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The Stromal Cell-derived Factor-1/CXCL12 3'A-gene Polymorphism is Related to the Increased Risk of Coronary Artery Disease: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND: Single-nucleotide polymorphism in the stromal cell-derived factor-1 (SDF-1)/CXCL12 gene had been associated with an increased risk of coronary artery disease (CAD). However, several published studies have shown inconsistent results.

AIM: A meta-analysis was assessed to evaluate the association between SDF-1 3'A-gene polymorphism and CAD in the literature.

METHODS: A systematic review was conducted in accordance with PRISMA guidelines and adhering to the Cochrane Handbook for Systematic Reviews. The literature search strategy was carried out on April 3, 2019, from PubMed, EBSCO, Google Scholar, and DOAJ during 2013–2018 period using various keywords related to SDF-1, CXCL12, polymorphism, and CAD. Original data from the group, case-control study, English full-text, and DNA polymorphism assessment using polymerase chain reaction were enrolled. Gene polymorphism in A-base nucleotide among patients with CAD and healthy subjects were evaluated. All data were analyzed using Review Manager 5.3 (Cochrane, Denmark) for meta-analysis.

RESULTS: Five eligible studies extracted for data analysis (2013–2018) based on the assessment of 2-independent reviewers. Several studies have been excluded due to irrelevant criteria evaluated. A significant result was found between SDF-1 3'A gene polymorphism with the increased risk of CAD in the overall effect evaluation using a fixed-effects model (odds ratio [OR]: 2.02; 95% confidence interval 1.54-2.65; I²: 34%; p<0.001) on the forest plot.

CONCLUSION: Our meta-analysis suggests that gene polymorphism in A-base nucleotide of SDF-1/CXCL-12 was associated with the susceptibility of CAD. However, a bigger-scale and well-design of case-control study should be conducted to clarify these conclusions.

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Introduction

Coronary artery disease (CAD) is one of cardiovascular disease which has been well known as the leading cause of death in both developed and developing countries [1]. CAD is an atherosclerotic disease that occurs in the coronary artery, which is manifested by stable angina, unstable angina, myocardial infarction, or sudden cardiac death [2]. The characteristic of pathological changes in atherosclerosis results from the endothelial injury or functional disorder, which is triggered by the abnormal accumulation of lipoproteins in the intima, as well as chronic inflammation [3]. As chronic inflammation, the immune system also plays critical roles in the initiation

and propagation of atherosclerosis [4]. Several studies have shown that the dysregulation of immune cells and chemokines results in the progression of atherosclerosis, plaque instability, and the subsequent onset of acute coronary syndrome (ACS, including unstable angina pectoris and acute myocardial infarction [MI]) [4], [5].

Atherosclerosis is manifested as foam cell accumulation beneath the endothelial cell as well as smooth muscle recruitment, which leads to thrombus formation [5]. Several chemokines have been known to promote this process; one of them is stromal cell-derived factor-1(SDF-1). SDF-1, also called as chemokine (C-X-C motif) ligand 12 (CXCL12), is one of the family members of CXC chemokine located on chromosome 10q11.21 and mostly known for its pivotal role in the smooth muscle

progenitor cells (SPCs) accumulation [6], [7]. MAPK and PI3K pathway also trigger the macrophage migration, particularly in the foam cell formation by binding of SDF-1 to CXCR4, a G-protein coupled receptor [8]. In addition, the SDF-1 expression also acts as a chemoattractant to recruit immune leukocyte cells, such as lymphocytes and monocytes, and, in turn, regulates the pro-inflammation cascade pathway which is responsible for plaque rupture and the occurrence of CAD such as MI [9].

Since lymphocytes and monocytes are prominent in the progression of atherosclerosis, it has been suggested that the disruption of SDF-1 function plays a critical role in the pathogenesis of CAD as well as could be used as a prognostic biomarker [10]. The disruption of SDF-1 has been proposed associated with the genetic variability caused by single nucleotide polymorphism (SNP) which leads to its overexpression in atheroma plaque [11]. There is strong evidence that SNP loci in the SDF-1 genes are associated with the risk of CAD due to a transition of G-to-A base (G>A) at position 801 in the 3'untranslated region (UTR) [11], [12]. However, a different race between Asian and Caucasian as well as the time of studies differ from the previous studies [11], [13]. Therefore, a systematic review and meta-analysis were performed to determine the relationship between SDF-1/CXCL12 3'A-gene polymorphism and risk of CAD from 5 years of current studies.

