Supplementation with high-dose trans-resveratrol improves ultrafiltration in peritoneal dialysis patients: a prospective, randomized, double-blind study

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**ABSTRACT**

**Background** Ultrafiltration (UF) failure mostly contributes to technical failure in peritoneal dialysis (PD) patients, and one of its responsible factors is peritoneal angiogenesis. Resveratrol has been proposed to have an angiogenesis-ameliorating effect on tumor patients. We hypothesize trans-resveratrol has beneficial effects on angiogenesis-related markers in PD patients.

**Methods** In this prospective, randomized, and double-blind trial, 72 patients were randomly assigned to 12-week treatment of low-dose or high-dose (150 or 450 mg/d) trans-resveratrol or a placebo. Visits were scheduled at 0, 4, 8, and 12 weeks after treatment. Clinical indices including 24-hour UF volume, UF rate, 24-hour urine volume, residual renal function, and dialysis adequacy ($kt/v$) were measured. Angiogenesis markers including vascular endothelial growth factor (VEGF), fetal liver kinase-1 (Flk-1), angiopoietin-2 (Ang-2), tyrosine kinase 2 (Tie-2), and thrombospondin-1 (Tsp-1) in peritoneal effluent were also assessed by enzyme-linked immunosorbent assay.

**Results** Finally, 64 out of 72 patients were analyzed, 18 in the high-dose group, 22 in the low-dose group, and 24 in the placebo group. Over the 12-week period, patients in the high-dose group [mean change from baseline (95% CI): 171.4 (141.3-201.5) (mL), $p = 0.003$ (Net UF); 11.3 (10.5-12.1) (mL/h), $p = 0.02$ (UF rate)] or the low-dose group [mean change from baseline (95% CI: 98.1 (49.5-146.7) (mL), $p = 0.007$ (Net UF); 6.5 (4.4-8.6) (mL/h), $p = 0.04$ (UF rate)] versus the placebo group had a significantly greater improvement in mean net UF volume and UF rate. The appearance rates of VEGF, Flk-1, and Ang-2 were more significantly reduced (appearance rates of Tie-2 and Tsp-1 increased) in the high-dose group versus the placebo group, but not in the low-dose group.

**Conclusion** Supplementation with trans-resveratrol is beneficial to improve ultrafiltration in PD patients, and high-dose supplementation may improve ultrafiltration by ameliorating angiogenesis induced by conventional lactate-buffered PD solutions.

**Introduction**

Peritoneal dialysis (PD) is a successful modality of renal replacement therapy, but ultrafiltration (UF) failure is common and mostly contributes to technical failure in PD patients. Peritoneal angiogenesis is one of responsible factors for UF failure. As is well-known, uratemia and bioincompatible characteristics of conventional lactate-buffered PD solutions can contribute much. Great efforts including antiangiogenesis therapy and some drugs (e.g., icodextrin and sTie-2-Fc\textsuperscript{1,2}) with the anti-angiogenesis effect are used to improve UF in recent years.

Vascular endothelial growth factor (VEGF), a potent angiogenesis stimulator, has also been shown to promote endothelial cell proliferation, cell migration, and tube formation. VEGF also induces vascular permeability, and this function is mainly mediated by fetal liver kinase-1 (Flk-1) (VEGFR2). As reported, the levels of VEGF and its type 2 receptor Flk-1 increase in human peritoneal mesothelial cells (HPMCs),\textsuperscript{3} animal model,\textsuperscript{4} and clinical studies\textsuperscript{5,6} under PD. In addition, the angiopoietin/tyrosine kinase 2 (Ang/Tie-2) system also plays an important role in initiation of angiogenesis in human omental tissue microvascular endothelial cells\textsuperscript{7} or PD rats.\textsuperscript{8} Thrombospondin-1 (Tsp-1), a natural angiogenesis inhibitor, counterbalances the effects of VEGF on endothelial cells. The inhibition of antiangiogenic Tsp-1 in endothelial cells could promote angiogenesis.\textsuperscript{9} Moreover, the VEGF/Tsp-1 balance could adjust angiogenesis in the remnant kidney\textsuperscript{10} and also affect diabetic retinopathy.\textsuperscript{11} Thus, angiogenesis is controlled by a dynamic balance between vessel regression and growth, and mediated by angiogenesis activators and inhibitors.

