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α-lipoic acid in patients with autosomal dominant polycystic kidney disease

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ABSTRACT

Objectives: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease characterized by multiple and bilateral cystic dilation of renal tubules. Hypertension, endothelial dysfunction, systemic inflammation, and accelerated atherosclerosis are alterations found at a very early stage of the disease and are responsible for increasing both cardiovascular risks and progression toward end-stage renal disease. The aim of the study was to evaluate the effects of the use of 1.6 g α-lipoic acid (ALA) daily for 3 and 6 on the main markers of systemic inflammation, endothelial dysfunction, and atherosclerosis, as well as on nutritional, cardiovascular, and psychocognitive parameters, in ADPKD patients with CKD stage G2/G3 Kidney Disease Improving Global Outcomes chronic kidney disease (KDIGO) compared to controls.

Methods: This was a controlled, longitudinal, prospective, interventional study with 59 patients with ADPKD. Of the patients, 33 were treated with ALA (1.6 g/d) for 6 mo and 26 were controls. Clinical, laboratory (inflammation and metabolic indexes), instrumental parameters (intima media thickness (IMT), renal resistive index (RRI), flow-mediated dilation (FMD), ankle-brachial index (ABI), and psycho-cognitive tests (Mini-Mental State Examination [MMSE], Hamilton Depression Rating Scale [HAM-D], Beck Depression Inventory-II [BDI-II]) were evaluated at baseline (T0), 3 mo (T1), and 6 mo (T2).

Results: Patients treated with ALA at T1 and T2 showed a significant reduction in serum glucose, insulin, homeostatic model assessment-insulin resistance, and serum uric acid ($P = 0.013$, $P = 0.002$, $P = 0.002$, $P < 0.001$; respectively) and significantly higher values of base excess ($P < 0.001$), compared with the control group. Moreover, the results showed a significant increase in bicarbonates ($P = 0.009$) and FMD ($P < 0.001$), and a significant reduction of C-reactive protein ($P < 0.001$) and RRI ($P = 0.013$). On the other hand, we did not assess a significant difference in IMT and ABI at T1 and T2. Psychocognitive tests (BDI-II, HAM-D, and MMSE) were significantly improved ($P = 0.007$, $P < 0.001$, $P < 0.001$; respectively) in patients treated with ALA for 6 mo compared with the control group. A significant difference in nicotinamide adenine dinucleotide phosphate oxidase 2 concentrations was observed between T0 and T2 only in ADPKD patients treated with ALA ($P = 0.039$, $P = 0.039$; respectively), although we did not find a significant difference in interleukin-6, interleukin -1β, and tumor necrosis factor-α concentrations in either group.

Conclusions: We suggest an early and careful monitoring of traditional and non-traditional cardiovascular risk factors in patients with ADPKD. Moreover, we suggest the use of ALA, an anti-inflammatory and antioxidant nutraceutical with few side effects. Additionally, it is important to evaluate the cognitive abilities, psychological health, and quality of life of patients with ADPKD, especially at the early stage of disease.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited monogenic disease characterized by the formation of cystic dilation of renal tubules, leading to a gradual subversion of the renal parenchyma until to end-stage renal disease (ESRD) [1,2]. Cardiovascular disease (CVD) is one of the main causes of morbidity and mortality in patients with ADPKD and endothelial dysfunction, systemic inflammation, and accelerated atherosclerosis are alterations found at a very early stage of the disease and are responsible for both increased cardiovascular risk and increased progression toward ESRD [3,4]. Moreover, several studies showed major cognitive impairment in patients with ADPKD and chronic kidney disease (CKD) compared with healthy controls (HC) and a higher prevalence of depression, especially in ESRD, which remains underdiagnosed. These factors together aggravate the patient's health and worsen their prognosis [5,6]. α-lipoic acid (ALA) is a small amphipathic molecule with an essential function in mitochondrial oxidative metabolism [7,8]. Its first clinical use was described in Germany in 1959 for the treatment of acute poisoning by amanita phalloides, but soon the same authors discovered its usefulness in the treatment of neurologic disorders [9]. Both ALA itself and its reduced form have many biochemical functions, acting as biological antioxidants, metal-chelating agents, reducing agents of oxidized forms of other antioxidants such as vitamin C and E and glutathione, and finally as modulators of many intracellular signaling pathways, such as insulin and nuclear factor-κB [10]. This molecule also demonstrated a positive effect on endothelial dysfunction [11] and on the reduction of oxidative stress after exercise [10,12]; moreover it has a protective effect against the development of atherosclerosis and inhibits the progression of an already formed atherosclerotic plaque [11,12]. For these reasons, ALA has been studied in many experimental studies as a potential therapeutic agent for many chronic diseases such as diabetes mellitus, hypertension [13,14], brain and cognitive disorders, and obesity [15]. ALA acts also as a cofactor of numerous enzymes such as pyruvate dehydrogenase, α-ketoacid dehydrogenase, and α-ketoglutarate dehydrogenase [16]. Generally, side effects are uncommon, even if these supplements could cause nausea, dizziness, or a rash. The aim of the study was to evaluate the effects of the use of ALA (1.6 g/d) for 3 and 6 mo on the main markers of systemic inflammation, endothelial dysfunction, and atherosclerosis, as well as on nutritional, cardiovascular, and psycho-cognitive parameters, in ADPKD patients with CKD stage 3 Kidney Disease: Improving Global Outcomes (KDIGO) (≤59 estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73 m^2), compared with a control group.

