Peer Review File
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Reviewer A

Comment 1: This paper is not scientific and cannot be recommended for publication.

Reply 1: Completely agree with your statement "the paper is not scientific"; however, the fact that this is not a typical scientific study is clear from the introduction; as described the three reported cases are part of the routine outpatient activity and their description could be of interest in the planning of future studies on this topic

Changes in the text: The sentence "The cases described have been part of a routine outpatient activity. Their description could be of interest in the planning of future studies on this topic." has been added to the newly added header "Presentation of Cases" (page 3 – 4, lines 62 - 71, together with the required statements as per author checklist).

Comment 2: SCI is not an established entity just a complex of many sorts of inflammatory diseases of highly different backgrounds and thus the usage of SCI is very risky.

Reply 2: Thank you for your comment. However, I do not agree. Chronic subclinical systemic inflammation has been described with an elevation of inflammatory cytokines in serum because of the failure to resolve acute inflammation, oxidative stress, or metabolic malfunction[1], although a consensus as to which markers best represent low-grade inflammation has not been reached yet[2]. Systemic chronic inflammation is associated with an increased risk of cardiovascular diseases, cancer, rheumatoid arthritis, diabetes, and neurodegenerative diseases[3,4]. This concept has been used by many authors in their papers and patients included in the present one fall into this group. Indeed, the paper published in Nature Medicine with a 2-year Impact Factor (2021) of 87.241 in 2019 describes this concept under the name of SCI as well[3].

Changes in the text: The sentence "Although a consensus as to which markers best represent low-grade inflammation has not been reached yet (10), SCI may be associated with an elevation of inflammatory cytokines in the serum (11)." has been added (page 1, line 18 -20).

Comment 3: The diet, exercise, and OEC cannot be a mainstay of treatment just supplementary treatment. The usage of OEC may be harmful.

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1 Ranneh Y, Akim AM, Hamid HA, Khazaai H, Mokhtarrudin N, Fadel A, Albujja MHK. Induction of Chronic Subclinical Systemic Inflammation in Sprague-Dawley Rats Stimulated by Intermittent Bolus Injection of Lipopolysaccharide. Arch Immunol Ther Exp (Warsz). 2019 Dec;67(6):385-400. doi: 10.1007/s00005-019-00553-6. Epub 2019 Jul 5. PMID: 31278602.

2 Calder PC, Ahluwalia N, Albers R, Bosco N, Bourdet-Sicard R, Haller D, Holgate ST, Jönsson LS, Latulippe ME, Marcos A, Moreines J, M'Rini C, Müller M, Pawelec G, van Neerven RJ, Watzl B, Zhao J. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br J Nutr. 2013 Jan;109 Suppl 1:S1-34. doi: 10.1017/S0007114512005119. PMID: 23343744.

3 Furman D, Campisi J, Verdin E et al.: Chronic inflammation in the etiology of disease across the life span. Nat Med 2019 Dec;25(12):1822-1832. doi: 10.1038/s41591-019-0675-0. Epub 2019 Dec 5. PMID: 31806905; PMCID: PMC7147972.

4 Zhou WBS, Meng J, Zhang J. Does Low Grade Systemic Inflammation Have a Role in Chronic Pain? Front Mol Neurosci. 2021 Nov 10;14:785214. doi: 10.3389/fnmol.2021.785214. PMID: 34858140; PMCID: PMC8631544.

Reply 3: Indeed, the used OEC is a food supplement and may hence only serve as supplementary treatment. As food, it is safe to use for the patient and no harmful effects have been reported during years of availability. Additionally, the paper does not suggest diet, exercise and OEC as the mainstay of the treatment; the paper would like to suggest their association with the recommended and scientifically validated standard treatment (when and if available). This concept has been added and therefore underlined in the conclusion section.

Changes in the text: The clarification that the used product is a food supplement has been added in the introduction (page 3, line 50-51). Also, it has been pointed out that this is a supplementary treatment (page 3, line 55: Three patients with inflammatory conditions and polyarthralgia were treated with this combinatory approach, additionally to recommended and scientifically validated standard treatment.)

Comment 4: In a patient with psoriasis, please show the photo of skin eruption before and after treatment, and also use the dermatological terms to describe the skin eruption.

Reply 4: Thank you for the suggestion. Figure 2 and 3 are added showing the skin eruptions before and after the treatment, as well as a dermatologic description.

