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

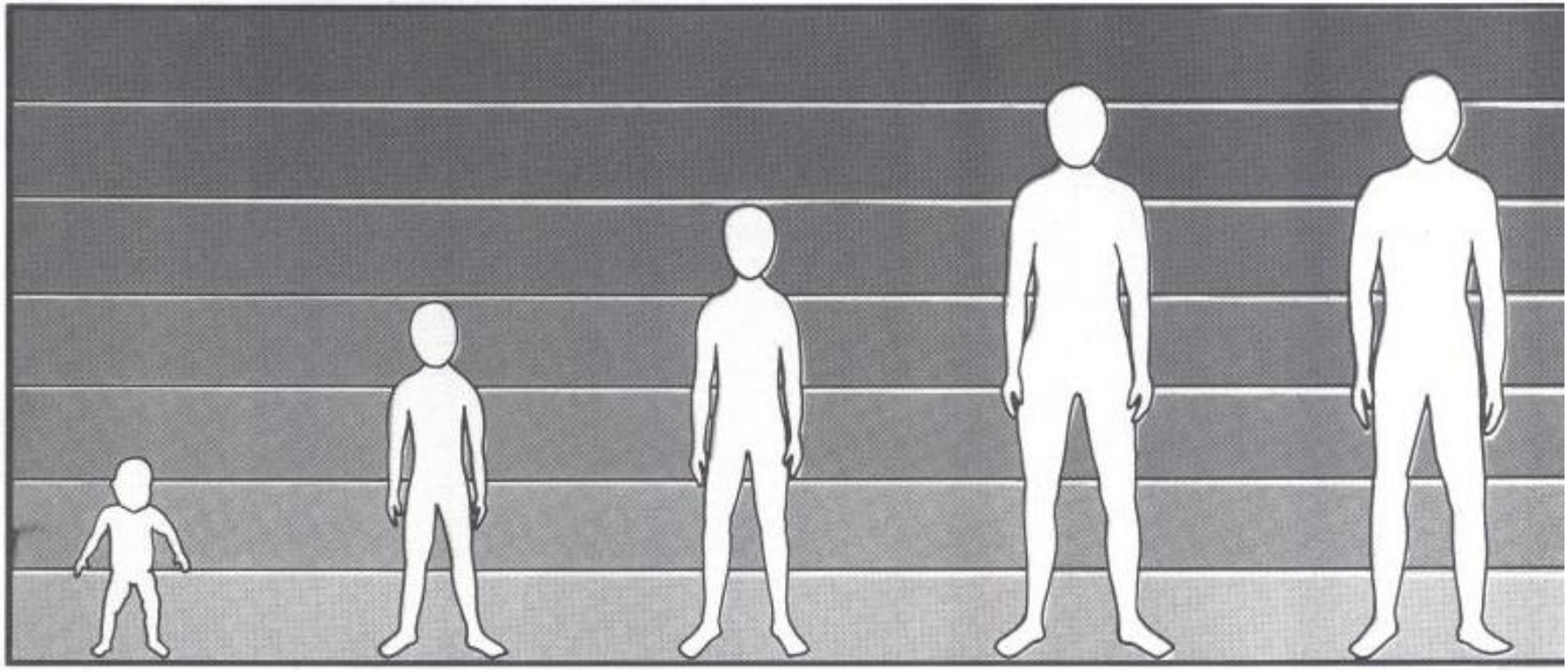
Linear growth / height:
Poor growth / short stature

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



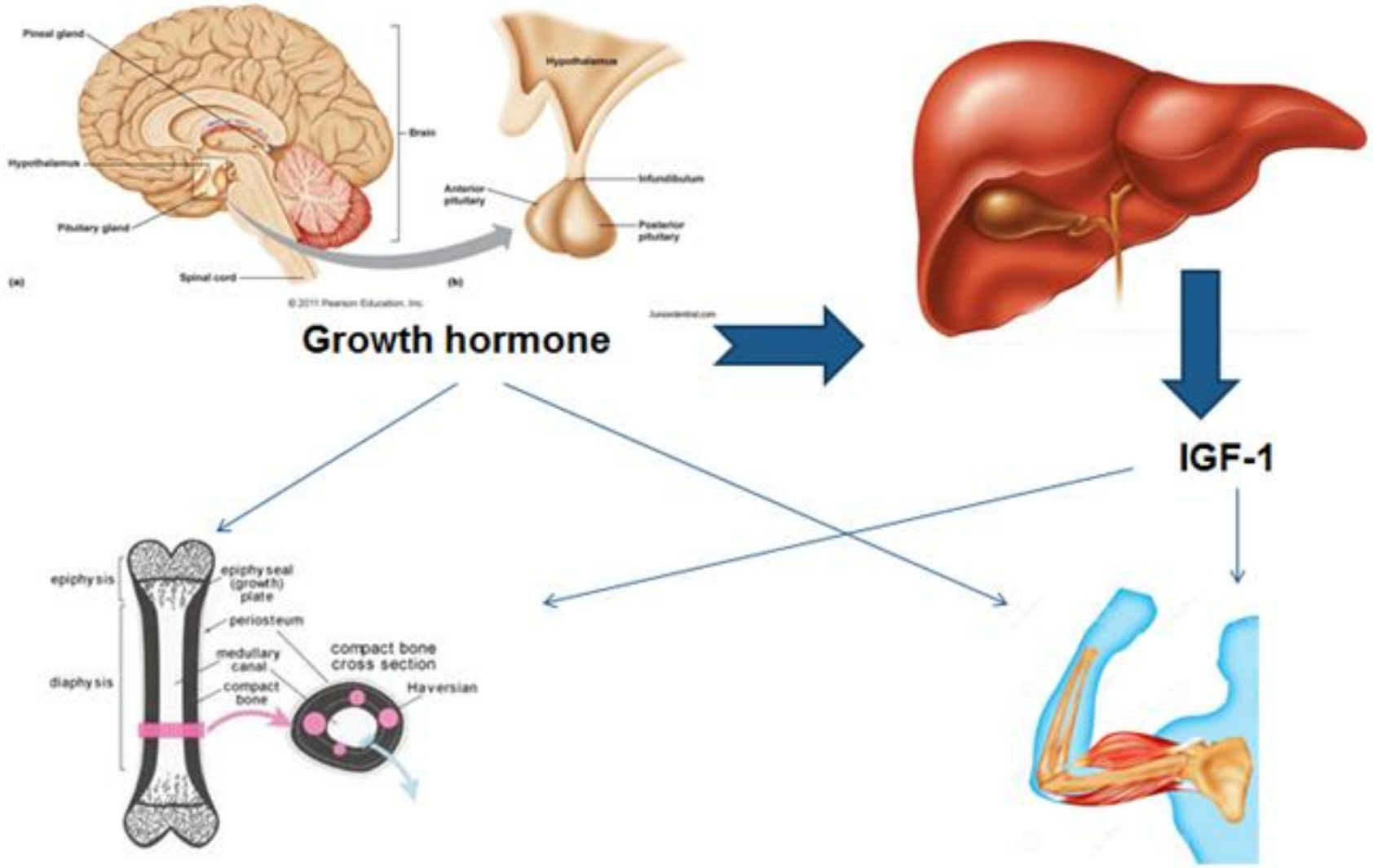
The increase in body size from birth to adult

Linear growth

Lean mass + fat mass

Bone development (length and thickness)