Materials and methods

The study protocol was approved by the Local Clinical Research Ethics Committee. The study conformed to the principles outlined in the Declaration of Helsinki and we obtained a written consent by each patient enrolled.

Study design

This was a longitudinal, prospective, interventional, controlled study with ADPKD patients at the University Hospital "Policlinico Umberto I" of Rome, Sapienza University of Rome, Italy. Patients were consecutively enrolled from July 2016 to June 2017. Clinical, laboratory, and instrumental parameters were evaluated at baseline (T0), 3 mo (T1), and 6 mo (T2).

Patients

The study enrolled 59 ADPKD patients (26 men). Of these patients, 33 were treated with ALA, and 26 were considered controls. The eGFR was evaluated according to the modification of diet in renal disease formula (MDRD) and CKD epidemiology [17]. We enrolled both normotensive and hypertensive patients. The state of arterial hypertension was defined by the use of hypotensive drugs (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium antagonists, α-lytic and/or diuretics) or by the presence of pressure values >140/80 mm Hg in three consecutive measurements.

Inclusion and exclusion criteria

Patients aged >18 y with diagnosis of ADPKD, defined according to the Pei's criteria [18], were included. We excluded patients who were affected by heart failure, psychiatric disorders, neoplastic diseases, acute coronary syndrome within 3 mo before the study, and those who were pregnant or nursing. Patients who refused to give consent and those with missing data also were excluded.

Laboratory measurements

Blood was drawn in the morning after an overnight fasting of ≥12 h. In all patients, the levels of fasting plasma glucose (mg/dL), insulin (mu U/mL), serum total cholesterol (TC; mg/dL), triglycerides (TGs; mg/dL), high-density lipoprotein (HDL; mg/dL), creatinine (mg/dL), serum nitrogen (mg/dL), serum uric acid (SUA; mg/dL), calcium (mg/dL), phosphorus (mg/dL), serum electrolytes (mEq/L), C-reactive protein (μg/L), and homocysteine (μmol/L) were measured using standard automated techniques. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation: LDL (mg/dL) = TC − HDL− (TG/5). Parathyroid hormone (PTH) was measured using a two-site assay that measures "intact" hormone (iPTH; pg/mL) and 25-hydroxyvitamin D (25-OH-VitD; ng/mL) was measured by radioimmunoassay. Serum albumin (g/dL) was determined by bromocresol purple method. Insulin resistance (IR) was assessed using the homeostasis model assessment-insulin resistance (HOMA-IR) originally described by Mathew et al. [19]. Microalbuminuria (30−300 mg/24 h) was assessed through a 24-h urine collection test. Arterial blood gas was performed using a blood gas analyzer (Nova Phox Plus C, Nova Biomedical, Waltham, MA, USA). Serum samples were used for the assay of inflammatory cytokines, interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and plasma nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX2). Their concentrations were assessed using the following enzyme-linked immunosorbent assay kits: human IL-1β, human IL-6, and human TNF-α (RayBiotech, Peachtree Corners, GA, USA), and human NOX2 (MyBiosource, San Diego, CA, USA). We used an ELISA (sandwich method) for the dosage of inflammatory cytokines, and a competitive immunoenzymatic method (competitive enzyme immunoassay) to dose NOX2.

