Relation of diabetes to coronary artery ectasia: A meta-analysis study

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Abstract

Objective: Previous studies have shown a significant negative association between diabetes and abdominal aortic aneurysm. However, the relation of diabetes to coronary artery ectasia (CAE) has not well established. The aim of the current study was to conduct a systemic review for evaluating the relationship between diabetes and CAE.
Methods: A systemic search of electronic databases (PUBMED, EMBASE, OVID, WEB OF SCIENCE, THE COCHRANCE LIBRARY) from 1970 to March 2013 was performed. Additionally, checking reference lists from identified articles, reviews, and the abstracts presented at related scientific meetings were also carried out. All case-control studies investigating appropriate prevalence data were included.
Results: Among 328 articles, 10 case-control studies were finally identified. The prevalence of diabetes in studied patients with CAE was 8% to 33%, while in those without CAE was ranged from 13.5% to 35%. Pooled analysis showed a reduced rate of diabetes amongst patients with CAE compared to those without (OR 0.65, 0.54-0.77, p<0.0001).
Conclusion: Our findings suggested that diabetes might play a protective role for the development of CAE, indicating that further study is needed to evaluate the association diabetes and CAE including underlying mechanisms and future medical interventional strategies.
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Key words: coronary artery ectasia, diabetes, meta-analysis

Introduction

Coronary artery ectasia (CAE) is a well-recognized but relatively uncommon finding encountered during diagnostic coronary angiography (1, 2). It is commonly defined as inappropriate dilation of the coronary arteries exceeding the largest diameter of an adjacent normal vessel more than 1.5 fold (2). The term ‘ectasia’ refers to diffuse dilation of a coronary artery whilst focal dilation is called as ‘coronary aneurysm’ (3). CAE has been considered as a rare coronary disorder associated with atherosclerotic coronary artery disease (CAD), and therefore subsequently also regarded as a variant of coronary atherosclerosis (4).

It has been reported that the prevalence of diabetes and CAE has significantly risen in recent years including Chinese population (5, 6). Although there is a close relation of diabetes and CAE to atherosclerotic disease, several previous studies indicated an increased prevalence of CAE and a low frequency of diabetes in patients with abdominal aortic aneurysm (AAA) (7-9). Moreover, a few case-control studies suggested that diabetes was found to be independently but inversely associated with CAE (10-13).

However, the association between diabetes and CAE remains largely unclear up to now, and previous published work in this area is limited by small sample size, more importantly inconsistent results (1, 14-16). Based on this condition, we scan the literature aiming to further delineate the association between diabetes and CAE using a meta-analysis according to PRISMA strategy.

Methods

The methods for this meta-analysis are in accordance with meta-analysis of observational studies in epidemiology: a proposal for reporting (17).

Search strategy

Two investigators performed a systematic literature search of PUBMED, EMBASE, OVID, WEB OF SCIENCE and THE COCHRANCE LIBRARY from 1970 to March 2013, using the MeSH

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terms "(coronary artery ectasia OR coronary artery aneurysm) and (diabetes mellitus OR diabetes)", and they worked independently. The last search was conducted on March 10, 2013. We also added a manual search using the reference lists of the relevant articles and the abstracts presented at related scientific societies meetings. No Language restriction was imposed.

Study selection

Inclusion criteria for studies were: (1) case-control studies, and (2) provision of sufficient data to calculate odds ratio (OR) or relative risk (RR) comparing diabetes in CAE patients to non-CAE patients. CAE was diagnosed by coronary angiography was defined as as inappropriate dilation of the coronary arteries exceeding the largest diameter of an adjacent normal vessel more than 1.5 fold (2).

Exclusion criteria for studies were: (1) studies conducted with less than 20 patients with CAE; (2) case report and observational studies without control groups, and (3) studies in which the data of diabetes rate in CAE or non-CAE group were not available.

Data extraction

Relating information from studies was extracted by two investigators independently by using a predefined data extraction form. The following data were sought from each article: first author, publication year, country of origin, the number of cases and controls, the type of objects, rate of diabetes and definition of diabetes for each study. The results were compared, and any discrepancies were resolved by consensus.

Statistical analysis

The odds ratio (OR) of CAE risk associated with the presence of diabetes was estimated for each study. An I^2 was performed to assess heterogeneity. If the result of the heterogeneity test was $p>0.05$, ORs were pooled according to the fixed-effect model (Mantel-Haenszel). Otherwise, the random-effect model (Dersimonian and Laird) was used. The significance of the pooled ORs was determined by Z-test. Publication bias was estimated using a funnel plot of study results against study precision. Statistical analysis was undertaken using the program Review Manager Version 5.0 (Cochrane Collaboration, Oxford, United Kingdom).

