

# Omega-3 intake in people with epilepsy under regular hemodialysis program: here to stay

Suplementação de ômega 3 em pessoas com epilepsia submetidas a um programa regular de hemodiálise: veio para ficar

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## ABSTRACT

Among the many risk factors suggested for sudden unexpected death in epilepsy (SUDEP), higher frequency of seizures is a very consistent issue. Furthermore, it has been established that hemodialysis-associated seizure is a complication of the dialysis procedure. Thus, since a possible relation between cardiovascular abnormalities and SUDEP among patients with chronic renal insufficiency in regular hemodialysis program should not be neglected, we propose in this paper that omega-3 fatty acids offer opportunities for prevention of sudden cardiac death or improved treatment in people with epilepsy under the regular hemodialysis program.

**Key words:** epilepsy, death, sudden, omega 3, hemodialysis.

## RESUMO

Dentre os fatores de risco sugeridos para a morte súbita inesperada em epilepsia (SUDEP), maior frequência de crises epiléticas é uma questão muito consistente. Além disso, tem sido estabelecido que as crises epiléticas associadas à hemodiálise são uma complicação do procedimento dialítico. Desse modo, como a existência de uma possível associação entre as alterações cardiovasculares e a SUDEP entre indivíduos com insuficiência renal crônica em tratamento dialítico não deve ser negligenciada, foi proposto neste artigo que o ômega 3 pode atuar na prevenção da morte súbita cardíaca ou melhorar o tratamento de pessoas com epilepsia inseridas em um programa regular de hemodiálise.

**Palavras-Chave:** epilepsia, morte súbita, ômega-3, hemodiálise.

The development of new treatments and effective strategies to prevent or reverse chronic human diseases must be the main goal of national health systems. This is easily established when the organization effectively translates findings in biomedical research into clinical practice and uses them on decision-makings in health policies. Translational medicine is the basis of this progress. This is a continued process that involves the direct application of discoveries from the bench to the development of studies in humans. It places together all results from these studies and applies them to clinical practice, in an attempt to improve health conditions and quality of life of the population. It may also facilitate the adoption of best medical practices by the community.

In practice, this interdisciplinary approach works well in several fields<sup>1</sup>, however it is still unusual among nephrologists and neurologists. In Nephrology, it is generally accepted that chronic renal failure is a worldwide public health problem. People with this condition undergo dialysis treatment, may require kidney transplant and have an increased risk of cardiovascular disease and hence sudden death<sup>2</sup>. In Neurology, the story is quite similar. Epilepsy is one of the most prevalent neurological diseases worldwide and mortality rates are considerably higher in those that bear it<sup>3-6</sup>.

Sudden unexpected death in epilepsy (SUDEP) is the main cause of death in people with chronic epilepsy<sup>3-6</sup>, accounting for 17.0% of them. It has an incidence among epileptic adults between 1:500 and 1:1,000 patient-years<sup>7</sup>. A single

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mechanism is not established for SUDEP, but evidences suggest that the major domain is cardiovascular dysregulation during and after seizures<sup>8-12</sup>. As these two chronic diseases are very common and have high rates of sudden death, we evaluated what would be the scenario if the same person had both conditions<sup>13</sup>. In order to do it, we investigated the relationship of seizure frequencies in people with end-stage renal disease (ESRD) under regular dialysis program<sup>14</sup>. Seven out of 189 ESRD cases had convulsive seizure during the dialytic program<sup>14</sup>, therefore it was evident that despite the belief that seizures were rare among ESRD individuals receiving dialysis, this was not the case. Indeed, this suggested that a clinical convergence of neurologists and nephrologists in the context would be helpful<sup>13-15</sup>.

We also looked at a possible link between epilepsy, cardiovascular abnormalities, and SUDEP among ESRD cases undergoing regular hemodialysis<sup>13,16</sup>. It was found that abnormalities of cardiac rhythm and SUDEP are unusual events in this specific population (7 out of 209)<sup>13,16</sup>. This data has to be cautiously interpreted as the numbers examined are small, but our conclusion is that the flame of translational science among health professionals directly involved with these people must be permanently lit. For these new considerations, experimental, epidemiological, and clinical studies should be carried out to establish the association between epilepsy, cardiovascular abnormalities, and sudden death in people on dialysis<sup>13,17</sup>.

Currently, the ultimate goal in neurology and nephrology research in regards to cardiovascular changes that may lead to sudden death is to develop new methods to prevent it and to establish actions other than medical that may be effective. Therapy or supplementation with a 'natural' substance has shown interesting and promising benefits in this regard: the omega-3 fatty acids (omega-3 FAs). A number of experimental and clinical studies could be put forward to demonstrate the effectiveness of omega-3 FAs in epilepsy and dialysis fields.

