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Biophysical integrated approach for the management of early stages of CKD in elderly patients: a 12-month controlled study

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Abstract

Background Chronic Kidney Disease (CKD) and its clinical evolution are an emerging issue, due to an increasingly aging population. Consequently, the evaluation of integrative strategies to manage the decline in renal function is warranted. The previous evidence indicates that a biophysical integrated approach can significantly improve renal function. Nevertheless, controlled trials assessing the clinical efficacy of this strategy are still needed.

Methods A 12-month controlled study was designed to assess the clinical outcome of a group of elderly patients affected by stage II/IIIa CKD randomly assigned to either control or biophysical treatment. In addition to the standard treatment with renin–angiotensin–aldosterone system inhibitors, the biophysical group underwent electromagnetic information transfer through aqueous system procedure every 3 months. Estimated glomerular filtration rate (eGFR), according to CKD–epidemiology collaboration formula, was calculated at baseline and every 3 months.

Results A total of 238 patients were included in the study, 118 (73.9 ± 3.8 years) in the biophysical therapy group and 120 (74.6 ± 4.2 years) in the control group. At baseline, mean eGFR was 69 ± 11.8 ml/min in the biophysical group and 70.7 ± 11.5 ml/min in the control group. After 1 year, eGFR was 74.1 ± 12.3 ml/min in the biophysical group, compared to 66.3 ± 11.9 ml/min in the control group, with a statistically significant difference between groups ($p < 0.0001$). The observed improvement in eGFR in the biophysical group was independent of age, gender, and antihypertensive treatment.

Conclusion This study shows a potential contribution of a biophysical integrated strategy to support renal function against its natural decline in the elderly, warranting further clinical evaluation.

Keywords Chronic kidney disease · Elderly · Biophysical therapy · Electromagnetic information transfer · eGFR

Introduction

Chronic Kidney Disease (CKD) and its clinical evolution are an emerging and extending issue due to the increasingly aging of population. CKD represents a serious concern in the management of elderly patients, either as a primary disease or as a common comorbidity occurring in a growing number of individuals with complex diseases. CKD is mainly associated with aging, and consequently, it is becoming more frequent due to progressive and increasingly aging populations, particularly in Western countries. CKD represents a true price of adaptation according to the allostatic load theory [1]. It contributes to a general functional decline [2] and thereby to an increase in cumulative biological risk, ultimately affecting both morbidity and mortality rates [3] through an increase in frailty [4]. Consequently, the evaluation of potential integrative strategies to prevent and manage the decline of renal function in the elderly is advisable. Evidence documents a significant improvement in renal function yielded by means of a biophysical integrated approach in recent years. The first report demonstrated the long-lasting improvement (a 10-year follow-up period) in renal function in a case of autoimmune nephritic syndrome obtained by means of a biophysical integrated approach [5]. Later, a

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significant improvement in estimated glomerular filtration rate (eGFR) following a biophysical integrated approach in 30 patients with early stage CKD treated for a period of 1 year was reported [6], and more recently, an open-label observational study has been performed on a group of 58 elderly patients with a positive outcome regarding the yearly assessment of eGFR [7]. Biophysical methods are novel and integrative emerging tools in clinical practice and several studies have reported on their potential beneficial use in the general management of pain [8], in particular on articular pain [9, 10], low back pain [11, 12], neck pain and disability [13] as well as in the management of psoriasis [14], and minor anxiety and depressive disorders [15].The working hypotheses is that biophysical treatments can exert their clinical effect through a resonance effect [16]. Resonance occurs between therapeutically delivered electromagnetic signals, endogenous or exogenous, and target tissues, organs, and/or the entire organism [17, 18], allowing the achievement of both local and systemic effects at the same time [19]. Nevertheless, prospective and randomized controlled trials assessing the clinical efficacy of this biophysical integrated strategy on the eGFR prognosis are still lacking. To address this, we designed a 1-year randomized controlled trial to assess the clinical outcome of a group of elderly patients affected by stage II/IIIa CKD randomly assigned either a biophysical protocol or control group.

