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Physical exercise as part of the rehabilitation in primary osteoporosis: insights into the signal transduction bone formation pathways

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Abstract: Primary osteoporosis, a geriatric bone metabolic condition affecting both the mineral density and the microarchitecture, comes with a complex burden. Bone turnover markers tidily reflect the changes of skeleton status that are part of the physiological process or theyhighlight the abnormal status including in osteoporosis in addition to other biomolecules evaluation such as hormones, inflammatory markers, myokines and adipokines. In this narrative review, we aimed to highlight several aspects regarding osteoporosis-related rehabilitation amid mitigating the role of physical exercise as bone formation booster. Bone turnover markers assays, by capturing the essence of the bone remodelling, registered a great progress during latest years, thus show-ing an enhanced index of applicability in daily practice (despite being known and studied for more than three decades). Irisin, a novel player in the muscle-bone-metabolism cross-talk, represents a muscle-derivate hormone that is expected to highlight the interplay between physical exercise and bone formation. Other concurrent signal transduction pathways include recently described biomarkers such as preptin or the spectrum associated with serotonin-LRP5-Wnt/beta catenin canonical and non-canonical loops. Current pitfalls of the topic include the personalized recommendation of physical activity due to severe co-morbidities, the lack of homogenous studies to measure the intervention and the consecutive bone health and great variations of using the bone turnover markers amid daily practice in different centers. To conclude, part of the monitoring protocol in

osteoporotic patients under specific medication against osteoporosis or during bisphosphonates drug holiday, bone turnover markers assays stands for a practical insight in every day practice. The contributing role of physical exercise to boost bone formation as reflected by these biomolecules is well understood across a multitude of signal transduction pathways. However, a current gap in practical use and surveillance of the prescription of physical activity, mechanical load and rehabilitation programs in these patients is confirmed so far.

Keywords: osteoporosis, bone, fracture, rehabilitation, physical exercise, bone turnover markers, osteocalcin.

1. Introduction

Primary osteoporosis, a geriatric bone metabolic condition affecting both the mineral density and the microarchitecture, comes with a complex burden due to fragility (also, named spontaneous or low trauma) fractures affecting menopausal women and adult males over 50 years. The disruption between bone formation and resorption should address the reduction/prevention of bone resorption as well as the increase of bone formation. An adequate way of approaching the bone formation includes, among others, the physical exercise as a general contributor to a better skeleton health in association with being a strong player in the cross-talk with the skeletal muscle and the metabolic regulation [1-3]. Musculoskeletal aging comes as a natural process that might take a pathologic outcome under the umbrella of various risk factors or lack of preventive measures including a healthy life style [4,5].

The dramatic epidemiologic impact of osteoporosis that is typically diagnosed in adults that might associate other co-morbidities such as metabolic or cardiovascular diseases and its increasing incidence in connection to the aging population in modern era justifies numerous insights seeking for a better outcome in this specific mater in order to elevate the overall quality of life and the prognostic [6-8]. A part from the medication against osteoporosis and vitamin D, respectively, calcium supplementation, sun exposure, an adequate intake of specific nutrients and maintaining an active life are mandatory [9-11].

Bone turnover markers tidily reflect the changes of skeleton status that are part of the physiological process or they highlight an abnormal status including in osteoporosis in addition to other biomolecules such as hormones, inflammatory markers, myokines, and adipokines [12-14].

In this narrative review, we aimed to briefly overview several aspects regarding osteoporosis-related rehabilitation amid mitigating the role of physical exercise as bone formation booster underlying a multitude of signal transduction pathways.

2.Evidence-based literature data

2.1. Bone turnover markers assays

Bone turnover markers, by capturing the essence of the bone remodelling, registered a great progress during latest years, thus showing an enhanced index of applicability in daily practice (despite being known and studied for more than three decades). They, however, embrace a large variation from one individual to another, from one condition to another; hence, their profile is primordially used in clinical studies rather than a single individual at a single point in time. Numerous factors may influence their level such as age, gender, hormonal status, ethnicity/population, co-morbidities, concomitant drugs (from glucocorticoids to specific medication against osteoporosis, etc.), methods of assessment, blood half time, fasting state, physical exercise, etc. [15-17].

