

Resveratrol Causes Gender-dependent and Bardoxolone Methyl-like Effects in Patients with IgA Nephropathy: Pilot Study

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Abstract

Antioxidant resveratrol showed nephron protective effects in different experimental models. However, human data are limited. Beneficial effects of resveratrol in patients with IgA nephropathy as suggested by in silico drug screening have not been evaluated. Our objective was to investigate the effect of resveratrol treatment on oxidative stress, renal function and albuminuria in IgA nephropathy patients. Twenty-seven IgAN patients were randomized to receive either resveratrol (2 x 5 mg/day) or placebo for 12 weeks, and were followed-up for additional 12 weeks. Male IgA nephropathy patients exerted initially higher urinary ortho-tyrosine concentration than females, indicative of increased oxidative stress, which may explain their worse prognosis. We noted that resveratrol treatment reduced urinary ortho-tyrosine excretion after 6 weeks, while it increased glomerular filtration rate and albuminuria in male but not in female IgA nephropathy patients. Due to these adverse effects our study was earlier terminated. Statin therapy had no impact on CCL11 or the anti-aging alpha-Klotho levels. In conclusion, increased glomerular filtration rate and albuminuria with resveratrol treatment could be resulted from hyperfiltration of the residual nephrons that occurred also after bardoxolone methyl administration in diabetic renal patients, and thus may negatively affect kidney function long-term.

Keywords: Resveratrol; IgA nephropathy; Oxidative stress; Urinary ortho-tyrosine; Albuminuria; Bardoxolone methyl

List of Abbreviations

CCL11: C-C motif chemokine (eotaxin-1)

CKD: Chronic Kidney Disease

eGFR: Estimated Glomerular Filtration Rate

GFR: Glomerular Filtration Rate

IgA: Immunoglobulin A

IgAN: Immunoglobulin A nephropathy

IQR: Interquartile Range

Nrf2: Nuclear factor erythroid 2-related factor 2

SD: Standard Deviation

Introduction

Although advantageous biochemical and physiological effects of resveratrol, which is the most intensively examined red wine polyphenol, were evidently demonstrated in several in vitro and in vivo animal studies, there are scarce human data available [1,2].

The burden of chronic kidney disease (CKD) associated with increased risk of cardiovascular morbidity and mortality reaches significant healthcare problem globally [3,4].

IgA nephropathy (IgAN) is the most common primary chronic glomerulonephritis presented with a large scale of clinical manifestations, from modest symptoms to even progressive renal failure, and end-stage renal disease long-term [5-7]. The precise pathomechanism of IgAN is unclear. Increased oxidative stress resulting from the excessive mesangial deposition of IgA molecule and consequent increases of pro-inflammatory processes has a key role [5,8,9]. There is poorer prognosis and increased liability for progression in male IgAN patients [6]. Also, the degree of oxidative stress appears to determine the long-term outcomes of IgAN [8,9].

CKD is characterized by increased oxidative stress [10]. Oxidative injury by superoxide or hydroxyl free radicals could take place not only free but also on protein-bound amino acids [10]. These oxidative derivatives of amino acids indicating the level of free radical production are stable markers of oxidative stress. For instance, ortho-tyrosine is generated from phenylalanine by hydroxyl free radical [10]. Beneficial impacts of resveratrol in CKD to attenuate oxidative stress [1,11] and inflammatory processes have been proposed, such as Nrf2 (nuclear factor erythroid 2-related factor 2) activation [1,12], the promotion of SIRT-1 expression and NF-κB suppression [13].

Among others, higher levels of the inflammatory C-C motif chemokine (eotaxin-1, CCL11) were found in CKD patients, which enhanced by other inflammatory cytokines may be responsible for the higher cardiovascular risk [14-16]. Resveratrol *in vitro* decreased CCL11 transcription and expression [16]. Resveratrol treatment both *in vitro* and *in vivo* animal studies enhanced renal expression of the anti-aging alpha-Klotho gene which is known to afford beneficial effects in CKD [17,18]. Consistent findings of decreasing CCL11 and increasing alpha-Klotho protein were suggested also with statin therapy [19-24].

Glomerular endocapillary proliferation is considered as negative prognostic sign of IgAN [25]. Signaling pathways responsible for this phenomenon could be efficiently altered by resveratrol and other substances as detected during *in silico* drug screenings [25].

We earlier showed that in patients with type 2 diabetes mellitus (T2DM) resveratrol treatment improved metabolism and reduced oxidative stress, as indicated by decreased ortho-tyrosine excretion [26].

