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Introduction

- Poor bone health is a major public health problem, at least in Western countries.
- Up to 60% of the variance in bone mass is determined by genetic factors.
- Environmental factors account for the remainder, including nutritional intake.

PLAN OF THIS TALK

- History of opinion made by EFSA in the field of bone health
- The problem of surrogate markers in bone health
- EFSA Guidances
- The GREES point of view
- Few words on cartilage health

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- The Panel concludes that a cause and effect relationship has not been established between the consumption of Femarelle® and increased BMD, increased bone formation, or decreased risk of osteoporosis or other bone disorders in post-menopausal women.

- The intervention study compared the effect of two intake levels (644 mg/day or 344 mg/day) of DT56a soy derivative on BMD in postmenopausal women.
- A significant difference between the two treatment groups for the change in BMD over the 12 month intervention period was observed for the lumbar spine (BMD increased in the group receiving 644 mg/day) but not for the femoral neck.

- A cause and effect relationship was established between the intake of calcium, either alone or in combination with vitamin D, and reducing the loss of BMD, which may contribute to a reduction in the risk of bone fracture.
- Based on large RCTs and meta-analyses with BMD and fracture as endpoint

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Definition

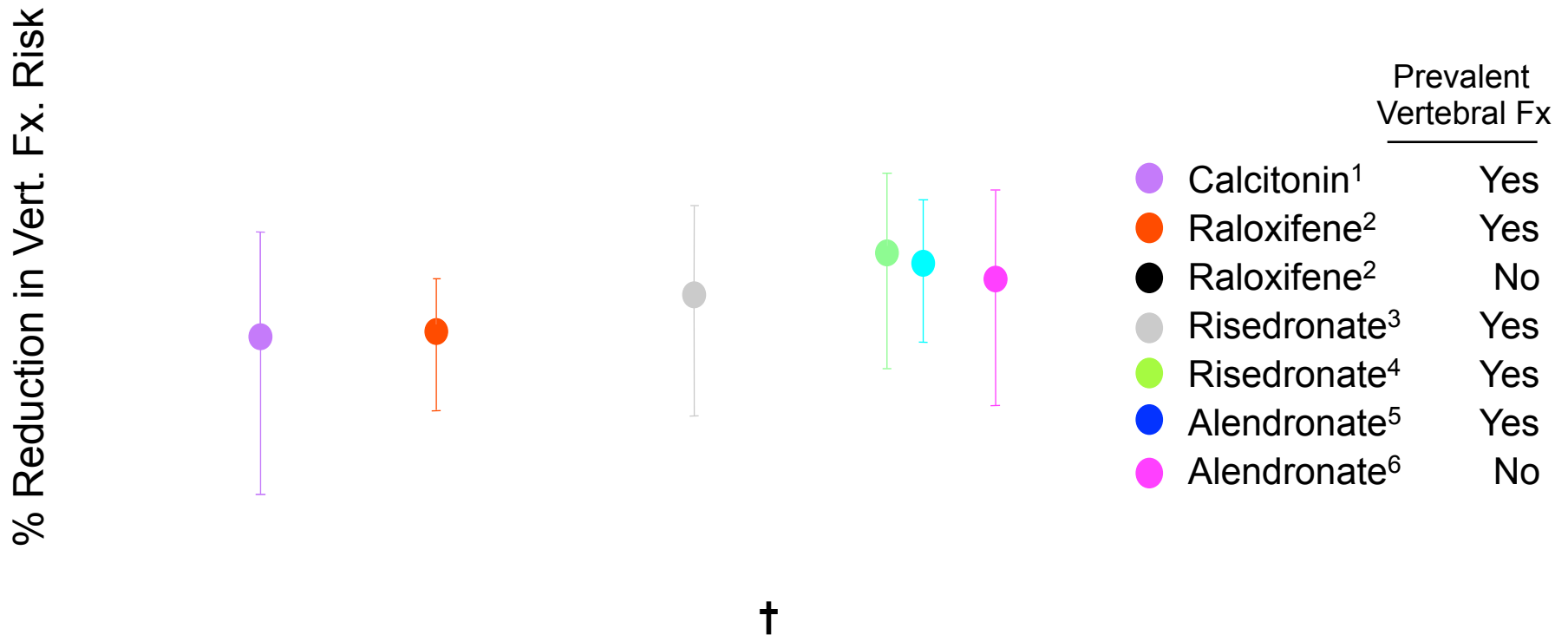
- A surrogate endpoint is "a biomarker intended to substitute for a clinical endpoint".
- Surrogate markers are used when the number of events is very small, thus making it impractical to conduct a clinical trial to gather a statistically significant number of endpoints.

