New biocomplex for nutrient-metabolic support of bone tissue

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Abstract. In the conditions of digitalization of agriculture and food industry, a prescription composition and innovative technology of a specialized product formulated as a biologically active additive have been developed to normalize metabolic processes in case of damage to the musculoskeletal system. Specialized product obtained by innovative tableting technology, which provides high consumer properties and preservation of prescription components. Innovative technological solutions allow us to divide prescription ingredients taking into account their chemical and pharmacological incompatibility, to deliver them to different parts of the gastrointestinal tract consistently at a given speed. It should be noted that glucosamine sulfate, which is part of the vitamin-mineral complex, is combined with macro and microelements: calcium hydroxyapatite, magnesium oxide, zinc oxide, D3 vitamin, manganese sulfate, which are characterized by unidirectional functional properties with respect to the correction and normalization of metabolic processes during damage motor apparatus. The effectiveness of the vitamin-mineral complex is confirmed by clinical trials by including it in the complex treatment of children with fractures of the long tubular bones, one capsule twice a day (children 3-7 years old) and one capsule three times a day (8-14 years). It was concluded that the appointment of a vitamin-mineral complex had a beneficial effect on the metabolism of bone remodelling, the rehabilitation period and, in general, the quality of life of sick children. New developments in the field of formulations and technologies were tested in terms of production at the enterprises of the Art Life company (Tomsk), certified according to the requirements of international standards 9001.22000 and GMP rules, ensuring competitiveness and stability of quality characteristics.

1. Introduction
The accumulated experience of traditional medicine is increasingly becoming an effective tool in the prevention and complex treatment of various diseases, among which special attention is paid to rickets in children and osteoporosis in the elderly and senile age. Equally important is the problem of traumatic injury of the musculoskeletal system. This is due to the development of a deficiency of essential micronutrients responsible for the correction of bone metabolic disorders in the indicated pathologies and, above all, calcium and D vitamin.

Calcium metabolism including its absorption and physiological functions is closely related to phosphorus and magnesium, which form the basis of the bone's mineral matrix. Calcium metabolism is controlled by a multicomponent hormonal system, where cholecalciferol and its hormonal derivatives play a strategic role.

Plant materials and preparations of biologically active substances were used as materials. We used generally available and special methods of research of quality, safety, efficiency and functional orientation of the developed product.
2. Research results

A vitamin-mineral biocomplex in the encapsulated form of a biologically active additive (BAA) was developed, the ingredients of which have synergistic properties in relation to the normalization of metabolic processes in bone pathologies, with the following amount of mg in a single capsule weighing 0.75 g: calcium hydroxyapatite, 24.41% - 350 (calcium - 85.4 ); magnesium oxide - 100 (magnesium - 60); chondroitin sulfate - 66; vitamin C - 60; silicon oxide - 8 (silicon - 3.7); zinc oxide - 1.5 (zinc - 1.2); manganese sulfate - 0.8 (manganese - 0.26); boron glycyrate, 5% - 0.5 (boron - 0.025); chromium picolinate - 8.5 mcc (chromium - 1.25); cholecalciferol (vitamin D3) - 1.6 mg.

The innovativeness of the technology lies in the matrix structure of the tablet, which is a system with adjustable speed and prolonged release of active substances. The novelty of technological solutions makes it possible to separate prescription components, taking into account their chemical and pharmacological incompatibility, to consistently deliver them to different target gastrointestinal sections to target cells at a given speed.

