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ORIGINAL ARTICLE

Clinical usefulness of nutraceutics with acetyl-L-carnitine, α-lipoic acid, phosphatidylserine, curcumin, C, E and B-group vitamins in patients awaiting for carpal tunnel release during COVID-19 pandemic: a randomized controlled open label prospective study

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Abstract: *Background and aim of the work:* Carpal Tunnel Syndrome (CTS) is provoked by the compression of the median nerve, leading to nerve ischemia, endoneural edema, venous congestion, and subsequent metabolic alterations. Conservative treatments could be considered. The present study investigates the efficacy of a specific blend of a 600 mg dietary integrator composed of acetyl-L-carnitine, α-lipoic acid, phosphatidylserine, Curcumin, C, E and B1, B2, B6 and B12 vitamins in patients with mild to moderate CTS. *Methods:* The present investigation involved the outpatients who were planned to undergo open surgical decompression of the median nerve awaiting surgery from June 2020 and February 2021. CTS surgery has been significantly reduced in our institutions during the COVID-19 pandemic. Patients were randomized into Group A (dietary integration 600 mg twice day for 60 days) and Group B (control group, no drug administration). Clinical and functional improvement was prospectively measured after 60 days . *Results:* One-hundred forty-seven patients completed the study, 69 from group A and 78 from group B. BCTQ was significantly improved with the drug administration, as well as BCTQ symptoms subscale, and the pain. BCTQ function subscale and Michigan Hand Questionnaire was not significantly improved. Ten patients in group A (14.5%) declared that they didn't need further treatment. No major side effects were noticed. *Conclusions:* Dietary integration could be considered as an option in patients who could not undergo surgery. Symptoms and pain could improve, but surgery remains the gold standard for recovery of function in mild to moderate CTS. (www.actabiomedica.it)

Key words: Carpal tunnel syndrome, nutraceutics, Median nerve compression, neuroprotection, Curcumin, Alpha-lipoic, vitamin, COVID-19.

Introduction

Carpal Tunnel Syndrome (CTS) is one of the most common peripheral nerve compression syndromes, affecting thousands of citizens worldwide. The prevalence of CTS has been reported to be around 5% in general population (1–5). It is caused by compression of the median nerve within the carpal tunnel, that reduces its blood flow, producing endoneural edema, venous congestion, ischemia, and subsequent metabolic alterations. The reperfusion injury of the median nerve, results in local oxidative stress which generates degenerative changes in nerve conduction (6–8). Patients suffering from CTS may experience numbness

and tingling, with or without pain, in at least two of the first three fingers of the hand. Symptoms often worsen overnight and compromise sleep quality (9). Though open or endoscopic surgical Median nerve decompression can completely resolve the clinical picture (8,10), it burdens on the health care system with an estimated cost, in the United States, of 2 billion Dollar each year (11). Conservative treatments of CTS are also possible such as local corticosteroid injections (12,13), splinting (14), laser therapy (15), shock wave (16) or oral nutraceuticals (17–19), with several limitations, but sometimes with promising results in term of pain improvement and functional recovery. Especially during the COVID-19 Era, the request for conservative treatments is abundantly growing up, to control pain in patients who cannot undergo surgery because of reduced elective surgical activity. Several molecules have been already investigated for their role of "neuroprotector" through oral administration, capable of limiting and correcting the nerve damage in mild to moderate CTS. One of these is Alpha-lipoic acid (ALA), which plays a critical role in mitochondrial energy metabolism, as a cofactor for α-ketoacid dehydrogenases. Its administration has been largely described for preventing and/or decreasing symptoms of diabetic polyneuropathies (20–22) and improving CTS symptoms, especially in the earlier stages of disease, thanks its potent antioxidant effect, scavenging free radicals, chelating metals and restoring intracellular glutathione levels (7,8,17,23). Another substance, L-acetyl-carnitine (LAC), which functions in the similar manner has been looked at. In fact, LAC has shown a free-radical scavenging effect, enhancing the activity of antioxidant factors thus protecting nerve cells against lipid peroxidation and promotes the production of membrane phospholipids, favoring nerves active regeneration (18,19,24). With regard to cell membrane component, also the intake of a naturally occurring phospholipid, such as phosphatidylserine (PS), has been proposed to improve nerve function, for its capacity to reduce cortisol levels and enhance well-being under acute physical and mental stress (25). PS doesn't play just a static structural role in neuronal membranes, but it is also involved in nervous excitability modulation, message transduction and neurotransmitter activity when exogenously supplied (26–29). Also Curcumin, a constituent of the spice turmeric (Curcuma Longa), has been reported to have significant neuroprotective effects, due to its anti-inflammatory and antioxidant properties (30–33). A role in raising antioxidant-related defenses has been recognized even to vitamins C and E (34,35). Also the potential usefulness of B-group vitamins for treating peripheral neuropathies, has been examined since 1970 demonstrating that they could determine a significant short-term reduction in pain, numbness and paresthesia (36–39). To date no study has analyzed the combined effect of all these selected molecules together, so the purpose of the present study is to investigate the efficacy of a dietary integrator composed of acetyl-L-carnitine (LAC), α-lipoic acid (ALA-R), phosphatidylserine (PS), Curcumin, C, E and B1, B2, B6 and B12 vitamins in patients with mild to moderate carpal tunnel syndrome, in terms of clinical and/or functional improvement.

