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ORIGINAL ARTICLE

Elevated plasma aldosterone is an independent risk factor for erectile dysfunction in men

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Abstract
Introduction Erectile dysfunction (ED) and cardiovascular disease (CVD) share a great number of common risk factors. There is growing evidence that aldosterone, an independent CVD risk factor, is associated with ED.
Aims The purpose of this study was to determine the relationship between plasma aldosterone and erectile dysfunction.
Methods This study recruited 287 participants, ranging from 18 to 84 years old; 217 were suffering from ED, diagnosed by the International Index of Erectile Function 5 (IIEF-5) scores. Based on IIEF-5 scores, patients were divided into one control group and three ED groups (mild ED; moderate ED; severe ED).
Main outcome measures The differences in principal characteristics, blood routine, sexual hormone, adrenal hormone, thyroid hormone, renal function, liver function and blood lipid were compared between ED and control groups.
Results Our study demonstrated that the difference of mean plasma aldosterone levels between ED group and the control group was statistically significant ($P < 0.05$). Stepwise logistic regression analysis of all the possible factors support the role of aldosterone as an independent risk factor for ED (OR 1.011; 95 % CI 1.003–1.018; $P = 0.004$). Similar statistical methods were applied to the comparison between moderate to severe ED group and control to mild ED group (OR 1.017; 95 % CI 1.009–1.024; $P < 0.001$). ROC curve and the area under the curve (0.718; 95 % CI 0.643–0.794; $P < 0.001$) were performed to assess the diagnostic effect and to compare the severity of risk with the known independent risk factors, such as age and cholesterol (0.704; 95 % CI 0.631–0.778; $P < 0.001$). When using a 374 pg/mL cut-off value from Youden index, the OR of ED group versus controls is 3.106 (95 % CI 1.458–6.617), while the OR of moderate to severe ED versus control and mild ED is 5.480 (95 % CI 3.108–9.662).
Conclusions We determined that elevated plasma aldosterone concentration is an independent risk factor for ED. Our findings also indicate that the aldosterone, a well-recognized contributor to vascular injury, might be a potential bond between ED and CVD.

Keywords Erectile dysfunction · Aldosterone · Cardiovascular disease · Risk factors

Introduction

Erectile dysfunction (ED), the most common male sexual dysfunction, is a worldwide medical problem of adult men. According to The Global Online Sexuality Survey, the prevalence of ED in the USA is 33.7 % in 2011, which is 27 % among all respondents in a national telephone survey of adult men in east Asians [1, 2]. Erection is the major sexual arousal phenomenon and is regulated by a complex network including neurological, vascular and tissue compartments [3]. ED has significant impacts on the quality of life for men of various ages. Moreover, ED is now regarded

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as an early marker of a significantly increased risk of symptomatic cardiovascular disease (CVD) [4–6].

The pathophysiology of ED might involve psychological, vascular, neurogenic, anatomic and hormonal factors [3]. Among etiological studies, the hormonal causes of ED are most controversial [7]. Except for some well-documented hormone disorders (e.g., hyperprolactinemia), the clinical association and molecular mechanism of endocrine hormones underlying the pathogenesis of ED remain poorly understood [7–9]. For example, it is unclear whether testosterone deficiency (TD) causes ED and whether a lack of dehydroepiandrosterone (DHEA/S) causes ED [7, 10, 11]. Likewise, elevated serum cortisol is also associated with ED, but it is difficult to determine whether hypercortisolism is the cause or the consequence of ED because ED is also a powerful stressor for glucocorticoids [12, 13]. Furthermore, hyperthyroidism is a common cause of acquired premature ejaculation, but its role in ED still remains ambiguous [14, 15].

