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Effect of Erythropoietin-stimulating agent on uremic neuropathy in hemodialysis patients: a single-center open-label prospective study

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Abstract

Background: Uremic neuropathy is a distal sensorimotor polyneuropathy caused by uremic toxins; its severity is correlated with the degree of renal insufficiency. Erythropoietin (EPO) and erythropoietin receptors (EpoR) are produced in the peripheral nervous system. This is a single-center open-label prospective study was designed to investigate the possible effect of erythropoietin-stimulating agents (ESAs) on uremic neuropathy. Twenty-four newly diagnosed end-stage kidney disease (ESKD) patients were selected, clinical assessment, laboratory, and neurophysiological study were done at 1 and follow-up after 3 months. Patients were divided into two groups (group A received ESA and group B did not receive ESA).

Results: Eighteen patients completed the study, eight patients (44.4%) did not have symptoms but had electrophysiological findings of neuropathy (subclinical neuropathy). After 3 months of hemodialysis, patients in group A showed improvement of some electrophysiological features (ulnar MNCV; $P = 0.016$).

Conclusions: The use of ESA may improve uremic neuropathy in patients with newly diagnosed ESKD who have been started on hemodialysis.

Keywords: Uremic neuropathy, Erythropoietin stimulating agents, ESKD

Background

Uremic neuropathy is a common complication of chronic kidney disease (CKD) [1]. Uremia may result in multiple organ damage with renal failure progression due to numerous uremic toxins. The significant neurotoxins accumulating in uremia are urea, creatinine, uric acid, and middle molecules and others [2]. Uremic neuropathy has an insidious onset, progressive course, and it has been estimated to be present in 60%-100% of ESKD patients on dialysis [3]. In general, neuropathy develops at glomerular filtration rates of less than 12 ml/min [3], and its severity is usually proportionate to the degree of renal insufficiency [4]. Progressive neuropathy is one of the indications for renal replacement therapy initiation and an essential indicator of insufficient dialysis [5]**.** Uremic neuropathy usually presents as a distal symmetrical sensorimotor affection of the lower-limb more than the upper-limb involving the large fibers [3]. Patients may also develop autonomic features, with postural hypotension, impaired sweating, diarrhea, constipation, or impotence. Nerve conduction studies demonstrate findings consistent with a generalized neuropathy of the axonal type [3]. Available therapies for uremic neuropathy, including dialysis and vitamin supplementation, are not satisfactory [2]. However, some observational studies showed a reduction in neuropathy prevalence with either an increase in frequency or dose of dialysis [6].

Anemia is a frequent complication of CKD, particularly among patients with diabetes. It is defined as a hemoglobin concentration below 13.0 g/dL for adult males and postmenopausal women, and hemoglobin

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[7] below 12.0 g/dL for pre-menopausal women [8]. EPO is a glycoprotein produced only from interstitial fibroblasts in the kidney [9]; it induces hematopoiesis by binding to EpoR [10], so a decrease in kidney mass in progressive CKD often results in impairment of EPO production, which leads to anemia [11]. ESA is the drug of choice to treat anemia in patients with CKD [12, 13]. In recent years, EPO and its receptor (EpoR) have been found in other tissues not involved in hematopoiesis as the brain, the reproductive tract [14–16], the lung, the spleen, and the heart [17]. Thus, EPO may be only an erythropoietic hormone and play a protective role in many organs. Interestingly, significant improvement of non-hemorrhagic stroke patients' outcome was noticed after receiving recombinant human EPO (rhEPO) intravenously within 8 h of the onset of symptoms [18]. Moreover, Epo and EpoR were found to be locally produced in cells of the peripheral nervous system, Epo is up-regulated in the sciatic nerve, particularly in Schwann cells after painful chronic construction injury [19]. This study was designed to investigate whether ESA therapy will improve uremic neuropathy using electrophysiological studies in newly diagnosed ESKD patients.

