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Analysis of Osteocalcin Concentration in Polyarthritic and Systemic Juvenile Idiopatic Arthritis with Combination of Diabetes Mellitus Type 1

Tashkent Medical Academy, Tashkent, Uzbekistan

Systemic Juvenile Idiopathic Arthritis

Alovxon Sulaymanovich Sulaymonov[1], Dilorom Rakhimjanovna Atayeva[1], Gulshan Xoldorovna Iskanova[1], Sayyera Shavkatovna Egamova[2], Akrom Alovxonovich Sulaymanov[3], Farrukh Rakhimjanovich Ataev[4]

[1]Tashkent Medical Academy, Department of Children's disease №2, Uzbekistan; [2]Tashkent Medical Academy, Department of Children's disease, Uzbekistan; [3]Tashkent Medical Academy, Department of Forensic Medicine, Uzbekistan; [4]Westminster International University in Tashkent, Uzbekistan.

ABSTRACT

Background & Aims: Low serum concentrations of the osteocalcin (OC), haemoglobin and osteoporosis is associated polyarthritic and systemic subtypes of the juvenile idiopathic arthritis (PJIA, SJIA) with the combination of type 1 diabetes mellitus (T1DM). We investigated the association of serum OC levels with JIA and the influence of T1DM on this association in participants. Our goal is to study, analyze, and update and introduce new therapeutic techniques into the underlying disease characteristics of chronic rheumatic diseases that are most commonly observed in childhood.

Methods: This study compares concentrations of osteocalcin (OC) between participants with PJIA, SJIA and type 1 diabetes (T1DM) (n=20) and age-, gender- and body mass index (BMI)-matched participants without T1DM (n=40) among patients with OJIA (oligoarthritic the juvenile idiopathic arthritis), and it explores relationships between OC concentrations JIA and T1DM. Quantitative evaluation of OC was measured in heparin-treated blood plasma by IMMULITE 2000 analyzers. This in vitro study used to monitor mineral metabolism and diagnose osteoporosis. The IMMULITE OC test allows determining only an unfragmented OC molecule, not fragmented ones.

Results: Concentrations of OC were very low in participants with PJIA, SJIA with the combination of T1DM. In OJIA patients without T1DM, concentrations of OC were roughly at normal average. Conclusions: In patients with PJIA and SJIA, lower OC concentrations were related to T1DM.OC was sufficient to predict and prevent osteoporosis in JIA patients with a combination of T1DM. Serum level of OC administered in patients with OJIA without T1DM was in the region of the normal range. No relationship was detected between serum OC levels and OJIA in participants.

Key Words: Juvenile idiopathic arthritis, Type 1 diabetes mellitus, Osteocalcin, Osteoblast-derived protein, Osteoporosis, Hyperglycaemia

INTRODUCTION

Osteocalcin (OC) also known as bone gamma-carboxy glutamic acid-containing protein (BGLAP), is a noncollagenous protein hormone found in bone and dentin, first identified as a calcium-binding protein in chick bone.[1] Because OC has gla domains, its synthesis is vitamin K dependent. In humans, OC is encoded by the BGLAP gene.[2,3] Its receptors include GPRC6A, GPR158, and possibly a third, yet-to-be-identified receptor.[4,5] OC is secreted solely by osteoblasts and thought to play a role in the body's metabolic regulation.[6] In its carboxylated form it binds calcium directly and thus concentrates in bone, but genetic evidence has revealed that it does not play an important role in bone

Corresponding Author:

Alovxon Sulaymanovich Sulaymonov, Tashkent Medical Academy, Department of Children's disease №2, Uzbekistan.