Erectile dysfunction and cardiovascular disease share a great number of common risk factors, including smoking, obesity, metabolic syndrome (MS), diabetes mellitus (DM), dyslipidemia and lack of exercise [7, 16, 17]. The relationship between the two conditions may originate from cardiovascular risk factors that affect endothelial function and atherosclerosis of both penile and coronary arteries [5]. Prior studies have demonstrated that elevated plasma aldosterone level is an independent risk factor for CVD and death in patients with CVD [18, 19]. Aldosterone is an adrenal hormone that controls blood pressure by acting on urinary tubule and binding directly to the mineralocorticoid receptors (MR) on blood vessels and myocardium [20]. MR is a ligand-activated transcription factor and plays a key role in the pathogenesis of cardiovascular disease [20]. The presence of MR in human penile corpus cavernosum tissue has been recently confirmed and its physiological effect in vitro is enhancing the noradrenaline-induced contraction [21, 22]. Thus, this indicates that aldosterone is one of the negative regulators for human erectile function. To date, however, no clinical evidence regarding the association between ED and aldosterone has been reported. Therefore, in this case–control study, ED patients are enrolled with consent to investigate whether elevated plasma aldosterone concentration is an independent risk factor for ED.

Methods

Patient enrollment

The study design was a retrospective case–control study. We identified patients of adult men with newly diagnosed ED who had visited the andrology department of Huashan Hospital, Fudan University, from January 1, 2014 to April 1, 2015. ED is diagnosed based on the results of a self-administered International Index of Erectile Dysfunction-5 (IIEF-5) questionnaire [23]. Patients were excluded if they received diagnosis of major psychiatric diseases, adrenal adenomas, hypophysoma, vascular disease, hypertension, diabetes mellitus and coronary heart disease, or used drugs that affected sexual function and aldosterone secretion, including spironolactone. Patients complained for psychological problems, such as depression or anxiety, were also excluded during inquiring diagnosis. Most of the enrolled cases had systematic inquiry and laboratory examination, including blood routine and tests for sexual hormone, adrenal hormone, thyroid hormone, renal function, liver function and blood lipid. For patients with elevated aldosterone concentrations beyond 400 pg/mL in more than two tests, further examination such as plasma electrolytes as well as adrenal CT scans was performed to exclude typical primary hyperaldosteronism (PHA) or secondary hyperaldosteronism. To ensure that the sample size of any laboratory parameter was over 200, 51 cases without plasma aldosterone examination were included. Finally, 287 cases (217 ED patients and 70 controls) completed the questionnaires, of which 236 had aldosterone levels examined.

Controls were matched with cases in terms of age and urbanization level. Controls were selected when the IIEF-5 score was larger or equal to 22. Controls were evaluated and confirmed to possess no history of ED. Moreover, the exclusion criteria are identical to that of the case group. The study design was reviewed and approved by the ethical committee of the Huashan Hospital, Fudan University.

Assessment of ED

The IIEF-5, 5-item version of the IIEF, was used to define the severity of erectile dysfunction in patients [23]. No ED: IIEF-5 score 22–25; mild ED: IIEF-5 score 12–21; moderate ED: IIEF-5 score 8–11; severe ED: IIEF-5 score 1–7.

Assessment of aldosterone

All measurements were performed at a central laboratory with strict quality control system at the Huashan Hospital, Fudan University. Aldosterone was measured using an ELISA kit (BioVendor) from baseline EDTA specimens, which were collected in the fasting state at 9:00 a.m. with the patient remaining in the upright posture for 2 h prior to sampling. The reference interval of normal plasma aldosterone concentration in upright position is between 80 and 370 pg/mL.

Statistical analysis

All statistical analyses in this study were conducted with the SPSS (Statistical Package for Social Sciences, Chicago, USA) software for Windows (version 20.0). Results are shown as mean and standard deviation (SD). All parameters underwent a Kolmogorov–Smirnov analysis for normality testing. For abnormal distribution data, Mann–Whitney *U* test was used. Normally, statistical comparisons between groups were carried out by means of Student's *t* test and Chi-square test. A stepwise logistic regression analysis was used to evaluate the risk factors for ED with age adjusted. All considered variables, specifically demographic data and all the laboratory examination parameters, were introduced in the univariate and multivariate model. Logarithmic transformation of plasma aldosterone levels was performed to fulfill the requirement of equal distribution of the residuals. Odds ratio (OR) and 95 % confidence intervals (CI) were presented. The conventional $P < 0.05$ was used to assess statistical significance.