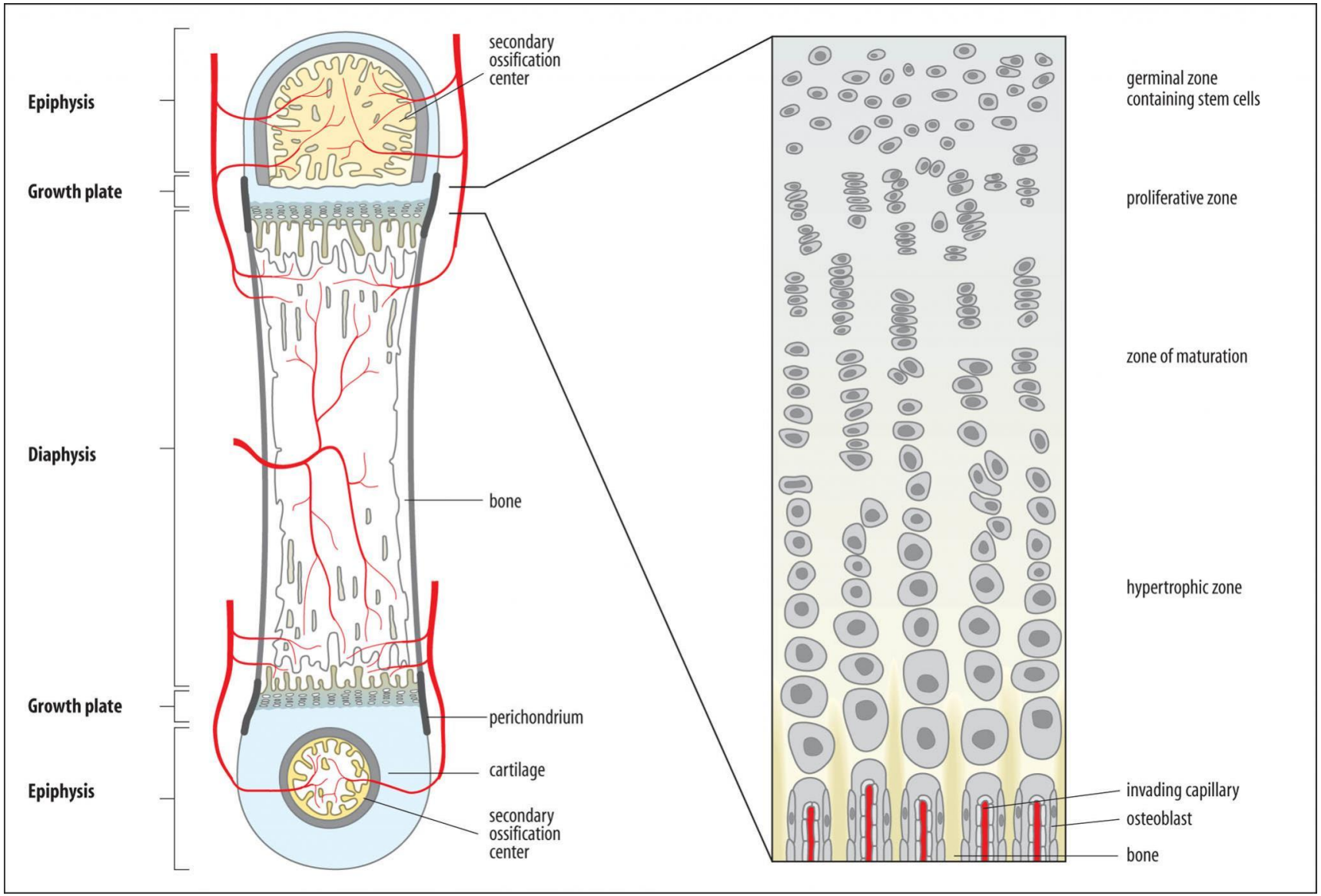
GH / IGF Axis


Pineal gland
Brain
Hypothalamus
Pituitary gland
Spinal cord
(a)
Hypothalamus
Infundibulum
Anterior pituitary
Posterior pituitary
(b)
Growth hormone
IGF-1
epiphysis
epiphyseal (growth) plate
periosteum
medullary canal
compact bone
diaphysis
compact bone cross section
Haversian

University of Glasgow

NHS Greater Glasgow and Clyde

GROWTH PLATE



Normal Pubertal Development

GIRLS

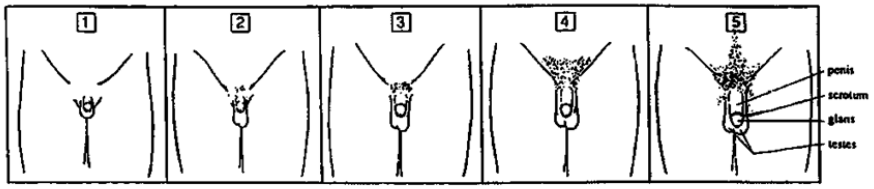
Breast enlargement (B2) by 10-11 years

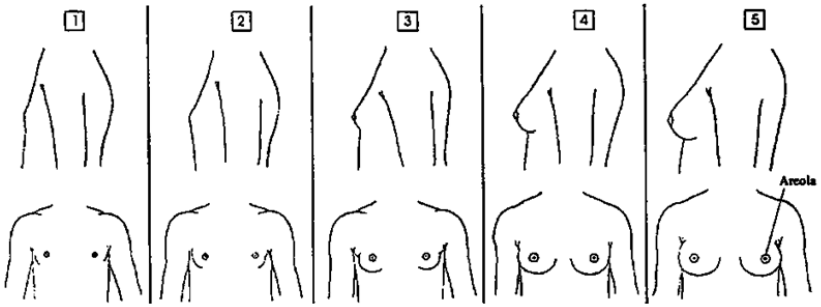
- Delayed puberty no breast development aged 13 years
- Delayed menarche no periods aged 14 years