Methods

Patients

In this prospective observational single-center study, 24 newly diagnosed ESKD patients, who recently started thrice-weekly in-center hemodialysis, were selected from the internal medicine inpatient department and the hemodialysis unit. All patients showed the criteria of ESKD and had been recruited at the first session of hemodialysis. We excluded patients with other causes of peripheral neuropathy other than uremic and diabetic neuropathy as radiotherapy, vasculitis, or drug induced. Their estimated glomerular filtration rate (GFR) was assessed according to modified diet renal disease (MDRD) formula. Of these patients, six patients were excluded, one died, and five were non-compliant. The patients were evaluated regarding serum creatinine, urea and hemoglobin levels. At the beginning of the research, all the 24 enrolled patients completed a questionnaire assessing neuropathy symptoms, and they underwent nerve conduction studies (NCS) upon initiation of hemodialysis. One patient died, 5 were non-compliant to follow-up and, 10 of the 18 patients were receiving subcutaneous ESA three times weekly, and eight patients did not receive ESA (the decision for taking ESA or not was determined by the dialysis center). Both groups were followed after 3 months hemodialysis; then, the above-mentioned questionnaire was again completed by the patients, and NCS were performed.

Clinical assessment

All cases were subjected to a detailed neurological assessment by a specialized neurologist looking for symptoms and signs of peripheral neuropathy. Diabetic Neuropathy Symptom Score (DNS) [20] is a four-item validated symptom score, with a high predictive value to screen for peripheral neuropathy in diabetes. Symptoms of unsteadiness in walking, neuropathic pain, paresthesia, and numbness are elicited—maximum score: 4 points; 0 points, polyneuropathy absent; 1–4 points, polyneuropathy present.

Overall Neuropathy Limitation Scale (ONLS) [21] was used to detect the affection of limb function. ONLS = arm disability score (range 0–5) + leg disability scale (range 0–7). Overall range: 0 (no signs of disability) to 12 (maximum disability). Both ONLS and DNS were done upon initiation and after 3 months of hemodialysis.

Nerve conduction studies

Neurophysiological assessment was performed by a clinical Neurophysiologist using Neuropack Manager (EP/EMG measuring system six-channel, version 08–14; manufacturer: Nihon Kohden, Tokyo, Japan, copyright 1997–2008). Standard stimulation using two surface electrodes was used for NCS, and skin temperature was kept between 32 and 34 °C during the examination. The applied techniques in NCS were orthodromic for sensory and motor nerves. Electrophysiological studies were carried out in right median, ulnar (motor nerve conduction velocity (MNCV) in m/s, the amplitude of compound motor action potential (CMAP) in mv, distal motor latency (DML) in milliseconds (ms), F-wave in ms, sensory NCV (SNCV) in m/s, distal latency in ms and amplitude of sensory action potential (SNAP) in mv) and radial nerves (SNCV, SNAP amplitude, and distal latency). Right deep peroneal and posterior tibial nerves were tested for recording MNCV, DML, the amplitude of CMAP, and the right sural nerve was done for SNCV, amplitude, and latency of SNAP. The neurophysiological assessment was done upon initiation and after 3 months of hemodialysis.

Ethical consideration

The study was approved by the Ethical Research Board of the School of Medicine, Egypt. Written consent was taken from all the participants or their relatives after being informed about the study's objectives, the examination, and the investigations. The confidentiality of their

information and their right not to participate in the study were considered. The study was conducted following the principles of the Declaration of Helsinki.

Statistical analysis

Data analysis was done with Statistical Package for Social Sciences Released in 2013. IBM SPSS Statistics for Windows, Version 18.0. Armonk, NY: IBM Corp. A descriptive statistical procedure was carried out to obtain mean and standard deviation for clinical, neurophysiological variables, and blood tests. All patients and patient subgroups' results were compared before and 3 months after hemodialysis using a *T*-test (paired sample *T*-test) and a significant level (two-tailed significance).

Results

Eighteen newly diagnosed ESKD patients completed the study, 10 were males (55.6%), and 8 were females (44.4%); their mean age was 42.5 ± 16.1 years old. Six patients were diabetic (33.3%) and 12 were non-diabetic (66.7%). Patients with diabetes were older than non-diabetic patients; (53.67 ± 12.66) (36.92 ± 15.02), respectively. The mean duration of diabetes (± SD) was 12.5 (± 6.22) years.

