Cell and Organ Transplantology. 2023; 11(1): 14-24.
https://doi.org/10.22494/cot.v11i1.150

Skeletal maturity as a biomarker for determining indications for regenerative interventional technologies in adolescent patients with hip and knee diseases

Holiuk Ye.[1], Melnyk M.[1], Filipchuk V.[1], Ostapenko T.[2], Strafun S.[1]

[1]*State Institute of Traumatology and Orthopedics, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine*
[2]*Ukrainian Scientific Center of Endocrine Surgery, Endocrine Organs and Tissue Transplantation, Ministry of Health of Ukraine, Kyiv, Ukraine*

*Corresponding author's e-mail: holyuk@yahoo.com

ABSTRACT

Our preliminary studies indicate the significant value of assessing skeletal maturity in adolescents, as it characterizes the development of the skeleton in an individual and can serve as a biomarker for regenerative potential in children and adolescents. This assessment significantly influences the choice of treatment tactics for diseases of the hip and knee joints. We have established a correlation between reparative regeneration processes and skeletal maturity in conditions such as slipped capital femoral epiphysis (SCFE), Perthes' disease, femoroacetabular impingement syndrome, spastic hip dislocation in patients with cerebral palsy, and Blount's disease. The intensity of regeneration processes during prepubertal development allows for the use of less invasive methods of surgical interventions.

THE PURPOSE *of the study was to develop a methodology for determining skeletal maturity as a biomarker for establishing indications for regenerative interventional technologies in adolescent patients with hip and knee joint diseases.*

MATERIALS AND METHODS. *The study group for the development of the examination methodology included 157 patients (86 boys and 71 girls) with hip joint pathology (hip dysplasia, Perthes' disease, juvenile epiphysiolysis of the femoral head, aseptic necrosis of the femoral head, and individuals without diagnosed hip joint pathology), as well as 129 patients (58 boys and 71 girls) with knee joint diseases (Blount's disease, axial deformities of the lower extremities, meniscal damage, and patients who were examined due to complaints of knee joint pain), aged between 10 to 18 years. The group for a differentiated approach to the use of regenerative interventional technologies consisted of 46 adolescent patients with diseases of the hip and knee joints (SCFE, Perthes' disease, Blount's disease, and pathology of menisci).*

RESULTS. *A methodology for the use of skeletal maturity as a biomarker for establishing indications for regenerative interventional technologies in adolescent patients with diseases of the hip and knee joints has been developed, which includes the following steps: establishing the period of sexual development of the patient based on the determination of skeletal maturity based on radiographs of the hip and knee joints, establishing additional risk factors (heredity, individual characteristics of the connective tissue, the presence of chronic systemic diseases) and the severity of the disease (according to the results of questionnaires). According to the results of the analysis of the application of the methodology of distinguishing skeletal maturity as a biomarker of indications for regenerative interventional technologies in adolescent patients with diseases of the hip and knee joints, it was established that in prepuberty only 3 out of 16 examined patients (which amounted to 19 %) have indications for regenerative interventional technologies, during the induction of puberty, 4 out of 9 examined patients (that is, almost 50 %) had the specified indications.*

CONCLUSION. *In the prepubertal period, we recommend the use of regenerative technologies in combination with one of the risk factors or in cases with a severe or moderate course of the disease. During the induction of puberty, regenerative technologies are recommended in the presence of one of the risk factors or in cases with a severe or moderate course of the disease. In the pubertal period, due to the reduction of the individual's regenerative potential, we recommend the use of regenerative technologies for all patients.*

KEY WORDS: *regenerative interventional technologies; diseases of the hip and knee joint; adolescent patients; skeletal maturity*

Reparative tissue regeneration of the musculoskeletal system is an ever-present problem of the science and practice of traumatology and orthopedics. In the structure of disability in adolescence, congenital and acquired diseases of the hip and knee joints occupy a significant share. In the absence of treatment or improper treatment in the coming months after the occurrence, damage to the joint tissues (articular cartilage and spongiosa, acetabulum lip, knee menisci, joint capsule, vessels feeding the head and neck) progresses to a severe dystrophic-destructive process, the result of which is a number of irreversible pathological processes and clinical conditions: tissue destruction of the bone articular end, capsule fibrosis, arthrogenic contractures, pain syndrome, permanent disability [1-3]. Thus, according to various authors, up to 40 % of patients in this category will need endoprosthesis in the future. A modern meta-analysis of literary sources indicates that in the structure of the final stages of osteoarthritis of the hip joint in young patients who require endoprosthesis, 30 % of all cases are the result of avascular necrosis of the femoral head (AVN), 26 % – dysplasia of the hip joint, 26 % – LCPD and SCFE, 14 % – unclassified [4]. In other words, more than half (52 %) of patients who need prosthetics by the age of 40 have been ill since childhood or adolescence.

An analysis of the long-term treatment results of such hip joint diseases as Legg-Calve-Pertes disease (LCPD), Slipped Capital of Femoral Epiphysis (SCFE), Developmental Dysplasia of the Hip (DDH) [5-6] showed that in most cases the hopes for the biological potential of adaptive and compensatory reactions in children and adolescents turned out to be unjustified. Modern analysis of literary sources indicates further specialization of adolescent medicine in pediatrics. This is due to a number of reasons, the main one being the peculiarities of the course and treatment of diseases during puberty. Pathology of the locomotor system in adolescence is no exception. Damage to the hip joint in this age period attracts considerable attention for a number of reasons:

• Significant prevalence of orthopedic diseases during puberty. According to the Society for Adolescent Medicine (2002), 7 % of citizens of this age group need orthopedic care. Similar screening programs were not conducted in Ukraine.

• The anatomical and functional features of the hip joint formation in normal puberty, in congenital and acquired diseases and after reconstructive and restorative operations performed on the hip joint at different age periods have not been sufficiently elucidated.

• Rapid progress of osteoarthritis of hip and knee joints in this age period.

• Reduction of adaptive capabilities of the body and hip joint, in particular, in this age period compared to children's.

• "Staying" of patients on the border of pediatric and adult orthopedics with problems of treatment continuity.

The treatment of these diseases and their residual problems remains an urgent issue today, since with the progression of the disease, the list of possible treatment tactics and their effectiveness decreases significantly, and the final technique – endoprosthesis – has a number of disadvantages and age restrictions. In addition to the diseases characteristic of this period (SCFE), there is deterioration in the course of congenital pathologies, in particular hip dysplasia. Modern technologies of their treatment, without a doubt, must take into account the peculiarities of the hip joint formation in this age. All of the above determines the relevance of this study.

Our previous studies [7-17] indicate the significant importance of skeletal maturity in adolescents, which characterizes the development of the skeleton in an individual and can be used as a biomarker of regenerative potential in children and adolescents, which significantly affects the choice of treatment tactics for the hip and knee joints diseases.

Thus, we established the dependence of reparative regeneration processes in children and adolescents on skeletal maturity in such diseases of the hip and knee joints in children and adolescents as SCFE, Perthes' disease, femoro-acetabular conflict syndrome, spastic hip dislocation in patients with cerebral palsy, Blount's disease. The intensity of regeneration processes in the prepubertal period of sexual development allows the use of less invasive methods of surgical interventions.