Materials and methods

Patients and study design

This was a randomized controlled trial (the protocol was not registered for this trial) and included patients aged ≥ 70 years presenting with stage II or IIIa CKD (i.e., eGFR > 45 ml/min/1.73 m^2). Exclusion criteria at enrollment were the presence of diabetes, the use of corticosteroid drugs, and the continuous use of any non-steroidal anti-inflammatory drugs. Patients were also excluded who had changes to their antihypertensive medication over the follow-up period. Informed consent was obtained from all participants and the study was performed in accordance with the declaration of Helsinki. In addition to the standard treatment with renin–angiotensin–aldosterone system (RAAS) inhibitors, the biophysical group underwent the electromagnetic information transfer through aqueous system procedure every 3 months over a period of 1 year, while the control group did not. Randomization was performed through the website http://www.randomization.com.

Evaluation of estimated glomerular filtration rate

After evaluation of the different methods currently available [20], we decided to employ the CKD–epidemiology collaboration (CKD–EPI) formula [21]. This is a simple and rapid method that allows eGFR estimation by inserting the value of serum creatinine through a dedicated website portal (www.mdrd.com) or by means of tables [22], along with gender, race, and age. Systematically, we employed the website www.mdrd.com. Serum samples for creatinine assessment were collected every 3 months, to monitor eGFR before each administration of the biophysical therapy in the therapy group as well as in the control group, and eGFR was calculated before the start of treatment (as baseline) and at the end of the 1-year follow-up period.

Laboratory tests

In a subset of patients (approximately half of patients in both control and biophysical groups), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. In 102 patients in the control group and 100 patients in the biophysical group, proteinuria was also undertaken at baseline and after 12 months.

Biophysical therapy group

Patients allocated to the biophysical protocol received a two-step treatment in addition to the standard treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs). As first step, the ‘regulation therapy’ program was selected on the touch screen of the Med Select 729 device (Wegamed, GmbH, Essen, Germany) to record the endogenous input signals at the renal , and then, the therapeutic electromagnetic output signals were delivered on an electromagnetic, full body carpet on which the patient laid down on for 10 min. As a second step, the ‘basic drainage therapy’ program was selected from the touch screen of the Med Select 729 device to record the endogenous input signals at the renal region and deliver the therapeutic output signals at the kidney’s site for 10 min. Along both steps, the output therapeutic signals were simultaneously recorded on a commercial available aqueous system (Nomabit Base, Named SRL, MB Italy) by placing the solution into the special built-in output coil of the Med Select 729 device according to the electromagnetic information transfer through aqueous system procedure [23]. This medical device works in the low-frequency range (between 0 and 20 kHz) window using a magnetic field with an intensity in the range of the Earth’s magnetic field, with a maximum output of 50 μT. It allows to record the input signals through

two electrodes and to deliver the output signals to the patient through two magnetic electrodes for local use (i.e., on target anatomical location), or through a magnetic carpet, where the patient can lay down (in this way the entire body can be treated). This device can, therefore, simultaneously deliver both a local and systemic treatment. The Nomabit Base aqueous solution was subsequently self-administered by the patient, to allow the recorded therapeutic information to be delivered based on a weekly plan beginning with a single drop on Monday and increasing by one drop/day up to six drops on Saturday; no therapy was administered on Sunday. The weekly protocol has been previously reported [9]. The Nomabit Base solution is composed of oligominerals and is currently used as a food supplement. This aqueous solution is provided with a dropper and stored in an aluminum-shielded container, which ensures that the signals are preserved on the aqueous solution and are protected from environmental, thermal, and electromagnetic pollution. This is an "off label" use of a common dietary supplement, which is already suited to be stored for a long period of time (up to 3 months after opening, as indicated by the manufacturer, avoiding the risk of affecting its characteristics).

Control group

Patients allocated to the control group did not receive any treatment in addition to the standard treatment with RAAS inhibitors. They were simply evaluated by serum creatine sampling with the same timing of the biophysical therapy group.