Ten patients (55.6%) received subcutaneous ESA thrice weekly, and eight patients (44.4%) did not receive ESA. Out of the total number of patients ($n = 18$), ten patients (55.6%) had clinical neuropathy (symptoms and signs), four were diabetic (22.2%), and six were non-diabetic (33.3%). Six patients (33.3%) had mixed (sensory and motor) neuropathy; as assessed by DNS and ONLS, 3 patients (16.7%) had pure sensory neuropathy by DNS while only one patient (5.6%) had pure motor neuropathy by ONLS (Fig. 1). All the patients in groups A and B had electrophysiological findings of neuropathy upon initiation of hemodialysis. The results were compared for patients who received ESA therapy (group A) and those who did not (group B).

Remarkably, eight patients (44.4%) (4 in group A, 4 in group B) did not have symptoms, but had electrophysiological findings of neuropathy (subclinical neuropathy). After 3 months of hemodialysis with ESA, patients in group A (n = 10) showed improvement of electrophysiological features in nearly all patients. This was also concurrent with clinical improvement in 4 of them. Also, there was significant improvement in Hb levels of the same group but did not reach normal values (Table 1).

The electrophysiological improvement was statistically significant in ulnar (MNCV; $P = 0.016$) and approaching significance with regard to the amplitude of ulnar CMAP ($P = 0.067$) in group A who received ESA in comparison to group B who did not receive ESA (Table1). Moreover, this improvement was significant in non-diabetic ESKD patients who received ESA (ulnar MNCV; *P = 0.050, and ulnar CMAP amplitude; P = 0.050)* (Table 2).

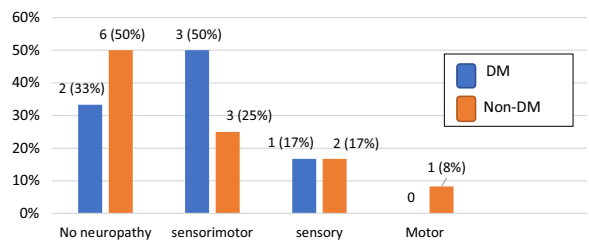

Fig. 1 Comparison of the clinical neuropathy pattern between diabetic and non-diabetic patients. *DM* diabetic patients, *Non-DM* non-diabetic patients

Discussion

Uremic neuropathy is a common under-investigated complication in patients with ESKD on dialysis. Uremic neuropathy occurs in 60–100% of dialysis patients [3]; it has a lower prevalence in non-dialysis CKD (ND-CKD) patients, which was reported to be 64% in one study [22]. Patients are mostly diagnosed late after being symptomatic in advanced axonal neuropathy, which is generally an irreversible nerve damage stage [22].

Aggarwal and his colleagues found that the prevalence of neuropathy increased with severity of renal dysfunction; among patients with ND-CKD [22].

Regarding nerve affection distribution, nerves of lower limbs are usually involved before upper-limb nerves [23]. It was proved that the dorsal sural nerve was the most affected nerve in different kinds of peripheral neuropathy [24]. Consequently, it is essential to detect early neuropathic changes by electrophysiological study and timely start proper treatment to retard nerve damage progression and prevent subsequent functional disability [25].

In this study, 55.6% of the patients had clinical neuropathy, which is consistent with Hassan and his colleagues, who found that two-thirds of CKD patients suffer from uremic neuropathy at the beginning of dialysis [26]. Remarkably, 44.4% of our patients did not have clinical manifestations of neuropathy, but they were found to have diagnostic electrophysiological findings of neuropathy (subclinical asymptomatic neuropathy). Therefore, early screening for neuropathy is crucial in ND-CKD patients regardless of the presence or absence of clinical features [23].

In our study, lower-limb nerves (common peroneal, posterior tibial; MNCV and CMAP amplitude and sural nerves) were severely affected than the upper-limb nerves, and these results are well-matched with the clinical manifestations of uremic neuropathy, which typically

Table 1 The effect of ESA on some of the neurophysiological findings and Hb levels in comparison to those of patients who did not receive ESA