Resveratrol, a naturally-existing polyphenol, has been proposed to have antiaging, antioxidant,
antiinflammatory, anti-carcinogenic, anti-platelet-aggregation, cardio-protective, neuro-protective, and cartilage-protective effects. Resveratrol also may affect the angiogenic pathways. These effects of resveratrol are largely mediated by the members of the sirtuin family. Previous studies find resveratrol is pro-angiogenic in the ischemic myocardium and antiangiogenic in cancers both in vitro and in vivo. Resveratrol can also attenuate tumor, metastasis, diabetic nephropathy, diabetic retinopathy, rheumatoid arthritis, and other diseases by modulating pathological angiogenesis in a sirtuin-independent pathway. Peritonea angiogenesis is also pathological. Resveratrol regulates angiogenesis by down-regulating relevant activators (e.g., VEGF, Flk-1, Ang-2) and up-regulating relevant inhibitors (e.g., Tie2, Tsp-1, Leptin, endothelin) in a dose-dependent manner in vitro and in animal experiments. Resveratrol modulates HPMCs-dependent angiogenic responses in the opposite direction via modulating the secretion of VEGF and IL-8/CXCL8. Moreover, HPMCs play an important role in peritoneal angiogenesis and fibrosis. In clinical studies, resveratrol is used orally among normal people, obese participants, and diabetes patients. However, there is no study about the use of resveratrol in the dialysis population. Luckily, resveratrol is highly-orally absorbed and well-tolerated by patients.

In this prospective, randomized, and double-blind study, we aim to evaluate whether or not trans-resveratrol has beneficial effects on UF and to investigate relevant markers of angiogenesis in PD patients.

Materials and methods

Study design

This 12-week prospective, randomized, and double-blind study was conducted at our dialysis center and approved by the local Ethics Committee (Approval No. 2014027). Written informed consent was obtained from all participants before enrollment. Participants were assigned into three groups via block randomization with a block size of six with an allocation ratio of 1:1 after the completion of baseline assessments. The allocation sequence was generated independently by the study statistician and concealed in opaque envelopes. Both investigators and participants were blind to the allocations. Block scheduling and envelope preparation were performed by a nurse not involved in the sampling and data analysis. The participants were advised on life-style modification, such as daily polyphenol intake. They were asked to abstain from consumption of trans-resveratrol-containing foods or drinks during the study.

Participants and methods

The participants were 18 years or older adults undergoing stable PD for at least three months. All participants were under continuous ambulatory PD (CAPD) with PD prescription for three exchanges a day. All participants used the same type of dialysis solution containing 1.5 mmol/L dialysate calcium, as well as constant PD prescriptions during the study period. They were randomly assigned to 12-week treatment with low-dose (150 mg) trans-resveratrol (ResVida®, DSM Nutritional Products Ltd., Kaiseraugst, Switzerland; one capsule of trans-resveratrol and two capsules of placebo) or a high dose trans-resveratrol (450 mg) (three capsules) daily, or to placebo (three capsules) as a control. The flow-chart of the study protocol is depicted in Figure 1.

The prescription of trans-resveratrol for patients undergoing dialysis was not mentioned in literatures. The dose selection in this study was based on pharmacodynamics, a pharmaceutical factory’s recommendation, and previous studies. According to pharmacodynamics, about 70% of orally-administered resveratrol (25 mg) can be rapidly (<30 min) absorbed and metabolized with a peak plasma level of metabolites ≈ 2 μM and a half-life of 9–10 h, and resveratrol is mostly metabolized in the liver. The pharmaceutical factory’s recommendation states that the safe dose is <450 mg/d. In previous studies, the dosage range for trans-resveratrol is about 10–3000 mg/d irrespective of the renal function.