Blood pressure measurements

Clinic blood pressure measurements were taken with a standard automatic sphygmomanometer according to Rodriguez et al. [20]. The mean values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) were then calculated for all participants. Hypertension was defined as having an SBP ≥ 140 mm Hg and a DBP ≥ 90 mm Hg at baseline; having a self-reported history of physician-diagnosed hypertension; or taking antihypertensive medication. We determined ankle-brachial Index (ABI), which is the measurement of the ratio of the SBP in the ankle and in the arm (normal values 0.9−1) [21].

Common carotid intima-media thickness assessment

Right and left carotid ultrasound was performed by an experienced sonographer who was unaware of the characteristics of the patients under examination. Participants were studied with the high-resolution B-mode ultrasound machine, Toshiba Aplio xV (Toshiba American Medical Systems, Inc., Tustin, CA, USA), equipped with a 5- to 12-MHz linear transducer with a 0.01-mm resolution, following a standardized vascular protocol. Intima-media thickness (IMT) was measured at three points on the far walls of both left and right distal common carotid arteries, carotid bulb, and the proximal portion of the internal carotid arteries [22]. The mean IMT was computed as the average IMT on both sides. The value of IMT was considered normal between 0.55 and 0.9 mm [23].

Flow-mediated dilation

According to the method described by Celermajer et al. [24], the endothelium-dependent vasodilation of the brachial artery was assessed using a B-mode ultrasound machine Toshiba Aplio xV (Toshiba American Medical Systems, Inc) equipped with a 55- to 12-MHz linear transducer, following a standardized protocol [25]. Flow-mediated dilation (FMD) was typically expressed as the change in post-stimulus diameter as a percentage of the baseline diameter. FMD: (diameter posthyperemia-basal diameter/basal diameter) × 100. The values of FMD were considered normal if >10%.

Psychological, compliance, and cognitive tests

All individuals completed standardized psychological and cognitive tests.

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) evaluates intellectual disorders and cognitive impairments. The MMSE consists of 30 items, referring to seven different

cognitive areas: orientation in time, orientation in space, recording of words, attention and calculation, commemoration, language, and constructional praxis [26]. The MMSE often is used as a screening tool in the investigation of patients with dementia and neuropsychological syndromes of different nature. The total score is between a minimum of 0 and a maximum of 30 points. A score ≤18 indicates severe impairment of cognitive skills; a score between 18 and 24 is an index of moderate to mild cognitive impairment, a score of 25 is considered borderline; from 26 to 30 is indicative of cognitive normality. The score is, however, indicative, being the calibration factors also related to age and educational level of the patient.

Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HAM-D) has proven its usefulness for many years as a tool for determining a patient's level of depression before, during, and after treatment. The HAM-D should be administered by a clinician experienced with working with psychiatric patients [27]. Although the HAM-D form lists 21 items, the scoring is based on the firsts 17. It generally takes 15 to 20 min to complete the interview and score the results. Eight items are scored on a scale ranging from 0 (*not present*) to 4 (*severe*). Nine are scored from 0 to 2. Since its development in 1960, the HAM-D has been widely used in clinical practice and has become a standard in pharmaceutical trials.

Beck Depression Inventory-II

The Beck Depression Inventory-II (BDI-II) is a self-assessment questionnaire consisting of 21 multiple-choice questions and is one of the most widely used psychometric tests for measuring the severity of depression. The BDI-II is designed for adults and adolescents of ≥13 y of age and is composed of items relating to symptoms of depression such as hopelessness and irritability, guilt, or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, pain, and lack of interest in sex. The BDI-II is a widely used test by health care professionals and researchers in a variety of settings and diseases [28].

Statistical analysis

Data management and analysis were performed using SPSS version 22 (IBM, Armonk, NY, USA). The normality of variables was tested using the Shapiro–Wilk method for normal distributions. All continuous variables were expressed as mean ± SD, categorical variables were expressed as number (%). Spearman's correlation was used to determine in bivariate correlation the relationship and the strength of association between the variables. A probability value of $P < 0.05$ was considered statistically significant.