Materials and Methods

Study design and subjects

This research was designed as a prospective randomize controlled open label study. The present investigation was performed on outpatients attending the hand surgery private practice of four hand surgeons from June 2020 and February 2021 who were planned to undergo open surgical decompression of the median nerve. The study was in accordance with the National ethics criteria and the Declaration of Helsinki. Considering that the administration of neuroprotective drugs as ALA-R, LAC, PS and B-Group Vitamins was already used in the pre-operative management protocols at our Institute, a formal ethical approval was not required. Considering the restrictions due to the COVID-19 pandemic, surgery for CTS release has been significantly reduced in our institutions. All patients in waiting list for carpal tunnel release (CTR) were potentially eligible for the study. The inclusion and exclusion criteria were as follows: a clinical diagnosis of mild-moderate idiopathic CTS, confirmed by electromyography as mild-moderate carpal tunnel syndrome, according with classification of Padua et al (40); clinical positive results in Tinel and Phalen tests; scheduled surgery to decompress the

median nerve between 18 and 65 years old. Patients with a positive history of diabetes, neuromuscular disease, hepatic impairment (MELD Score > 9), renal impairment (Cr clearance < 90ml/min), psychiatric disorders, previous pharmacological treatment of CTS and/or previous splinting, confirmed diagnosis of arthritis of the hand, previous wrist/hand traumas in the last year and allergy or contraindication to the study drugs, undergoing litigation, were excluded from the study. Pregnant and breastfeeding women were also excluded. Patients with a COVID19 positive test during the study period were also excluded. Patients who declared to have discontinued the therapy (more than 10 missed intakes) or who had independently taken another therapy were excluded from the study. CTS is a disease that typically worsens, as a result we excluded patients who performed electromyography more than three months before the start of the study. All participants gave a written or verbal informed consent before being involved into the study. During the first visit, demographic data (age, sex, BMI) and general medical history were collected. All patients were aware that surgery was the only resolutive treatment for mild to moderate CTS and it could not be replaced by any pharmacological therapy until today. The surgeon carefully explained to the patient risk and benefits from surgery and informed consent for surgical treatment was collected. Patients in waiting list were telephone called between June 2020 and November 2020 to inform them they would not undergo surgery at least for the next two months and they were questioned for their willingness to participate to the study involving a symptomatic nutraceutical drug. Those who answered affirmatively were asked to complete questionnaires sent by email, on the more symptomatic hand in case of bilateral disease.

Groups assignment

Patients were randomized into two groups, with a 1:1 allocation ratio: Group A (ALA-R, LAC, PS, Curcumin, C, E and B-Vit, 600 mg twice day for 60 days) and Group B (control group, no drug administration). Randomization process was performed in blocks of 10. The randomization scheme was generated by using the Web site Randomization.com (http:/www.randomization.com). Patients were asked about the two items: pain and functionality, both of day and night. The General Practitioner or the surgeon, according to the patient's preference, managed eventual side effects.

Procedures

The drug was prescribed in patients from group A. General Practitioners of all participants were informed about their patient's participation.

All patients were invited to complete the questionnaires again after two months and send back to the surgeon. Patients who forgot to complete the questionnaire received a reminder telephone call. Patients who did not sufficiently complete each questionnaire (<90%) were subsequently excluded. Adherence to therapy was also assessed through that second telephone call.