The main objective of this study was to investigate the effect and possible mechanisms of resveratrol treatment on oxidative stress, renal function, and albuminuria in IgAN patients.

Patients and Methods

Study participants

Study protocol and all procedures were conducted according to the guidelines laid down in the Declaration of Helsinki, and were approved by the Research Ethics Committee, University of Pécs (certificate number: 4583). Written informed consent was obtained from all participants. Originally, our double-blind, placebo-controlled, randomized, parallel-group, prospective, 12-week long study was scheduled to involve 100 IgAN patients, however, interim analysis of 27 patients indicated that resveratrol treatment is likely to increase albuminuria, therefore, examinations were subsequently terminated. Enrolled IgAN patients were randomly assigned to receive the product containing Resveratrol (N=15; male: 9, female: 6) or Placebo N=12; male: 6, female: 6).

Caucasian patients with histologically determined IgAN were included. Further inclusion criteria were as follows: age>18 yrs, CKD stage 1 and 2 (estimated glomerular filtration rate (eGFR) \geq 60 ml/min/1.73 m²; eGFR was calculated by CKD-EPI formula [27], treatment with angiotensin-converting enzyme-inhibitor and/or angiotensin II receptor blocker, no significant changes in proteinuria and eGFR over the past three months.

The Control group involved healthy (non-IgAN) subjects (employees of our clinic). The Control group was matched with that of the IgAN patients.

Exclusion criteria implied pregnancy, lactation, acute infection, malignancy, alcohol or drug abuse, overt autoimmune disease, severe liver or cardiac (New York Heart Association III-IV) disease.

Study protocol

At baseline, urinary creatinine and albumin, ortho-tyrosine concentrations, and 24 hours creatinine clearance were measured in urine samples collected for 24 hours prior to baseline. First morning

urine samples were also obtained from patients to assess urinary albumin concentration and albumin/creatinine ratio.

Blood samples were taken to determine main laboratory parameters, including: glucose, sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, alanine transaminase, aspartate amino transferase, alkaline phosphatase, lactate dehydrogenase, gamma glutamyl transferase, bilirubin, blood count, IgA.

Fructosamine, hemoglobin A1c, insulin, C-peptide, parathyroid hormone, triglyceride, low density lipoprotein, high density lipoprotein, total cholesterol, prothrombin, high-sensitivity C-reactive protein, reticulocyte number, iron, transferrin, transferrin saturation, ferritin, erythropoietin were measured only at baseline. The levels of ortho-tyrosine, alpha-Klotho and CCL11 were also quantified.

Patients were randomly subjected to resveratrol or placebo treatment. Patients of the Resveratrol group were administered orally 5 mg BID resveratrol pills, while patients of the Placebo group were given orally 2x1 pills per day.

Aforementioned urinary and routine blood measurements were re-conducted after 6 weeks and 12 weeks.

Medical records and physical examination were taken, and eGFR was calculated by CKD-EPI formula at all visits [27].

In the Resveratrol group, routine blood measurements and urinalysis (including urinary albumin concentration and albumin/creatinine ratio) were also conducted after 3 months of open label wash-out period.

The primary endpoints were the changes of oxidative stress, eGFR and proteinuria. The secondary endpoints were the changes of CCL11 and alpha-Klotho.

Analytical procedures

Routine blood and urinary measurements were carried out according to standard clinical laboratory procedures in the Department of Laboratory Medicine, Medical School, Univ. of Pécs (Pécs, Hungary).

Oxidative stress was determined by measuring urinary and plasma ortho-tyrosine levels as described previously [10], using a reverse-phase HPLC (Shimadzu LC-10 ADVP HPLC system, Shimadzu USA, OR, USA) equipped with a fluorescence detector (Shimadzu RF-10 AXL). Tyrosine and its isomers were excited at 275 nm and their emission was measured at 305 nm. Urinary amino acid concentrations were normalized to urinary creatinine levels.

CCL11 levels were measured using Human CCL11/Eotaxin Quantikine ELISA Kit (R&D Systems, Minneapolis, MN, USA). Alpha-Klotho levels were measured using Human soluble α -Klotho Assay Kit (Immuno-Biological Laboratories Co., Fujioka, and Gunma, Japan).

Materials

Both resveratrol and placebo gelatin capsules were obtained from Argina Ltd. (Fót, Hungary). The resveratrol (5 mg per each) capsule contained >98% *trans*-resveratrol; placebo capsules contained only the microcrystalline cellulose vehicle. Resveratrol and placebo capsules were counted (originally 60 capsules per box) to verify patient compliance at the end of the trial.

