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Expert consensus on the role of nutraceuticals in bone, joints, and muscle health

Sunil Katoch, Raju Easwaran, Hemant Thacker, Amulya Kumar Singh, Pradeep Moonot, Amitava N Mukherjee, Santosh Shetty, Kaushal C Malhan, Vasudev Prabhu, Niranjana R Rathod, Moazzam Jah, Sridhar Gangavarapu, Naidu MJ, Pranay Bhushan and Anish Desai

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Abstract

In recent times orthopedic surgeons have faced three common dilemmas in their day-to-day practice. These include changing patient profiles (fitness addict senior citizens), challenges in patient care (nonhealing osteoporotic fracture), and extensive use of whey proteins and other supplements by youngsters. Nutraceuticals science plays a vital role and is a valuable tool for orthopedicians in these scenarios complementing well with the standard of care. The recent COVID-19 pandemic and widespread misinformation have brought to the forefront limitations of science, social media's influence, and nutraceutical medicine's role in enhancing health and well-being.

As nutraceuticals are in focus from all healthcare stakeholders - doctors, patients, and service providers an expert consensus is required to enhance bone, joints, and muscle health. A group of national orthopedics experts came together to achieve this consensus. The literature review on pharmacology, clinical data, and experts' experience in using nutraceuticals, formed the base of this consensus. This expert consensus will help bridge the void due to the absence of national and international guidelines on integrating modern and nutraceutical medicine. It will facilitate better patient care for bone, joint, and muscle health.

Keywords: Dietary supplements, undenatured type II collagen, glucosamine, bio-active collagen peptides, tocotrienols, amino acids, branched-chain

1. Introduction

We live in an ever-increasing aging population and an increased number of people with sedentary and unhealthy lifestyles resulting in ~1.3 billion patients with musculoskeletal disorders and 138.7 million DALYs (disability-adjusted life years) [1]. The health and strength of our musculoskeletal system are influenced by a balanced diet and a steady stream of nutrients.

Understanding nutraceutical science and its role in bone and muscle health, risk factors associated with premature aging, and senescence can provide better patient care. The two significant tissues in the human body are bone (~3.5 kg in an adult (dry weight (~ 1 kg collagen), and muscles (~40% of body mass) [2]. Collagen, proteoglycans, and minerals, i.e., calcium and phosphorus, are three critical components of bone, while muscles store ~40% of body amino acids; and glycogen and facilitate lipid metabolism [3]. Joint cartilage comprises collagen, proteoglycan, and elastin fibers [4].

Thus, a constant and appropriate intake of macro and micronutrients (vitamins & minerals) is required to keep bone, muscle, and joints healthy and active. In addition, effective prevention and therapy strategies with fewer side effects are highly desirable for life-long chronic conditions, e.g., osteoarthritis, osteopenia and osteoporosis, joint pains and stiffness, muscle cramps, etc. Several studies have shown the benefits of supplementing the diet with "Nutraceuticals.

Osteoarthritis (OA) is one of the significant health concerns for middle-aged and older adults due to its high prevalence and effect on activities of daily living [5].

Corresponding Author:
Anish Desai
Clinical Pharmacologist and
Pharmaceutical Physician,
Director, IntelliMed Healthcare
Solutions, Mumbai,
Maharashtra, India
dranishdesai@pharmaserv.in

The pathological changes are observed in the cartilage of the significant weight-bearing joints, i.e., knees, hips, and vertebra. Treatment approaches of OA help reduce pain and inflammation, facilitate mobility, and sustain the quality of life (QoL). Osteoporosis is associated with increased bone turnover and decreased bone mass with skeletal fragility, resulting in increased fracture risk. It is estimated that globally, every third woman and one in five men over 50 will suffer from an osteoporotic-induced bone fracture [6].

