

The dysfunctional muscle-bone unit in juvenile idiopathic arthritis

J.M. Burnham^{1,2}, J. Shults², H. Sembhi¹, B.S. Zemel¹, M.B. Leonard^{1,2}

¹The Children's Hospital of Philadelphia, Philadelphia, PA, USA; ²University of Pennsylvania School of Medicine, Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA, USA

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Introduction

Juvenile idiopathic arthritis (JIA), the most common pediatric rheumatic disease, is a chronic inflammatory disorder that causes joint inflammation, swelling, pain, immobility, and osteoporosis¹. The bone loss that occurs in JIA is clinically significant, both early and late in the course of the disease. We recently demonstrated that childhood-onset arthritis is associated with a significantly elevated risk of fracture, particularly during the adolescent years and over the age of 45². The degree of trabecular density and cortical bone strength deficits in JIA is likely multifactorial. Inflammatory cytokines, such as tumor necrosis factor α (TNF- α), are produced in the inflamed joints and released systemically. TNF- α directly inhibits osteoblast differentiation, function, and survival and promotes osteoclastogenesis. Inflammation may further diminish bone accrual indirectly by inducing muscle loss³. TNF- α stimulates protein degradation, inhibits myogenic differentiation, and causes myoblast apoptosis.

The mechanostat theory states that a bone adapts to the mechanical forces to which it is subjected in order to keep the strain on the bone at a constant set point⁴. Therefore, investigators have hypothesized that interventions to improve muscle mass and strength in JIA will optimize bone health³. However, there have been no longitudinal studies that have rigorously tested the connection between muscle and bone deterioration in JIA. Our objectives were to 1)

characterize changes in muscle mass and cortical bone strength in a sample of prevalent JIA subjects over 12 months; and 2) determine whether improvements in muscle mass over 12 months are associated with improvements in cortical bone strength in JIA, compared with healthy controls.

Methods

Tibia peripheral QCT (Stratec XCT 2000) measurements were obtained at 0 and 12 months in 42 subjects with JIA (21% male), and 192 controls (48% male), ages 5-21 years. Cortical cross-sectional moment of inertia (CSMI), a measure of bone strength, was assessed at the 38% site. Muscle CSA was assessed at the 66% site. Height and BMI were converted into age- and sex-specific standard deviation scores (SDS) using national reference data. Generalized estimating equations with interaction terms and adjusted for sex, age, follow-up duration, and tibia length were used to determine the magnitude of CSMI and muscle CSA deficits in JIA, and to assess the relation between changes in muscle CSA and CSMI.

Results

Mean \pm SD age at the baseline visit was 10.4 \pm 3.6 yr and 12.9 \pm 4.2 yr in JIA and controls, respectively. Height and BMI SDS were similar between JIA and controls. In JIA, baseline CSMI and muscle CSA were 14.4% (95% CI: 5.8-22.3%; $p=0.001$) and 6.4% (1.4-11.2%, $p=0.01$) lower than controls, respectively. In the healthy controls, muscle CSA and CSMI increased 1.2% (0.3-2.1%, $p=0.005$) and 2.9% (1.6-4.2%, $p<0.001$), respectively, over 12 months of follow-up. The absolute muscle accrual over 12 months was 2.0% (0.3-3.6%, $p=0.02$) greater in JIA compared with controls. However, CSMI deficits in JIA remained unchanged over 12 months, compared with controls. The strong relation

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Corresponding author: Jon M. Burnham, M.D., M.S.C.E. The Children's Hospital of Philadelphia, Pediatrics, Room 1579 CHOP North, 3535 Market Street, Philadelphia PA 19104, USA
E-mail: burnhams@email.chop.edu

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between muscle CSA and CSMI in controls at 12 months ($\beta=0.77$, 0.62-0.91, $p<0.001$) was attenuated in JIA ($\beta=0.45$, 0.16-0.74, $p=0.002$). This difference in slopes between the JIA subjects and healthy controls was statistically significant ($p=0.01$).

Conclusions

This is the first longitudinal study to formally test the "functional muscle-bone unit" in health and disease. JIA results in marked muscle mass and cortical bone strength deficits. Improvements in muscle mass do not produce the expected gains in CSMI in JIA. Childhood arthritis may create lifestyle changes that decrease either the frequency, duration, or intensity of biomechanical loading during physical activity. These changes may alter the dynamic stimulus applied to cortical bone and impact structural adaptation⁵. Additionally, disease-specific factors and/or therapies may diminish the normal cortical response to mechanical stimuli during growth.

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