Statistical analysis

Urinary ortho-tyrosine excretion, urinary ortho-tyrosine/creatinine ratio, eGFR, UAC, ACR, CCL11 showed not normal distribution, alpha-Klotho showed normal distribution by Kolmogorov-Smirnov test. For comparisons of Visit results either Mann-Whitney test (in case of parameters showing not normal distribution) or one-way ANOVA and *Bonferroni post hoc* test (in case of parameters showing normal distribution) was used.

Mann-Whitney test was performed to compare changes at group-level. The changes of eGFR and albuminuria were compared between Resveratrol and Placebo groups, as well as between male and female patients. Results are expressed as the percentage of 6 week or 12 week, taking Baseline as 100 % due to the low number of cases and high variability of the initial data.

Results of variables showing normal distribution are expressed as mean ± standard deviation (SD), while median (IQR, interquartile range) values were presented for parameters with not normal distribution. Relationships between clinical variables showing not normal distribution were examined by Spearman's rho correlation.

Statistical analyses were performed using IBM SPSS Statistics, Version 22 software, and p<0.05 was defined as statistically significant, as indicated in the result section and figure legends.

Results

Baseline characteristic

At baseline, main clinical characteristics of male (Table 1A) and female (Table 1B) patients were similar between the Resveratrol group and the Placebo group.

(A)				
Male	Resveratrol (n=9)		Placebo (n=6)	
	Median	IQR	Median	IQR
Age (year)	34	20	55.5	27
Body weight (kg)	87	27	89	32
High-sensitivity CRP (mg/l)	2.3	5.9	1.2	3.1
Creatinine (µmol/l)	80	47	83.5	37
eGFR (ml/min/1.73 m ²)	101	51	93.5	42
Parathormone (pmol/l)	4.2	3.3	4.3	2.6
Erythropoietin (mU/ml)	7.7	5.7	7.6	6.7
Total cholesterol (mmol/l)	5.3	1.4	4.9	1.7
LDL cholesterol (mmol/l)	2.7	1.6	2.9	2
HDL cholesterol (mmol/l)	1.3	0.7	1.5	0.8
Triglycerides (mmol/l)	1.2	1	0.9	1.4
Urinary albumin/creat (morningvoid) (mg/mmol)	8.7	25	22.5	71
Blood pressure (syst) (mmHg)	135.5	16	135	22

Blood pressure (diast) (mmHg)	72.5	9	74	13
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Table 1(A): Baseline characteristics of patients in the Resveratrol and the Placebo group.

(B)				
Female	Resveratrol (n=6)		Placebo (n=6)	
	Median	IQR	Median	IQR
Age (year)	51.5	12	48.5	14
Body weight (kg)	78.9	30	71.3	23
High-sensitivity CRP (mg/l)	1.9	6.7	1.9	2.5
Creatinine (µmol/l)	78	22	78.5	21
eGFR (ml/min/1.73 m ²)	79.5	33	76.5	27
Parathormone (pmol/l)	4.1	1.6	2.9	1.4
Erythropoietin (mU/ml)	7.7	18	10.3	6.3
Total cholesterol (mmol/l)	5	1.5	4.7	1.6
LDL cholesterol (mmol/l)	3.4	1	2.8	1.2
HDL cholesterol (mmol/l)	1.8	0.7	1.6	0.9
Triglycerides (mmol/l)	1.2	0.9	1.3	1.6
Urinary albumin/creat (morningvoid) (mg/mmol)	34.1	74	11.3	38
Blood pressure (syst) (mmHg)	129	16	129.5	9
Blood pressure (diast) (mmHg)	78.5	10	70	20

Table 1(b): Baseline characteristics of patients in the Resveratrol and the Placebo group.

Data are expressed as median values and interquartile ranges (IQR) in male (A) and female (B) patients with IgA nephropathy. Estimated glomerular filtration rate was calculated by the CKD-EPI formula [27].

CRP, C-reactive protein; eGFR, estimated glomerular filtration rate

There were no significant differences between Resveratrol group vs. Placebo group and Male vs. Female patients.

The Control group was matched to IgAN patients regarding age (54.0 yrs (IQR:6) vs. 47.5 yrs (IQR:19); p=NS), regarding eGFR (85.18 ml/min/1.73 m² (IQR:19) vs. 83.00 ml/min/1.73 m² (IQR:37); p=NS), and regarding body weight (80.3 kg (IQR:20.8) vs. 83.5 kg (IQR:20.0); p=NS).