Regulated indicators of nutritional value are established for individual packaging of a specialized product, along with a characteristic of its functional properties (table 1).

| Indicators, mg in 1 capsule | Volume          |
|----------------------------|-----------------|
| Vitamin C (ascorbic acid)  | 48 - 72 (60)    |
| Vitamin D3 (cholecalciferol), mcg | 1.12 - 2.08 (1.6) |
| Magnesium                  | 48 - 72 (60)    |
| Calcium                    | 68- 102 (85.4)  |
| Zinc                       | 0.96 - 1.44 (1.2) |
| Manganese                  | 0.23 (at least 0.23) |

Calcium being in the form of hydroxyapatite is actively absorbed from the intestine into the bloodstream; it is well absorbed by the body and effectively realizes its functions during the formation of bone tissue. This is achieved due to the balanced content of calcium and phosphorus in hydroxyapatite (1:1) and calcium in relation to magnesium (2:1) in the prescription formula dietary supplement. The remaining micronutrients - vitamins and minerals included in the formulation, ensure the balance of calcium and its participation in the metabolic processes of the bone-joint and ligament apparatus. Calcium hydroxyapatite prevents bone resorption by inhibiting parathyroid hormone and forms the basis of the bone's mineral matrix. Proceeding from its main function, calcium preparations are successfully used for the prevention and complex treatment of diseases of the joints, rickets in children, and osteoporosis in the elderly and elderly, and are recommended to accelerate the healing of traumatic bone injuries. In addition, calcium is actively involved in other, multiple bone tissue exchange reactions: it provides muscle contraction, transmission of nerve impulses, activates the hormonal pool.

Magnesium as it was mentioned above is a synergist of calcium in the metabolic processes of bone tissue. As a cofactor, it participates in numerous enzymatic reactions of the organism, which determines its systemic nature in relation to the correction of metabolic disorders. The specific properties of magnesium are directed to the regulation of phosphorus metabolism and the formation of bone strength, muscle contraction and relaxation.

Zinc is necessary for the normal functioning of the skeletal system, being part of hormones and enzymes. It has a specific effect in stimulating the immune system and killer antitumor cells.

Manganese is one of the participants in the formation of bone and connective tissue, the regulation of gluconeogenesis. It promotes the growth and regeneration of bone cartilage; it is included in the structure of the main component of the joints - glucosamine (spongy sugar-like substance). It inhibits the development of arthritis, leading to destruction of the joints.

D3 vitamin controls the absorption and utilization of phosphorus and calcium in the gastrointestinal tract and their metabolic transformations aimed at ensuring the integrity of the bone. It is necessary for building and maintaining skeletal structure, which is very important for the risks of osteoporosis and traumatic injuries of the bone tissue.
Boron is an active participant in the exchange of calcium and potassium. Vitamin through its antioxidant, antibacterial, other vital properties, has a positive effect, together with other components of the formulation, on the functioning of the musculoskeletal system as a whole.

Evidence-based medical studies confirming the effectiveness and functional orientation of the biocomplex were conducted. Thirty-five sick children took part in the tests; 14 girls and 21 boys of age groups of 2–6 and 7–14 years old with fractures of long tubular bones. Children of the control group (19 people) were prescribed classical treatment, the main group (16 people) received cryotherapy together with diet therapy in the form of dietary supplements: 1 capsule 2 times a day (3-7 years old) and 1 capsule 3 times a day (8-14 years old) during the meal.

The studies were carried out at the Department of Pediatric Surgical Diseases of the Siberian State Medical University under the direction of Doctor of Medical Sciences, Professor G V Slizovsky.

We used generally available and special test methods: biochemical analysis of blood serum, X-ray, laser Doppler flowmetry.

The results of biochemical tests are presented in table 2.

Table 2. Biochemical blood parameters of children of 3-7 and 8-14 years old with fractures of long tubular bones (X ± m).