Methods

Literature eligibility criteria

Eligibility criteria were created based on the PICO framework. PICO criteria used in this study as follows: (1) Patient: Adult people; (2) Interest: CAD; (3) Control: non-CAD; and (4) Outcome: The polymorphism of SDF-1/CXCL12 AA-genes. The articles used in this study included all literature that provided full-text articles regarding the comparison of SDF-1/CXCL12 3'A-gene polymorphism and non-polymorphism in CAD patients. We exclude review, animal, anatomic, cadaveric, qualitative, and economic studies. Articles made by the same author in the same institution were performed sample evaluation to prevent sample duplication. We included studies published in Bahasa and English. Other languages were translated using google translate and decided by the author whether they include them or not. Five-year studies (2013–2018) were included to provide the current results.

This review included studies with adult participants (age 18 years or older) of both genders who have suffered CAD. CAD was defined as is the narrowing or blockage of the coronary arteries, usually caused by atherosclerosis. There are different terms used regarding CAD in this study, such as MI and coronary heart disease (CHD). The reviewed interest was SDF-1 3'A-gene polymorphism. SDF-1 3'A-gene polymorphism is defined

as a presence of SNP (rs1065297, rs1801157, rs266089, rs197452, rs2839693, and/or rs10793538) in HHEX gene located on chromosome 10q24 participants of all nationalities, ethnic, and race were included in this study.

Methods for identifying evidence

We extracted the eligibility criteria (PICO) into keywords using Boolean operator. In this study, we used keywords ((stromal cell-derived factor-1) odds ratio (OR) stromal cell-derived factor 1) OR SDF-1) OR SDF1) OR CXCL 12) OR CXCL-12) OR CXCL12) AND (coronary artery disease) OR CAD) OR CHD) OR CHD) AND (polymorphism) OR gene mutations)) in PubMed, EBSCO, Google Scholar, and Directory of Open Access Journal (DOAJ) database to find the eligible studies.

The study selection process was performed by two independent authors (IPYP and EM) to reduce the possibility of discarding relevant studies. The decision of another author was used when a disagreement occurred. Duplicate records were removed. Titles and abstracts were screened and irrelevant studies were removed. Studies that passed the first screening were further evaluated for the compliance of the inclusion and exclusion criteria of this review. Finally, the studies were further evaluated for their quality before included in this review.

Study selection

In the first phase, the title of the literature was examined and irrelevant studies such as review articles, non-experimental studies, as well as anonymous authors, were removed. In the next phase, the full-text of potentially relevant literature was retrieved and examined for compliance with the eligibility criteria of this review; the selected literature must meet the inclusion and exclusion criteria such as case-control study, including OR, as well as full-text articles. Finally, the selected literature was assessed for their evidence before being included in the final review (Figure 1).

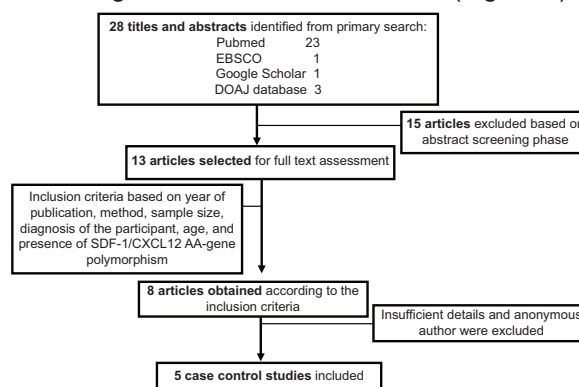


Figure 1: The PRISMA diagram of literature selection in this study

Data collection

Literature that was identified merged and managed for further analysis. All of the selected literature

was thoroughly read and apprehended to extract the principle of the literature. An electronic data collection form was used to collect data from each author. The collected data by each author will be merged and be managed with software Review Manager 5.3. The data items were the author's name, year of publication, method, sample size, diagnosis of the participant, age, and presence of SDF-1/CXCL12 AA-gene polymorphism. They were calculated for the OR and were analyzed.

