

## Original Article

# Decreased circulating levels of sirtuin-1 in patients with aortic dissection

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**Abstract:** Sirtuin-1 (SIRT1) has long been associated with beneficial metabolic effects and vascular homeostasis. However, the role of endogenous SIRT1 in patients with aortic dissection (AD) has not been fully elucidated. This study measured for the first time serum SIRT1 levels in AD patients and control subjects and explored the correlations between its serum levels and various clinic parameters. SIRT1 concentrations in plasma of 46 patients with AD and 74 control subjects were measured by Enzyme-linked immunosorbent assay (ELISA). Anthropometric parameters, blood lipids, creatinine, blood urea nitrogen, uric acid (UA) and fasting glucose were measured. Circulating levels of SIRT1 were significantly decreased in AD patients than in control subjects ( $1.52 \pm 0.64$  versus  $1.87 \pm 0.68$  ng/ml,  $P = 0.01$ ). Interestingly, analysis of the data showed a negative correlation between SIRT1 levels and UA in all subjects ( $r = -0.22$ ;  $P = 0.02$ ). In addition, plasma SIRT1 levels tended to correlate negatively with UA in AD patients ( $r = -0.28$ ;  $P = 0.06$ ). To conclude, circulating concentrations of SIRT1 are significantly decreased in AD patients and negatively correlated with UA. Our results suggest that SIRT1 may play a role in the pathogenesis of AD and could be a potential biomarker for AD.

**Keywords:** Aortic dissection, sirtuin-1, uric acid

## Introduction

Aortic dissection (AD) is a life-threatening cardiovascular disease with an incidence of about 2.6 to 3.6 cases per 100,000 person-years [1]. There is a growing body of evidence from multiple clinical studies revealed that 20% of the patients with AD die before reaching hospital and 30% die during hospital admission [2, 3]. Pathologically, AD is characterized as blood penetrates the intima and enters the media layer, which causes the formation of a false lumen within the middle tunic. Acute onset of severe chest or back pain is the most common symptom of acute AD occurring in 90% of patients. Depending on the site of rupture, a Stanford-A type AD involves the ascending aorta and progresses distally to involve various extents of the arch and thoracoabdominal aorta. A Stanford-B type AD involves the descending thoracic aorta and/or abdominal aorta. Recent data demonstrate that Stanford-A type AD occurs in almost 60% of all cases with a mortality reaching 90% if untreated [4].

Besides, acute Stanford-A type AD has a mortality of 20% at one day, 30% at 2 days, 40% at 7 days and 50% at 30 days [5]. Therefore, AD typically requires emergent medical treatment which involves replacement of the aorta and arterial stent implantation. Despite recent advances, the in-hospital mortality for AD in International Registry of Acute Aortic Dissection (IRAD) study remains approximately 20% over the past 20 years [6]. Therefore, finding a biomarker for this disease would be important in exploring pathogenic mechanisms and indentifying patients who could benefit from early treatment.

Sirtuin-1 (SIRT1), one of histone deacetylases that consume one molecule of nicotinamide adenine dinucleotide+ during each deacetylation cycle [7], which has been implicated in the processes of antioxidant and anti-inflammatory. It is well known that SIRT1 plays an important role in metabolic health by deacetylating many target proteins in numerous tissues, including endothelium, liver, adipose tissue, muscle and

heart. SIRT1 has received extensive and growing attention recently for its potential role in extending longevity and ameliorating degenerative diseases [8, 9]. Interestingly, accumulating evidence has demonstrated that SIRT1 deacetylates and alters the function of key molecules involved in atherosclerosis and vascular homeostasis [8, 10]. It was also suggested that SIRT1 acts as a regulator of macrophage foam cell and neointima formation by reducing medial degeneration and vascular smooth muscle cell (VSMC) proliferation and migration [8, 11]. Previous study has shown that SIRT1 overexpression ameliorates angiotensin II (AngII)-induced VSMC hypertrophy [12]. Additionally, lack of SIRT1 and resultant oxidative damage in apolipoprotein E-deficient mice contribute to enhanced atherosclerosis [8]. Of note, mice lacking SIRT1 in VSMC had drastically high mortality caused by aortic dissection after angiotensin II infusion [13]. Thus, SIRT1 level is a valuable biomarker for the structural integrity of the aortic wall.

In light of these observations, we hypothesized that circulating SIRT1 level may be associated with AD. In the current study, we examined SIRT1 level in AD patients and control subjects. We also assessed the potential of relationship between SIRT1 and clinical parameters.

