Growth & Development In Children With Chronic Conditions

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Nutritional Status & Monitoring In Paediatrics, Nutricia
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Potential conflict of interest:

Previous research and fellowship funding by:

NovoNordisk UK
NovoNordisk Australia
Normal growth and puberty

Impact on non-nutritional factors on growth and puberty

Clinical evidence of abnormalities in paediatric Crohn’s disease

Strategies to improve growth and puberty
Nutritional Outcomes

Linear growth / height:
Poor growth / short stature

Puberty:
Delayed puberty, poor progression through puberty, absent puberty, pubertal regression, poor growth during puberty

Weight / body mass index / body composition:
Low lean mass, preserved fat mass

Bone development
Poor bone development
Growth & development

The increase in body size from birth to adult

Linear growth

Lean mass + fat mass

Bone development (length and thickness)
GROWTH PLATE

- Epiphysis
- Growth plate
- Diaphysis
- Growth plate
- Epiphysis

- Secondary ossification center
- Germinal zone containing stem cells
- Proliferative zone
- Zone of maturation
- Hypertrophic zone
- Invading capillary
- Osteoblast
- Bone

- Perichondrium
- Cartilage
Normal Pubertal Development

**GIRLS**
Breast enlargement (B2) by 10-11 years
- Delayed puberty no breast development aged 13 years
- Delayed menarche no periods aged 14 years

**BOYS**
Testes enlargement (4 ml) by 11-12 years
- Delayed puberty testes < 4 ml aged 14 years
14 yrs
Late stage of puberty

12 yrs
Early stage of puberty
Bone age for assessment of skeletal maturity

Bone defects eg arthritis

Obesity

Comparison between methods
Bone growth parallels linear growth

LONGITUDINAL BONE GROWTH

Poor growth in childhood chronic condition will have an impact on bone accrual which is already affected in chronic ill health +/- GC therapy
The muscle-bone cross talk is bi-directional. Interaction is at a biomechanical and biochemical level.

Brotto et al Bone 2015
DXA BMD or BMC
T-score (NOT APPROPRIATE FOR CHILDREN)
Z-score (Age and sex matched)

Interpret bone density data for size
(eg height and/or bone age)

Decisions on introduction of bone protective therapy however not dependent on DXA BMD (especially a single “abnormal” result)

Newer generation DXA allows assessment of spine to identify vertebral fractures which are common in children treated with long term steroid therapy
% fat mass changes throughout growth

Taylor RW et al Am J Clin Nutr 2002

% fat mass maybe falsely elevated in children with reduction in muscle mass
(Low muscle mass and normal / marginally elevated fat mass)
Mechanism of poor growth and bone development in chronic illness
Cytokines  Glucocorticoid  Undernutrition
Cytokines  Glucocorticoid  Undernutrition

Bone/growth plate
Cytokines Glucocorticoid Undernutrition

Bone/growth plate GH/IGF axis
Cytokines  Glucocorticoid  Undernutrition

- Bone/growth plate
- GH/IGF axis
- Gonadal axis
- Muscle mass
Cytokines  Glucocorticoid  Undernutrition

Bone/growth plate  GH/IGF axis  Gonadal axis  Muscle mass
Cytokines           Glucocorticoid             Undernutrition

Bone/growth plate
GH/IGF axis
Gonadal axis
Muscle mass
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- Bone/growth plate
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Bone/growth plate  GH/IGF axis  Gonadal axis  Muscle mass
GH / IGF Axis In Chronic Illness

Common to see
- Hormone insensitivity (esp GH)
- Hormone insufficiency

Defect transient and reversible

30-40% of children with chronic inflammatory conditions may have abnormal GH levels to GH stimulation test

Pivotal role of TNF and IL1 on growth impairment at the level of the growth plate

IL6 impact on bone

MacRae et al J Endocrinol 2006
Inflammation And Nutrition In IBD Growth Failure

Balinger AB et al Gut 2000
Clinical evidence of poor growth in chronic illness
Chronic Diseases In Childhood

Effect on growth

- Disease specific aspects
  - Drugs
  - Nutrition
  - Metabolic state
  - Hypogonadism

- Common aspect
  - Inflammation

Karlberg et al, Eur J Clin Nutr, 1994
Growth in cystic fibrosis


Rogan MP et al Proc Natl Acad Sci U S A. 2010
Growth failure can precede symptoms of chronic illness
In Crohn’s disease, average time to symptoms is 12 months
Poor growth during follow-up should alert to poorly managed underlying disease

Kanof ME et al Gastroenterology 1988
Puberty & pubertal growth in IBD

Girls with IBD: Delayed puberty
Boys with IBD: Poor pubertal growth

Mason et al Horm Res Paediatr 2015
Fig. 2 Serum IGF-I-values during enteral nutrition (**P = 0.005 compared with 0 weeks).
Long term gastrostomy feeding in CD

Duncan et al Acta Paediatr 2018
Gastrostomy feeding in CF

Table 2
Nutritional status at baseline and after initiation of gastrostomy feedings among 18 subjects followed up for a minimum of 18 months after gastrostomy