Relation of BMD to Fracture Risk

**How important is
change in BMD with
treatment?**

- Treatments for osteoporosis increase BMD & reduce risk
- Is the reduction in fracture risk with treatment due to the increase in BMD?

Relationship between the Risk of Vertebral Fracture and Increases in BMD*



*Not head-to-head comparison; †vs placebo. Error bars represent 95% confidence intervals.

¹Chesnut CH, et al. *Am J Med.* 2000;109:267-276; ²Ettinger B, et al. *JAMA.* 1999;282:637-645; & data on file, Eli Lilly and Company; ³Harris ST, et al. *JAMA.* 1999;282:1344-1352; ⁴Reginster J-Y, et al. *Osteoporosis Int.* 2000;11:83-91; ⁵Black DM, et al. *Lancet.* 1996;348:1535-1541; ⁶Cummings SR, et al. *JAMA.* 1998;280:2077-2082.

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- This draft guidance document was endorsed by the NDA Panel on 15 25 March 2011, and is released for public consultation from 26 April 2011 to 31 August 2011.

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Objective

- To define the relevant biomarker for bone health
- To provide recommendations for the design and the methodology of clinical studies which need to be fulfilled to assert claims related to bone health.

Methods

- Two 1-day meetings organized by the Group for the Respect of Ethics and Excellence in Science (GREES)
- Literature search up to August 2010 using keywords including health claims, nutrition, bone, osteoporosis, clinical study methodology, surrogate endpoint.

Results

- The GREES panel considers that :
 - clinical data in humans are indispensable, and that health claims cannot be accepted solely on the basis of animal data;
 - different levels of health claims should be considered based both on the endpoint used and on the information provided by animal studies.

Results

- Pre-clinical models
- Acceptable health claims in human bone health
- Design of clinical studies

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Pre-clinical models

- The assessment of bone strength is considered to be the most relevant in the field of bone health claims.
- The assessment of bone health would benefit from the measurement of bone strength *in vivo*.
- No validated non-invasive tools capable of measuring bone strength *in vivo* are available to date.
- Biomechanical tests of resistance to fracture provide an objective measure of overall bone strength.

Pre-clinical models

- Objectives:
 - To assess a direct effect of the food product on bone strength
 - To better understand the mechanism of action of the food product
 - To validate surrogate variables used in human animal data to see if these variables reflect bone strength

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Acceptable health claims

- The GREES panel considers that
 - six different health claims could be accepted for an effect of food products on bone health.
 - different wording to reflect the level of evidence of the effect could be used depending on the effect that is (always), may (demonstrated only under certain circumstances) or might be (logically expected benefit from physiology but yet not demonstrated) beneficial for bone health.

1. Improvement of calcium bioavailability

- Defined as the proportion of calcium in foods which is absorbed and utilised for normal metabolic functions.
- Could have an article 13 claim:
 - “X increases calcium absorption”
 - “X increases calcium bioavailability”.

2. Maintenance of bone metabolism

- Through an effect on osteoclast regulatory proteins
- Markers of osteoclastogenesis include RANKL and OPG
- Markers of osteoclast number include TRAcP and Cat K
- Would not fulfil a claim related to article 14.
- Might have the label under the article 13: “X contributes to the maintenance of bone metabolism”.

3. Maintenance or changes in bone turnover marker

- Reference markers of bone formation (s-PINP) and resorption (s-CTX)
- Might have the claim:
 - “X maintains normal bone remodelling that could contribute to the normal structure and function of bones”
 - “X increases markers of bone formation that could contribute to the normal structure and function of bones”
 - “X decreases markers of bone resorption that could contribute to the normal structure and function of bones”.

3. Maintenance or changes in bone turnover marker

- BTMs are only indicators of fracture risk,
- Change in BTM induced by a product is not necessarily associated with a change in fracture risk or bone strength.
- Animal models are useful to assess if changes in BTMs due to the intake of the food product are associated with an increase in bone strength.

