Simple renal cyst and abdominal aortic aneurysm

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Objective: **To summarize the association of simple renal cyst (SRC) with abdominal aortic aneurysm (AAA), we reviewed currently available clinical studies with a systematic literature search and meta-analytic evaluation.**

Methods: **To identify all case-control studies evaluating the association of SRC with AAA, databases including MEDLINE and Embase were searched through April 2015 using web-based search engines (PubMed and Ovid). For each study, data regarding SRC prevalence in both the AAA and control groups were used to generate unadjusted odds ratios (ORs) and 95% confidence intervals. When an adjusted OR (by the use of multivariable logistic regression) was available, we preferentially abstracted the adjusted OR rather than an unadjusted OR.**

Results: **Of 139 potentially relevant articles screened initially, 5 eligible case-control studies enrolling a total of 2897 participants were identified and included. A pooled analysis of seven estimates from the five studies demonstrated a statistically significant 2.54-fold prevalence of SRC in patients with AAA relative to subjects without AAA (OR, 2.54; 95% confidence interval, 1.93-3.34; *P* < .00001).**

Conclusions: **Our meta-analytic evaluation demonstrated 2.5-fold prevalence of SRC in patients with AAA relative to subjects without AAA, which suggests that SRC is associated with AAA. (J Vasc Surg 2016;63:254-9.)**

The idea that the proteolytic process of abdominal aortic aneurysm (AAA) formation is not limited to the aortic wall but part of a systemic disorder with involvement of several tissues arose approximately 30 years ago and is to date still under evaluation.[1] An imbalance between blood proteases and antiproteases, resulting from chronic smoking, can damage connective tissue in the groin as well as in the lung,[2] and increased blood proteolytic activity may play a role in the development of both AAA and adult inguinal hernia.[3] Although coexisting abdominal wall hernia (AWH) and simple renal cyst (SRC) has been proposed as a possible predictor for AAA development, limitations of clinical evidence, presuming an underlying systemic connective tissue disorder, remain to date small sample sizes of the studies.[1] A number of meta-analyses,[4-6] however, have demonstrated obvious evidence regarding the association of AWH with AAA. Furthermore, it has been debated for the last 30 years whether AAA forms part of the extrarenal, vascular manifestations of autosomal dominant polycystic kidney disease (ADPKD). A recent systematic review by Bailey et al[7] included 18 papers (23 cases of ADPKD and AAA). Two studies assessed aortic diameter in patients with ADPKD and controls, one finding increased aortic diameter in ADPKD (2.7 cm vs 2.3 cm; $P < .02$)[8] and the other finding no difference.[9] We previously proposed a novel hypothesis[10] that matrix metalloproteinases (MMPs), synthesized and secreted by kidney tubules of ADPKD, play a critical role in development of concurrent AAA. It is also important to consider the upstream genetics driving these processes.[7] Because the association of SRC with AAA is a more recent topic of interest, neither systematic reviews nor meta-analyses have been conducted to date as far as we know. To summarize the association of SRC with AAA, we reviewed currently available clinical studies with a systematic literature search and meta-analytic evaluation in this article.

METHODS

All case-control studies evaluating the association of SRC with AAA were identified using a two-level search strategy. First, databases including MEDLINE and Embase were searched through April 2015 using web-based search engines (PubMed and Ovid). Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles and a search of reviews and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analysis. Search terms included cyst or cysts and AAA. Studies considered for inclusion met the following criteria: the design was a case-control study; the study population was (1) patients with AAA and subjects without AAA or (2) patients with SRC and subjects without SRC; and main outcomes included (1) SRC prevalence and (2) AAA prevalence. For each study, data regarding SRC prevalence in both the AAA and control groups were used to generate unadjusted odds ratios (ORs) and 95% confidence intervals (CIs). When an adjusted OR for SRC or AAA prevalence (by the use of multivariable logistic regression) was available, we preferentially abstracted the adjusted OR rather than an unadjusted OR. Mathematically, an OR of SRC prevalence for patients with AAA vs subjects without AAA is equal to an OR of AAA prevalence for patients with SRC vs subjects without SRC (Appendix, online only). We took the OR of AAA prevalence hence to be representative of the OR of SRC prevalence. Study-specific estimates

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(ORs of SRC prevalence for patients with AAA vs subjects without AAA) were combined using inverse variance-weighted averages of logarithmic ORs in both fixed- and random-effects models. Between-study heterogeneity was analyzed by means of standard χ^2 tests. Where no statistically significant heterogeneity was identified, the fixed-effect estimate was used preferentially as the summary measure. All analyses were conducted using Review Manager version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Search results. Of 139 potentially relevant articles screened initially, 112 were excluded on the basis of titles and abstracts, and the remaining 27 articles were retrieved for detailed reviews. Of them, 5 eligible case-control studies[1,11-14] enrolling a total of 2897 participants were identified and included. Study design and patient characteristics are summarized in Table. In addition, we identified an autopsy study[15] to confirm the degree of contribution to aortic circumference of renal cysts.

SRC prevalence in AAA patients. Gindera et al[1] determined and compared the incidence of SRC in 236 patients with known AAA (treated at their institute) and 236 randomly chosen patients with aortoiliac occlusive disease (AOD) recruited as a control group. SRC was significantly more frequent in the AAA group than in the AOD group (68.6% vs 37.3%; adjusted OR, 2.110; 95% CI, 1.325-3.359; $P = .002$).

