# Developmental Abnormalities, Blood Pressure Variability and Renal Disease In Riley Day Syndrome

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## Abstract

Riley Day syndrome, commonly referred to as familial dysautonomia (FD), is a genetic disease with extremely labile blood pressure due to baroreflex deafferenation. Chronic renal disease is very frequent in these patients and was attributed to recurrent arterial hypotension and renal hypoperfusion. Aggressive treatment of hypotension, however, has not reduced its prevalence.

We evaluated the frequency of kidney malformations as well as the impact of hypertension, hypotension and blood pressure variability on the severity of renal impairment. We also investigated the effect of fludrocortisone treatment on the progression of renal disease.

Patients with FD appeared to have an increased incidence of hydronephrosis/reflux and patterning defects. Patients younger than 4 years old had hypertension and normal eGFR. Patients with more severe hypertension and greater variability in their blood pressure had worse renal function (both, p<0.01). In contrast, there was no relationship between eGFR and the lowest blood pressure recorded during upright tilt. The progression of renal disease was faster in patients receiving fludrocortisone (p<0.02).

Hypertension precedes kidney disease in these patients. Moreover, increased blood pressure variability as well as mineralocorticoid treatment accelerate the progression of renal disease. No association was found between hypotension and renal disease in patients with FD.

## Keywords

hypertension; renal failure; blood pressure instability; familial dysautonomia; afferent baroreflex failure

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# INTRODUCTION

Riley Day syndrome, commonly referred to as familial dysautonomia (FD), is an autosomal recessive disease caused by a deficiency of the protein IKAP.[1] We have recently shown that patients with FD have a selective developmental defect in the afferent baroreceptor pathways,[2] which leads to extremely labile blood pressure.

Patients with FD have a very high incidence of renal disease, which frequently begins at an early age.[3] Previous cross-sectional studies showed that one third of patients had elevated serum creatinine levels[3] and of those that survive beyond age 25, 20% required dialysis or renal transplant.[4] The cause of renal failure in these patients is unknown. Based on limited pathology data, a gross anatomical congenital abnormality was thought to be unlikely because most patients were found not to have obstructive uropathy or obvious kidney malformations and prior to the development of renal failure do not have significant proteinuria.[3]

It was previously postulated that the cause of renal disease in patients with FD was renal hypoperfusion due to frequent hypotension.[4] However, episodic hypotension, particularly in the young, is unlikely to cause chronic kidney disease (CKD).[5–7] Furthermore, the aggressive use of mineralocorticoids and alpha-1-agonists to treat orthostatic hypotension[8,9] has paralleled an increase rather than a decrease in the prevalence of renal failure in these patients.[3,4]

Hence, there is an urgent need to understand the mechanisms involved in the pathogenesis, severity and progression of renal disease in patients with FD. Hypertension is a well-known cause of CKD progression in children,[10] but blood pressure variability has recently received considerable attention as a mechanism of target organ damage. Thus, we examined the potential contribution of blood pressure variability on the severity of CKD. We hypothesized that patients with more variable blood pressures would have worse renal function. In addition, because treatment with mineralocorticoids is potentially nephrotoxic, we also analyzed whether treatment with fludrocortisone contributes to the fast progression of renal disease.

# METHODS

## STUDY POPULATION

Sixty-five patients with typical clinical features of FD who were homozygous for the common mutation[1] and 14 normal controls matched for age participated in these studies (Table 1). Data was extracted from medical records of patients with FD followed at the Dysautonomia Center. The Institutional Review Board of N.Y.U. approved all procedures and all subjects signed informed consent.