Purpose of the study and Outcomes

The aim of this study was to evaluate the efficacy of a dietary integrator composed of acetyl-L-carnitine (LAC), α-lipoic acid (ALA), Curcumin, C, E and B1, B2, B6 and B12 vitamins in patients with mild to moderate carpal tunnel syndrome. The primary endpoint was to evaluate the Boston Carpal Tunnel Questionnaire (BCTQ) in each group at the end of the treatment (2 months). BCTQ is a validated device composed of 19 items scoring to 1 to 5, widely adopted for CTS evaluation (41), which is composed by two sub-questionnaires: functional assessements (eight items) and symptoms assessment (11 items). The scores of every single question are added up and the average is calculated. The secondary outcome included the assessment in each group at the end of the treatment (2 months) of individually evaluated BCTQ subscales, Michigan Hand Questionnaire (MHQ) (42), pain assessment measured with the visual analogue scale (VAS). Side effects and the general satisfaction were also assessed. Eventual side effects and adverse events were reported and assessed through.

Statistical Analysis

The study was aimed to detect at least a 15% improvement on the BCTQ with respect to the mean the expected average baseline value for the population, which was expected to be about 2.9 points (SD 1.0) (13).

The minimal improvement expected was decided according to the recent literature, on the base of the reported expectations of clinical improvement with conservative non-invasive treatment of CTS (13).

On the base of our clinical experience and considering reports in literature, an improvement greater than 0.45 point on the overage value of total BCTQ score was considered an acceptable improving effect for a symptomatic treatment.

The power of the study was fixed at 85%, with 5% two-tailed significance. In the recent literature, the loss at follow-up is assumed to be up to 15%. However, considering the presence of COVID-19 pandemic, we assumed a 20% loss at follow-up.

Given 85% power, 5% two-tailed significance, and assuming 20% loss to follow-up, 180 patients were required, 90 patients in each group.

Continuous and ordinal data underwent Shapiro-Wilk normality test. Normally distributed data were analyzed through t-Student test. Non-parametric tests were considered in case of non-normally distributed data. Wilcoxon signed rank test (paired analysis) was used to compare the variation of pain and BCTQ values between T0 and T1. Mann-Whitney U test was used to compare the final assessment results between group A and B (independent samples). Chi-square test for categorical variables. A P value < 0.05 was considered statistically significant. Dedicated SPSS (version 20.0.0) statistical calculation software (SPSS Inc, Chicago, IL) was employed. Data were described using means ± SD for quantitative variables and numbers and percentages for qualitative variable. Only one decimal digit was reported and was rounded up.

Results

181 patients (82M, 99F) met the inclusion criteria during the enrollment period, 90 from group A (drug administrated) and 91 from group B (control group). However, 147 patients completed the study, 69 from group A (33M, 36F) and 78 from group B (37M, 41F).

Higher drop-out rate (21 patients, 23%) was recorded in group A. .

- 21 patients discontinued the therapy:
  - 3 of them missed more than 10 intakes,
  - 3 took a different neuroprotective or neurotrophic drug,
  - 4 discontinued because of minor side effects (3 case of head ache and 1 case of nausea).
  - Only 4 patients declared to have discontinued the intake because of no impact on symptoms.
  - 7 patients were lost at follow-up.

In group B (control group) 13 patients (14%) were lost at follow-up and did not completed the study. The study flowchart is shown in Figure 1.

The mean age was 61 years old (±13.6) in group A and 66 years old (±10.7) in group B. The BMI was 24.1 (±4.5) in group A, 26.5 (±5.2) in group B. Smokers were 15 (%) in group A and 20 (%) in group B. Demographic features are summarized in the Table 1.
About the primary endpoint, a significant different was found in term of BCTQ score ($p<0.05$).
However, looking separately the two subscales of BCTQ (secondary endpoints), we observed a significant difference in Symptoms BCTQ score in response to the administration of the drug (from 31.4±6.5 to 26±8 in group A, $p<0.0001$; from 31.4±7 to 30.3±7.3 in group B, $p=0.1443$).
Nevertheless, non-significant differences were found in Function BCTQ score in both groups (from 25.5±8.5 to 25.3±8.5 in group A, $p=0.70394$; from 25±7 to 25±7.3 in group B, $p=0.8181$).
Comparing the last follow-up assessments between group A and group B, we found a statistically significant difference in Symptoms BCTQ ($p=0.0003$) and a non-significant difference in Function BCTQ ($p=0.96012$).
As far as the other secondary endpoints, non-significant differences were found in term of MHQ score in both groups ($p>0.05$).
Furthermore, referred pain measured through VAS score was improved in response to the administration of the drug, changing from a mean value of 6.0±1.4 to 4.2±1.6 ($p<0.00001$). Not significant changes were observed in control group (6.1±1.5 to 6.2±1.4,