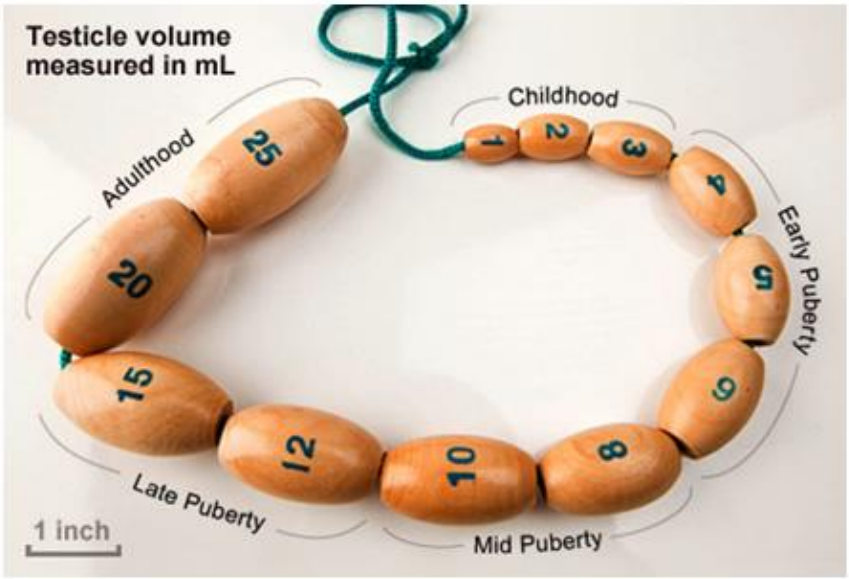
BOYS

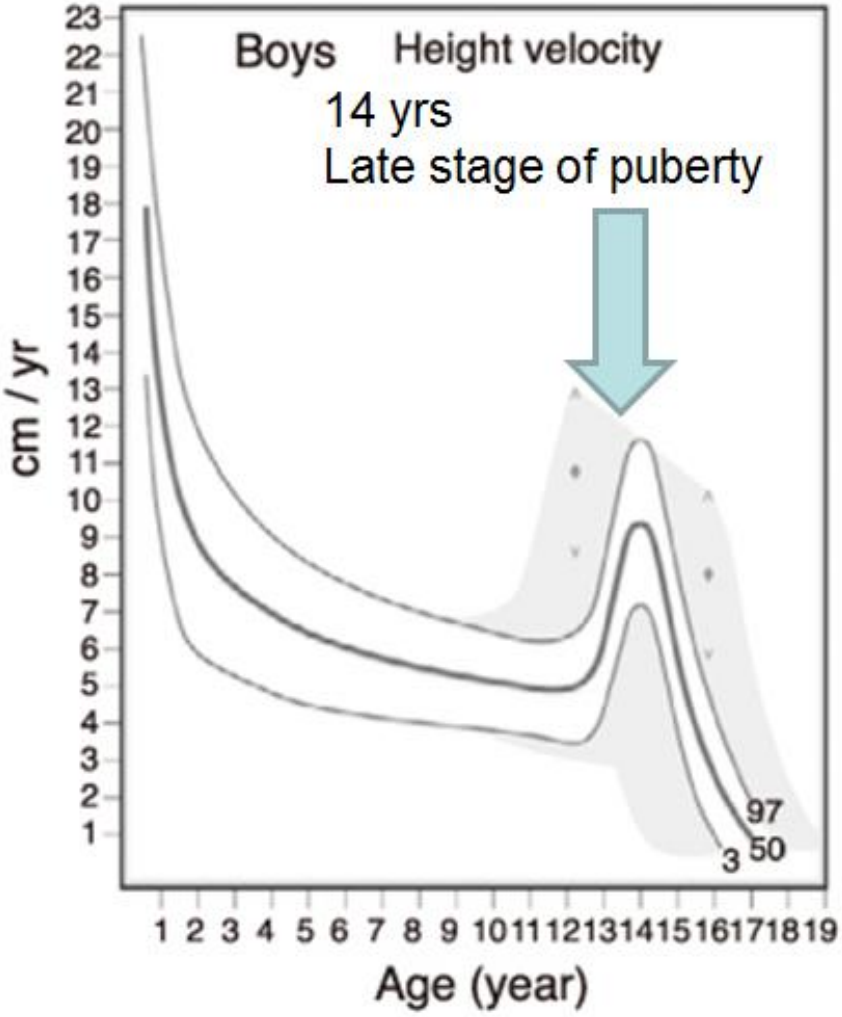
Testes enlargement (4 ml) by 11-12 years

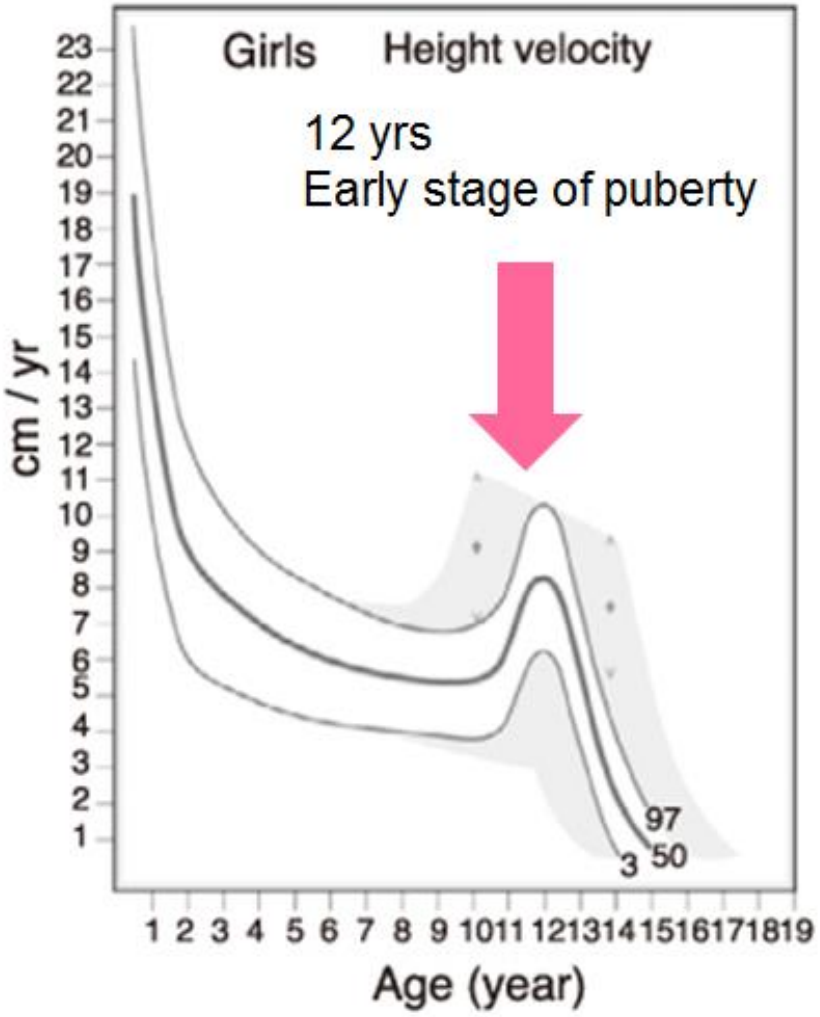
- Delayed puberty testes < 4 ml aged 14 years








Boys Height velocity
14 yrs
Late stage of puberty
cm / yr
Age (year)
97
50
3


Girls Height velocity
12 yrs
Early stage of puberty
cm / yr
Age (year)
97
50
3

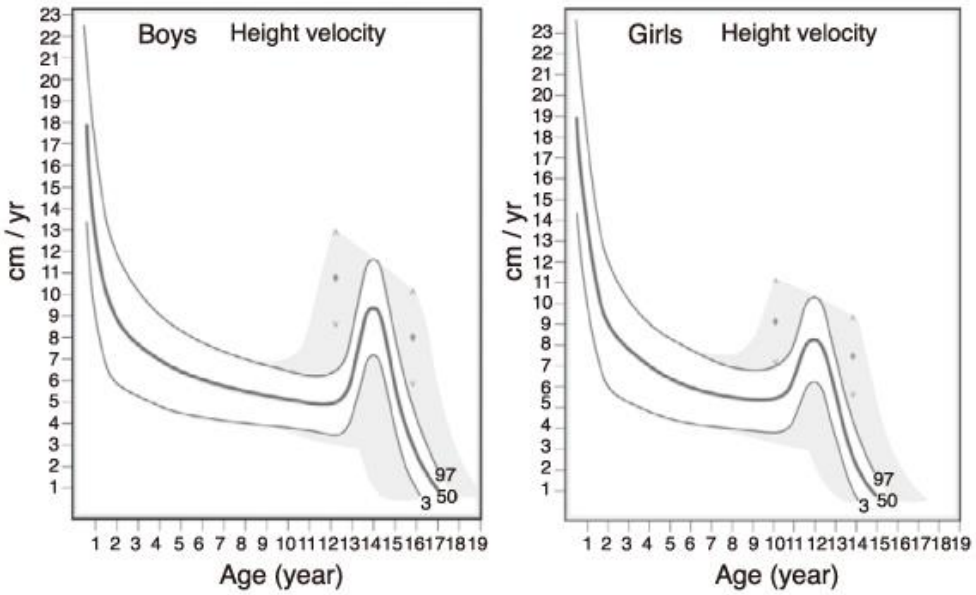
Bone age for assessment of skeletal maturity