## MEASUREMENTS

**OFFICE BLOOD PRESSURES**—The average of three systolic and diastolic blood pressure values measured in the left arm using an automated sphygmomanometer cuff (Colin Press-Mate 7800, Colin Medical Instruments Corp., San Antonio, TX) while the

patients were in the supine position during an office visit taken after at least 20 minutes of rest was used as the baseline blood pressure. Mean blood pressure (MBP) was calculated as the diastolic pressure plus 1/3 of the pulse pressure. *Head up tilt*: Fifty-five patients then underwent 60-degree passive head-up tilt with footplate support for 10 minutes. Blood pressure was recorded every minute. The three lowest systolic blood pressure readings during tilt were averaged and used as a measure of the severity of orthostatic hypotension. Our five youngest patients with FD (age 2±0.5 years, range 1 month to 4 years) did not undergo head-up tilt testing.

**AMBULATORY BLOOD PRESSURES—**Fifty-five patients underwent ambulatory blood pressure monitoring while outpatients performing their usual daily activities. Blood pressure was measured at 20-minute intervals throughout the day and night using a validated ambulatory blood pressure monitor (90207 monitor, SpaceLabs, Washington, USA). Our 5 youngest patients with FD did not undergo ambulatory monitoring, as they were too young to carry the monitor. Nineteen patients with FD were unable to complete the recording. Complete data, with acceptable rates of successful blood pressure measurements, were obtained in 35 cases. The cohort of 35 patients that completed the ambulatory recordings was appropriately representative of the total population (average age, 25±2 years, 16 males: 19 females, mean eGFR 86±6 ml/min). Recently, blood pressure instability was defined as transient fluctuations in blood pressure that occur in response to specific stimuli such as standing or emotions, while variability was defined as the variation in blood pressure overtime.[11] In patients with FD, however, the profound abnormality in afferent baroreflex function, makes it difficult to distinguish between variability and instability. Hence, we used the standard deviation and the coefficient of variation (i.e., the SD/Mean × 100) of ambulatory blood pressures during 24 hours as an estimate of both instability and variability.

**RENAL FUNCTION—**Renal function was assessed from the serum concentration of creatinine and BUN levels measured in venous blood. Samples were taken while subjects were seated during an office visit. All measurements were performed in the same clinical laboratory. GFR was estimated (eGFR) using the Cockcroft Gault equation,[12] the Schwartz pediatric calculation,[13] and the Modified Renal Disease in Diet Equation.[14] Data from the Cockcroft-Gault equation[12] are reported here because they correlated best with urine creatinine clearance values ($R^2 = 0.65$, $p<0.01$, n = 11). Thirty-patients with FD had proteinuria captured in a clean urine sample using dipstick measurements. The remaining 30 patients were unable to give urine samples at the office because owing to lack of adequate bladder control.

**STATISTICS—**Linear regression analysis with Pearson correlation coefficients was used to assess the relationship between variables. Unpaired *t*-tests were used to compare differences between groups. We compared the rate of progression of renal disease in fludrocortisone naive patients and in patients treated with fludrocortisone in the 5-year period between the ages of 16 and 21. All data are presented as mean ± SEM. A *p<0.05* value was considered statistically significant.

# RESULTS

**General patient population characteristics—**As previously published,[3,4] the average eGFR was lower and BUN levels were higher in patients with FD than in controls (Table 1). Urine samples showed trace amounts of protein (5 – 10 mg/dl) in 5%, proteinuria of >30 mg/dl in 12 % and proteinuria of > 300 mg/dl in 3% of patients, who had advanced renal failure (eGFR between 19 and 29 ml/min).

## EXPLORATION OF A DEVELOPMENTAL DEFECT

To examine whether patients with FD have primary renal disease we reviewed the available renal ultrasounds of 41 patients with FD performed under the age of 5. We found that 4 patients (10%) had hydronephrosis/reflux and 3 (7%) had patterning defects, including a single kidney, both kidneys on the same side and horseshoe kidney. While our sample size is not large enough for appropriate statistical comparisons, the incidence of patterning defects appears to be higher than in normal children.[15,16] Serum creatinine (range 0.2 to 0.5 mg/dL) and BUN levels (range 11 to 15 mg/dL) were normal in all cases, at the time they had their ultrasound, and they had no proteinuria.

