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Presence of simple renal cysts is associated with increased risk of aortic dissection: a common manifestation of connective tissue degeneration?

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ABSTRACT

Objective Aortic dissection is a multifactorial disease whose primary pathology is connective tissue degeneration of the aorta's medial layer. It was hypothesised that the presence of renal cysts, another possible manifestation of connective tissue weakness, would be associated with increased risk of aortic dissection.

Methods The incidence of simple renal cysts on CT angiography in 518 patients with aortic dissection (AD group) and 1366 healthy subjects (control group) who underwent CT for routine health screening was compared. To reduce the effects of selection bias and confounding variables, data were adjusted by propensity score matching.

Results The prevalence of simple renal cysts was 37.8% in the AD group and 22.0% in the control group, a statistically significant difference ($p<0.0001$). The prevalence of renal cysts was even greater in patients with the following characteristics: intramural haematoma, type B dissection, normal blood pressure or advanced age. In the 311 matched cohorts after propensity score matching, the prevalence of simple renal cysts was still significantly higher in the AD group than in the control group (33.8% vs 25.7%, $p=0.023$). Multivariate analysis confirmed that the presence of renal cysts (OR 1.49, $p=0.0245$) could be a marker of having a common underlying mechanism with aortic dissection.

Conclusion Patients with aortic dissection have an increased burden of renal cysts compared with healthy controls. This finding suggests that the connective tissue weakness that predisposes patients to renal cysts may be associated with aortic dissection.

INTRODUCTION

Aortic dissection is a life-threatening condition in which early diagnosis, treatment and close follow-up are critical for survival. The underlying cause of aortic dissection is multifactorial. Connective tissue weakness, so-called 'cystic medial degeneration', is a chief predisposing factor for aortic dissection. Therefore, any disease process or other condition that undermines the integrity of the elastic component of the media predisposes the aorta to dissection. In addition to connective tissue diseases such as Marfan syndrome, long-standing hypertensive–atherosclerotic processes are well-known risk factors for aortic dissection.[1 2] The structural integrity of the aorta relies on extracellular matrix proteins, which are regulated by proteolytic enzymes.[3] Matrix metalloproteinases (MMPs) play an important role in the turnover of the extracellular matrix in normal and pathological aortas.[4] In fact, it has been demonstrated that MMPs play an important role specifically in aortic dissection.[5 6]

Simple renal cysts are discrete lesions that are typically cortical and extend outside the parenchyma, distorting the renal contour. The prevalence of simple renal cysts has been reported to be 5–41% based on different studies.[7 8] The pathogenesis of simple renal cysts is unclear. Several previous studies have reported that MMPs were detectable in renal cystic fluids and that treatment with metalloproteinase inhibitors resulted in a significant reduction in cyst number and weight.[9 10] A recent study demonstrated that the presence of simple renal cysts is associated with increased risk of aortic aneurysm.[11] Additionally, autosomal dominant polycystic kidney disease is characterised by increased risk of aneurysmal formation and aortic dissection.[12 13] Therefore, it is conceivable that aortic dissection and simple renal cysts in part share a common pathophysiological mechanism. We hypothesised that the structural weakness that predisposes a patient to the development of simple renal cysts may be associated with the development of aortic dissection. We compared the prevalence of simple renal cysts between patients with aortic dissection and healthy subjects who underwent abdominal CT during a health screening programme. To the best of our knowledge, this is the first study to evaluate whether simple renal cysts occur more frequently in patients with aortic dissection since they share in part their pathophysiological mechanism.

MATERIALS AND METHODS

Study population and design

We reviewed the records of patients with aortic dissection and/or intramural haematoma (AD group) diagnosed from December 1994 to March 2009 and healthy subjects (control group) who underwent abdominal CT as part of a routine health screen from December 1994 to December 2006 at the Samsung Medical Center. Of 594 patients with aortic dissection who did not have end-stage renal disease, hydronephrosis, autosomal dominant polycystic kidney disease and renal cell carcinoma, 76 people (12.7%) with other causes of aortic dissection such as Marfan syndrome,

Ehlers–Danlos syndrome, pregnancy, mycotic aneurysm, bicuspid aortic valve, trauma and iatrogenic events were excluded. The remaining 518 patients were the AD group in our study (300 men and 218 women; mean age 58±13 years). Of 1386 healthy subjects identified, we excluded 20 patients (2%) who had a predisposing factor for renal cyst formation such as end-stage renal disease, hydronephrosis and autosomal dominant polycystic kidney disease. The medical records and the results of health screening tests of the control group revealed that they did not have any disease except hypertension and diabetes. Therefore, 1366 subjects became the control group (1177 men and 189 women; mean age 50±8 years).