The male Control group was matched to male Resveratrol group regarding age (54.0 yrs (IQR:10) vs. 34.0 yrs (IQR:20); p=NS), regarding eGFR (87.3ml/min/1.73 m² (IQR:47) vs. 101.0ml/min/1.73 m² (IQR:51); p=NS), and regarding body weight (84 kg (IQR:21) vs. 87.0 kg (IQR:26.5); p=NS).

The female Control group was matched to female Resveratrol group regarding age (54.0 yrs (IQR:7) vs. 51.5 yrs (IQR:12); p=NS), regarding eGFR (79.6 ml/min/1.73 m² (IQR:15) vs. 79.5 ml/min/1.73

m² (IQR:33); p=NS), and regarding body weight (76 kg (IQR:27.5) vs. 78.9 kg (IQR:30); p=NS).

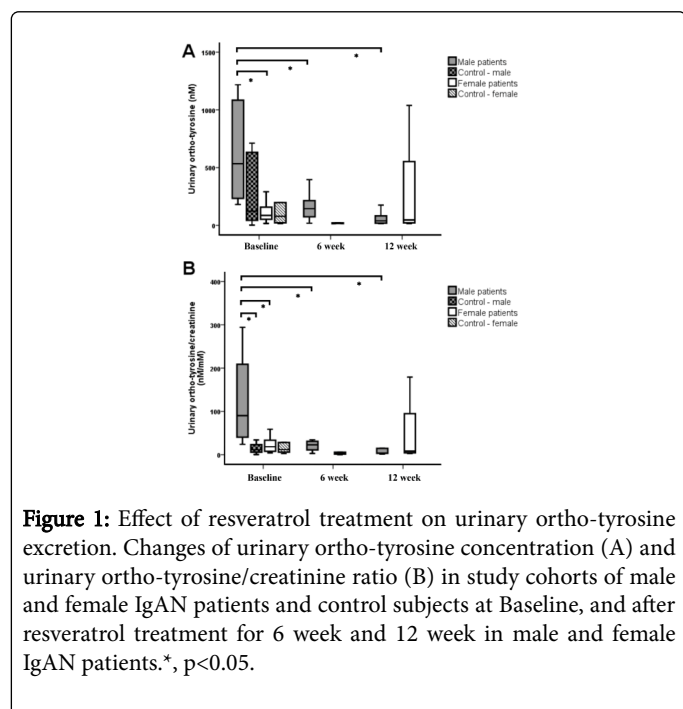
However, there was also no difference between male and female subjects in the Control group concerning age (54.0 yrs (IQR:10) vs. 54.0 yrs (IQR:7); p=NS), eGFR values (87.26ml/min/1.73 m² (IQR:47) vs. 79.6 ml/min/1.73 m² (IQR:15); p=NS) and body weight (84 kg (IQR:21) vs. 76 kg (IQR:27.5); p=NS).

Gender-dependent effect of resveratrol treatment on urinary ortho-tyrosine excretion

At Baseline, there were no differences in urinary ortho-tyrosine concentration and ortho-tyrosine/creatinine ratio between male and female subjects in the Control (non-IgAN) group (Figure 1A and 1B). However, male IgA patients in the Resveratrol group had higher urinary ortho-tyrosine concentration than females (p=0.018), as well as urinary ortho-tyrosine/creatinine ratio compared to male (non-IgAN) controls (p=0.019) at Baseline. In contrast, female IgAN patients showed comparable urinary ortho-tyrosine concentration and ortho-tyrosine/creatinine ratio with female (non-IgAN) controls at Baseline (Figure 1A and 1B).

Resveratrol treatment after 6 week significantly decreased both urinary ortho-tyrosine concentration and urinary ortho-tyrosine/creatinine ratio in male IgAN patients (p=0.017 and p=0.008 vs. Baseline, respectively). However, these changes were not found in female IgAN patients of the Resveratrol group (Figure 1A and 1B).

After 12 week of resveratrol treatment, both urinary ortho-tyrosine concentration and urinary ortho-tyrosine/creatinine ratio were still substantially lower in male IgAN patients (p=0.001 and p=0.004 vs. Baseline, respectively) but were not altered in female IgAN patients of the Resveratrol group (Figure 1A and 1B).



