

## Why We Need the New Paradigm of the Chronic Skeleton Diseases?

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### Commentary

Chronic skeleton diseases, such as osteoporosis and osteoarthritis, are among the most common medical problems. Complications associated with these diseases cause disabilities and significant deterioration of the quality of life, thus presenting a big public health issue, and also a big financial burden not only for the patient and their family but for the whole society. They have been ignored for many years and were considered as a consequence of natural aging. Unfortunately, even today the situation is not much better. Regarding osteoporosis, various pharmacological treatments introduced in the last twenty years didn't solve nor decreased the problem of osteoporosis [1,2]. On the contrary, new problems appeared such as drug's adverse event and fractures after a long-term of pharmacotherapy. Regarding the osteoarthritis, symptomatic treatment with temporary effect is still a standard approach and hip's and knee's replacement still the only choice for many patients. But even that is not solving the problem and the most of patients suffer the whole life.

Despite the recent significant improvement of the knowledge about the skeleton biology which clearly indicating an importance of prevention, it is still neglected as well as the education with the aim to increase awareness of prevention.

Such clinical practice regarding bone and joint diseases is mostly due to lack of basic education about the physiology of the skeleton and biological mechanisms that affect the skeleton. Until recently the skeleton

was not even considered an organ, so it is not surprising that there is still no specialization in clinical medicine to deal with the musculoskeletal disease. Orthopedics, physical medicine, rheumatology, and endocrinology only deal with parts of this large and complex organ, so it is no wonder that the clinical approach is only partial.

Fortunately, the intensive scientific activities in last two decades provide a significant advance in the understanding of skeleton physiology, the influence of metabolic and biomechanical factors on a bone which indicates the necessity of changing clinical approach towards the principles of personalized and integrative medicine. So, the new paradigm is needed.

Skeleton is a complex organ which is constantly adjusting to bio-mechanical and metabolic balance. Due to gravity, it absorbs significant load which is permanently changing during the daily activity. Skeleton is specifically designed to reduce the load by distributing it equally to all parts. In the case of skeleton deformities like hip dysplasia, spinal and foot deformities or any disproportion which causes overload (sport, sedentary life style, etc.); certain parts of the skeleton will be exposed to overload which will cause damage to cartilage. Under abnormal mechanical stimuli the balance of the chondrocyte metabolism (degradation and synthesis of matrix molecules) is disturbed leading to matrix loss and degeneration of cartilage. If the overload exceeds the regenerative capacity of chondrocytes, regeneration will be replaced by scarring process which will, by the time, cause a deterioration of cartilage properties and its capacity to absorb the load. Due to the fact that there are no nerves in the cartilage, there is no pain or any signal until the overload has been extended to the ligaments, tendons and bone causing chronic inflammation of joints, which we recognize as osteoarthritis. Biomechanical imbalance is getting worst by the time, causing “domino effect” regarding other parts of skeleton. Therefore, in most cases, osteoarthritis is not limited on one joint. Additionally, due to the fact that biomechanical stimuli significantly influence bone remodeling the biomechanical imbalance will cause deterioration of bone microarchitecture with consequent decreasing of bone strength and osteoporosis.

Besides the biomechanics, genetic factors and metabolic balance have also a significant influence on skeleton, particularly on bone, but on cartilage as well. It is documented for example that diabetes is an independent predictor for severe osteoarthritis [3]. It is well known that premature menopause, most of hormonal diseases and number of chronic inflammatory diseases negatively influence on bone remodeling and bone strength. At the beginning osteoporosis was considered mostly as the result of metabolic and hormonally diseases, but buy the time, it become clear that the most of osteoporosis cases are caused by combination of biomechanical, biochemical balance and genetic.

So, osteoporosis is a much more complex problem, then it was though before. The problem of osteoporosis is an increased fracture risk as a result of the poor bone strength. Bone strength primarily depends on the quality of collagen and bone architecture, not so much on bone mass. So, the definition of osteoporosis which has been issued on the “Consensus conference” 1994, by which osteoporosis is defined as the metabolic bone disease characterized with the low bone mass and low bone density, needs to be changed. It would be much better to define osteoporosis as the pathological condition of poor bone strength and consequent increased risk of fracture. Therefore, the major goal of treatment should be an improvement in bone strength and decrease bone fragility. Consequently, the clinical approach which has been based on the pharmacotherapy needs to be changed. Drugs, such as bisphosphonates, SERM-s, Teriparatide, or Denosumab, are affecting

bone turnover, but not stimulating the rejuvenation of the bone collagen and thus does not improve the quality of bone matrix nor improve the bone architecture. That could explain the poor effect of pharmacotherapy. Such drugs could be beneficial in the case of metabolic bone diseases which cause a pathological increase of bone reabsorption, such as Paget disease, but this is not the case in most of the patients with osteoporosis. Moreover, anti-reabsorptive drugs, like bisphosphonates and denosumab suppress bone remodeling rate in general, not only bone reabsorption than also bone formation, and might cause deterioration of bone strength and increase the risk of fractures. That could explain evidence about fractures after long-term of pharmacotherapy. So, the clinical approach should be changed. The goal needs to be the improvement a quality of collagen, and bone microarchitecture.