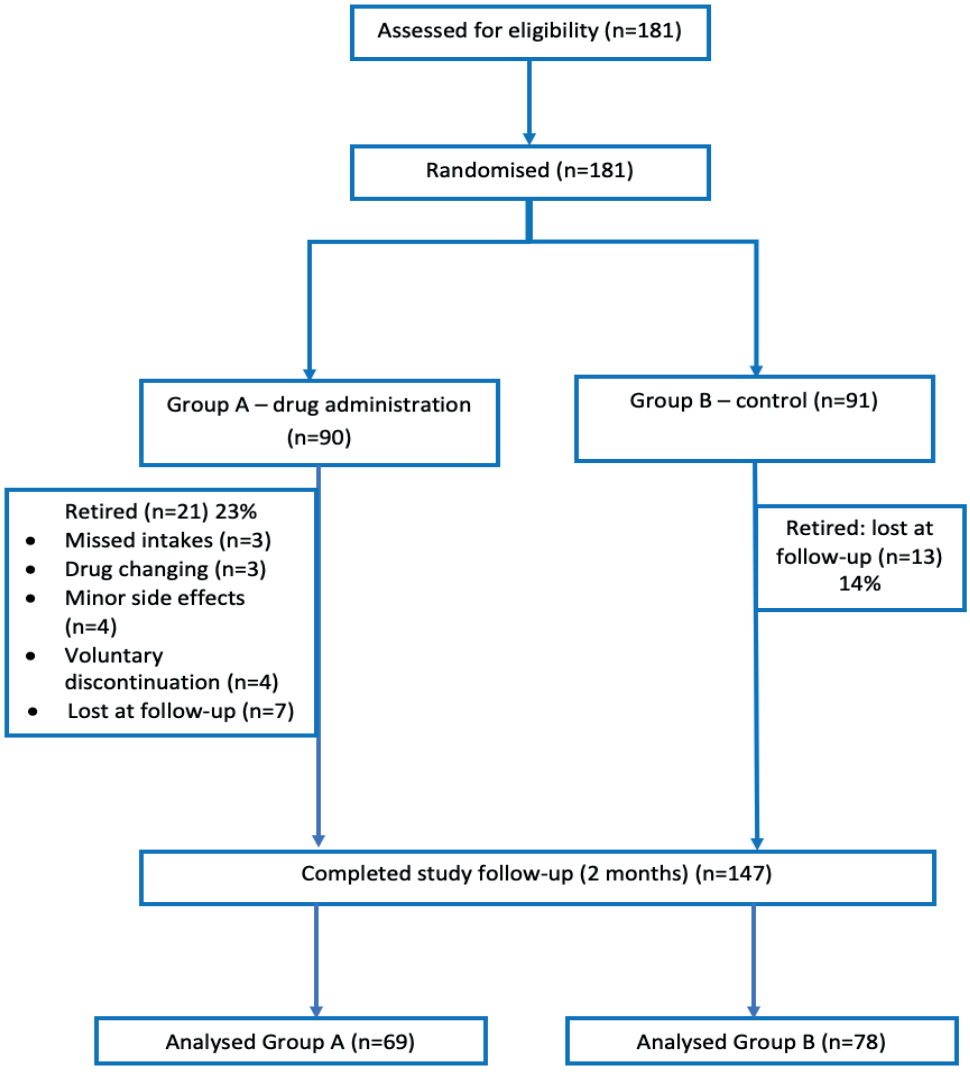

Figure 1. Study flow chart

Table 1. Clinical and demographic features

Demographics	Group A	Group B	p value
Number of patient	69	78	
Gender	36 F, 33 M	41 F, 37 M	.962
Age (years)	61.1 (±13.6)	66.2 (±10.7)	.678
Body mass index	24.1 (±4.5)	26.5 (±5.2)	.234
Duration of symptoms (months)	19.6 ±5.3	17.8 ± 5.1	.562
Number of smokers	15 (21.7%)	20 (25.6%)	.579
History of chronic alchool consumption	2 (2.9%)	2 (2.6%)	.901
Comorbidities with impact on peripheral nervous system *	8 (11.6%)	10 (12.8%)	.820
Other comorbidities **	25 (36.2%)	25 (32.1%)	.593

