL-8 in people with unstable angina and acute myocardial infarction. Increased IL-17 triggered by inflammation has a role in causing instability in people with artery coronary disease. |
| NO | Heading                                                                 | Writer                                                                 | Study design | Subject                                                                 | Exposure/cytokine parameters                                                                 | Outcome on cardiovascular function | Result                                                                                                                                                                                                                      | Conclusion                                                                                                                                                                                                                     |
|----|------------------------------------------------------------------------|------------------------------------------------------------------------|--------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6  | IL-6 but not TNF is linked to coronary artery calcification in patients with chronic kidney disease | Joanna Kaminska, Marek Stopinski, Krzysztof Mucha, Anna Jędrzejczak, Marek Gołębiowski, Monika A. Niewczas, Leszek Pączek, Bartosz Foroncewicz | Cohort       | 57 patients with chronic kidney disease (CKD):                         | • Chronic kidney disease (CKD)                                                               | Artery calcification               | • IL-6 levels in the unstable angina group = (53.63 ± 31.92 pg/ml) and in the acute myocardial infarction group = (46.91 ± 16.11 pg/ml)                                                                 | • IL-6 is related to calcium score  
  • Chronic inflammation such as coronary artery calcification contributes to the mortality rate of cardiovascular patients with impaired kidney function |
| 7  | Association between interleukin-6 and the risk of cardiac events measured by coronary computed tomography angiography | Lei Zhao, Xilin Wang, Yuhai Yang                                     | Cohort       | 303 patients:                                                           | • Coronary Artery Disease  
  • IL-6                                                               | Atherosclerotic coronary plaques       | • Subjects with high IL-6 levels showed higher atherosclerotic load than subjects with lower IL-6 levels (p<0.001)  
  • Greater IL-6 levels were associated with a higher incidence of MACE and mortality than lower IL-6 levels (p<0.0001).                      | Subjects with elevated levels of IL-6 have a higher risk of atherosclerosis and MACE |
| NO | Heading                                                                 | Writer                                                                                   | Study design       | Subject                                                                 | Exposure/cytokine parameters                                                                 | Outcome on cardiovascular function                                                                 | Result                                                                                                                                                                                                 | Conclusion                                                                                                                                                               |
|----|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 8  | Associations of inflammatory markers with coronary artery calcification: results from the Multi-Ethnic Study of Atherosclerosis | Nancy Swords Jennya, Elizabeth R Brown, Robert Detrano, Aaron R Folsom, Mohammed F Saad, Steven Shea, Moyses Szklo, David M. Herrington, David R Jacobs Jr. | Cross sectional    | 6783 multi-ethnic participants                                         | • coronary artery calcification (CAC), C-reactive protein, fibrinogen • IL-6                                                                 | • artery calcification • atherosclerotic                                                                 | • CRP has a relative risk of 1.13 for CAC based on age, gender and ethnicity. • IL-6 has a relative risk of 1.22 and fibrinogen 1.18 based on gender and ethnicity. | • Inflammatory markers have a weak relationship with CAC. • Inflammatory markers and CAC have different pathophysiologies. |
| 9  | Role of superoxide dismutase in vascular inflammation and in coronary artery disease | V. Lubrano, P. Di Cecco, G.C. Zucchelli                                                  | Cross sectional    | • 36 coronary artery disease (CAD) patients (33 men and 3 women) • 19 normal subjects (16 men and 3 women) • Measurement of extracellular superoxide (EC-SOD) levels, CRP • Measurement of IL-6 and TNF-α levels mm | Impairment of coronary artery function | • The levels of EC-SOD in the control and CAD groups were the same. • There was a significant difference in levels of radical peroxide (p<0.01), hs-CRP (p<0.01), and hs-IL-6 (p<0.001) between subjects with CAD and control groups. • There was an increase in hs-IL-6 levels in subjects with more impaired coronary arteries (p<0.05). • Hs-IL-6 concentrations are associated with CRP (p<0.05, r=0.14) and peroxide radicals (p<0.05, r=0.1) • Average levels of IL-6: control = (1.05±0.2 pg/ml) 1 artery involved = (2.7±0.7 pg/ml) 2 artery involved = (2.6±1.7 pg/ml) | EC-SOD has a small role to play in CAD prevention. • hs-IL-6 can be used as a marker in efforts to prevent and characterize artery coronary disease. |
| NO | Heading                                                                 | Writer                                | Study design       | Subject                                                                 | Exposure/cytokine parameters                                                                 | Outcome on cardiovascular function | Result                                                                 | Conclusion                                                                 |
|----|-------------------------------------------------------------------------|---------------------------------------|--------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------|
| 10 | Biomarkers of endothelial dysfunction, cardiovascular risk factors and atherosclerosis in rheumatoid arthritis | Patrick H Dessein, Barry I Joffe, Sham Singh | Cross sectional   | 74 people with rheumatoid arthritis 80 healthy individuals (control) | Rheumatoid arthritis hs-CRP, IL-1, IL-6, and TNF-α                                            | Marker levels of endothelial function impairment (ICAM-1, VCAM-1, ELAM-1) | 3 artery involved = (3.3±1.0 pg/ml) 4 artery involved = (3.5±0.6 pg/ml) | • Average levels of TNF-α: control = (2.50±1.1 pg/ml) 1 artery involved = (1.05±0.3 pg/ml) 2 artery involved = (1.34±0.2 pg/ml) 3 artery involved = (0.98±0.4 pg/ml) 4 artery involved = (3.90±1.5 pg/ml) |