### Materials and methods

#### *Study subjects*

The study groups consisted of randomly selected 74 control subjects and 46 AD patients. AD patients were recruited from the Department of Internal Medicine, Tongji Hospital in Wuhan (Hubei, People's Republic of China). Diagnosis of AD was based on previous history, transthoracic echocardiography and contrast-enhanced CT. We excluded participants with Marfan syndrome, history of aortic valve, coronary artery bypass surgery, traumatic aortic dissection or iatrogenic aortic dissection on admission. Furthermore, those with coronary heart disease, heart failure, peripheral artery disease, cerebrovascular event, acute or chronic infection and malignancy were excluded.

The study protocol was approved by the Ethical Committee of Tongji Hospital. Written informed consent was obtained from each participant before inclusion in this study. This study was

conducted in accordance with the principles expressed in the Declaration of Helsinki.

#### *Physiological and biochemical parameters*

Information on sex, age, ethnicity, cigarette smoking, medical history was obtained through self-administered. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Subjects were considered to be hypertensive if their systolic blood pressure (SBP) was  $\geq 140$  mmHg or diastolic blood pressure (DBP)  $\geq 90$  mmHg or they were ongoing therapy of hypertension. Fasting concentrations of total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), plasma glucose, blood urea nitrogen (BUN), creatinine and uric acid (UA) were measured at the Department of Clinical Laboratory at Tongji Hospital.

#### *Measurement of SIRT1 level*

After 12 h of fasting, blood samples of subjects were taken into tubes and centrifuged at 3000 rpm for 5 min at 4°C. Plasma samples of subjects were analyzed for the levels of SIRT1 by using enzyme-linked immunosorbent assay (ELISA) kits according to a protocol provided by the manufacturer (Abcam). Samples from each patient were measured in parallel and in duplicate to avoid interassay variance.

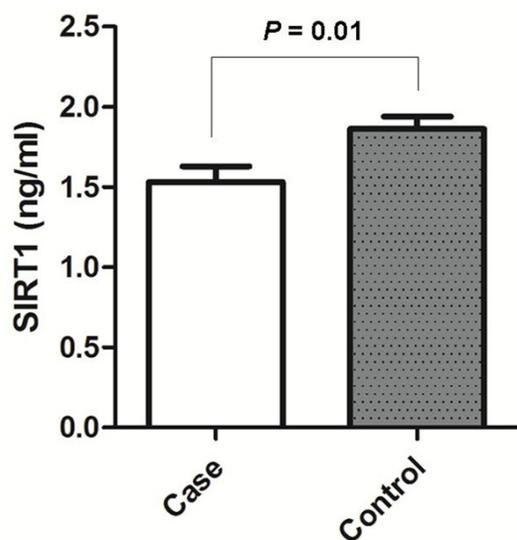
#### *Statistical analysis*

The Kolmogorov-Smirnov test was used to evaluate if the data were distributed normally. Among the numerical variables, those that were normally distributed were expressed as mean  $\pm$  standard deviation and those that were not normally distributed were expressed as median. For normally distributed parameters, the independent sample t test was used, whereas for parameters that were not normally distributed, the Mann-Whitney U test was used. Categorical values were compared by the Chi-square test or Fisher's test when appropriate. The relation between the parameters was analyzed using Spearman correlation analysis. Two-tailed *P* values  $< 0.05$  were considered significant. The software SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, United States) was used for statistical analysis.

**Table 1.** Baseline characteristics of the study subjects

Characteristics	AD group (n = 46)	non-AD group (n = 74)	P value
Age (years)	55.9 ± 12.4	54.0 ± 8.3	0.29
BMI (kg/m <sup>2</sup> )	24.6 ± 2.2	24.0 ± 2.2	0.17
Male (%)	35 (76.1)	52 (70.3)	0.53
Smoking (%)	27 (58.7)	33 (44.6)	0.09
Hypertension (%)	42 (91.3)	64 (86.5)	0.31
Hyperlipidemia (%)	20 (43.5)	36 (48.6)	0.58
BUN (mmol/L)	5.6 ± 1.7	5.4 ± 1.7	0.41
Creatinine (μmol/L)	90.2 ± 43.7	84.8 ± 36.9	0.47
UA (μmol/L)	412.8 ± 106.4	351.0 ± 102.7	<0.01
TC (mmol/L)	4.79 ± 1.10	4.61 ± 0.81	0.31
TG (mmol/L)	1.88 ± 1.64	1.49 ± 1.11	0.13
LDL (mmol/L)	2.65 ± 0.66	2.58 ± 0.59	0.60
HDL (mmol/L)	1.47 ± 0.29	1.47 ± 0.34	0.96
Glucose (mmol/L)	6.9 ± 2.1	6.1 ± 1.2	0.01

Data are shown as means ± SD or n (%).