Results

Patient characteristics

This study involved 217 patients with ED and 70 controls with normal erectile function. Tables 1 and 2 outline the baseline characteristics of the subjects. The mean age is 36.41 ranging from 18 to 84 years old. According to Wald–Wolfowitz test, differences between ages of ED group (38.15 ± 12.07 years) and control group (31.01 ± 8.16 years) were not statistically significant ($P > 0.05$). The proportion of mild, moderate and severe ED were 53.0, 26.7 and 19.35 %, respectively. Among the total population, aldosterone (mean 358.3 pg/mL) has a wide range (126.8–645.0 pg/mL) with a standard deviation of 90.70. Although aldosterone level possesses a normal distribution in the raw data, we generated a logarithm transformation to refine the data for further analysis [24].

Table 1 Principal patient characteristics of total population

	Valid (*n*)	Min	Max	SD	Mean
Age (years)	287	18	84	11.65	36.41
IIEF5 score	287	2	25	6.32	14.53
E2 (pmol/L)	261	21.7	288.5	40.22	107.04
T (nmol/mL)	265	0.67	45.04	6.06	18.11
TSH (mIU/L)	266	0.18	13.88	1.25	1.91
ALD (pg/mL)	236	126.8	645.0	90.70	358.30
HGB (g/L)	233	6.1	187.0	14.39	157.67
BUN (mmol/L)	229	1.8	10.6	1.31	5.30
ALT (U/L)	232	9.0	150.0	19.96	29.94
TC (mmol/L)	229	2.43	7.34	0.83	4.62
HDL (mmol/L)	229	0.69	6.91	0.45	1.22
FBG (mmol/L)	251	3.9	19.3	1.53	5.48

E2 estradiol, *T* testosterone, *TSH* thyroid stimulating hormone, *ALD* aldosterone, *HGB* hemoglobin, *BUN* blood urea nitrogen, *ALT* glutamic pyruvic, *TC* serum total cholesterol, *HDL* high-density lipoprotein, *FBG* fasting blood glucose

Normality test found some attributes that were not in normal distribution, such as LH, follicle-stimulating hormone (FSH), prolactin (PRL), cortisol, dehydroepiandrosterone (DHEA), thyroid stimulating hormone (TSH), hemoglobin (HBG), fasting blood glucose (FBG), blood urea nitrogen (BUN), glutamic pyruvic (ALT), glutamic oxaloacetic transaminase (AST), serum total triglyceride (TG) and high-density lipoprotein (HDL). These data were analyzed through nonparametric tests. Pairwise comparison was performed between ED groups and control group, as shown in Table 2. In the ED group ($P < 0.05$), FSH, PRL and DHEA were reduced while aldosterone, white blood cells (WBC) counts, platelet counts, FBG, BUN, serum total cholesterol (TC), TG and low-density lipoprotein LDL were elevated. Significant differences were found between the two groups in the presence of elevated blood lipid and glucose. Sexual hormones and thyroid hormones are nearly identical between the two groups.

Risk factors for ED

To determine whether aldosterone is an independent risk factor for ED, logistic regression analysis was performed. All the laboratory examination parameters were inputted into a logistic regression model and run in a stepwise forward LR manner. After the selection of the model, five variables, specifically age, LH, DHEA, aldosterone and platelet, were kept in the equation ($P < 0.05$) while the others were excluded. The upper part of Table 3 shows the selected variables in the equation. In this model, the adjusted OR of aldosterone to ED is 1.011 (95 % CI 1.003–1.018; $P = 0.004$), and the OR of age to ED is 1.168 (95 % CI 1.056–1.292; $P = 0.003$). Considering the decentralization of aldosterone value and the instability of variance, univariate and multivariate logistic regression analyses were applied after logarithmic transformation of plasma aldosterone values (Table 4). Receiver operating characteristic (ROC) curve of age and aldosterone was plotted to evaluate the ability to recognize ED (Fig. 1a). The ROC curve for plasma aldosterone possessed an area under the curve value of 0.632 (95 % CI 0.519–0.745; $P = 0.043$; Table 5), showing that plasma aldosterone concentration may not qualify as a marker for ED.