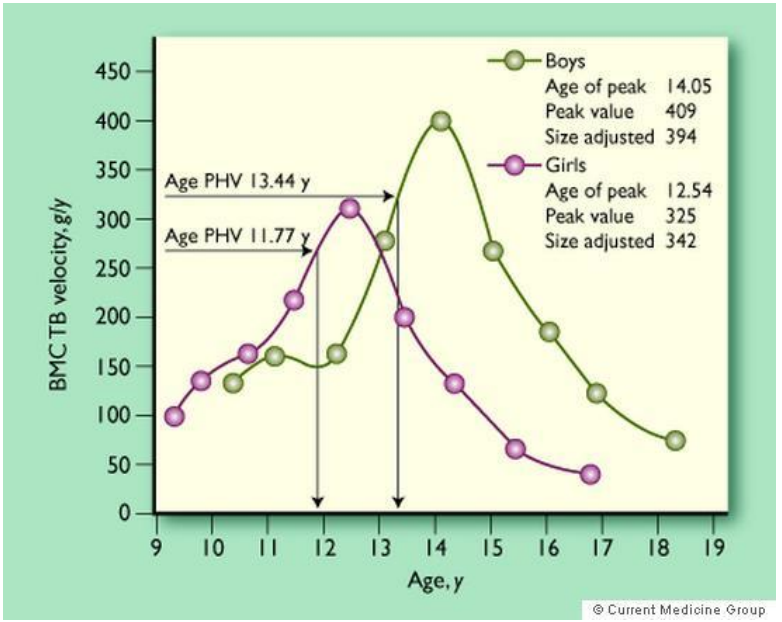
Bone defects eg arthritis

Obesity

Comparison between methods

Bone growth parallels linear growth

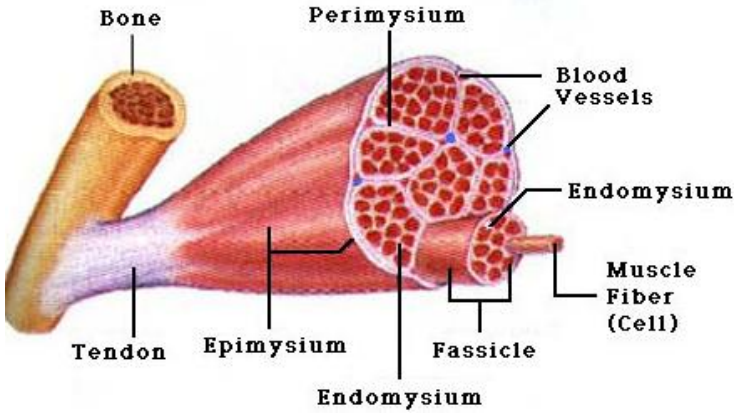


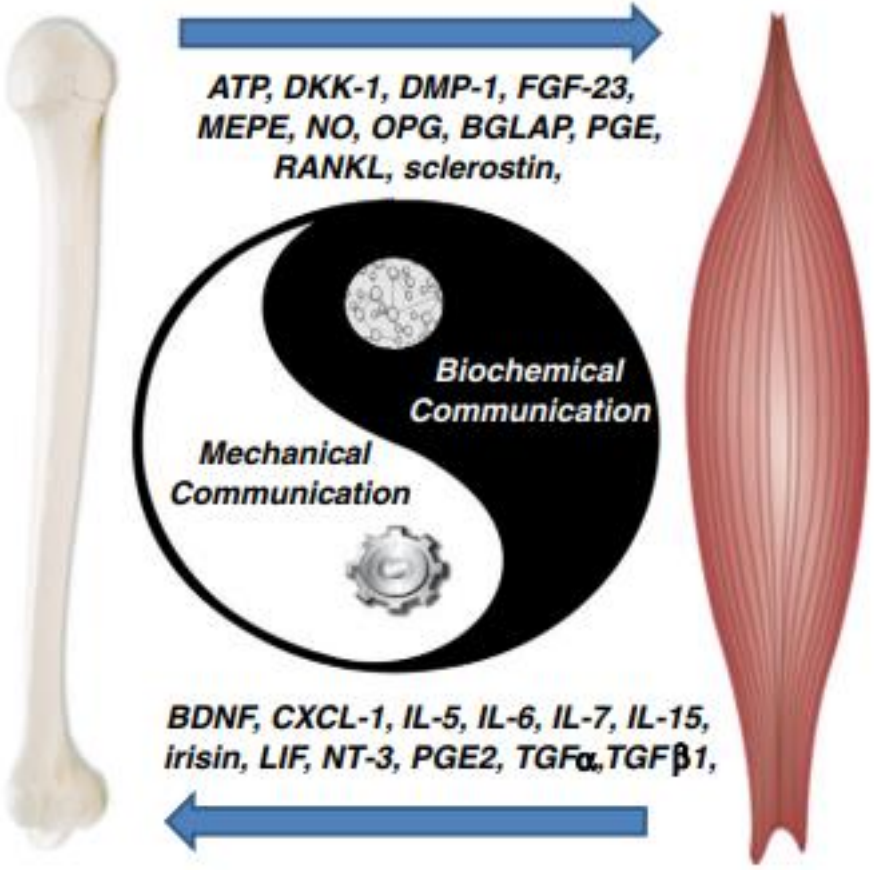


LONGITUDINAL BONE GROWTH

Poor growth in childhood chronic condition will have an impact on bone accrual which is already affected in chronic ill health +/- GC therapy

Muscle-Bone Cross Talk

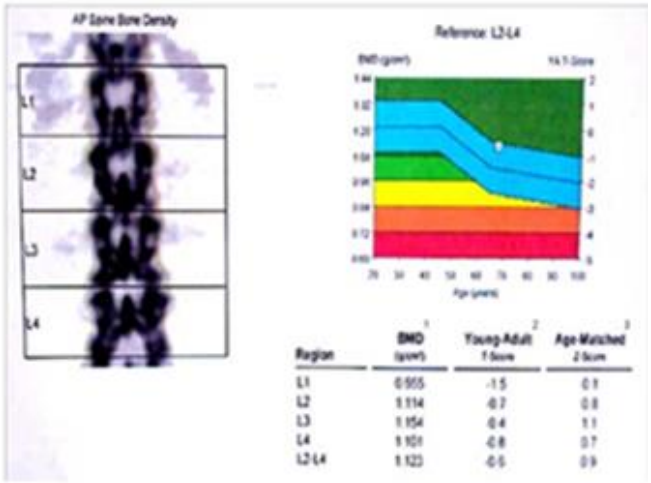




The muscle-bone cross talk is bi-directional
Interaction is at a biomechanical and biochemical level

