



University
of Catania



School of Medicine, Human Anatomy and Histology Section

Prof. G. Musumeci (✉), B.S, M.S, Ph.D.
E-mail: g.musumeci@unict.it

Dear Reviewers,

Thank you for your letter and for the comments concerning our manuscript titled “**Exercise as medicine to be prescribed in osteoarthritis**” By **Silvia Ravalli, Paola Castrogiovanni, Giuseppe Musumeci. Manuscript NO: 46866**. Now we are resubmitting our manuscript for your kind consideration for possible publication in **World Journal of Orthopedics**.

Point by point reply

Reviewer 1:

The general style and writing of the paper should be more formal and avoid superfluous language, e.g. "renowned for being beneficial for the entire body" and "there was a time where it was intended as a way of life rather than thought as working out".

[Reply: As kindly suggested, we removed some sentences and modified the text.](#)

Please omit unscientific and subjective comments such as "What can be caught from this brief overview is how astounding is the process that leads us to be seated eight hours a day, in office chairs, in order to provide food and essential goods."

[Reply: As kindly suggested, we removed subjective comments.](#)



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The introduction provides a lot of historical perspective that may not be relevant or useful for readers.

Reply: We appreciate this honest suggestion, but we would like to maintain this part of the introduction as we consider it could be interesting for some readers, although it has just historical meaning.

The introduction would benefit from further development in a few ways. First, the authors did not define "exercise" in the introduction. There would be value in doing that and fleshing out the distinction between acute exercise effects (i.e., transient effects tied to a bout of exercise/activity) and chronic exercise effects. Will mechanisms for the respective effects be distinct?

AND

So what constitutes an "active lifestyle"?

Reply: Thank you for your wise comments. We added this paragraph: "Leading an active lifestyle implies to avoid sedentary habits and include dynamic movements as part of daily routine. This lifestyle does not only refer to sport practice but also to positive everyday activities ranging from walking to housekeeping. Exercising is part of this concept and represents a planned activity focussed on be beneficial for mental and physical health. The type of exercise itself could vary depending on the group of muscles or parts of the body interested, the frequency, intensity and duration of the movement, the equipment used to perform it and the personal abilities required for the scope. Physical training can be addressed to exert specific functions: maintain healthy shape, reduce weight, boost strength and flexibility, improve mood, treat pathological conditions and prevent diseases. Different effects of training can be observed analysing short term responses, following a single or acute bout of training, or long-term adaptations, deriving from repeated and

Department of Biomedical and Biotechnological Sciences
Direction and Administrative Offices
Via Santa Sofia 64, 95125 Catania
C.F./VAT 02772010878
Tel. 095/7384236; 095/7384245; 095/7384084



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chronic bouts of exercise[2]. Intensity and duration of acute training are involved in the dose-dependent and transient stimulation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system, which are responsible of mobilisation of energy reserves, increase of heart rate and blood pressure as well as improvement of mental vigilance and activation of the immune system. Repeated exercise, followed by recovery, appears to be associated, in the long term, with adaptive and optimised control of neuroendocrine factors, anti-inflammatory states, increased production of growth factor and enhanced neural plasticity[3]. Acute and chronic exercise effects have been investigated, for example, on inflammatory states[4], cardiovascular system[5], skeletal muscle proteome[6] and cognitive performance[7-8].”

Second, more information on the evidence-based health benefits of exercise would be useful. For example, exercise benefit patients with heart failure (citation: Pandey A, Parashar A, Kumbhani DJ, Agarwal S, Garg J, Kitzman D, Levine BD, Drazner M, Berry JD. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circulation: Heart Failure*. 2015 Jan;8(1):33-40), improves mood symptoms (citation: Ng QX, Venkatanarayanan N, Loke W, Yeo WS, Lim DY, Chan HW, Sim WS. A meta-analysis of the effectiveness of yoga-based interventions for maternal depression during pregnancy. *Complementary therapies in clinical practice*. 2019 Feb 1;34:8-12), and it may also have cognitive benefits and even improve ADHD symptoms (citation: Ng QX, Ho CY, Chan HW, Yong BZ, Yeo WS. Managing childhood and adolescent attention-deficit/hyperactivity disorder (ADHD) with exercise: a systematic review. *Complementary therapies in medicine*. 2017 Oct 1;34:123-8).

Reply: Thank you for these suggestions. We cited these articles as references number 17, 18 and 19: “Data in literature highlight that exercise has a therapeutic role for diseases such as diabetes,

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obesity, pain, neurological disorder and heart failure[14-17]. Furthermore, physical activity has been reported as consistent therapeutic intervention in neuropsychiatric conditions; for example, it is able to improve mood symptoms in depressed pregnant women[18] and may benefit patients with attention-deficit/hyperactivity disorder[19].”