THE PURPOSE of study: the determination of skeletal maturity has significant prospects for determining indications for the regenerative technologies application, which became the reason for the development of an examination methodology and a differentiated approach.

MATERIALS AND METHODS

The study group for the development of the methodology consisted of 157 patients (86 boys and 71 girls) with hip joint pathology (hip dysplasia, Perthes' disease, SCFE, aseptic necrosis of the femoral head, and without diagnosed hip joint pathology) and 129 patients (58 boys and 71 girls) with diseases of the knee joints (Blount's disease, axial deformities of the lower extremities, meniscal injuries, and patients who were examined for complaints of pain in the area of the knee joint) aged 10 to 18 years. Patients' parents signed an informed consent to participate in the study without fail.

The following research methods were used:

- clinical research;
- determining the quality of life of patients according to questionnaires;
- determining the skeletal maturity based on radiographs of hip and knee joints.

The clinical examination consisted in identifying the following parameters, which were included in the thematic patient's medical record form (**Fig. 1**).

To assess the quality of life in children and adolescents with hip joint pathology, we used a questionnaire developed by us previously (**Fig. 2**) [18].

To assess the quality of life in children and adolescents with diseases of the knee joint, the KOOS-Child scale [19], translated into Ukrainian, was used (**Fig. 3**).

THEMATIC PATIENT'S EXAMINATION RECORD №____

Treatment facility: _____
Inpatient record No: _____
Diagnosis: _____
Date of arrival at the clinic: _____
Date of discharge: _____
Date of completion: _____

I. Passport information

1. Full name _____
2. Gender: Male / Female
3. Date of birth: _____
4. Age (years): _____
5. Place of birth: _____
6. Nationality: _____

II. Complaints of the patient (must be underlined)

1. Pain in the lower limb: Yes / No
2. Gait disorder: Yes / No
3. Movement restrictions: Yes / No
4. Shortening of the limb: Yes / No

III. Risk factors and life history (emphasis required)

1. Presence of systemic diseases in the family: Yes / No
   If so, which ones?
2. Presence of patients with osteoarthritis in the family: Yes / No
   If so, who has _____
3. The presence of the ligamentous laxity: Yes / No
   If so, who has _____

IV. Medical history:

1. Onset of the disease (year, month): _____
2. Duration of the disease (months): _____
3. Previous treatment: _____

V. Objective examination (to be completed by a doctor)

Date: _____

1. Constitution: Normosthenic, hypersthenic, hyposthenic
2. Height: _____ cm.
3. Weight _____ kg.
4. The presence of weakness of the ligamentous apparatus Yes / No
5. Stage of sexual development according to Tanner _____
6. Skeletal maturity of the hip (knee) joints at the time of onset of the disease (scores)_____
8. Skeletal maturity of the hip (knee) joints at the time of admission (points) _____

Fig. 1. Thematic patient's examination record form.

1. Does your child have pain?
44 = none
40 = there is, but the child ignores it (does not pay attention)
30 = is only after long running, jumping, does not limit normal needs (walking, climbing stairs, transport, sitting)
20= yes, limiting usual needs (walking, climbing stairs, transport, sitting)
10 = frequently and significantly restricts movement in some places takes pain medication
0 = is constant, or requires constant pain medication

2. Does your child have a limp (lameness)?
4 = none
3 = barely (almost imperceptibly and occasionally)
2 = constant but moderate
1 = heavy constant
0 = does not walk without additional support

3. How far can your child walk?
4 = unlimited
3 = 1.5 km
2= 500-700 m
1 = only at home
0 = does not walk

4. Is there a limitation of mobility of the hip joint?
4 = none
3 = barely
2 = moderate
1 = significant
0 = very significant (joint almost immobile)

5. Does your child have problems going down the stairs?
4 = none
3 = barely
2 = moderate
1 = significant
0 = cannot walk up the stairs

6. Does your child have problems climbing stairs?
4 = none
3 = barely
2 = moderate
1 = significant
0 = cannot walk up the stairs

7. Are there any problems while walking?
4 = none
3 = barely
2 = moderate
1 = significant
0 = cannot go for a walk

8. Are there problems during mobile games with other children (football, classes, running, etc.)?
4 = none
3 = barely
2 = moderate
1 = significant
0 = cannot be played

9. Are there problems when squatting?
4 = none
3 = barely
2 = moderate
1 = significant
0 = cannot squat

10. Are there problems when changing the direction of movement (turning the body while standing on one leg)?
4 = none
3 = barely
2 = moderate
1 = significant
0 = cannot turn the body while standing on one leg

Fig. 2. Questionnaire for children and adolescents with hip joint diseases

Today's date: _____ Date of birth: _____

Name: _____

INSTRUCTIONS
These questions collect information about how your injured knee affects you. Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please select the best answer you can.

KNEE PROBLEMS

Symptoms. *The questions should be answered in the context of symptoms during the last week.*

S1. During the past 7 days, how often has your knee been swollen?
☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

S2. During the past 7 days, how often has your knee made any noise/sounds?
☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

S3. During the past 7 days, how often did your knee get stuck?
☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

S4. During the past 7 days, how often have you been able to fully straighten your knee on your own?
☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

S5. During the past 7, days how often have you been able to fully bend your knee on your own?
☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

Stiffness. The following questions refer to the degree of stiffness of the joint during the last week. Stiffness is a feeling of limitation or slowing down of movements in the knee joint.

S6. During the past 7 days, how much difficulty have you had moving your knee just after waking up in the morning?
☐ No difficulty ☐ A little ☐ Sometimes ☐ A lot ☐ Extreme difficulty

S7. During the past 7 days, how much difficulty have you had later in the day moving your knee after being sedentary for a while?
☐ No difficulty ☐ A little ☐ Sometimes ☐ A lot ☐ Extreme difficulty

PAIN

P1. During the past month, how often have you experienced knee pain?
☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ All the time

How much knee pain have you experienced **in the past 7 days** during the following activities?

Check the best answer for each item

P2. Twisting/pivoting on your injured knee when walking/standing/running
☐ No pain ☐ A little pain ☐ Middle pain ☐ A lot of pain ☐ Extreme pain

P3. Fully straightening your injured knee
☐ No pain ☐ A little pain ☐ Middle pain ☐ A lot of pain ☐ Extreme pain

P4. Fully bending your injured knee
☐ No pain ☐ A little pain ☐ Middle pain ☐ A lot of pain ☐ Extreme pain

P6a. Walking up stairs
☐ No pain ☐ A little pain ☐ Middle pain ☐ A lot of pain ☐ Extreme pain

P6b. Walking down stairs
☐ No pain ☐ A little pain ☐ Middle pain ☐ A lot of pain ☐ Extreme pain

P8a. Sitting with your injured knee bent
☐ No pain ☐ A little pain ☐ Middle pain ☐ A lot of pain ☐ Extreme pain

P9. Standing upright on both legs for any amount of time
☐ No pain ☐ A little pain ☐ Middle pain ☐ A lot of pain ☐ Extreme pain

DIFFICULTY DURING DAILY ACTIVITIES

The following questions relate to joint function. By this we mean your ability to move around and your ability to care for yourself. For each of the following activities, please indicate the degree of difficulty you have experienced in the past week because of your knee.