Table 2 Characteristics and relevant laboratory data between groups

	Control ($N = 70$)	ED ($N = 217$)	Mild ED ($N = 115$)	Moderate ED ($N = 58$)	Sever ED ($N = 42$)
Sexual hormones					
E2 (pmol/L)	103.3 ± 42.6	108.3 ± 39.4	107.8 ± 38.2	115.1 ± 41.4	100.6 ± 39.3
LH (IU/L)	4.86 ± 2.01	5.47 ± 4.16	5.24 ± 3.43	4.89 ± 1.95	4.87 ± 2.96
FSH (IU/L)	4.24 ± 2.12	5.49 ± 4.18*	5.37 ± 4.30*	5.34 ± 3.56	5.90 ± 4.78
PRL (ng/mL)	12.58 ± 6.58	11.16 ± 6.88*	10.76 ± 4.85*	11.53 ± 9.11	11.72 ± 7.96
T (nmol/mL)	18.86 ± 5.11	17.87 ± 6.34	18.91 ± 6.60	17.34 ± 5.07	15.94 ± 6.69*
Thyroid hormones					
TSH (mIU/L)	1.80 ± 1.00	1.95 ± 1.32	2.01 ± 1.14	1.97 ± 1.91	1.78 ± 0.73
FT3 (pmol/L)	5.36 ± 0.54	5.28 ± 0.51	5.34 ± 0.50	5.25 ± 0.47	5.15 ± 0.58
FT4 (pmol/L)	16.41 ± 2.18	16.15 ± 2.20	16.04 ± 2.14	16.59 ± 2.18	15.86 ± 2.33
Adrenal hormones					
Cortisol (μg/dL)	18.11 ± 18.3	15.33 ± 5.20	15.63 ± 5.23	14.87 ± 5.38	15.18 ± 4.92
DHEA (μmol/L)	9.27 ± 2.59	8.06 ± 3.49*	8.48 ± 3.84*	7.90 ± 2.96*	7.36 ± 3.19*
ALD (pg/mL)	328.0 ± 69.5	365.6 ± 93.8*	335.9 ± 76.68	372.8 ± 97.8*	422.6 ± 97.2**
Blood routine					
HGB (g/L)	158.3 ± 9.7	157.6 ± 15.1	156.6 ± 10.6	158.7 ± 23.1	158.6 ± 11.3
WBC (10^9/L)	5.85 ± 1.29	6.35 ± 1.73*	6.03 ± 1.56	6.73 ± 1.74*	6.68 ± 1.96*
PLT (10^9/L)	189.8 ± 30.1	204.0 ± 51.5*	202.5 ± 56.8	204.7 ± 46.4	206.7 ± 44.6
Blood glucose					
FBG (mmol/L)	5.07 ± 0.37	5.59 ± 1.69**	5.29 ± 0.97	5.67 ± 1.52*	6.21 ± 2.75**
Renal and liver function					
BUN (mmol/L)	4.83 ± 1.11	5.40 ± 1.33*	5.30 ± 1.33	5.42 ± 1.37*	5.58 ± 1.29*
CR (μmol/L)	78.9 ± 11.62	81.1 ± 10.79	80.8 ± 9.71	80.4 ± 12.25	82.6 ± 11.36
ALT (U/L)	29.8 ± 24.12	30.0 ± 19.17	27.8 ± 20.39	31.6 ± 15.69	33.2 ± 19.78
AST (U/L)	20.9 ± 7.97	20.8 ± 7.74	19.9 ± 7.57	21.6 ± 7.63	22.2 ± 8.16
Blood lipid levels					
TC (mmol/L)	4.15 ± 0.59	4.71 ± 0.84**	4.48 ± 0.78*	4.72 ± 0.75**	5.20 ± 0.90**
TG (mmol/L)	0.99 ± 0.49	1.58 ± 1.29**	1.31 ± 0.88*	1.63 ± 1.04**	2.18 ± 1.99**
HDL (mmol/L)	1.22 ± 0.23	1.22 ± 0.48	1.26 ± 0.63	1.17 ± 0.22	1.17 ± 0.28
LDL (mmol/L)	2.29 ± 0.66	2.87 ± 0.76**	2.72 ± 0.70*	2.88 ± 0.72**	3.22 ± 0.85**