A bone biopsy might equally reflect the skeleton dynamics, but this harbours side effects and lack of availability in many centres, thus it has a limited use in every day

practice based on an individualized decision [15,18,19]. Bone turnover markers showed their utility in various bone metabolic conditions such as osteoporosis, osteomalacia, Paget's disease of the bone, bone disease in primary and secondary (renal) hyperparathyroidism, respectively, bone metastasis, etc. [20-22].

Overall, the bone formation profile mainly includes the products of osteoblasts as follows: alkaline phosphatase (preferably, the sequence with bone specificity), osteocalcin, and P1NP (procollagen Type 1 N-terminal propeptide), while the most common bone resorption markers are serum CrossLaps or CTX (C-telopeptides of type I collage), urinary N-telopeptides of type I collagen, and tartrate-resistant acid phosphatase type 5b (TRACP-5b) [23-25].

2.2. Osteogenic effects of physical activity

These mentioned aspects have been studied in pre- and post-menopausal osteoporosis, as well as secondary types such as glucocorticoid-induced osteoporosis or the form that is associated with early long term untreated hypogonadism. One of the most important practical points in addressing this issue is represented by the methods of quantification of the physical exercise protocols in order to achieve a good level of statistical evidence across similar studies' methods and protocols. The outcomes are usually represented by the assays concerning the serum and/or urinary bone turnover markers profile, hormones of mineral metabolism, particularly, PTH (parathormone), and central DXA (Dual-Energy X-Ray Absorptiometry) results [26-28].

For instance, a randomized controlled study of small cohort size published in 2023 and enrolled premenopausal women; P1NP, and osteocalcin as bone formation markers were assessed after three months, respectively, after six months of intervention (namely, a daily brisk walk of 10,000 steps plus 60 jumps by using an accelerometer-based wearable device) versus controls (who underwent usual lifestyle without any specific intervention) revealed statistically significant differences in the level of the mentioned bone turnover markers as well as the six-month femoral neck bone mineral density (BMD) according to DXA scans. The P1NP reduction also statistically significant correlated with the femoral neck BMD elevation (correlation coefficient of $r = -0.73$, $p < 0.001$). Hence, this type of intervention might prove useful for boosting bone formation [29].

Alternatively, pulsed electromagnetic field (PEF) in addition to the physical exercise was also proved helpful in adult men and menopausal women with osteoporosis and osteopenia [30,31]. One recent controlled study (N = 95 males diagnosed with osteoporosis and osteopenia with a mean age of 51.26 years) showed across three subgroups of analysis (PEF plus exercise; placebo PEF plus exercise, respectively, PEF alone) that after twelve weeks total hip and lumbar BMD was statistically significant increased in all three groups (group 1 and 2 > group 3), respectively, associated with an elevation of bone turnover markers (group 1 and 2 > group 3) [32].

Another type of potentially useful intervention in osteoporosis is Nordic walking. This was especially useful in type 2 diabetic or pre-diabetic females and those associating non-alcohol fatty liver disease [33,34]. Also, a randomized controlled trial showed the effects of practicing recreational team handball according to a planned exercise programme provided for untrained menopausal osteoporotic women. This 16-week study on 67 females identified a statistically significant lumbar BMD increase of +1.5%, respectively, of bone mineral content (of +2.3%) in addition to an elevation of serum P1NP and osteocalcin levels in studied group versus controls [34]. This type of activity might help not only the bone turnover, but, also, it might increase the postural balance, thus preventing the falls as important contributors to osteoporotic fractures [35-37]. Of note, fall prevention also includes establishing an adequate supplementation of vitamin D, and calcium, as well as correction of the glucose profile anomalies and associated variations during day time, vision disturbances and blood pressures changes as part of an optimum life style in this specific matter [38-40].