Effect of resveratrol treatment on urinary ortho-tyrosine excretion in male IgAN patients

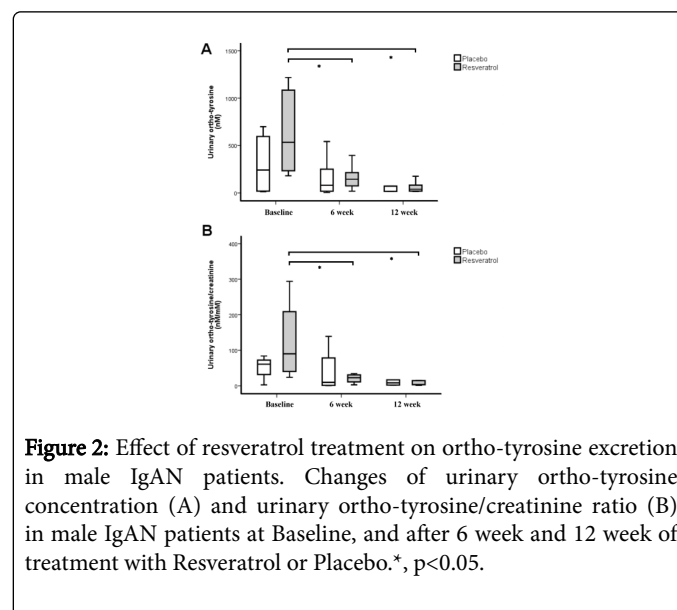
At Baseline, in male IgAN patients there were no differences in the urinary ortho-tyrosine concentration and urinary ortho-tyrosine/creatinine ratio between the Resveratrol and the Placebo group (Figure 2A and 2B).

However, the administration of resveratrol for both 6 week and 12 week considerably reduced both urinary ortho-tyrosine concentration and urinary ortho-tyrosine/creatinine ratio in male IgAN patients compared to Baseline data (for 6 week p=0.017 and p=0.008; for 12 week p=0.001 and p=0.004, respectively) (Figure 2A and 2B).

At 6 week and 12 week, urinary ortho-tyrosine concentration and urinary ortho-tyrosine/creatinine ratio remained unaltered in untreated male IgAN patients of the Placebo group (Figure 2A and 2B).

Effect of resveratrol treatment on eGFR

To demonstrate the effect of resveratrol treatment on renal function, changes of eGFR, expressed as median values of 6 week/Baseline and 12 week/Baseline ratios were calculated.



At 6 week, resveratrol treatment increased eGFR in male IgAN patients compared to the Placebo group, as indicated by higher 6 week/Baseline ratio (p=0.026) (Figure 3A).

However, 12 week/Baseline ratios were similar between the Resveratrol and the Placebo group (Figure 3A).

After 3 months open label wash out period, eGFR was reverted in male IgAN patients of the Resveratrol group, as indicated by Wash out Visit/Baseline ratio compared to 6 week/Baseline ratio (p=0.028) (Figure 3A).

We found no changes of eGFR in female IgAN patients with resveratrol treatment, as indicated by comparable 6 week/Baseline and 12 week/Baseline ratios between the Resveratrol and Placebo group at 6 week and 12 week (Figure 3B).

Effect of resveratrol treatment on albuminuria

To demonstrate the effect of resveratrol treatment on albumin excretion, changes of urinary albumin and albumin/creatinine ratio, expressed as median values of 6 week/Baseline and 12 week/Baseline ratios were calculated.

Surprisingly, there was an increase of albuminuria in male IgAN patients after resveratrol treatment compared to the Placebo group at 6 week, as indicated by higher 6 week/Baseline ratios of the albumin/creatinine ratio ($p=0.006$) (Figure 4A), and the urinary albumin concentration (452.2(1783)% vs. 16.7(59)%, $p=0.018$) (data not shown).