According to the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Glossary of Terms, a 'muscle cramp' is an involuntary, painful contraction associated with electrical activity [7]. In the case of a 'muscle cramp,' also named a 'true muscle cramp, the commencement is sudden, generally occurring at rest, and often is nocturnal. The calves are the most affected area, but cramps are also observed in the fingers and hands. Muscle cramps impact QoL due to impairment in physical functioning, sleep, mental health, energy levels, and social isolation. The proposed mechanisms may be disturbances in nerve function, energy metabolism, plasma volume, and electrolytes. Oxidative stress can damage membrane conduction which may result in nerve dysfunction.

Sarcopenia is a common geriatric syndrome characterized by progressive skeletal muscle mass and function decline. It results in loss of muscle strength, impairment of tendon, ligament, bone, and cartilage function, destabilization of the joints, and increased risk of arthritis. The prevalence of sarcopenia ranges from 5.5–25.7% in Asian countries.

It is associated with many adverse outcomes in older adults, including falls, mobility impairment, frailty, physical disability, and death. It requires early detection and intervention.

1.1 Management of Osteoarthritis

Undenatured Collagen Type II collagen (UC-II)

UC-II is a novel nutraceutical ingredient effective in treating RA (rheumatoid arthritis) and OA [3]. It is the primary form of collagen in cartilage. In patients who do not qualify for surgery, UC-II is the preferred option as it helps in delaying Total Knee replacement (TKR) and improves mobility and Quality of Life (Figure 1) [8]. This effect occurs due to the induction and migration of T regulatory cells (Tregs) at

Peyer's patches to the joint area of inflammation and damage. Tregs produce anti-inflammatory cytokines that stimulate chondrocytes to synthesize cartilage matrix components.

Undenatured collagen type II in a dose of 40 mg/day provides maximum clinical benefits, and the response rates decreased with a further increase in daily dosage. UC-II supplementation shows its beneficial effects in 2–3 weeks and is advised to be used for 1–6 months with/without food. To date, no major safety concerns have been observed in different studies. Thus, the unique mechanism of action, simplicity of administration, and apparent safety make it highly appealing to use UC-II in OA.

Glucosamine, Chondroitin Sulfate, Hyaluronic Acid, and Curcumin

Glucosamine, a biological constituent, is used as an oral supplement for its chondroprotective effect [9]. It is widely used with chondroitin sulfate across the USA, Europe, and Asian countries, for knee OA as it helps pain relief and facilitates joint preservation. Chondroitin sulfate (CS) is a natural glycosaminoglycan found in the cartilage and extracellular matrix. It is effective in managing OA due to its anti-inflammatory activity [10]; it helps maintain structural and functional aspects of the joint cartilage, including elasticity, by slowing breakdown; and reducing pain. It is widely used in combination with glucosamine for OA.

Hyaluronic acid (HA) is synthesized in the joint tissues by synoviocytes, fibroblasts, and chondrocytes. It is present in the synovial fluid and the extracellular matrix of cartilage and is responsible for synovial fluid's viscoelasticity and lubricating properties. In OA, there is a decline in synovial fluid quantity and viscoelastic properties, increasing the cartilage's susceptibility to injury. Hyaluronic acid performs a multitude of biophysical, biochemical, and cell regulatory roles in joint synovial tissues. HA (visco-supplementation) supplementation in OA patients has been widely used to reduce joint pain [10]. It is also effective in treating symptoms associated with synovitis (knee pain), relief of synovial effusion or inflammation, and improving muscular knee strength. Curcumin's antioxidant and anti-inflammatory effects are effective in patients with osteoarthritis [11]. It has been shown to have similar efficacy to non-steroidal anti-inflammatory drugs and glucosamine.

