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ORIGINAL ARTICLE

Influence of short-term selenium supplementation on the natural course of Hashimoto's thyroiditis: clinical results of a blinded placebo-controlled randomized prospective trial

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Abstract
Background The real efficacy of selenium supplementation in Hashimoto's thyroiditis (HT) is still an unresolved issue.
Objectives We studied the short-term effect of L-selenomethionine on the thyroid function in euthyroid patients with HT. Our primary outcome measures were TSH, thyroid hormones, thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TGAb) levels and thyroid echogenicity after 6 months of L-selenomethionine treatment. The secondary outcome measure was serum CXCL10 levels.
Methods In a placebo-controlled randomized prospective study, we have enrolled untreated euthyroid patients with HT. Seventy-six patients were randomly assigned to receive L-selenomethionine 166 μg/die (SE $n = 38$) or placebo (controls $n = 38$) for 6 months. TSH, free T_4 (FT_4), free T_3 (FT_3), TPOAb and CXCL10 serum levels were assayed at time 0, after 3 and 6 months. An ultrasound examination of the left and right thyroid lobe in transverse and longitudinal sections was performed. A rectangular region, the region of interest, was selected for analysis.
Results TSH, FT4, FT3, TPOAb, thyroid echogenicity and CXCL10 were not statistically different between SE and control groups at time 0, after 3 and 6 months. In the SE group, FT_4 levels were significantly decreased ($P < 0.03$) after 3 months, while FT_3 increased ($P < 0.04$) after 3 and 6 months versus baseline values. In the control group, the FT_3 decreased after 3 and 6 months ($P < 0.02$) compared to baseline.
Conclusion The short-term L-selenomethionine supplementation has a limited impact on the natural course in euthyroid HT. Our results tip the balance toward the ineffectiveness of short-term L-selenomethionine supplementation in HT.

Keywords Hashimoto's thyroiditis · 1-selenomethionine · Thyroid function · Thyroid echogenicity · CXCL 10 levels

Introduction

Hashimoto's thyroiditis (HT) is the most common thyroid disorder and the most prevalent cause of hypothyroidism in the USA [1]. It is an autoimmune disease with the higher risk of developing a second autoimmune disorder [2, 3]. Nevertheless, one century after its initial description, HT is still multifaceted disease of multifactorial etiology not yet completely understood [4, 5]. HT is a disorder of T cell-mediated immunity with genetic and environmental factors involvement. Chemokines, chemotactic cytokines responsible for the attraction and recruitment of different cell types during leukocyte infiltration, are the histopathological hallmark of autoimmunity, and CXCL10 seems to have a major role in thyroid autoimmunity [6]. The natural

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history of euthyroid HT is a gradual progression toward overt autoimmune hypothyroidism [7]. Clinical manifestations of the disease are defined primarily by low levels of thyroid hormones, and therefore, it is treated by hormone replacement therapy, which usually consists of levo-thyroxine (LT4). The thyroid expresses several specific selenoproteins of which some are implicated in thyroid hormone metabolism, and others play an antioxidant defense role. The principal selenoproteins, including glutathione peroxidase (GPXs) thioredoxin reductases (TRs) and deiodinases, are expressed in the thyroid gland in large quantities. The three deiodinase isoforms (D1, D2 and D3) catalyze conversion of T4 into T3 [8]. Selenium supplementation has been proposed for HT treatment, and data from the literature are most likely to indicate that selenium might contribute to decrease the dosage of LT4, might reduce antibody levels and may be associated with different clinical favorable effects [9–15]. Published results are still conflicting depending on basal selenium status, dose, time and form of selenium used for intervention. Evidence for sex-specific selenium action, lack of beneficial effects in pregnancy and contribution of genetic polymorphisms (selenoprotein S) has been shown [16]. Metanalysis of four studies was unable to support the efficacy of selenium supplementation in people with HT [17]. These data highlight the need for randomized placebo-controlled trials to evaluate the effects of selenium in people with HT and to provide reliable evidence for clinical decision making.

We therefore have designed a blinded placebo-controlled randomized prospective study including 76 patients with newly developed HT to evaluate the efficacy of L-selenomethionine supplementation on the natural course of HT. Primary outcome was to study the effect of L-selenomethionine supplementation on thyroid hormones, antibodies, TSH levels and thyroid echogenicity. Secondary outcome of the study was the evaluation of a possible modulation by L-selenomethionines of the autoimmune mechanism by measuring CXCL10 levels.