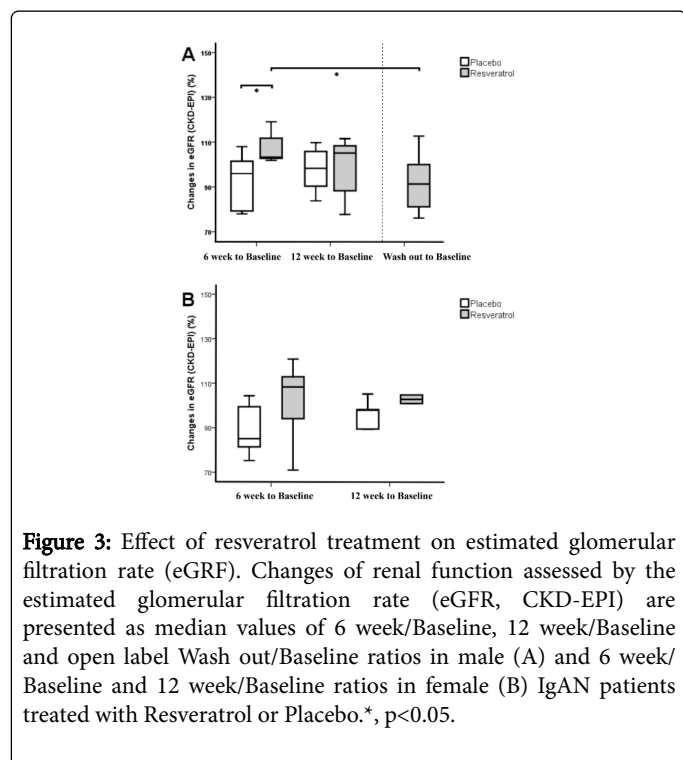


Figure 3: Effect of resveratrol treatment on estimated glomerular filtration rate (eGRF). Changes of renal function assessed by the estimated glomerular filtration rate (eGFR, CKD-EPI) are presented as median values of 6 week/Baseline, 12 week/Baseline and open label Wash out/Baseline ratios in male (A) and 6 week/Baseline and 12 week/Baseline ratios in female (B) IgAN patients treated with Resveratrol or Placebo. *, $p<0.05$.

The higher 6 week/Baseline albumin/creatinine ratio remained unaltered in male IgAN patients after resveratrol treatment at 12 week, although 12 week/Baseline ratios were not statistically significant compared to the Placebo group (Figure 4A).

At 12 week, resveratrol treatment resulted in higher urinary albumin concentration in male IgAN patients compared to the Placebo group, as indicated by increased 12 week/Baseline ratio (698.9 (1364)% vs. 44.4 (75.4)%, $p=0.011$). There were no differences in the urinary albumin concentration between 6 week/Baseline and 12 week/Baseline ratios in male IgAN patients of the Resveratrol group.

The changes of albumin/creatinine ratio were reversible in male IgAN patients, as indicated by open label Wash out/Baseline ratio of the Resveratrol compared to 6 week/Baseline ratio in Placebo groups ($p=NS$) (Figure 4A).

As shown in Figure 4B, resveratrol treatment had no impact on albumin/creatinine ratio in female IgAN patients at 6 week or 12 week compared to the Placebo group, as indicated by the unaltered 6 week/Baseline and 12 week/Baseline ratios (Figure 4B). Similarly, there were no changes in the urinary albumin concentration with resveratrol

treatment in female IgAN patients at 6 week or 12 week 33.5(96)% vs. 107.1(184)%, $p=NS$.

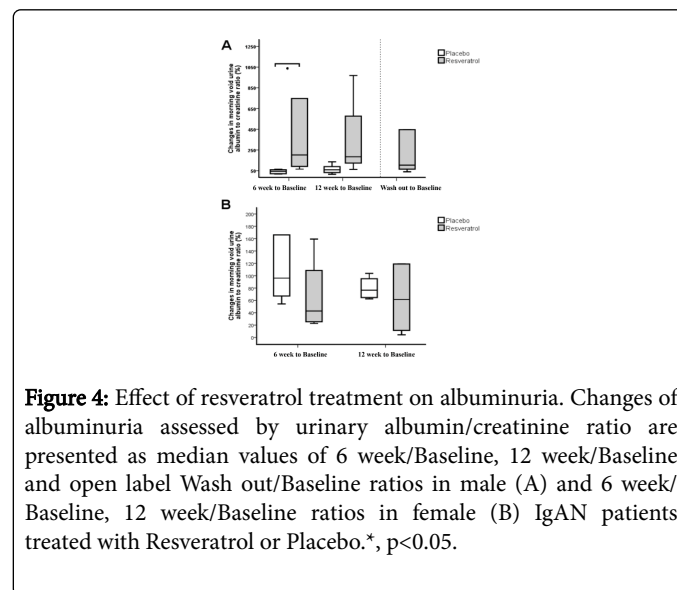


Figure 4: Effect of resveratrol treatment on albuminuria. Changes of albuminuria assessed by urinary albumin/creatinine ratio are presented as median values of 6 week/Baseline, 12 week/Baseline and open label Wash out/Baseline ratios in male (A) and 6 week/Baseline, 12 week/Baseline ratios in female (B) IgAN patients treated with Resveratrol or Placebo. *, $p<0.05$.

Effect of statin treatment on CCL11 and alpha-Klotho

There were regular statin-users in both the Resveratrol ($N=6$) and the Placebo group ($N=4$), therefore we investigated the potential modifying effect of statin treatment on CCL11 and alpha-Klotho. However, neither CCL11 nor alpha-Klotho levels showed significant differences between statin-users and non-users at baseline (Figure 5A and 5B).

