Detecting reasons for recurrent deformity in treatment of patients with vitamin D-resistant rickets using diagnostic imaging

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ABSTRACT

Purpose: To assess age related manifestations of the femur and tibia in patients with vitamin D-resistant rickets (VDR) and explore causes for recurrent deformity using imaging modalities.

Methods: Computed tomography (CT), magnetic resonance imaging (MRI) and dual energy X-ray densitometry (DEXA) were used to assess conditions of long bones of lower limbs in patients with vitamin D-resistant rickets aged from 4 years to 30 years preoperatively and after limb lengthening.

Results: Age related MRI findings showed specific structure of the femur and tibia in patients with VDR pre-operatively and after operative treatment. Abundant irregular osteoid formed in femoral and tibial physes was shown to reveal complicated nature of bone deformity causing recurrence in patients with VDR at childhood. CT findings allowed us to detect early cortical injury, measure its length with forming Looser's zones, examine significant differences in density measurements of Looser's zones preoperatively and after deformity correction using transosseous osteosynthesis.

Conclusion: Recurrent deformity can develop in patients with VDR due to progression of the disease, irregular osteoid deposited in the medial and lateral metaepiphysis, osteoid area measuring over 50% of epiphyseal cross section, insufficient regenerate mineralization, and formation of Looser's zones.

1. Introduction

Pediatric treatment of post-rickets deformity is rather challenging, requires several stages and lasts for many years.¹ VDR (hypophosphatemic) is the most frequently encountered form of rickets among metabolic disorders. The prevalence of the disease is 1:20000.² Patients with rickets-like diseases develop lower limb deformities due to disturbed physal metabolism making diagnosis difficult at childhood.^{3,4} Thanks to the method of transosseous compression-distraction osteosynthesis pioneered by G.A.Ilizarov the new practice has initiated a qualitatively new approach and greater possibilities for rickets deformity correction.^{5–7} Application of additional osteogenesis stimulation and fixation techniques in patients with VDR allowed for obtaining new rewarding evidence.^{8–12} A few publications report errors, complications

and recurrence rate of lower limb deformity but no detailed roentgen-morphological assessment of factors causing recurrent deformity in patients with skeletal metabolic conditions has been reported.^{1,13} The purpose of our study was to get answers to the questions as follows,

1. Are there any age related specific features in osseous structures preoperatively and after lengthening in patients with VDR?
2. What are the reasons for recurrent deformity in patients with VDR after surgical treatment?

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Fig. 1. Total and local bone density measured from CT scans of the knee joints. Topodramm (a), axial plane (b) of the proximal metaphysis of the right tibia in a 21-year-old patient.

2. Methods

2.1. Population

The study included results of treatment and examinations of 62 patients with VDR (phosphate diabetes) aged from 4 years to 30 years. There were 25 female patients (40%). Patients aged from 11 to 16 years (34%) prevailed in the study group. Eighteen patients (29%) started operative treatment at the age of 4–6 years, 17 patients (27%) at the age of 7–10 years, four patients (6%) were operated on at the age of 16–25 years, and two cases (3%) at the age of 25–30 years. All patients received treatment from 1980 to 2011. All patients were seen and diagnosed by geneticist. Treatment of patients included both conservative and operative techniques. Conservative treatment was tailored and depended on severity, course of the disease, and the patient's age and included conventional vitamin D therapy or oxidevitum as an alternative, calcium, phosphorus, vitamins A, C, E and group B medications.¹⁴ Phosphorus buffer systems have been recently used. Surgical correction was produced in stable clinical and laboratory remission. Clinical examination showed deficient height, pains in lower limb bones.

2.2. Methods of treatment

All patients were treated with transosseous osteosynthesis using the Ilizarov external fixation only or in combination with intramedullary hydroxyapatite coated wires.¹⁵ A choice for surgical correction techniques and beginning of the treatment was exercised with regard to the patient's age, severity, type and level of a deformity, number of involved segments. Comprehensive metabolic panel and urine test. Patient's age was disregarded in severe bone deformity to prevent further changes in the joints and spinal column. However, recent evidence suggests that other factors of bone origin participate in maintaining phosphorus homeostasis, including fibroblast growth factor 23, matrix extracellular phosphoglycoprotein, and frizzled-related protein 4. These factors are collectively known as phosphatonins.¹⁶ Calculations using center of rotation of angulation offered by D.Paley (2002) were applied when planning a surgical intervention to identify a level, plane of osteotomy and number of osteotomies.⁶ The technique of transosseous osteosynthesis with Ilizarov external fixation combined with intramedullary hydroxyapatite coated wires was used for majority of the patients.