Methods

Study design

We performed a blinded placebo-controlled randomized prospective study. The study was conducted from January 2013 to January 2015.

Patients

Over a period of 24 months, 110 Hashimoto's thyroiditis (HT) patients referred to the Endocrinology Unit of the Second University of Naples, Medical Center, were recruited and 76 subjects (female, aged 17–64 years) completed the study. All subjects were living in Campania district area (Southern Italy). Newly diagnosed subjects who had elevated plasma TPOAb and Tg antibodies (TgAb) above 350 IU/ml, who had thyroid parenchyma heterogeneity with reduced echogenicity, with normal TSH, FT3 and FT4 serum levels, in absence of L-thyroxine supplementation, were considered as HT patients with euthyroidism and were selected and asked for their informed consent to participate in the study. A baseline visit was made in which personal data, past medical history and symptoms were collected. All cases underwent the following study protocol to assess thyroid function, antithyroid antibodies and thyroid ultrasound and CXCL10. The review committee of the Second University of Naples approved the study protocol, and all patients gave written informed consent.

Exclusion criteria

Male patients, patients living outside Campania district area, patients with overt hyperthyroidism who were on antithyroid drugs, patients with hypothyroidism who were on L-thyroxine treatment, patients on any other medication, which may alter the thyroid and immunity status of the patients and pregnant patients were excluded from the study.

Randomization

Patients have been randomized into two age-matched groups; 38 patients received 166 μg L-selenomethionine/day, orally (Syrel, IBSA Farmaceutici Italia, Milan, Italy, selenium 83, 0 μg/cps), for 6 months, and 38 patients received placebo. An independent physician using a computer-generated system carried out randomization.

Collection of samples

Serum was collected in the morning, in same species standard sampling tubes with separator gel. Samples, blind of identification, treatment or placebo group, were immediately sent to the Laboratory Facility of the School of Medicine of the Second University of Naples for analysis of FT4, FT3, TSH, AbTPO and AbTG. The measurements were taken on the same day in primary tubes, after blood centrifugation at 3200 rpm for 15 min.

Measurement of CXCL10

Serum was frozen (−20 °C) and, blind of identification, shipped on dry ice to the Endocrine Services Laboratory, University of Pavia, for analysis of CXCL10. The CXCL10 level was measured using commercially available kits

(R&D Systems). The mean minimum detectable dose of CXCL10 was 1.67 pg/ml. The intra- and interassay coefficients of variation were 3.0 and 6.9 %, respectively. Samples were assayed in duplicate. Quality control pools of low, normal or high concentrations were included in each assay.

Biochemical data

Blood samples were drawn initially, after 3 and 6 months of the treatment. The blood level of FT4, FT3, TSH, AbTPO and AbTG was analyzed by using the 1235 Auto DELFIA automatic immunoassay system (Perkin Elmer, Wallace Oyo, Mustionkatsu 6, Fi-20750 Turku, Finland) following the manufacturer's instructions.

Thyroid ultrasound

Thyroid ultrasound was performed initially, after 3 months and at the end of the treatment by the same blinded investigator (G. V.). The images were obtained with GE Logiq P5 ultrasound machine. The frequency of the transmitter was set to 10 MHz, and harmonic imaging option was turned off. All the images were recorded in DICOM format. During the test, the patient remained in the supine position and the doctor applied ultrasound heads to the right and left side of the thyroid. For each subject, four ultrasound images were taken. Those were images of the right and left lobe of the thyroid in both transverse and longitudinal section. Each ultrasound image was analyzed in great detail and, then, an expert radiologist selected for analysis a rectangular region, the region of interest (ROI), which covered the thyroid lobe in individual sections. Each time, the ROI included the greatest possible and most representative area of the patient's thyroid lobe [18].

Data analysis

The data were tabulated on a spreadsheet and analyzed with SPSS statistics 17 software. We calculated mean and standard deviation for continuous variables. Group means were compared by *t* test. *P* values <0.05 were considered statistically significant.