Results

Patient's characteristics at T0 are shown in Table 1. In all, 59 ADPKD patients (33 males) with a mean age of 45.1 ± 10.7 y were enrolled. Of the patients, 33 (18 males) were treated with ALA and 26 (15 males) were controls. No differences were observed between the two groups at T0 (Table 1). At T1, after 3 mo of therapy with ALA, the patients treated with ALA demonstrated significantly lower values of serum glucose, insulin, HOMA-IR, and SUA ($P = 0.008$, $P = 0.042$, $P = 0.004$, and $P < 0.001$, respectively) and significantly higher values of base excess (BE; $P = 0.003$), compared with the control group (Table 1, Figs. 1, 2). We also observed an

Table 1
Patients' characteristics at T0 (baseline), at T1 (after 3 mo of treatment with α-lipoic acid), and at T2 (after 6 mo of treatment with α-lipoic acid)

Parameters	Group A (n = 33)	Group B (n = 26)	*P*- value	Group A (n = 33)	Group B (n = 26)	*P*- value	Group A (n = 33)	Group B (n = 26)	*P*- value
	T0			T1			T2		
BMI (kg/m^2)	23.27 ± 3.08	23.62 ± 2.41	0.07	22.65 ± 2.28	22.81 ± 2.35	0.792	23.41 ± 2.94	24.19 ± 2.60	0.291
Creatinine (mg/dL)	1.31 ± 0.41	1.33 ± 0.30	0.808	1.30 ± 0.22	1.38 ± 0.40	0.333	1.29 ± 0.41	1.42 ± 0.30	0.163
Serum uric acid (mg/dL)	4.92 ± 0.97	4.55 ± 1.13	0.191	4.27 ± 0.94	5.34 ± 1.59	***0.004***	5.06 ± 0.96	6.21 ± 1.32	***<0.001***
CRP (mg/L)	4.07 ± 3.33	4.48 ± 2.84	0.614	3.07 ± 2.5	4.52 ± 3.56	0.073	2.42 ± 1.27	6.30 ± 2.86	***<0.001***
FMD %	11.21 ± 9.16	11.38 ± 9.48	0.944	12.1 ± 4.84	8.95 ± 8.37	0.075	15.85 ± 11.6	6.06 ± 2.12	***<0.001***
RRI	0.61 ± 0.19	0.60 ± 0.11	0.812	0.60 ± 0.09	0.62 ± 0.06	0.334	0.58 ± 0.06	0.63 ± 0.09	***0.013***
BDI-II	12.73 ± 6.69	12.85 ± 5.50	0.941	10.41 ± 3.45	12.35 ± 4.5	0.066	8.39 ± 2.31	12.38 ± 5.61	***0.007***
HAM-D	17.52 ± 17.52	17.00 ± 6.43	0.762	11.33 ± 11.14	13.5 ± 11.7	0.470	11.09 ± 2.77	19.50 ± 5.32	***<0.001***
Mini- Mental	25.30 ± 2.68	24.48 ± 2.29	0.235	26.00 ± 3.94	24.66 ± 2.6	0.142	27.90 ± 4.38	23.61 ± 1.53	***<0.001***

ABI, ankle-brachial index; ADPKD, autosomal dominant polycystic kidney disease; BDI, Beck Depression Inventory; BMI, body mass index; CRP, C-reactive protein; FMD, Flow-mediated dilation; HAM-D, Hamilton Depression Rating Scale; RRI, renal resistive index
Data shown as mean ± SE or n (%).
Group A: ADPKD patients treated with α-lipoic acid; Group B: ADPKD patients as controls.