Effect of resveratrol treatment on CCL11 and alpha-Klotho

Resveratrol treatment had no effect on CCL11 levels irrespective of genders (Figure 6A). The serum level of CCL11 remained unaltered in both male patients (Baseline: 247.25(33.13) pg/ml vs. 12 week: 247.75(122) pg/ml, $p=NS$) and female patients (Baseline: 277.75(155.5) pg/ml vs. 12 week: 325.5(206) pg/ml, $p=NS$).

The alpha-Klotho levels were also unaltered after resveratrol treatment (Figure 6B) in both male (Baseline: 872.5 ± 181.08 pg/ml vs. 12 week: 776.25 ± 288.56 pg/ml, $p=NS$) and female patients (Baseline: 856.67 ± 393.94 pg/ml vs. 12 week: 809.17 ± 328.56 pg/ml, $p=NS$).

Effect of resveratrol treatment on the relationship of urinary ortho-tyrosine excretion and CCL11 levels

In male IgAN patients after resveratrol treatment, we found positive correlation between CCL11 levels and both urinary ortho-tyrosine excretion ($r=0.829$, $p=0.042$) and urinary ortho-tyrosine/creatinine ratio ($r=0.829$, $p=0.042$) at 12 week. Conversely, relationship between CCL11 levels, and urinary ortho-tyrosine concentration and urinary ortho-tyrosine/creatinine could not be observed in any female IgAN patients of the Resveratrol or the Placebo group.

Discussion

Here we presented data of a pilot study, which was terminated earlier due to the unfavorable interim analysis results showing that resveratrol treatment increased albuminuria.

Our previous report showing that male IgAN patients exerted higher level of oxidative protein damage and oxidative stress markers assessed by fluorescence method [7] together with the initially higher urinary ortho-tyrosine excretion observed here, clearly indicate increased oxidative stress status in male IgAN patients compared to females. Our findings appear to support the notion that increased oxidative stress may be responsible, at least in part, for the poorer prognosis recognized in male IgAN patients [6,8,9,28-30].

Here we demonstrate that while administration of trans-resveratrol (5 mg BID) significantly reduced oxidative stress, it also increased eGFR and albuminuria in male IgAN patients; whereas any of these effects could not be detected in female IgAN patients.

On the other hand, increase of eGFR and albuminuria in male IgAN patients seemed reversible effects of resveratrol treatment, as indicated by reduced eGFR and ACR values after 3 months open label wash out period.

Several reports proposed that resveratrol by suppressing oxidative stress could beneficially alter numerous pathophysiological processes in CKD [1,11,13]. Our present data revealed to corroborate this notion only in male IgAN patients. Accordingly, we found significant relationship between urinary ortho-tyrosine/creatinine ratio and CCL11 levels after 12 weeks of resveratrol treatment in male but not in female IgAN patients.

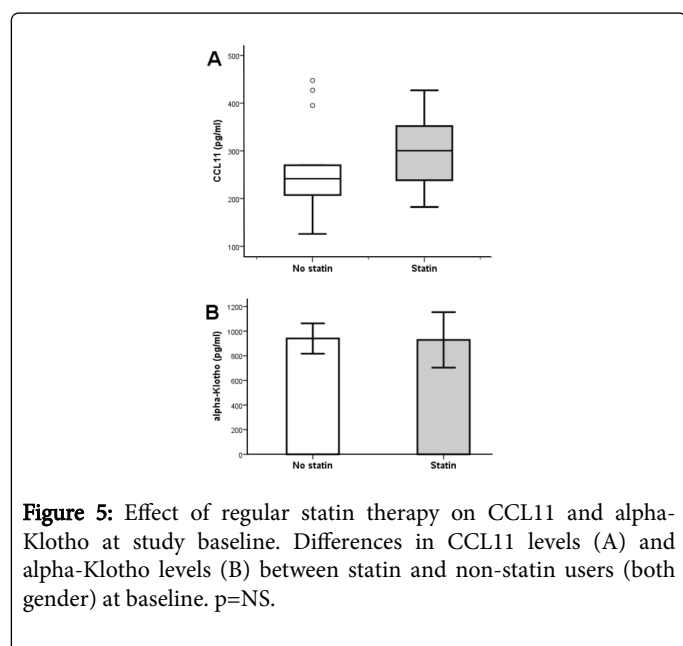


Figure 5: Effect of regular statin therapy on CCL11 and alpha-Klotho at study baseline. Differences in CCL11 levels (A) and alpha-Klotho levels (B) between statin and non-statin users (both gender) at baseline. p=NS.