Brotto et al Bone 2015

DXA- bone mass



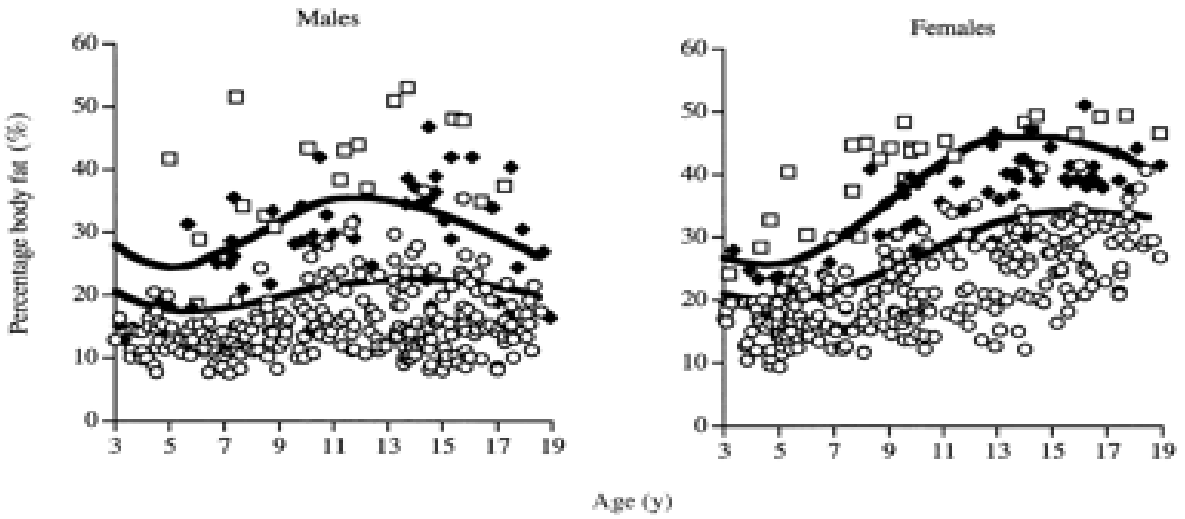
DXA BMD or BMC
T-score (NOT APPROPRIATE FOR CHILDREN)
Z-score (Age and sex matched)