Nerve ($n=10$)	0_A	3_A	p	Nerve ($n=8$)	0_B	3_B	p
Median ($n=10$)				Median ($n=8$)			
MNCV	49.51 ± 5.77	47.3 ± 5.6	0.094	MNCV	47.89 ± 7.53	47.05 ± 6.87	0.300
CMAP	5.97 ± 2.34	5.36 ± 2.15	0.469	CMAP	7.34 ± 4.72	6.28 ± 3.64	0.392
Ulnar ($n=10$)				Ulnar ($n=8$)			
MNCV	44.87 ± 6.7	50.02 ± 5.55	**0.016**	MNCV	49.04 ± 4.95	48.01 ± 6.43	0.431
CMAP	5.97 ± 2.08	7.38 ± 2.08	0.067	CMAP	5.54 ± 1.86	5.8 ± 1.54	0.705
Peroneal ($n=8$)*				Peroneal ($n=7$)*			
MNCV	40.91 ± 5.57	38.95 ± 4.96	0.188	MNCV	40.26 ± 7.89	39.16 ± 8.61	0.358
CMAP	2.38 ± 1.65	3.64 ± 2.8	0.134	CMAP	4.09 ± 2.49	3.28 ± 2.63	0.203
Tibial ($n=7$)*				Tibial ($n=7$)*			
MNCV	41.31 ± 2.31	43.37 ± 4.64	0.126	MNCV	41.14 ± 8.92	37.96 ± 6.67	0.202
CMAP	3.97 ± 1.49	7.01 ± 5.28	0.262	CMAP	3.87 ± 1.49	3.70 ± 1.97	0.733
Median ($n=7$)*				Median ($n=7$)*			
SNCV	46.51 ± 5.8	48.57 ± 5.5	0.263	SNCV	47.27 ± 9.23	45.97 ± 7.8	0.440
Ulnar ($n=7$)*				Ulnar ($n=6$)*			
SNCV	45.3 ± 6.44	46.5 ± 12.6	0.740	SNCV	46.88 ± 12.0	46.52 ± 12.4	0.935
Radial ($n=7$)*				Radial ($n=6$)*			
SNCV	48.2 ± 7.53	54.06 ± 4.6	**0.009**	SNCV		49.62 ± 10.36	0.527
Sural ($n=5$)*				Sural ($n=4$)*			
SNCV	37.92 ± 6.7	24.56 ± 22.44	0.352	SNCV	45.73 ± 5.44	46.53 ± 3.69	0.763
Hb (g/dl)	7.92 ± 1.08	9.36 ± 0.8	**0.000**		8.33 ± 1.74	8.91 ± 1.09	0.139

0_A baseline finding in patients received ESA, 3_A finding after 3 months hemodialysis with ESA supplement, 0_B baseline finding in patients who did not receive ESA, 3_B finding after 3 months dialysis without ESA, *MNCV* motor nerve conduction velocity in m/s, *CMAP* compound motor action potential amplitude in mv, *SNCV* sensory nerve conduction velocity in m/s. *These drops in records are attributed to technical difficulties (ulcers, edema or AV fistula) in the tested side at one or the 2 sessions. Ulnar MNCV, Radial SNCV and Hb level showed statistically significant improvement in group A

Table 2 Effect of ESA therapy on some of neurophysiological findings in non-diabetic patients in comparison to those of diabetic patients

Nerve ($n=6$)	0_c	3_c	p	Nerve ($n=4$)	0_D	3_D	P
Median ($n=6$)				Median ($n=4$)			
MNCV	53.08 ± 3.51	50.48 ± 4.88	0.099	MNCV	42.15 ± 1.93	42.52 ± 3.93	0.559
CMAP	6.98 ± 2.55	5.27 ± 2.56	0.170	CMAP	4.45 ± 0.68	5.5 ± 1.69	0.228
Ulnar ($n=6$)				Ulnar ($n=4$)			
MNCV	47.25 ± 4.02	53.35 ± 3.57	**0.050**	MNCV	41.3 ± 9.13	43.03 ± 3.97	0.267
CMAP	5.38 ± 2.32	7.77 ± 2.14	**0.050**	CMAP	6.85 ± 1.49	6.8 ± 1.99	0.881
Median ($n=5$)*				Median ($n=2$)*			
SNCV	48.92 ± 5.12	51.54 ± 2.63	0.325	SNCV	40.5 ± 1.41	41.1 ± 1.27	0.105
Ulnar ($n=5$)*				Ulnar ($n=2$)*			
SNCV	45.54 ± 2.99	49.52 ± 7.72	0.351	SNCV	40.7 ± 14.57	38.95 ± 23.6	0.523
Radial ($n=5$)*				Radial ($n=2$)*			
SNCV	47.98 ± 4.63	53.5 ± 3.67	**0.018**	SNCV	45.75 ± 15.9	45.45 ± 8.41	0.426