Quality study assessment

Studies that complied with inclusion and exclusion criteria were assessed for their quality to ensure the validity and reliability of the studies. This process was done independently by two authors using a standardized critical appraisal tool to minimize the possibility of bias in the study selection. The critical appraisal tool in this study was the Joanna Briggs Institute (JBI) critical appraisal tool based on study design. A decision of the third and fourth authors was used when a disagreement occurred.

The cutoff point was used to determine the quality of the study. The cutoff point in this review was half of the total score in each JBI critical appraisal checklist. The low-quality study was defined as a score below the cutoff point while conversely was termed as a high-quality study.

Synthesis of results

All relevant literature regarding SDF-1/CXCL12 3'A-gene polymorphism and risk of CAD were included

in the narrative synthesis. The OR of outcome was pooled and analyzed. Meta-analyses were performed using software Review Manager 5.3. Fixed effect model was used because the included studies were homogenous. The narrative synthesis was conducted systematically to gain a different perspective based on the previous current studies (2013–2018).

Results

The study results yielded five studies to be analyzed (Table 1) which can be included in the study [14], [15], [16], [17], [18]. All five articles were observational case-control studies. We did not find any randomized clinical trial study comparing SDF1 AA-gene polymorphism in CAD patients and control. All five articles were considered as a good quality based on our judgment. The article searching process was carried out based on the PRISMA principle (Figure 1).

According to Table 1, all of the studies are using polymerase chain reaction technique to determine the polymorphism of the SDF-1 gene. A total of 1819 cases and 2030 control were included from five different studies during the 2013–2018 period. Based on those studies, there were 155 SNP of AA gene among CAD patients, compared with 104 SNP of AA gene in non-CAD patients. The OR analysis for risk assessment was ranging from 1.10 to 7.37 among studies. However, to evaluate the overall effect regarding those studies, the meta-analysis using forest-plot was conducted (Figure 2).

Table 1: The summary of studies in this meta-analysis for the main comparison among variables

Study author	Type of study	Methods	Subject condition	Case	n	Control	n	Outcome
Mansoori <i>et al.</i> , 2017	Observational study, case-control	PCR	One-hundred-twenty Iranian adult patients with myocardial infarction and 120 healthy individual	MI/CAD	120	No MI/CAD	120	CAD: 7 SDF1 AA gene, No CAD: 1 SDF1 AA gene
Borghini <i>et al.</i> , 2014	Observational study, case-control	PCR	Two-hundred of myocardial infarction patients and 230 healthy individuals	MI/CAD	200	No MI/CAD	230	CAD: 12 SDF1 AA gene, No CAD: 21 SDF1 AA gene
Gu <i>et al.</i> , 2013	Observational study, case-control	PCR	Five-hundred-ninety-two patients with CAD and 625 healthy individuals	CAD	592	No CAD	625	CAD: 101 SDF1 AA gene, No CAD: 54 SDF1 AA gene
Eba <i>et al.</i> , 2018	Observational study, case-control	PCR	Three-hundreds-ten chromosomes of CAD patients and 370 chromosomes of healthy individuals	CAD	310	No CAD	370	CAD: 14 SDF1 AA gene, No CAD: 6 SDF1 AA gene
Zhang <i>et al.</i> , 2017	Observational study, case-control	PCR	Five-hundred-ninety-seven patients with diagnosis of CHD patients and 685 healthy individual	CAD	597	No CAD	685	CAD: 21 SDF1 AA gene, No CAD: 22 SDF1 AA gene

PCR: Polymerase chain reaction, CAD: Coronary artery disease, MI: Myocardial infarction, SDF1: Stromal cell-derived factor-1.

