

Isoflavones and bone

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The appearance of scales for the prediction of the absolute risk of fragility fracture and the consequent definition of thresholds for pharmacological intervention has significantly limited the number of women eligible for treatment among those who are in their first years of the menopause. What is certain is the deterioration that many of them suffer in terms of bone metabolism as a consequence of rapid hypogonadism, but there are no defined strategies for the use of drugs to limit this phenomenon. In its day, hormone therapy solved this problem, but its limitations to use in women with symptoms sufficient to affect quality of life has left many users without an efficacious option. It is true that life style changes, especially diet and exercise, alleviate the problem, but they are not an entirely satisfactory solution. The advances which are being made in the action mechanism of plant extracts, both in the form of pure molecules prepared to the equal quality of medicines, or foods in which they are found in sufficient concentrations (functional foods), are raising new expectations. There has been significant progress in the knowledge of the molecular mechanisms of many of these substances, especially the isoflavones. Although there are differences between their components, we know that they are capable of activating estrogen receptors, particularly isoform β , and that this is followed by the activation of different signalling pathways in various experimental models, essentially cellular. The fundamental question, however, is what is their true clinical significance.

On this point the evidence is more limited and to date, still confusing. On the one hand is the

unfinished business of the symptoms, where there are few clinical studies of quality, and those that there are present difficulties derived from their inclusion of groups with low numbers of participants or of other methodological drawbacks. On the other, there is the question of their eventual efficacy in limiting chronic diseases which more or less clearly have their roots in hypogonadism, such as cardiovascular disease or osteoporosis. The questions in relation to the former have recently been reviewed¹, and with respect to the latter, particularly welcome is the article by García-Martín et al. in this issue². With a control group and with a randomised double blind design, the authors conclude that after a year of follow up the supplementation with 50 mg/day of isoflavones improves the bone parameters evaluated by ultrasound. There are favourable changes overall in some of the markers for bone metabolism evaluated, although without differences between the two groups. Perhaps the inclusion of a high number of cases would have revealed the suggested advantage of the isoflavones. It is curious that the intervention is associated with a decrease in osteoprotegerin (OPG). This finding is contrary to that published by other groups³, and *a priori*, is in opposition to the protection seen in the ultrasound parameters. Therefore, what cannot be discounted is that this data has even greater value, given the highly varied provenance of the OPG, and of its growing value as biomarker for cardiovascular disease, as the same group has just well reviewed⁴.

A literature review regarding the actions of the isoflavones in bone, however, shows that were are dealing with an area in which there are significant discrepancies. For example, a recent clinical trial

did not find a protective effect on the bone in women who took tablets containing 200 mg of isoflavones for two years⁵, and a meta-analysis which examined the action on bone mineral density came to similar conclusions⁶. However, another meta-analysis found there to be protection, albeit reduced⁷. Also, with regard to biochemical markers for bone metabolism, a recent meta-analysis found a slight protective action in relation to resorption⁸. Finally, there is very little information on the effect on ultrasound parameters, and again, in this, the value of the García-Martín study should be highlighted.

How to cast some light on this apparently tricky matter? Evidently, more clinical research is required, but this does not seem to be a simple task due to a series of conditions particular to these types of preparations.

On the one hand, is the great variety of molecules and the differences between their effects, including the metabolic capacities of the individual, which is not the same between, for example, the isoflavones genistein and biochanin A. And in terms of individual metabolism, it is also important to note that equol, a metabolite of daidzein, is generated by the action of intestinal flora, but only in certain individuals. There are no exact figures, but it is calculated that between 35% and 50% of individuals are capable of producing it. This adds an important factor to the variability of the results of therapeutic actions, given that equol is considered to be one of the most powerful isoflavones. In this area, it would have been useful if the García-Martín² study had included details of the mixture of isoflavones used.

But on the other hand, there is the response threshold. A meta-analysis which examined the action on vasomotor symptoms found a clear dose-dependent action in a period which reached up to 160 mg/day of isoflavones, with a threshold of acceptability of approximately 80 mg/day⁹. There are also differences between purified isoflavones and soya protein, at least in the matter of cardiovascular protection, as has been demonstrated in the analysis of the American Heart Association¹⁰.

In conclusion, therefore, this is a promising field, but one in which order needs to be imposed. What needs to be clarified is what isoflavones should be used, purified or not, at what dose and, probably, what type of user will obtain, or not, some protective effect. Studies such as that of García Martín are particularly welcome, given their good design which contributes to the accumulation of more evidence.

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