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

DXA-body composition



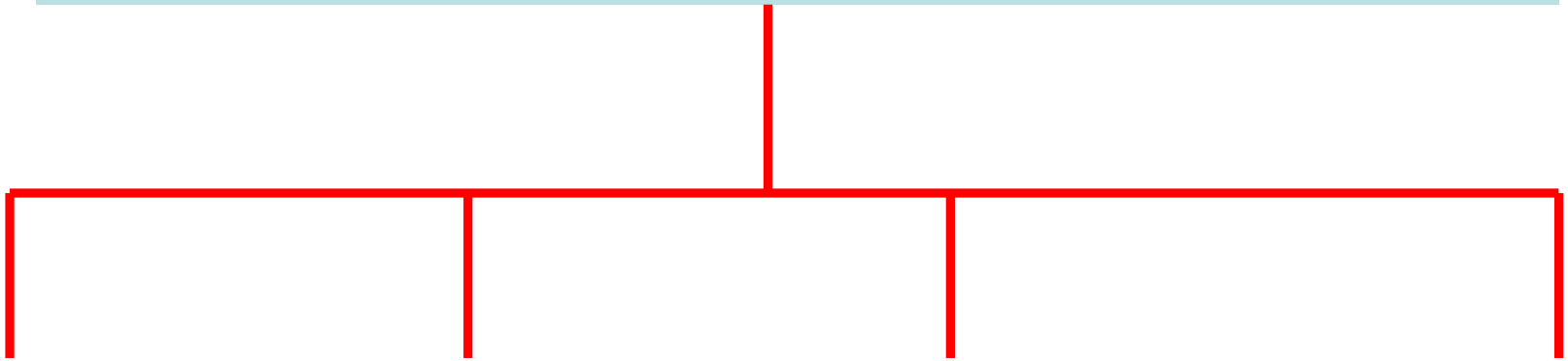
% fat mass changes throughout growth

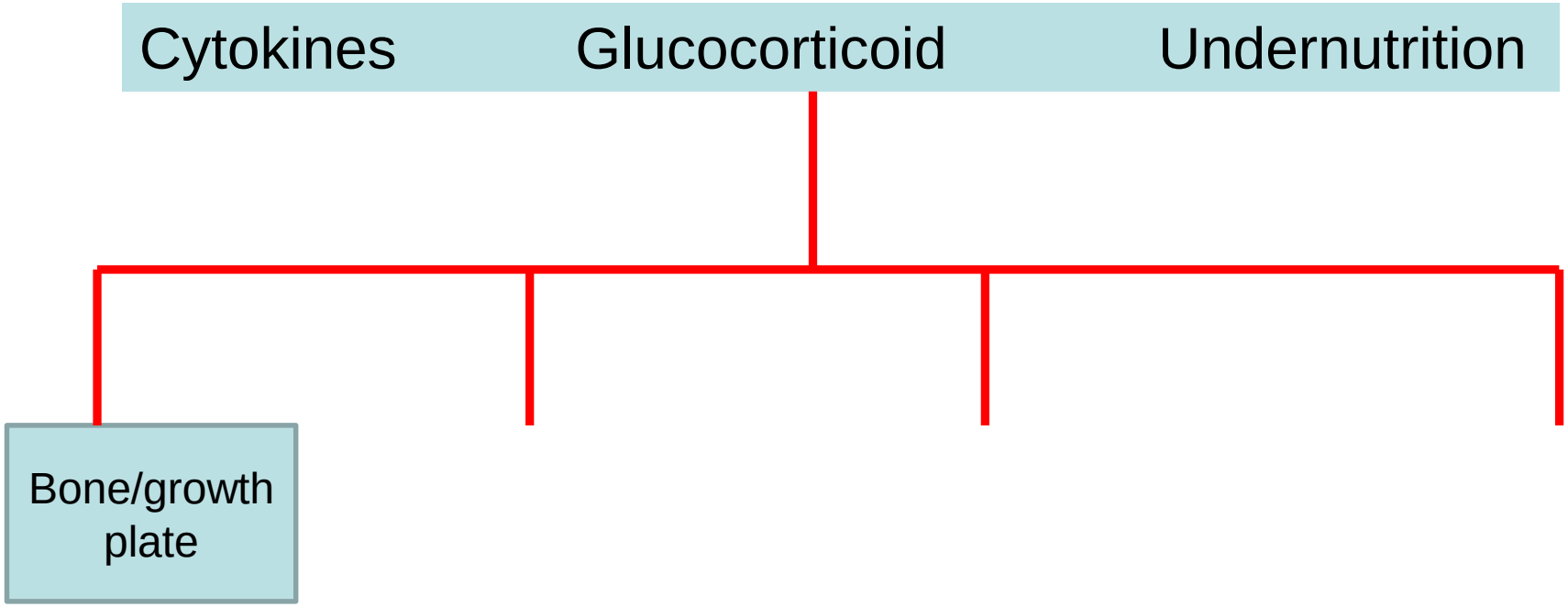
Taylor RW et al Am J Clin Nutr 2002

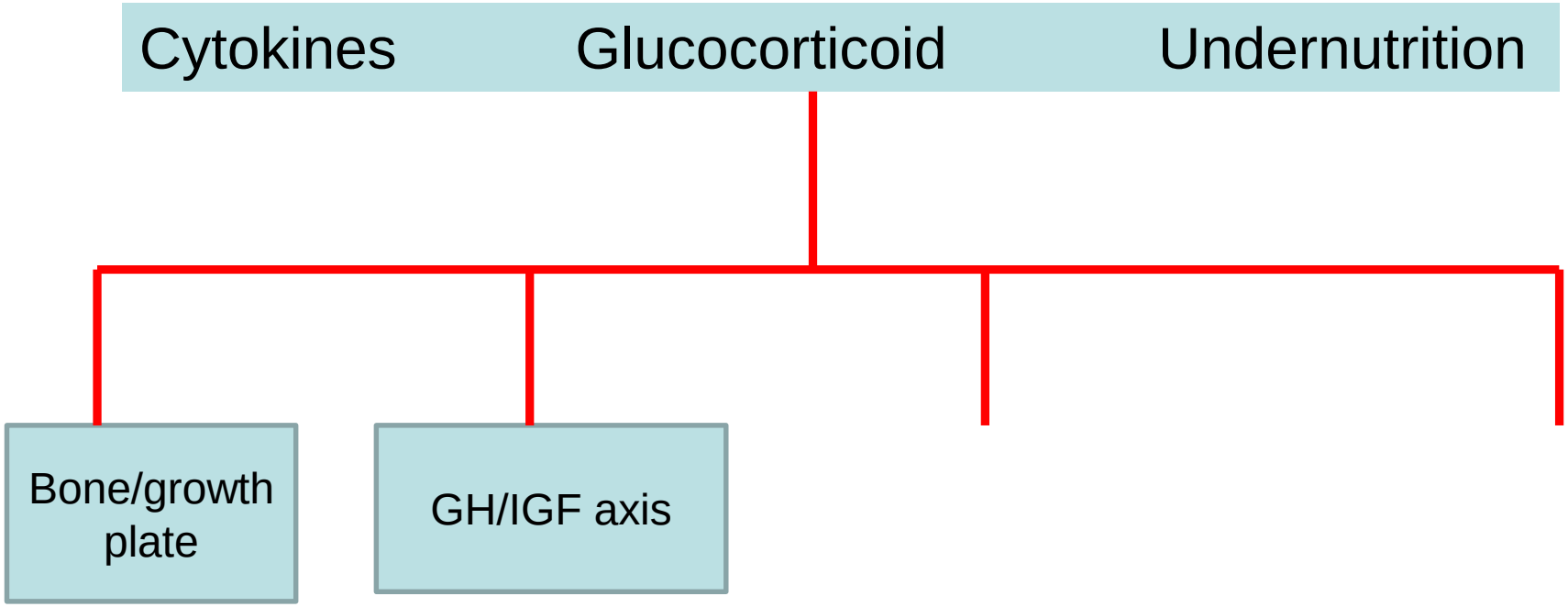
% fat mass maybe falsely elevated in children with reduction in muscle mass
(Low muscle mass and normal / marginally elevated fat mass)

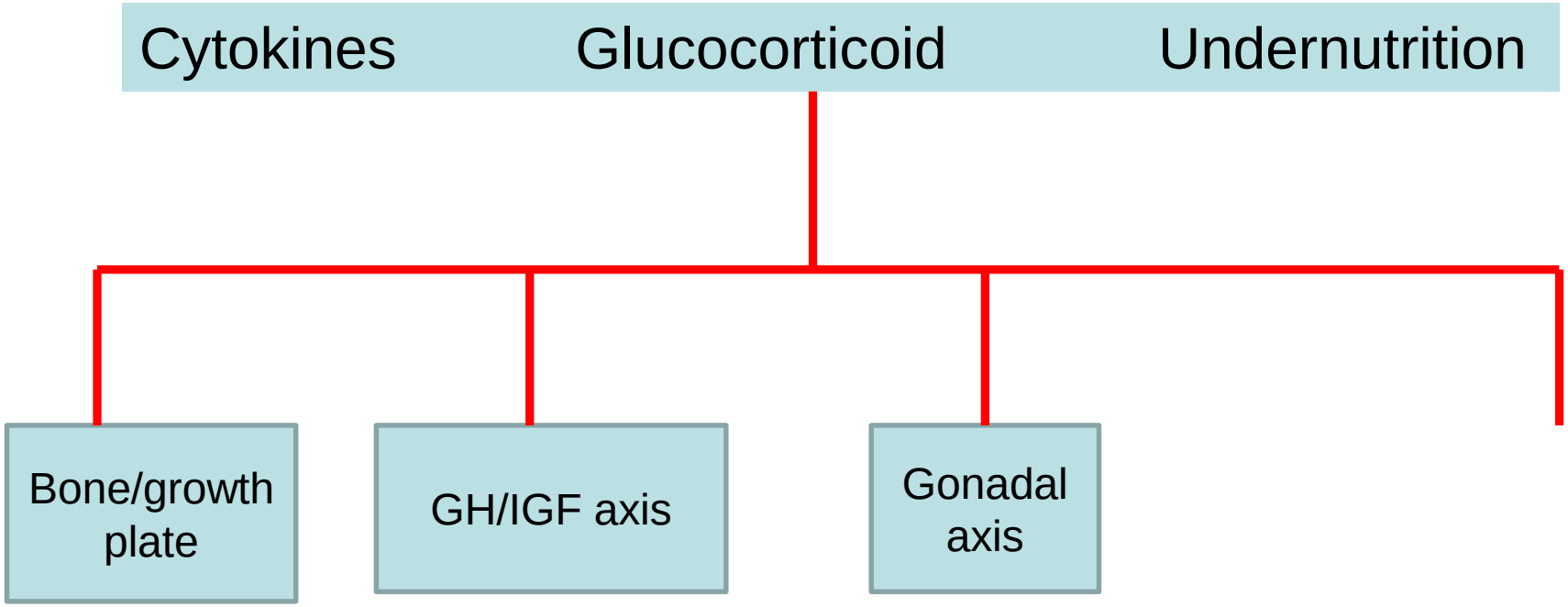
Mechanism of poor growth and bone development in chronic illness