A1. During the past 7 days, how much difficulty have you had walking down stairs?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A2. During the past 7 days, how much difficulty have you had walking up stairs?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A3. During the past 7 days, how much difficulty have you had standing up from a chair?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A4. During the past 7 days, how much difficulty have you had to stand
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A5. During the past 7 days, how much difficulty have you had to bend down and pick up an object from the floor?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A6. During the past 7 days, how much difficulty have you had to walking on a flat surface
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A7. During the past 7 days, how much difficulty have you had getting in to/out of a car?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A8. During the past 7 days, how much difficulty have you had to go shopping
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A9. During the past 7 days, how much difficulty have you had to put on socks/stockings
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A10. During the past 7 days, how much difficulty have you had to get out of bed?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A11. During the past 7 days, how much difficulty have you had to remove socks/stockings
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A12. During the past 7 days, how much difficulty have you had to change knee position when lying in bed?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A13. During the past 7 days, how much difficulty have you had getting in to/out of the bathtub/shower?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A14. During the past 7 days, how much difficulty have you had to sit in a chair with your injured knee bent?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A15. During the past 7 days, how much difficulty have you had to get up/sit down in a wheelchair
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A16. During the past 7 days, how much difficulty have you had to carry heavy bags/backpacks etc?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

A17. During the past 7 days, how much difficulty have you had to do light chores such as cleaning your room, filling/emptying the dishwasher, making your bed, etc?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

DIFFICULTY DURING SPORTS AND PLAYING

The following questions are about your physical function that requires significant effort. The question should be answered in the context of complications related to the knee joint during the last 7 days

SP1. During the past 7 days, how much difficulty have you had to squat down during play or sports activities?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

SP2. During the past 7 days, how much difficulty have you had to run during play or sports activities?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

SP3. During the past 7 days, how much difficulty have you had to jump during play or sports activities?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

SP4. During the past 7 days, how much difficulty have you had to twist/pivot because of your injured knee during play or sports activities?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

SP5. During the past 7 days, how much difficulty have you had to kneel because of your injured knee?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

SPN6. During the past 7 days, how much difficulty have you had to keep your balance when walking /running on uneven ground?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

SPN7. During the past 7 days, how much difficulty have you had playing sports because of your injured knee?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

HOW HAS YOUR INJURY AFFECTED YOUR LIFE?

Q1. How often do you think about your knee problem?
☐ Never ☐ Rarely ☐ Some ☐ Sometimes ☐ All the time

Q2. How much have you changed your lifestyle because of your injured knee?
☐ Not at all ☐ A little ☐ Some ☐ A lot ☐ Very much

Q3. How much do you trust your injured knee?
☐ Completely ☐ A lot ☐ Some ☐ A little ☐ Not at all

Q4. Overall, how much difficulty do you have with your injured knee?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

Q5. How much difficulty have you had getting to school or walking around in school (climbing stairs, opening doors, carrying books, participating during recess) because of your injured knee?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

Q6. How much difficulty have you had to do things with friends because of your injured knee?
☐ No difficulty ☐ A little ☐ Some ☐ A lot ☐ Extreme difficulty

Thank you very much for completing all the questions in this questionnaire!

Fig. 3. Knee Injury and Osteoarthritis Outcome Score – Child (KOOS-Child) Questionnaire.

The next step was to determine the skeletal maturity of the knee and hip joints based on their radiographs. Determining the skeletal maturity of the knee and hip joints was carried out according to the methods developed by us previously [20-22]. We propose the X-ray markers of knee joint maturity, including patella (**Fig. 4**), proximal tibial epiphysis (**Fig. 5**), proximal fibular epiphysis (**Fig. 6**), distal femoral epiphysis (**Fig. 7**), and tibial tuberosity (**Fig. 8**).

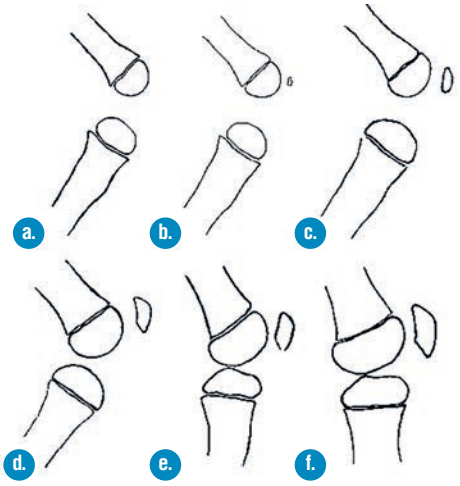

Fig. 4. Indicators of skeletal maturity of patella: a – only the cartilage model of the patella is available (1 point); b – the appearance of ossification nuclei of the patella (2 points); c – the patella has an elongated shape in the form of an oval (3 points); d – the patella has the shape of a biconvex disk, which is more flattened on the upper edge (4 points); e – the upper edge of the patella is slightly concave, the back-lower surface of the patella is flat and forms an obtuse angle with its lower edge (5 points); f – patella has the shape of a parallelogram (6 points).

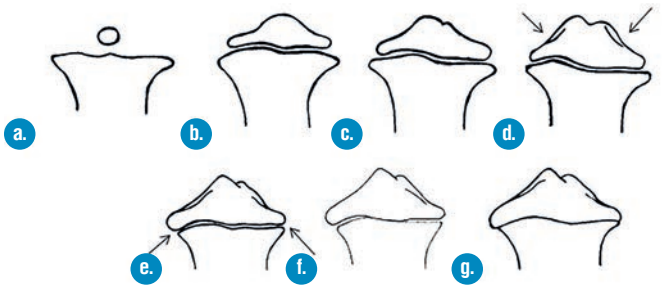

Fig. 5. Indicators of skeletal maturity of proximal tibial epiphysis: a – appearance of the center of ossification, usually rounded, and sometimes triangular in shape (1 point); b – the pineal gland takes on a triangular shape (2 points); c – formation of intercondylar elevation (3 points); d – the appearance of lines on the plateau of the tibial epiphysis (4 points); e – the epiphysis is aligned with the diaphysis in width (5 points); f – partial synostosis (6 points); g – complete synostosis (7 points).