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mineralization. In its uncarboxylated form, OC acts as a hormone in the body, signalling in the pancreas, fat, muscle, testes, and brain.[7] In the pancreas, OC acts on beta cells, causing beta cells in the pancreas to release more insulin.[8] In fat cells, OC triggers the release of the hormone adiponectin, which increases insulin sensitivity.[9] In muscle, OC acts on myocytes to promote energy availability and utilization and in this manner favours exercise capacity.[10] In the testes, OC acts on Leydig cells, stimulating testosterone biosynthesis and therefore affect male fertility.[11] In the brain, OC plays an important role in development and functioning.[12] An Acute Stress Response (ASR) (colloquially known as the fight or flight response) stimulates OC to release from bone within minutes in mice, rats, and humans. Injections of high levels of OC alone can trigger an ASR in the presence of adrenal insufficiency.[13] As OC is produced by osteoblasts, it is often used as a marker for the bone formation process. It has been observed that higher serum OC levels are relatively well correlated with increases in bone mineral density during treatment with anabolic bone formation drugs for osteoporosis, such as teriparatide. In many studies, OC is used as a preliminary biomarker on the effectiveness of a given drug on bone formation. For instance, one study which aimed to study the effectiveness of a glycoprotein called lactoferrin on bone formation used OC as a measure of osteoblast activity.[14] The demonstration that osteoblasts are endocrine cells stimulating insulin secretion and that this function was fulfilled by OC came from a classical cell biology experiment.[15] OC is carboxylated on three glutamine acid residues within the osteoblasts before being released into the bone extracellular matrix, however, both the carboxylated and uncarboxylated forms of OC can be found in the general circulation.[16] Since the gamma carboxylase enzyme responsible for this post-translational modification is not expressed in bacteria, the use of recombinant, bacterially produced OC, allowed to address this aspect of OC biology. Recombinant and therefore uncarboxylated OC, but not carboxylated one, was able to induce Insulin expression in pancreatic islets thus indicating that it is the uncarboxylated form of OC that is acting as a hormone.[17,18] OC circulates physiologically in several carboxylation states, two of which are reliably quantifiable in humans.[19] OC is synthesized by osteoblasts and is post-translationally g- carboxylated on three Gla residues in a vitamin K-dependent manner to carboxylated OC (cOCN). It is thought carboxylated osteocalcin (cOCN) has effects on bone mineralization and bone turnover while attached to calcium in bone.[20,21] Clinically, lower circulating concentrations have been associated with insulin resistance, suggesting the need to evaluate these relationships in people both with and without T1DM, T2DM.[22,23] The number of all people who currently have SJIA is estimated to be between 5 and 15 people in every 100,000.[24-26] OC also known as Bone Gla Protein is a non-collagenous, 49 amino acid long single-chain protein (MW 5.8 kDa), containing three γ-carboxyglutamic acids.[27-30] It is secreted solely by osteoblasts and its biosynthesis is vitamin K dependent.[31,32] During bone formation, newly synthesized OC is incorporated into the bone matrix, and a small fraction is secreted directly into the circulation, but its function remains elusive. Circulating OC concentrations have been broadly used for evaluating the rate of bone turnover in metabolic bone diseases such as hyperparathyroidism, Paget's disease and renal osteodystrophy.[33-36]

The term 'juvenile idiopathic arthritis' has been adopted as an umbrella term to indicate disease of childhood-onset (arbitrarily before the 16th birthday) characterised primarily by arthritis persisting for at least 6 weeks and currently has no known cause.[37] The circulating level of OC (10–25%) reflects the rate of bone formation. In juvenile idiopathic arthritis (JIA), a decrease in bone mass has been described in a high percentage of children with increased risk of osteoporosis.[38] This study aimed to explore the early changes in the predictors of bone turnover (OC) in children with JIA, without clinical symptoms and/or radiological signs of osteoporotic fractures.

MATERIALS AND METHODS

Study design and study subjects

This retrospective study included sixty patients with SJIA (40 girls and 20 boys) according to the International League of Associations for Rheumatology (ILAR) criteria[28] and was consecutively selected from Rheumatology, Rehabilitation and Endocrine Department, Tashkent Medical Academy, for the study. Twenty participants withT1DM were matched 2:1 for age, gender and BMI category to 40 who did not have of type 1 diabetes mellitus (T1DM). All participants had SJIA. Identification of participants with diagnosed T1DM (HbA1c > 6.3%, FBG > 6.5 mmol/L) was completed through clinical chart review. Those in the non-T1DM group did not have a clinical diagnosis of T1DM, use any antidiabetic medications, or have an HbA1c over 6.3%. Any participants with acute medical illnesses, neurodegenerative or neuropsychiatric diagnoses, active cancer, bone disease were excluded. Participants were screened using the standardized Mini-Mental State Exam (sMMSE) to exclude those with cognitive impairment; those with scores of less than 24 were excluded.[27] The disease duration ranged from 2 months to 5.2 years. Children excluded from the study were those older than 16 years and younger than 4 years, Children with any clinical or radiological finding of osteoporosis, with secondary causes of low bone mass, such as a clinical history of rickets, hypoparathyroidism, hyperthyroidism or hypothyroidism, poor gastrointestinal absorption, and renal or hepatic insufficiency.