In the present study, 150 and 450 mg/d trans-resveratrol were chosen as the two doses were suggested to be safe yet effective and tolerant enough. We did not find any resveratrol-related adverse events, and the patients were well-tolerated at both doses. The placebo was indistinguishable by color, form, or taste from the active drug. Trans-resveratrol and placebo were both taken at 19:00–21:00 p.m.

Inclusion and exclusion criteria

The inclusion criteria are as follows: (1) diagnosis of end-stage renal disease (ESRD); reception of current conventional maintenance PD (three exchanges a day) for more than three months; ≥ 18 years old; voluntary participation; signed consent form. The exclusion criteria are as follows: peritonitis or tunnel infection during the study period; current pregnancy or lactating mothers; severe hepatic or intestinal dysfunction; excessive alcohol or caffeine intake (>210 and 140 mL/d alcohol for men and women, respectively; >450 mg/d caffeine); uncontrolled psychiatric disease; history of trans-resveratrol allergy. The patients using the solutions including 4.25%
Dianeal, Physioneal, Icodexcin, or amino-acid-containing were also excluded.

**Assessment of peritoneal transport kinetics and measurement of UF**

Net UF volume (in mL) and UF rate (in mL/h) were measured at both baseline and 12 weeks after treatment. The modified peritoneal equilibration test (PET) was performed at the sitting position. In brief, the infusion of 2.0 L of 4.25% dialysis solution was considered as the “zero” dwell time. The effluent was collected at 0, 60, and 240 min, and venous blood was collected at 60 min. Then the effluent and blood samples were sent for measurements of glucose, urea, creatinine, and sodium. At the completion of the 4-h dwell, the dialysate-to-plasma ratio of creatinine (D/P4Cr) was measured, and at 1 h, the dialysate-to-plasma ratio of sodium (D/P1Na) was measured.

Net UF volume during the PET was measured. For volume determination, 1 g of fluid was considered equivalent to 1 mL of fluid. All bags were weighed by a nurse before instillation and after drainage. The UF in each dwell was assessed below. Each full solution bag was weighed both before and after instillation, while the difference between the two weights was recorded as the instillation volume. Each full drainage bag was weighed after the completion of the 4-h dwell, and the empty drainage bag was weighed after dumping the effluent. The difference between these two weights plus 150 mL of the sampling volume taken during the study was recorded as the drainage volume. UF volume was calculated as “drainage volume - instillation volume”. UF rate was also calculated as “net UF volume/actual dwell time”.

**Demographic and laboratory measurements**

We measured basic laboratory parameters, such as hemoglobin, serum phosphorus, and high sodium at baseline levels. Blood samples were collected on the morning of the dialysis day. Measurements were done via standard methods. **kt/v** and Body mass index \( [\text{BMI} = \text{weight (kg)} / \text{height (m}^2\text{)}] \) were also calculated and recorded. Information about age, sex, and primary kidney disease for renal failure, duration of PD, and PD prescription was gathered from medical records. The history of smoking and drinking was inquired from the patients. Comorbidity was scored on the number of comorbid conditions using the comorbidity index.

Angiogenesis markers including VEGF, Flk-1, Ang-2, Tie-2, and Tsp-1 from peritoneal dialysate effluent (PDE) were analyzed by an enzyme-linked immunosorbent assay (ELISA) kit (Quantikine®; R&D Systems, Minneapolis, MN) according to the manufacturer’s directions. All PDE samples for the biomarker assessment were collected.
from the overnight PDE (from exchanges with 2 L 2.5% Dianeal dialysate) at the night preceding the PET and were stored at −70°C until analysis. For correlation and comparisons, the appearance rate of each angiogenesis marker in the dialysate was calculated as “marker concentration × drained volume/dwell time” [pg (ng)/min].

Safety assessment
Safety was assessed by a review of reported adverse events and abnormal laboratory test results.

Statistical analysis
Calculations show that a sample of 64 patients is adequate enough (α = 0.05 in a two-sided t-test) for the proposed tests. The results of UF volume and UF rate from baseline to 4, 8, and 12 weeks are plotted with two panels of mean and error bars of each variable. The results are expressed as mean ± standard deviation (SD) and p < 0.05 indicates significance. Differences in means were tested using one-way analysis of variance (ANOVA) or the Mann–Whitney test as appropriate.