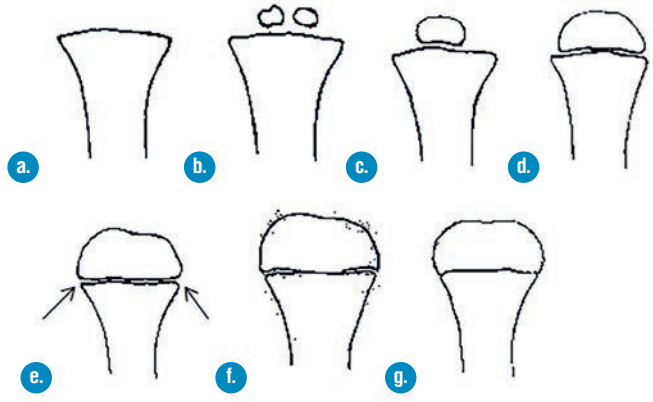

Fig. 6. Indicators of skeletal maturity of proximal fibula: a – cartilaginous model of the epiphysis of the fibula (1 point); b – the appearance of points of ossification of the epiphysis (2 points); c – the epiphysis of the fibula has the shape of an oval placed horizontally (3 points); d – the epiphysis of the fibula has the shape of a dome (4 points); e – the width of the epiphysis is aligned with the dialysis (5 points); f – partial synostosis (6 points); g – complete synostosis (7 points).

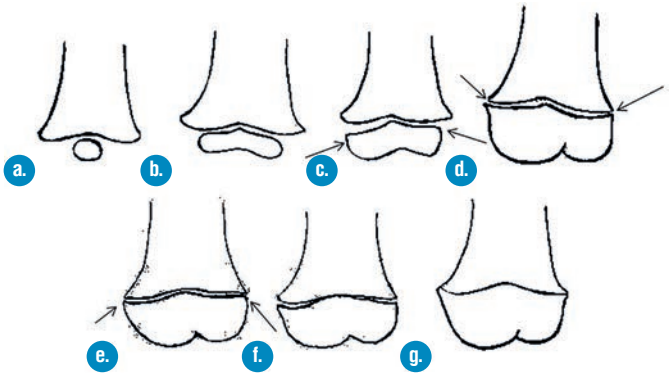

Fig. 7. Indicators of skeletal maturity of distal femur: a – ossification core of mostly rounded shape (1 point); b – elongation of the pineal gland in width, the pineal gland acquires a dome-shaped shape (2 points); c – condyles are visualized as separate formations (3 points); d – the line of the medial condyle moves towards the lateral condyle and the growth zone, the proximal medial corner of the epiphysis sharpens (4 points); e – the width of the epiphysis is aligned with the dialysis (5 points); f – partial synostosis (6 points); g – complete synostosis (7 points).

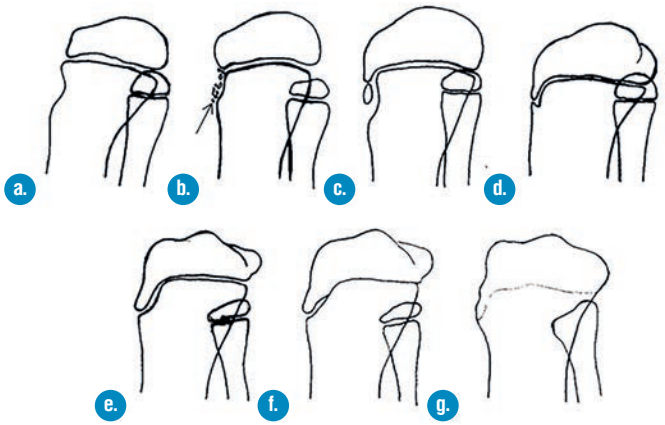

Fig. 8. Indicators of skeletal maturity of tibial tuberosity: a – absence of ossification points of the humerus (1 point); b – the appearance of numerous points of ossification of the humerus (2 points); c – fusion of ossification points into one large one (3 points); d – fusion of the ossification point of the humerus with the front-lower edge of the epiphysis and the formation of a «beak» (4 points); e – lengthening and thickening of the «beak» formed by the ridge and the front-lower edge of the epiphysis (5 points); f – partial synostosis (6 points); g – complete synostosis (7 points).

We also propose the X-ray markers of hip joint maturity, including femoral head (**Fig. 9**), greater trochanter (**Fig. 10**), acetabulum (**Fig. 11**), Y-cartilage (**Fig. 12**), ishiopubic synchondrosis (**Fig. 13**), os pubis (**Fig. 14**), ishium (**Fig. 15**) and trochanter minor (**Fig. 16**).

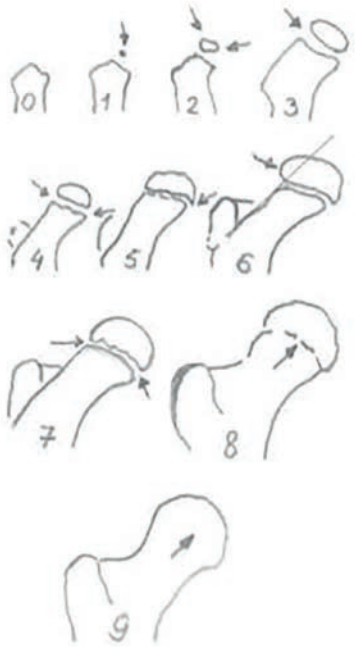

Fig. 9. Indicators of femoral head maturity: 0 points – the head is not visualized; 1 point – point nucleus of ossification; 2 points – an increase in the transverse size of the head and the acquisition of a rounded shape by the epiphysis; 3 points – the formation of a concave surface of the meta-epiphysis adjacent to the growth zone; 4 points – acquisition of a rectangular shape by the growth zone; 5 points – formation of the «beak» of the lower part of the pineal gland; 6 points – «normalization» of the Klein line; 7 points – the formation of a convex-concave ratio of the metaphysis and epiphysis; 8 points – partial synostosis; 9 points – complete synostosis.

Fig. 10. Indicators of greater trochanter maturity: 1 point – single or multiple nuclei of ossification without a clear shape; 2 points – the appearance of two relatively large nuclei of oval-shaped ossification projecting one on the other; 3 points – the fusion of ossification nuclei into a single bone formation, the apophyseal growth zone acquires a rectilinear shape; 4 points – the appearance of additional ossification points for the apex of the greater trochanter; 5 points – creeping of the lower-medial pole of the apophysis on the neck, or the appearance of the second contour of the back part of the acetabulum (depends on the torsional development of the hip); 6 points – partial synostosis of the great acetabulum; 7 points – complete synostosis, «fusion» of the acetabulum with the diaphysis of the femur.

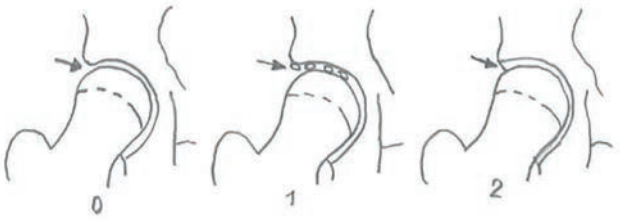

Fig. 11. Indicators of acetabulum maturity: 0 points – the contour of the roof is flat or slightly wavy, secondary points of ossification are not detected; 1 point – the appearance of numerous ossification points in the projection of the acetabulum; 2 points – synostosis of secondary ossification points with the roof of the acetabulum.