Demographics and Clinical Characteristics

Demographic and clinical characteristics of the study group both at the time of enrolment and at follow-up are described in Table 1. Sociodemographic, clinical and anthropometric data for patients and controls were obtained through complete medical history, physical, medicational and articular examinations. Articular Disease Severity Score (ADSS)[48,49] were obtained from all patients. The joint index used was the whole 71 joint count.[50] The number of arthritis and systemic inflammation response was recorded through complete medical history, physical and articular examinations. Anthropometric data including weight, height, and BMI, were collected from medical records. Body fat percentage was measured by bioelectric impendence[29] Insulin was measured using an enzyme-linked immunosorbent assay (ELISA; ab200011 DeFactum, Tashkent, Uzbekistan) and glucose was measured using a standard glucometer (DeFactum, Tashkent, Uzbekistan). Homeostatic model of insulin resistance (HOMA-IR) was calculated using the formula: [fasting insulin (micro μ/L) x fasting glucose (nmol/L)]/22.5[30] HbA1c, cholesterol and triglycerides were assessed by standard lab testing at Sunnybrook Health Sciences Centre.

Osteocalcin Measurements

This study measured OC. Fasting blood was drawn (0900h ± 30 mins) and collected blood samples were centrifuged at 4° C, 1000 rpm for 10 minutes. Serum was separated and stored at -80° C until assayed. Serum concentrations of OC were quantified by ELISA (Immulite 2000).

Statistical Analyses

Differences between groups with and without T1DM were tested with independent samples t-tests. To explore potential confounders, participant characteristics were compared between those with T1DM and those without using an independent samples t-test for continuous measures or a chi-squared test for categorical measures, and relationships between participant characteristics and serum OC measures were assessed using non-parametric tests (Spearman's rho or Mann-Whitney U tests) because they are less sensitive to possible outlier effects in small sample sizes. Potential confounders thus identified were included in analyses of covariance (ANCOVA) to test the independent effect of T1DM on serum OC concentrations. Differences between study groups were evaluated by Student's *t*-test for normally or Mann-Whitney *U* test for non-normally distributed variables, and chi-squared statistic for proportions. McNemar for parametric and the Wilcoxon signed-rank test on nonparametric were used to comparing the baseline. For all statistical testing, two-sided probability values were reported and statistical significance was established at $P < 0.05$. We explored relationships between OC types and clinical characteristics in subgroups with and without T1DM using non-parametric tests. Post-hoc models were run in subgroups not using an insulin preparation. We assessed interactions between T1DM and participant characteristics in predicting OC concentrations as interaction terms in ANCOVA models.

RESULST

Participant characteristics

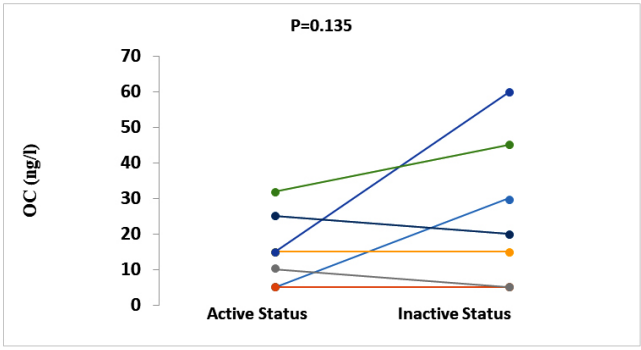
Characteristics of the 20 participants with T1DM and of the 40 without T1DM are reported in Table 1. Participants with T1DM had significantly different metabolic, fitness and lipid profiles compared to participants without T1DM (Table 1)

Table 1: Baseline characteristics of study participants

Characteristics	PJIA orSJIA+T1DM (n = 20)	JIA without T1DM (n = 40)	p
Age (y)	8.12 ±3.2	8.0 ±3.1	<0.001
BMI (kg/m²)	20.6 ± 3.1	21.1 ± 3.4	0.027
Height (cm)	125.2 ± 4.3	128 ± 3.9	<0.001
Fasting glucose (mmol/L)	6.96 ± 1.42	4.85 ± 1.2	0.005
Fasting insulin (pmol/L) must be < 174 pmol/L	169.8 ± 66.2	133.5 ± 32.43	<0.01
HOMA-IR	8.8±0.7	4.8± 0.1	0.03
HbA1c (%)	7.12± 0.89	6.01± 1.83	<0.01

Correlation of OC and disease state

OC levels were lower in the active than in the inactive phase, but without statistical significance P=0.135. Baseline characteristics and BMD measurements of the study participants (n = 60) (Fig. 1).