2.3. Irisin: a novel player in the muscle-bone-metabolism cross-talk

Irisin, a muscle-derivate hormone represent a cutting edge in exploring osteoporosis and an important part of the signal transduction pathways connecting metabolism to bone cells, once released from the muscle upon activation via physical training (or cold exposure) [41]. Important correlations with bone status have been described in healthy humans of any age, as well as osteoporotic individuals (with or without fragility fractures), but on limited level of statistical evidence so far [42-44].

This cross-talk has been recently explored in murine experiments whereas streptozocin-induced type 1 diabetes mellitus displayed a reduced trabecular bone microarchitecture that was partially restored by irisin exposure. Moreover, this microstructure improvement associated with a decrease of diabetes-related high sclerostin (sclerostin suppresses osteocalcin in diabetic mousses and humans), hence, confirming a new pathway between physical activity and bone formation via irisin-sclerosin cross-talk [45].

Among the limited number of publications with concern to the clinical data on humans in the promising field of irisin applications we mention a study from 2022 in newly diagnosed type 2 diabetes patients (N = 66 subjects) versus controls (N = 82 humans) whereas serum irisin, as well as bone turnover markers P1NP, CTX and osteocalcin were lower in diabetic persons versus controls and irisin was lower in diabetic osteoporotic versus diabetic non-osteoporotic individuals. Multivariate regression showed that irisin was an independent predictor for osteoporosis/osteopenia in the studied group [46]. Other interventional studies in rats showed that reduced levels of bone formation markers and irisin in ovarectomized rats increased upon administration of irisin which stands for a future irisin applicability in humans who cannot practice physical exercise, hence, expecting a double benefit for the metabolic rate and the bone turnover [47].

2.4. Preptin as cutting edge biomarker: from pancreatic beta-cell to bone cells

A novel peptide (hormone) has been identified as serving to the metabolic-bone connection. Preptin is co-secreted with insulin from pancreatic beta-cells and controls glucose-related insulin release. It is derivate from pro-IGF2 (Insulin-like Growth Factor). Preptin levels are found high in diabetic patients, as well as those diagnosed with metabolic syndrome or polycystic ovary syndrome (hence, suggesting that it might be involved in their pathogenic traits). Moreover, in type 2 diabetes, prepeptin seems to boost the bone mineral density by acting on osteoblasts levels which release osteocalcin. Preptin is stimulated by physical exercise and it was found low in osteoporotic (non-diabetic) subjects. Its blood level was associated with serum osteocalcin [48-50].

Moreover, murine experiments showed in ovariectomized rats a deficiency of estradiol and preptin that were correlated with higher bone resorption markers and pro-inflammatory cytokines and decreased osteopontin. Estradiol administration and moderate physical exercise improved these parameters as did the exposure to alendronate to act against osteoporosis [51]. Additionally, other murine studies showed in obese mice with estrogen deficiency an increase bone formation upon simvastatin use in association with exercise [52]. As adropin, preptin seems a promising biomarker of bone-metabolic exploration and further clinical trials are necessary to pinpoint their applications in daily clinical practice [53-55].

2.5. Interleukins profile

Mechanical loading upon physical exercise induces an increase of interleukin-11 that elevates bone formation and decrease adipogenesis. Experimental studies with Wnt inhibitors that block Wnt signal transduction pathway proved a lowering of interleukin-11 levels with reduced bone mass, another important interplay between metabolic loops and bone formation [56]. Moreover, mechanical stress-induced interleukin-11 stimulates *IL-11* gene transcription and this converts the signal to the activation of Wnt-beta catenin

pathways by inhibiting Dkk2 expression [57]. Glucocorticoids inhibit *IL-11* gene activation via interaction with nuclear glucocorticoids receptors [58,59]. Another pathway of boosting interleukin-11 expression upon mechanical stimulation involves bone morphogenic proteins (BMPs) through BMP-Smad signaling [60,61].