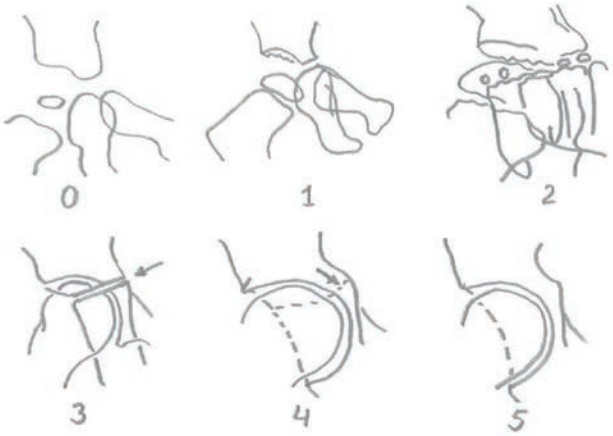

Fig. 12. Indicators of Y-cartilage maturity: 0 points – U-shaped cartilage in the form of a wide band of illumination, its lower contour in the form of an angle with the apex turned downward; 1 point – narrowing of the U-shaped cartilage, its contours are rectilinear with pronounced locking plates; 2 points – appearance of secondary ossification points; 3 points – partial synostosis in the medial sections; 4 points – residual enlightenment; 5 points – complete synostosis.

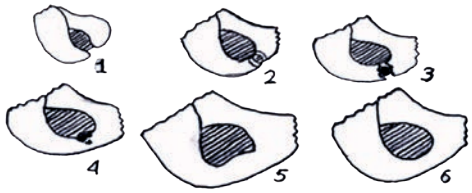

Fig. 13. Indicators of ishio-pubic synchondrosis maturity: 1 point – a significant gap between bones, lack of congruence of surfaces; 2 points – reduction of the gap, the cartilaginous tissue between the ends of the branch of the ischial bone and the lower branch of the pubic bone is displayed in the form of two bands of illumination, which are closed at the ends; 3 points – the appearance of a «calcified callus» of the joint; 4 points – partial synostosis of the joint; 5 points – complete synostosis, a small compaction is differentiated at the level of the former synchondrosis; 6points – remodeling of the bone: the branches of the ischial and pubic bones are a single entity.

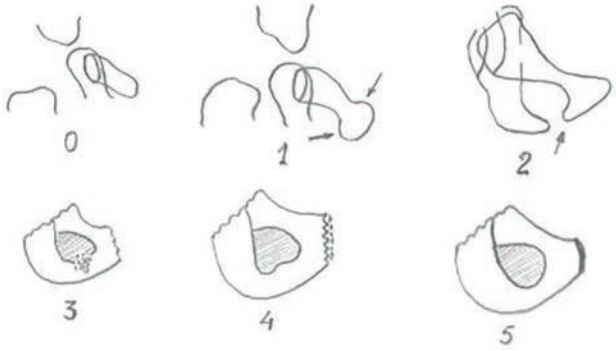

Fig. 14. Indicators of os pubis maturity: 0 points – the lower branch of the pubic bone is not visualized; 1 point – the lower branch of the pubic bone is short with rounded ends; 2 points – an increase in the length of the ossified lower branch to 2/3 of its anatomical length; 3 points – the final phase of ossification of the pubic bone – closure of the pubic-gluteal synchondrosis; 4 points – the appearance of «waviness» of the contours of the symphyseal surface of the pubic bones (sometimes with the presence of one small secondary point of ossification at the upper and lower edges); 5 points – fusion of secondary ossification points with the symphyseal surface, which acquires an even contour.

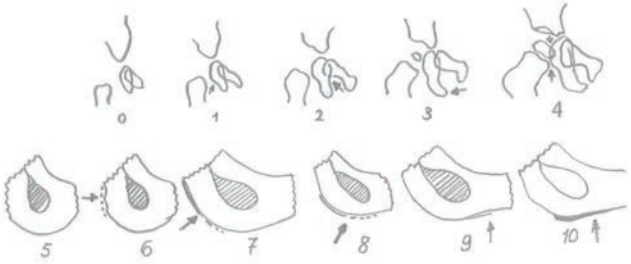

Fig. 15. Indicators of ishium maturity: 0 points – incisura acetabuli is not differentiated; 1 point – appearance of the contour of the incisura acetabuli; 2 points – the appearance of the contour of the medial surface of the body of the ischium (the first contours of «teardrops»); 3 points – further enchondral ossification of the ramus ischii with the formation of a «hook»; 4 points – «creeping» of the upper-lateral parts of the body of the ischium on the contour of the epiphysis; 5 points – the appearance of a wavy contour of the upper surface of the body of the ischium; 6 points – the appearance of a wavy contour of the lower surface of the branch of the ischial bone; 7 points – the appearance of ossification points for the tubercle of the ischial bone in the form of narrow sclerosed bands; 8 points – an increase in the length of the ossification points; 9 points – fusion of separate points of ossification into a single wide sickle-shaped strip of ossified apophysis of the ischial hump; 10 points – complete synostosis of the apophysis.

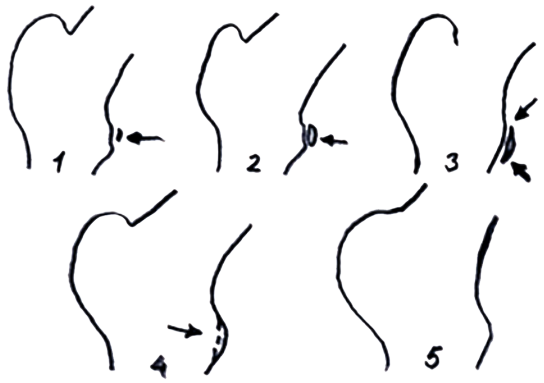

Fig. 16. Indicators of trochanter minor maturity: 0 points – absence of the contour of the small rotator cuff; 1 point – ossification nucleus without a certain shape; 2 points – the core of the ossification in the form of a vertically elongated semicircle: convex medially, straight laterally; 3 points – the formation of a concavity on the lateral surface of the small acetabulum; 4 points – partial synostosis of the small acetabulum; 5 points – complete synostosis of the acetabulum and diaphysis.

According to the results of determining the skeletal maturity, the period of sexual development of the patient was determined according to the algorithms for the assessment of skeletal maturity developed by us (**Fig. 17-18**).

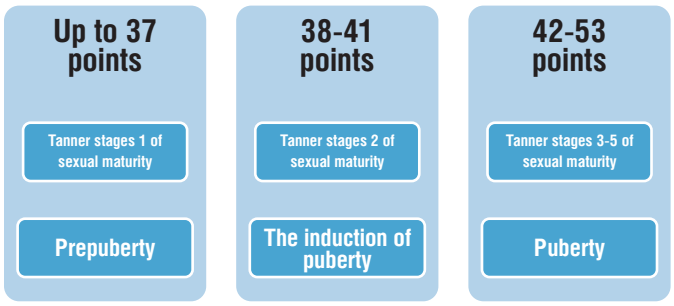

Fig. 17. Algorithm for assessing skeletal maturity based on radiographs of the hip joint in children and adolescents.