Results

Selenium does not change TSH and AbTPO in HT living in Campania district

A total of 110 patients were enrolled in the study. After the application of the exclusion criteria, eleven subjects resulted not eligible for the study, 29 patients dropped out during the study period because they were lost to follow-up, and seventy-six HT completed the study. All subjects were living in Campania district (Southern Italy). Thirty-eight received placebo, and the other 38 received L-selenomethionine 166 μg/day, orally for 6 months. The mean age in both groups was similar (SE 40.0 ± 12.1 yr; placebo, 46.0 ± 14.1 yr). All were euthyroid, taking no l-T_4 supplementation. The mean baseline TSH levels were 2.7 ± 0.8 μU/ml (SE) and 2.0 ± 0.4 μU/ml (controls) (Fig. 1a). At study entry, the mean TPOAb concentrations were not statistically different in both groups (SE, 2070 ± 575 IU/ml; controls, 3049 ± 757 IU/ml) (Fig. 1 b). The mean baseline FT_3 and FT_4 serum concentrations were similar in both groups before selenium or placebo supplementation (Fig. 1c, d, respectively). In both groups, TSH baseline concentrations, using statistical test, were not statistically different after 6 months of treatment with selenium or placebo (Fig. 1 a). In SE group, FT_3 levels were increased ($P < 0.04$) after 3 and 6 months of L-selenomethionine supplementation compared to the baseline values at study entry (Fig. 1c), and FT4 serum levels were significantly reduced after 3 months ($P < 0.03$) but not after 6 months when we compare baseline with final measurement (Fig. 1 d). In the control group, FT_3 serum concentrations were decreased after 3 and 6 months ($P < 0.02$) compared to that at study entry (Fig. 1c). No significant differences in TgAb were found in SE and controls before and after 6 months compared with study entry values and between groups (data not shown).

Selenium supplementation and ultrasound pattern in HT

The ultrasound pattern in all patients revealed the typical hypoechoic thyroid tissue (Fig. 2). Thyroid echogenicity was studied by ROI, a rectangular region that covered the thyroid lobe in individual sections selected for analysis (Fig. 2). Each time the ROI included the greatest possible and most representative area of the patient's thyroid lobe evaluation method and in SE and controls, we did not find significant changes after 6 months. A thyroid ultrasound before (Fig. 2a) and after L-selenomethionine (Fig. 2b) of a representative subject is shown in Fig. 2. A thyroid ultrasound image showing a typical distribution of the ROI (white) marked by a specialist physician in a representative patient at study entry is depicted in Fig. 2 a, b showed the thyroid ultrasound image with a typical distribution of the ROI (white) marked by a specialist physician after 6 months of treatment in the same representative subject. Last image (Fig. 2c) depicted ROI values in controls and in SE.