Cytokines Glucocorticoid Undernutrition




Cytokines
Glucocorticoid
Undernutrition
Bone/growth plate


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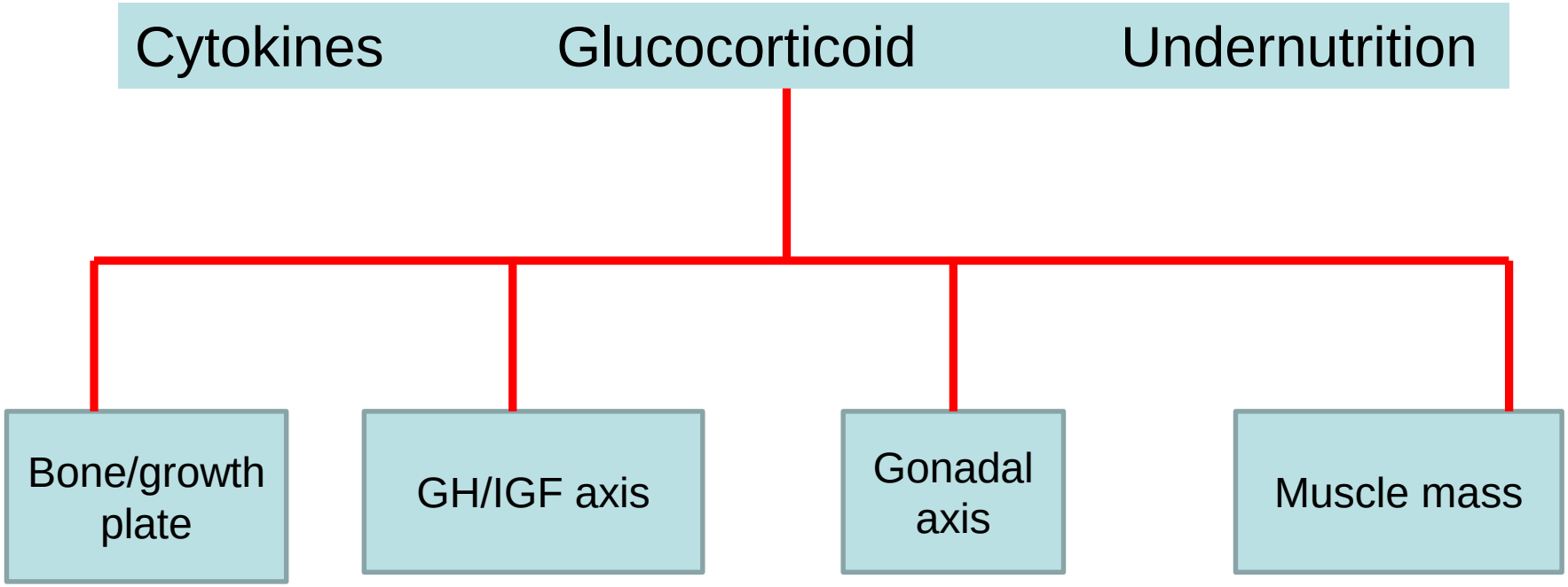
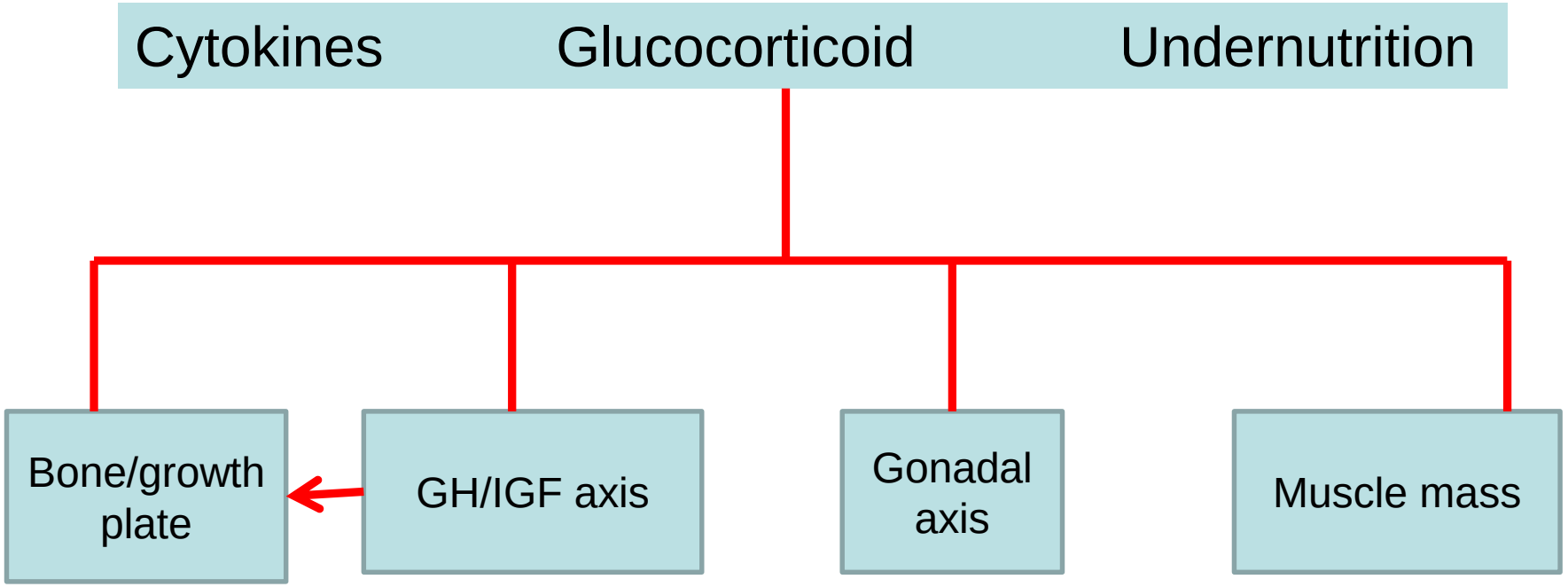
Undernutrition
Bone/growth plate
GH/IGF axis
Gonadal axis