Patient characteristic with respect to BMI and BMD

The Body Mass Index (BMI) and Bone Mineral Density (BMD) measurements at spine and femur were significantly

different between T1DM (n = 20) and No T1DM (n = 40) patients (Table 2). The clinical picture in patients with active phase of SJIA is represented in Table 3.

Table 2

Parameters	PJIA, SJIA+T1DM (n = 20)	JIA without T1DM (n = 40)	p value
Age (Years)	8.12 ±3.2	8.0 ±3.1	0.999
BMI (Kg/m²)	16.5±2.5	14.5±2.5	< 0.001
Spine BMD (g/cm²) T Score	0.884 ± 0.17 −1.91 ± 1.61	1.087 ± 0.14 −0.46 ± 1.33	< 0.0001
Femur BMD (g/cm²) T Score	0.778 ± 0.11 −1.28 ± 1.17	0.936 ± 0.12 −0.32 ± 1.06	0.0002
Calcium (mg/dL)	8.21 ± 1.86	8.89 ± 1.23	0.89
Phosphorous (mg/dL)	5.89 ± 1.49	5.12 ± 1.89	0.71
OC (ng/mL)	10.83 ± 2.1	17.71 ± 2.44	< 0.0001

Table 3

Indicators	The number of patients participated in clinical research (n=60)	
	PJIA or SJIA+T1DM (n = 20) %	JIA without T1DM (n = 40) %
Articular manifestations		
Narrow joint spaces	80,9%	12,5%
New bone formation	56,4%	14,9%
Juxta articular osteopenia	68,9%	26,2%
Morning stiffness	98,2%	56,9%
Tenosynovitis		
Synovial membrane proliferation and thickening	86.9%	36.6%
Periarticular soft tissue swelling	89.7%	46.6%
Swollen joints	85,7%	63,2%
Disability index	98,7% (high)	12,5% (high)
Arthralgia	79,8%	25,2%
Arthritis that involves ≤ 4 joints	12,8%	89,9%
Deformities	59,8%	11.3%
Erosion	89,8%	8.3%
Limitation of range of motion	88.5%	21.3%
Tenderness of joints	78.9%	12.6%
Joint contractures	86.3%	36.9%
Increased heat in one or more joints in all subtypes	86.6%	23.6%
Extra-articular manifestations		
Anaemia	92.6%	33.5%
Fatigue	76.8%	23.4%
Lethargy	82.3%	26.5%
Thrombocytosis	26.1%	2.6%
Increased ESR	69.8%	23.2%
Lymphadenopathy (generalized)	26.4%	4.9%
Hepatosplenomegaly	42.3%	12.1%
Serositis	59.6%	26.3%
Hepatitis	65.3%	36.3%
Fever (spikes once or twice daily)	84.2%	21.4%
Salmon-pink rash	66.9%	26.1%
Soft tissue swelling	56.8%	22.1%
Pericarditis	26.8%	3.9%
Pleuritis	33.2%	4.1%
Anterior uveitis	69.2%	13.4%
Low body height	13.5%	5.3%
Poor appetite	76.8%	26.4%
Reduced physical activity	59.8%	12.8%
Limping	86.9%	26.3%
Flu-like symptoms	56.3%	26.2%