|    |                                                                         |                                       |                    |                                                                          |                                                                                              |                                    |                                                                       | People with rheumatoid arthritis have worse endothelial function than controls, but also have higher levels of hs-CRP and cytokines. In persons with rheumatoid arthritis, IL-6, rheumatoid titer levels, and GFR may predict the probability of impaired endothelial function. |
| NO | Heading                                                                 | Writer                                                                 | Study design       | Subject                                                                 | Exposure/cytokine parameters                          | Outcome on cardiovascular function | Result                                                                                                                                                                                                 | Conclusion                                                                                                                                                                                                 |
|----|------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------|-------------------------------------------------------------------------|--------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11 | Markers of inflammation are cross-sectionally associated with microvascular complications and cardiovascular disease in type 1 diabetes "the EURODIAB Prospective Complications Study" | MT Schram, N Chaturvedi, CG Schalkwijk, JH Fuller, CDA Stehouwer     | Cross sectional    | 543 subjects with type 1 diabetes were divided into 2 groups:           | • Type 1 Diabetes mellitus  
• IL-6, CRP, and TNF-α | 
• Cardiovascular disease  
• Albuminuria  
• Retinopathy | • In rheumatoid arthritis survivors, VCAM-1 is linked to intima-media carotid artery thickness (p=0.02) and plaque thickness (p=0.04).  
• Markers of inflammation are cross-sectionally associated with microvascular complications and cardiovascular disease in type 1 diabetes.  
• Reduced inflammatory activity can help to reduce vascular problems in people with type 1 diabetes. |
| NO | Heading | Writer | Study design | Subject | Exposure/cytokine parameters | Outcome on cardiovascular function | Result | Conclusion |
|----|---------|--------|--------------|---------|-------------------------------|-----------------------------------|--------|------------|
| 12 | Associations between serum uric acid and adipokines, markers of inflammation, and endothelial dysfunction | S Bo, R Gambino, M Durazzo, F Ghione1, G Muss0, L Gentile, M Cassader, P Cavallo-Perin, and G Pagano | Cross sectional | 100 healthy men | • Uric acid, resistin, hs CRP, leptin, nitrotyrosine • Adiponectin, IL-6, TNF-α | Endothelial dysfunction marker levels: • E-selectin • Intercellular adhesion molecule-1 (ICAM-1) • Vascular adhesion molecule-1 (VCAM-1) | • Subjects with higher uric acid levels had worse metabolic patterns and higher prevalence rates suffering from metabolic • Uric acid levels are inversely proportional to nitrotyrosine levels and directly proportional to TAS | |
| NO | Heading                                                                 | Writer                                                                                     | Study design | Subject                                                                 | Exposure/cytokine parameters | Outcome on cardiovascular function | Result                                                                                           | Conclusion                                                                                           |
|----|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|--------------|--------------------------------------------------------------------------|------------------------------|------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| 13 | Serum levels of interleukin-22, cardiometabolic risk factors and incident type 2 diabetes: KORA F4/FF4 study | Christian Herder, Julia M Kannenberg, Maren Carstensen-Kirberg, Cornelia Huth, Christa Meisinger, Wolfgang Koenig, Annette Peters, Wolfgang Rathmann, Michael Roden, Barbara Thorand | Cross sectional and Cohort | Cross sectional = 1107 people Cohort = 504 people | Type 2 Diabetes mellitus, glucose status, HDL, GFR, IL-22 levels, IL-1R | Male sex, smoking, low HDL levels, low GFR, and low IL-1RA levels are associated with high IL-22 levels (p<0.05) | The average IL-22 levels in type 2 diabetics was 6.28 (1.95; 12.35) pg/ml and in the control group was 6.45 (1.95; 11.80) pg/ml | Increased IL-22 levels are inversely related to various parameters linked with cardiometabolic disease risk, but not with the risk of type 2 diabetes. Although IL-22 cannot be utilized as a biomarker for type 2 diabetes in humans, it has the potential to be used as a marker for cardiovascular disease if more study is done on it. |
| NO | Heading                                                                 | Writer                                                                 | Study design | Subject                              | Exposure/cytokine parameters                                      | Outcome on cardiovascular function | Result                                                                 | Conclusion                                                                 |
|----|-------------------------------------------------------------------------|------------------------------------------------------------------------|--------------|--------------------------------------|------------------------------------------------------------------|-------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 14 | Relationship between IL-27 and coronary arterial lesions in children with Kawasaki disease | Feifei Si, Yao Wu, Fang Gao, Siqi Feng, Ruixi Liu, Qijian Yi            | Cross sectional | 81 children with Kawasaki disease (48 men, 33 women) | • Kawasaki disease  
• Levels of IL-27, IL-17A, IL-10, IL-6, IL-1β, TNF-α in serum | Coronary artery lesions | • Serum levels IL-27 (p=0.004), IL-6 (p<0.05), IL-1β (p<0.05), and TNF-α (p<0.05) were higher in the Kawasaki Disease patient group accompanied by coronary artery lesions than the Kawasaki Disease patient group without coronary artery lesions.  
• There is a relationship between WBC (r=0.185), CRP (r=0.291), PCT (r=0.400), IL-10 (r=0.454), IL-17A (r=0.618), IL-6 (r=0.263), IL-1β (r=0.13) and TNF-α (r=0.372) with IL-27 in subjects with KD  
• Levels of serum IL-6 in KD with coronary artery lesions = (234.20±133.10) pg/ml and in KD without coronary artery lesions group = (110.50±73.70) pg/ml  
• Levels of serum TNF-α in KD with coronary artery lesions = (56.00±15.40) pg/ml and in KD without coronary artery lesions | • Increased IL-27 may be the cause of increased pro-inflammatory cytokines in acute KD  
• IL-27 may have a key role in the progression of coronary artery lesions in persons with acute KD. |
| NO | Heading | Writer | Study design | Subject | Exposure/cytokine parameters | Outcome on cardiovascular function | Result | Conclusion |
|----|---------|--------|--------------|---------|-----------------------------|-----------------------------------|--------|------------|