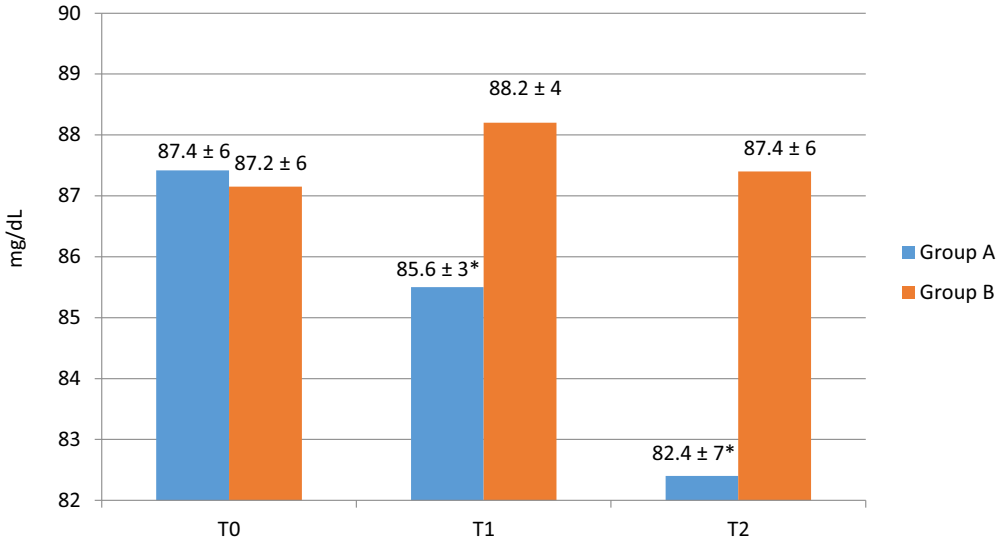

Fig. 1. Serum glucose at baseline (T0) and during follow-up at 3 (T1) and 6 mo (T2) in ADPKD patients treated (group A) and not treated (group B) with a-lipoic acid. *$P < 0.01$ group A vs group B. ADPKD, autosomal dominant polycystic kidney disease.

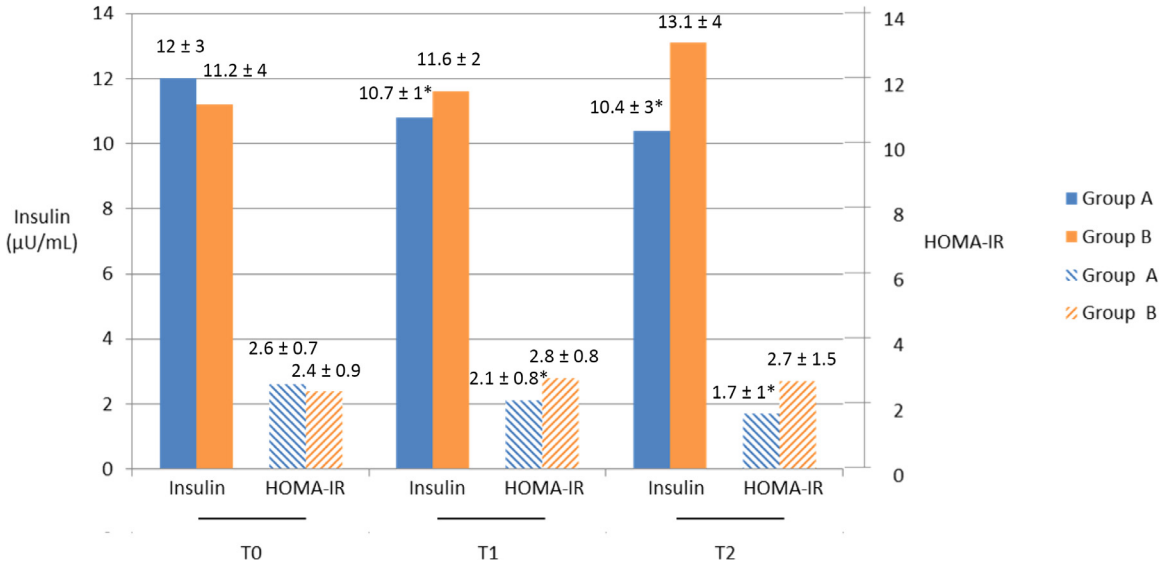

Fig. 2. Plasma levels of insulin and HOMA-IR at baseline (T0) and during follow-up at 3 (T1) and 6 mo (T2) in ADPKD patients treated (group A) and not treated (group B) with α-lipoic acid. *$P < 0.01$ group A vs group B. ADPKD, autosomal dominant polycystic kidney disease; HOMA-IR, homeostasis model assessment-insulin resistance.

increase in concentrations of bicarbonates ($P = 0.08$) and FMD ($P = 0.07$; Table 1, Fig. 3) values and a decrease in serum CRP ($P = 0.073$) in treated patients compared with the controls, even if not statistically significant. We reported an improvement in all psychological and cognitive tests (BDI-II, HAM-D, MMSE) in patients treated with ALA compared with the control group, but no statistical significance (Table 1). At T2, after 6 mo of therapy with ALA, significantly lower values of insulin concentration ($P = 0.004$), serum glucose ($P = 0.013$), HOMA-IR ($P = 0.002$), BE ($P = 0.001$; Figs. 1 and 2) and a higher value of bicarbonates ($P = 0.009$; Fig. 3) were observed. We also observed a significant reduction in CRP ($P < 0.001$) and renal resistive index (RRI; $P = 0.013$) and a significant increase in FMD ($P < 0.001$; Table 1), although we did not detect a significant difference in IMT and ABI at T2 ($P = 0.982$ and $P = 0.419$, respectively). BDI-II, HAM-D, and MMSE tests were significantly improved ($P = 0.007$, $P < 0.001$, and $P < 0.001$, respectively) in patients treated with ALA for 6 mo compared with the controls (Table 1). There was a significant difference in NOX2 between T0 and T2 only in those ADPKD patients treated with ALA ($P = 0.039$), although we did not observe a significant difference in IL-6, IL-1β, and TNF-α concentrations in either group (Table 2). We did not observe any side effects in the present study.