Based on these findings, we cannot rule out a primary congenital defect or the possibility of some subtle developmental defect of the kidney. However, not all patients develop renal failure and not all progress at the same rate. Therefore, we examined potential factors that contribute to the progression of renal failure in these patients.

## BLOOD PRESSURE ABNORMALITIES AND RENAL DISEASE

**Hypertension vs hypotension and the severity of renal disease—**To examine whether the severity of renal disease in patients with FD was related to the level of hypertension or hypotension during an office visit, we analyzed the relationships between eGFR and blood pressures. Patients with the highest blood pressures in the supine position had the lowest eGFR (systolic diastolic, mean, Fig 1). There was no correlation between the lowest blood pressure during head up tilt and the severity of renal disease (figure 1, n = 60).

**Hypertension and renal function—**To ascertain whether the hypertension preceded the appearance or was a consequence of renal disease, we analyzed renal function and blood pressure in our 5 youngest patients with FD (mean age 2±0.5 years, range 1 month to 4 years). All 5 had normal serum creatinine levels for age (mean 0.3±0.0 mg/dl, range 0.2 to 0.4 mg/dl, compared to standard controls of the same body weight [17]) and no proteinuria. They all had severe episodic hypertension (average blood pressure 150±9/106±10 mmHg) suggesting that hypertension is present before measurable changes in renal function.

**Blood pressure variability over 24 hours and renal disease—**Blood pressure variability is thought to have an important role in the progression of organ damage. All patients who underwent ABP monitoring showed very pronounced variability in their blood pressure. The coefficient of variation, a measure of blood pressure variability that takes into account the underlying mean blood pressure, was inversely correlated with eGFR (Fig. 3). The highest SBP value captured in the recording correlated with eGFR, but the lowest did

not (R). Out of the 24 hours, patients were hypertensive (SBP >140 mmHg) 50±4% and hypotensive (SBP <80 mmHg) 1.2±0.5% of the time. The percentage time spent with SBP in the hypertensive range correlated with eGFR while the time with hypotension did not. This suggests that it is the degree of hypertension and the amount of time spent hypertensive that are factors associated with renal disease.

### FLUDROCORTISONE TREATMENT AND RENAL DISEASE

Finally, we examined the impact of fludrocortisone treatment on the progression of renal function from a review of medical records. We identified 14 patients (in the cohort of 60) who at age 16 started treatment with 0.2 mg/day of fludrocortisone for at least 5 years and found 13 patients (sex/BMI matched) who were not treated with mineralocorticoids from age 16 to 21 years. It should be noted here, that the decision to treat with fludrocortisone was made empirically by the treating physician when the patient complained of fatigue in an interview. Standing SBP was similar in the two groups at baseline (treated 109±9 mmHg vs. untreated 88±7 mmHg, NS).

As shown in figure 3, mean eGFR was similar in both groups at age 16. Average eGFR dropped from 70±6 ml/min (±SEM) to 53±6 ml/min after 5 years of treatment with fludrocortisone (i.e. 24% reduction). Over the same time period, average eGFR in non-fludrocortisone treated patients was essentially unchanged (74±4 ml/min to 74±6 ml/min). Individual rates of change in eGFR over the five-year period were calculated for each patient in each group. Confirming this, the non-fludrocortisone patients showed a flat slope (1.9±1.9 ml.min/year) and the fludrocortisone treated patients had a significantly faster slope of decline in eGFR over time (−2.2±0.8 ml.min/year, p<0.03). Average yearly supine blood pressures in the patients taking fludrocortisone were not consistently higher than in those not taking fludrocortisone (figure 3), suggesting mineralocorticoid stimulation itself may adversely affect the kidney.

## DISCUSSION

The main findings of our study in patients with FD are that hypertension precedes CKD, and that the severity of CKD is influenced by blood pressure variability. Our findings also suggest that IKAP deficiency could affect kidney development, as the incidence of renal malformations may be increased in these patients. In contrast, the severity of hypotension has no relationship with renal function and treatment with fludrocortisone is associated with a faster progression in renal disease. These findings underscore the urgent need to develop new treatment guidelines to delay the progression of renal disease in patients with FD. Hypertension should probably be treated more aggressively, and non-pharmacological measures like head-up sleeping and physical counter maneuvers to treat orthostatic hypotension should be implemented.