Statistical analysis

Based on results obtained from a previous study performed on 58 CKD patients [7], we estimated that a sample size of 240 patients (in this two-arm study) would allow us to have a 90% statistical power in detecting a mean change in eGFR of 5 ml/min (10% compared to baseline values). Student's paired *t* test was used to compare mean differences in eGFR values in patients from baseline and 1 year, while Student's unpaired to *t* test was used to compare differences in eGFR between male and female patients. Statistical analysis was performed using the MedCalc software (Mariakerke, Belgium) and Instat Software (GraphPad, San Diego, CA, USA). A p value of <0.05 was considered statistically significant.

Results

Baseline clinical characteristics of CKD patients

A total of 238 patients were included in the study, 118 (mean age: 73.9 ± 3.8 years) in the biophysical therapy group and 120 (mean age: 74.6 ± 4.2 years) in the control group. Almost all patients had arterial hypertension and were treated with ARB or ACE inhibitors. Clinical characteristics of control and biophysical group patients are presented in Table 1. Baseline clinical characteristics were similar in the control and biophysical group. Furthermore, no difference was observed in baseline eGFR values, proteinuria, CRP, or ESR between the control and biophysical groups.

Table 1 Baseline clinical characteristics of control and biophysical groups

Characteristic	Control ($N=120$)	Biophysical ($N=118$)	P value
Age (years)	74.6 ± 4.2	73.9 ± 3.8	0.19
Female gender, *n* (%)	75 (62.5)	77 (65.3)	0.69
Hypertension, *n* (%)	116 (96.7)	113 (95.8)	0.75
eGFR (ml/min per 1.73 m^2)	70.7 ± 11.5	69 ± 11.8	0.25
CRP (mg/dl)	1.02 ± 0.99	1.00 ± 1.2	0.93
ESR (mm/h)	24.8 ± 10.9	24.9 ± 16.7	0.92
Proteinuria, *n* (%)	16/102 (15.7)	15/100 (15)	1
ARB, *n* (%)	49 (42.2)	47 (41.6)	1
ACE inhibitor, *n* (%)	67 (57.8)	66 (58.4)	1

eGFR was measured in all patients for both groups; CRP was only available in 53 patients in the control group and 50 patients in the biophysical group; ESR was only available in 69 patients in the control group and 63 patients in the biophysical group and proteinuria was only available in 102 patients in the control group and 100 in the biophysical group

Data are presented as mean ± standard deviation or number and percent

ARB angiotensinogen receptor blocker, *ACE* angiotensin-converting enzyme inhibitor, *eGFR* estimated glomerular filtration rate

Effect of biophysical treatment vs. control on eGFR and proteinuria

After 1 year of biophysical therapy, there was a highly significant increase in eGFR (ml/min/1.73 m^2) in the biophysical group (69 ± 11.8 at baseline vs. 74.1 ± 12.3 at 1 year, $p = 0.0013$) equating to an improvement of 5.1 ml/min/1.73 m^2, increasing further, when compared to the control group at 1 year (66.3 ± 11.9 vs. 74.1 ± 12.3, $p < 0.0001$; net difference of 7.8 ml/min/1.73 m^2; Fig. 1a). In contrast, in the control group, eGFR worsened (decreased) after 1 year (70.7 vs. 66.3, $p = 0.004$). While no difference was observed between the proportion of patients with proteinuria at baseline (15.7 vs. 15%, $p = 0.99$), proteinuria markedly decreased in both groups by 12 months, with no significant difference between groups (Fig. 1b). Sub-analysis of male and female patients did not reveal any difference in eGFR or proteinuria at the start or after 1 year in either the control or biophysical group. Furthermore, stratifying control and biophysical populations by ARB or ACE inhibitor treatment did not identify any significant differences in eGFR or proteinuria at baseline or follow-up.

Effect of biophysical treatment vs. control on CRP and ESR

After 1 year of biophysical therapy, there was a highly significant decrease in CRP was observed in the biophysical group compared to the control group (0.54 ± 0.8 mg/dl vs. 1.1 ± 1 mg/dl, $p = 0.0007$; Fig. 2a). Similarly, in the biophysical group, ESR was also significantly decreased after 12 months in the biophysical-treated group compared to control (16.3 ± 10.8 mm/h vs. 27.5 ± 10.6 mm/h, $p < 0.00001$; Fig. 2b). Sub-analysis of male and female patients did not reveal any difference in CRP or ESR at the start or after 1 year in either the control or biophysical group. Furthermore, stratifying control and biophysical populations by ARB or ACE inhibitor treatment did not identify