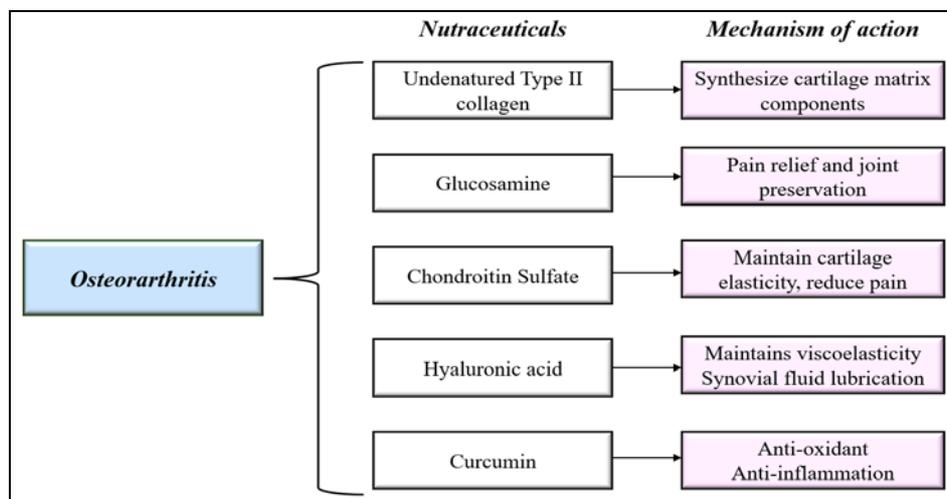


Fig 1: Role of nutraceuticals in osteoarthritis

1.2 Management of Osteoporosis

Bioactive Collagen Peptides

Bone is a living, dynamic metabolic system of approximately

70% inorganic salts and 30% organic matrix by weight; however, collagen (mainly type I collagen) makes up over 90% of the organic component. It is collagen that generates

the bone density that gives our bones the ability to withstand stress. Collagen is a protein that provides a framework of soft tissue that calcium adheres to, creating a hardened framework. Calcium is still essential, but taking large doses can be ineffective without enough collagen supplementation. In postmenopausal osteoporosis, the decreased rate of collagen synthesis leads to a change in the quality of collagen fibers, which weakens them. So, collagen supplementation plays an essential role in the therapy of osteoporosis.

Bioactive collagen peptide (BCP) has a unique action mechanism compared to other anti-osteoporosis drugs. It stimulates $\alpha_2\beta_1$ receptors on the pluripotent stem cells and increases insulin growth factor - 1 (IGF-1) levels in the extracellular matrix. These two actions facilitate the differentiation of stem cells into osteoblasts, i.e., bone/osteoid-forming cells. The newly formed osteoblast cells result in a favorable OPG/RANKL ratio (Osteoprotegerin/ Receptor activator of nuclear factor kappa-B ligand) which

inhibits the differentiation of stem cells into osteoclasts (Figure 2). The net effect of BCP is to increase the number of osteoblast cells and decreases the number of osteoclast cells [12].

BCP increases bones' organic component and improves vertebrae's metabolism, microarchitecture, and biomechanical resistance. Bioactive collagen peptide supplementation leads to a statistically significant decrease in the excretion of bone collagen breakdown products compared to placebo treatment. Moreover, the effect of therapy with collagen peptides was persistent for at least three months after the last administration, suggesting an anabolic effect of collagen peptide treatment. Bioactive collagen peptides significantly increase the bone's organic substance, and the following mineralization increases BMD and improves bone stability. It helps prevent postmenopausal osteoporosis and osteoporosis and osteopenia in general.