* Rheumatoid arthritis, cervical spine disease

** Hypercholesterolemia, hypertension, glaucoma, history of cardiac infarction and other cardio-vascular diseases

p=0.11876). We found a statistically significant difference comparing the last follow-up pain assessments between the two groups (p=0.0002).
Finally, regarding patients' general satisfaction, at the last follow-up we asked the patients "how is your illness? Have you noticed some changes about your illness? Do you think do you need a further treatment?" Ten patients in group A (14.5%) declared that they have noticed an improvement of their disease and they have felt that they didn't need further treatment. In Group B all patients asked to be surgically treated. Results are summarized in Table 2.

Discussion

The usefulness of oral supplementation in CTS has been already investigated by other authors, in some studies with promising results (7,8,24,43). Concerning our study, oral supplementation with LAC, ALA-R, PS, Curcumin, C, E and B-Group Vitamins twice a day, in CTS patients waiting for surgical treatment, has a deep impact on symptoms. In fact our results showed that at last follow-up (two months) although there was not significant improvement in functional score (MHQ and Function BCTQ subscale) related to nutraceutical administration, the purely symptomatic aspect, assessed by VAS score and Symptoms BCTQ subscale, resulted in a statistically significant difference, in contrast with control group. Also the patient satisfaction confirm these results, in fact differently from control group, 14.5% of patients from group A, perceived a symptomatic improvement to do not consider surgery need to be made. These data indicate that the beneficial effects on pain observed in this study were not due to chance. As already evidenced, inflammation plays a central role in compressive neuropathies pathogenesis, such as CTS (44). In fact local compression, with chronic endoneural ischemia, produces a deep local inflammatory reaction and oxidative stress with oedema, infiltration of hematogenous immune cells and induction of various soluble factors like cytokines and chemokines, resulting in degenerative changes in the nerve (44). Even if surgical carpal tunnel release can definitely reduce symptoms, conservative treatment could be just as effective in low grade CTS (8,45). The latter should be considered above all if surgery is not feasible in the short term, because of the growing waiting lists, just like during the COVID-19 pandemic. Previous studies have reported the neuroprotective and anti-inflammatory effects of ALA, capable of limiting and to correct the clinical course of CTS. In a study of 112 subjects with moderately severe CTS, Di Geronimo et al. (17) described a

Table 2. Results. Data represent the mean ± SD, median, interquartile range. Significant p values are marked in bold.

	Drug administration (Group A)			**Control (Group B)**			**T0 (Group A vs Group B)**	**t1 (Group A vs Group B)**
	t0	**t1**	**p value (t0 vs t1)**	**t0**	**t1**	**p value (t0 vs t1)**	**p value (t0 vs t0)**	**p value (t1 vs t1)**
BTCQ total score	29.0 (±4.8) 28.0 25.3 – 32.1	26.1 (±5.6) 24.3 21.9 – 29.7	**0.001**	28.7 (±6.9) 29.0 24.5 – 32.2	30.1 (±6.9) 30.5 24.8 – 33.2	0.497	0.384	**0.039**
BTCQ Function score	25.5 (±8.5) 25.0 19.0 – 33.0	25.3 (±8.5) 25 19 - 31	0.704	25.0 (±7.0) 25.0 21.0 - 30.0	25 (±7.3) 25.0 21.0 - 29.0	0.818	0.936	0.960
BTCQ Symptoms score	31.4 (±6.5) 32.0 27.0 - 36.0	26.0 (±8.0) 25.0 20.0 - 31.0	**<0.00001**	31.4 (±7.0) 31.0 27.0 – 35.0	30.3 (±7.3) 31.1 26.1 – 36.1	0.144	0.810	**0.0003**
MHQ score	46.9 (±12.0) 52.0 38.0 - 59.0	49.1 (±12.4) 52.0 40.0 - 60.0	0.407	46.4 (±11.2) 50.0 39.3 - 55	46.4 (±11.2) 48 40.5 - 55	0.857	0.503	0.174
Pain (VAS score)	6.1 (±1.4) 5.8 5.2 – 6.9	4.2 (±1.6) 4.1 3.1 – 5.4	**0.0007**	6.1 (±1.5) 5.9 4.9 – 7.4	6.2 (±1.4) 6.1 5.1 – 7.3	0.687	0.904	**0.0002**