Due to the fact that biomechanical stimuli significantly influence bone remodeling, a biomechanical imbalance will cause deterioration of bone microarchitecture with consequent decreasing of bone strength and osteoporosis. Therefore, the correction of the biomechanics and regular biomechanical stimulation are crucial in the treatment and prevention of osteoarthritis, but also for the treatment of osteoporosis. That explains the needs for a holistic approach to the skeleton as a whole.

Regards to the significant diversity among people, relating to biochemical and biomechanical balance as well as genetics, personalized approach is necessary.

### **What Should Be Goals of Successful Treatment?**

1. To increase bone strength and joint's functional ability. This means to improve bone quality and to regenerate the cartilage because that will improve mobility and reduce the risk of fractures.
2. Prevent complications
3. Reduce symptoms
4. Achieve the optimal biomechanical and biochemical balance, to prevent further damages.

To achieve those goals the change of clinical approach is needed based on the new paradigm which is founded on the following principles:

1. Due to the fact that the functional ability of skeleton depends on the quality of all of its parts, the holistic concept it is always necessary, treating the skeleton as a whole.
2. Due to a significant variability among the people in terms of diversities in genetic, biochemical and biomechanical balance, the treatment needs to be based on personalized assessment and on the principle of integrative medicine be a combination of methods to achieve a synergistic effect.

The good example of the new paradigm is model popularly named „BaR“- a holistic concept based on the principles of personalized medicine and integrative medicine, which I've introduced in the clinical practice ten years ago. The name „BaR“ comes from the two the most important goals of the treatment. “B” stands for biomechanics and biochemical balance and, “R” for regeneration. It is an integrated, holistic approach to treatment using a combination of methods in order to improve “biomechanics”, provide regular

biomechanical stress to the bone, as well as good metabolic balance, and to stimulate the regeneration of cartilage and bone formation.

Despite that the current treatment capacity is still limited, a long clinical experience on thousands of patients convinced me that by application of „BaR“ concept, it is possible to achieve much better results than by convention approach, particularly if it is applied on time. The „cornerstone“ of „BaR“ treatment, we are doing in our clinical practice, is a combination of a special exercise program „Tae do“ and MBST- nuclear magnetic resonance therapy. „Tae do“ exercise is based on the Taekwondo principles [4]. Strong, intermittent, rhythmic contractions of the muscles send an appropriate biomechanical signal to bone cells to create a good microarchitecture. MBST- nuclear magnetic resonance therapy stimulates regeneration of cartilage and bone formation. MBST uses the well-known magnetic resonance technology to increase production of the bone matrix, by stimulating osteoblasts, specific cells which create the collagen which makes a bone matrix. Also, there are MBST programs which stimulate chondrocytes with consequent regeneration of cartilage. This method can be combined also with others, depends on the character of skeleton disease and clinical status. Due to the fact that „Tae do“ exercise and MBST have no adverse effect, it can be used also as prevention, not only as a treatment. Moreover, the best would be to introduce that at an early stage, before complication appeared.

But, „BaR“ concept is not limited to some particular technology or drug, and it can be easily upgraded with new technologies which will come. However, to be able improving the treatment ability, besides the development of new drugs and methods, the concept based on the personalized and integrative medicine is needed, due to the fact that a skeleton is a complex organ. Therefore, the new paradigm needs to be introduced in the clinical practice without any delay.

That is in spite of the fact that there is no prospective, double-blind randomized, placebo-controlled clinical trial of the „BaR“ concept. The fact is that there is a lot of scientific and clinical evidence regarding the effect of biomechanical influences on a bone, confirming the need for implementing this concept in clinical practice. Also, there are solid scientific and clinical evidence confirming that MBST- nuclear magnetic resonance therapy activate chondrocytes, osteoblast, and fibroblasts with consequent regenerative effect on cartilage and bone formation with long term reduction of pain and improvement of mobility [5-29]. Recent studies also showed that nuclear magnetic resonance (MBST) shifts the oscillation of the circadian clock light independently, alters the cellular redox environment and affects the circadian expression of Hif-1alfa. Both, the circadian clock and the hypoxic signaling pathway play central roles in the generation and progression of osteoarthritis [30].

It also important to be recognized, that there is a general problem in a clinical evaluation of the skeleton due to the fact that there is no possibility of measuring bone strength or quality of osteoid, as well as the quality of cartilage. Thus, the best evidence of a successful treatment of osteoporosis would be the resistance of the bone on the strong force which happens in severe trauma, but it is not possible to make a double-blind, prospective, placebo-controlled clinical study based on purposely exposing patients to accidents with potential fracture trauma.

Also, the effect of exercise on the bone structure cannot be measured by randomized, placebo control study, because the intensity of exercise and the impact of the muscle contraction on the bone cannot be measured.

So, two people who are doing the same exercise program can have a significantly different result, because of big variation in an intensity of the muscle contraction, which cannot be standardized and measured, as it can be done in the case of a drug for example.

Hence, there is an objective problem regarding the clinical evidence in the case of a skeleton. But, taking in consideration all scientific and clinical data related to skeleton, as well as a positive long clinical experience in application of “BaR” method, which should not be ignored, it can be concluded that despite all limits, there are more than enough reasons for the acceptance of the new paradigm in the clinical approach to the skeleton, based on a holistic and personalized approach.

## Conflict of Interest

Author Dalibor Krpan declares that he has no conflict of interest.

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