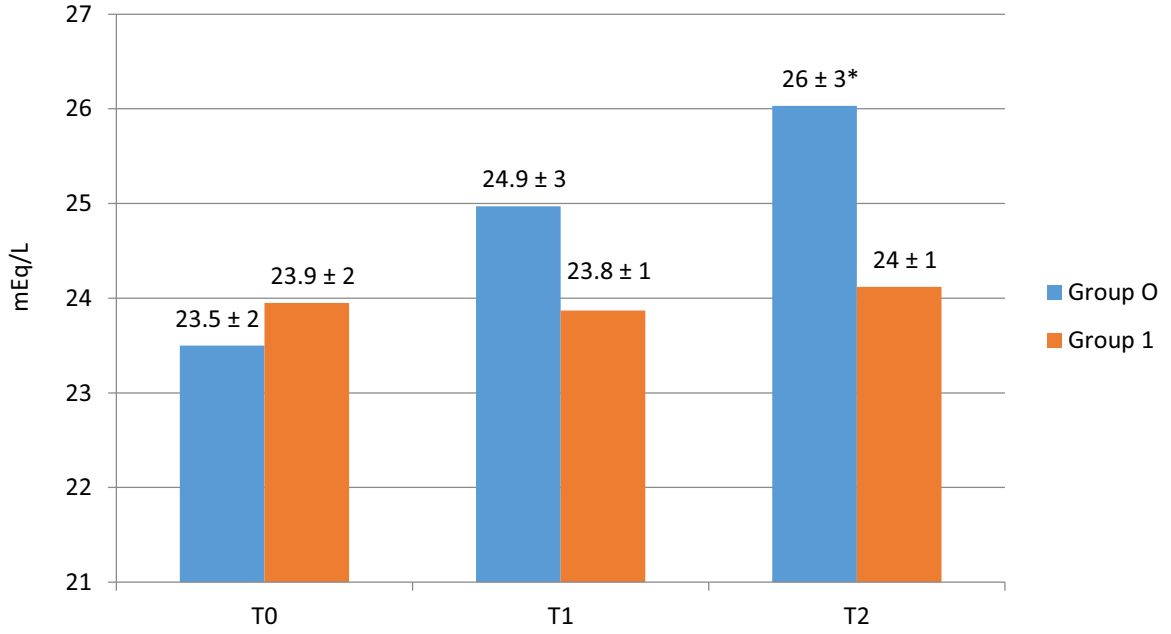

Fig. 3. Bicarbonate ($HCO3^-$) levels at baseline (T0) and during follow-up at 3 (T1) and 6 mo (T2) in ADPKD patients treated (group A) and not treated (group B) with α-lipoic acid. *$P < 0.01$ group A vs group B. ADPKD, autosomal dominant polycystic kidney disease.

Table 2
Patients' characteristics al T0 (baseline) and T2 (after 6 mo of treatment with α-lipoic acid)

Parameters	Group A (n = 33)			Group B (n = 26)		
	Baseline	Follow-up	*P*-value	Baseline	Follow-up	*P*-value
IL-6	40.76 ± 87.96	36.25 ± 74.06	0.834	32.92 ± 65.56	61.01 ± 133.75	0.336
IL-1-ß	1.61 ± 2.11	1.57 ± 2.01	0.937	2.99 ± 6.71	2.71 ± 6.07	0.875
TNF-α	52.34 ± 64.29	52.06 ± 66.66	0.986	64.84 ± 101.24	77.36 ± 120.52	0.933
NOX2	0.55 ± 0.14	0.48 ± 0.13	**0.039**	0.54 ± 0.12	0.56 ± 0.15	0.597

ADPKD, autosomal dominant polycystic kidney disease; IL, interleukin; NOX2, nicotinamide adenine dinucleotide phosphate oxidase; TNF, tumor necrosis factor
Data show as mean ± SD or n (%).
Group A: ADPKD patients treated with α-lipoic acid; Group B: ADPKD patients as controls.
Bold value is used for values less than 0.05 (high statistical significance).