0 baseline finding in non-diabetic patients, 3 finding 3 months after dialysis and treatment with ESA in non-diabetic patients, *MNCV* motor nerve conduction velocity in m/s, *CMAP* compound motor action potential amplitude in mv, *SNCV* sensory nerve conduction velocity in m/s. *These drops in records are attributed to technical difficulties (ulcers, edema or AV fistula) in the tested side at one or the 2 sessions. Ulnar MNCV, CMAP and Radial SNCV showed statistically significant improvement in group C

involve the lower limbs more than the upper limbs [27]. Also, Krishnan and Kiernan have described a change in sural sensory potential as the most sensitive nerve conduction abnormality in patients with CKD [28]. Additionally, the decrease in CMAP amplitude suggests that the demyelinating process is associated with axonal degeneration [23]. Also, the sural nerve was undetectable in diabetic CKD patients, and this could be explained by the effect of diabetes [29, 30], taking into consideration that all the enrolled patients in our study have a long-standing type 2 diabetes mellitus (12.5 (±6.22) years).

Regarding motor affection in the upper-limb nerves, the ulnar nerve MNCV was affected while the median nerve was in the normal range; this contrasts with what Hassan and his colleagues found in anemic pre-dialysis patients, the ulnar nerve was normal at the beginning of their study while median, peroneal and tibial nerves were affected [26]. Another study reported that the facial nerve was more sensitive to uremic neuropathy than median and peroneal nerves while the ulnar nerve was the least involved in patients with end-stage renal disease of varying severity and duration (the frequency was 82, 68, 36 and 22%, respectively) [31].

Uremic toxins are believed to participate in the pathogenesis of uremic neuropathy; subsequently, both peritoneal and hemodialysis have proven partial reduction of uremic neuropathy progression [23]. Early studies noticed a decrease in neuropathy occurrence with either increased frequency or dose of dialysis [6]. Ghazan and his colleagues found that intensive home hemodialysis (5–6 nights/week) clears more uremic toxins than other conventional renal replacement therapy improving neurological symptoms [23]. Similarly, another study found that daily hemodialysis enhanced improvement of neuromuscular function in ESKD patients more than conventional thrice-weekly hemodialysis [32]. This improvement may be due to frequent daily elimination of the smaller sized molecules (urea and creatinine) and converting more toxic substances to the less harmful smaller molecules [32]. Likewise, conventional thrice-weekly hemodialysis usually results in fluctuations in body fluid volume and solutes, which is different from normal body hemostasis. Increasing dialysis frequency may simulate the normal renal physiology in the healthy population lower fluctuations of solute concentrations and body fluid volume [33].

In our study, we had made our best to ensure that all the patients received the same dialysis dose. All patients underwent conventional thrice-weekly hemodialysis with almost similar dialysis doses regarding the length of treatment, frequency of dialysis, and hemodialyzer that diminishes the possibility of neurophysiological improvement because of hemodialysis only.

Upon initiation of the study, we noticed low MNCV of ulnar, common peroneal, and posterior tibial nerves. After 3-month hemodialysis (thrice weekly) with ESA therapy, both ulnar and posterior tibial nerves showed improvement that was statistically significant in the ulnar nerve (MNCV $P=0.016$ and CMAP $P=0.067$). Also, NCS of the radial nerve's sensory branch was within the normal range upon initiation of the study and showed statistically significant improvement after 3-month hemodialysis with ESA therapy (SNCV $P=0.009$). On the other hand, patients in group B (who did not receive ESA) had no improvement in almost all electrophysiological studies.

These results concur with Hassan and his colleagues, who found significant improvement of MNCV of the median, peroneal, and tibial nerves ($p=0.04$, $p=0.03$, $p=0.04$, respectively) after 5 months of ESA therapy [26]. Also, Sobh and his colleagues described a significant increase in MNCV in six patients who underwent chronic hemodialysis with 3 months of ESA therapy [34].