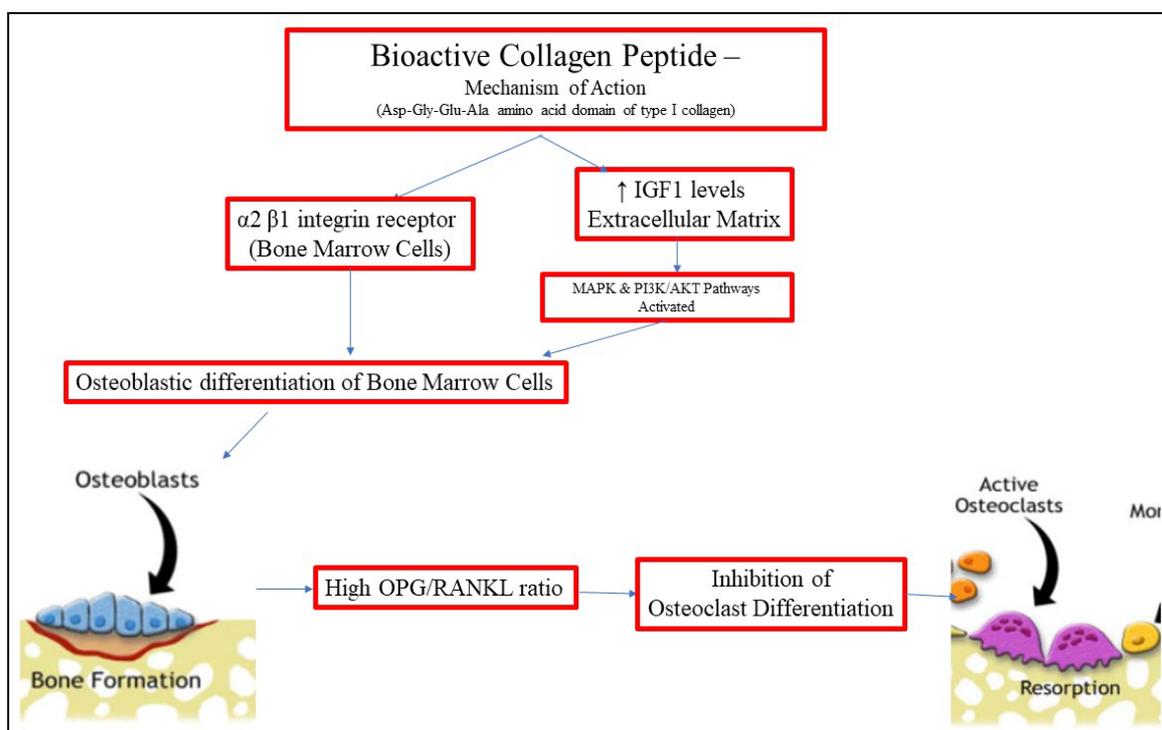


Fig 2: Mechanism of action of Bioactive Collagen Peptide

Asp-Aspartate; Gly-Glycine; Glu-Glutamate; Ala-Alanine; IGF-1-Insulin Growth Factor; OPG-Osteoprotegerin; RANKL - Receptor activator of nuclear factor kappa-B ligand; MAPK -Mitogen-activated protein kinase; PI3K- phosphatidylinositol 3-kinase and Akt - protein kinase B.

1.3 Management of Muscle Cramps

Vitamin E (alpha-tocopherol) is an essential antioxidant that helps membrane repair and, as a membrane-based antioxidant, is necessary for muscle homeostasis. The tocopherols are saturated, while tocotrienols are unsaturated forms of vitamin E. Tocotrienols, the Vitamin E of the 21st Century, have superior anti-inflammatory and antioxidant activity compared to tocopherols and are likely to result in better outcomes. Fish oil supplements (Cod liver oil) provide ω -3 FAs (docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [13]. They have effects of anti-inflammation, anti-oxidation, protecting vascular endothelial cells, etc. (Figure 3).

Wheat germ oil

It is derived from the germ part of wheat. It contains omega-6 (44 and 65% (Linoleic Acid), omega-3 (in a lower proportion, 4–11 % (alpha-linolenic acid) fatty acids, and it is known to have the highest tocopherol (Vitamin E) content among other edible oils [14]. It is used widely for its anti-inflammatory properties. L-Carnitine plays a crucial role in mitochondrial β -oxidation, improving AKT activation and downstream cellular signaling pathways involved in skeletal muscle atrophy process prevention. It exerts beneficial action on increased protein synthesis and reduced muscle degradation [15, 16].