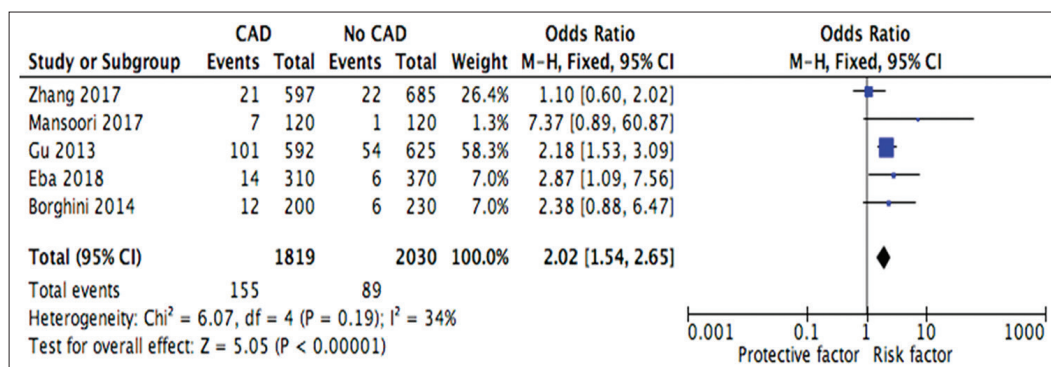


Figure 2: Forest plot regarding single-nucleotide polymorphism in stromal cell-derived factor-1/chemokine (C-X-C motif) ligand 12 gene

The forest plot in Figure 2 showed that the fixed effect model analysis was used due to the p -value >0.05 in the heterogeneity test ($I^2 = 34\%$; $X^2 = 6.07$; $p = 0.19$). The test for overall effect was assessed based on pooled OR, whereas finding statistically significant about 2.02 times higher risk for CAD compared with patients without SNP in SDF-1 gene ($p < 0.00001$; 95% confidence interval: 1.54–2.65) (Figure 2).

To exclude the risk of publication bias, funnel plot assessment was conducted (Figure 3). According to the funnel plot, it can be assumed that all results of five different studies are symmetrical and this indicates the results of the study having a low publication bias (Figure 3).

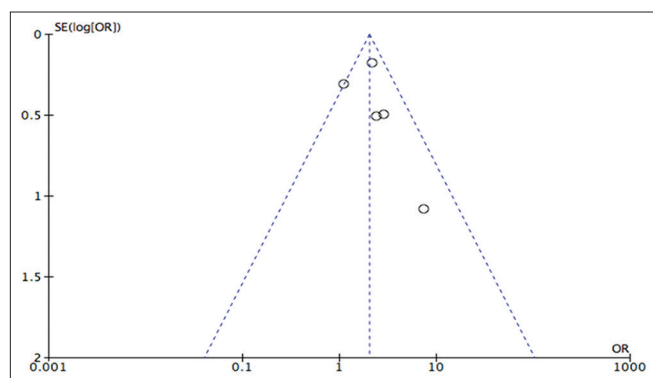


Figure 3: Funnel plot assessment among five different studies regarding single-nucleotide polymorphism in the stromal cell-derived factor-1 gene

Discussion

Our meta-analysis from 5 eligible studies indicated a significant association between the 3'A-gene polymorphism in SDF-1 and risk of CAD. However, several pieces of evidence regarding those associations were inconclusive based on risk analysis. According to results, we can assume that genetic polymorphism will change the level expression of SDF-1 in the bloodstream. Genetic phenotyping analysis studies recently have addressed the association between the variation of 10q11.21 locus harboring SDF-1 gene, also known as CXCL-12, and CAD. SDF-1 belongs to a chemoattractant family and responsible for SPCs and endothelial progenitor cells (EPCs) and implicated in atherosclerosis plaque formation. SDF-1 also has a role in neutrophil and lymphocyte recruitment to atherosclerosis lesion and affects plaque stabilization. The SDF-1 3'A polymorphism (rs1065297, rs1801157, rs266089, rs197452, rs2839693, and/or rs10793538) in HHEX gene is a newly identified SNP which involves guanine (G) to adenosine (A) transition at UTR of SDF-1 gene. This mutation regulates change in SDF-1 expression and been linked to CAD susceptibility [10], [19], [20].

