Journal of Nephrology (2021) 34:23–25
https://doi.org/10.1007/s40620-020-00744-x

EDITORIAL

Setting the clock back: new hope for dialysis patients. Sodium thiosulphate and the regression of vascular calcifications

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Published online: 16 May 2020

Keywords Vascular calcifications · Hemodialysis · Sodium thiosulphate · Dialysis vintage

The current year 2020 will remain in our memory as the one marked by the ravaging COVID-19 pandemic and a worldwide lockdown—the time when our routine activities were turned upside down.

Yet, things happen, our patients are still there, studies continue to be published.

One of them deserves particular attention, as it brings new hope for dialysis patients.

The study, entitled "Sodium thiosulphate and progression of vascular calcification in end-stage renal disease patients: a double-blind, randomized, placebo-controlled study" was published in the first 2020 issue of Nephrology Dialysis Transplantation, and selected as "editor's choice" for this issue [1].

In itself, the study is "just" a small randomised controlled trial, performed as an exploratory study, and for which power calculations were not even done; sixty patients were randomised to receive either 25 g/1.73 m^2 of sodium thiosulphate, or 100 mL of 0.9% sodium chloride, in the last fifteen minutes of dialysis. The trial lasted 6 months. Its main end-point, reduction of aortic calcifications, was not met. However, the patients receiving sodium thiosulphate displayed a significant reduction in their iliac artery calcifications, according to a validated score, while calcifications increased, in the meantime, in the patients on placebo. The favourable effect was not limited to the iliac arteries, since in treated patients arterial stiffness and carotid intima–media thickness tended to decrease and there was no increase in cardiac valvular calcifications. The latter parameters displayed a significant difference between treated and untreated patients. The data, as the authors state, are widely scattered, and statistical significance is "just met", if statisticians allow a layman's definition, for the main result of decrease in iliac calcifications (-137 ± 641 versus 245 ± 755; $P = 0.049$). It is therefore quite far from being a perfect trial. However, it is an important study, not because of its superb design, or its outstanding statistics, but because it introduces an important idea, and for the hope it brings.

In fact, the study follows scattered previous evidence suggesting that sodium thiosulphate, the basic treatment for calciphylaxis may be effective not only in halting progression, but also in reversing vascular calcifications [2, 3].

No other treatment has so-far been able to perform this miracle: early hope with kidney transplantation was not confirmed in the long term, and although parathiroidectomy, new phosphate binders and calcimimetics were all able to retard the progression of vascular calcifications, none was able to set back the biological clock.

Dialysis patients get old too soon. We are pained, often overcome with a sense of impotence. each time we see a scan of one of our veterans, The patient whose recent CT scan is reported in Fig. 1 is almost paradigmatic of this frustrating situation: he is relatively young, i.e. in his mid-sixties, has a good nutritional status, on target for calcium, phosphate and PTH balance (his PTH has remained below 300 ng/mL, in keeping with strict Japanese indications).

He has a nearly 30-year history of renal replacement therapy and a failed kidney graft; he is hyperimmunized and failed to respond to previous attempts of desensitization. In spite of being on on-line high-flow hemodiafiltration with a Daugirdas 2 Kt/V of over 1.4, he suffers from disabling dialysis-related amyloidosis. He knows that should his vascular

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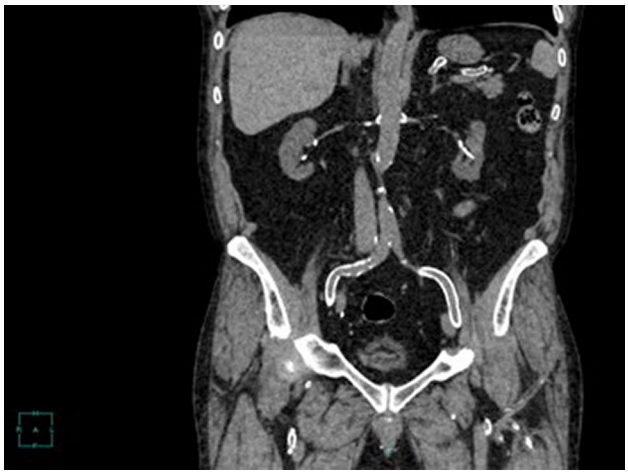

Fig. 1 Extensive vascular calcifications in a patient with a long dialysis vintage

disease progress further, he will not be grafted again. In our in-hospital dialysis ward in central France, where the median age is approximately seventy-four, and a high percentage of patients suffer from diabetes and/or obesity (median Charlson Index of 9), over 15% of the patients have experienced a minor or major distal amputation. In the last 4 years, ten patients experienced one episode of calciphylaxis and were treated with sodium thiosulphate. As in the study being discussed here, no severe side effects were found, provided dialysate sodium had been adjusted to avoid overload.

In addition to the two studies cited in the paper, in which, respectively, eighty-six patients were treated for 4 months and twenty-two patients for 5 months, both reporting positive results without relevant side effects, we were able to retrieve three further studies that, albeit with different deigns, reported, once more in the absence of relevant side effects, a positive effect on arterial stiffness (in twenty-four patients randomised for receiving treatment for 5 months [4]), leg pain related with vascular calcifications (18 heavily calcified patients, treated for 6 months [5]), and coronary artery calcifications (17 patients treated for 3 months [6]). In one further study, in which sodium thiosulphate was added to the dialysis fluid, a "positive impression" was reported in six cases [7]. Significantly, the data are in keeping with the few, albeit convincing, animal and in vitro studies published.

Why were these promising studies not followed up? Sodium thiosulphate is not expensive, at least in Europe; it is readily available, provided that the pharmacy cooperates in its preparation, and can be safely handled, provided that attention is paid to the management of the dialysis session. In patients with calciphylaxis, in our center we perfuse a standard dose of 25 g in the last thirty minutes of dialysis, modulating sodium and bicarbonate concentration in the dialysate. While this simple manoeuvre is not time consuming, attention is needed, and this may be perceived as "complicated" in an overcrowded dialysis ward.

As usual, in this era of evidence-based medicine, the question that arises is whether we should wait for a "perfect", large-scale randomised controlled trial, or for irrefutable evidence on the promising new alternatives [8], or, in the absence of alternatives, and, more importantly, in the absence of severe side effects of a drug we routinely use with slightly different indications [9],we should wisely select those of our patients who would, to the best of our clinical knowledge, benefit more from halting or regressing vascular calcifications?

There is no "right answer" to this question; however, to cite a pivotal paper that appeared in 2002 in The BMJ, "Evidence does not make decisions, people do". We wholeheartedly agree.

Funding No external funding was obtained for this editorial; the Centre Hospitalier Le Mans supported language review.

Compliance with ethical standards

Conflict of interest None of the authors reports any conflict of interest for this editorial paper.

Ethical approval No ethical approval is needed for this editorial paper. The patient cited in Fig. 1 supported written consent for publication of his anonymous data and images.

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