The effects of lipoic acid supplementation on the estimated glomerular filtration rate in patients with chronic kidney disease

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Some studies reported positive effects of lipoic acid (LA) in kidney disease. The present study investigated the effect of oral LA supplementation at a daily dose of 600 mg over a period of 30 days on the estimated glomerular filtration rate (eGFR) in stage 3, 4 and 5 chronic kidney disease (CKD) patients.

The studies were carried out in patients before dialysis (ND), patients treated with peritoneal dialysis (PD), and in a group of healthy volunteers. eGFR was calculated based on the results of serum creatinine test. The commercial preparation Neurolipon-MIP 600, which contains a racemic mixture of LA as the pharmacologically active substance was used in this clinical trial.

The results demonstrated that in the group of ND patients supplemented with LA for 30 days, the serum creatinine concentration (Cr) decreased by 17.9 µmol/L on average and thus eGFR increased by 1.54 ml/min per 1.73 m^2. In addition, the studies evidenced that LA did not affect the eGFR in PD patients.

The present study indicates that the use of LA in CKD patients can be an efficient therapeutic strategy protecting the kidney form progressive reduction of its function and allowing for postponement of inevitability of renal replacement therapy, which is of great importance for patient's quality of life. Furthermore, the studies revealed potential new pharmacological properties of LA. However, these are preliminary studies and confirmation of the present results and hypothesis requires further investigations.

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Key words:
- chronic kidney disease
- lipoic acid
- estimated glomerular filtration rate

Wpływ suplementacji kwasem liponowym na szacowany wskaźnik filtracji kłębuszkowej u pacjentów z przewlekłą niewydolnością nerek

Wyniki wielu badań wskazują, że kwas liponowy (LA) posiada właściwości nefroprotekcyjne. W niniejszej pracy przeprowadzono więc badania dotyczące wpływu doustnej suplementacji LA w dawce dziennej 600 mg przez okres 30 dni na szacowany wskaźnik filtracji kłębuszkowej (eGFR) u chorych z przewlekłą niewydolnością nerek (CKD). Badaniem objęto pacjentów w stadiach 3-5 CKD: (1) nie poddawanych dializie (ND); (2) poddawanych dializie otrzewnowej (PD). Grupę kontrolną stanowili zdrowi ochotnicy. Do badań użyto leku stosowanego w praktyce klinicznej o nazwie Neurolipon-MIP 600, który jako substancję farmakologicznie aktywną zawiera racemat LA.

Uzyskane wyniki wskazują, że w grupie pacjentów ND po 30 dniach suplementacji LA doszło do obniżenia stężenia kreatyniny w osoczu o 17,9 µmol/L i tym samym podwyższenia wartości eGFR o 1,54 ml/min/1,73 m^2. Natomiast LA nie miał wpływu na wartość eGFR u pacjentów poddawanych PD.

Otrzymane wyniki wskazują więc, że stosowanie LA u chorych z CKD może okazać się skuteczną strategią terapeutyczną pozwalającą na zwolnienie postępującej utraty czynności nerek i odsunięcie w czasie konieczności rozpoczęcia leczenia nerkozastępczego, co ma niebagatelne znaczenie dla jakości życia i komfortu pacjenta. Badania te wskazują ponadto na nowe właściwości farmakologicznego działania LA. W celu lepszego rozpoznania mechanizmów działania LA i potwierdzenia prezentowanych tu hipotez niezbędne są dalsze badania.

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Słowa kluczowe:
- przewlekła niewydolność nerek
- kwas liponowy
- szacowany wskaźnik filtracji kłębuszkowej

Introduction

Diseases of affluence or *Western diseases* are the terms sometimes given to diseases which, in general, are thought to be a result of increased wealth in the society. Diseases of affluence of the 21st century are usually believed to include cardiovascular disease, hypertension, obesity and diabetes, and recently also chronic kidney disease (CKD) has been added to this list. It is noteworthy that contemporary nephrology has become the most interdisciplinary field of medicine because of the complex nature of causes and complications associated with kidney diseases [1].