ED erectile dysfunction, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *PRL* prolactin, *DHEA* dehydroepiandrosterone, *WBC* white blood cells, *PLT* blood platelet, *BUN* blood urea nitrogen, *CR* creatinine; transaminase, *AST* glutamic oxaloacetic transaminase, *TG* serum total triglyceride, *LDL* low-density lipoprotein. Normal reference value: E2 (pmol/L) 28.0–156.0; LH (IU/L) 1.70–8.60; FSH (IU/L) 1.50–12.40; PRL (ng/mL) 3.86–22.80; T (nmol/mL) 9.90–27.80; TSH (mIU/L) 0.550–4.780; FT3 (pmol/L) 3.50–4.50; FT4 (pmol/L) 11.50–22.70; Cortisol (μg/dL) 6.20–19.40; DHEA (μmol/L) 1.91–13.40; ALD (pg/mL) 80.0–370.0; HGB (g/L) 130–175; WBC (10^9/L) 3.5–9.5; PLT (10^9/L) 125–350; FBG (mmol/L): 3.9–5.8; BUN (mmol/L) 2.50–7.0; CR (μmol/L) 50–130; ALT (U/L) 9–50; AST (U/L) 15–40; TC (mmol/L) 2.80–5.90; TG (mmol/L) <1.80; HDL (mmol/L) 0.80–1.80; LDL (mmol/L) 1.30–3.70

* $P < 0.05$; ** $P < 0.001$

Risk factors for moderate to severe ED

Table 2 shows significantly increased plasma aldosterone concentration in the severe ED group, raising the question of whether aldosterone is related to the occurrence of moderate to severe ED. Thus, logistic regression analysis was performed again with dependent variables of moderate to severe ED versus control and mild ED. In this logistic regression model, five variables were selected: age, aldosterone, WBC, AST and TC. LH, DHEA and platelet were excluded from the equation, while age and aldosterone remain selected. The OR of crude aldosterone values is 1.017 (95 % CI 1.009–1.024; $P < 0.001$), and the OR of age is 1.118 (95 % CI 1.059–1.181; $P < 0.001$). It is important to note the OR of TC in this model for moderate to severe ED is 3.046 (95 % CI 1.617–5.735; $P = 0.001$), which is similar to the results of a previous large-scale investigation [25]. The univariate and multivariate logistic

Table 3 Variables in the equation for logistic regression analysis

	B	SE	Wals	*df*	Sig.	Exp (B)	95 % CI
Age[a]	0.155	0.051	9.134	1	.003	1.168	1.056–1.292
LH[a]	−0.439	0.149	8.695	1	.003	0.645	0.482–0.863
DHEA[a]	−0.296	0.100	8.678	1	.003	0.744	0.611–0.906
ALD[a]	0.011	0.004	8.281	1	.004	1.011	1.003–1.018
PLT[a]	0.020	.009	4.934	1	.026	1.020	1.002–1.038
Age[b]	0.112	0.028	16.168	1	.000	1.118	1.059–1.181
ALD[b]	0.016	0.004	18.555	1	.000	1.017	1.009–1.024
WBCb	0.390	0.157	6.136	1	.013	1.476	1.085–2.009
AST[b]	0.061	0.027	4.927	1	.026	1.063	1.007–1.122
TC[b]	1.114	0.323	11.896	1	.001	3.046	1.617–5.735

[a] ED group versus control group

[b] Moderate to sever ED group versus mild ED and control group

Table 4 Logistic regression analysis of Ln ALD (OR 95 % CI)

	Univariate analysis	Multivariate analysis[c]
Ln ALD[a]	3.640 (1.117–11.863)	5.114 (1.454–17.981)
Ln ALD[b]	13.408 (4.116–43.681)	22.965 (6.337–83.224)

[a] ED group versus control group

[b] Moderate to sever ED group versus mild ED and control group

[c] The analysis is adjusted for age

regression analyses were used with logarithmic transformation of aldosterone values (Table 4). We also performed ROC curve in this section with three variables: age, aldosterone and TC (Fig. 1b). Unlike the curve in the previous section (Fig. 1a), aldosterone has the largest area under curve (0.718; 95 % CI 0.643–0.794; $P < 0.001$), while TC has the second largest (0.704; 95 % CI 0.631–0.778; $P < 0.001$; Table 5).