Thirty patients underwent gradual deformity correction and developed distractional regenerate bone and acute deformity correction was produced in 32 cases.

2.3. Diagnostic imaging

Computed tomography (CT), magnetic resonance imaging (MRI) and dual energy X-ray densitometry (DEXA) were used for assessment

of 62 patients with VDR preoperatively and at a long-term follow-up. CT scanning was performed using CT Somatom AR.HP (Siemens, Erlangen, Germany). MRI assessment was performed using a 1.5-T MRI Magnetom Symphony Maestro Class unit (Siemens, Erlangen, Germany). Mineral density (MD) of the distractional regenerate bone was measured using Lunar DPX NT bone densitometer (General Electric, USA).

3. Results

1. Preoperative CT findings showed irregular trabecular patterns and greater distance between them in the femur and tibia metaepiphyses of 80% of the patients with VDR. Absence of typical cancellous bone pattern, thin cortex and lower density values in epiphyses and medial femur and tibia metadiaphyses were observed in patients aged 13–16 years. Bone density in the proximal tibial epiphysis showed greater values in all patients with D-resistant rickets aged 17 years–23 years as compared to the one in the distal femoral epiphyses.

Preoperative assessment of bone structure in patients with VDR aged 24 years–40 years showed areas of heterogeneous cancellous bone in both epiphyses and metaphyses. Bone structure of tibial and femoral metaepiphyses in patients with VDR aged 11 years–16 years appeared as scattered bone trabeculae medially and irregular sclerotic areas at one-to-two-year follow-ups. Patients aged 18 years–23 years showed greater sclerotic changes in the proximal tibial epiphyses and less changes in the distal femoral metaphyses at one-to-three year follow-up which is showed in Fig. 1.

Minimal bone density measurements were observed in the proximal tibial epiphysis of patients with VDR aged 24 years–30 years and deemed to be associated with extensive cysts at the level.

2. Bone regeneration (new bone formation) was shown to delay building periosteal and endosteal “bridges” in patients with VDR who underwent acute deformity correction with the total decrease in bone mineral density. Complete organotypical remodeling occurred two to three years later. Application of intramedullary wires was practical for reducing treatment length.

A greater diversity in regenerate bone structure was observed during gradual deformity correction in patients with VDR. Areas of fine mesh and coarse trabecular structure with lucent cysts were observed.

Densitometric findings showed maximal values of mineral density in the middle part of the femoral regenerate bone of patients with VDR at four-to-five day follow-up. A greater increase in the density was observed in the middle part of the femoral and tibial regenerate bone at four-to-six month as compared to distal regenerate portions.

3. Preoperative MRI scans of patients with VDR aged to five years

Fig. 2. Osteoid area measured from coronal T2WI- (a) and axial T2WI-MRI scans of the knee joints of a 15-year-old patient. With VDR. Measuring osteoid density in coronal and axial planes (b).

showed proliferation of pathologically changed cartilaginous tissue with increased MR-signal on T1FL2D (FLASH). Patients aged from 9 years to 12 years showed non-mineralized areas (osteoid) at physes extending to femoral and tibial epiphyses and metaphyses revealing irregular, grotesque forms that were well visualized with T1FL2D FS in the coronal plane preoperatively

MRI scans (T2TSE) of patients aged from 13 years to 16 years showed a great number of clumpy areas with regular contours and high MR-signal in the femur and tibia epimetaphyses after treatment. To determine an extent of rickets process we suggested calculating a ratio of pathological cartilaginous area (osteoid) and the total epiphyseal, metaphyseal area using MRI scans of the knee joints in Fig. 2.

Round heterogeneous foci of an area measuring to $2.3 \pm 0.03 \text{ cm}^2$, having obvious wavy contours, and being hyperintensive with T1FL2D FS, T2TSE were observed in condyles of patients with D-resistant rickets aged 25 years–30 years after the treatment.