The positive correlation of ortho-tyrosine/creatinine ratio with CCL11 after resveratrol treatment suggests that altered inflammatory state could be a consequence of reduced oxidative stress.

However, in IgAN patients effects of resveratrol treatment on alpha-Klotho could not be noticed which seems dissimilar with the results of *in vivo* animal studies showing that resveratrol affects the renal expression of Klotho gene [18].

In addition, evidences demonstrating the effects of statin treatment to decrease the level of the inflammatory chemokine CCL11 and to increase the level of the anti-aging protein alpha-Klotho could not be verified in our present study [19-24].

Increased eGFR found here with resveratrol treatment could be possibly, due to the enhancement of single nephron hyperfiltration as a result of increased renal blood flow; similar that seen in animals where resveratrol caused endothelium-dependent renal vasodilation through its antioxidant properties [31,32].

Nevertheless, resveratrol treatment reduced oxidative stress associated with increased eGFR in male IgAN patients.

It is noteworthy that results of the 52-week BEAM study conducted in CKD patients with T2DM showed similar increases of eGFR and albuminuria after bardoxolone methyl treatment, which is also known to possess antioxidant and Nrf2 activator capacity [33].

It is conceivable to suggest that there could be common mechanisms by which resveratrol and bardoxolone methyl could provoke increased urinary albumin excretion, as we summarized our hypothesis in Figure 7.

In addition, increased proteinuria found here with resveratrol treatment was also noticed in bardoxolone methyl-treated CKD patients with T2DM in the BEACON trial [34,35].

Consequently, in kidney failure augmented hyperfiltration of the residual nephrons may lead to increased proteinuria and advanced decline of the renal function [36,37] (Figure 7).

In conclusion, our results suggest that resveratrol treatment, as bardoxolone methyl therapy was indicated earlier in CKD patients with T2DM is not recommended in patients with IgA nephropathy. Limitations include the small number of cases due to increased albuminuria observed by the interim analysis leading to early termination of this study.

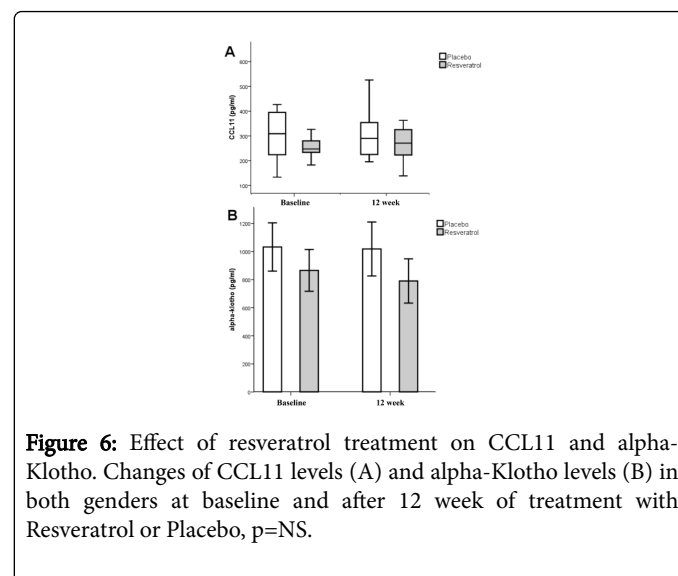


Figure 6: Effect of resveratrol treatment on CCL11 and alpha-Klotho. Changes of CCL11 levels (A) and alpha-Klotho levels (B) in both genders at baseline and after 12 week of treatment with Resveratrol or Placebo, p=NS.

Acknowledgements

The present scientific contribution is dedicated to the 650th anniversary of the foundation of the University of Pécs, Hungary.

Disclosure Statement

László G. Mészáros is the owner of Argina Ltd (Fót, Hungary), the vendor of resveratrol capsules. All other authors declare that they have no conflicts of financial interest.

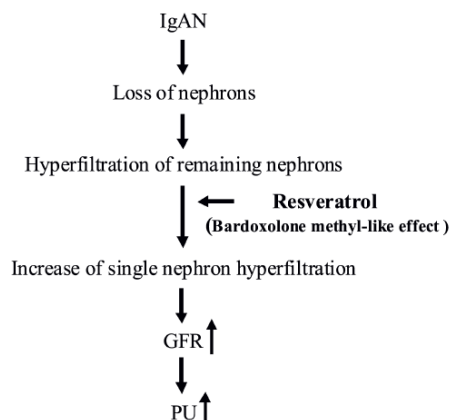


Figure 7: Possible mechanisms by which resveratrol treatment leads to increased glomerular filtration rate (GFR) and proteinuria in IgA nephropathy.

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