Comparisons among quartiles were assessed with the χ² test. Changes from baseline to 12 weeks in the angiogenesis markers were analyzed with a linear mixed model and a spatial-power covariance structure. The non-inferiority of high-dose versus low-dose (450 vs. 150 mg/d) was assessed on basis of 95% confidence intervals (CIs) for the least-squares-means difference (LSMD) derived from a mixed-effects model. All statistical analyses were evaluated on SPSS 18.00 (IBM Corporation, Armonk, NY).

Results
Characteristics of studied patients
During the 12-week study period, 8 out of 72 patients were excluded (6 in the high-dose group, 2 in the low-dose group) because of switching to hemodialysis (n = 3), reception of kidney transplantation (1) and poor adherence (4). Basic laboratory data and sociodemographic characteristics of the entire study population are depicted in Table 1. There is no significant difference in any of the characteristics at baseline among the three groups.

Table 1. Sociodemographic and clinical data in different groups.

| Characteristics                      | Trans-resveratrol 150 mg Daily (n = 22) | Trans-resveratrol 450 mg Daily (n = 18) | Placebo (n = 24) | p-Values |
|---------------------------------------|----------------------------------------|----------------------------------------|------------------|----------|
| Age (Yr)                              | 57.1 ± 9.9                             | 55.2 ± 10.7                            | 54.5 ± 10.6      | 0.18     |
| Sex (male%)                           | 59.1                                   | 61.1                                   | 62.5             | 0.97     |
| Primary kidney disease (%)            |                                        |                                        |                  | 0.99     |
| Nephritis                             | 59.1                                   | 61.1                                   | 66.7             |          |
| Hypertensive nephrosclerosis          | 4.5                                    | 0                                      | 4.2              |          |
| Diabetic nephropathy                  | 13.6                                   | 16.7                                   | 8.3              |          |
| Polycystic kidney disease             | 9.1                                    | 11.1                                   | 8.3              |          |
| Other                                 | 13.7                                   | 11.1                                   | 12.5             |          |
| Diabetes mellitus (%)                 | 9.1                                    | 11.1                                   | 8.3              | 0.95     |
| Body Mass index (kg/m²)               | 66.7 ± 10.3                            | 69.1 ± 11.9                            | 65.6 ± 9.4       | 0.29     |
| Duration of PD (month)                | 35.3 ± 22.7                            | 38.1 ± 25.9                            | 34.8 ± 19.2      | 0.35     |
| PD prescription (three exchange %)    |                                        |                                        |                  | 0.91     |
| 1.5% Dianeal                          | 45.5                                   | 38.9                                   | 41.7             |          |
| 2.5% Dianeal                          | 54.5                                   | 61.1                                   | 58.3             |          |
| Type of fluid for overnight (2.5% Dianeal %) | 68.2                                   | 72.2                                   | 70.8             | 0.96     |
| Peritoneal transport type (%)         |                                        |                                        |                  | 0.69     |
| High (fast)                           | 0                                      | 0                                      | 0                |          |
| High (average)                        | 31.9                                   | 38.9                                   | 41.7             |          |
| Low (average)                         | 63.6                                   | 61.1                                   | 58.3             |          |
| Low (slow)                            | 4.5                                    | 0                                      | 0                |          |
| Drinking (%)                          | 18.2                                   | 22.2                                   | 25.0             | 0.85     |
| Drinker (%)                           | 50.0                                   | 38.9                                   | 54.2             | 0.61     |
| Residual renal function (mL/min/1.7m²)| 8.7 ± 4.3                              | 8.9 ± 5.1                              | 7.8 ± 5.2        | 0.23     |
| Total kTVcrea                         | 1.73 ± 0.49                            | 1.68 ± 0.52                            | 1.71 ± 0.55      | 0.16     |
| Peritoneal kTVcrea                     | 1.64 ± 0.51                            | 1.62 ± 0.48                            | 1.65 ± 0.47      | 0.72     |
| Mean urine volume (mL)                | 366.8 ± 212.3                          | 387.1 ± 195.9                          | 374.6 ± 203.4    | 0.09     |
| Net ultrafiltration volume (mL)       | 415.5 ± 109.5                          | 396.4 ± 133.6                          | 388.7 ± 124.3    | 0.47     |
| Ultrafiltration rate (mL/h)           | 21.7 ± 8.3                             | 20.6 ± 9.2                             | 20.3 ± 8.7       | 0.21     |
| Mean hemoglobin (g/L)                 | 12.4 ± 5.7                             | 11.8 ± 2.1                             | 12.2 ± 5.0       | 0.12     |
| Mean serum phosphorus (mmol/L)        | 1.5 ± 0.4                              | 1.4 ± 0.3                              | 1.4 ± 0.2        | 0.17     |
| Mean serum sodium (mmol/L)            | 136.5 ± 8.7                            | 139.1 ± 4.9                            | 139.1 ± 4.9      | 0.33     |
| Comorbidity index                     | 5.7 ± 1.3                              | 5.9 ± 2.1                              | 5.5 ± 1.7        | 0.15     |