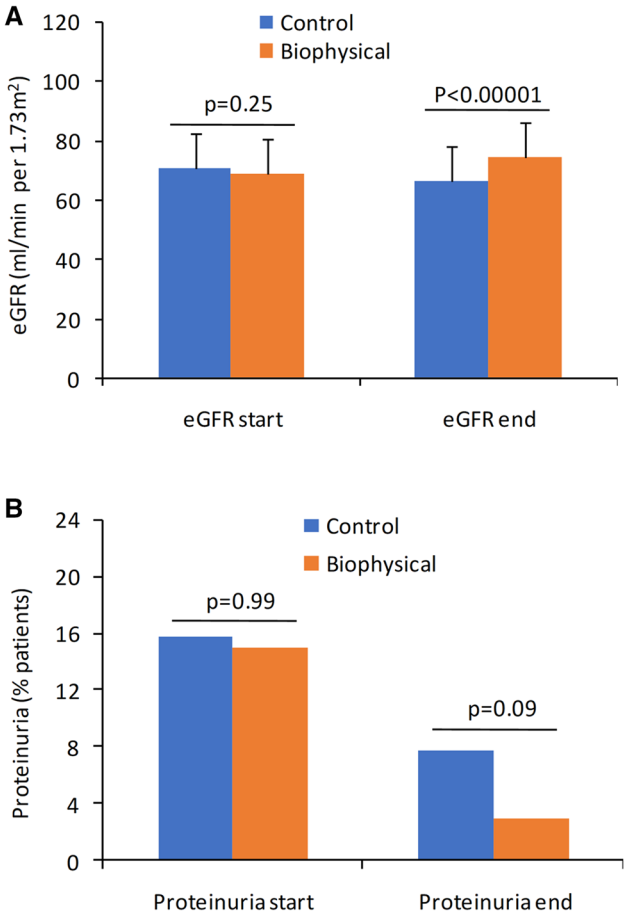

Fig. 1 Measurement of eGFR and proteinuria in elderly CKD patients in control and biophysical groups at start and after 12 months. Data are presented as mean ± SD

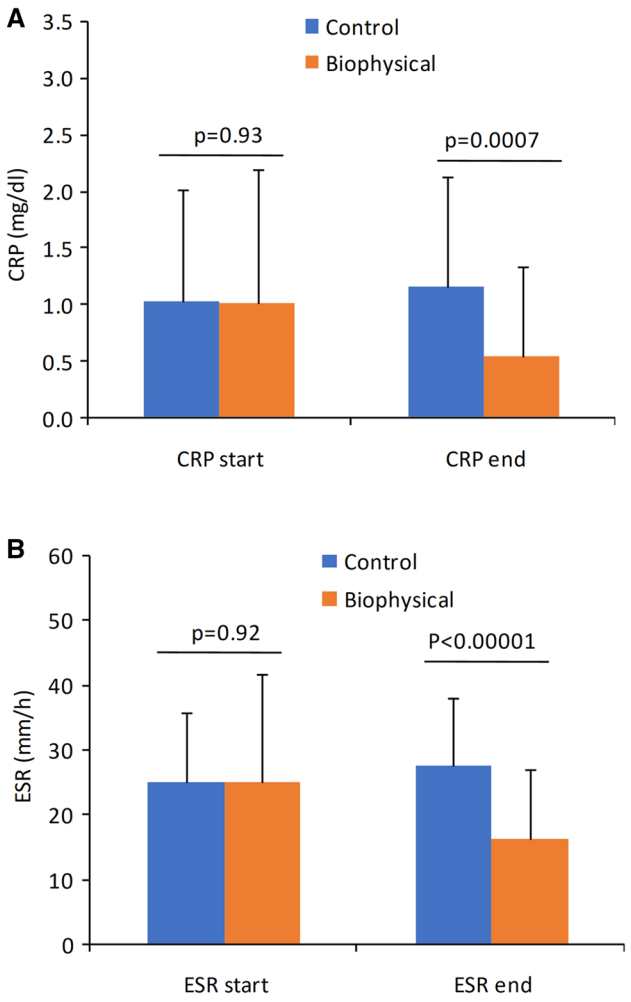

Fig. 2 Measurement of CRP and ESR levels in elderly CKD patients in control and Biophysical groups at start and after 12 months. Data are presented as mean ± SD

any significant differences in CRP or ESR at baseline or follow-up.