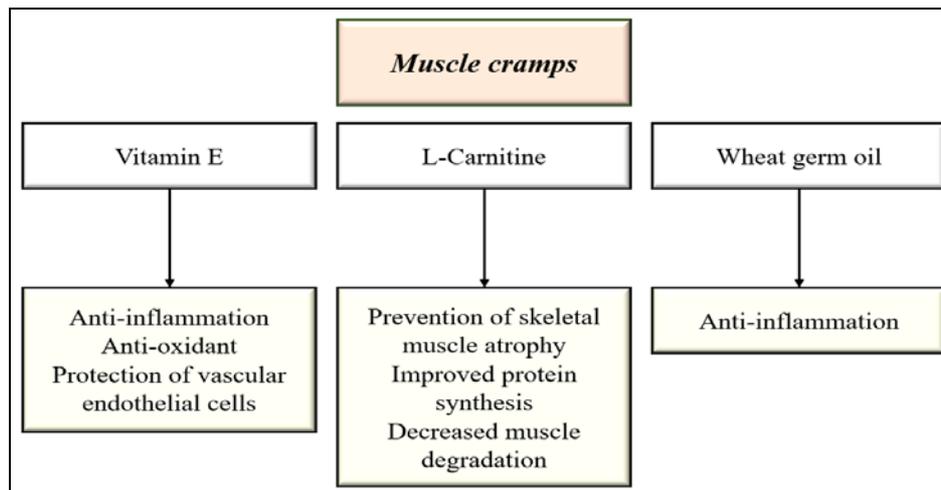


Fig 3: Role of nutraceuticals in Muscle Cramps

1.4 Management of Sarcopenia and Exercise-Induced Muscle Damage

Physical exercise positively impacts muscle mass and function in subjects with sarcopenia and aged ≥ 60 years [17]. Dietary supplement of whey protein fortified with vitamin D helps to cater to higher protein requirements of 1.2 g/kg body weight/day.

Exercise-induced muscle damage (EIMD) is typically caused by unaccustomed exercise and results in pain, soreness, inflammation, and reduced muscle function. These adverse outcomes may cause discomfort and impair subsequent performance or training quality, particularly in individuals with limited time to recover between training sessions. Several approaches, including massage, cryotherapy, and stretching, have been used to overcome the signs and symptoms of EIMD, with mixed results [3]. Long-term consumption of antioxidants and several chronic supplementation strategies (Omega-3 polyunsaturated fatty acids and vitamin D₃) may help reduce symptoms of exercise-induced muscle damage and improve muscle function in many patients.

1.5 Evolution of Orthopedics and the role of nutraceuticals

Orthopedics or orthopedics? The age-old debate on spelling in musculoskeletal medicine keeps raging, though both convey the surgeon's intention to help a child overcome his deformity [18]. In the previous century, orthopedic surgeons' primary work revolved around children with deformities, as the average lifespan was in the mid-twenties. Recently, it has evolved as the primary focus is on adults and a role far beyond surgery to involve bone, joints, muscle health and well-being, and preventive medicine.

1.5.1 Changing orthopedic patient profiles

In the current times, it is pretty common to get the following three types of patient profiles in an outpatient setting of an orthopedic surgeon:

1. A 60-plus-year-old young male patient with a right knee ligament tear due to a half marathon aspires to compete in the senior Olympics in another three months.
2. 60-plus-year-old female with osteoporosis and spinal fracture refractory to standard of care treatment (including lack of stability to locking plate device) and

3. 20-plus- year-old fitness freak male striving to develop six-pack abs along with daily consumption of whey proteins and other supplements under the guidance of his trainer.

These patients are well-read on their disorders. Nutraceuticals' pharmacology and clinical data help an orthopedic surgeon individualize treatment with standard care.

1.5.2 Nutraceuticals for enhancing health and well-being

The anatomical and physiological functions of bone, joints, and muscles are primarily governed by a continuous supply of specific nutrients such as collagen, protein, and amino acids—intake of BCAA (branched-chain amino acids) and proteins results in muscle synthesis. Antioxidants and omega-3 polyunsaturated fatty acids, vitamin D₃, curcumin, etc., reduce exercise-induced inflammation [3]. This approach supports muscle health in age-related frailty and sarcopenia and helps build muscle mass in fitness freak youngsters. In muscle cramps, supplementation with tocotrienols, cod liver oil, wheat germ oil, and vitamins is required [7].

Supplementation with calcium and vitamin D formulation and appropriate catabolic or anabolic treatment for osteoporosis helps improve bone mineral density and reduces the risk of fractures [6]. This process is further facilitated by using bioactive collagen peptides (Type 1), which help replenish bones' collagen backbone [12]. Type II collagen supplementation helps slow down osteoarthritic joints' wear and tear and supports collagen synthesis and the standard of care treatment [8].