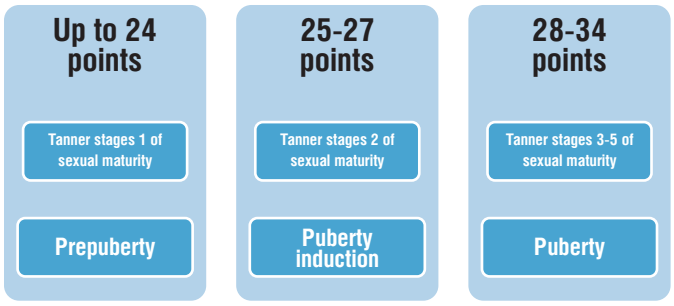

Fig. 18. Algorithm for assessing skeletal maturity based on radiographs of the knee joint in children and adolescents.

This methodology was applied for a differentiated approach to the application of regenerative technologies in 46 adolescent patients with diseases of the hip and knee joints (SCFE, Perthes' disease, Blount's disease, pathology of the menisci of the knee joint).

RESULTS AND DISCUSSION

To evaluate the results of the examination of 286 children and adolescents with diseases of the hip and knee joints when using regenerative technologies, the following criteria were used:

The period of sexual development:

- prepuberty;
- induction of puberty;
- puberty.

Presence of risk factors:

- diseases of the joints in the hereditary anamnesis;
- systemic diseases in hereditary anamnesis;
- connective tissue dysplasia.

Determining the patient's condition and degree of the disease course severity is based on the results of questionnaires and additional objective research methods:

- unsatisfactory condition (severe course) – 4 points;
- satisfactory condition (average degree of severity) – 3 points;
- good condition (mild severity of the disease) – 2 points;
- excellent condition (no disease manifestations) – 1 point.

The assessment of the survey results for the own questionnaire for the hip joints pathology was carried out as follows:

- < 60 points – unsatisfactory;
- 60-69 points – satisfactory;
- 70-79 points – good;
- > 80 points – excellent.

The assessment of survey results for the Knee Injury and Osteoarthritis Outcome Score Child (KOOS-Child) scale was carried out according to the following formulas for each block of questions:

Pain: 100 – average score ($P_1 – P_{10}$) × 100 / 4 = Index of pain syndrome;

- Symptoms: 100 – average score ($S_1 – S_5$) × 100 / 4 = Index of symptoms;

- Function, daily life: 100 – average ($A_1 – A_{17}$) × 100 / 4 = Index of function and daily life;

- Sports and recreational activities: 100 – average score ($SP_1 – SP_4$) × 100 / 4 = Index of sports life and recreational activities;

- Quality of life: 100 – average score ($Q_1 – Q_4$) × 100 / 4 = Index of quality of life.

The order of the assessment of examination results of children and adolescents with diseases of the hip and knee joints in order to determine the indications for the use of regenerative technologies is as follows (**Fig. 19**):

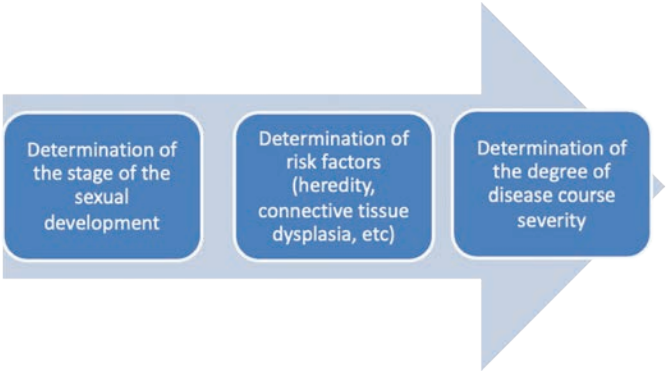

Fig. 19. The scheme of the order of assessment of the examination results of children and adolescents with diseases of the hip and knee joints in order to determine the indications for the use of regenerative technologies.

The following results were obtained: the period of prepuberty was identified in 96 examined patients, the period of puberty induction – in 58 patients, the period of puberty – in 132 patients. We considered the regenerative potential of prepubertal patients as good, patients in the period of puberty induction – satisfactory, and patients in the pubertal period of sexual development – limited.

We recommend the use of regenerative technologies in the pubertal period of sexual development in all patients, due to a decrease in their own regenerative potential.

In the period of puberty induction and pre-puberty, to determine the indications for the use of regenerative interventional technologies, we recommend taking into account additional risk factors and quality of life indicators according to questionnaires.

In the period of puberty induction, the use of regenerative technologies is recommended in the presence of one of the risk factors, or in the case of a severe or moderate course of the disease.

In the period of prepuberty, the use of regenerative technologies is recommended in the presence of one of the risk factors in combination with a severe or moderate course of the disease.

The scheme of recommendations for the use of regenerative technologies in pediatric and adolescent patients with diseases of the hip and knee joints can be presented as follows (**Fig. 20**).

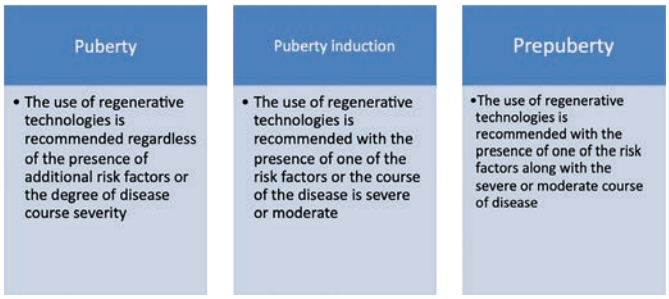

Fig. 20. Scheme of recommendations for the use of regenerative technologies in pediatric and adolescent patients with diseases of the hip and knee joints.

A differentiated approach to the application of regenerative interventional technologies was used in 46 patients and the following results were obtained (**table 1**):

Table 1. Results of patient examination to determine indications for the application of regenerative interventional technologies.

Stage of sexual development	Number of patients	Risk factors/ number of patients		Patient condition by degree of course severity/number of patients		The use of regenerative interventional technologies/ number of patients is recommended	
Prepuberty	16	Yes	10	4 points	2	Yes	3
				3 points	1		
				2 points	5	No	7
				1 point	2		
		No	6	4 points	0	No	6
				3 points	1		
				2 points	4		
				1 point	1		
Puberty induction	9	Yes	3	4 points	1	Yes	3
				3 points	1		
				2 points	1	No	0
				1 point	0		
		No	6	4 points	0	Yes	1
				3 points	1		
				2 points	3	No	5
				1 point	2		
Puberty	21	Yes	15	4 points	3	Yes	21
				3 points	8		
				2 points	4		
				1 point	0		
		No	6	4 points	1	No	0
				3 points	2		
				2 points	2		
				1 point	1		

Thus, according to the analysis results of the application of the methodology for determining skeletal maturity as a biomarker of indications for regenerative interventional technologies in adolescent patients with diseases of the hip and knee joints, it was established that in prepuberty only 3 out of 16 examined patients (which amounted to 19 %) had indications to regenerative interventional technologies. During puberty induction 4 out of 9 examined patients (that is, almost 50 %) had these indications. In the period of puberty, we recommend the use of regenerative interventional technologies regardless of the presence of additional risk factors and the patient's condition according to the severity of the disease course.

