IN-SILICO APPROACH TO ELUCIDATE THE PATHWAYS LEADING TO PRIMARY OSTEOPOROSIS: AGE-RELATED VS. POSTMENOPAUSAL

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Introduction

Primary osteoporosis (OP) is the most common form of OP and includes gonadal insufficiency-related OP (type I), such as postmenopausal osteoporosis (PMO), and senile OP (type II), also called age-related OP (ARO).
Understanding the etiology of the disease and in particular discerning which factors are intrinsic to ARO and which are intrinsic to PMO is key to treatment design, since both can concur in postmenopausal women but only some can be counteracted by medication.
We have implemented a previously developed bone cell population model (BCPM) of bone remodeling [1] to analyze the effect of all those factors. The comparison between the clinical results of bone loss observed in men and women with age [2] and the in-silico results of the simulation of ARO (for men) and ARO+PMO (for women), was used to elucidate the importance of each factor independently or in conjunction with others.

Methods

The BCPM developed by Martin et al. [1] (see Fig.1), has been implemented and modified to consider the effecs of ARO and ARO + PMO.

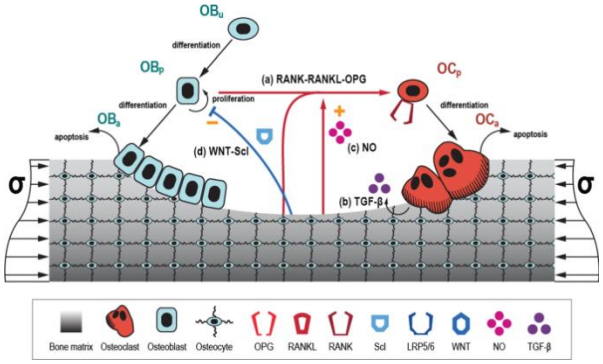

Fig. 1: Scheme of the bone cell population model.

Regarding ARO, the literature suggests: (1) a gradual increment of sclerostin production with age [3] and (2) a decrement of concentration of TGF-β (transforming growth factor beta) within bone matrix [4] as the cause of bone density loss (BDL). For PMO, three factors were discussed in the literature to produce BDL as a consequence of the drop of oestrogen after menopause: (3) increment of RANKL expression, (4) increased RANK responsiveness of osteoclasts, (5) decrease of OPG secretion by osteoblasts [5]. These effects have been modelled using a linear function of time in the case of sclerostin increase and bilinear functions of time in all other cases. The results of the BCPM were fitted to the clinical data of BDL corresponding to men (ARO) and women (ARO+PMO) [2] using a gradient-based optimization algorithm, so obtaining the temporal functions of the five factors that minimized the error between the clinical and the in-silico results.

Results

Fig.2 shows the best fit of the model to the clinical data.

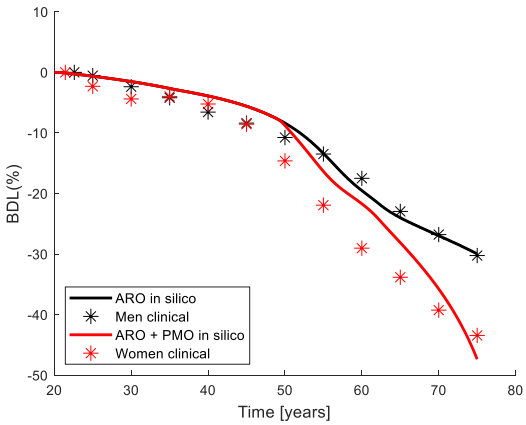

Fig. 2: Comparison of in-silico and clinical results [2].

Discussion

The proposed BCPM was able to reproduce the clinical results of BDL for both men and women. Here, we hypothesized that BDL due to ARO is similar in men and women, since ARO is caused by a decrease in androgens and estrogens respectively, and both processes have a similar effect on sclerostin and TGF-β [6]. Moreover, the increase of sclerostin explained BDL in ARO better than the decrease of TGF-β. In PMO, the three effects suggested in the literature produced equivalent results in our BCPM model in terms of BDL, although it is likely that they affect other biological processes whose effects are not considered here.

References

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Acknowledgements

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