**Figure 1.** Circulating levels of SIRT1 were significantly decreased in AD patients than in control subjects.

## Results

### Baseline characteristics

Demographic and clinical characteristics of subjects are summarized in **Table 1**. In total, 46 patients with AD and 74 control subjects who met the inclusion criteria were enrolled. According to the table, there was no significant difference in age, BMI and the frequency of male between the study groups ( $P > 0.05$ ). AD patients had marginal significantly higher ratio

of smokers than control subjects ( $P = 0.09$ ). BUN, creatinine and morbidity of hypertension were not significantly different between the AD patients and control subjects ( $P > 0.05$ ). Plasma UA levels in AD patients were markedly higher than those in control subjects ( $412.8 \pm 106.4$  versus  $351.0 \pm 102.7$  μmol/l,  $P < 0.01$ ). No significant difference in TC, TG, LDL or HDL was detected between case and control groups ( $P > 0.05$ ). However, AD patients had higher fasting glucose values compared to the control subjects ( $6.9 \pm 2.1$  versus  $6.1 \pm 1.2$  mmol/l,  $P = 0.01$ ).

### Relationship between SIRT1 and AD

The serum SIRT1 concentrations are shown in **Figure 1** between the AD and control groups. Circulating SIRT1 levels in AD patients were markedly lower than those in control subjects ( $1.52 \pm 0.64$  versus  $1.87 \pm 0.68$  ng/ml,  $P = 0.01$ ) (**Figure 1**).

### Relationship between SIRT1 and clinical parameters

We analyzed the correlation between plasma levels of SIRT1 and clinical parameters in all subjects (**Table 2**). There was no correlation between SIRT1 levels and glucose, creatinine, BUN, HDL, LDL, TG, TC, BMI or age in all subjects ( $P > 0.05$ ). However, analysis of the data showed a negative correlation between SIRT1 levels and UA in all subjects ( $r = -0.22$ ;  $P = 0.02$ ). In addition, plasma SIRT1 levels tended to correlate negatively with UA in AD patients ( $r = -0.28$ ;  $P = 0.06$ ) (**Figure 2**). In contrast, no significant correlation was observed in control subjects between SIRT1 levels and any clinical parameters ( $P > 0.05$ ).

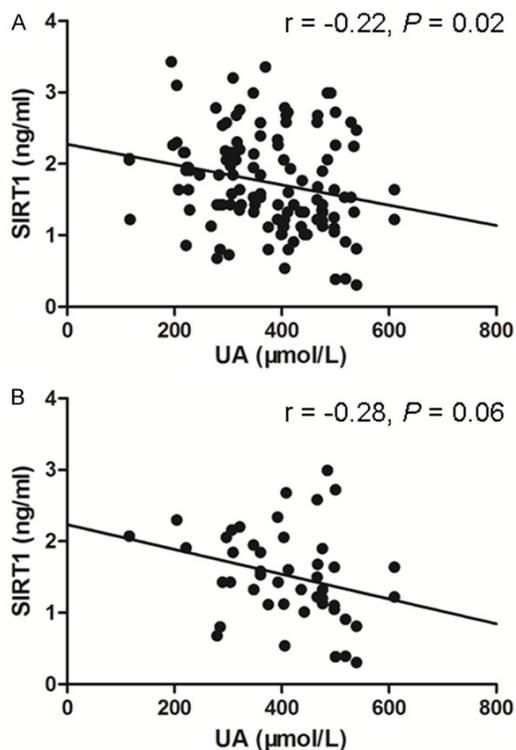
## Discussion

The current study provides the first evidence that decreased levels of SIRT1 are associated with the prevalence of AD in Chinese population. Moreover, we demonstrate for the first time that plasma SIRT1 levels tended to correlate negatively with UA. Although the functional role of SIRT1 in the arterial system is incompletely known, these observations indicate that SIRT1 acts as a useful marker for evaluation of AD risk.

**Table 2.** Correlation between circulating SIRT1 levels and clinical parameters

	All subjects (n = 120)		Control (n = 74)		AD (n = 46)	
	Coefficient	P value	Coefficient	P value	Coefficient	P value
Age	0.14	0.14	0.20	0.08	0.12	0.39
BMI	0.03	0.75	-0.07	0.56	0.25	0.09
DBP	0.08	0.37	0.06	0.63	0.24	0.10
SBP	-0.08	0.38	0.01	0.96	-0.22	0.15
Creatinine	0.12	0.21	0.08	0.49	0.22	0.14
BUN	0.10	0.29	0.10	0.36	0.15	0.32
UA	-0.22	0.02	-0.10	0.38	-0.28	0.06
HDL	-0.02	0.83	-0.02	0.88	-0.02	0.89
LDL	0.04	0.63	-0.05	0.67	0.20	0.19
TG	-0.04	0.65	-0.03	0.82	0.02	0.90
TC	-0.01	0.89	-0.04	0.77	0.07	0.63
Glucose	-0.02	0.80	0.19	0.09	-0.13	0.38

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triacylglycerol.