In epilepsy, despite the need to perform clinical trials with higher doses and longer periods of omega-3 FAs to definitively assess their anti-seizure effects, it is already well-established that their supplementation reduces the convulsion frequency, promotes neuroprotection and positive neuroplastic changes in animal models and in some people with uncontrolled epilepsy<sup>18-23</sup>. Omega-3 FAs *per se* is able to improve vascular and cardiac hemodynamics, triglycerides, autonomic control, inflammation, thrombosis, arrhythmia and to reduce the risk of cardiac death, which may have implications for SUDEP prevention<sup>24,25</sup>.

It has been postulated that omega-3 FAs supplementation in people with refractory epilepsy may not only reduce seizures but also their cardiac arrhythmias and hence SUDEP<sup>26</sup>. In these lines, a pilot, randomized, double-blind two-period crossover clinical trial of high-dose omega-3 FAs in 11 subjects with refractory seizures was carried out<sup>27</sup>. This was the first trial to demonstrate the beneficial effects of

omega-3 FAs on cardiac risk factors and heart rate variability in people with epilepsy. It provided evidence that fish oil may reduce the risk of SUDEP in epilepsy<sup>27</sup>, which was also confirmed experimentally<sup>28-30</sup>.

In dialysis, omega-3 FAs have been clinically and experimentally assessed due to their proven benefits in advanced chronic kidney disease (CKD), such as renoprotection in IgA nephropathy, cardioprotection via a variety of mechanisms including triglyceride levels and blood pressure reduction, maintenance of dialysis access patency, sparing of inflammation-associated muscle loss, and reduced mortality<sup>17,31,32</sup>. In these lines, we fully agree with this and have recently confirmed it in a trial (Rui Alberto Gomes, PhD Thesis — unpublished data). Briefly, we evaluated the omega-3 FAs effects on individuals under hemodialysis treatment with low quality of life and high mortality risk. Patients received daily supplementation of 2 g omega-3 FAs in oral capsules, for three months, in a six-month period. Biochemical analysis was carried out at three points, generating three groups of variables (before, during, and after omega-3 FAs supplementation). A reduction of inflammatory markers, with significant reduction of white blood cells in peripheral blood, in the glycemic, C-reactive protein and triglyceride levels, was seen. There was also a quality of life (QoL) score improvement on the SF-36 instrument, especially in the physical health dimension (Rui Alberto Gomes, PhD Thesis — unpublished data).

Given the importance of these results, the 2005 Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines specifically encourage further research on the effects of kidney failure and/or dialysis on omega-3 FAs metabolism and blood/tissue levels. It also calls the attention for clinical trials designed to evaluate the effects of omega-3 FAs supplementation on cardiovascular risk and outcomes<sup>17,31-33</sup>. It is important to note that sudden cardiac death is the most common cause of death in ESRD individuals under regular dialysis program usually caused by ventricular arrhythmias, such as ventricular tachycardia and fibrillation<sup>34</sup>. Therefore, omega-3 FAs supplementation can be of value in a preventive strategy for cardiovascular abnormalities in individuals undergoing dialysis. This is due to its antiarrhythmic properties as well to its well-established ability to reduce the risk of cardiac death<sup>35</sup>.

The scientific field exploring omega-3 FAs is innovative, evolving, and promising. It needs, however, to be remembered that humans cannot synthesize omega-3 FAs. Thus, it must be obtained from the diet<sup>36</sup>. The only aliments that provide large amounts of omega-3 with low levels of contaminants (i.e., methylmercury) are oily sea fish as anchovies, herring, mackerel, salmon, sardines, and trouts<sup>37,38</sup>. Guidelines have converged on consistent recommendations for the general population to consume at least 250 mg/day of long-chain omega-3 FAs or at least two weekly servings of oily fish<sup>35</sup>. On that basis, fish is one of the most important

foodstuffs we can choose for cardiovascular and brain health. For individuals who do not tolerate fish or want a diet with no contaminants but at the same time are keen to enjoy the benefits of omega-3 FAs, options include fish oil supplements or the intake of some food, such as walnuts or oils (flax, canola, and soybean)<sup>39,40</sup>.

While we are unable to prevent ESRD and epilepsy or to reverse the clinical scenario when they are installed, the use of omega-3 FAs could be an option to prevent cardiovascular abnormalities and hence sudden cardiac death in these patients. There is still the need to confirm the utility, and to establish intake recommendations and optimal dosing of omega-3 FAs<sup>32</sup>, however it is more than time to institute a task force to assess the state of knowledge (clinical management, research directions, and educational, social, and cultural efforts) in order to put into practice these strategies.

Finally, these creative efforts about omega-3 FAs offer opportunities for preventing sudden cardiac death or improved

treatment in people with epilepsy under regular hemodialysis program. With this proposal, we should not forget the famous words of philosopher Socrates: "We do not live to eat but eat to live".

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