Discussion

The benefit observed by biophysical therapy has already been demonstrated in 30 patients with early stage CKD treated for a period of 1 year [6], as well as in an open-label observational study in a group of 58 elderly patients with CKD stage I/II [7]. We have confirmed these results and extended them further including a larger sample size ($N = 150$), using a randomized, double-blind, trial design in patients affected with more severe CKD (stage II/IIIa).

Patients receiving biophysical treatment benefited from an increase in eGFR by 7.8 ml/min/1.73 m^2 compared to the untreated control group after 1 year. Proteinuria was also decreased to a greater extent in the biophysical group after 12 months, but the difference between groups did not attain statistical significance. This improvement was also independent of age, gender, or anti-hypertensive therapy. Moreover, while renal function improved in the biophysical group over the 12 months (net increase in eGFR of 5.1 ml/min/1.73 m^2), it actually worsened by a similar margin (-4.4 ml/min/1.73 m^2) in the control group. This rapid reduction in GFR in the control group may have been linked to the burden of hypertension in these patients (almost all patients were being treated for hypertension). Corroborating this, in a retrospective study in the US by Al-Aly et al. (2010), including 4171 patients who had rheumatoid arthritis and early stage 3 CKD, approximately half of them ($n = 2141$, 51.3%) had moderate CKD (decline of 1–4 ml/min/year) or severe CKD (decline of > 4 ml/min/year) with a mean loss in eGFR of -2.4 ± 0.9 and -7.5 ± 3.9, respectively [24]. In another study undertaken in the US in a cohort of community dwelling older adults ($n = 4380$), Rifkin and colleagues (2008) showed a lower decline in $eGFR_{creat}$ (-0.4 ± 3.6 ml/min/year) and $eGFR_{cys}$ (-1.8 ± 2.6 ml/min/year); however, patients showing rapid decline in eGFR (> 3 mL/min/1.73 m^2/year) were older and more likely to have hypertension, diabetes mellitus, and cardiovascular disease at baseline [25]. Actually, only a small proportion of patients had hypertension in this study (about 10%), in contrast to our study.

In addition to an improvement in renal function, we also observed a significant decrease in the inflammatory measures CRP and ESR in the biophysical group, but not in the control group. Although both CRP and ESR levels did not indicate any overt underlying inflammatory burden (both measures were in the normal range), a 50% reduction in levels of both these measures was observed after 12 months in the biophysical group only. The previous studies have observed an association between CRP, ESR, and GFR [26, 27]. We have also previously observed a significant improvement in knee osteoarthritis following biophysical treatment, although inflammatory measures were not assessed in that study [10].

Our findings have important clinical relevance. Since a reduction in eGFR rate correlates with all-cause mortality and the incidence of cardiovascular disease, it significantly impacts upon public health [28]. Therefore, any rapid, non-invasive therapeutic approach that can result in an increase in eGFR should be considered as an integrative and useful tool for the management of public health and as an aid to successful aging.

The precise mechanism by which biophysical treatment exerts these observed renoprotective effects is not yet understood. The observed reduction in CRP and ESR point towards additional anti-inflammatory effects beyond improvement in renal function. Whether changes in these measures may be associated with kidney function in the long term remain to established.

Biophysical therapies very likely exert their effect through a resonance phenomenon [16]. Resonance occurs between therapeutically delivered signals, endogenous or exogenous, and target tissues, organs and/or entire organism, which allows the achievement of local and/or systemic effects simultaneously [19]. We have previously discussed these theoretical underlying mechanisms in detail [16, 23].