We conducted a retrospective cohort study comparing the incidence and characteristics of simple renal cysts between AD and control groups. This study was approved by the local institutional review board; informed consent was waived for this retrospective study.

Diagnostic criteria

Aortic dissection was identified using multidetector CT angiography. On CT imaging, classical aortic dissection was defined as the existence of an intimal flap separating the true and false lumens of the aorta. Intramural haematoma was defined as a thickening of the aortic wall with high attenuation extending in a longitudinal, non-spiral fashion. The lumen of an aorta with an intramural haematoma, in contrast to aortic dissection, is rarely compromised and does not have an intimal flap or show wall enhancement after contrast administration. A simple renal cyst was defined on CT scan as a thin-walled, low-attenuation, oval to round lesion with a diameter ≥5 mm without evidence of enhancement or septation. We recorded the number of renal cysts, mean area of the cysts, largest transverse diameter, summation of the diameters and bilateral kidney involvement.

Hypertension was defined as a systolic blood pressure >140 mm Hg or self-reported hypertension irrespective of pharmacological treatment. Diabetes mellitus was defined as a history of type 1 or type 2 diabetes mellitus treated either pharmacologically or by diet. Obesity was defined as a body mass index (weight (kg)/height^2 (m^2)) >25 based on Asian criteria.

Statistical analysis

To reduce the effect of selection bias and potential confounding in this observational study, we adjusted for significant differences in baseline patient characteristics using propensity score matching. To estimate the propensity score, we used logistic regression to obtain the predicted probability of developing an aortic dissection. The predictive ability of each propensity score model was assessed by C statistics (0.86), indicating good discrimination between groups. We determined the success of the matches by examining standardised mean differences in the observed confounders between matched groups. Small differences (<10%) support the assumption of balance between groups.

Following propensity score matching, we assessed the balance in baseline covariates between groups with the Wilcoxon signed rank test for continuous variables and the McNemar test for categorical variables. A p value <0.05 was considered significant. Mean values, percentages and ORs are presented with 95% CIs. Analysis was performed using a Statistical Analysis Software package (SAS version 9.1.3, SAS Institute, Cary, North Carolina, USA).

RESULTS

Study population characteristics

Entire cohort

Of 518 individuals in the AD group, 375 (72.4%) had a classical aortic dissection and 143 (27.6%) had an intramural haematoma. According to the Stanford classification, 212 (56.5%) patients had type A classical aortic dissection, while 163 (43.5%) patients had type B. The incidence of type A intramural haematoma was 55 (38.5%); the incidence of type B was 88 (61.5%). Baseline characteristics of all subjects are summarised in table 1. Mean age was 58±13 years in the AD group and 50±8 years in the control group. Men comprised 57.9% of the AD group and 86.2% of the control group. There were significant differences between AD and control groups with respect to hypertension (73.0% vs 16.3%, p<0.0001) and obesity (36.5% vs 33.3%, p<0.0001). There was no significant difference in the prevalence of diabetes mellitus between groups (9.1% vs 7.2%, p=0.1673). Creatinine levels were significantly higher in the AD group (1.2±1.2 mg/dl vs 1.1±0.2 mg/dl, p<0.0007).

Propensity-matched cohort

Propensity score matching yielded 311 matched patient pairs. In this matched cohort, 223 (71.7%) had classical aortic dissection and 88 (28.3%) had intramural haematoma. According to the Stanford classification, 109 (48.9%) patients had type A classical aortic dissection, while 114 (51.1%) had type B classical aortic dissection. The prevalence of type A intramural haematoma was 29 (33.0%); the prevalence of type B was 59 (67.0%). Using matched cohorts eliminated all significant differences between the AD group and the control group for any covariate according to the use of statistical methods appropriate for matched data (table 1).