<table>
<thead>
<tr>
<th></th>
<th>No. of years before gastrostomy</th>
<th>6 to 18 mo after gastrostomy</th>
<th>18 to 30 mo after gastrostomy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Percentile</td>
<td>Range</td>
<td>Percentile</td>
</tr>
<tr>
<td>Weight</td>
<td>2</td>
<td>1,6</td>
<td>12</td>
</tr>
<tr>
<td>Height</td>
<td>5</td>
<td>1,34</td>
<td>6</td>
</tr>
<tr>
<td>Weight as % of ideal</td>
<td>88</td>
<td>80,92</td>
<td>90</td>
</tr>
</tbody>
</table>

Rosenfeld M et al J Am Diet Assoc 1999

Barclay A et al Eur J Clin Nutr 2007
Biologic Therapy In CD And Growth

Catch up growth
No growth issues
Persistent poor growth
Deterioration in growth

Malik et al J Pediatr Gastroenterol Nutr 2011
Adult height in childhood onset CD

Mean deficit of the study population

± 95% CI for the UK population

Frequency

Height difference, cm Between MPH and Final Height

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Mean difference (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumed risk</td>
<td>Placebo or non-steroidal drugs Mean linear growth velocity ranged across control groups from 5.5 to 8.5 cm/y</td>
<td>-0.48 cm/y (-0.65 to -0.30) less growth in the ICS group</td>
<td>5717 (14 trials)</td>
<td>★★★★★☆-2,3</td>
<td>moderate</td>
</tr>
<tr>
<td>Corresponding risk</td>
<td>Inhaled corticosteroids Mean reduction in linear growth velocity was 0.48 cm/y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear growth velocity in first year of treatment (cm/y)</td>
<td>Change from baseline in height over first year of treatment (cm) Mean change from baseline in height over a 1-year period ranged across the control groups from 4.7 to 8.6 cm/y</td>
<td>-0.61 cm (-0.83 to -0.38) less growth in the ICS group</td>
<td>3275 (15 trials)</td>
<td>★★★★★☆-2,3</td>
<td>moderate</td>
</tr>
<tr>
<td></td>
<td>Mean reduction in change in height over a 1-year period was 0.61 cm</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Change in height standard deviation score (SDS) in first year of treatment</td>
<td>Mean change in height SDS score across control groups from -0.09 to 0.5</td>
<td>-0.13 (-0.24 to -0.01) less growth in the ICS group</td>
<td>258 (4 trials)</td>
<td>★★★★★☆-2,3</td>
<td>moderate</td>
</tr>
<tr>
<td></td>
<td>Mean reduction in change in height SDS score was 0.13</td>
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<td></td>
<td></td>
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</table>

*Zhang L et al Cochrane Database Syst Rev 2014*
Growth with long term oral GC

10 year old boy with DMD on daily oral GC since age 6 years
8 year old boy with undiagnosed chronic lung condition on GC since age 2 years
Bone morbidity with long term GC therapy

Multiple VF with severe back pain

VF identified from screening x rays, no pain
Delayed puberty in chronic illness

Importance of puberty for
- Psychosocial adjustment (matched with peers)
- Improved bone and muscle mass accrual
- Adolescent growth spurt

Examine puberty routinely
Refer for pubertal induction in those with delayed puberty

13 ½ year old CF
Considered for lung transplant
On Pred 5 mg daily currently and have been on daily Pred for last 2 years (Sick day steroid plan in place)

DXA BMD: No VF but total body and LS BMD about -1.5 SD

Pubertal assessment G1 P1 2 ml testes (left), right (previous orchidectomy from torsion of testes)
Who is at risk?
- Those treated with oral GC for more than 6 months (12 months very high risk)
- ICS above licenced indication
- Beware those on multiple modes of GC (eg topical, inhaled, intra-articular)

Physiological replacement 10 mg/m$^2$/day of hydrocortisone
- Pred 1 mg equivalent to Hydrocortisone 4 mg
- Dexamethasone 1 mg equivalent to 20 mg Hydrocortisone

Need sick day steroid plan

Weaning plan if planning to discontinue and testing adrenal axis
Long term GH use in JIA

Improvement in adult height with long term use of GH in JIA but subjects remained short at attainment of adult height

GH adverse effect (with GH therapy): Glucose abnormalities, T2DM in about 30-40%

Growth hormone use in JIA & other chronic conditions is not a licenced indication

Bechtold S et al J Clin Endocrinol Metab 2007
Childhood chronic disease mediated by chronic inflammation, poor nutrition and use of steroid can impact on growth and bone development via:
- Systemic mechanisms
- Direct impact on target organs

Targeting nutrition & disease are important strategies to improve such outcomes.

Assessing and addressing puberty routinely in adolescents with chronic condition is paramount.
Clinical pathway

Regular height and weight monitoring (at least 6 monthly)

Assess puberty routinely from age 11-12 years
- Refer to endocrinology if no evidence of puberty by 13 years
- Mindful of window of opportunity to improve linear growth

Address other endocrine consequences of chronic illness esp long term steroids
- Bone health
- Secondary adrenal insufficiency
- Glucose and metabolic abnormalities.
Glasgow Children’s Hospital Charity, NovoNordisk UK

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QUESTIONS

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