The role of systemic sclerosis on the coronary artery disease risk: a systematic review and meta-analysis

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Received October 16, 2016; Accepted November 16, 2016; Epub September 15, 2017; Published September 30, 2017

Abstract: Several studies assessed the association between systemic sclerosis (SSc) and coronary artery disease (CAD) risk. However, the results were controversial. We searched PubMed, Embase, and Wanfang databases to find relevant articles. The association of SSc and CAD risk was estimated by OR with 95% CI. Nine studies with 5247 cases and 383468 controls were eventually included. SSc was significantly associated with CAD risk (OR = 2.37, 95% CI 1.72-3.26, \(P<0.00001\); \(I^2 = 79\%\)). In the subgroup analysis by race, SSc was significantly associated with CAD risk in Caucasians (OR = 2.20, 95% CI 1.57-3.07, \(P<0.00001\); \(I^2 = 79\%\)) and Asians (OR = 4.24, 95% CI 1.06-16.90, \(P = 0.04\); \(I^2 = 67\%\)). When the studies without adjustment were excluded, the result was still positive (OR = 2.23, 95% CI 1.57-3.17, \(P < 0.00001\); \(I^2 = 86\%\)). In conclusion, this meta-analysis suggested that SSc patients might have higher CAD risk.

Keywords: Systemic sclerosis, coronary artery disease, association

Introduction

Coronary artery disease (CAD) is a major disease of morbidity and mortality [1]. Previous studies have found some risk factors for CAD, including smoking and inflammation [1]. Ridker et al. found that base-line plasma concentration of C-reactive protein predicts the risk of future myocardial infarction and stroke [2]. Inflammation may modulate the thrombotic responses by upregulating procoagulants, downregulating anticoagulants and suppressing fibrinolysis [3]. Reduction in inflammatory levels was associated with a proportional reduction in cardiovascular events [4]. Thus, inflammation play an important role in the development of CAD.

Systemic sclerosis (SSc) is a disease with unknown etiology. Inflammation play an important role in the development of SSc. Several studies assessed the association between SSc and CAD risk [5-13]. However, the results were controversial. Thus, we decided to perform a meta-analysis to determine the association between SSc and CAD risk.

Methods

Publication search

We used the following electronic databases to search for eligible literature: PubMed, Embase, and Wanfang, and the searching keywords included: “systemic sclerosis” and “coronary artery disease”. We additionally searched the references of all articles retrieved. There was no language restriction.

Inclusion and exclusion criteria

We considered studies meeting the following criteria eligible for included in the present meta-analysis: (1) estimation the association between SSc and CAD risk; (2) with a case-control or cohort study; (3) sufficient original data for calculating odds ratio (OR) with its 95% confidence interval (CI). The major reasons for exclusion included: (1) comment, review, or abstract; (2) animal study; and (3) duplicates. As for publications containing same data series, we only selected the latest one.
Data extraction and quality assessment

Two independent reviewers extracted the data utilizing a standard approach. Any discrepancy was resolved through discussion. The following data were extracted: name, year of publication, race, age, gender, smoking, number of cases, number of controls, and covariates.

The included studies were assessed independently by two authors using the Newcastle-Ottawa Scale (NOS). Scores ranged from 0 to 9 stars.

Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 11, STATA, College Station, TX) and Review Manager (Version 5.0, Copenhagen, Nordic Cochrane Centre, The Cochrane Collaboration, 2010). We used ORs and 95% CIs to measure the association of SSc and CAD risk. Heterogeneity across studies was examined with the Chi-square-based Q-statistical test. The significance of the pooled OR was determined by the Z test. Subgroup analysis was conducted by race. The cumulative meta-analysis and sensitivity analysis were performed. Publication bias was investigated with Egger's test. The statistically significant level of all tests was set at \( P < 0.05 \).

Results

Study characteristics

A total of 24 studies were retrieved from the literature databases (Figure 1). Among them, 2 duplicate studies were excluded on the basis of their abstracts. After further reading the full text of each study, 13 additional studies were excluded for not meeting the inclusion criteria. As a result, 9 studies were eventually included. Two studies were included Asians and other studies included Caucasians. A total of 5247 cases and 383468 controls were included in this meta-analysis. The general characteristics of the included studies are shown in Table 1. The quality assessment demonstrated that the included studies had high quality.

Quantitative synthesis

The main results were shown in Table 2. SSc was significantly associated with CAD risk (OR = 2.37, 95% CI 1.72-3.26, \( P < 0.00001 \); \( I^2 = 79\% \); Figure 2). In the subgroup analysis by race, SSc was significantly associated with CAD risk in Caucasians (OR = 2.20, 95% CI 1.57-3.07, \( P < 0.00001 \); \( I^2 = 79\% \)) and Asians (OR = 4.24, 95% CI 1.06-16.90, \( P = 0.04 \); \( I^2 = 67\% \)). When the studies without adjustment were excluded, the result was still positive (OR = 2.23, 95% CI 1.57-3.17, \( P < 0.00001 \); \( I^2 = 86\% \)). When the studies with adjusting for age and gender were included, we also found positive result (OR = 3.10, 95% CI 2.09-4.60, \( P < 0.00001 \); \( I^2 = 39\% \)).

As shown in Figures 3 and 4, cumulative meta-analysis and sensitivity analysis suggested that
Systemic sclerosis and coronary artery disease

The result was stable. The shape of the funnel plot showed symmetry (Figure 5). Egger’s test found no evidence of publication bias ($P = 0.44$).

Discussion

This meta-analysis study with 5247 cases and 383468 controls assessed the association of SSc and CAD risk. We observed that SSc was significantly associated with CAD risk. In the subgroup analysis by race, SSc was significantly associated with CAD risk in Caucasians and Asians, respectively. When the studies with adjustment were included, the result was still positive. Additionally, cumulative meta-analysis and sensitive analysis indicated that the results of this meta-analysis were reliable.