Prevalence of simple renal cysts

The prevalence of simple renal cysts was 37.8% in the AD group and 21.9% in the control group (p<0.0001). In the matched

Table 1 Comparison of the baseline characteristics of the aortic dissection (AD) and control group

	Total population				Propensity-matched population			
	AD (n=518)	Control (n=1366)	p Value	Standardised difference	AD (n=311)	Control (n=311)	p Value	Standardised difference
Age, years	58±13	50±8	<0.0001	60.38	53±12	53±9	0.9218	−2.32
Male, n (%)	300 (57.9)	1177 (86.2)	<0.0001	57.16	238 (76.5)	229 (73.6)	0.2987	−6.82
Hypertension, n (%)	378 (73.0)	222 (16.3)	<0.0001	127.60	181 (58.2)	179 (57.6)	0.7815	1.30
DM, n (%)	47 (9.1)	98 (7.2)	0.1673	6.61	25 (8.0)	32 (10.3)	0.3270	−8.27
Obesity, n (%)	189 (36.5)	455 (33.3)	<0.0001	6.59	136 (43.7)	120 (38.6)	0.1763	10.35
Creatinine (mg/dl)	1.2±1.2	1.1±0.2	0.0007	13.12	1.0±0.4	1.0±0.2	0.1580	5.30
Presence of renal cyst, n (%)	196 (37.8)	300 (22.0)	<0.0001	–	105 (33.8)	80 (25.7)	0.0230	–

Data are presented as mean±SD or n (%).
DM, diabetes mellitus; standardised difference, standardised mean difference of covariates between groups.