Diabetic patients are predisposed to diabetic neuropathy and vasculopathy; their peripheral nervous system becomes more affected, especially the sensory part, in the uremic patients [26]. This may explain the marked affection of CKD diabetic patients that was observed upon initiation of the study in comparison to non-diabetic CKD patients. After 3-month hemodialysis with ESA therapy, we recorded a significant improvement of ulnar and posterior tibial nerves (MNCV and CMAP amplitude) in non-diabetic CKD patients. On the other hand, diabetic CKD patients did not show improvement in almost all nerves after hemodialysis with ESA therapy.

We suggest that the absence of diabetic patients' improvement may be explained by the additional harmful effect of uncontrolled diabetes on peripheral nerves. Furthermore, the findings of improvement in motor more than sensory parameters after 3 months of treatment of ESA may be attributed to the early and augmented affection of sensory nerves by both diabetic and uremic neuropathies [26]. These findings coincide with Hosseini-Zare MS and his colleagues, who found that although ESA therapy had corrected the anemia in mild-to-moderate CKD patients with diabetic neuropathy, neurophysiological parameters did not improve after 6 months of ESA therapy [35].

The improvement in nerve conduction velocity could be related to ESA's direct action through EPO receptors on human neuronal cells [19]. Campana and colleagues revealed the presence of EPO receptors in Schwann cells and axons in the peripheral nervous system of animal models [19]. Similarly, Keswani and his colleagues found that acrylamide-treated rats (a neurotoxic substance causes severe motor and sensory axonal degeneration)

were given ESA showed significantly less sensory and motor axonal degeneration compared to those were given a placebo [36], suggesting that ESA prevents axonal degeneration.

Conclusions

It is essential to detect early uremic neuropathic changes by electrophysiological study and timely start proper treatment to retard nerve damage progression and prevent subsequent functional disability. Uremic toxins are believed to participate in the pathogenesis of uremic neuropathy, subsequently increasing the frequency or dose of dialysis associated with a reduction in neuropathy.

Three-month therapy with ESA may improve sensorimotor polyneuropathy in ESKD patients on hemodialysis. This effect seems to be more prominent in upper limbs and in non-diabetic patients compared to diabetic patients. This non-hematopoietic effect of ESA may be related to its direct action on EPO receptors in human neuronal cells, Schwan cells, and nerve axons promoting axonal regeneration and remyelination. Thus, early detection of uremic neuropathy in ESKD patients by neurophysiological study allows prompt management and prevents progression. Further studies are required for a longer duration on a larger number of patients to emphasize ESA's effect on uremic neuropathy.

Some potential limitations of this study should be acknowledged: follow-up duration was short, small sample size and single center-based experience, so further multicenter studies are required for a longer duration on a larger number of patients to emphasize ESA's effect on uremic neuropathy.

Abbreviations

EPO: Erythropoietin; EpoR: Erythropoietin receptors; ESA: Erythrocyte stimulating agent; ESKD: End-stage kidney disease; CKD: Chronic kidney disease; rhEPO: Recombinant human EPO; GFR: Glomerular filtration rate; MDRD: Modified diet renal disease; NCS: Nerve conduction study; DNS: Diabetic Neuropathy Symptom Score; ONLS: Overall Neuropathy Limitation Scale; MNCV: Motor nerve conduction velocity; CMAP: Compound motor action potential amplitude; DML: Distal motor latency; SNCV: Sensory nerve conduction velocity; SNAP: Sensory nerve action potential amplitude; Hb: Hemoglobin; DM: Diabetic patients; ND-CKD: Non-dialysis chronic kidney disease.

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Author contributions

NA recruited the cases and collected all the needed data. Prof. AK, MY and AH revised the clinical data obtained and the results. Finally, NA and WH wrote the manuscript which was revised by the other authors to be ready for publication. NA is the corresponding author who is responsible for the publication. All authors read and approved the final manuscript.

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Availability of data and materials

Data can be available for publication only by special approval from the Minia University.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Research Board of Minia School of Medicine, Egypt. The ethics approval date was September 24th, 2012, the reference number is not available. Written consent was taken from all the participants or their relatives after being informed about the study's objectives, the examination, and the investigations. The confidentiality of their information and their right not to participate in the study were considered. The study was conducted following the principles of the Declaration of Helsinki.

Consent for publication

A consent for publication was obtained from all the participants included in the study.

Competing interests

None of the authors have any competing interests (financial or non-financial).

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