IKAP is abundant in the normal kidney.[18] While the cause of the renal failure in patients with FD is unknown, we found a possible increased incidence of rare kidney malformations[15] and hydronephrosis,[16] which has not been reported before. Other subtle defects may also be possible. As patients with FD have an afferent sensory defect,[19] it is likely that there are abnormalities in the peristalsis of the genitourinary tract, a common

problem in congenital disorders. [20] Renal biopsy data in patients with FD showed a marked reduction in the number of sympathetic nerve terminals innervating the renal arterioles[3]. These findings suggest that patients with FD may have an intrinsic renal abnormality that makes the nephrons more vulnerable to blood pressure oscillations or mineralocoticoid damage, even before measurable increases in serum creatinine levels. As the extent of renal damage was so closely related to the magnitude of blood pressure variability, the defining feature of afferent baroreflex dysfunction, it is tempting to speculate that this type of autonomic abnormality is particularly hazardous to the kidney. Several lines of evidence support this hypothesis. First, there is epidemiological data suggesting that blood pressure variability and instability may be independent risk factors for end-organ target damage.[11,21] Second, in animal models of baroreceptor deafferentation, which results in a cardiovascular phenotype startlingly similar to the FD phenotype, the extent of end organ target damage is directly related to the degree of blood pressure variability.[22] Finally, and particularly relevant for patients with FD, CKD has been reported in patients who have paroxysmal hypertension and surges in circulating catecholamines caused by damage to the afferent baroreflex pathways after radiation therapy to the neck[23] or as a result of a pheochromocytoma.[24,25]

Based on the association between the degree of renal disease and the orthostatic fall in blood pressure it was previously postulated that low blood pressure was the cause of renal failure in FD.[3,4] Our data, however, suggest that the main factor responsible for the severity of renal failure in these patients is hypertension rather than hypotension. This is in line with histopathology reports in these patients showing changes typical of hypertensive nephrosclerosis.[3,26] Since patients with FD who have the greatest orthostatic fall in blood pressure do not always have the lowest blood pressure standing, the orthostatic fall is more a measure of blood pressure variability/instability rather than the severity of hypotension *per se*. Moreover, episodic hypotension, particularly in the young, is unlikely to cause CKD.[5–7]

Despite aggressive treatment of orthostatic hypotension in the last 20 years,[8,9] the incidence or renal failure has increased, not decreased in patients with FD.[4] Indeed, in our current survey, half the patients had elevated serum creatinine levels. There appears to be an increased incidence of arterial hypertension in patients with FD, perhaps as a result of treatment with fludrocortisone, which became widespread in the early 1990's. This could conceivably account for the increase incidence of CKD.[27] In addition, because activation of mineralocorticoid receptors in the kidney causes inflammation, fibrosis and oxidant injury[28] fludrocortisone probably also has a direct nephrotoxic effect (figure 3).

Our study has limitations. First, the use of estimates of GFR derived from serum creatinine levels rather than 24 hour urine creatinine clearance measures which are technically difficult to obtain because of the high incidence of incontinence in patients with FD. As GFR calculations often overestimate renal function, it is likely that we are underestimating the true extent of renal disease. It is also possible that we are underestimating the true severity of renal disease in patients who were volume expanded after treatment with fludrocortisone. We are also aware of the limitations of using qualitative assessment of proteinuria and how hydration can affect the interpretation of the test. Of note, almost all patients had gastrostomy tubes to ensure adequate fluid intake. Multiple correlation analyses to

determine whether the several factors we identified as being related to renal failure were independent or interrelated would be useful. Unfortunately, these analyses were not possible because of the relatively small sample size.

A recent trial showed that tight blood pressure control in children (with target blood pressures in the low range of normal) delays the progression of CKD.[10] This is challenging in FD, because antihypertensive drugs may worsen symptoms of orthostatic hypotension.[29] Prospective studies focused on controlling paroxysmal and sustained hypertension as well as blood pressure variability are warranted.