According to previous professional guidelines, excretory kidney function was classified into five stages. Stage 5 of CKD

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is often called end-stage kidney disease or end-stage renal disease (ESRD). Among diseases of affluence, CKD occupies a special place because it can be either a cause or a complication of the remaining diseases of this group. It suffices to notice that the impaired renal function has been found to be an independent risk factor of adverse cardiovascular disease (CVD) outcomes and all-cause mortality in a large spectrum of CVD patients [2]. It is also known that the most common causes of ESRD include diabetes and high blood pressure [3].

One of the most common complications of diabetes, diabetic neuropathy (DN) occurs in ca. 50% of diabetic patients. DN affects all peripheral nerves including pain fibers, motor neurons and the autonomic nervous system. Neuropathic pain is difficult to treat. The currently available evidence (randomized, placebo controlled studies) indicates that lipoic acid (LA) is a drug which significantly and in clinically relevant manner reduces neuropathic pain [4-6].

The present study for the first time investigated the effect of oral LA supplementation on the estimated glomerular filtration rate (eGFR) in stage 3, 4 and 5 CKD patients. The studies were conducted in non-dialyzed CKD patients, in patients treated with peritoneal dialysis (PD), and in a group of healthy volunteers. Thus, the aim of our studies was to answer the question whether LA is able to improve renal function in non-dialyzed and dialyzed chronic kidney disease patients

In each study group, the creatinine concentration was assayed before and after LA supplementation and then eGFR was calculated. Moreover, other parameters: albumin, HCO_3^- and lipid profile and blood pressure were determined.

Material and Methods

The studies were conducted on clinically stable patients with chronic kidney disease (CKD) treated in the Rydygier's Hospital Fressenius Nephrocare II in Kraków and on a control group of healthy volunteers. Study protocol was approved by Local Medical Ethics Committee and informed consent was obtained from all participants. The studies were carried out in three groups: I- patients with chronic renal failure, who were not treated with dialysis (non-dialyzed, ND); II – patients with end stage renal failure undergoing peritoneal dialysis (PD); and III- healthy volunteers with no clinical history of kidney diseases (control).

Group I (ND) comprised 13 patients (6 women and 7 men), at the mean age of 70.5 ± 11.5 years. The following etiological causes of uremia were identified: glomerulonephritis (2), pyelonephritis (5), polycystic kidney disease (2), hypertensive nephropathy (3), rheumatoid arthritis (1).

Group II (PD) consisted of 15 patients (7 women and 8 men) with end stage chronic kidney disease on peritoneal dialysis, with the mean age of 40.7 ± 9.4. Etiological causes of uremia in this group included: glomerulonephritis (6), pyelonephritis (4), hypertensive nephropathy (4), nephrolithiasis (1).

Group III comprised 15 healthy control subjects (11 women and 4 men) aged 41.7 ± 8.0 years with no clinical history of renal diseases. The control group was composed of employees of the Rydygier's Hospital Fresenius Nephrocare II and the Chair of Medical Biochemistry, Jagiellonian University, Medical College.

Exclusion criteria in all groups were: cancer, diabetes, liver disease, immune deficiency.

All study participants were supplemented orally with a capsule of lipoic acid (LA) at a daily dose of 600 mg (once a day, after breakfast) in the commercial preparation Neurolipon-MIP 600 for 30 days. Blood from the patients and from the controls was collected twice: 1 day before the first and 1 day after the last dose of LA. Fasting blood samples were collected in the Rydygier's Hospital Fresenius Nephrocare II in Krakow. In each study group, the concentration of creatinine, albumin, HCO_3^- and lipid profile were determined before and after LA supplementation. Moreover, blood pressure and body mass index (BMI) were estimated.

Biochemical parameters (creatinine concentration and other parameters) were measured with Olimpus AU 680 apparatus using routine laboratory methods.

The estimated glomerular filtration rate (eGFR) was calculated using the equation: eGFR [ml/min/1.73m^2]=186 x creatinine concentration x age in years x factor, which is 0.742 for women and 1.0 for men.