Song and Park[11] compared the incidence of SRC in 271 patients with AAA and 1387 patients without AAA (controls) using computed tomography (CT) angiography and abdominal CT as a health-screening program. The AAA group had significantly greater prevalence of SRC than the controls (55% vs 19%; $P = .001$). After propensity score matching (n = 164), the prevalence of SRC was still significantly greater in the AAA group (56% vs 29%; $P = .032$). In multivariate analysis, SRC was one of the independent predictors of AAA (adjusted OR, 2.64; 95% CI, 1.05-6.63; $P = .038$).

Of 170 consecutive patients with aortoiliac disease treated by Pitoulias et al,[12] 110 had AAA and 60 had AOD. Univariate analysis showed that incidence of SRC was one of the significant predictive factors for presence of AAA (unadjusted OR, 6.135; 95% CI, 3.049-12.346; $P < .001$), and multivariate analysis identified SRC as one of the independent predictive factors for the presence of AAA (adjusted OR, 4.386; 95% CI, 2.10-9.091; $P < .001$).

Ito et al[13] conducted a retrospective chart review on the clinical data of 396 consecutive patients undergoing CT scans for preoperative evaluation of thoracic and cardiovascular surgery. In comparing patients with SRC (n = 164) with those without (n = 233), there was a statistically significant difference between the presence of SRC and AAA (AAA presence, 43.5% vs 23.3%; $P < .001$) on univariate analysis. In comparing patients with AAA with those without, although AAA was not associated with SRC in patients <65 years old (SRC prevalence, 37.5% vs 29.4%; $P = .564$), the presence of SRC was the strongest association with AAA among patients belonging to the 65- to 74-year-old group (adjusted OR, 4.15; 95% CI, 1.72-10.03; $P = .002$) and ≥75-year-old group (adjusted OR, 3.00; 95% CI, 1.16-7.73; $P = .023$) on multivariate analysis.

Yaghoubian et al[14] conducted a retrospective cohort study comparing the incidence of SRC on CT scan in 100 patients with AAA with that in 100 patients without AAA (matched by age and gender). Of patients with AAA, 54% had SRC compared with only 30% in the control group (unadjusted relative risk, 2.74; 95% CI, 1.53-4.9; $P = .0005$). On multivariate analysis, AAA was one of the independent predictors of SRC (OR, 2.05; 95% CI, 1.08-3.88; $P = .028$).

A pooled analysis of seven estimates from these five studies demonstrated a statistically significant 2.54-fold prevalence of SRC in patients with AAA relative to subjects without AAA in the fixed-effects model (OR, 2.54; 95% CI, 1.93-3.34; $P < .00001$; Fig). There was minimal trial heterogeneity ($P = .48$) and accordingly no difference in the pooled result from random-effects modeling.

SRC and aortic diameter/circumference. Gindera et al[1] revealed that AAA diameter of >55 mm or <55 mm had no significant association with the development of SRC (71.1% vs 66.4%; unadjusted OR, 1.242; 95% CI, 0.715-2.158; $P = .441$). Univariate analysis by Pitoulias et al[12] failed to show any predictive value of SRC for AAA diameter (unadjusted OR, 1.379; 95% CI, 0.604-3.149; $P = .446$). Multiple linear regression analyses in the study by Kurata et al[15] of 108 adult autopsy cases demonstrated that the number of renal cysts was correlated with both thoracic and abdominal aortic circumference (coefficient for thoracic, 0.299 [$P = .002$]; coefficient for abdominal, 0.296 [$P = .003$]) and circumference/height (coefficient for thoracic, 0.309 [$P = .002$]; coefficient for abdominal, 0.300 [$P = .003$]), which was more predominant in female subjects (coefficient for thoracic circumference, 0.446 [$P = .004$]; coefficient for abdominal circumference, 0.481 [$P = .002$]; coefficient for thoracic circumference/height, 0.419 [$P = .011$]; coefficient for abdominal circumference/height, 0.483 [$P = .003$]) than in male subjects (coefficient for thoracic circumference, 0.225 [$P = .086$]; coefficient for abdominal circumference, 0.144 [$P = .276$]; coefficient for thoracic circumference/height, 0.282 [$P = .035$]; coefficient for abdominal circumference/height, 0.154 [$P = .257$]).

SRC characteristics. Gindera et al[1] showed that number of cysts was significantly greater in AAA compared with AOD patients (2.7 ± 2.5 vs 1.8 ± 1.1; $P < .001$), and a bilateral kidney involvement was found in the majority of AAA cases (58.0% vs 29.5%; unadjusted OR, 3.296; 95% CI, 1.894-5.737; $P < .001$). Mean diameter of cysts was, however, similar between the groups (15.8 ± 10.9 vs 13.5 ± 9.9 mm; not significant).

In the analysis by Song and Park,[11] the AAA group had a significantly greater number of cysts per patient (2.8 ± 2.1 vs 1.7 ± 1.2; $P = .001$), bilateral renal involvement (46% vs 26%; $P = .001$), maximum diameter of each cyst (26.3 ± 17.4 vs