| 15 | Effect of ABCA1 promoter methylation on premature coronary artery disease and its relationship with inflammation | Fang An, Chao Liu, Xiujuan Wang, Tan Li, Hao Fu, Buhe Bao, Hongliang Cong, Jihong Zhao | Cross sectional | 90 patients with premature coronary artery disease, 90 healthy people | *ABCA1* transcriptional activation rate, CRP, cfDNA/NETs, HDL, IL-1β | Premature coronary artery disease (pCAD) | People with premature coronary artery disease had a higher *ABCA1* transcriptional activation rate than the healthy group (44.24% ± 3.66 vs. 36.05% ± 2.99, p<0.001). The methylation of the *ABCA1* promoter is a risk factor for coronary artery disease (OR=2.87, 95% CI: 1.802–4.594, p<0.001). *ABCA1* promoter methylation levels were positively correlated with IL-1β, cfDNA/NETs, and CRP (r=0.385; 0.404; 0.389; p<0.001), and negatively correlated with HDL (r=0.488, p<0.001). The higher the level of *ABCA1* promoter methylation, the lower HDL levels and high levels of *ABCA1* promoter methylation are risk factors for the development of premature coronary artery disease. The methylation of the *ABCA1* promoter is influenced by inflammatory cytokines and cfDNA/NETs, which leads to the development of premature coronary artery disease. | |
| NO | Heading                                                                 | Writer                                                                 | Study design | Subject                                                                 | Exposure/cytokine parameters                                                                 | Outcome on cardiovascular function | Result                                                                                                                                                                                                 | Conclusion                                                                                           |
|----|-------------------------------------------------------------------------|------------------------------------------------------------------------|--------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| 16 | Epicardial adipose tissue is a predictor of decreased kidney function and coronary artery calcification in youth- and early adult onset type 2 diabetes mellitus | M Reinhardt, T R Cushman, MS Thearle, J Krakoff                     | Cross sectional | 149 Americans (92 women, 57 men of whom 95 were diagnosed with type 2 diabetes) | • Type 2 diabetes mellitus  
• Epicardial fat  
• Pericardial fat  
• IL-6 levels,  
• Calcification of coroner’s arteries  
• Kidney function | • BMI was associated with pericarial fat volume and epicardial fat volume (r=0.26, p=0.001; r=0.37, p=0.0001).  
• In the control group, the volume of epicardial fat associated with coronary artery mass (r=0.51, p<0.0001)  
• The presence of IL-6 levels and coronary artery calcification were associated with epicardial fat volume (β=0.05±0.02 cm³, p=0.03; β=0.02±0.01 pg/ml/cm³, p=0.002).  
• In the group of young type 2 diabetes mellitus subjects, pericardial fat volume is a risk factor for heart disease and can be a predictor of poor kidney function in young type 2 diabetes mellitus patients. | Epicardial fat volume is a risk factor for heart disease and can be a predictor of poor kidney function in young type 2 diabetes mellitus patients. |
| NO | Heading                                                                 | Writer                                                                 | Study design | Subject                                                                 | Exposure/cytokine parameters | Outcome on cardiovascular function | Result                                                                 | Conclusion                                                                 |
|----|------------------------------------------------------------------------|------------------------------------------------------------------------|--------------|------------------------------------------------------------------------|------------------------------|-----------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 17 | Is serum Interleukin-17 associated with early atherosclerosis in obese patients? | Giovanni Tarantino, Susan Costantini, Carmine Finelli, Francesca Capone, Eliana Guerrieri, Nico1ina La Sala, Saverio Gioia, Giuseppe Castello2 | Cross sectional | 80 obese people with normal liver enzyme levels                      | • Obesity  
• C-reactive protein  
• Eotaxin-3 CCL4/ MIP1β, fibrinogen, ferritin  
• IL-8, IL-17, and TNF-α | Thickness of carotid intima-media                             | • There was an association between inflammatory cytokine IL-6 levels and serum IL-17 levels (p<0.0001), TNF-α (p<0.0001), IFN-γ (p < 0.0001)  
• IL-17 levels are associated with IL-8 (95%CI: p<0.0001), eotaxin (95%CI: p<0.0001), and CCL4/MIP1β (95%CI: p<0.0001)  
• Examination of serum eotaxin levels (p=0.0059) and visceral fat (p=0.0010) can predict carotid intima media thickness. | • The thickness of the carotid intima media and the IL-17-related eotaxin have a strong association.  
• The link between visceral fat, serum eotaxin levels, and carotid intima media thickness supports the idea that IL-17 produced by visceral fat tissue can cause atheromatous vascular smooth muscle cells to secrete eotaxin. |
| 18 | Association of systemic inflammation with epicardial fat and coronary artery calcification | Soren Gauss, Lutz Klinghammer, Alina Steinhoff1, Dorette Raaz-Schrauder, Mohamed Marwan, Stephan Achenbach, Christoph D. Garlichs | Cross sectional | 391 people at high risk of coronary artery disease                  | • Epicardial fat volume and inflammatory markers  
• (IL-17, IL-15, IL-13, IL-12, IL-10, IL-8, IL-7, IL-6, IL-4, IL-2, IL-1α, IP-10, Eotaxin, MIP-1, MCP-1, G-CSF, GM-CS, hs-CRP, TNF-α, IFN-γ) | Calcification of coronary arteries | • Epicardial fat volume and CAC have a significant correlation (p=0.001; r=0.37)  
• Coronary artery calcification and epicardial fat volume were significantly related to age (r=0.32), gender | • Epicardial fat volume indicates the development of atherosclerosis as measured through coronary artery calcification scores  
• Systemic inflammatory marker levels do not predict |
| NO | Heading                                                                 | Writer                                                                 | Study design       | Subject                                                                 | Exposure/cytokine parameters                                                                 | Outcome on cardiovascular function                                                                 | Result                                                                 | Conclusion                                                                 |
|----|-------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| 19 | Comparison of inflammation, arterial stiffness and traditional cardiovascular risk factors between rheumatoid arthritis and inflammatory bowel disease | Fenling Fan, Abby Galvin, Lu Fang, David Andrew White, Xiao-lei Moore, Miles Sparrow, Flavia Cicuttini, Anthony Michael Dart | Cross sectional    | • 43 rheumatoid arthritis patients                                       | • Rheumatoid Arthritis                                                                      | • Endothelial dysfunction, Arterial stiffness                                              | (p<0.001), diabetes (p=0.036), smoking (p<0.001), and hypertension (p<0.001). | increased coronary artery calcification and epicardial fat volume. |