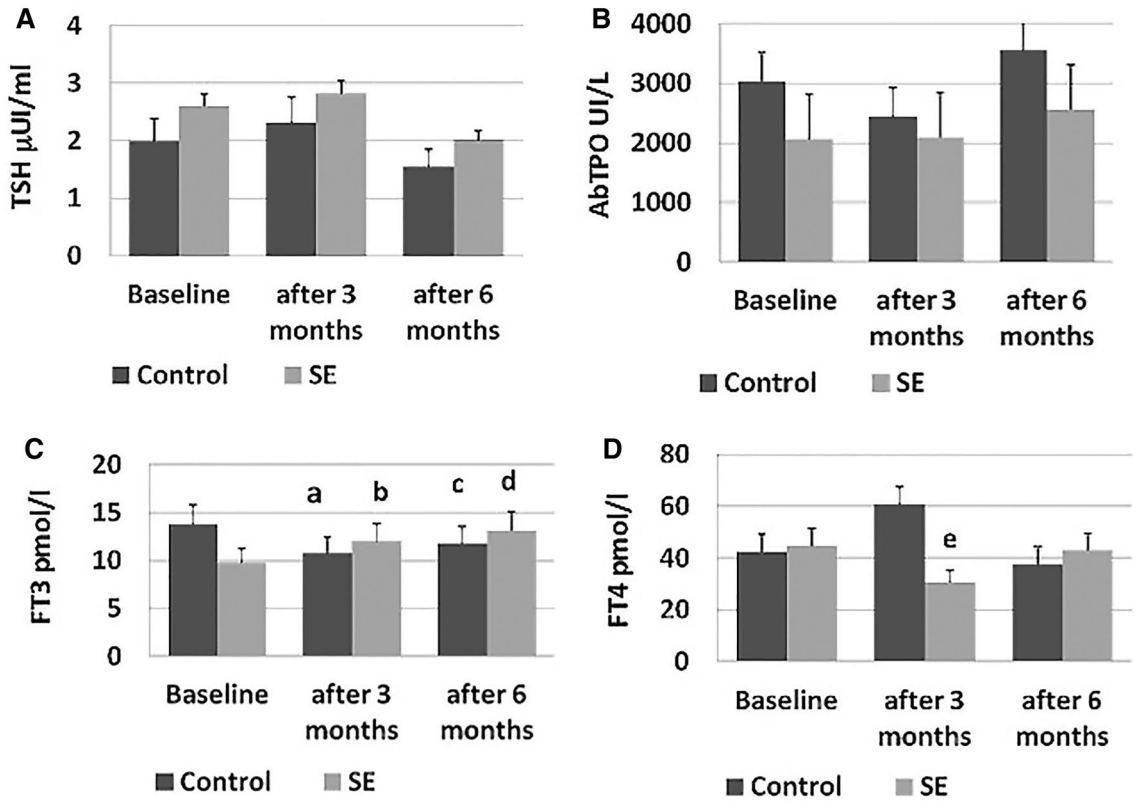

Fig. 1 TSH, TPOAb, FT3 and FT4 concentrations at study entry and 6 months after treatment with 166 mg/daily L-selenomethionine (SE) or placebo (Control). *P* values are calculated by Student *t* test. Only data of individuals who completed the study were included in the final analyses. **a** $P < 0.02$ control at baseline versus control after 3 months; **b** $P < 0.04$ SE at baseline versus SE after 3 months of treatment; **c** $P < 0.02$ control at baseline versus control after 6 months; **d** $P < 0.04$ SE at baseline versus SE after 6 months; and **e** $P < 0.025$. SE at baseline versus SE after 3 months of treatment

Selenium supplementation and CXCL10 serum levels in HT

CXCL10 serum levels were not different between the study groups at the study entry and did not change significantly in SE and controls after 3 and 6 months of observation (Fig. 3).

Discussion

The focal point of our study was to assess the effect of short-term administration of L-selenomethionine (166 µg/day/orally for 6 months) on the natural course of HT. L-selenomethionine was administered in HT women with normal thyroid function taking no hormone replacement therapy and compared to HT women with normal thyroid function, sex and age-matched controls, under treatment with placebo. All subjects were living in Campania district (Southern Italy), where there is a mild shortage of selenium in the soil, and the risk of thyroid disease is increased [15, 19–22]. The main finding of this study has been that TSH, the thyroid hormones levels and TPOAb, thyroid echogenicity and CXCL10 concentration were not statistically different at baseline level and after 3 and 6 months of SE or placebo supplementation, respectively. We found that HT subjects treated with L.-selenomethionine have shown an increase in FT_3 serum levels after 3 and 6 months, while FT4 significantly decreased after 3 months but not after 6 months compared to the baseline values. We also have demonstrated that thyroid-specific TPOAb concentrations and CXCL10, in patients with autoimmune thyroiditis with euthyroidism under selenium substitution for 6 months, did not change compared to their levels at study entry and compared to control group, as well as thyroid ultrasound echogenicity was unmodified.

The thyroid gland presents the highest selenium concentration of all tissues and selenium-dependent iodothyronine deiodinases produce active thyroid hormone, triiodothyronine, from its inactive precursor, L-thyroxine [20, 21, 23]. The increased action of deiodinases would result in increased conversion of T4 to T3. In our study, we observed increased levels of serum FT3 and reduced levels of FT4 in SE patients but not in the placebo group after 3 and

