

ABSTRACT

## World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2020): ESCEO-WHO Collaborating Centre for Public Health Aspects of Musculoskeletal Health and Aging Symposium Abstracts (ESCEO-WHOCC)

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### ESCEO-WHOCC1

#### GUT MICROBIOTA AND INFLAMMATION/INFLAMMAGING C. Franceschi<sup>1,2</sup>

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Human aging is characterized by a chronic, low-grade inflammation, a phenomenon that I suggested to term "inflammaging." Inflammaging is a highly significant risk factor for both morbidity and mortality in the elderly people, as most if not all age-related diseases (ARDs) and geriatric syndromes (GSs) share an inflammatory pathogenesis. The last development of this inflammatory theory of aging ("garbaging") suggests that the most important/causal inflammatory stimuli fueling inflammaging are to be identified in the lifelong, persistent exposure to exogenous, non-self microbial agents and environmental pollutants and to the age-related dysregulation of the production of endogenous, self and quasi-self (gut microbiota, GM) "molecular garbage". Such garbage is continuously/physiologically produced as a consequence of cell death (necroptosis; altered and misplaced molecules), metabolism and GM function, but also continuously neutralized by the remodeling and adaptive capability of the body (degradation of inflammatory molecules/molecular fragments; production of anti-inflammatory molecules) which quickly and efficiently down-regulate inflammatory responses in young subjects but fail to do so in older bodies. The causal role in inflammaging of age-related dysbiosis is suggested by animal data showing that aged GM contributes to systemical inflammaging after transfer to germ-free mice. I will illustrate the following points: i) the complex age-related remodeling of GM lifelong and the peculiar shotgun GM signature we found in centenarians (100+) and semi-supercentenarians (105+); ii) recent data obtained within the framework of the European project NU-AGE showing that taxa enriched by adherence to the Mediterranean Diet for one year were positively associated with: a) markers of lower frailty and improved cognitive function, and negatively associated with inflammatory markers including C-reactive protein and Interleukin-17; b) an increase in short/branch chained fatty acid production and lower production of secondary bile acids, p-cresols, ethanol and carbon dioxide; c) key-stone interaction positions in the GM network; iii) a parsimonious, mechanistic model of GM focused on GM biodiversity as a major characteristic of complex ecological systems which is a robust predictor of healthy/non-healthy status in aged humans.

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### ESCEO-WHOCC2

#### ROLE OF GUT MICROBIOTA IN NON-COMMUNICABLE DISEASE AND OSTEOARTHRITIS MANAGEMENT

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The prevalence of musculoskeletal diseases such as osteoarthritis (OA) increases not only because of longer life expectancy but also because of the modern lifestyle and diets which promote chronic low-grade inflammation and obesity. Adverse alterations of the gut microbiota (GMB) composition, called microbial dysbiosis, may favor metabolic syndrome and inflammaging, two important components of non-communicable diseases onset and evolution. The potential relationships between GMB and risk factors, pathogenesis and medications of OA will be discussed. The contribution of GMB is supported by observational or dietary intervention studies in animal models of OA and in humans. In addition, GMB interacts with several well-recognized risk factors of OA. Lastly, GMB is a critical determinant of drug metabolism and bioavailability and may influence the response to OA medications. Further research is needed to determine whether interventions targeting GMB or its metabolites may move the field of OA from symptomatic management to individualized interventions targeting its pathogenesis.

### ESCEO-WHOCC3

#### CLINICAL APPLICATION OF BONE TURNOVER MARKERS IN POST-MENOPAUSAL OSTEOPOROSIS

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**Introduction** It is well known that elevated blood biochemical bone turnover markers (BTMs) are associated with increased fracture risk, rate of bone loss, and poor treatment adherence, but their clinical utility is presently unclear. A consensus group was gathered with the aim to provide guidance to clinicians regarding the use of BTMs in patient evaluation in postmenopausal osteoporosis, in the monitoring of treatment efficacy and adherence to osteoporosis medication, and in fracture risk prediction.

**Methods:** A working group with osteoporosis specialists and clinical scientists was invited by the Scientific Advisory Board of European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), to discuss and provide recommendations regarding the use of BTMs in clinical practice.

**Results:** Serum bone formation marker PINP and resorption marker  $\beta$ CTX-I were considered the preferred markers for evaluating bone turnover in clinical practice due to their high specificity to bone, documented performance in clinical studies, widespread use and acceptable analytical variability. However, as a result of low sensitivity and specificity, BTMs were considered to have no place in diagnosing osteoporosis, but could provide some guidance in patient evaluation where high values may indicate the need to investigate some causes of secondary osteoporosis. Measuring serum  $\beta$ CTX-I and PINP can slightly improve fracture prediction, with a gradient of risk of about 1.2 per SD increase in the BTM in addition to known clinical risk factors and bone mineral density. For an individual patient, assessing BTMs are not particularly useful in projecting treatment efficacy or bone loss. In contrast, it is recommended that BTMs PINP and  $\beta$ CTX-I could be used to monitor treatment adherence to oral bisphosphonates. An observed suppression of the serum BTMs to levels in the lower 50% of the reference interval in healthy and young premenopausal women or greater than the least significant change is strongly associated with treatment adherence.

**Conclusion:** The currently available evidence suggests that the main clinical utility of BTMs is for evaluating adherence to oral bisphosphonate therapy.

#### ESCEO-WHOCC4

#### ALGORITHM FOR THE ASSESSMENT OF ANTI-OSTEOPOROSIS TREATMENTS BY BONE TURNOVER MARKERS

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Virtually all of the currently used treatments for osteoporosis exert their effects by modifying bone cell activity; anti-resorptives decrease bone turnover by initially suppressing osteoclastic bone resorption followed by a consequential decrease in bone formation. An opposite direction and pattern is observed with the anabolic, teriparatide, whereby an increase in osteoblastic bone formation is followed by a somewhat smaller increase in bone resorption. It is not unreasonable, therefore, to consider that bone turnover markers (BTM) might be of clinical utility in the assessment of such treatments, and recent guidelines have recommended the use of serum PINP and  $\beta$ CTX-I as they are responsive to treatment and have low within-subject variability.

A commonly proposed approach to determine if the change in the bone marker is physiologically relevant (and not due to measurement or sampling error) is to compare the observed change with the least significant change (LSC, usually defined as 2.77 times the intra-individual coefficient of variation). Another approach that has been proposed is to define