significant improvement in both symptoms and functional scores after a 90-days treatment with a fixed association of alpha-lipoic acid and gamma-linolenic acid, furthermore they reported a statistically significant improvement in electromyographic examinations. Another randomized controlled trial in 2019 (8) involving 134 patients, showed that the use of ALA-R, in full dose for two months, had a favorable impact on pain, both night and day in subjects with mild-moderate CTS. Also Pajardi et al. (43) in 2014 investigated the effectiveness of oral supplementation with a combination product, containing ALA, Curcumin, and B-group vitamins in patients with CTS, scheduled to undergo surgical decompression. According to the study this nutraceutical combination, administrated twice a day both before and after surgery, is effective in reducing nocturnal symptoms and the clinical positivity of Phalen's Test. Curcumin, in fact, has been also reported to have significant neuroprotective effects, inhibiting production of several inflammatory mediators (e.g., NF-κB, IKK-β, COX-2, iNOS, TNF-α, and IL-6) and protecting from oxidative stress (32,33,46). Although the usefulness of B-group vitamins is still controversial, they are often used as conservative therapy in CTS. A Cochrane systematic review by Ang et al. (39) demonstrated, with moderate evidence, that B-group vitamins, at high doses, may produce a significant short-term reduction in pain and paresthesia in peripheral neuropathies. The supplementation with LAC also has been widely investigated for its antinociceptive and neuroprotective effects in peripheral neuropathies. In fact L-Acetylcarnitine, the acetyl ester of L-carnitine, plays an essential role in the metabolism of fatty acids in mitochondria (47), but aside from its role in fatty acid ß-oxidation, has been reported to modulate the activity of nerve growth factor (NGF) in the nervous system in rats (48) and to perform a free-radical scavenging effect, protecting nerve cells against lipid peroxidation and favoring nerves active regeneration (18,19). Cruccu et al. in 2017 in a multicentre examiner-blinded study (24) investigated the effects of LAC supplementation, 500 mg BID in 82 patients with CTS of mild to moderate severity, reporting statistically significant improvement in neurophysiological measures (sensory conduction velocity) and in BCTQ Score, with a greater improvement in Symptom subscale. These results confirmed the neuroprotective action and central anti-nociceptive properties of LAC in mild-moderate CTS. Otherwise Curran et al. in 2019 (49), reported no significative improvement, compared to placebo control group, in patients affected with severe CTS, treated with LAC, following a surgical carpal tunnel release. Also the intake of a cells membrane phospholipid, Phosphatidylserine (PS), has been recently investigated for its capacity to reduce physical and mental stress and improve nerve function (25). PS in fact, as evidenced in different studies, takes part in modulation of nervous excitability and neurotransmitter activity, normalizing the hyper-responsivity of the hypothalamic-pituitary-adrenal axis (HPAA) to a stressor (26–28). The results of our study suggest that mild to moderate CTS patients, scheduled to undergo surgical decompression of the median nerve, who receive oral supplementation with LAC, ALA-R, PS, Curcumin, C, E and B-Group Vitamins twice a day, before surgery, could have a significative improvement in their symptoms. There are several limitations to this study which need to be mentioned. First, this study presented a small follow-up, so a long term recurrence of symptoms could not be excluded. Anyway, in that case a second treatment period could be effective again. Further studies with a longer follow-up should be considered to evaluate the maintenance of beneficial effects. Second, the lack of blinding could have introduced bias, due to the knowledge of which intervention was being received, even if our results were in line with those reported in literature. Furthermore, our study did not compare the effect of the combination product with that of each compound alone (i.e., ALA-R, LAC, Curcumin, C, E and B-group vitamins alone). The treatment was associated with good satisfaction levels and compliance, suggesting the potential clinical usefulness of this supplementation in patients who could not undergo surgery (because of major health problems) or did not undergo surgery for personal convictions (50).

Conflict of Interest: Each author declares that he has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Informed consent: The involved subject gave informed consent to participate and patient anonymity has been constantly preserved.

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