Increased awareness of a healthy diet and fitness regimen has triggered several people to adopt them wholeheartedly. This lifestyle change also helps them overcome the stresses of their work and other life activities. Fitness regimens and different types of exercise workouts induce exercise-induced inflammation in muscle tissues.

1.5.2 Nutribiography – the way ahead

The need of the hour is that every patient presenting to an orthopedic clinic needs to undergo a "nutribiography," that is, the effect that an individual's dietary history and supplementation can have on his clinical signs and symptoms and pathogenesis of their disorder [19]. It improves outcomes with nutraceuticals, drugs, and surgical options for musculoskeletal disorders.

1.6 Nutraceuticals for disease prevention and enhancing patient care

Over the generations, there has been a gradual transition in the mindset of people and the healthcare system toward preventive medicine and primordial prevention (a step further ahead from preventive medicine (prevent the occurrence of risk which predisposes a person to a disease) ^[20]. Nutraceuticals have a role in geroprotection, i.e., slowdown, inhibition, or reversal of age-related decline (as a composite of disease, dysfunction, and, ultimately, death) ^[19]. Geroprotection can be achieved by maintaining bone, joints, and muscle health using appropriate nutraceuticals and lifestyle approaches.

One needs to have balanced diet with optimal protein, calcium, bioactive collagen peptide intake, vitamin D sufficiency, and regular weight-bearing physical exercise to optimize bone health. Bone mineral density, strength, and microstructure directly relate to protein intake and bioactive collagen peptides. Skeletal muscles have a critical role in physical activity, mobility, and whole-body metabolism, with muscle mass and quality directly linked to improved health and even lifespan. Optimizing nutrition and tailored exercises are an established, effective ergogenic practice for fitness freak/ athletic performance. Training and nutritional approaches are effective in patients with muscle dysfunction associated with aging and numerous musculoskeletal conditions, as they help increase muscle mass and functioning. Thus, a mixed macronutrient supplementation containing protein, carbohydrates, fat, and BCAA stimulates muscle protein synthesis (MPS) ^[3].

The prevailing cultural beliefs in our society emphasize and prefer the use of nature-based and traditional remedies. This view got further reinforced by the widespread use of nutraceuticals and supplements to improve immunity, health, and well-being over the past two years (COVID-19 pandemic). Changing times, changing patient profiles, and changing needs of patients and the healthcare system; require an orthopedic surgeon to optimally leverage benefits offered by nutraceutical science to enhance patient care.

1.7 Nutraceuticals - Patient Engagement, Education and Enhancing Treatment Compliance and Quality and Regulations

Every healthcare setting needs systems and processes for a detailed assessment and counseling for their patient's nutritional and other lifestyle habits. An open and unbiased discussion should be conducted to identify and overcome the misbeliefs of patients about nutraceuticals and other supplements. Integrating nutraceuticals with the standard of care should be governed by an evidence-based approach based on realistic expectations with mid to long-term goals. Patient engagement and education can achieve the desired clinical outcomes and enhance treatment compliance with appropriate doses and duration ^[21].

Regulations for nutraceuticals are evolving and flexible in contrast to therapeutic drugs ^[22]. Bold claims, widespread misinformation, and multiple brands with different price points confuse patients ^[23]. Sometimes, the patient buys a formulation at a lower price with questionable quality, which impacts efficacy and safety results. As regulation changes happen, increased physicians' awareness of nutraceutical science, clinical data, manufacturing processes, and patient education will help overcome some of these challenges.

2. Need for Expert Consensus

Globally there has been a rise in the use of nutraceuticals for

health and well-being. However, misinformation, the inertia of a healthcare practitioner, inappropriate doses, and duration of nutraceuticals may impair patient outcomes. Hence experts decided to generate a consensus to enable a wider group of physicians and patients to gain the benefits of nutritional science. This consensus will help clinicians on the role of nutraceuticals in an orthopedic setting.