Table I

Clinical and biochemical parameters before and after lipoic acid (LA) supplementation at a dose of 600 mg for 30 days in all three studied groups: patients with chronic kidney disease non-dialysed (ND); patients with chronic kidney disease undergoing peritoneal dialysis (PD) and healthy subjects (Control). The concentration of urea, phosphate and total calcium was not measured in control group. *statistically significant (p≤0.05) difference between the values in the same group before and after LA supplementation.

Parametry kliniczne i biochemiczne przed i po 30 dniach doustnej suplementacji kwasem liponowym (LA) w dawce 600 mg u osób biorących udział w badaniu: (ND) pacjenci z rozpoznaną chroniczną niewydolnością nerek, nie poddawani dializie; (PD) pacjenci z rozpoznaną chroniczną niewydolnością nerek, poddawani dializie otrzewnowej; (Control) zdrowi ochotnicy. W grupie zdrowych ochotników nie badano stężenia mocznika, fosforanów i wapnia całkowitego w osoczu krwi.
*różnica znamienna statystycznie dla p≤0,05 w tej samej grupie badanych przed i po suplementacji LA.

	ND		PD		Control	
	Before LA (mean +/- SD)	After LA (mean +/- SD)	Before LA (mean +/- SD)	After LA (mean +/- SD)	Before LA (mean +/- SD)	After LA (mean +/- SD)
BMI	23.57 ± 2.75		25.26 ± 4.82		24.4 ± 3.6	
SBP	124.6 ± 11.0	132.9 ± 18.4	135.9 ± 19.9	126.4 ±16.9	116.0 ± 18.4	120.0 ± 15.6
DBP	76.1 ± 6.8	77.1 ± 8.3	85.5 ± 12.3	82.7 ±11.9	74.0 ± 11.7	77.5 ± 10.1
Pulse	75.6 ± 9.6	74.1 ± 8.6	75.9 ± 12.8	73.3 ±9.2	66.3 ± 6.0	67.6 ± 6.4
Creatinine [µmol/l]	323.2 ± 128.7 *	305.3 ± 123.4	730.3 ± 261.2	760.2 ± 259.9	78.8 ± 9.1	79.9 ± 8.2
eGFR [ml/min]	18.6 ± 9.8 *	20.6 ±10.5	7.0 ± 2.7	6.7 ± 2.3	71.7 ± 7.9	70.4 ± 8.2
Total calcium [mmol/l]	2.3 ± 0.1	2.3 ± 0.1	2.24 ± 0.22	2.25 ± 0.19	-	-
Urea [mmol/l]	19.3 ± 6.4	20.9 ± 8.2	21.70 ± 3.28	19.95 ± 6.70	-	-
Phosphate [mmol/l]	± 0.2	1.1 ± 0.3	1.68 ± 0.35	1,84 ± 0.54	-	-
Albumin [g/l]	39.4 ± 4.0	40.0 ± 3.9	35.71 ± 2.73	35.57 ± 3.01	43.4 ± 2.2	43.3 ± 2.1
HCO_3^- [mmo/l]	22.9 ± 2.7	22.0 ± 3.1	22.47 ± 2.18	22.39 ± 2.32	26.2 ± 2.3	26.9 ± 1.7
Total cholesterol [mmol/l]	4.6 ± 0.8	4.7 ± 0.9	4.82 ± 1.08	4.76 ± 0.67	5.1 ± 0.5	5.1 ± 0.7
LDL [mmol/l]	2.5 ± 0.7	2.7 ± 0.7	2.76 ± 0.91	2.72 ± 0.51	3.0 ± 0.5	3.2 ± 0.5
HDL [mmol/l]	1.2 ± 0.2	1.1 ± 0.3	1.24 ± 0.24	1.05 ± 0.24	1.5 ±0.3	1.4 ± 0.2
Triglicerydes [mmol/l]	1.8 ± 0.7	1.7 ± 0.5	1.76 ± 0.66	2.14 ± 1.17	1.3 ± 0.4	1.0 ± 0.4

Statistical analysis

Statistical analysis was carried out using STATISTICA 10.0 Software (Statsoft, Inc, USA). The significance of differences in the examined parameters in patients with chronic renal failure before and after LA supplementation was estimated using t--Student's test. The differences were considered statistically significant when $p<0.05$.