A meta-analysis found that carotid intima-media thickness was significantly increased in the SSc population compared with controls [14]. Timar et al. found that augmentation index and pulse wave velocity were both elevated in SSc patients than that in controls [15]. Many inflammatory factors, such as tumor necrosis factor-alpha, interleukin-6, and C-reactive protein, have been demonstrated to be increased in patients with SSc [16]. Inflammation is a component of the pathophysiology of both SSc and CAD. Therefore, SSc patients may have higher CAD risk.

Some advantages of this study were noted. First, cumulative meta-analysis and sensitivity analysis were well investigated. Result from cumulative meta-analysis and sensitivity analysis suggested that results of this study is stable. Second, funnel plots and Egger’s tests were used to find potential publication bias. The results indicated that there was no significant publication bias. Third, more than 39000 subjects were included in this study.

Some limitations of this study should be acknowledged. First, lacking of the original data of the eligible studies limited the evaluation of the subgroup analyses by gender, age, and other factors. Second, all the studies were

Table 1. Characteristics of the included studies

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Race</th>
<th>Mean age</th>
<th>Female (%)</th>
<th>Smoking (%)</th>
<th>No. of case</th>
<th>No. of control</th>
<th>Adjusted for</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Angelo</td>
<td>1969</td>
<td>Caucasian</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>58</td>
<td>58</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Youssef</td>
<td>1995</td>
<td>Caucasian</td>
<td>63</td>
<td>100</td>
<td>13</td>
<td>31</td>
<td>31</td>
<td>NA</td>
<td>5</td>
</tr>
<tr>
<td>Khurma</td>
<td>2008</td>
<td>Caucasian</td>
<td>51</td>
<td>82</td>
<td>6</td>
<td>17</td>
<td>17</td>
<td>NA</td>
<td>5</td>
</tr>
<tr>
<td>Mok</td>
<td>2011</td>
<td>Asian</td>
<td>53</td>
<td>94</td>
<td>11</td>
<td>53</td>
<td>106</td>
<td>Age, sex, dysglycemia, hypertension, LDL and HDL cholesterol levels</td>
<td>8</td>
</tr>
<tr>
<td>Ngian 1</td>
<td>2012</td>
<td>Caucasian</td>
<td>48</td>
<td>14</td>
<td>20</td>
<td>850</td>
<td>8802</td>
<td>Age, sex</td>
<td>8</td>
</tr>
<tr>
<td>Ngian 2</td>
<td>2012</td>
<td>Caucasian</td>
<td>57</td>
<td>54</td>
<td>9</td>
<td>850</td>
<td>15787</td>
<td>Hypertension, hypercholesterolemia, diabetes, smoking and body mass index</td>
<td>8</td>
</tr>
<tr>
<td>Man</td>
<td>2012</td>
<td>Caucasian</td>
<td>59</td>
<td>86</td>
<td>14</td>
<td>865</td>
<td>8643</td>
<td>Body mass index, smoking, hypertension, diabetes, hyperlipidaemia, NSAID and glucocorticoid use</td>
<td>8</td>
</tr>
<tr>
<td>Zoller</td>
<td>2012</td>
<td>Caucasian</td>
<td>NA</td>
<td>42</td>
<td>NA</td>
<td>1068</td>
<td>336479</td>
<td>Age, period, socioeconomic status, hospitalization of chronic lower respiratory diseases, obesity, alcohol, hypertension, diabetes, arterial flutter, heart failure, and renal disease</td>
<td>8</td>
</tr>
<tr>
<td>Nordin</td>
<td>2013</td>
<td>Caucasian</td>
<td>61</td>
<td>90</td>
<td>NA</td>
<td>111</td>
<td>105</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Chu</td>
<td>2013</td>
<td>Asian</td>
<td>51</td>
<td>76</td>
<td>20</td>
<td>1344</td>
<td>13440</td>
<td>Age, sex, and underlying comorbidities</td>
<td>8</td>
</tr>
</tbody>
</table>

HDL, high density lipoprotein; LDL, low-density lipoprotein; NSAID, non-steroidal anti-inflammatory drugs; NOS, Newcastle-Ottawa Scale; NA, not available.

Table 2. Results of this meta-analysis

<table>
<thead>
<tr>
<th>Test of association</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Heterogeneity</th>
<th>I^2 (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>2.37 (1.72-3.26)</td>
<td>&lt; 0.00001</td>
<td>79</td>
<td>&lt; 0.00001</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>2.20 (1.57-3.07)</td>
<td>&lt; 0.00001</td>
<td>79</td>
<td>&lt; 0.00001</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4.24 (1.06-16.90)</td>
<td>0.04</td>
<td>67</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Adjust</td>
<td>2.23 (1.57-3.17)</td>
<td>&lt; 0.00001</td>
<td>86</td>
<td>&lt; 0.00001</td>
<td></td>
</tr>
<tr>
<td>Adjust for age and gender</td>
<td>3.10 (2.09-4.60)</td>
<td>&lt; 0.00001</td>
<td>39</td>
<td>0.19</td>
<td></td>
</tr>
</tbody>
</table>
Systemic sclerosis and coronary artery disease

In conclusion, this meta-analysis suggested that SSc patients might have higher CAD risk.

Disclosure of conflict of interest

None.

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References

Systemic sclerosis and coronary artery disease

Figure 4. Sensitivity analysis for the association between SSc and CAD risk.

Figure 5. Funnel plot for the association between SSc and CAD risk.


Systemic sclerosis and coronary artery disease