3. Methodology

A panel of 14 experts (13 orthopedic surgeons and one physician) from India with experience in research and publications in peer-reviewed journals and speakers at national/ regional conferences came together. The objective of this forum was to discuss recent and ongoing medical research that had implications for the re-evaluation of routine medical practice and generate a consensus on the role of nutraceuticals for bone, joint, and muscle health.

Experts shared views and experiences on nutraceuticals in bone, joints, and muscle health. Based on the data discussed and expertise shared by the experts, three consensus statements were developed, which are provided below.

4. Expert Opinion

The expert panel discussed and agreed on the following points:

There is an unmet need in patients with osteoporosis or osteopenia for calcium and Vitamin D treatment. Exercise and bioactive collagen peptides are the preferred intervention for these patients. Rising reports of adverse events of whey protein supplements in fitness-conscious people (e.g., renal ADRs) are a significant concern. Hence a science-based protein formulation and intake are required to avoid whey protein and other protein formulations with questionable rationale.

There has been a shift in clinical practice with changes in patient profiles and a move towards a preventive approach. Most of these patients seek nutraceuticals, fitness, and preventative strategy for disease management. The new mantra for practice is, 'Don't wait for complications/ aggravation of disease before starting nutraceuticals.' It is a fact that healthy muscle leads to healthy bones and joints. The three core principles for managing patients are exercise, muscle health (Neuromuscular interventions), and nutraceuticals. The health of vastus medialis obliquus muscle (VMO) is used clinically to monitor bone and muscle health.

Pharmacotherapy is time bound, with drugs preferred to be used for a shorter duration due to safety concerns. Pain killers are often perceived as 'plain killers.' Patients with bone disorders and co-morbid conditions like diabetes are suitable profiles for nutraceuticals. Nutraceuticals should be used to address bone, joints, and muscle health (Osteopenia/ osteoarthritis + arthritis + sarcopenia). The right dose, time, and place of use of Nutraceuticals will optimize treatment outcomes. Condition-based nutraceutical management requires an appropriate amount and formulation backed by clinical data. Every patient needs to undergo a science-based nutritional evaluation and counseling to improve their awareness.

There is a need to use the correct dose of UC-II for clinical benefits through immune-mediated action in grade 2 and 3 osteoarthritis. The use of UC-II in low or high doses leads to inadequate response. A pure and bioavailable formulation of curcumin in the correct dosage should be used for appropriate clinical benefits.

5. Expert Consensus

The expert consensus statements have been presented in Table 1 and figure 4.

Table 1: Consensus Statements

Serial Number	Consensus Statements
Consensus 1	Integrate nutraceuticals with standard drugs to maximize outcomes. UC-II collagen, glucosamine, chondroitin sulfate, hyaluronic acid, and curcumin are effective in osteoarthritis. Bioactive collagen peptides are recommended for osteoporosis. Vitamin E (Tocotrienols), fish oil supplements, wheat germ extract, and L-carnitine relieve muscle cramps. Branched-chain amino acids control sarcopenia. Antioxidants, omega-3 polyunsaturated fatty acids, and vitamin D ₃ help recover from exercise-induced muscle damage.
Consensus 2	Optimize nutraceuticals to prevent musculoskeletal diseases and enhance health and well-being.
Consensus 3	'Think Nutrition First' and optimize nutrition in every patient to align with their needs, changing profile, and lifestyle.