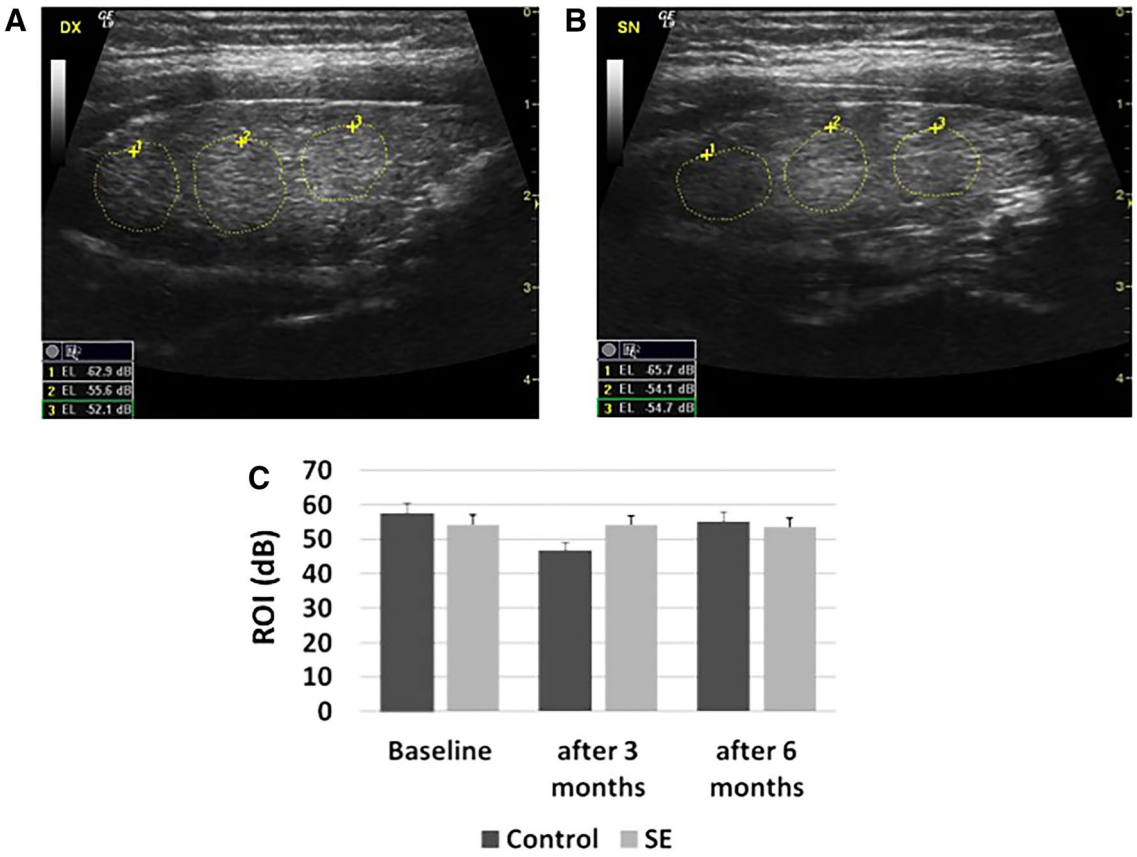

Fig. 2 Effect of L-selenomethionine on thyroid echogenicity using the ROI before and after 3 and 6 months of treatment in patients with Hashimoto's thyroiditis. **a** thyroid ultrasound image showing a typical distribution of the ROI (*white*) marked by a specialist physician in a representative patient at study entry; **b** thyroid ultrasound image showing a typical distribution of the ROI (*white*) marked by a specialist physician in a representative patient after 6 months of treatment; **c** ROI values in controls and in SE

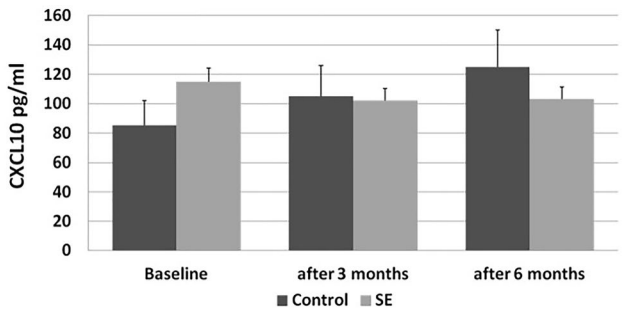

Fig. 3 CXCL10 concentrations at study entry and 6 months after treatment with 166 mg/daily L-selenomethionine or placebo. *P* values are calculated by Student *t* test