Aldosterone is an independent risk factor for ED

The mean concentration of plasma aldosterone increased with the severity of ED. Thus, it is hypothesized that aldosterone may have a linear correlation with the IIEF-5 score in ED patients. Scatter diagram indicates the possibility of a linear correlation. Linear regression model showed a Pearson correlation coefficient of 0.409 ($P < 0.001$). Based on the ROC curve of aldosterone, we calculate the Youden Index of every point. The maximum value of Youden Index (sensitivity = 0.653, specificity = 0.759) corresponds to a plasma aldosterone concentration of 374 pg/mL, which was selected as the cut-off point. Further statistical analysis, such as fourfold Table (2 × 2 Chi-square), was performed using this cut-off value. The OR of ED group versus controls is 3.106 (95 % CI 1.458–6.617), while the OR of moderate to severe ED versus controls and mild ED is 5.480 (95 % CI 3.108–9.662).

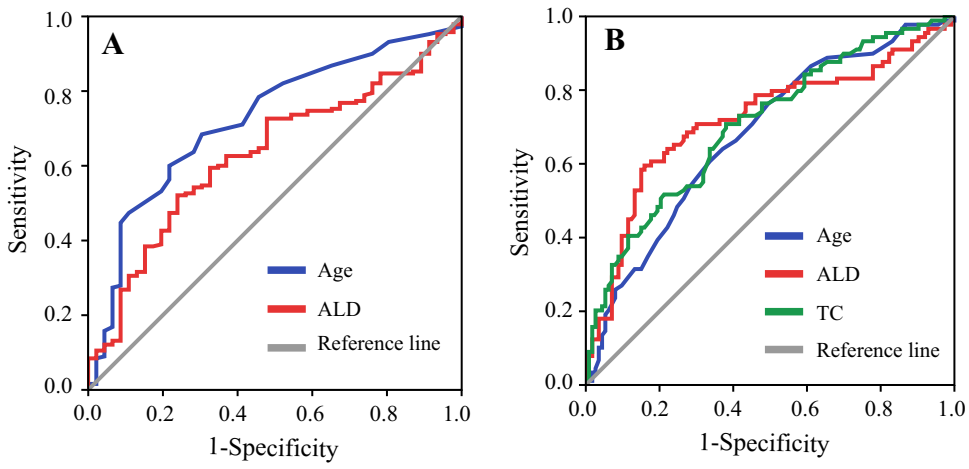

Fig. 1 ROC curve of plasma aldosterone. **a** ROC curve of age and aldosterone was plotted to evaluate the ability to recognize ED. **b** ROC curve of age, aldosterone and total cholesterol, for recognizing moderate to severe ED. *ROC* receiver operating characteristic

Table 5 Area under ROC curve

Variates	Area under curve	SE	Sig.	95 % CI
Age[a]	0.719	0.047	0.001	0.627–0.812
ALD[a]	0.632	0.058	0.043	0.519–0.745
DHEA[a]	0.285	0.045	0.001	0.196–0.373
AGE[b]	0.689	0.038	0.000	0.614–0.763
ALD[b]	0.718	0.039	0.000	0.643–0.794
WBC[b]	0.655	0.040	0.000	0.577–0.732
AST[b]	0.595	0.041	0.023	0.515–0.675
TC[b]	0.704	0.038	0.000	0.631–0.778

[a] ED group versus control group

[b] Moderate to sever ED group versus mild ED and control group

Discussion

In the present study, we recruited ED patients and normal controls with hormone screening to investigate our first hypothesis that aldosterone is an independent risk factor for ED. Our data determined that the difference of plasma aldosterone between ED group and the controls was statistically significant. Stepwise logistic regression analysis of all the possible factors supports the role of aldosterone as an independent risk factor. ROC curve and the area under the curve were performed to assess the diagnostic effect and to compare the severity of the risk with the known independent risk factors such as age and cholesterol. Similar statistical methods were applied to the comparison between moderate to severe ED group and control to mild ED group. The OR of the moderate and severe ED group to control and mild ED group is greater, while its area under cure also increased. When using a 374 pg/mL cut-off value from Youden index, the OR of ED group versus controls is 3.106, while the OR of moderate to severe ED versus control and mild ED is 5.480. Together, our data collectively demonstrated that elevated plasma aldosterone concentration is an independent risk factor for ED.