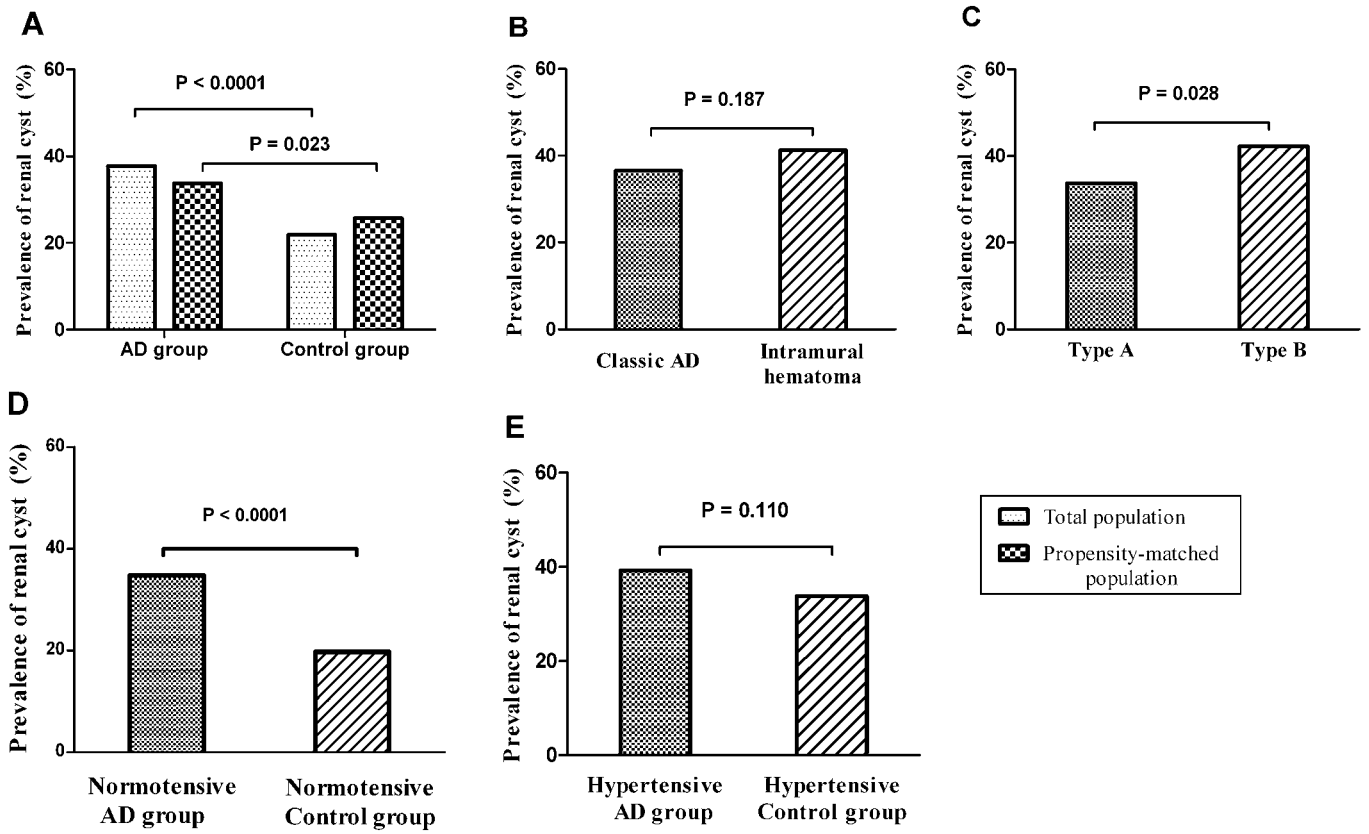

Figure 1 Prevalence of renal cysts. (A) Prevalence of renal cysts in the AD (aortic dissection) group versus the control group in total and propensity-matched populations. (B) Prevalence of renal cysts in patients with classical AD versus patients with intramural haematoma. (C) Prevalence of renal cysts between type A and type B ADs. (D) Prevalence of renal cysts in normotensive AD subjects versus normotensive controls. (E) Prevalence of renal cysts in hypertensive AD subjects versus hypertensive controls.

cohort, the AD group still had a higher prevalence of simple renal cysts than the control group (33.8% vs 25.7%, p=0.0230) (figure 1A). In subgroup analysis of the entire cohort, patients with intramural haematoma had a higher prevalence of simple renal cysts than did patients with classical aortic dissection (41.3% vs 36.5%) (figure 1B), although this was not statistically significant (p=0.1870). With regard to the site of aortic involvement, patients with type B dissections had a significantly higher prevalence of simple renal cysts than patients with type A dissection (42.2% vs 33.7%, p=0.0280) (figure 1C). The prevalence of simple renal cysts was significantly higher in normotensive patients in the AD group (48 out of 140) than in normotensive control patients (225 out of 1144) (34.7% vs 19.7%, p<0.0001) (figure 1D). Of 600 individuals with hypertension, 39.2% (148 out of 378) of the AD group and 33.8% (75 out of 222) of the control group had simple renal cysts (p=0.1100) (figure 1E).

Interestingly, the prevalence of renal cysts in the AD group increased significantly with age, whereas it increased only marginally in the control group (figure 2). In multivariate analysis, the presence of simple renal cysts was significantly associated with increased risk of aortic dissection. This finding was confirmed by multiple logistic regression analysis of the matched cohorts (table 2).

Characteristics of simple renal cysts

We next analysed the characteristics of simple renal cysts in our subjects (table 3). The AD group had a larger sum of the diameters of all renal cysts (49.8±63.3 mm vs 25.7±19.8 mm, p<0.00004). The number of cysts per person (2.7±2.8 vs 1.6±1.2, p<0.0001) and the presence of bilateral involvement (44.6% vs 23.3%, p<0.0001) were higher in the AD group. Furthermore, maximal diameter (22.9±16.7 mm vs 19.7±13.6 mm, p=0.07998), mean diameter (17.5±10.6 mm vs 16.8±10.5 mm, p=0.42811) and mean area (410.0±590.7 mm^2 vs 333.5±521.8 mm^2, p=0.22429) of cysts were greater in the AD group than in the control group. However, none of these differences was statistically significant. Partial Spearman correlation analysis demonstrated a significant correlation between aortic dissection and number of renal cysts