Notes: Differences in proportions were tested using the Pearson Chi-square test; differences in means were tested using an one-way analysis of variance or Mann–Whitney.

n, number; PD, Peritoneal Dialysis.
Net UF volume and UF rate

After 12 weeks, the high-dose group [Mean change from baseline (95% CI): 171.4 (141.3–201.5) (mL), \( p = 0.003 \) (Net UF); 11.3 (10.5–12.1) (mL/h), \( p = 0.02 \) (UF rate)] and the low-dose group [Mean change from baseline (95% CI): 98.1 (49.5–146.7) (mL), \( p = 0.007 \) (Net UF); 6.5 (4.4–8.6) (mL/h), \( p = 0.04 \) (UF rate)] versus the placebo group show significantly larger mean net UF volume and UF rate. The high-dose versus the low-dose is associated with a more significant improvement in mean change from baseline in net UF volume both (188.3 ± 58.5 vs. 115.0 ± 108.2, \( p = 0.02 \)) and UF rate (12.2 ± 1.0 vs. 7.4 ± 4.6, \( p = 0.04 \)) (Figure 2).

Some angiogenesis and inflammatory markers

The appearance rates of VEGF, Flk-1, and Ang-2 in the dialysate are significantly lower in the high-dose group versus the placebo group, and the appearance rates of Tie-2 and Tsp-1 are increasing significantly. However, none of these influencing angiogenesis markers are significantly different between the low-dose and the placebo groups (Table 2).

The non-inferiority assessment shows a significant reduction in the appearance rates of VEGF (LSMD, -115, 95% CI, -151 to -79; \( p < 0.05 \)), Flk-1 (LSMD 1010.5, 95% CI, -1821.1 to -199.9; \( p < 0.01 \)), and Ang-2 (LSMD, -335.5, 95% CI, -381.3 to -288.7; \( p < 0.05 \)), as well as a significant increase in the appearance rates of Tie2 (LSMD, 786.6, 95% CI, 237.6 to 1335.6; \( p < 0.01 \)) and Tsp-1 (LSMD, 137.8, 95% CI, 114.6 to 161.0; \( p < 0.05 \)) in the high-dose group versus the low-dose group. On the contrary, the IL-6 appearance rates are not significantly different among the three groups (\( p > 0.05 \)).

Adverse effects

Adverse events including diarrhea, constipation, muscle cramps/pain, fatigue, headache, and memory loss were observed after the use of trans-resveratrol. Adverse events led to discontinuation of medication in the trans-resveratrol groups (because of diarrhea in two cases, muscle pain in one case, and headache in one case).

Discussion

Based on previous observations about a beneficial effect of resveratrol on anti-angiogenic responses in human peritoneal mesothelial cells (HPMCs),12 and a hypothesis that trans-resveratrol could improve ultrafiltration via the anti-angiogenesis effect in PD-treated patients, here we tested the oral supplementation with trans-resveratrol in PD patients. To the best of our knowledge, this is the first report demonstrating the effects of trans-resveratrol on UF and neoangiogenesis in PD patients with ESRD. We did find a significant difference in either net UF volume or UF rate between the groups with and without oral trans-resveratrol administration. This UF improvement induced by high-dose trans-resveratrol (450 mg) was associated with less neo-angiogenesis with an up-regulation of activators (VEGF, Flk-2, and Ang-2) and down-regulation of inhibitors (Tie-2 and Tsp-1) in the dialysate.