Results

Literature search

A total of 340 potentially relevant papers concerning the association between CAE and diabetes were screen for retrieval (including 12 articles obtained from the manual search). After a careful review, 305 papers that were not relevant to CAE or diabetes were excluded. Then, in the remaining 35 studies, 25 studies were excluded for the following reasons: 4 were cases-report studies, 4 were reviews, 10 did not have control group and 7 did not make it possible estimate the diabetes rate. Finally 10 case-control studies were included in this meta-analysis (Fig. 1) (10-16, 18-20). We established a database according to the extracted information from each article. The information was presented in Table 1. The included studies were published from 1997 to 2011. These studies involved 8220 patients, with a total diabetes rate of 17.8% (1461/8220). The cumulative sample size of the control group was 5957, of which 1870 were diabetes (31.4%). Of the total 1250 CAE group, only 211 were diabetes (16.7%). Other necessary information was also listed in the forest plots of the meta-analysis. We considered the confounding factors. Nevertheless, insufficient data were obtained from the included primary manuscripts. Thus, subgroup analyses regarding the confounding factors had not been conducted.

Pooled estimates

We analyzed the heterogeneity for the included studies. The test value of χ^2 was 11.02 with 9 degrees of freedom. The I^2 was 18% and p=0.27. Thus, fix-effect model was used for diabetes and CAE risk as follows: the combined OR was 0.65 (95%CI 0.54-0.77) and the test for overall effect Z value was 4.77 ($p<0.0001$, Fig. 2A). The funnel plot does not suggest significant bias in the studies available for inclusion (Fig. 2B). The results suggest that there is an inverse association between diabetes and CAE.

Discussion

In this study we evaluated the association between diabetes and CAE on case-control studies by carrying out a quantitative meta-analysis. The results suggest that diabetes might be a protective factor for the occurrence of CAE.

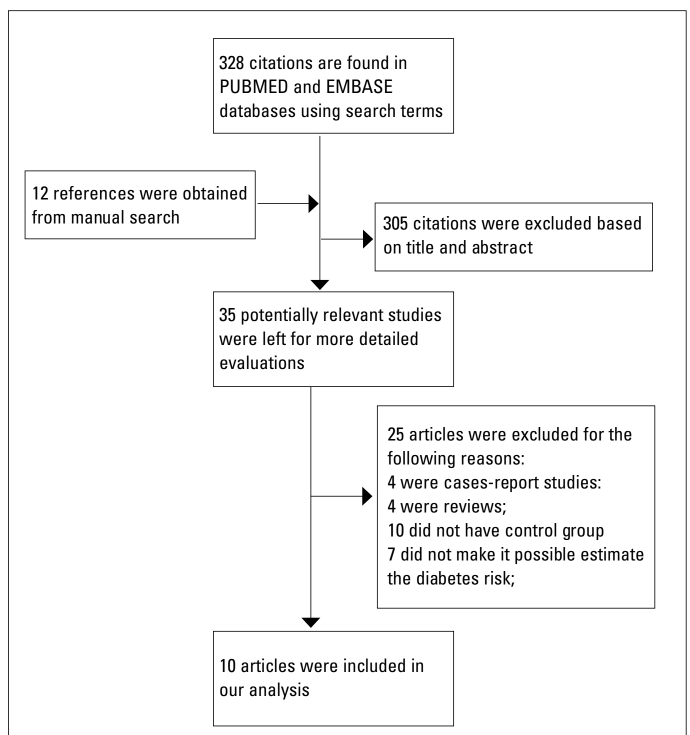

Figure 1. Flow diagram of selection of studies for inclusion in this meta-analysis

Table 1. Characteristics of included studies

First author	Publication year	Country	CAE (n) (DM%; Male%) Age, years	Non-CAE(n) (DM%; Male%) Age, years	Objects	DM defined
Pinar et al. (12)	2003	Spain	147 (22.4%; 91.2%) (60.8±11.7)	4185 (35.1%; 72%) (63.3±10.7)	underwent CAG	appeared in histories
Waly et al. (19)	1997	Egyptian	45 (33%; 95,6%) (37-72) years	230 (31%; 93.9%, (30-78) years	underwent CABG	not defined
Baman et al. (11)	2004	USA	243 (18%; 83%) age no data	541 (26%; 60%) age no data	Underwent CAG	On going therapy or hyperglycemia, or diet control
Güneş et al. (16)	2006	Turkey	122 (16.4%; 66.3%, 58±11)	152 (22.3%; 61.3%) (58±11)	Underwent CAG	not defined
Demo et al. (18)	1997	Greece	203 (15.8%; 92.6%) (57.3±10)	165 (20%; 87.3%) (57.6±10)	Underwent CAG	not defined
Andro et al. (10)	2004	Greece	190 (14.7%; 78.4%) (56.2±9.5)	341 (22.3%; 76.5%) (56.5±9.6)	Underwent CAG	FBG(120 mg/dL) or receiving insulin, oral hypoglycemic.
Sağlam et al. (13)	2008	Turkey	112 (8%; 67%) (59±12)	62 (22.6%; 66%) (57±9)	Underwent CAG	not defined
Yao et al. (15)	2010	China	25 (12%; 72%) (59.2±8.5)	50 (32%; 80%) (59.4±10.3)	Underwent CAG	FBG (110 mg/dL) or ongoing treatment
Şen et al. (20)	2009	Turkey	97 (14.4%; 71.%) (58.1±9.5)	194 (15.5%; 76%) (58.4±8.8)	Underwent CAG	FPG(126 mg/dL) or being on a diet, or ongoing treatment
Boles et al. (14)	2011	Sweden	66 (19.7%; 69.7%) (65±8)	37 (13.5%; 35.1%) (66±11)	Underwent CAG	not defined

