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Claimed effects, outcome variables and methods of measurement for health claims proposed under Regulation (EC) 1924/2006 in the framework of bone health

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ABSTRACT

Several foods or food components have been the object of application for authorization of health claims on bone health, pursuant to Regulation (EC) 1924/2006. For most of them, the European Food Safety Authority (EFSA) has issued negative opinions mainly for reasons pertaining to an insufficient substantiation of the claim, including the choice of not appropriate outcome variables (OVs) and methods of measurement (MMs). The present manuscript refers to the collection, collation and critical analysis of OVs and MMs related to bone health compliant with the Regulation. The definition of the keywords, the PubMed search strategies and the creation of databases of references were performed to critically analyse the OVs and their MMs on the basis of the literature review. The assessment of each OV and related MM was defined according to its appropriatness in relation to the claimed effects proposed. The results obtained are relevant for the choice of the best OVs and MMs, to be used not only for the substantiation of health claims on bone health, but also in general research performed with different purposes. Moreover, the results can be used by EFSA during the update of guidance for the scientific requirements of health claims on bone health.

1. Introduction

Bone health is an important factor in determining an adequate quality of life. In fact, in spite very few people die as a direct result of bone disease, these diseases can have a significant impact on the everyday lives of those who suffer from the disease, other than being responsible for high healthcare costs [1]. Among bone diseases, defined as conditions that result in the impairment of normal bone function and can make bones weak, the most common is osteoporosis, characterized by low bone mass and deterioration of bone structure, which predisposes to an increased risk of fractures especially in the elderly and mostly in postmenopausal women [2]. It has been estimated that

Abbreviations: ALP, Alkaline Phosphatase; BMC, Bone Mineral Content; BMD, Bone Mineral Density; CPII, C-terminal type II procollagen peptide; CT, Computed Tomography; CTXII, C-terminal crosslinking telopeptide; DXA, Dual energy X-ray Absorptiometry; ECLIA, Electrochemiluminescence Immunoassay; ECM, Extra-Cellular Matrix; ELISA, Enzyme-Linked Immunosorbent Assay; FRAX, Fracture Risk Assessment Tool; GH, Growth Hormone; HPLC, High Pressure Liquid Cromatography; MRI, Magnetic Resonance Imaging; OA, Osteoarthritis; PICP, C-terminal type I procollagen peptide; PIINP, N-terminal type II procollagen peptide; PINP, N-terminal type I procollagen peptide; pQCT, Peripheal Quantitative Computer Tomography; PTH, Pararathyroid Hormone; QCT, Quantitative Computer Tomography; RCTs, Randomized Controlled Trials; RR, Relative Risk; SPA, Single Photon Absorptiometry; VAS, Visual Analogue Scale; VFA, Vertebral Fracture Assessment; WHO, World Health Organization; WOMAC, Western Ontario and McMaster Universities

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osteoporosis causes up to 9 million fractures annually worldwide [3].

Following fractures, like hip fractures in the elderly, most people are not able to return to their activities of daily living, with a loss of independence that can have negative consequences on the emotional domains of the quality of life for both the individuals who suffer them and for their families [4,5].

In spite bone health can be influenced by genetic factors, controllable lifestyle factors such as diet and physical activity are responsible for a notable portion of bone mass and structure [6]. Regarding nutrition, it has been shown that a balanced diet can help increase or preserve bone mass. In particular, calcium and vitamin D intake are now known to be major contributors to bone health, even if also other nutrients can play a role in this scenario. That is why most of the dietary guidelines recommend the daily consumption of calcium and vitamin D-rich sources such as dairy foods [7,8].

In this scenario, many foods or food component have been the object of applications for authorisation of health claims pursuant to Regulation (EC) 1924/2006. Some of these applications have received a positive opinion by the European Food Safety Authority while other received negative opinions due to different reasons. These may include an insufficient characterization of the food/food component, the choice of an inappropriate claimed effect. However, most of the negative opinions were due to an insufficient substantiation of the claim, for reasons related to the sample size, the statistical analysis, the characteristics of the subjects, as well as the choice of outcome variables (OVs) and/or methods of measurement (MMs).

In this scenario, a project has been developed with the aim of improving the quality of applications provided by applicants to EFSA, through an appropriate choice of OVs and MMs, as described in Martini et al. [9]. This manuscript referes to the collection, collation and critical analysis of OVs and MMs related to bone health.