Examples of application the methodology in patients are presented in **Figs. 21-23**.

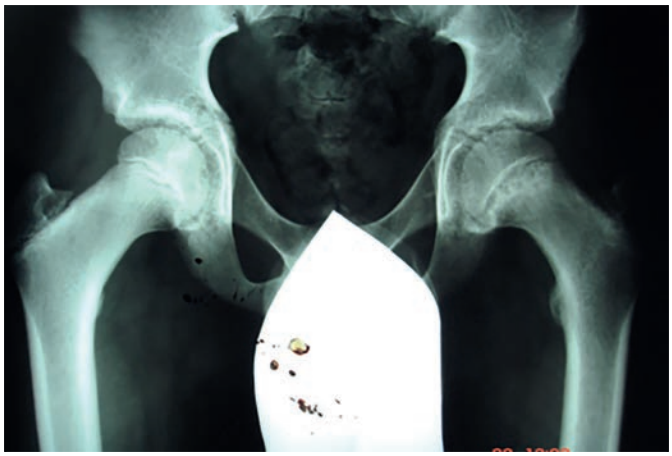

Fig. 21. Direct radiograph of the hip joints of patient B., 15 years old with SCFE, 1st displacement degree.

The patient is in a prepubertal period of sexual development according to the results of determining the skeletal maturity, there are no additional risk factors, according to the results of using the questionnaire – 72 points (2 points according to the degree of severity of the course of the disease). That is, the use of regenerative interventional technologies is not recommended for this patient. It is recommended to perform a traditional surgical intervention – physiodesis of the head of the left femur.

Fig. 22. Direct radiograph of the hip joints of patient Sch., 17 years old. with SCFE, 3rd displacement degree.

The patient is in a prepubertal period of sexual development according to the results of determining the skeletal maturity, therefore, he is indicated for the use of regenerative interventional technologies, regardless of additional risk factors, along with traditional surgical intervention – physiodesis of the head of the left femur and corrective osteotomy of the proximal part of the femur.

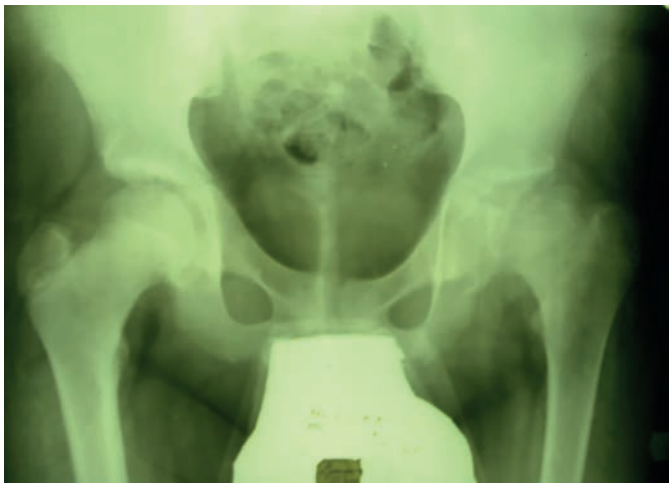

Fig. 23. Direct X-ray of hip joints of patient K., 12 years old. with Perthes disease on the left, the 3rd group of femoral head lesions according to Catterall.

The patient is in a period of puberty induction according to the results of determining the skeletal maturity, a severe course of the disease. Therefore, he is indicated for the use of regenerative interventional technologies along with traditional surgical intervention – corrective osteotomy of the proximal part of the left femur.

It should be noted that to date there are publications in which the analysis of the compatibility of the mechanisms of aging and the reduction of regenerative potential, in particular of bone tissue, and the prospects for the application of regenerative technologies depending on age [23] are carried out. The use of regenerative technologies in diseases of the hip and knee joints in adult patients is already quite common in clinical practice [24-28]. At the same time, approaches to the use of these techniques in pediatric and adolescent patients currently require additional study. Modern research and literature analysis indicate the relevance of the use of regenerative technologies both in pediatric practice in general [29] and in diseases and injuries of bones and articular cartilage in children and adolescents in particular [30].

CONCLUSION

1. ***A methodology for assessing skeletal maturity as a biomarker for establishing indications for regenerative interventional technologies in adolescent patients with diseases of the hip and knee joints has been developed, which includes the following steps: determining the period of sexual development of the patient based on the determination of skeletal maturity based on radiographs of the hip and knee joints, establishing additional risk factors (heredity, individual characteristics of the connective tissue, the presence of chronic systemic diseases) and the severity of the disease (according to the results of questionnaires).***
2. ***We recommend the use of regenerative technologies in all patients in the pubertal period of sexual development due to a decrease in their own regenerative potential. In the period of puberty induction, the use of regenerative technologies is recommended in the presence of one of the risk factors, or in the case of a severe or moderate course of the disease. In the period of prepuberty, the use of regenerative technologies is recommended with the presence of one of the risk factors in combination with a severe or moderate course of the disease.***
3. ***According to the analysis results of the methodology for assessing skeletal maturity as a biomarker in adolescent patients with diseases of the hip and knee joints, it was established that in prepuberty only 3 out of 16 examined patients (which amounted to 19 %) had indications for regenerative interventional technologies, in the period of puberty induction 4 out of 9 examined patients (that is, almost 50 %) had these indications.***

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

УДК 611.7:611.728.2+611.728.3:612.66:616.71-003.93

Скелетна зрілість, як біомаркер встановлення показань до регенеративних інтервенційних технологій у пацієнтів підліткового віку з захворюваннями кульшового та колінного суглобів

Голюк Є. Л.[1], Мельник М. В.[1], Філіпчук В. В.[1], Остапенко Т. А.[2], Страфун С. С.[1]

[1]*ДУ «Інститут травматології та ортопедії Національної академії медичних наук України», Київ, Україна*
[2]*Український науково-практичний центр ендокринної хірургії, трансплантації ендокринних органів та тканин МОЗ України, Київ, Україна*

РЕЗЮМЕ

Наші попередні дослідження вказують на вагоме значення оцінки скелетної зрілості у підлітків, яка характеризує розвиток скелета в окремо взятої особи та може використовуватися, як біомаркер регенеративного потенціалу у пацієнтів дитячого та підліткового віку, який суттєво впливає на вибір тактики лікування при захворюваннях кульшового та колінного суглобів.

Раніше нами було встановлено залежність процесів репаративної регенерації у дітей та підлітків від скелетної зрілості при таких захворюваннях кульшового та колінного суглобів, як юнацький епіфізеоліз головки стегнової кістки, хвороба Пертеса, синдром феморо-ацетабулярного конфлікту, спастичний звих стегна у пацієнтів з ДЦП, хвороба Блаунта. Інтенсивність процесів регенерації в препубертатному періоді статевого розвитку дозволяє застосовувати менш інвазивні методи оперативних втручань.