Multiple reasons account for the increase in plasma aldosterone including aldosterone-producing adenoma (APA), idiopathic hyperaldosteronism (IHA), adrenal hyperplasia, familial hyperaldosteronism, renal artery stenosis, heart failure and any other factors that activate the renin–angiotensin–aldosterone system (RAAS). Patients with previous diagnosis of hypertension, coronary heart disease or adrenal tumor are excluded from the study to minimize the interfering cofounders. Strikingly, however, the mean concentration of aldosterone is still significantly higher than the control group after ruling out the known causes of hyperaldosteronemia. It should be noted that elevated plasma aldosterone is frequently accompanied by some other metabolic parameters in our data. Lamounier-Zepter reported that human adipocytes produce a yet uncharacterized mineralocorticoid-releasing factor which stimulates adrenal aldosterone production, meaning that obesity might be associated with the elevation of aldosterone levels [26]. Excessive food intake, especially fat and carbohydrates, is associated with the increase in RAAS components [27, 28]. Animal experiments proved that fructose-rich diets are associated with higher aldosterone levels, but fewer metabolic alterations would occur when rats were administered spironolactone [29]. However, the effects of high sodium diet on plasma aldosterone levels remains controversial [28]. In other words, diets might have various impacts on plasma aldosterone levels, which may be influenced by mechanisms other than the sodium homeostasis feedback mechanism and blood pressure [28].

In addition to diet, psychological disorders could also contribute to the increase in plasma aldosterone levels, which suggests that aldosterone forms the connection between vascular disease and psychological dysfunction [30, 31]. Emanuele et al. [30] have reported that depressed subjects exhibited greater mean aldosterone levels than control subjects and that hyperaldosteronism could be a common feature among depressed patients. Since ED itself is also a powerful stimulator for aldosterone production, the plasma aldosterone levels might be in a positive feedback loop in ED patients.

Multiple studies support the concept that aldosterone deficiency plays a role in the pathogenesis of ED [32, 33]. In adrenalectomized male rats, the erectile function is significantly decreased and subsequently improved following hormone replacement therapy with aldosterone and hydrocortisone [33]. Autoimmune Addison's disease (AD) is characterized by insufficient production of glucocorticoids and mineralocorticoids and frequently associated with sexual dysfunctions, which could be reversed after initiating hormone replacement therapy with cortisol and aldosterone [32, 34]. One theory is that aldosterone deficiency induces the compensatory elevation of Ang II, which could reduce nitric oxide (NO) bioavailability and contribute to the development of ED [35, 36]. Furthermore, hypoadrenalism leads to systemic arterial hypotension and hypovolemia, resulting in the reduced pressure and perfusion that are necessary to maintain erection [32].

On the contrary, some studies and our data indicate that elevated plasma aldosterone concentration may facilitate the development of ED [22, 37]. The presence of MR in human hPCC, endothelial and vascular smooth muscle cells is beyond dispute and its physiological effect toward ED is currently being investigated [21, 22, 38, 39]. It has been demonstrated that aldosterone infusion impairs endothelial-mediated vasodilation, while the MR antagonist improves it, thus supporting that excessive aldosterone has negative effects on epithelial cells [40, 41]. A possible mechanism is that aldosterone can decrease endothelial