Calcification of coronary arteries is negatively correlated with IL-13 (r=-0.10) and G-CSF (r=-0.12)

Epicardial fat volume is positively correlated with IP-10 (p=0.002), MCP-1 (p=0.037)

The development of coronary artery calcification is significantly related to the expansion of epicardial fat (p<0.001)

Results showed no association between increased coronary artery calcification, epicardial fat volume, cytokines indicating systemic inflammation.

TNF-, IL-10, IL-1β, IL-6, and von Willebrand factor (vWF) levels were greater in patients with IBD and rheumatoid arthritis compared to controls.

In rheumatoid arthritis CRP levels are higher than IBD.

There is no link between inflammatory markers and arterial stiffness.
| NO | Heading                                                                 | Writer                                                                 | Study design | Subject                                                                 | Exposure/cytokine parameters                                                                 | Outcome on cardiovascular function                                                                 | Result                                                                                                                                                                                                 | Conclusion                                                                                       |
|----|-------------------------------------------------------------------------|------------------------------------------------------------------------|--------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| 20 | Association of influenza virus infection and inflammatory cytokines with acute myocardial infarction | Xiuru Guan, Wei Yang, Xijuan Sun, Lanfeng Wang, Benjiang Ma, Hongyuan Li, Jin Zhou | Case control | 120 acute myocardial infarction (AMI) patients 160 controls          | • Influenza virus<br>• Titer IgG<br>• levels of TNF-α, IL-18, IL-10, IL-6, IL-2, ET-1, IFN-γ, sVCAM-1, sICAM-1 | Acute Myocardial Infarction (AMI)                                                                 | • The AMI group has positive IgG antibody titers for IV-B and IV-A (IV-B: OR: 10.2, 95% CI: 5.7–20.0; IV-A: OR: 3.1, 95% CI: 1.5–6.4)<br>• The risk of AMI is related to the | AMI is associated to influenza virus infection.<br>The development of atherosclerosis in inflammatory cytokines plays a role in triggering AMI |
| NO | Heading                                                                 | Writer                                                                                                                                  | Study design | Subject                                                                                     | Exposure/cytokine parameters                                                                 | Outcome on cardiovascular function                                                                 | Result                                                                                                                                                                                                 | Conclusion                                                                                                                                                                                                 |
|----|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 | Plasma concentration and expression of adipokines in epicardial and subcutaneous adipose tissue are associated with impaired left ventricular filling pattern | Kacper Toczyłowski, Tomasz Hirnle, Dorota Harasiuk, Piotr Zabieliski, Anna Lewczuk, Iwona Dmitruk, Monika Ksiazek, Artur Sulik, Jan Gorski, Adrian Chabowski, Marcin Baranowski | Cross sectional | 55 male patients with Coronary Artery Disease (CAD) | • Fat tissue  
• TNF-α, IL-6, apelin, visfatin, resistin, adiponectin level, leptin in plasma  
• Expression of mRNA and protein in epicardial fat tissue and subcutaneous fat tissue | Decreased left ventricular filling function | Diabetes and obesity are linked to lower levels of plasma adiponectin, higher levels of leptin, higher levels of leptin and IL-6 expression, and higher levels of visfatin expression in epicardial fat tissue (p<0.001).  
• Decreased diastole function in the left ventricle is inversely proportional to the increase in plasma IL-6 concentration \((\beta=-0.28\pm0.13; p=0.03)\) for the initial diastole velocity and \((\beta=-0.34\pm0.13; p=0.014)\) for the ratio of blood flow speed at the peak of the initial diastole versus the speed of blood flow at the end of diastole | Adipokin expression in subcutaneous fat tissue and epicardial fat tissue is associated with heart function  
Diastole dysfunction in the left ventricle is strongly associated with systemic adipokin levels |
Two studies confirmed the presence of impaired cardiovascular function in rheumatoid arthritis patients. One study found that rheumatoid arthritis sufferers had an increase in IL-6 (p=0.024) levels as well as a 29% decrease in myocardial flow reserve. This study was supported by other studies that showed an increased in IL-6 in people with rheumatoid arthritis can lead to impaired function in the endothelial (p≤0.03). 