Changes in the text: Figure 2 has been added in page 5, line 103 to show the skin eruptions before the treatment. On page 6, line 120, the sentence "The psoriatic lesions have gone into complete remission (figure 3)" has been added. Figure enumeration changed consecutively.

Reviewer B

The author presents three case reports of patients with various inflammatory conditions treated with diet, exercise and OEC. These are appealing examples of an holistic approach. There are some questions that were raised while reading the manuscript.

Comment 1: Why are the interventions not introduced in the introductions, for example the choice for the different diets, exercises and the background of the OEC ingredients.

Reply 1: Thank you for your comment, the requested information which will give further background has been added in the Introduction section.

Changes in the text: The explanation of dietary and exercise approaches has been added on page 1-2 in lines 21-28: "In order to start the effective treatment of SCI conditions, it would be enough to apply some changes to the lifestyle. The main ones consist of changes in the dietary pattern: diet rich in vitamins, minerals, fiber, antioxidants, folates, polyphenols and omega-3 fatty acids and low in trans fatty acids, simple sugars, animal proteins and processed foods correlates inversely with pro-inflammatory cytokine levels; furthermore, an overall reduction in caloric intake, the constant performance of moderate aerobic physical activity, individually adapted based on the patient´s preferred and manageable type of activity, and better stress management should be added."
To explain the background of the OEC formulations, a further description of the ingredients has been included on page 2 in line 31 – 38 with the following sentences: Bromelain, a cysteine protease derived from pineapples, and trypsin, a serin protease isolated from porcine pancreas, are enzymes

with a broad spectrum of application. A common addition is the flavonoid rutin, a powerful antioxidant and anti-inflammatory plant secondary metabolite present in e.g. Sophora japonica, the Japanese pagoda tree (15). Proposed mechanisms of action include activation of the ubiquitous antiprotease alpha-2-macroglobulin, enabling binding of cytokines and controlling signaling pathways (16, 17), and direct proteolytic effects on surface receptors or advanced glycation end products (AGEs) (18).
References were added and enumeration has been changed consecutively.

Comment 2: Also in person 2, why was at visit 4/5 only CRP measured?

Reply 2: Thank you for your comment. We introduced the required additional data into the manuscript.

Change in text: Addition to table 2: Visit 4 and 5 visits were split and data added.
Table 2: Anthropometric and blood parameters at visit 1 after 8 weeks of initial treatment, at visit 2 after 8 weeks of combined treatment and at the final visit 3. OEC therapy was then interrupted for 8 weeks and resumed for another 8 weeks. CRP was measured 2 and 8 weeks after resumption of OEC therapy (visit 4 and 5).

	Visit 1 anamnesis	**Visit 2 diet + exercise therapy**	**Visit 3 diet + exercise therapy + OEC**	**Visit 4 OEC**	**Visit 5 OEC**
Weight (kg)	63.5	62.8	63.2	64.1	63.5
BMI	22.2	22	22.1	22.3	22.2
FM (%)	18.5	17.00	19.00	18	18.5
CRP (mg/dL)	6.5	6.3	2.1	4.5	1.5
VAS	6	7	1	5	3

BMI: Body Mass Index; CRP: C-reactive protein; FM: Fat Mass; VAS: visual analogue scale

Comment 3: Concerning the methodology it would have strengthened the treatment if a run-in and run out period was included with an extra analysis of the parameters.

Reply 3: I completely agree with this observation; however, the three cases are part of the routine outpatient activity and the decision to publish the data was taken at a later stage.
Patient files have been reviewed but unfortunately blood chemistry date are not available for all of them.

Changes in text: None.

Comment 4: Finally, please show the waiver of the ethical review board that no informed consent is needed. The author state that this is not needed because it is not possible to identify subjects from the data included in this report on three cases. The subjects were treated so they were subject to action and a permission of the medical ethical committee is necessary including informed consent.
I think that the issue of the informed consent should be solved before this report can be published.

Reply 4: All the patients give their informed consent to the treatment when that was proposed; after that, the consent to the publication of the case was asked and obtained from each one of the included patients; the ethic committee was not consulted as the cases were sporadic clinical cases, completely independent of each other and there was not a specific study protocol in which they were included and that can be presented to the ethic committee.

Changes in text: None.