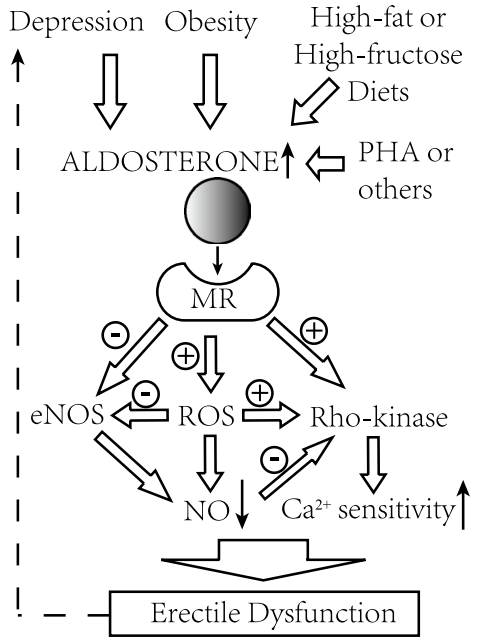

Fig. 2 Current understanding of the association between ED and aldosterone. *PHA* primary hyperaldosteronism, *MR* mineralocorticoid receptor, *eNOS* endothelial NO synthase, *ROS* reactive oxygen species

glucose-6-phosphate dehydrogenase (G6PD) expression and its activity both in vitro and in vivo, resulting in increased production of reactive oxygen species (ROS) and decreased bioactivity of NO [42]. In another study on rat vascular smooth muscle cells (VSMC), aldosterone has been shown to enhance NADPH oxidase activity and upregulate Nox4 mRNA expression, both of which are important superoxide-producing enzymes in vascular pathology [39, 43]. More specifically, in the context of the penis, the smooth muscle contraction is partially mediated by RhoA, a small monomeric G-protein belonging to the Ras superfamily of GTPases, as well as its effector Rho-kinase [44, 45]. Recently, Tokuyama et al. [46] reported that RhoA/Rho-kinase pathway could be activated by aldosterone in an MR-dependent manner. The activation of RhoA/Rho-kinase increases myosin light chain (MLC) phosphorylation, followed by increases in Ca^{2+} sensitivity and vasoconstriction [47]. Physiologically, an elevated Rho-kinase basal activity plays a key role in the maintenance of vasoconstriction in the flaccid state of penis, and the process could be facilitated by ROS and inhibited by NO [48–50]. However, injection of specific Rho-kinase antagonist into corpus cavernosum sinuses significantly improves erection through a NO-independent pathway [44]. These indicate that the NO and Rho-kinase signaling might be independent pathways in regulating erection with no correlation to each other. In addition to downregulating NO bioactivity via ROS, aldosterone could also directly suppress the endothelial NO synthase (eNOS) activity via ROS production and Ser 1177 dephosphorylation in an MR-dependent manner [51] (Fig. 2). Moreover, it is reported that aldosterone has no direct contractile or relaxant activity on isolated hPCC tissue, but acts to significantly augment the noradrenaline-induced contraction [22]. In other words, aldosterone could enhance the contraction of hPCC tissue through the α-receptors for noradrenaline [22].

The first limitation of this study was a relative small sample size of ED patients. Furthermore, the large variation of aldosterone levels affected the odds ratio of the variable during logistic regression analysis. The cross-sectional retrospective study design failed to establish cause and effect relationship between aldosterone and ED. Moreover, due to economic problems, the plasma concentration of renin, angiotensin and electrolyte has not been routinely examined in the current project. Thus, the activity of renin–angiotensin system is elusive, even if patients did not have a diagnosis of hypertension or diabetes mellitus. Therefore, further research is required to expand the sample size and to investigate the association between the serum aldosterone level and the prognosis of ED patients with PDE-5 inhibitors treatment.

Conclusions

In conclusion, the present study demonstrated that elevated plasma aldosterone concentration is an independent risk factor for ED. In addition to the well-known causes of hyperaldosteronism, diets and psychological stress account for the nonspecific increase in aldosterone levels. Specifically, aldosterone participates in the pathogenesis of ED through multiple pathways, such as NO and Rho-kinase signaling pathways in hPCC, endothelial and vascular smooth muscle cells. Further research is required to explore the possibility of treating ED with angiotensin converting enzyme inhibitor or spironolactone.

Author contributions G.X., H.W.J. and Q.D. designed the project; S.H.M and F.W. collected and analyzed data; F.W. and T.F.Y. wrote the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This study has been approved by the appropriate ethics committee (institutional review board) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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