CABG - coronary artery bypass grafting; CAE - coronary artery ectasia; CAG - coronary artery grafty; DM - diabetes mellitus; FPG - fasting plasma glucose

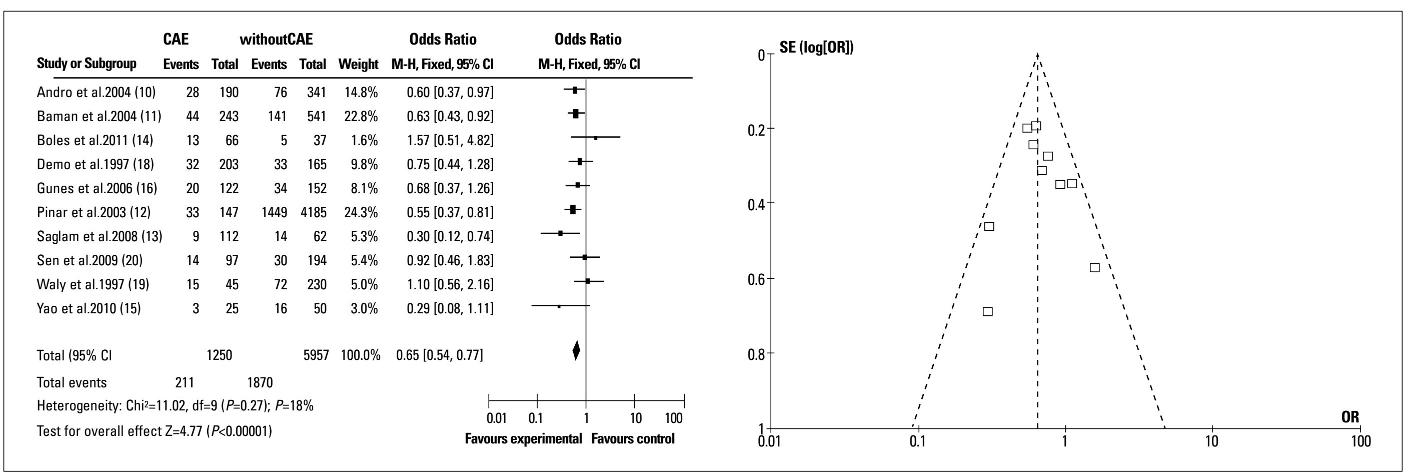

Figure 2. Odds Ratio and funnel plot of diabetes prevalence of subjects with CAE and Non-CAE. (A) Odds Ratio of DM incidence; (B) Funnel plot of DM incidence

CAE is a multifactorial disease and the pathogenesis and precise mechanism remain unknown. More and more lines of evidence indicate that CAE is tightly involved in inflammation (4, 21-23). Pathological specimen showed that aneurysmatic coronary segments having a marked degradation of the medial collagen and elastin fibers and disruption of the internal and external elastic lamina (24). Researchers speculated that enzymatic degradation of the extracellular matrix (ECM) of the media appears to play a key role in the causative mechanisms (25). Matrix degrading enzymes may cause severe disruption of the internal elastic lamina providing a gateway for the inflammatory cells to extend from the intima into the media, elaborate matrix proteases, degrade the collagen and elastin fibers, weaken the arterial wall integrity, and ultimately promote an ectatic transformation of the wall (26-28).

Although diabetes significantly increases the risk of atherosclerosis and CAE has been considered as a form of atherosclerosis, the association between diabetes and CAE is not well-defined. Prior clinical observational studies have showed a high incidence of CAE but a low frequency of diabetes in patients with abdominal aortic aneurysm (AAA) (8, 29, 30). There may be some common pathological mechanisms in both CAE and AAA. Similar to the present study, the result of recent meta-analysis also suggested that diabetes might be a protective factor for the development of AAA (7). Patients with those CAE and diabetes share many common traditional risk factors, but it seems unlikely that exposure to those factors alone dictate the pattern of arterial disease. Based on the above characteristics of CAE, diabetes is likely to influence the development of CAE through the following aspects.