## Acknowledgments

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## Summary Table

| What is known about the topic |
|---|
| - Riley Day syndrome commonly known as Familial dysautonomia (FD) is a genetic disease caused by a deficiency of the protein IKAP that affects the development of baroreceptor afferents |
| - Patients with FD have extremely labile blood pressure |
| - Patients with FD have a high incidence of renal disease, the cause of which is unclear |
| What this study adds |
| - Patients with FD have an increased incidence of rare kidney malformations, suggesting that the protein IKAP may play a role in renal development |
| - Labile hypertension and increased blood pressure variability are associated with worse renal function |
| - Fludrocortisone, a drug commonly used in the treatment of orthostatic hypotension, is associated with a faster decline in renal function. |
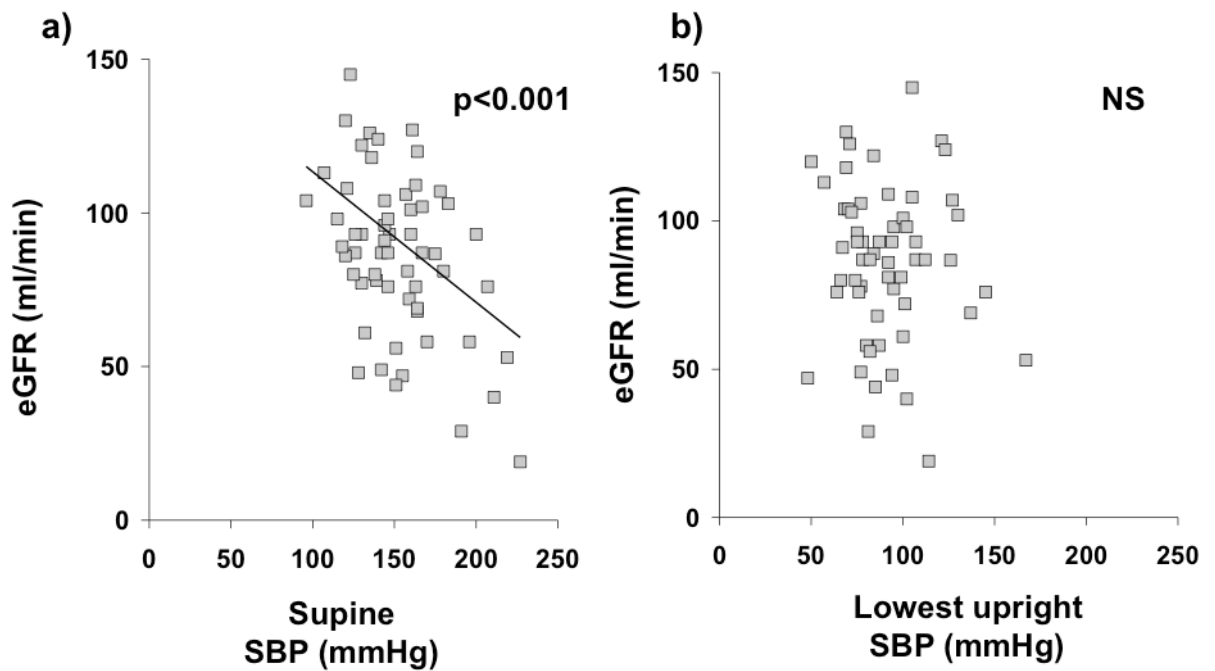