The article appears rather one-sided at the moment. The potential drawbacks to exercise should be briefly discussed, for e.g. exercise for which a skeletal muscle is not adequately conditioned results in focal sites of injury distributed within and among the fibres. Exercise can cause physical injuries and exercise with eccentric contractions can be particularly damaging.

Reply: We appreciated the advice. We added this paragraph: “It is important to take into consideration that exercise can involve a risk of injury (fractures, muscle strain, torn ligaments), especially when movements are performed improperly, or equipment is not correct. Strenuous training could impair the immune system and may be responsible for structural changes of the heart and large arteries, loss of electrolyte balance and cardiac or respiratory distress[35]. Those who over exercise can experience high levels of depression, fatigue and confusion, since overtraining affects blood levels of neurotransmitters, including glutamine, serotonin and dopamine. Insomnia can also be caused by exercise-induced cortisol level. Because of the psychological stress about performance and body image, symptoms of anxiety and aggression, eating disorders, as well as drugs and alcohol addictions, are common in athletes and team players[36].”

Several caveats require further discussion: it is important to emphasize that exercise must be tailored in terms of its intensity, frequency and duration of exercise, especially in special patient populations e.g. the elderly who struggle with frailty and patients with heart failure.

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Reply: As kindly suggested, we added this part: “Training programs need to be tailored paying attention to some special patient categories, due to physiological and pathological reasons: pregnant women, for example, cannot perform strenuous activities that could put at risk their pregnancy. Children and elderly are not always able to perform complex or exhausting movements and incur more easily in injuries. In the same manner, chronic or pre-existing pathological conditions, like cardiovascular, metabolic, musculoskeletal and neurological disorders, must be evaluated”.

Second, most of the published literature in support of this contention are pilot studies or non-randomized with generally small numbers. There are no direct comparisons and many studies did not examine the long-term effects of exercise.

Reply: Thank you for this observation. We removed some citations and we added other more appealing and recent studies:

14 Abdelbasset WK, Tantawy SA, Kamel DM, Alqahtani BA, Soliman GS. A randomized controlled trial on the effectiveness of 8-week high-intensity interval exercise on intrahepatic triglycerides, visceral lipids, and health-related quality of life in diabetic obese patients with nonalcoholic fatty liver disease. *Medicine (Baltimore)*. 2019; 98: e14918 [PMID: 30896648 DOI: 10.1097/MD.00000000000014918].

15 Jones GT, Macfarlane GJ, Walker-Bone K, Burton K, Heine P, McCabe C, McNamee P, McConnachie A, Zhang R, Whibley D, Palmer K, Coggon D. Maintained physical activity and physiotherapy in the management of distal arm pain: a randomised controlled trial. *RMD Open*. 2019; 5: e000810 [PMID: 30997149 DOI: 10.1136/rmdopen-2018-000810].

16 Rafferty MR, Prodoehl J, Robichaud JA, David FJ, Poon C, Goelz LC, Vaillancourt DE, Kohrt WM, Comella CL, Corcos DM. Effects of 2 Years of Exercise on Gait Impairment in People With



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[Parkinson Disease: The PRET-PD Randomized Trial. J Neurol Phys Ther. 2017; 41: 21-30 \[PMID: 27977518 DOI: DOI: 10.1097/NPT.000000000000163\]](#)

[17 Pandey A, Parashar A, Kumbhani DJ, Agarwal S, Garg J, Kitzman D, Levine BD, Drazner M, Berry JD. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail. 2015; 8: 33-40 \[PMID: 25399909 DOI: 10.1161/CIRCHEARTFAILURE.114.001615\]](#)

Reviewer 2:

This is a good editorial underlying the importance of physiotherapy or appropriate exercise for most illnesses but especially for osteoarthritis. Although I see that an English certificate has been obtained, the English is not good and detracts from the message of the paper. The manuscript has to be rewritten by a native English speaker.

[Reply: Thank you for your kind comment, we apologize for the mistakes. We applied corrections throughout the whole text.](#)

Comments from reviewers are all valuable and very helpful for revising and improving the editing of our paper and for this reason we acknowledge the editor for the suggestions whereby the paper has improved considerably.

Thank you for your time and for considering our paper.

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We look forward to hearing from you soon.

Yours Sincerely,

A handwritten signature in black ink, enclosed in a thin black rectangular border. The signature appears to be 'G. Musumeci'.

Giuseppe Musumeci (on behalf of all authors).

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