To date, however, there are no mechanistic studies documenting the effect of low-frequency electromagnetic waves in patients with kidney disease. However, the effect of extremely low-frequency pulsed magnetic fields (ELFPMF) has recently been examined in a model of diabetic nephropathy, in streptozotocin-treated rats [29]. In this study, the down-regulation of vascular endothelial growth factor A (VEGF-A) and up-regulation of connective tissue growth factor (CTGF) induced by 6-week ELFPMF exposure in the renal cortex indicate that ELFPMF may aggravate the symptoms of diabetic nephropathy. However, 6-week exposure to ELFPMF stimulation partially prevented the development of glomeruli degeneration in streptozotocin-treated rats with diabetic nephropathy following histology and electron microscopy examination. Both positive and negative effects of ELFPMF on the development of diabetic nephropathy in diabetic rats were observed. The positive effect observed by ELFPMF may have an important role in the development of diabetic nephropathy in diabetic rats, and this effect may be derived from the correction of pathogenic diabetes-induced mediators [29]. Indeed, the immune-modulating effects of low-frequency electromagnetic fields are recognized [30]. Future studies are needed to characterise the mechanisms through which the biophysical effect derived from low electromagnetic waves exerts these protective effects (e.g., anti-proteinuric effects).

This study shows a potential contribution of a biophysical integrated strategy [31] to support renal function against its natural decline in the elderly. It is well known that CKD itself has to be considered as a biomarker of premature aging [32], as well as a model of premature aging [33]. Aging of population raises the relevance of age related functional impairment as well as the increasing number of comorbidities or side effects due to multiple medications [34] requiring personalized treatments. The complex dynamics of aging aimed to preserve stability through dynamic changes [35] frequently leads to frailty [36] and claim to be supported to delay functional impairment of important homeostatic regulators such as renal function. It would be useful to assess the possible contribution of this biophysical integrated strategy on renal function impairment due to diabetes or polycystic kidney disease.

Study limitations

This study has several limitations that need be addressed. Although the follow-up period of 1 year was sufficient time to detect a significant change in eGFR compared to untreated controls, it would be worthwhile to see whether this rate of improvement can be maintained over 2 and 3 years. We chose to use eGFR to measure change in renal function; however, other renal disease measures (e.g., proteinuria) could be useful in future studies to confirm the present findings and explore potential mechanisms of action. Measurement of GFR is recognized worldwide as the most accurate way of assessing kidney function [37]. In this study, we estimated GFR using the formula from the chronic kidney disease–epidemiology collaboration (CKD–EPI) study [21]. A next step could be the measurement of GFR with (99 m) Tc-diethylene triamine pentaacetic acid [(99 m)Tc-DTPA] [38].

Diabetes was an exclusion criterion for this study and almost all patients were receiving antihypertensive medication. It would be interesting and important to explore the potential benefit from biophysical therapy in patients with CKD and diabetes as well as patients with and without hypertension. Patients included in the present study who presented with early stage CKD (stages II and IIIa) in the older population. Our study would have benefited from a larger sample size to explore whether younger patients with more and less severe CKD can also benefit from biophysical treatment. We have to also consider that the observed results may have occurred by chance, i.e., a false positive. However, our previous observations in other settings do strengthen our confidence that these results did not occur by chance [5, 7, 9, 11, 13, 15]. To address these limitations, we are currently undertaking and finalizing a larger controlled trial including approximately 700 patients that are not limited to the elderly population, as well as a sub-group of 150 patients with follow-up of 5 years. Additional studies will also help explore potential underlying mechanisms to explain these observed benefits.

Conclusion

In summary, in CKD patients, biophysical treatment afforded a statistically significant and clinically relevant increase in eGFR compared to age- and gender-matched control population. This improvement in renal function was independent of age, gender, or use of RAAS inhibitors. Despite the relatively short follow-up period (1 year), it was still a sufficient amount of time to detect a clinically significant improvement in renal function compared to untreated controls. Besides the improvement in eGFR, we also observed a significant reduction in CRP and GFR in a sub-group of patients. These preliminary results warrant further larger and longer clinical evaluation to extend the use of this integrative strategy for successful aging and in preventive medicine for general population, since early stages of CKD is increasing in prevalence in the general population [39].

Further studies in larger and more patient populations including those with later stages of CKD are warranted. Whether this integrative therapeutic approach can have an impact on overall survival still remains to be determined.

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Compliance with ethical standards

Conflict of interest None declared.

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