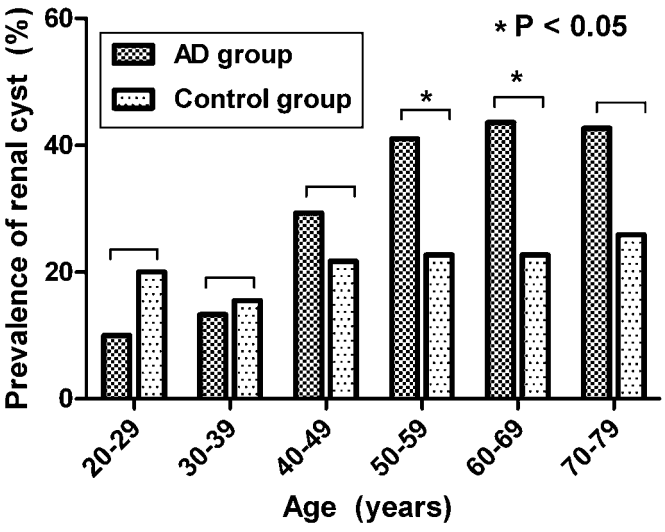

Figure 2 Association between the presence of renal cysts and ageing.

Table 2 Multivariate analysis

	Total population		Propensity-matched population	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.06 (1.04 to 1.07)	<0.0001	1.00 (0.98 to 1.01)	0.5445
Sex	5.00 (3.55 to 7.05)	<0.0001	0.93 (0.66 to 1.31)	0.6899
Hypertension	11.38 (8.68 to 14.91)	<0.0001	0.93 (0.79 to 1.10)	0.3954
DM	0.59 (0.37 to 0.96)	0.0320	0.76 (0.44 to 1.30)	0.3089
Obesity	1.14 (0.86 to 1.50)	0.3660	1.24 (0.90 to 1.70)	0.1903
Creatinine	3.19 (1.90 to 5.37)	<0.0001	1.12 (0.67 to 1.89)	0.6629
Renal cyst	1.49 (1.12 to 1.98)	0.0070	1.49 (1.05 to 2.11)	0.0245

DM, diabetes mellitus.

(correlation coefficient=0.14570, p=0.0036). Multiple logistic regression analysis also demonstrated a significant association between bilateral cysts and risk of aortic dissection (table 4). These findings suggest that the burden of renal cysts is increased in patients with aortic dissection.

DISCUSSION

Our analysis demonstrated increased prevalence of simple renal cysts in patients with aortic dissection compared with healthy subjects. Multivariate analysis demonstrated that renal cysts were independently associated with development of aortic dissection. These results suggest a common mechanism underlying development of aortic dissection and renal cysts.

In accordance with previous studies, our study showed a higher prevalence of hypertension in patients with aortic dissection. Data analysis from the International Registry of Acute Aortic Dissection showed that three-quarters of patients with aortic dissection have a history of hypertension.[14] An association has been reported between simple renal cysts and hypertension, including higher systolic and diastolic blood pressures.[15 16] Therefore, it is possible that higher blood pressure in subjects with renal cysts leads to aortic dissection. However, our results negate this possibility and suggest the following, since we found a significant difference in the prevalence of renal cysts between normotensive AD and control subjects, but not between hypertensive AD and control subjects. In subjests with hypertension, increased transmural wall tension, shear stress or associated atherosclerosis most probably predispose the patients to aortic dissection more potently than the structural weakness associated with renal cysts. Additionally, the increased incidence of simple renal cysts in patients with aortic dissection was not related to an increased risk of hypertension. We can speculate that general connective tissue weakness manifested as simple renal cysts plays an important role, primarily in normotensive patients with aortic dissection.

Interestingly, we found that the prevalence of renal cysts in the AD group increased significantly in patients older than 50 compared with the control group. Based on this finding, we hypothesise that the contribution of renal cysts to the pathogenesis of aortic dissection is largely dependent on the degenerative processes associated with ageing.

Table 3 Comparison of renal cyst characteristics between the aortic dissection (AD) and control group

	AD (n=195)	Control (n=300)	p Value
Bilateral involvement, n (%)	87 (44.6)	70 (23.3)	<0.0001
Total number of cysts, n (%)	2.7±2.8	1.6±1.2	<0.0001
Maximal size of cyst (mm)	22.9±16.7	19.7±13.6	0.0800
Sum of cyst diameters (mm)	49.8±63.3	25.7±19.8	<0.0001
Mean size of cyst (mm)	17.5±10.6	16.8±10.5	0.4281
Mean area of cyst (mm^2)	410.0±590.7	333.3±521.8	0.2243

Data are presented as mean±SD or n (%).