4. Changed architectonics of lower limb bones in 17 patients with VDR appeared as pathologically restructured areas (Looser's zones) extended to the shaft.¹⁷ That were addressed with Ilizarov external fixation and intramedullary wires.^{10–12,17} Looser's zones were shown to complete after deformity correction. CT scans first allowed for detecting specific features of bone structure of the completed Looser's zones with three-dimensional reconstruction. Thick rolls were visualized in periosteum in the cases with VRT-reconstruction. Looser's zones were most evident with minimal density measurements in patients aged 12 years–16 years.
5. A recurrent deformity has been shown to develop in 54 patients with VDR rickets due to:
 - 5.1. Progression of the disease with irregular formation of osteoid zones in the medial and lateral metaepiphysis; increase in osteoid area of more than 50% of epiphyseal cross section;
 - 5.2. Insufficient mineralization of the regenerate bone in the distal tibia with mineral density of the distractional regenerate bone measuring not more than $750.14 \pm 35.70 \text{ g/cm}^2$
 - 5.3. Formation of Looser's zone and bone deformity.

4. Discussion

Classical radiological rickets manifestations are well known, however, there have been several specific pathomorphological changes revealed in the long bones of lower limbs in patients with VDR, and CT, MRI and DEXA that are not routinely used for the condition were employed for detailed evaluation of the femur and tibia metaepiphyses.¹⁸ Radiological findings allowed us to pinpoint age-related radiological dynamics in the femoral and tibial physis in patients with VDR. Scattered abundant osteoid deposited in femoral and tibial metaepiphysis

served a reason for a complicated deformity in pediatric patients with VDR.¹⁹ With greater osteoid deposits that persisted at the age of 14 years–15 years prognosis of classical operative deformity correction was rather problematic. A few publications on MRI assessments of rickets cases described specific features of physal structure¹⁸ however, we first performed MRI studies for patients with different types of rickets that allowed for detecting age-related pathomorphological manifestations in the femur and tibia structure preoperatively and at a long-term follow-up.²⁰

CT findings allowed us to identify an injury to the cortex at an early stage with forming Looser's zones and its dimensions that was practical for the choice of operative intervention.¹⁷ CT and MRI scans have considerably extended the possibilities of morphological assessment of Looser's zones and their restructuring after the deformity correction.

This is the first study of patients with VDR that employed current imaging modalities to assess age related dynamics in pathological changes taking place in the bones of lower limbs to identify risk factors for recurrence following surgical deformity correction. Our sample size has enabled us to detect changes in bone structure of children aged 4 years–15 years that should be considered when planning age and techniques for surgical treatment. In addition to that, we have studied quantitative and qualitative characteristics of Looser's zones that are also to be considered in treatment of these patients. Thanks to current imaging modalities we revealed causes that could contribute to recurrence. However, the study does have a number of limitations. First, we had a comparatively small number of adult patients with VDR rickets whose knee bone architectonics was assessed with CT. But these changes were very specific and we can suppose that considerable changes occurring in the femur and tibia metaepiphysis can lead to early deforming arthritis and extensive metaphyseal areas in condyles. Second, not all the patients underwent CT and MRI assessments, however, the findings have enabled us to identify specific changes in physis and Looser's zones.

Our study is consistent with previous studies of surgical treatment of patients with different types of VDR that have demonstrated possibilities with transosseous osteosynthesis techniques used to correct deformities of lower limbs.^{8,9} However, the series reported methodological principles and did not look into risk factors for recurrence. Several publications reported possibilities with MRI to study bone condition in rickets-like diseases and osteomalacia.¹⁸ The previous work of Shevtsov et al., shown that MRI plays a substantial role in identifying physal changes to be considered for a choice of treatment technique.²⁰

5. Conclusion

A review of radiomorphological manifestations of lower limb long bones in patients with vitamin D-resistant rickets before and after deformity correction showed that recurrent deformity can develop due to

progression of the disease with irregular formation of osteoid zones in the medial and lateral or lateral and posterior metaepiphysis, insufficient mineralization of the regenerate bone with an overall decrease in the bone density, and formation of Looser's zones, and increase in osteoid area of more than 50% of epiphyseal cross section.

Declarations of interest

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