| Indicators | Survey terms | 3-7 years old | 8-14 years old | Children with fractures | With standard treatment |
|------------|--------------|---------------|-----------------|------------------------|------------------------|
|            |              | n= 11         | n= 5            | n= 14                  | n= 5                   |
| APh, un/l  | Before       | 241.42 ±13.60 | 234.22 ±10.33   | 217.79±10.32           | 237.81±11.25           |
|            | treatment    | p1 <0.05      | p1 <0.05        | p1 <0.05               | p1 <0.05               |
|            | 14th day     | 220.85 ±13, 60| 204.22 ±11,10   | 208,85±19,62           | 205,58 ±10,74          |
|            | after        | p1 <0.05      | p1 <0.05        | p1 <0.05               | p1 <0.05               |
|            | treatment    | 131,14 ±14, 19| 140,70 ±7,11    | 129,80±8,54            | 130,70 ±11,18          |
|            | 30th day     | p1 <0.05      | p1 <0.05        | p1 <0.05               | p1 <0.05               |
|            | after        | p4 <0.05      | p4 <0.05        | p4 <0.05               | p4 <0.05               |
|            | treatment    | p5 <0.05      | p5 <0.05        | p5 <0.05               | p5 <0.05               |
| Ca2+, mmol/l| Before       | 1,26±0,07     | 1,20±0,06       | 1,31±0,12              | 1,12±0,01              |
|            | treatment    | 1,14±0,03     | 1,12±0,11       | 1,08±0,05              | 1,20±0,10              |
|            | 14th day     | 1,06±0,02     | 1,08±0,07       | 1,18±0,01              | 1,06±0,10              |
|            | after        | 1,82 ±0,07    | 1,56 ±0,07      | 2,03±0,08              | 1,56±0,07              |
|            | treatment    | p1 <0.05      | p1 <0.05        | p1 <0.05               | p1 <0.05               |
|            | 14th day     | 1,55 ±0,03    | 1,83 ±0,13      | 1,82±0,04              | 1,60±0,06              |
| P, mmol/l  | Before       | 1,31 ±0,03    | 1,46 ±0,09      | 1,40±0,02              | 1,41±0,07              |
|            | treatment    | p1 <0.05      | p1 <0.05        | p1 <0.05               | p1 <0.05               |
|            | 14th day     | p4 <0.05      | p4 <0.05        | p4 <0.05               | p4 <0.05               |
|            | after        | p4 <0.05      | p4 <0.05        | p4 <0.05               | p4 <0.05               |
|            | treatment    | 1,82±0,08     | 1,56±0,07       | 2,03±0,08              | 1,56±0,07              |
|            | 14th day     | 1,55±0,03     | 1,83±0,13       | 1,82±0,04              | 1,60±0,06              |
|            | after        | p1 <0.05      | p1 <0.05        | p1 <0.05               | p1 <0.05               |
|            | treatment    | p4 <0.05      | p4 <0.05        | p4 <0.05               | p4 <0.05               |
|            | 30th day     | 1,31±0,03     | 1,46±0,09       | 1,40±0,02              | 1,41±0,07              |
|            | after        | p1 <0.05      | p1 <0.05        | p1 <0.05               | p1 <0.05               |
|            | treatment    | p4 <0.05      | p4 <0.05        | p4 <0.05               | p4 <0.05               |

Note: APh- alkaline phosphatase, Ca 2+ - ionized calcium, P - inorganic phosphorus; p1 - the level of statistical significance of differences in comparison with indicators in healthy children of the corresponding age, p2 - when using BAA therapy and the standard method of therapy, p3 - children of 3-7 and 8-14 years old.

Figure 1 shows the dynamics of changes in the concentration of osteocalcin as a marker of bone remodelling and metabolic processes of bone tissue.
Figure 1. Dynamics of changes in the concentration of osteocalcin in children with a traumatological profile under the influence of a bioactive complex.

It was shown that the bioactive complex increases the osteocalcin level and stabilizes its concentration in the blood. These data indicate the activation of reparative osteogenesis and the acceleration of the formation of inert callus, create conditions for restoring the integrity and regeneration of bone tissue.

The materials obtained in the work indicate the following positive changes in the body of sick children under the influence of diet therapy:

- normalization of the concentration of inorganic phosphorus in the serum;
- increased alkaline phosphatase activity and the amount of inorganic phosphorus;
- reduction of pain and a negative attitude to taking dietary supplements, limiting the need for the use of analgesics;
- reduction in the volume of post-traumatic soft tissue edema and the absence of any side effects;
- shortening the rehabilitation period for post-immobilization contractures, increasing the range of motion in the joint of the injured limb.

The available literature data and materials from our own research have suggested a possible mechanism for the nutrient correction of metabolic bone disorders (figure 2).