Discussion

Patients with ADPKD present high cardiovascular risk. In fact, inflammation and endothelial dysfunction can induce important development of atherosclerosis. Results from the present study demonstrated an improvement of the main cardiovascular risk factors in ADPKD patients treated with ALA compared with the control group. We also observed a significant reduction of insulin concentrations, serum glucose, and HOMA-IR.

IR depends on multiple factors, including lifestyle, obesity, and genetic predisposition. Several studies [29,30] have found a correlation among IR, atherogenesis, arterial wall thickening, and endothelial dysfunction leading to greater cardiovascular risk. A higher IR in patients with ADPKD was shown previously [31], but the pathogenetic mechanism has not yet been fully elucidated, although Mao et al. [32] showed a role of polycystin in regulating insulin secretion, as it is expressed also in pancreatic β cells. We also showed an increase of BE and bicarbonate values after treatment. Metabolic acidosis is associated with CKD and it can determine an increase in protein catabolism, mineral metabolism diseases, and IR. In fact, it is a known cardiovascular risk factor and a progression factor toward ESRD [33].

In the present study, we assessed a reduction of CRP, a systemic marker of inflammation after ALA administration. Although the causes of inflammation have been well described in CKD, the effects of inflammation on vascular functions have not yet been fully elucidated. However, because recent evidence [34] supports the hypothesis that systemic inflammation is a pathogenetic key mechanism in the development and progression of atherosclerosis and in the onset of cardiovascular events, CRP seems to be more than a simple marker. Indeed, CRP can directly influence the vascular endothelium through many mechanisms, including an increase in the expression of adhesion molecules, reduction of nitric oxide (NO) expression in endothelial cells, and the alteration of LDL. For these reasons, the increased CRP is considered an independent risk factor for CVD [35], especially in patients with ADPKD, where an early systemic inflammation has been documented, promoting cardiovascular risk and progression of renal disease [36–38].

In the present study, we described a significant reduction in NOX2 between T0 and T2 only in ADPKD patients treated with ALA, although we did not observe a significant difference in IL-6, IL-1β, and TNF-α in either group. Studies over the past 2 decades have indicated the presence of an inflammatory component in ADPKD human and murine models [36]. Menon et al. [37] reported that hypertensive patients with ADPKD and an eGFR between 25 and 60 mL/min had higher levels of inflammatory markers such as CRP and IL-6 compared with HCs (normotensive ADPKD and hypertensive ADPKD with eGFR of >60 mL/min) [36]. Gardner et al. [38] found IL-1β, TNF-α, and IL-2 in cyst fluid of human kidneys; whereas monocyte chemoattractant protein-1 (MCP-1), a chemokine that regulates monocyte/macrophage migration, was detected in urine of patients with ADPKD, as reported also by Zheng et al. [39], and urinary MCP-1 levels correlated positively with the rate of subsequent cyst growth in patients with ADPKD, as confirmed more recently by Messchendorp et al. [40]. NOXs are enzymes present in the vascular wall, and their primary task is to produce reactive oxygen species (ROS) superoxide, physiologically at low levels, in vascular cells [41]. Recent evidence showed overactive NOX systems in the initiation and progression of vascular disease via an excessive ROS production by cells of the artery wall at levels that are cytotoxic [42–43]. These ROS may lead to activation of proinflammatory pathways, depletion of antioxidants, and oxidative damage to proteins, lipids, and DNA. Among the NOX isoforms, NOX2 is believed to have the greatest implication in vascular disease. Overexpression of NOX2 in mice results in significantly increased superoxide production, and NOX2 knockout mice show significantly reduced ROS levels [44]. Therefore, increased activation of NOX2 could contribute to diminished bioavailability of NO, and thus, endothelial dysfunction and vascular cell hypertrophy [45]. NOX2 upregulation could also explain the oxidative stress observed in patients with ADPKD, including endothelial dysfunction [41,46]. ALA is an effective free radical scavenger, synthesized in mitochondria, acting as cofactor of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. Some studies showed that ALA, with its free radical scavenging effect, could protect kidneys from ischemia reperfusion and cisplatin or methotrexate-induced nephropathy, preventing lipid peroxidation and neutrophil infiltration of the renal tissue [47]. Moreover, some authors showed that ALA treatment decreases plasma levels of proinflammatory cytokines [48]. Proinflammatory cytokines stimulate nitric oxide synthase (*iNOS*) gene expression, leading to excessive production of NO and resulting in renal injury. Yamada et al. [49] showed that ALA inhibits the induction of *iNOS* gene expression at a post-transcriptional step via iNOS mRNA stabilization. This may provide useful therapeutic effects through the suppression of iNOS induction. In the present study, we showed a significant improvement in endothelial dysfunction markers as SUA, FMD, and RRI, after treatment with ALA.