**Figure 1. Supine hypertension, orthostatic hypotension and renal function**
The significant relationship between the severity of hypertension when supine and the degree of renal disease in 55 patients with FD is shown in graph a (y = −0.5181x + 147.68, $R^2$ = 0.1568, p<0.001). The lack of association between the lowest upright blood pressure and renal disease is shown in graph b (p=0.75).
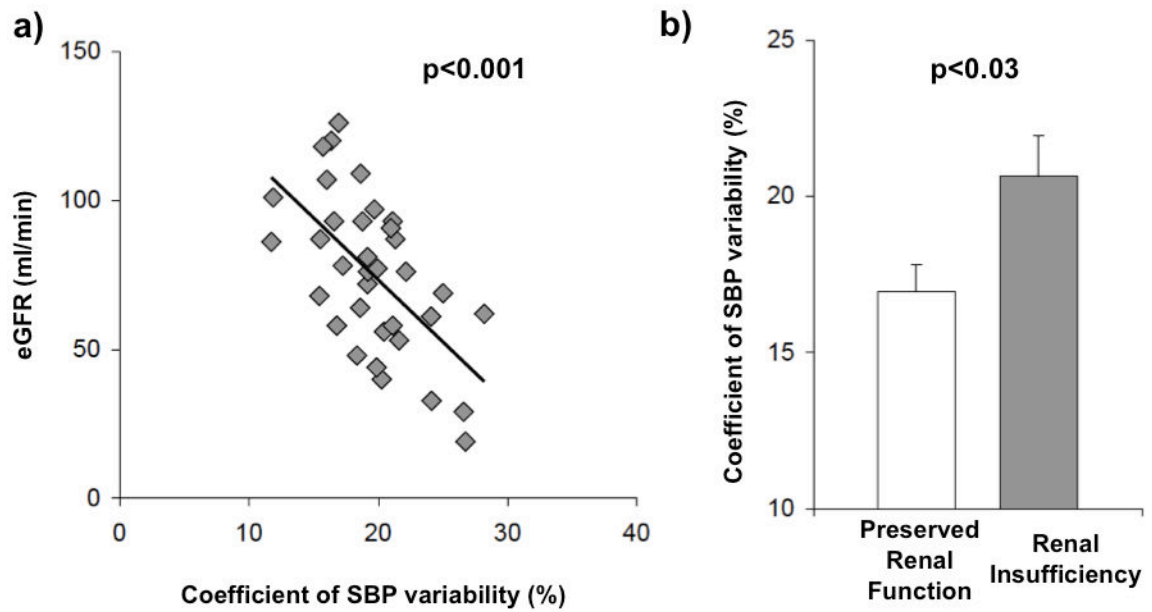
**Figure 2. Blood pressure variability and renal disease**
Linear regression graph shows an inverse relationship between the coefficient of systolic blood pressure variability assessed over 24 hours and renal function (y = −4.1695x + 156.65, $R^2 = 0.3664$, n = 35). Bar chart b shows that patients with renal insufficiency (serum Cr 1.0±0.1 mg/dL, eGFR 55±4 ml/min, n=10) had higher coefficients of systolic blood pressure variability than age, sex, height and weight matched patients with preserved renal function (Serum Cr 0.6±0.1 mg/dL, eGFR: 122±6 ml/min, mean ± SEM, n=12).
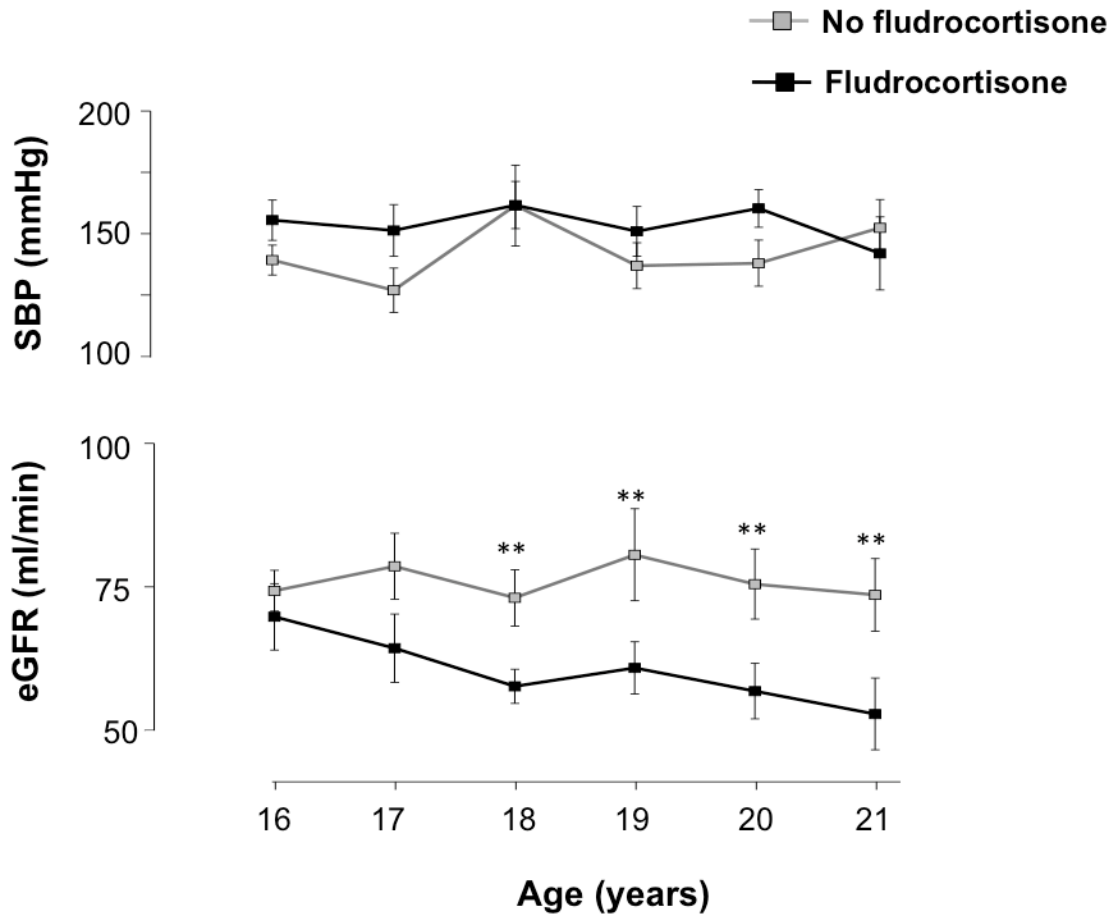
**Figure 3. 5-year rate of progression of renal disease in patients treated with fludrocortisone and those not**