Also the information is of interest that calcium, in combination with vitamin D, induces the synthesis of calcitonin which is a hormone with analytical activity.

Recommendations on the use of BAA for the prevention and complex treatment of traumatic injuries of bones, joints and ligaments, rickets in children and systemic osteoporosis in adults have been developed. This pathology is particularly pronounced in women over 45 years of age due to the restructuring of the hormonal background and a decrease in the biosynthesis of estrogens, ensuring calcium absorption. Systemic osteoporosis in 90% of cases is the cause of bone fractures (including the femoral neck) in the group in question.

With the preventive purpose the recommendation is to take 1 capsule 2 times a day, preferably in the afternoon (in the evening) after a meal. The most effective uptake at a specified time is associated with circadian fluctuations in the biosynthesis of parathyroid hormone and the cyclical nature of bone resorption. Therapeutic dose is calculated according to the recommendations.
The formulation and technology of the biocomplex were tested at the enterprises of Art Life (Tomsk). The developed product has passed the state examination and is registered in the Federal Register of Supplements. The technical documentation is approved, and the industrial production is organized. The quality and relevance of BAA is guaranteed by the implementation of a Management System for the enterprises of the company in accordance with the requirements of ISO 2001, 22000 standards and GMP rules.

3. Conclusion
Thus, the use of a biocomplex as a nutritional factor has a positive effect on recovery processes and functions of nearby joints in children with fractures of long tubular bones, the rehabilitation period can improve the quality of life of sick children with a trauma profile and is of medico-social importance.

References
[1] Avstrievkikh A N, Vekovtsev A A and Pozniakovsk V M 2005 Healthy food products: new technologies, quality assurance, efficiency of use (Novosibirsk: Sib. univ publishing house)
[2] Vekovtsev A A, Tohiriyon B, Chelnakova D A and Pozniakovsk V M 2017 Scientific substantiation and clinical approbation of a new dietary supplement formula in patients with deforming osteoarthrosis Bulletin of SUSU. Food and Biotechnology series 5(1) 59–65
[3] Kuzhelivsky I I, Urazova O I, Slizovsky G V and Maslikov V M 2008 Dynamics of osteocalcin and hemostasiological blood parameters on the background of cryotherapy in children with fractures of long tubular bones Siberian Medical Journal 5 30-3
[4] Musoev D S 2015 Osteosynthesis in the treatment of diaphyseal fractures of long tubular bones in children Avicenna Bulletin 3 64(64) 37-41
[5] Popov V P, Zdrelko V P, Trukhachev I G and Popov A V 2014 Complications of plateau
osteosynthesis in patients with fractures of the long tubular bones The genius of orthopedics 2 5-9
[6] Tutelyan V A, Spirichev V B, Sukhanov B P and Kudasheva V A 2002 Micronutrients in the diet of a healthy and sick person. Handbook of vitamins and minerals (Moscow: Kolos)
[7] Zhevachevsky N G 2016 The art of being healthy (Novosibirsk: Publishing House “Advertising and Publishing Company Novosibirsk”)
[8] Weaver C M, Gordon C M, Janz K F et al. 2016 The National Osteoporosis Foundation’s position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations Osteoporosis International 27(4) 1281–386
[9] Karpouzos A, Diamantis E, Farmaki P, Savvanis S and Troupis T 2017 Nutritional Aspects of Bone Health and Fracture Healing Journal of Osteoporosis 2017 4218472
[10] Cooper C, Dawson-Hughes B, Gordon C M and Rizzoli R 2015 Healthy Nutrition, Healthy Bones: How nutritional factors affect musculoskeletal health throughout life International Osteoporosis Foundation
[11] Tucker K L 2014 Vegetarian diets and bone status American Journal of Clinical Nutrition 100(1) 329S–35S
[12] Flodin L, Cederholm T, Saaf M et al. 2015 Effects of proteinrich nutritional supplementation and bisphosphonates on body composition, handgrip strength and health-related quality of life after hip fracture: A 12-month randomized controlled study Public health, nutrition and epidemiology BMC Geriatrics 15(1) 149