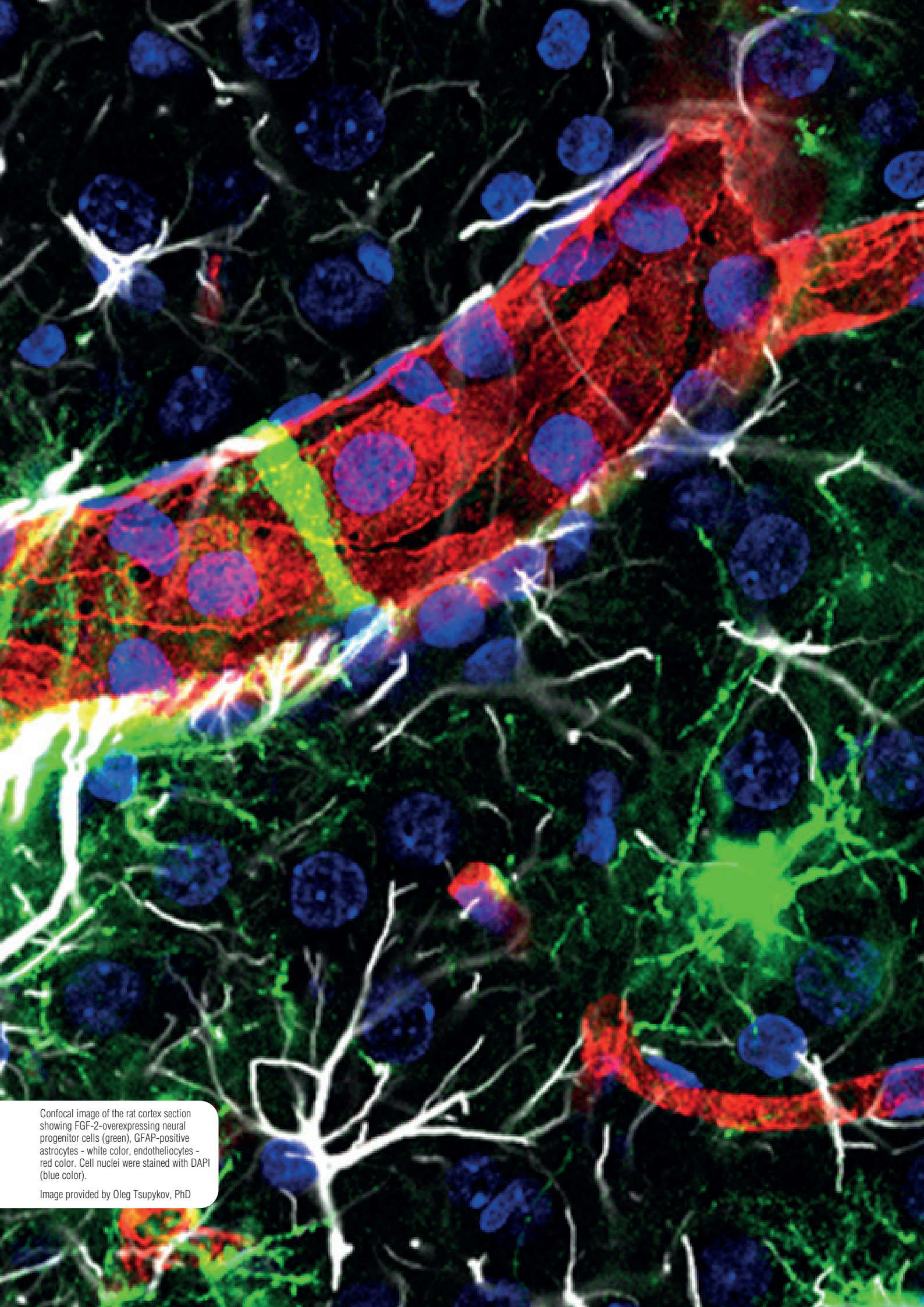
***МЕТА ДОСЛІДЖЕННЯ**: розробити методологію застосування визначення скелетної зрілості, як біомаркера для встановлення показань до регенеративних інтервенційних технологій у пацієнтів підліткового віку з захворюваннями кульшового та колінного суглобів.*

***МАТЕРІАЛИ ТА МЕТОДИ**. Групу для розробки методології обстеження склали 157 пацієнтів (86 хлопчиків та 71 дівчинка) з патологією кульшових суглобів (дисплазія кульшових суглобів, хвороба Пертеса, юнацький епіфізеоліз головки стегнової кістки, асептичний некроз головки стегнової кістки, та без діагностованої патології кульшових суглобів) років та 129 пацієнтів (58 хлопчиків та 71 дівчинка) з захворюваннями колінних суглобів (хвороба Блаунта, осьові деформації нижніх кінцівок, пошкодження менісків та пацієнти, які обстежувалися на предмет скарг на біль в ділянці колінного суглоба) віком від 10 до 18 років. Групу диференційованого підходу до застосування регенеративних інтервенційних технологій склали 46 пацієнтів підліткового віку з захворюваннями кульшового та колінного суглобів (юнацький епіфізеоліз головки стегнової кістки, хвороба Пертеса, хвороба Блаунта, патологія менісків колінного суглоба.*

***РЕЗУЛЬТАТИ**. Розроблено методологію застосування скелетної зрілості, як біомаркера для встановлення показань до регенеративних інтервенційних технологій у пацієнтів підліткового віку з захворюваннями кульшового та колінного суглобів, яка включає наступні кроки: встановлення періоду статевого розвитку пацієнта на основі визначення скелетної зрілості за рентгенограмами кульшових та колінних суглобів, встановлення додаткових факторів ризику (спадковість, індивідуальні особливості сполучної тканини, наявність хронічних системних захворювань) та ступеню важкості захворювання за даними опитувальників. За результатами аналізу застосування методології визначення скелетної зрілості, як біомаркера показань до регенеративних інтервенційних технологій у пацієнтів підліткового віку з захворюваннями кульшового та колінного суглобів, встановили, що в препубертаті лише у 3 з 16 обстежених пацієнтів (що склало 19 %) є показання до регенеративних інтервенційних технологій, а в періоді індукції пубертату 4 з 9 обстежених пацієнтів (тобто, майже 50 %) мали зазначені показання.*

***ВИСНОВКИ**. В періоді препубертату ми рекомендуємо застосування регенеративних технологій при наявності одного з факторів ризику в поєднанні з важким чи середньої тяжкості перебігом захворювання. В періоді індукції пубертату застосування регенеративних технологій рекомендуємо при наявності одного з факторів ризику або при важкому чи середньої тяжкості перебігу захворювання. В пубертатному періоді статевого розвитку в зв'язку зі зниженням власного регенеративного потенціалу ми рекомендуємо застосування регенеративних технологій у всіх пацієнтів.*

***КЛЮЧОВІ СЛОВА**: регенеративні інтервенційні технології; захворювання кульшового та колінного суглоба у підлітків; скелетна зрілість*



Confocal image of the rat cortex section showing FGF-2-overexpressing neural progenitor cells (green), GFAP-positive astrocytes - white color, endotheliocytes - red color. Cell nuclei were stained with DAPI (blue color).

Image provided by Oleg Tsupykov, PhD