Black squares show average yearly estimated glomerular filtration rates (eGFR) and mean blood pressures (MBP) in 14 patients who began treatment with 0.2 mg of fludrocortisone per day at age 16 and continued on the same dose until age 21. Grey squares show average GFR and MBP between the ages of 16 to 21 in 13 patients with FD who did not receive fludrocortisone. ** p<0.02 (ANOVA)

**Table 1**

Clinical laboratory results and autonomic function tests

|  | CONTROLS | FD | p |
|---|---|---|---|
| n | 14 | 60 |  |
| Males:females | 8:6 | 26:34 | NS |
| Age (years) | 20±2 | 22±1 | NS |
| Height (cm) | 155±4 | 147±2 | NS |
| Body mass (kg) | 62±6 | 41±2 | <0.001 |
| Serum creatinine (mg/dL) | 0.6±0.1 | 0.8±0.1 | NS |
| eGFR (ml/min) | 129±7 | 92±4 | <0.02 |
| BUN (mg/dL) | 11±0.1 | 21±1.9 | <0.002 |
| **SUPINE** |  |  |  |
| Systolic BP (mmHg) | 118±3 | 153±4 | <0.001 |
| Diastolic BP (mmHg) | 68±2 | 89±3 | <0.001 |
| Heart rate (bpm) | 66±3 | 83±2 | <0.001 |
| **UPRIGHT** |  |  |  |
| Systolic blood pressure (mmHg) | 117±3 | 93±4 | <0.001 |
| Diastolic blood pressure (mmHg) | 71±2 | 41±3 | <0.001 |
| Heart rate (bpm) | 86±3 | 75±2 | <0.02 |

Data are mean ± SEM