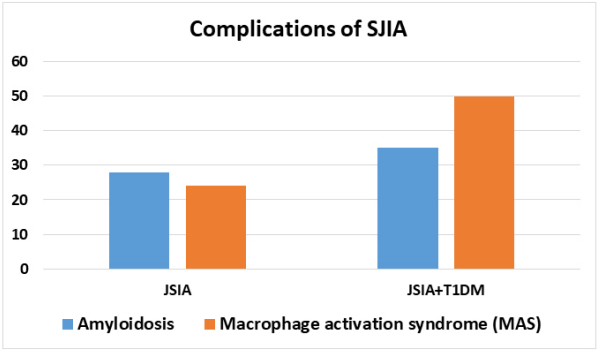


Diagram 2

Table 4

Variables JIA	PJIA or SJIA+T1DM (n = 20)	JIA without T1DM (n = 40)	p value
Serum laboratory			
Ca (mg/dl)	8.87 ± 0.54	9.07 ± 1.44	0.3
Ph (mg)	5 ± 1.63	4.8 ± .89	0.6
ALP (U/l)	149.52 ± 72	200.08 ± 74.39	0.001
OC (ng/ml)	1.20 ± 0.94	4.01 ± 1.32	0.4

Table 5: Ca: total calcium, Ph: phosphorus, ALP: alkaline phosphatase, OC: Osteocalcin

Characteristics, no. (%) or mean ± SD	PJIA or SJIA+T1DM patients (20)	JIA patients without T1DM (40)
Disease subtype		
Oligoarthritis	9	18
Polyarthritis	6	13
Systemic	5	9

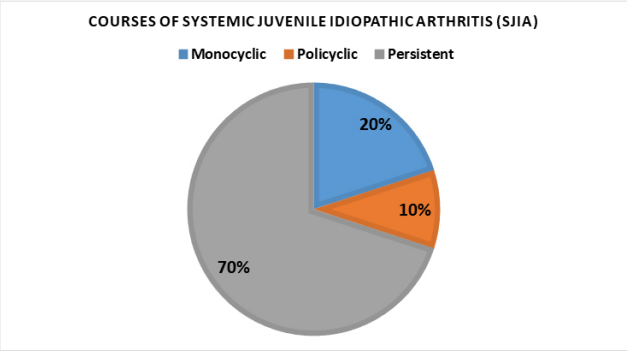


Diagram 3

Table 6: Densitometry of patients

Disease Densito metry manifestations	T1DM	OJIA	PJIA	SJIA	T1DM+ PJIA	T1DM+SJIA
normal bone mineral density	98%	96%	84%	76%	60%	50%
low bone mass (osteopenia)	2%	4%	5%	20%	20%	25%
osteoporosis	1%	1%	1%	4%	20%	25%

Table 7: Densitometry of patients

Disease Medicines	T1DM	OJIA	PJIA	SJIA	T1DM+ PJIA	T1DM+SJIA
Glucocorticoid (Prednisoloneoral, intravenous, intra-articular)	18%	26%	84%	96%	70%	80%
TNF alpha blockers (Etanercept)	5%	59%	86%	30%	72%	36%
Anti- interleukin-6 agents (Tocilizumab)	6%	67%	86%	56%	46%	56%
Anti-interleukin-1 agents (Anakinra)	8%	76%	84%	50%	56%	60%
T-cell regulatory agents (Abatacept)	6%	59%	86%	52%	65%	60%
Disease-modifying antirheumatic drug (Methotrexate)	2%	64%	85%	90%	70%	75%
NSAIDS (Ibuprofen per oral or topical)	11%	65%	81%	84%	80%	85%
Insulin (subcutaneous)	98%	0%	0%	0%	98%	95%
Antibiotics (Ceftriaxone)	42%	40%	55%	60%	80%	85%
Betamethasone dipropionate and betamethasone sodium phosphate (Diprospan subcutaneous)	25%	35%	75%	84%	60%	85%
Enzyme drug (Pancreatin)	78%	6%	24%	46%	60%	70%
Cristalloid (Combisol or Reosorbilact)	12%	15%	45%	70%	80%	95%
Methylxanthine phosphodiesterase inhibitor (Trental)	11%	21%	61%	84%	70%	85%
Ferrum III component drug (Maltofer)	12%	15%	45%	60%	70%	75%

Table 8: Skeletomuscular functional insufficiency

Degree Disease	*Skeletomuscular functional insufficiency I degree*	*Skeletomuscular functional insufficiency II degree*	*Skeletomuscular functional insufficiency III degree*
T1DM	11%	41%	71%
OJIA	21%	51%	12%
PJIA	12%	45%	21%
SJIA	84%	90%	70%
T1DM+ PJIA	60%	91%	70%
T1DM+SJIA	84%	90%	70%