Results

The patients and controls well tolerated LA treatment and no serious adverse events were reported in this trial. All studied biochemical parameters and blood pressure before and after 1 month of LA supplementation are presented in Table 1.

The obtained results indicated that LA at a dose of 600 mg administered for 30 days did not affect in a significant manner the level of most of the studied parameters, i.e. blood pressure, and urea, HCO_3^- and albumin concentration or lipid profile in patients with chronic renal failure either non--dialysed or undergoing peritoneal dialysis or in control subjects. However, the most interesting results are connected with the effect of LA on the kidney function expressed as the creatinine concentration and eGFR. In the non-dialyzed (ND) group of patients with chronic renal failure before LA supplementation, the mean creatinine concentration was 323.2 µmol/l and after LA it decreased significantly to the value of 305.3 µmol/l. In consequence of the reduction of creatinine concentration, eGFR increased after LA supplementation (18.6 vs. 20.6 ml/min). In the case of patients with chronic renal failure undergoing peritoneal dialysis (PD), the initial creatinine concentration was 730.3 µmol/l and after LA administration it even increased to 760.2 µmol/l. It was accompanied by a slight decrease in eGFR (from 7.0 to 6.7 ml/min). The changes of kidney function parameters in PD group were not statistically significant. The effect of LA supplementation on the creatinine concentration and eGFR value in healthy control group was negligible (Tab. I).

Table II shows a comparison of the effect of LA at a dose of 600 mg administered for 1 month in all three studied groups on the kidney function expressed as the change in creatinine concentration and eGFR value. The positive effect of LA supplementation manifested in a statistically significant decrease in serum creatinine concentration and an increase in eGFR was found only in patients with chronic renal failure in the pre-dialysis stage.

Discussion

The present results demonstrated that in ND patients supplemented with LA for 30 days, the serum creatinine concentration decreased by 17.9 µmol/L on average and thus eGRF increased by 1.94 ml/min per 1.73 m^2. In contrast, LA at the same dose did not affect the eGFR in PD patients.

Normal GFR in adults is 90 mL/min per 1.73 m^2 or higher. As already mentioned earlier, according to previous professional guidelines on assessing the severity of impairment of excretory kidney function, CKD was classified into five stages. New guidelines for the assessment of excretory kidney function published in January 2013 were based on eGFR as a marker of kidney function [7]. eGFR categories were designated with the letter "G". The categories from G1 to G5 are equivalent to the former five stages for assessing the severity of CKD. Briefly, the category G1 is characterized by GFR≥90 mL/min per 1.73 m^2, while the category G2 by GFR 60 to 89 mL/min per 1.73 m^2. An estimated glomerular filtration rate of 60-89 mL/min/1.73 m^2 (stages G1 and G2) in the absence of other evidence of kidney disease does not signify CKD and does not indicate that further tests are required. The category G3 was subdivided into G3a (GFR 45-59 mL/min per 1.73 m^2) and G3b (GFR 30-44 mL/min per 1.73 m^2). Patients showing GFR 15-29 mL/min per 1.73 m^2 are included in the category G4. Patients of category G5 have GFR<15 mL/min per 1.73 m^2. In people with GFR<60 ml/min/1.73 m^2 (GFR categories G3a-G5) kidney failure is confirmed. Thus presently, GFR is the best measure of kidney function used to determine the stage of kidney disease.