In contrast to G allele, mutation at A allele is found to correlate with SDF-1 overexpression. The effect of high SDF-1 production, however, remains controversial and the results vary across ethnic groups. There were only a few studies about SDF-1 3'A polymorphism existed, and some demonstrated a protective role of high SDF-1 expression in AA genotype groups on CAD risk [21]. Conversely, studies by Mansoori *et al.* and Gu *et al.* demonstrated completely different findings in which SDF-1 3'A polymorphism related SDF-1 upregulation expressed significantly higher in the CAD group than in the non-CAD group [15], [16]. Based on those findings, we conducted a meta-analysis to further elaborate and analyze this diversity in study findings.

We performed meta-analysis from the five newest different studies analyzing SDF-1 3'A gene polymorphism in diverse ethnic background, Iranian, Chinese, Indian, and Italian population. The pooled OR from these five case-control studies suggested that the presence of SDF-1 3'A gene polymorphism as a genetic risk factor for CAD [14], [15], [16], [17], [18]. The present finding was in contrast to a former meta-analysis by Wu *et al.* which elaborated association between rs1801157/SDF-1 gene polymorphism and CHD [19]. In this aforementioned study, they did not specifically analyze the AA phenotype, instead they did five genetic subgroup analysis of AA, GG, AG versus GG, AA/AG versus GG, and AA versus AG/GG phenotypes, and eventually jump into the conclusion that rs1801157/SDF-1 gene polymorphism was not increased susceptibility to CHD and may serve as protective factor for MI. However, a meta-analysis by Wu *et al.* possessed strong heterogeneity across studies due to a difference in CHD subtype defines across studies and the number of respondents recruited [19]. This meta-analysis showed a current study from 5 years period (2013 to 2018) and also resulted in low publication bias based on the funnel plot.

The present study exclusively focused on the AA phenotype polymorphism, which was yet explored in other studies and may serve as a good foundation to a more solid and reliable meta-analysis in the near future. Nevertheless, there were still some issues that could be attributed to the limitation of the current study. First, the lack of available studies on this related field caused inevitably a small sample size of only 1819 total CAD cases. Another limitation was related to heterogeneity in the case of selection due to there were only five eligible studies during 2013–2018. Although all studies defined CAD cases based on coronary angiography findings, in three studies patients was diagnosed with MI and later confirmed by the invasive study to have CAD, whereas in studies by Eba *et al.* and Zhang *et al.*, there was no clear explanation about the occurrence of MI in CAD groups [14], [18]. At the end, all those subjects shared a common underlying pathogenic process, atherosclerosis, and the SDF-1 gene polymorphism, therefore strongly correlated with CAD [14], [15], [16], [18].

SDF-1 is a chemokine that regulating neutrophil migration to the atherosclerosis lesion [22], [23]. Damàs *et al.* yielded a result that increased in SDF-1 level associated with anti-inflammatory and matrix-stabilizing effects in MI [22]. This effect might be a result from potent chemoattractant properties of SDF-1 in recruiting EPC through binding with CXCR4 and CXCR7 receptors [23]. However, a higher plasma SDF-1 level was associated in reduced frequency of CD34⁺ cell phenotypes, a circulating cell marker associated with progenitor cell activity [24]. Previous studies have found that SDF-1 binds to the CXCR4 receptor found on CD34⁺ cells and triggers CD34⁺ cell release from the bone marrow [25]. The CD34⁺ cell itself is responsible for angiogenesis and neovascularization to mediate ischemic healing after CAD [26]. Based on those results, we can assume that SDF-1 3'A-gene polymorphism associated with its overexpression, whereas inversely reduced the CD34⁺ cell phenotype as one of the protective factors against CAD. Even this meta-analysis showed a statistically significant association between SDF-1 3'A gene polymorphism and risk of CAD, lack number of participants included during 5 years study was a study limitation compared with the previous studies.

Authors' Contributions

IPYP, AAWL, and IMM are responsible for the conceptual framework, data analysis, and interpreting the results. GARP, IMJRA, IKR, and PEM are responsible for statistical analysis in this study. In addition, AB, SHR, and IBAPM are responsible for criticizing the results as well as English improvement.

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