According to a study, greater IL-6 levels were linked to a higher calcium level (p<0.05) and the development of calcification of the corona’s arteries in individuals with chronic kidney disease (p<0.05). There were 2 other studies with samples of people with diabetes mellitus that showed an increased association of IL-6 and the risk of cardiovascular disease. The first researcher proved that the elevated risk of cardiovascular disease was caused by an increase in IL-6 in patients with type 1 diabetes mellitus (Z score=-0.28, 0.06 with CI=95% and a value of p<0.001). Another study found that the volume of epicardial fat in young early-adult-onset diabetes mellitus patients is linked to the presence of coronary artery calcification and IL-6 levels (β=0.05±0.02 pg/ml/cm³, p=0.03; β=005 ± 0.01 pg/ml/cm³, p=0.002).

There was one study that reported an increase in IL-6 in obesity conditions at risk of cardiovascular disease, where coronary flow reserve in obese people was lower than that of people without obesity (p=0.02) and a multivariate analysis revealed that IL-6 was a determinant of coronary flow reserve (p<0.02). In addition, one study showed that if a person has a high level of IL-6, he will have a higher atherosclerotic load (p<0.001) and increase the risk to develop a major adverse cardiac events (MACE) (p<0.0001).

Three studies reported that cardiovascular patients may experience an increased in IL-6 which ultimately increases the risk of developing the disease. Research Lubrano et al. (2006), found that subjects with coronary artery disease who had higher levels of IL-6 had more impaired coronary arteries than those who had lower levels of IL-6 (p<0.05). The study was supported by other studies proving that people suffering from coronary artery disease with higher levels of IL-6 are at risk of developing impaired diastole function in the left ventricle (β=-0.28±0.13; p=0.03) for the initial diastole velocity and (β=-0.34±0.13; p=0.014) for the ratio of blood flow speed at the peak of the initial diastole versus the speed of blood flow at the end of diastole. One study reported that people with acute myocardial infarction infected with influenza virus had markers of atherosclerosis and higher levels of IL-6 than the control group (p=0.01). Other studies also confirmed that IL-6 can be an independent predictor for acute myocardial infarction for someone who has suffered from cardiovascular disease (p=0.03).

Another study proving that an increased cytokine IL-6 can also increase the risk of cardiovascular disease was also conducted by Jenny et al. (2010), against a multiethnic sample in America. According to the findings, increased levels of IL-6 had a relative risk of 1.22 based on gender and ethnicity for causing coronary artery calcification.

**TNF-α**

Six studies found a link between an increase in TNF-α, which occurs in an elevated risk of cardiovascular disease and inflammatory diseases. One study in people with chronic kidney failure showed that elevated concentrations of TNF-α (p<0.01) were associated with vascular cellular adhesion molecule-1 (VCAM-1) (p<0.05) where an increased in VCAM-1 will increase the risk of calcification of the corona’s arteries. 

This study is also supported by other studies where the increased risk of cardiovascular disease is caused by an increase in TNF-α in patients with type 1 diabetes mellitus (Z score=-0.28, 0.06 with CI=95% and a value of p<0.001). The study Si F et al. (2017), showed serum TNF-α levels, higher in the Kawasaki Disease patient group accompanied by coronary artery lesions than the Kawasaki Disease patient group without coronary artery lesions (p<0.05).

Two studies showed that increased levels of TNF-α in someone suffering from cardiovascular disease will aggravate the progression of the disease. One study proved an increase in TNF-α in people with coronary artery ectasia with influenza virus had higher levels of TNF-α and markers of atherosclerosis than the control group (p=0.01).