3. Maintenance or changes in bone turnover marker

- Effect on BTMs together with
 - animal studies that showed improved bone strength or
 - a relationship between changes in BTMs induced by the food product and bone strength
- Could have the claim:
 - “X contributes to the maintenance of normal bone remodelling (or increases bone formation or decreases bone resorption) that is associated with bone strength
 - “X contributes to the maintenance of normal bone remodelling (or increases bone formation or decreases bone resorption) that increases bone strength”
 - “X increases bone strength”

4. Maintenance or improvement in bone structure

- Methods include *in vitro* μ CT, *in vitro* μ MRI, *in vivo* pQCT, and *in vivo* high-resolution MRI
- Assessment of bone structure is not sufficiently validated to be a reliable surrogate of bone strength.
- Animal models are needed to assess the relationship between changes in bone microarchitecture induced by the food product and any increase in bone strength.

4. Maintenance or improvement in bone structure

- Effect on microarchitecture together with
 - animal studies that showed improved bone strength or
 - a relationship between changes in microarchitecture induced by the food product and bone strength
- Could have the claim:
 - “X improves bone microarchitecture that increases bone strength”
 - “X increases bone strength”

5. Maintenance or increase in bone mineral density

- BMD is only a surrogate marker for bone strength or fracture risk,
- Changes in BMD with a food product are not clearly associated with changes in bone strength or fracture risk
- Increase in BMD may not be associated with an increased bone strength or decreased fracture risk

5. Maintenance or increase in bone mineral density

- A food product with a positive effect on BMD could have the claim:
 - “X increases BMD. A low BMD is associated with an increased risk of fracture”
 - “X maintains BMD. A low BMD is associated with an increased risk of fracture”.

5. Maintenance or increase in bone mineral density

- Effect on BMD, together with
 - animal studies showing an improvement in bone strength or
 - a relationship between BMD changes induced by the food product and bone strength
- Could have the claim:
 - “X increases (or maintains) BMD that could reduce the risk of fracture”
 - “X increases (or maintains) BMD that increases bone strength”
 - “X increases bone strength”.

6. Reduction of the risk of fracture

- According to the regulation it cannot be claimed as such without mentioning the effect on a risk factor.
- A reduction in the fracture risk is obviously supportive for a claim on the reduction of an identified risk factor.

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1. Population

- Representative of the population targeted for the food product.
- The tested population must be equivalent to the user population with respect of ethnicity, age, physiological status (such as menopause for example), life habits (such as exercise) and diet.
- No densitometric criteria are required for inclusion.

2. Design

- The ideal design would be a multicentre RCT.
- The control could be a placebo, another active product or nothing, depending on the tested food.
- When possible, subjects and/or investigators should be blinded of the intervention.
- When RCT is not possible (in practice or from an ethical point of view):
 - Well-designed prospective cohort studies
 - Case-control studies
 - Observational studies
 - Cross-over studies
 - All acceptable if accompanied by other data (e.g. animal data, effect on multiple surrogate endpoints).

3. Duration of study

- Should be predetermined
- Should depend on the outcome

4. Statistical analysis

- Intention-to-treat analysis
- Beta risk equal to or less than 20%.
- Sample size of the study must be calculated prior to the start of the study.
- Possible confounding variables should be managed using appropriate statistical analysis.
- Within group (end vs baseline) and between groups comparisons should be made.

5. Diet habit & lifestyle

- Critical effect modifiers must be controlled
- Intakes of other nutrients or foods, on which the tested nutrient is dependent, must be optimized.
- Any supplementation with other food products known to have an effect on bone (e.g. calcium and/or vitamin D) should be consistent within all patient groups.

6. Observance

- Should be monitored during the study

7. Safety

- All adverse experiences should be fully documented with separate analysis of adverse events, dropouts and patients who died while being on the study.

Conclusion

- The level of health claim may differ according to
 - the surrogate end-point used
 - additional animal studies provided to support the claim.
- The ideal study design is a RCT but, in some particular cases, prospective cohort, case-control or observational studies can be acceptable.
- General principles of the consensus reached are in line with the principles adopted in the EFSA's published opinions.
- This consensus is subject to future modifications when new validated surrogate markers will be available.

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On the basis of the data available, the Panel concludes that a cause and effect relationship has not been established between the consumption of glucosamine, either as glucosamine hydrochloride or as glucosamine sulphate, either alone or in combination with chondroitin sulphate and maintenance of normal joints in the general population.

- General vs specific population
- Validated tools in the general population
- Effect on structure (X-ray)
- Surrogate markers

GENERAL CONCLUSION

- No definitive answer.
- No definitive guidelines.
- Improvement in surrogate is necessary.
- Collaborations are very important.

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