As is well-known, angiogenesis is regulated by numerous activators and inhibitors as well as different angiogenic factors depending on the circumstance. We find higher levels of angiogenic activators (VEGF, Flk-2, and Ang-2) and lower levels of angiogenic inhibitors (Tie-2 and Tsp-1) in the effluent of patients treated with 1.5 or 2.5% Dianeal versus 450 mg trans-resveratrol, but not between the placebo group and the low-dose group. We hypothesize that high-dose trans-resveratrol administration could have the efficacy on angiogenesis. Structure–function relationship studies show that loss of UF capacity is associated with the occurrence of angiogenesis in the peritoneum both in rat models and in long-term PD patients. For most patients, exposure to glucose and especially glucose degradation products is the driving factor of angiogenesis. Many additives and substances have been studied to counteract these alterations.

The precise mechanism explaining the inhibitory effect of trans-resveratrol on angiogenesis has not been sufficiently clarified. Among many known activators, VEGF is...
believed to be the most prevalent efficacious and long-term signal that can stimulate Flk-mediated angiogenesis in vitro and in vivo. In endothelial cells, trans-resveratrol inhibits VEGF-VEGFR2-mediated endothelial cell responses via suppressing the phosphorylation of the MAP kinase or proteinkinase C (PKC) or COX enzymes.23,24 The anti-angiogenic activity of resveratrol in human umbilical vein endothelial cells (HUVECs) may also be associated with the activation of the glycogen-synthase kinase 3b (GSK3b), which leads to the down-regulation of the b-catenin signaling pathway and eventually to the decreased production of VEGF.25 Resveratrol also has the anti-angiogenic effects by up-regulating TSP-1 expression in melanoma-endothelial cells under co-culture.26

As reported, resveratrol at the given dose of 250 mg/day has no beneficial effect on angiogenesis,19 which is not found in the low-dose group of our study. In our study, the antiangiogenesis effect was seen in the high-dose group but not in the low-dose group. We think that the high-dose is more advantageous in anti-angiogenesis than the low dose or regular dose. This view was confirmed previously19 that 0.5 or 1.0 g/d resveratrol was sufficient to exert anti-carcinogenic and anti-angiogenic effects. Apart from the above-mentioned effects, resveratrol could also improve angiogenesis by adjusting the morphology of adipose tissues. As reported, the visceral fat percentage is significantly increased with the progress of PD.27,28 Adipocytokine up-regulation is accompanied by increase of visceral fat percentage. These adipocytokines including ptn and iponectin could affect the peritoneal angiogenesis.

Here we found a significant improvement of UF in the low-dose group although the relevant angiogenesis makers were not significantly changed. We think many factors besides peritoneal angiogenesis are associated with UF.29 Inflammation is one contributor to angiogenesis and UF failure,30 while inflammation could be suppressed by resveratrol in vitro and in vivo.31–33 Besides anti-inflammation, the cardio-protective effect34 and glycemic-control effect35 both could improve UF, since glucose is an osmotic gradient and the impaired cardiac function has a negative effect on UF.

In summary, trans-resveratrol (150 and 450 mg) can safely and effectively improve UF in PD-treated patients. Besides other advantages, the high-dose (450 mg)
supplementation may improve UF by ameliorating angiogenesis induced by conventional lactate-buffered PD solutions.

The present randomized controlled study is limited by the relatively small sample size and the relatively short follow-up time (12-week). The trans-resveratrol concentration in blood or effluent samples was not measured or monitored during the whole study. Further studies with more subjects, long-term anti-angiogenic and anti-fibrotic effects of resveratrol will help to confirm the findings of this study.

Declaration of interest

The authors report no conflicts of interest. The authors alone were responsible for the content and writing of the paper.

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