2.6. Serotonin and LRP5-Wnt/beta catenin signal transduction pathway

Serotonin (5-hydroxytriptamine, a tryptophan metabolite), also named "two faces" molecule, displays opposite effects with regard to the bone turnover: central serotonin does not actually reach the skeleton, but indirectly contributes to the bone formation (as part of the cross-talk between the bone and the central nervous system, respectively, adrenergic system), while peripheral serotonin (mostly, gut-derivate which is biochemically identical to the central molecule, but peripheral and central serotonin is synthetized by two distinct genes, *Tph1* and *Tph2*, and it does not cross the blood-brain barrier) directly acts on each bone cell since osteoblasts, osteoclasts, and osteocytes hold serotonin receptors (serotonin-reuptake transporter) and the effect is to enhancing bone resorption; of note, all bone cells may synthetize serotonin [62-64].

The overall dominant effect of gut serotonin is negative on bone formation. The correlations between the bone status and the serum serotonin (as neuroendocrine biomarker) are less practical and its blood level does not serve as bone turnover marker since the most important skeleton contribution of 5-hydroxytriptamine is locally, being mediated via paracrine pathways [65-67]. These mentioned skeleton aspects might explain the bone loss and osteoporosis/osteoporotic fractures in selective serotonin reuptake inhibitors (SSRI) users [68-71]. For instance, INCUR study (one-year prospective, observational trial on 800 subjects and 64 of them experienced a fracture during the study) showed that subjects (who were nursing home residents) were at higher risk of fractures in association with SSRIs use (adjusted odds ratio of 1.76, 95% confidence interval 1.04-2.98, $p = 0.045$) [72].

On a deeper level, Lrp5 (low-density lipoprotein receptor-related protein 5, encoded by *Lrp5* gene) inhibits the synthesis of gut serotonin which stands for a positive effect to bone formation (via suppressing *Tph1* gene). In bone, Lrp5 acts as co-receptor to the canonical Wnt/beta catenine pathway that plays a major role in bone formation. Specifically, when Wnt binds to Fz receptors (from osteoblasts) that cause beta-catenin stabilization, the process is followed by the transcription of osteoprotegerin in osteoblasts in order to reduce the bone resorption. Supplementary, Wnt/beta-catenin signaling enhances osterix expression which represents a transcription factor that elevates osteoblasts differentiation. On the contrary, non-canonical influence on Wnt/beta-catenin is expressed by molecules such as Wnt5a (causing an increase of osteoclasts activity) [73-75].

Additionally, central serotonin acts as a neurotransmitter as it does dopamine and they both have been studied in relationship not only to depression, but with the pivotal role of physical exercise in acting against depression and supplementary positive (indirect) influence on the bone mass. Moreover, central serotonin has been linked to the metabolism since its synthesis takes place in neurons that express leptin receptor ObRb (leptin inhibits the synthesis of serotonin by suppressing its gene activity, namely *Tph2* gene) [76].

2.7. Endocrine considerations

Bone health is connected to a multitude of hormones and they regulate the adult turnover and remodeling, as well as the peak bone mass acquisition and bone growth; the regulation of bone mass accrual is controlled by the estrogens, leptin (which cross-talks to the metabolism) and PTH. Physical exercise increases the production of hepatic IGF1 that is released into the blood stream; hence, it also contributes to the bone formation and a more active skeletal muscle. This comes in addition to the neural control of the bone via sympathetic pathways as contributors to the bone formation, too [77-79]. Other myokines

are acting as hormones, as part of the muscle-bone-metabolism interplay such as myostatin, and apelin; additionally, adipokines have been shown to take a part in osteoporosis pathogenic traits (for example, traditional molecules as adiponectin and leptin in addition to the novel biomarkers like visfatin, omentin-1, vaspin, nesfatin-1, and lipocalin-2) [80-82]. Notably, physical activity improves the skeleton muscle status, as well, including in elderly; this comes with changes of the muscle biomarkers such as the troponin T isoform which is associated with fast-twitch muscles [83]. Pathological conditions such as prolonged hypercorticism, primary hyperparathyroidism or long term untreated thyrotoxicosis (as seen in TSH suppressive therapy following surgery for differentiated thyroid cancer) are prone to bone resorption and increased osteoporotic fracture risk [84,85].