2. Materials and methods: search strategy

OVs and MMs were collected from the relative Guidance document [10], from the applications for authorization of health claims under Articles 13.5 and 14 of Regulation 1924/2006 related to bone health, as well as from comments received during public consultations. As described in Martini et al. [9], the OVs and their MMs were included only if the food/food constituent(s) was sufficiently characterized and the claimed effect was considered to be beneficial. Following this decision tree, 3 claimed effects with 8 OVs were evaluated under Article 13.5, whereas 2 disease risk reduction claims and 1 claimed effect referred to children development were selected under the Article 14. For each OV, a database of references was created on PubMed and was used for the critical analysis of the OVs and the MMs. Each OV and related MM was ranked in one of the following categories: (i) appropriate; (ii) appropriate only/better if in combination with other OV or MM; (iii) not appropriate per se; (iv) not appropriate in relation to the specific claimed effect proposed by the applicant(s), (v) not appropriate alone, but useful as supportive evidence for the scientific substantiation of the claimed effect.

3. Results: critical evaluation of outcome variables and methods of measurement

3.1. Function health claims Art 13 (5)

3.1.1. Improvement/maintenance of bone mass

3.1.1.1. Bone mineral density. It is well assessed that bone is a metabolically active tissue and its mass results from the co-existing activity of osteoblasts and osteoclasts, leading to a balance between bone deposition and resorption during adult life. Thus, the bone mass is the total amount of trabecular and cortical bone, the last representing 20% of total bone in the body [11]. Bone mass is considered as a synonym of bone mineral density (BMD); indeed, based on the evaluation methodology, bone mass amounts to the sum of two components: areal BMD, which is a two-dimensional measurement expressed in g/cm^2, usually obtained through Dual energy X-ray Absorptiometry (DXA) scans, and volumetric BMD, expressed in g/cm^3, which is a 3D measure given by Quantitative Computer Tomography (QCT). Volumetric BMD can discriminate between cortical and trabecular bone, thus emerging as qualitative, other than quantitative medical tool only. Physiologically, BMD reaches its peak in the early adulthood in both males and females and subsequently declines with the aging starting from the fifth decade [12]. Thus, lifestyle (e.g. cigarette smoking, excessive alcohol consumption, prolonged immobilization) or genetic factors can accelerate this process. At the opposite, bone mass increases in response to mechanical stimuli (e.g. physical activity and gravity), that are able to at least maintain bone homeostasis. Bone mass is also influenced by ethnic differences and sex [13]. BMD distribution describes the local mineral content of the bone matrix, reflecting mineralization kinetics, bone turnover, and average bone matrix age. Any deviations from normal BMD distribution has significant biological and clinical relevance.

To evaluate the appropriateness of BMD as OV of improvement/maintenance of bone mass, the literature deriving from database #1 was critically evaluated (Table 1).

BMD measurement is widely carried out both in physiologic and in pathologic context to evaluate bone strength and a well consolidated tool for fracture risk assessment and management [14]. The peak bone mass (i.e. the total amount present in the body at the accomplishment of skeletal growth) is a significant determinant of fracture risk especially in the elderly when risk of falling is an additive risk for fractures. Considering that vertebral fracture is the hallmark of osteoporosis, bone mass, and in particular its component, i.e. areal BMD, is a valuable parameter for diagnosis and follow-up of osteoporosis in the presence or in the absence of pharmacological intervention. Sites where BMD is frequently measured are hip, lumbar spine and femoral neck [13]. BMD analysis is recommended in case of previous fractures in adult life occurring spontaneously, history of parental hip fractures, current smoking, glucocorticoids exposure, daily alcohol intake malnutrition, premature menopause (< 45 years) and pathologies as rheumatoid arthritis, osteoporosis, type I diabetes, chronic liver disease, osteogenesis imperfecta, long-standing untreated hyperthyroidism and hypogonadism. By considering that the absolute risk of fracture is not the same between women and men and that it is also influenced by age, BMD measurement must be adjusted for sex and age. BMD measurements can be expressed quantitatively by comparing the results to those obtained in healthy young adults, or age-matched adults of the same sex. The former comparison defines whether a person has a bone mass reduction or osteopenia, while the latter defines, in part, a person's future fracture risk, relative to a cohort of the same age and sex. Thus, BMD values are expressed as z-scores, the number of standard deviations reflecting how a patient's BMD differs from the average BMD corresponding to their age and sex in the whole population. Currently, WHO defines the scores of BMD as follows: a T-score ≥ -1 means normal bone, a T-score between -1 and $-2{,}5$ denotes osteopenia and a T score $\leq -2{,}5$ stands for osteoporosis [15]. Thus, even if the evaluation of BMD alone is sufficient for the assessment of bone mass and bone health status, a combination of BMD and vertebral fracture assessment (VFA) or, even better, a combination of BMD, VFA and FRAX significantly increases the efficacy in identifying individuals who need treatment [14]. In conclusion, BMD can be used as appropriate outcome variable for the scientific substantiation of health claims in the context of improvement/maintenance of bone mass.

3.1.1.1.1. Dual energy x-ray absorptiometry. DXA, also known as bone densitometry or bone density scanning, can accurately analyze bone and non-bone tissue, providing a quantification of BMD, bone mineral content (BMC), fat mass and soft lean mass. It is considered the gold standard by WHO for measuring bone mass [16]; it has been

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