Another condition that can increase TNF-α levels is obesity. The study showed that, from the results of multivariate analysis in a sample of people with obesity, TNF-α levels are a determinant of coronary flow reserve (p<0.02) where with increasing levels of TNF-α there will be a decrease in coronary flow reserve.
IL-1β

Three studies reported a level that increases the risk of cardiovascular disease is IL-1β, whereas one study showed an increased association of IL-1β and cardiovascular disease risk in inflammatory diseases. The study Si F et al. (2017), showed serum IL-1β levels is higher in Kawasaki Disease patient group accompanied by coroner artery lesions than the Kawasaki Disease patient group without coroner artery lesions (p<0.05).13

Another study confirmed that people with cardiovascular disease itself were at risk of increased levels of IL-1β which worsened the disease. An increase in IL-1β in coronary artery ectasia compared to atherosclerosis and control (p<0.05) can result in increased flow in right coronary artery and left anterior descending coronary artery (p<0.01).26 Other studies reported an increased in IL-1β (p<001) as a risk factor for increased levels of ABCA1 promoter methylation (r=0.385, p<0.01) where the higher the level of ABCA1 promote methylation, the higher the risk of premature coronary artery disease.27

IL-17

Research in the obese group showed that at higher eotaxin levels there was an increase in carotid intima thickening (p=0.0059), an increase in IL-17 was related with an increase in serum eotaxin levels (95%CI: p<0.0001), which is a risk factor for atherosclerosis.28 This study was supported by another study found an increase in the cytokine IL-17 (p<0.05) in unstable angina patients and acute myocardial infarction compared to the control group.29

IL-18

One study showed that people with acute myocardial infarction infected with influenza virus had higher levels of IL-18 and atherosclerosis marker markers (p=0.01) than the control group.23

IL-2

The study from Guan et al. (2012), proved that there was an increased in IL-2 and marker markers of atherosclerosis in acute myocardial infarction sufferers infected with influenza virus (p=0.01).26

Cytokine levels that affect cardiovascular function

The summary for cytokines that have increased in inflammatory conditions and their effect on the cardiovascular system can be seen in Table 2. One study showed that compared to type 1 diabetes mellitus without cardiovascular disease, type 1 diabetes mellitus patients with cardiovascular disease had higher levels of inflammatory cytokines (IL-6: 2 pg/ml and 1.5 pg/ml; TNF-α: 3 pg/ml and 2 pg/ml for).17

In the Kawasaki Disease with coronary artery lesions group, IL-6 levels were 228.26 ± 303.97 pg/ml and TNF-α levels were 9.21 ± 31.10 pg/ml, while the Kawasaki Disease group without coronary artery lesions had IL-6 levels was 39.18 ± 107.20 pg/ml and TNF-α levels were 0.21 ± 0.22 pg/ml.12 Another similar study showed that the Kawasaki Disease with coronary artery lesions group, the levels of IL-6, IL-1β, and TNF-α were 234.1 ± 133.1 pg/ml, 33.8 ± 18.7 pg/ml, 56.0 ± 15.4 pg/ml, while the Kawasaki Disease group without coronary artery lesions the levels of IL-6, IL-1β, and TNF-α were 110.5 ± 73.7 pg/ml, 3.6 ± 0.6 pg/ml, and 21.6 ± 4.6 pg/ml.13

One study in the obese group showed that the group with decreased coronary flow reserve, the average levels of IL-6 and TNF-α were 4.6 (3.6 – 6.1) ng/l and 12 (10.5 – 15.0) ng/l, higher than the group without a normal coronary flow reserve rates where IL-6 ang TNF-α levels were three (2 – 3.8) ng/l and ten (8.8 – 11.5) ng/l.19

One study using samples of patients with cardiovascular disease proved that the group with simple lesions on the coronary arteries, the IL-6 levels were 46.62 ± 16.33 pg/ml and the group with complex lesions, the levels of IL-6 were 53.24 ± 33.30 pg/ml.24 One study showed that the average IL-6 concentration in the group with narrowed lumen diameter in 1 coronary artery was 2.7 ± 0.7 pg/ml, 2 arteries was 2.6 ± 1.7 pg/ml, 3 arteries was 3.3 ± 1.0 pg/ml, and four arteries was 3.5 ± 0.6 pg/ml and also the average concentration of TNF-α in the group with narrowed lumen diameter in one coronary artery was 1.05 ± 0.3 pg/ml, two arteries was 1.34 ± 0.2 pg/ml, three arteries was 0.98 ± 0.14 pg/ml, and four arteries was 3.9 ± 1.5 pg/ml.21 The group with premature coronary artery disease also showed a higher average IL-1β level of 57.74 ± 12.55 pg/ml compared to the healthy group of 47.66 ± 14.77 pg/ml.27
In this present study, the investigation of inflammatory cytokines that associated to cardiovascular system disease was done. According to the review that has been conducted, it was found that the increased in some cytokines can cause impaired function in cardiovascular system, especially in the coroner’s arteries. There were three most widely reported inflammatory cytokines: IL-1β, IL-6 and TNF-α. Elevated IL-6 may be at risk of causing lesions of artery coronaria.\textsuperscript{12,13,16,18,20,24,25} IL-6 increased the angiotensin II receptors activity and expression of adhesion molecules in endothelial cells, triggering inflammation of blood vessels.\textsuperscript{29} The development of atherosclerosis and vascular diseases is complicated by blood vessel inflammation.\textsuperscript{30,31} Pro-inflammatory cytokine may enhance the risk factor of cardiovascular system through narrowing blood vessel resulted to high blood pressure. The increased level of pro-inflammatory cytokines can be a trigger for decreased function and cause the disease in the cardiovascular system.