**Figure 2.** Correlations of plasma SIRT1 levels with UA concentration in all participants (A) (n = 120) and AD patients (B) (n = 46).

Our results extend the knowledge on SIRT1 expression in AD and control subjects and are in accordance with data obtained in rodents [13]. Supporting our findings, SIRT1 expression

was reduced in human atherosclerotic plaques in a very recent study [8]. Furthermore, reduced SIRT1 associated with increased vascular smooth muscle cells apoptosis. Previous studies shown that vascular smooth muscle cells apoptosis can increase atherosclerosis, reduce relative fibrous cap thickness, and associate with increased atherosclerosis necrotic core and medial degeneration [14-16]. In contrast, vascular smooth muscle cells from mice expressing inactive SIRT1 showed increased oxidized LDL-induced DNA damage and senescence. Noteworthy, SIRT1 over-expression alleviated vascular remodeling in

mouse thoracic and renal aortas induced by AngII infusion, and significantly inhibited reactive oxygen species (ROS) generation, vascular inflammation, and collagen synthesis in arterial walls [12]. Additionally, recent studies showed that SIRT1 improves endothelial function to prevent atherosclerosis by improving endothelium relaxation through activating endothelial nitric oxide synthase [17, 18]. Therefore, by demonstrating the relation between SIRT1 and the above parameters, the present study may give a clue for developing novel treatment strategy to decrease the risk of AD development. Further elucidations of the role of SIRT1 in the pathophysiology of AD are warranted.

Uric acid is the metabolic end product of purine metabolism in humans, which have pro-inflammatory effects. Recently, accumulating evidence has shown that serum uric acid is positively associated with increased cardiovascular risk, including atherosclerosis and aneurysm [19, 20]. It has also been reported that increased serum uric acid level might be associated with aortic dissection [21, 22]. Previous study revealed that serum uric acid could be used as a predictor for cardiovascular disease related mortality and all-cause mortality [23]. In post-menopause, serum uric acid levels are associated with increased risk of death and major adverse cardiovascular events [24]. Interestingly, it has been shown that higher serum uric acid was associated with greater

increase in pulse wave velocity in longitudinal study [25]. Consistently, our data show that circulating SIRT1 correlated negatively with serum uric acid in AD patients and all subjects. Furthermore, we demonstrate that serum uric acid is dramatically increased in AD patients versus control subjects in the present study. Taken together, these data suggest that SIRT1 not only represents an AD biomarker but also might have antioxidant properties.

The functional significance of SIRT1 in the pathogenesis of AD seems to be poorly understood. SIRT1, belong to the family of silent information regulator 2, has been shown to be expressed in various tissues including adipose tissue, liver, brain, skeletal muscle, pancreas and so on. The expression of SIRT1 is regulated in a context-dependent manner by various stresses, transcription factors and post-translational modifications. It is well known that SIRT1 has attracted extensive attention as a mediator of health and longevity. Recent evidence indicate that activated SIRT1 improves the insulin sensitivity of liver, skeletal muscle and adipose tissues and protects the function and cell mass of pancreatic  $\beta$ -cells [26]. Besides, accumulating studies have found that SIRT1 plays a key role in the development of cardiovascular and atherosclerosis. The mechanisms of SIRT1 on cardiovascular disease, including reduction of inflammation, improvement of endothelial function, defense against oxidative stress, promotion of autophagy, delay of cellular senescence and inhibition of foam cell formation, are starting to become clear [27]. By contrast, despite comparable blood pressure increases, mice lacking SIR1 in vascular smooth muscle had drastically high mortality caused by aortic dissection [13]. Aortas from smooth muscle SIRT1 knockout mice had severely disorganized elastic lamellae with frequent elastin breaks, increased oxidant production, and aortic stiffness compared with wild-type mice [13]. Preclinical studies mentioned above have provided much evidence that SIRT1 has helpful effects in vasculature. Nevertheless, the role of SIRT1 in human with AD is currently unknown. Although the exact molecular mechanisms of SIRT1 in AD development remain elusive, our data demonstrate that the clinical relevance of SIRT1 associate with AD in humans.

In summary, our results indicate for the first time that circulating SIRT1 concentrations were

significantly decreased in patients with AD. Moreover, serum SIRT1 levels are correlated negatively with serum uric acid. These phenomena emphasize the complexity of SIRT1 biology. Future studies from other research conducted in different population are required to establish this association.

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### Disclosure of conflict of interest

None.

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## Sirtuin-1 and aortic dissection

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