Table 9: Effect of medical conditions on circulating osteocalcin concentration

Condition	Effect on circulating osteocalcin	Other information
T1DM	Decrease	Correlates with disease stage and adequate insulin therapy
OJIA	No change	There is no need to specific therapy
PJIA	No change (15%)	Correlates with adequate hormonetherapy, rehabilitation with antiosteoporosis drugs and vit K supplementation
SJIA	Decrease	Correlates with adequate hormonetherapy, rehabilitation with antiosteoporosis drugs and vit K supplementation
T1DM+ PJIA	Decrease	Correlates with adequate hormonetherapy, rehabilitation with antiosteoporosis drugs and vit K supplementation
T1DM+SJIA	Decrease	Correlates with adequate hormonetherapy, rehabilitation with antiosteoporosis drugs and vit K supplementation

Prednisone dose

All participants are followed over five years of rehabilitation. Bone mass index is measured with dual-energy x-ray absorptiometry (DEXA) at the beginning of the study, at the middle of the five years, and the end of five years. New diagnoses of osteoporosis and osteoporotic fractures are recorded during this time and the following graph is plotted based on the data recorded (Table 2- Table7).

DISCUSSION

Juvenile idiopathic arthritis is an HLA-associated synovial inflammation that can cause arthralgias/arthritis in children. In this study, we evaluated levels of OC as indicators of SJIA activity. We found that: (1) Reduced OC levels have been found in children with chronic rheumatic diseases, (2) children with SJIA who have an improvement in their disease activity have an improvement in bone mineral density, heralded by an increase in serum OC values, (3) serum OC levels were lower in the active phase than in the inactive phase of SJIA (Table 8, 9), (4) The degree of anaemia and microcytosis was directly related to JRA activity and the most severe anaemia was seen in patients with active systemic JIA (Fig 1-4), (5) Osteoporosis is characterized by loss of bone mass associated with increased fragility and risk of fractures.[39] It is diagnosed by measuring a real bone mineral density (BMD, g/cm2).[44] It is important to detect the early changes of bone mass in JIA to identify patients at risk to develop reduced bone mass and osteoporotic fracture.[40] Biochemical markers of bone turnover are indirect indices of skeletal metabolism. A range of biochemical markers have been investigated for applicability to determine bone health in children with JIA.[41] OC (OC) is the major non -collagenous protein of the bone matrix. OC is predominantly synthesized by mature osteoblasts and is mainly incorporated into the bone matrix. The circulating level of OC (10–25%) reflects the rate of bone formation.[42] Deoxypyridinoline (DPD) is one of two major cross-links in the collagen molecule. It is excreted in the urine and is considered a bone-specific resorption marker[43] JIA strongly affects the skeletal system in certain patients, which may lead to either localized or generalized osteoporosis.[44]

There are relatively few deaths from osteoporosis observed in pediatric younger people, i.e., in the younger group of people we have identified; however, it creates the most conducive environment for disease due to pain, regular exercise interference, risk of fracture, and long-term outcomes. This is in agreement with previous studies wgo reported that the serum level of OC was significantly lower in JIA patients compared to healthy control.[45-47] We demonstrated that there was a significant decrease in the serum level of OC in patients with SJIA and T1DM compared to control group.Several studies in the literature demonstrated that chronic inflammatory processes result in generalized bone-mass loss, bone demineralization, and progressive radiological abnormalities. The bone articular complications consist of juxta-articular osteopenia, subchondral and marginal bone erosions.[48] Discovered that osteocalcin serum test maintained to detect the level of osteoporosis of JIA with combination T1DM. Throughout the research performed the blood test on 60 patients. Of the 20 patients with the JIA+T1DM, 18 had positive test results and 2 had negative test results. Of the 40 patients without the T1DM, 8 had positive test results. Test sensitivity is 18/18+2=0.9 or 90% for patients with diseases. Test specificity is 32/32+8=0.8 or 80%. Sensitivity and specificity are determined by test parameters and are thus intrinsic to the text itself.osteocalcin acts as a hormone to affect insulin sensitivity and energy expenditure; only the undercarboxylated form of osteocalcin is active.

CONCLUSION

Key aspects of OC measurement are activities aimed at eliminating these active diseases, normalizing joint function, normal development, and preventing joint injuries using adequate therapy.

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