3. Discussions

3.1. Pitfalls of expecting physical exercise to boost the bone formation

While the pathogenic rational of prescribing physical exercise in osteoporotic patients, particularly, in seniors seems justified, there is a fine line of being harmful to individuals that might be frail when suffering from many co-morbidities (for instance, of neurological, oncologic or rheumatologic type, etc.) in association with osteoporotic fragility fractures. Thus, the recommendation of daily activity is rather a matter of individualized (personalized) approach than a generalized intervention; also, this prescription does not replace the specific medical drugs acting against complicated osteoporosis to prevent further bone loss and novel (incidental) fractures [86-90].

Another pitfall of analyzing the serum/urinary bone turnover profile is represented by the expected influence of the anti-osteoporotic drugs that might hide the actual effects of the physical/mechanical effects if concurrent to the drugs [91-93]. Surveillance of the bone turnover markers profile stands for one of the most challenging, yet, very useful strategy to address the response to anti-osteoporosis medication in daily practice [94,95]. For instance, anti-resorptive medication (bisphosphonates or denosumab) is expected to suppress the bone turnover markers, while in patients under teriparatide, a bone forming agent, an increase of bone formation markers followed by the bone resorption markers highlights the anabolic window amid first 6-12-24 months of exposure (a maximum two-year protocol is allowed for a lifetime) [96,97]. Notably, bisphosphonates drug holiday represents a useful treatment gap to follow the profile of these mentioned biomarkers; their increase might be a surrogate of bone loss thus helping the decision of drug re-continuation [98-100].

3.2. COVID-19 pandemic (bone-metabolic) insights

During restriction amid recent COVID-19 pandemic, the outside physical activity has been reduced and an encouragement of using home-based activity was registered. In addition to a large scale of COVID-19 related medical and surgical entities, osteoporotic subjects seemed to be affected as well [101-103]. Devices such as SuperJump allowed a high impact activity combining an aerobic and anaerobic training via an elastic trampoline. A 20-week study upon its use in women with normal menses showed a significant reduction of CTX and increase of osteocalcin, showing to be a good starting point in acting against sedentary lifestyle [104].

Overall, we mention a gap between the multitude of pathogenic connections that have been found between the improvement of bone status upon physical exercise in experimental studies and the clinical evidence according to adequate levels of statistical evidence. A recent meta-analysis addressed this issue. The authors included 100 clinical studies across 120 types of physical exercise. In healthy menopausal women, the most efficient protocol to boost bone formation included moderate to high intensity interventions (most important being the ones that addressed both high intensity resistance and impact training). The potential bias comes from limited and heterogeneous

publications with respect to bone turnover markers and BMD assays upon different physical interventions [105].

3.3. Current limits and further expansion

As limitations of using the assessments with concern to the bone turnover markers as daily assays for various practitioners we mention their price, availably, reimbursement protocols, and a lack of a homogenous spectrum of testing between different centers [106-108]. Another bias comes from experimental data that are yet inconclusive in humans. Further randomized controlled studies are mandatory.

4. Conclusion

Part of the monitoring protocol in osteoporotic patients under specific medication against osteoporosis or during bisphosphonates drug holiday, bone turnover markers and biomolecules assays stands for a practical insight. The contributing role of the physical exercise to boost bone formation as reflected by these biomolecules is well understood across a multitude of signal transduction pathways. However, a current gap in practical use and surveillance of the prescription of physical activity, mechanical load and rehabilitation programs in these patients is confirmed so far.

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