Firstly, in contrast to the proteolysis and matrix destruction seen in CAE, diabetes is characterized by increased matrix volume resulting in changes such as basement membrane thickening and mesangial expansion (31). Advanced glycation end-products (AGEs) are modifications of proteins or lipids that become nonenzymatically glycated and oxidized after contact with aldose sugars (32). AGEs can alter properties of the large matrix proteins collagen, vitronectin, and laminin, through AGE-AGE intermolecular covalent bonds, or cross-linking (33, 34). AGE cross-linking on type I collagen and elastin causes an increase in the area of ECM, resulting in increased stiffness of the vasculature (35, 36). Renal hypertrophy and extracellular matrix accumulation are early features of diabetic nephropathy. Hyperglycemia enhances mesangial cell proliferation and fibronectin expression is demonstrated to be associated with the process (37). By intracoronary ultrasound, researchers found that diabetics with atherosclerosis have less compensatory coronary artery enlargement than non-diabetics and the researchers considered it can explain the diffuse and accelerated course of coronary artery disease in these patients (38). Patients with a longer duration of diabetes who were treated with insulin had (paradoxically) less reference segment and stenosis plaque accumulation and hyperglycemia increases plasminogen activator inhibitor 1 expression and attenuates AAA diameter had been demonstrated by animal experimental studies (39, 40), lowering of serum glucose levels with insulin treatment diminishes this protective effect (41). Other researchers argued that diabetes promotes negative arterial wall remodeling or at least impairs compensatory arterial enlargement during the course of the atherosclerotic process (10).

Secondly, the enzymes largely responsible for ECM degradation are the matrix metalloproteinases (MMPs). MMPs are proteinases that participate in extracellular matrix remodeling and degradation. Numerous studies confirmed that CAE, AAA and Kawasaki disease patients have elevated expression, activity, or protein levels of MMPs (42-47). The phenomenon suggests that imbalances in MMPs or MMP/tissue inhibitor of MMP (TIMP) may play important pathophysiological roles in the development of this dilated artery disease. Instead, researchers showed that MMPs production is down regulated in vascular smooth muscle cells, monocytes and serum or plasma levels in diabetes (48-51). Golledge et al. (52) followed 198 patients (20 with diabetes) who had 30-45 mm AAA with yearly aortic ultrasound for 3 years. They found diabetes was independently associated with reduced AAA growth, and further study found that a mechanism by which the aortic media may be protected from decreasing MMPs secretion in vitro laboratory experiments.

Finally, diabetes are likely to be taking drugs such as hypoglycaemic agents, statins and angiotensin converting enzyme inhibitor/angiotensin receptor blocker for coexisting with CAD, hypertension and renal impairment. Investigators found that the use of such medication may have negative effects on the development of aneurysmal disease. For example, angiotensin II type 1 receptor blockers, telmisartan and irbesartan limited AAA enlargement in animal models (53) and pre-treatment or post-treatment with rosiglitazone reduced aortic aneurysms expansion and rupture concomitant with decreased expression of inflammatory mediators in mouse model (54). A retrospective study also found that patients receiving statins had a decreased AAA growth rate compared with those patients not receiving statins [0.9 mm/y (interquartile range, -1.0 to +1.0) vs. 3.2 mm/y (interquartile range, 2.0-4.9), $p<0.0001$], the difference in the rate of growth was maintained after adjusting for potential confounding factors (55).

The clinical implication of diabetes against CAE may help to identify high-risk group for screening and may help demonstrate the differing cellular mechanisms behind CAE and atherosclerotic disease, and in turn rationalize the search for pharmacological intervention of CAE.

Study limitations

There are several limitations of this meta-analysis. First of all, one pivotal factor is that most of the studies included in this meta-analysis were not initially designed to specifically address the association between diabetes and CAE. Herein, these data are inherently limited by the selection bias, which occurs with recruitment for these enrolled studies. The larger sample of prospective case-control may provide a real assessment of the relevance of diabetes and CAE. Moreover, the pooled studies differed in inclusion and exclusion criteria, definition of diabetes or CAE, which may be the major source of heterogeneity. Besides, CAEs vary in size and numbers in coronary arteries. However, whether the severity of CAE is linked to diabetes has not been investigated in this meta-analysis. Finally, this meta-analysis provided association, not causal, evidence and mandates caution when interpreting our results.

Conclusion

In summary, the present meta-analysis showed a negative association of diabetes with CAE, suggesting that diabetes may be a protective factor for CAE. Further work into prevalence associations and biological mechanisms is apparently required, with specific attention to the hypoglycaemic management and concurrent medications.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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