Cell adhesion molecules (VCAM1 and ICAM-1) promote leukocyte adhesion and migration to the subendothelial space.\textsuperscript{32} In addition, increased levels of IL-6 can also cause disruptions in the flow in the coronary arteries.\textsuperscript{3,19,22} The complex interaction between TF and Von Willebrand Factor (vWF), vascular dysfunction and endothelial damage is triggered by inflammation of various cells in the walls of blood vessels.\textsuperscript{33,34} IL-6 can trigger the expression of tissue factor (TF) (index for coagulation), chemokines, and adhesion molecules on endothelial cell surfaces.\textsuperscript{35,36} Increased damage to endothelial cells can lead to a decrease in nitric oxide levels released into blood vessels resulting in impaired vascular function and decreased blood flow.\textsuperscript{37,38} In addition, the decreased in coronary flow reserve (CFR) can be caused by narrowing of the coroner’s arteries or it could be due to endothelial dysfunction that occurs before the narrowing of the arteries. Multivariate analysis shows that microvascular dysfunction is not a risk factor for the early phase of atherosclerosis in asymptomatic obese individuals, but rather the role of inflammation.\textsuperscript{39}

The increased in IL-6 not only occurs in infectious disease conditions, but there are also other conditions that can cause an increased in IL-6, namely obesity and increased volume of epicardial fat.\textsuperscript{18,19} Cytokines such as TNF-α and IL-6 can be produced by fat cells which are mediaters in the occurrence of inflammatory responses in subjects with obesity.\textsuperscript{40}

### Table 2. Summary for cytokines that have increased in inflammatory conditions and their effect on the cardiovascular system.

| Inflammatory conditions                      | Cytokine   | Cardiovascular outcome                                      | Number of studies |
|---------------------------------------------|------------|-------------------------------------------------------------|-------------------|
| Kawasaki disease                            | IL-6       | Coronary artery lesion                                      | 2 (9.5%)          |
|                                             | TNF-α      | Coronary artery lesion                                      | 1 (4.8%)          |
|                                             | IL-1β      | Coronary artery lesion                                      | 1 (4.8%)          |
| Rheumatoid arthritis                        | IL-6       | Decrease in myocardial flow reserve                         | 2 (9.5%)          |
|                                             | TNF-α      | Coronary artery lesion                                      | 1 (4.8%)          |
|                                             | IL-1β      | Coronary artery lesion                                      | 1 (4.8%)          |
| Chronic kidney disease                      | IL-6       | Artery coronary calcification                               | 2 (9.5%)          |
|                                             | TNF-α      | Artery coronary calcification                               | 1 (4.8%)          |
| Diabetes mellitus type 1                    | IL-6       | Artery coronary calcification                               | 1(4.8%)           |
|                                             | TNF-α      | Artery coronary calcification                               | 1 (4.8%)          |
| Obesity                                     | IL-6       | Decrease in coronary flow reserve                           | 1 (4.8%)          |
|                                             | TNF-α      | Decrease in coronary flow reserve                           | 1 (4.8%)          |
|                                             | IL-17      | Atherosclerosis                                               | 2 (9.5%)          |
| Coronary artery disease cause by inflammation| IL-6       | Atherosclerosis                                               | 3 (14.3%)         |
|                                             | TNF-α      | Atherosclerosis                                               | 2 (9.5%)          |
|                                             | IL-1β      | Atherosclerosis                                               | 2 (9.5%)          |
| Acute myocardial infarction invaded with Influenza virus | IL-18 | Atherosclerosis                                               | 1 (4.8%)          |
|                                             | IL-2       | Atherosclerosis                                               | 1 (4.8%)          |
An increased level of TNF-α can trigger the formation of lesions on the coroner’s arteries that can lead to atherosclerosis and acute myocardial infarction.\textsuperscript{13,16,23} TNF-α can accelerate the occurrence of apheresis by triggering increased expression of Monocyte Chemotactic Protein-1 (MCP-1), E-selectin, VCAM-1, and ICAM-1.\textsuperscript{43} In addition, TNF-α can increase the expression of NF-κβ, so that Fractalkine expression can also increase which triggers the formation of atherosclerosis lesions.\textsuperscript{42}

TNF-α can cause impaired function in endothelial and microvascular cells and potentially decrease flow in the coronary artery.\textsuperscript{19,26} Decreased in artery coronaria due to the increased of TNF-α caused by TNF-α can decrease the availability of nitric oxide in endothelial cells so that the ability of vasodilation of blood vessels is also impaired. In addition, TNF-α causes an increased in apoptosis of endothelial cells that result in injury to blood vessels.\textsuperscript{31}