Table 4 Multiple logistic regression for the risk of aortic dissection

	OR (95% CI)	p Value
Age	1.11 (1.08 to 1.14)	<0.0001
Sex	3.18 (1.65 to 6.15)	0.0006
Hypertension	7.95 (4.80 to 13.18)	<0.0001
DM	0.48 (0.19 to 1.19)	0.1124
Obesity	1.49 (0.89 to 2.50)	0.1328
Creatinine	3.09 (1.19 to 8.07)	0.0211
Bilateral renal cysts	2.47 (1.45 to 4.11)	0.0008

DM, diabetes mellitus.

Aortic dissection is associated with degenerative changes in the medial layer of the aortic wall. Dysregulation of MMP production and activity leads to extracellular matrix degradation and medial layer degeneration. The role of MMPs in the pathogenesis of degenerative abdominal and thoracic aortic aneurysms is well established.[17] Although dissections are studied far less extensively than are degenerative aneurysms, there is ample evidence that MMPs play a role in aortic dissection.[6 18 19]

The prevalence of simple renal cysts in the general population ranges from 5% to 41%, depending on the study.[20 21] The pathogenesis of simple renal cysts is poorly understood. Previous studies have shown that MMPs are associated with renal simple cyst formation.[9 10] MMP-2 and MMP-9 are synthesised and secreted by cultured kidney tubules from polycystic mouse models and are abundant in the cystic fluid of human renal biopsy samples. Furthermore, treatment with MMP inhibitors has been shown to result in significant reduction of cyst number and kidney weight. In another study, MMPs synthesised in polycystic kidney disease were shown to play a role in the development of a concurrent abdominal aortic aneurysm.[22]

A recent study reported that the presence of simple renal cysts is associated with an increased risk of aortic aneurysm.[11] Additionally, autosomal dominant polycystic kidney disease is associated with aortic dissections. Therefore, aortic dissection and simple renal cysts may share a common pathophysiological mechanism. The common denominator of aortic dissection and renal cysts could be genetic variation of 8202A/G in the MMP-9 gene, which is known to be associated with aortic dissection (adjusted OR 4.26, 95% CI 1.70 to 10.66).[23 24] The unsolved issue from these studies, however, is whether this polymorphism is involved in the development of simple renal cysts. A prospective study is warranted to ascertain a common pathophysiological mechanism between aortic dissection and simple renal cyst.

Our findings do have an important clinical implication; we recommend that patients with renal simple cysts require more strict control of other correctable risk factors for aortic dissection and more prudent follow-ups are necessary for patients with aortic dilatation and renal simple cysts.

Study limitations

The present study was conducted retrospectively in a single centre, which may have caused selection bias. In addition, our study population may not be reflective of the general population. Ideally, selection bias should be avoided first by study design. However, the fact that this was a relatively large population-based analysis increases our confidence in the results. Additionally, we adjusted covariates by propensity score matching to minimise the effect of selection bias and potential confounding. The validity of matching was tested

with C statistics with a good correlation of 0.86. We could not exclude completely the relationship of any medication history in developing renal cysts. Our study provides only limited evidence for the mechanisms underlying this association: we did not perform immunohistochemical studies or measure MMP levels in aortic dissection tissue or renal cystic fluid to explore causal relationships between connective tissue abnormalities, aortic dissection and renal cysts.

CONCLUSION

Patients with aortic dissection, including intramural haematoma, have an increased burden of simple renal cysts compared with healthy controls. The structural weakness that predisposes patients to the development of simple renal cysts may be associated with medial degeneration of the aorta, which in turn leads to aortic dissection. A prospective study is required to determine whether aortic dissection and simple renal cysts do in fact have a common pathogenesis. Such a study should also evaluate whether the presence of renal cysts can be considered a risk factor for aortic dissection.

Competing interests None.

Ethics approval This study was approved by the local institutional review board.

Provenance and peer review Not commissioned; externally peer reviewed.

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