**High level of irisin as a marker of malnutrition in head and neck cancer patients subjected to radiotherapy**

**General Recommendation:** Reject - very poor

**Comments to Editor:**
The authors have not adequately revised this manuscript, which should have initially been rejected due to the concerns with the study rationale, design, methods, and the conclusions made by the authors.

**Comments to Author:**
The authors have not adequately revised this manuscript and there are still major concerns with the study design, rationale, methods, and presentation of the results. There are the following major concerns that cannot be corrected by changing the written content of the manuscript:

1. It is not clear why the authors studied the association between levels of the peptide, irisin, which is a PGC1 proliferator-activated receptor coactivator1-dependent myokine, and malnutrition and why they chose this particular patient group. Irisin is a myokine that is secreted from skeletal muscle in response to exercise, and stimulates conversion of white adipose tissue to brown adipose tissue.
2. This is a study on the association between irisin and nutritional status in only 50 patients with head and neck cancer - of unknown type - following radiotherapy - assessed using the subjective short nutrition assessment tools, the Nutrition Risk Screening 2002 NRS-2002 and Subjective Global Assessment Form SGA. These methods have been poorly described and it is not clear that they are relevant.
3. Patients with malignancy, particularly of the head and neck, will have difficulty eating and will lose weight and may become cachectic. Weighing the patient, measuring muscle mass and adiposity are all established methods of assessing weight loss.
4. Irisin and myostatin have been previously described as markers of muscle strength/mass, which is different to malnutrition, but the authors have not made this clear. See, - Planella-Farrugia C, Comas F, Sabater-Masdeu M, et al. Circulating Irisin and Myostatin as Markers of Muscle Strength and Physical Condition in Elderly Subjects. Front Physiol. 201910871. 5. No subjective anthropometric methods have been used to evaluate muscle mass. 6. These authors have stated that they used bioelectrical impedance analysis BIA for fat but without clearly describing the method. 7. Although the authors mention white adipose tissue WAT and brown fat, they have not evaluated these in the patients studied. 8. Serum levels of irisin were measured by ELISA. The methods are poorly described and no controls were used. No details have been given of the source and dilution of the primary irisin antibodies used. 9. The main Background sections and Discussion sections are long and repetitive.
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