IL-1β triggers inflammation in endothelial cells.\textsuperscript{43} IL-1 induces the attachment of molecules such as VCAM-1, ICAM-1 which can lead to recruitment of leucocytes. IL-1 also stimulates chemokines such as monocyte chemoattractant protein (MCP)-1 (C-C motif chemokine ligand [CCL]-2) which is a chemoattractant for mononuclear phagocytes, implying a role for IL-1 in cardiovascular disease. When exposed to inflammatory stimuli, atheroma cells secrete IL-1.\textsuperscript{43,45} Moreover, IL-1β may increase the risk of lesions in the coroner’s arteries\textsuperscript{13} because IL-1 β induces IL-6 production. The increased of IL-6 production will trigger the liver to produce fibrinogen and plasminogen activator inhibitors that stimulate in the formation of thrombus accumulation as a precursor to atherosclerosis.\textsuperscript{46} In addition, increased levels of IL-6 triggered by IL-1 β also cause impaired vascular function and decreased blood flow.\textsuperscript{37,38}

Elevated levels of inflammatory cytokines can also be caused by cardiovascular disease itself and lead to increased progression of more severe disease, such as calcified coronary artery lesions, increased coronary artery luminal narrowing, and coronary artery flow disturbances.\textsuperscript{21,22,23,26,26}

There are several inflammatory cytokine that associated with cardiovascular disease, high risk patient should modify their lifestyle such as healthy diet and light continuous exercise to minimize the cardiovascular disease risk. Health general checkup frequently also play important role to control the risk of cardiovascular disease.

However, in the process, the scoping review that has been carried out has several limitations, the articles included do not all have the determination of cytokine levels that can cause impaired cardiovascular function and the determination of the type of disorders in cardiovascular function is not done specifically. Further study is urgently needed such as systematic review with meta-analysis to provide the higher evidence level about this topic.

Future research
Research that has been done shows that levels of inflammatory cytokines that can trigger disorders of the cardiovascular system vary widely, this seems to be strongly influenced by many factors. Further research is needed to determine the levels of inflammatory cytokines that can trigger disorders of the cardiovascular system by considering confounding factors such as type of inflammatory disease, age, BMI, and lifestyle so that more appropriate data is obtained for determining inflammatory cytokine levels.

Conclusion
Based on the results of this review, it is known that inflammatory cytokines can cause impaired function in cardiovascular system. This means that cardiovascular disease prevention approaches can be taken through controlling factors that can trigger an increase in inflammatory cytokines, especially inflammatory diseases and infections.

Data availability
All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines
Figshare: PRISMA-ScR checklist for Inflammatory cytokines affecting cardiovascular function: a scoping review. https://doi.org/10.6084/m9.figshare.20277921.v1.47

Figshare: PRISMA flowchart Inflammatory cytokines affecting cardiovascular function: a scoping review. https://doi.org/10.6084/m9.figshare.20277972.v1.48

Figshare: Table Review Inflammatory cytokines affecting cardiovascular function: a scoping review. https://doi.org/10.6084/m9.figshare.20277975.v1.49

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).
39. Vaccarino V, Khan D, Votaw J, et al.: Inflammation is related to coronary flow reserve detected by positron emission tomography in asymptomatic male twins. J. Am. Coll. Cardiol. 2011; 57: 1271–1279.

40. Berg A, Sherer P: Adipose tissue, inflammation, and cardiovascular disease. Circ. Res. 2005; 96: 939-949. Publisher Full Text

41. Hotamisligil G, Arner P, Caro J, et al.: Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J. Clin. Invest. 1995; 95: 2409–2415. PubMed Abstract | Publisher Full Text

42. Zhang H, Zhang C: Vasoprotection by Dietary Supplements and Exercise: Role of TNFα Signaling. Exp. Diabetes Res. 2011; 2012: 1–6. Publisher Full Text

43. Bevilacqua M, Pober J, Wheeler M, et al.: Interleukin-1 activation of vascular endothelium effects on procoagulant activity and leukocyte adhesion. Am. J. Pathol. 1985; 121: 393–403.

44. Libby P, Ordovas J, Auger K, et al.: Endotoxin and tumor necrosis factor induce interleukin-1 gene expression in adult human vascular endothelial cells. Am. J. Pathol. 1986; 124: 179–185. PubMed Abstract

45. Libby P, Ordovas J, Birinyi L, et al.: Inducible interleukin-1 expression in human vascular smooth muscle cells. J. Clin. Invest. 1986; 78: 1432–1438. PubMed Abstract | Publisher Full Text

46. Libby P: Interleukin-1 Beta as a Target for Atherosclerosis Therapy Biological Basis of CANTOS and Beyond. J. Am. Coll. Cardiol. 2017; 70(18): 2278–2289. PubMed Abstract | Publisher Full Text

47. Bramantoro T: PRISMA-SCR Inflammatory cytokines affecting cardiovascular function: a scoping review. figshare. Dataset. 2022. Publisher Full Text

48. Bramantoro T: PRISMA-Scr flowchart Inflammatory cytokines affecting cardiovascular function: a scoping review. figshare. Figure. 2022. Publisher Full Text

49. Bramantoro T: Table Review Inflammatory cytokines affecting cardiovascular function: a scoping review. figshare. Dataset. 2022. Publisher Full Text
The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com