CKD is a worldwide health problem. This disease is characterized by a progressive and irreversible loss of kidney function. Dialysis and transplantation are the main therapeutic options. Progression of CKD is defined as a shift towards a higher GFR category. It is known that GFR reduction by 10 mL below 60 mL/min per 1.73 m^2 is accompanied by an increased risk of sudden cardiac death by 11-17% [8,9]. Thus, the goal of the treatment of CKD is to slow down the advancing decline of kidney function and postponement of inevitability of renal replacement therapy, which is of great importance for patient's quality of life. Of no little importance is also the fact that dialysis is a costly procedure. No wonder then that the timing of dialysis initiation and dosing strategy are a focus of intensive research. The Canadian Society of Nephrology clinical practice guidelines for timing the initiation of chronic dialysis published in 2014 stated that for adults (aged>18 yr) with an eGFR of less than 15 mL/min per 1.73 m^2 an intent-to-defer strategy is strongly recommended over an intent-to--start-early approach for the initiation of chronic dialysis. An intent-to-defer strategy requires close monitoring of patients for uremic symptoms or other complications or a decline in eGFR to 6 mL/min per 1.73 m^2 or less, which would serve as an indication for starting dialysis. Other complications mentioned in these guidelines included: symptoms of uremia, fluid overload, hyperkalemia and acidemia refractory to conservative treatment [10].

It also appears that the present results indicating that oral administration of LA at a daily dose of 600 mg in the preparation Neurolipon-MIP 600 allows for achievement of clinical improvement manifested by an increased eGFR in CKD patients not treated with dialysis bring new hopes for patients with renal failure. Our observations agree with animal studies demonstrating that LA treatment prolongs survival and attenuates acute kidney injury in a rat model of sepsis [11,12]. Also, animal studies indicated that LA could efficiently prevent cyanate toxicity [13]. It is worth reminding that cyanate and its active form isocyanate are formed mainly in the process of nonenzymatic urea biodegradation and belong to the uremic toxins. The positive effects caused by LA in kidney disease were also demonstrated in clinical trials. Khabbazi et al. documented a positive effect of LA in patients with ESDR on hemodialysis [14]. In another study, LA at a daily dose of 600 mg significantly reduced CRP concentration without influencing the oxidative stress [15].

The same studies showed that one of putative mechanisms of biological action of LA is based on its influence on sulfane-sulfur metabolism, leading to hydrogen H_2S release [16-18]. It was demonstrated that both sulfane sulfur and H_2S protected the kidney against various forms of injury [19]. Iciek et al. showed that LA supplementation increased the sulfane sulfur content in erythrocytes of ESRD patients treated with PD [20].

Thus, it seems that LA is a potential candidate for a safe and efficacious medication in kidney diseases which reveals potential new pharmacological properties of LA.

Conclusion

To sum up, the obtained results indicate that in patients on renal replacement therapy, LA supplementation did not influence creatinine concentration or eGRF value, which indicates that LA administration in this group of patients is not reasonable. However, LA administration in non-dialyzed patients seems promising since the obtained results indicate that 30-day LA supplementation in these patients led to the mean reduction of creatinine concentrations by 19.7 µmol/L which correspond to the mean eGRF increase by 1.54 ml/min per 1.73 m^2.

Table II

Comparison of changes in creatinine concentration and eGFR values after and before lipoic acid (LA) supplementation in all studied groups (p≤0.05).

Porównanie zmian w stężenia kreatyniny i wartości eGFR po i przed suplementacją kwasem liponowym (LA) w we wszystkich badanych grupach (p≤0,05).

	ND	PD	Control
	mean ± SD	mean ± SD	mean ± SD
Creatinine change [µmol/l]	-17.9 ± 27.3	29.9 ± 98.9	1.1 ± 2.8
eGFR change [ml/min]	1.9 ± 2.2	-0.3 ± 1.3	-1.2 ± 2.9

It evidences that unlike in dialyzed patients, LA supplementation in non-dialyzed ones is advisable because it can improve efficiency of already implemented therapeutic strategies aimed to slow down the progressing loss of renal function and to postpone the inevitability of renal replacement therapy. These pilot findings are based on a small number of patients, therefore, confirmation of the present results and hypothesis requires further investigations.

Conflict of interest

The authors do not have any conflict of interest regarding this manuscript.

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