6 months of selenium supplementation, suggesting a higher activity of deiodinases induced by L-selenomethionine. This result could be consistent with the self-reported well-being status and TSH normal levels of the patients taking L-selenomethionine, even if the real impact of this observation needs to be considered with caution. Our result seems to be, somehow, similar to what observed in a previous study showing that selenium supplementation (100 mg sodium selenite/day) in a group of 36 elderly Italian subjects significantly decreased plasma total T4 concentrations, consistent with increased deiodinase activity, although there was no change in serum concentrations of TSH [24]. We have also shown no significant change in TSH level in SE and placebo groups. On the contrary, another study, conducted in Italy, has demonstrated that SE supplementation (80 mg/day) decreased AbTPO levels but only after 12 months [12]. We can speculate that the discrepancy of our results compared to that of Nacamulli et al. could be maybe due to different time of SE supplementation associated with lower selenium dietary intake. In fact, it is demonstrated that the soil of the Volcanic grounds, rising near Naples and in the surrounding area, where our patients were living, presents lower selenium content that could also influence our results [19]. European countries present lower selenium content of the soils compared to North America, which may explain the mild to moderate selenium deficiencies observed in Europe. A prospective placebo-controlled clinical study

with selenium in autoimmune thyroid diseases (AITD) conducted in the selenium-deficient area of Bavaria in southern Germany, by Gärtner [25] showed, in 70 HT under L-thyroxine replacement therapy, a 36 % reduction in antiTPO levels in the selenium-treated group, whereas a further reduction of up to 60 % was seen in a subgroup of patients with basal antiTPO levels above 1200 IU/ml. South Greece, more precisely the region around Athens (Attiki), is selenium and iodide sufficient [26] and in patients with HT under L-thyroxine replacement therapy treated with selenomethionine for 6 months was observed a 55.5 % decrease in antiTPO, but no correlation with thyroid hormone was found [27]. A 9.9 % reduction in serum antiTPO levels has been reported during the first 6 months of 200 mg selenium in the form of L-selenomethionine supplementation in 55 HT patients with normal or elevated TSH and normal free T4 by Mazokopakis EE et al. [28]. On the basis of the best available evidence, selenium supplementation seems to be associated in some cases with a decrease in TPOAb titers [29] and with improvement in mood and/or general well-being. Evidence suggests a different pattern of response to selenium supplementation in HT relative to baseline TPOAb titers, and selenium ground content [30]. However, the role of the reduction in antiTPO titers on the natural course of HT is still controversial. Despite all this data, up to now, the level of evidence for the efficacy of selenium supplementation in the management of people with HT remains unclear to high risk of bias [17].

Our secondary outcome measure was the evaluation of the effect of selenium supplementation on the whole autoimmune response in HT, studying its influence on CXCL10 levels. The autoimmune response involves the activation of peripheral co-stimulatory signals and the action of cytokines and chemokines in the recruitment, trafficking, and in situ maintenance of specific subsets of activated lymphocytes. Chemokines, chemokine receptor and its interferon (IFN)γ-dependent chemokines (CXCL10, CXCL9, CXCL11), although representing distal steps in the disease process, do play a key role in the immune pathogenesis of HT, Graves' disease and Graves' ophthalmopathy [5, 6]. In mild GO, a 6 month course of selenium supplementation is effective in improving mild manifestations and preventing progression to more severe forms [31]. However, our results showed that selenomethionine supplementation did not modified CCXL10 levels in the early stage of HT and are in contrast to what observed by Pilli et al. [32]. The discrepancy of the results maybe could be due to the relatively small sample size of the previous study [32]. Moreover, this data need to be considered, with caution, when novel therapies with novel molecules targeting the various agents involved in the pathogenesis of AITD are proposed [33].

In conclusion, taking into account the literature data, our expectancy was an extension of the euthyroid phase in HT. Our blinded placebo-controlled randomized prospective study in newly developed HT with euthyroidism showed a limited effect of the short-term L-selenomethionine administration on the natural history of this disease, considering the unchanged levels of TSH, AbTPO and CXCL10. In light of our findings above, we may conclude that now this expectancy appears to be unlikely and suggests cautions in the use of L-selenomethionine in HT.

Compliance with ethical standards

Conflict of interest The authors have nothing to declare.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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