FMD is a technique for quantifying endothelial dysfunction and has a prognostic value for cardiovascular risk [50]. FMD directly evaluates the function of the arterial wall, considering the bioavailability of NO, a molecule produced by the endothelium with antiatherogenic functions, plaque stabilization, and vessel tone regulation [51]. Recently, some authors showed an essential role of the cilia in proper development of the vascular system [52]. Insufficient expression of PC1 or PC2 could be associated with functional or structural abnormalities of the vascular system, determining a reduced release of NO with altered endothelial response to shear stress and reduced vasodilation. The RRI is a renal and systemic vascular damage marker that reflects the vascular atherosclerotic

changes and is associated with cardiovascular events and mortality in patients with CKD [53,54]. In fact, clinical trials in patients with CVD showed significant and independent association of RRI with all-cause mortality and cardiovascular events, with no significant effect on renal function and kidney disease with the exception of atherosclerosis [55]. Several studies [55,56] showed higher RRI in hypertensive and normotensive patients with ADPKD compared with controls, whereas Ramunni et al. [57] showed that in patients with ADPKD, without renal failure, the RRI values were significantly higher in hypertensive than in normotensive patients.

We also observed a significant reduction of SUA in patients with ADPKD treated with ALA. SUA is an independent risk factor for atherosclerosis and CVD, and it could play a causative role in oxidative stress influencing the endothelial dysfunction and promoting the development of inflammation and atherosclerosis [58,59]. Moreover, in patients with ADPKD, SUA may be considered an independent risk factor for all-cause and cardiovascular mortality and it may be associated with earlier onset of larger kidney volume, hypertension, and increased risk for ESRD [60–62]. In the present study, we did not describe a significant difference in IMT and ABI, indexes of subclinical atherosclerosis, perhaps because patients with ADPKD are still in the early stage of disease [63].

Other important aspects that we evaluated were the psychological and cognitive parameters. We showed a mildly moderate depression at T0 with a cognitive state considered borderline; whereas we observed an improvement in mood and cognitive functions in patients with ADPKD after 6 mo of ALA treatment (T2) compared with the control group. Patients with CKD, especially those with ADPKD, have a high prevalence of psychological and cognitive deficits [5]. The clinical presentation can be variable, from the most serious forms, often associated with ESRD, which may be characterized by motor slowdown and cognitive deficits that may reduce adherence to treatment, diseases of the cerebral white matter, clinically silent cerebral infarcts, hematochemical and electrolyte alterations, and metabolic acidosis, frequently observed in these patients [6]. Milder forms also may be present and characterized by psychological disorders such as depression, by psychological disorders such as depression, that could reduce the quality of life and compliance of these patients [64]. Moreover, in patients with ADPKD, quality of life is decreased with respect to the physical (fatigue, pain, etc) and psychological effects of the disease. Depression and anxiety are mainly due to uncertainty of prognosis, genetic guilt, precariousness of parental future, feelings of powerlessness, and hopelessness [5]. So, the importance of using standardized methods for evaluation over time of a patient's psychocognitive functions is obvious.

Limitations

The main limitation of the present study was its relatively small cohort of patients with ADPKD. Therefore, additional prospective follow-up studies with a larger number of patients are necessary to confirm these results. A significant proportion of patients was on several medications with potential effects on different metabolic indices that may have possibly confounded the results. Moreover, the follow-up period was relatively short.

Conclusions

In patients with ADPKD, early assessment and careful monitoring of traditional and non-traditional cardiovascular risk factors are important. In addition to the treatment of cardiovascular risk factors, the use of ALA, an anti-inflammatory and antioxidant nutraceutical with few side effects, is recommended in patients with ADPKD who have high cardiovascular risk factors at an early stage of disease. Moreover, we underline the importance of an assessment of cognitive functions, psychological state of health, and quality of life, especially during the early stages of disease, to implement therapeutic interventions and to improve the quality of life of these patients.

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