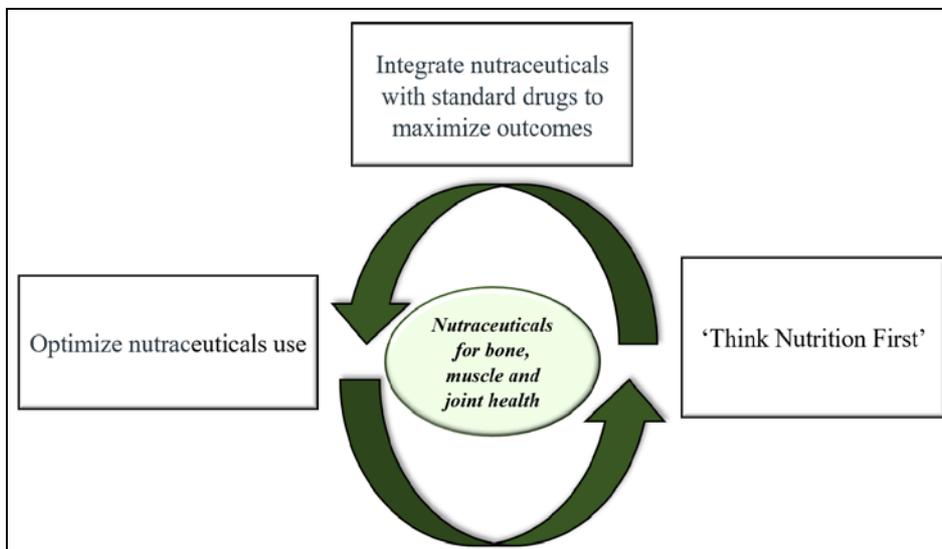


Fig 4: Expert consensus on nutraceuticals for bone, muscle, and joints health

6. Conclusion

Healthcare physicians can enhance patient care by using nutraceuticals for musculoskeletal health and aging. It will help manage 60 plus fitness addict senior citizens, 60 plus senior citizens nonresponsive to the standard of care, and 20 plus fitness freak youngsters. The importance of "nutriobiography" and geroprotection is critical in the outpatient clinic of every orthopedician [12]. Nutriobiography and nutraceutical science will help every clinician/ surgeon optimize/ individualize the intervention approaches and help advance patient care, and facilitate geroprotection.

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Authors Details

Sunil Katoch

Senior Consultant, Department of Orthopaedics (Spine Surgery), MAX HealthCare, New Delhi, India

Raju Easwaran

Director, Shree Meenakshi Orthopaedics & Sports Medicine Clinic, Arthroscopy, Sports Medicine & Joint Preservation Surgery, Indore, Madhya Pradesh, India

Hemant Thacker

Consultant Physician & Cardio Metabolic Specialist, Director &

Head of Department Medicine at Bhatia Hospital, Additional Director of Medicine at Jaslok Hospital & Senior Consultant Breach Candy & Reliance HN Hospital, Mumbai, Maharashtra, India

Amulya Kumar Singh

Senior Orthopaedic Surgeon, Akshat Seva Sadan Clinic, Patna, Bihar, India

Pradeep Moonot

Senior Orthopaedic Surgeon, Breach Candy Hospital Trust Mumbai, Maharashtra, India

Amitava N Mukherjee

Senior Orthopaedic and Joint Replacement Surgeon, Med7 Clinic, Kolkata, West Bengal, India

Santosh Shetty

Head of Department of Arthroplasty and Joint Replacement for Surana Group of Hospitals & Thunga Group of Hospitals, Mumbai, Maharashtra, India

Kaushal C Malhan

Director Orthopaedic Surgeon at Fortis Hospital Mulund, Mumbai, Maharashtra, India

Vasudev Prabhu

Orthopedic and Joint Replacement Surgeon, Apollo Hospitals Sheshadripuram Bengaluru, Karnataka, India

Niranjan R Rathod

Rathod Orthopaedic Hospital, Mumbai, Maharashtra, India

Moazzam Jah

Arthroscopy & Sports Injury Clinic, Nishat Hospital, Lucknow, Uttar Pradesh, India

Sridhar Gangavarapu

Senior Consultant Orthopedic Surgeon & Head of Department, Medicover Hospitals, New Delhi, Delhi, India

MJ Naidu

Orthopedic Surgeon, MJ Naidu Super Speciality Hospital, Vijayawada, Andhra Pradesh, India

Pranay Bhushan

Orthopedic Surgeon, Advanced Ortho Care, Allahabad, Prayagraj, Uttar Pradesh, India

Anish Desai

Clinical Pharmacologist and Pharmaceutical Physician, Director, IntelliMed Healthcare Solutions, Mumbai, Maharashtra, India