Cytokines
Glucocorticoid
Undernutrition
Bone/growth plate
GH/IGF axis
Gonadal axis
Muscle mass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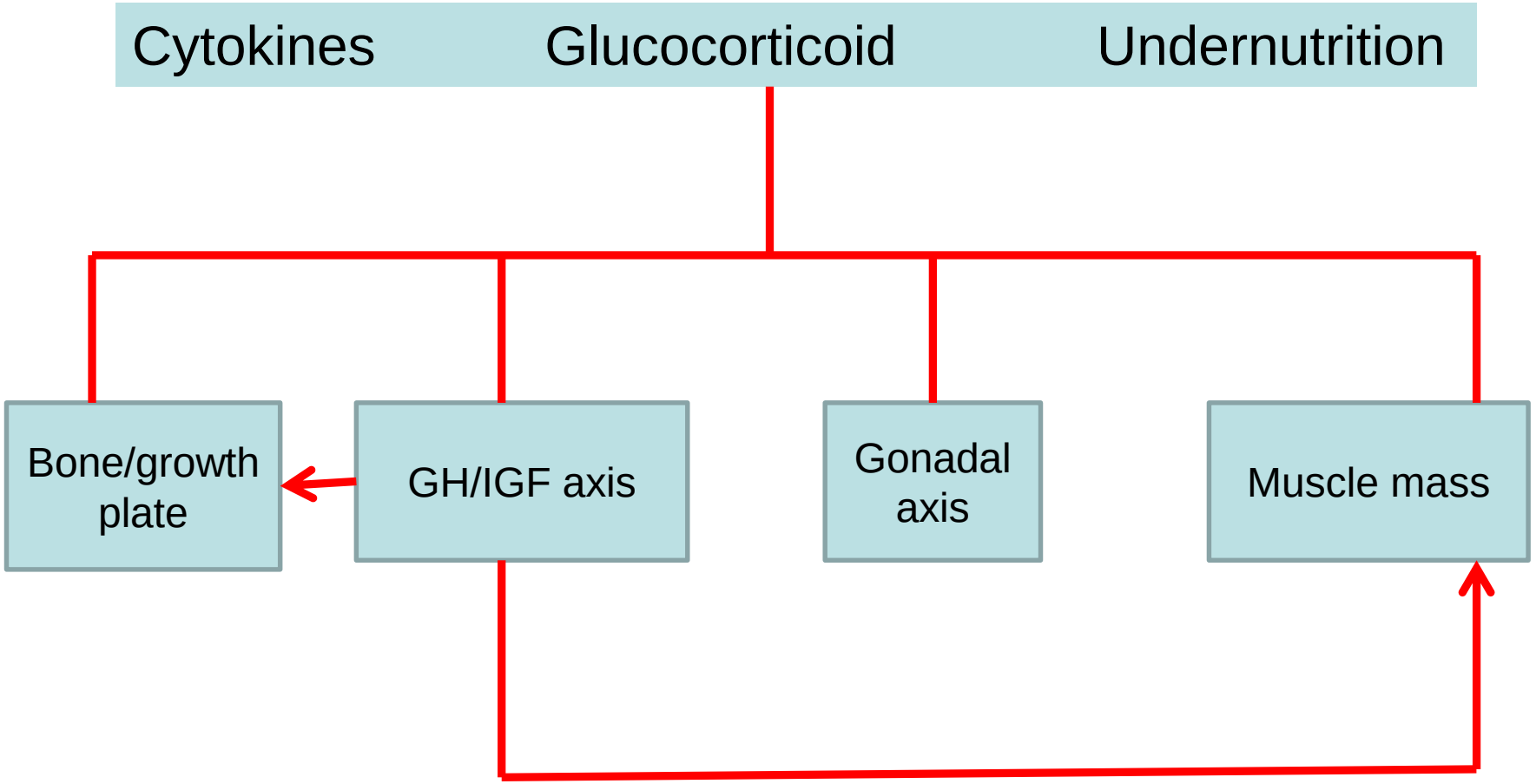
Muscle mass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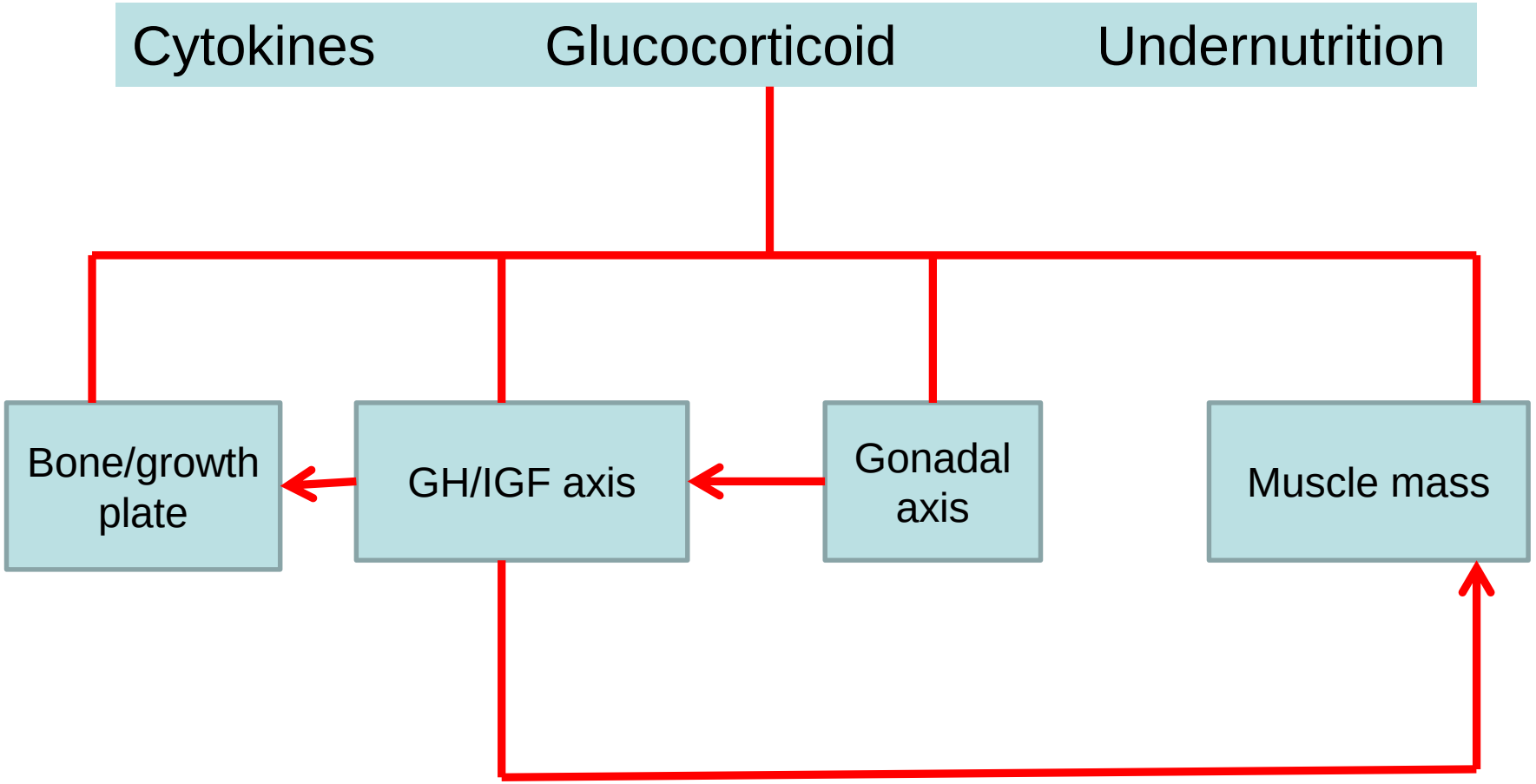
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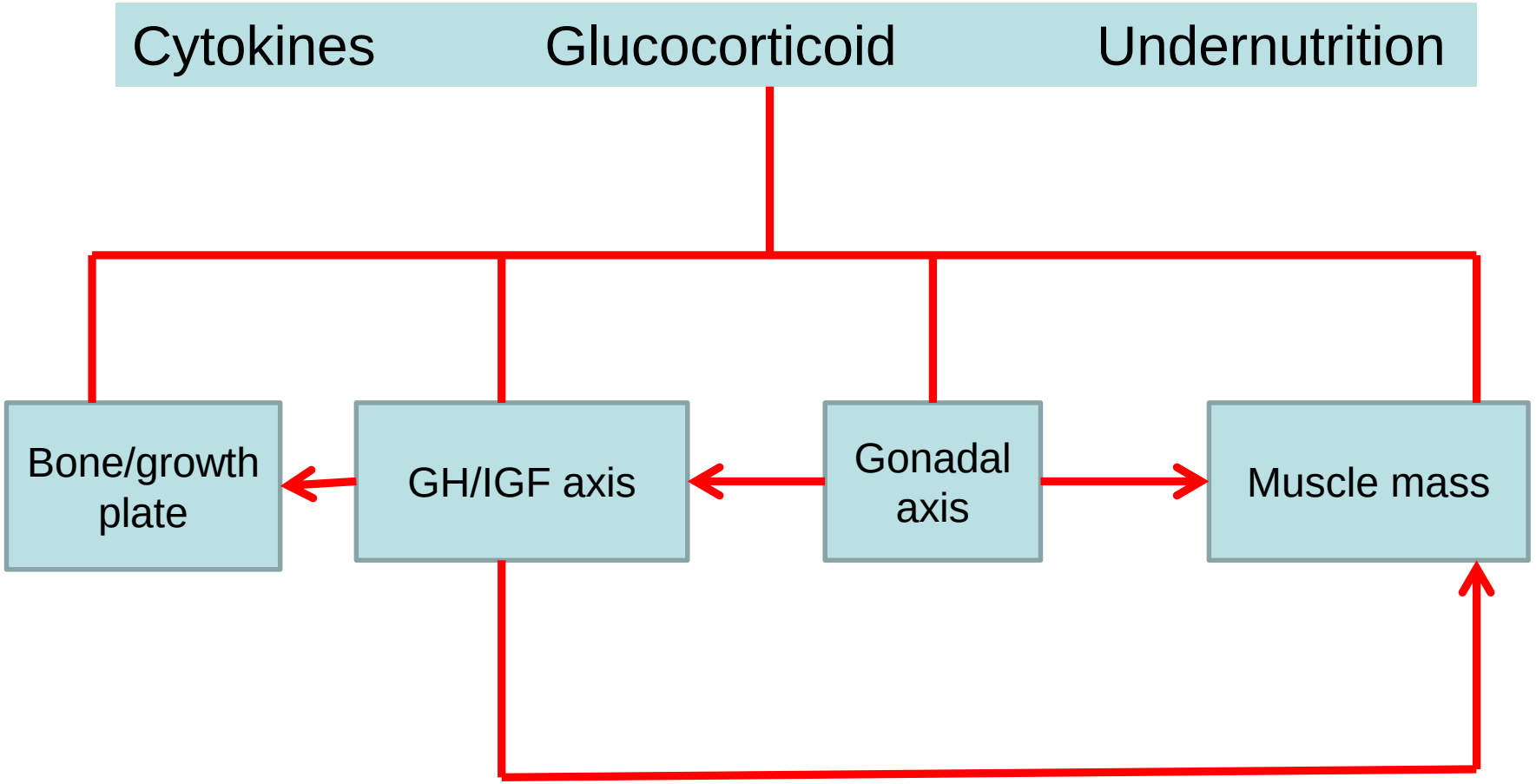
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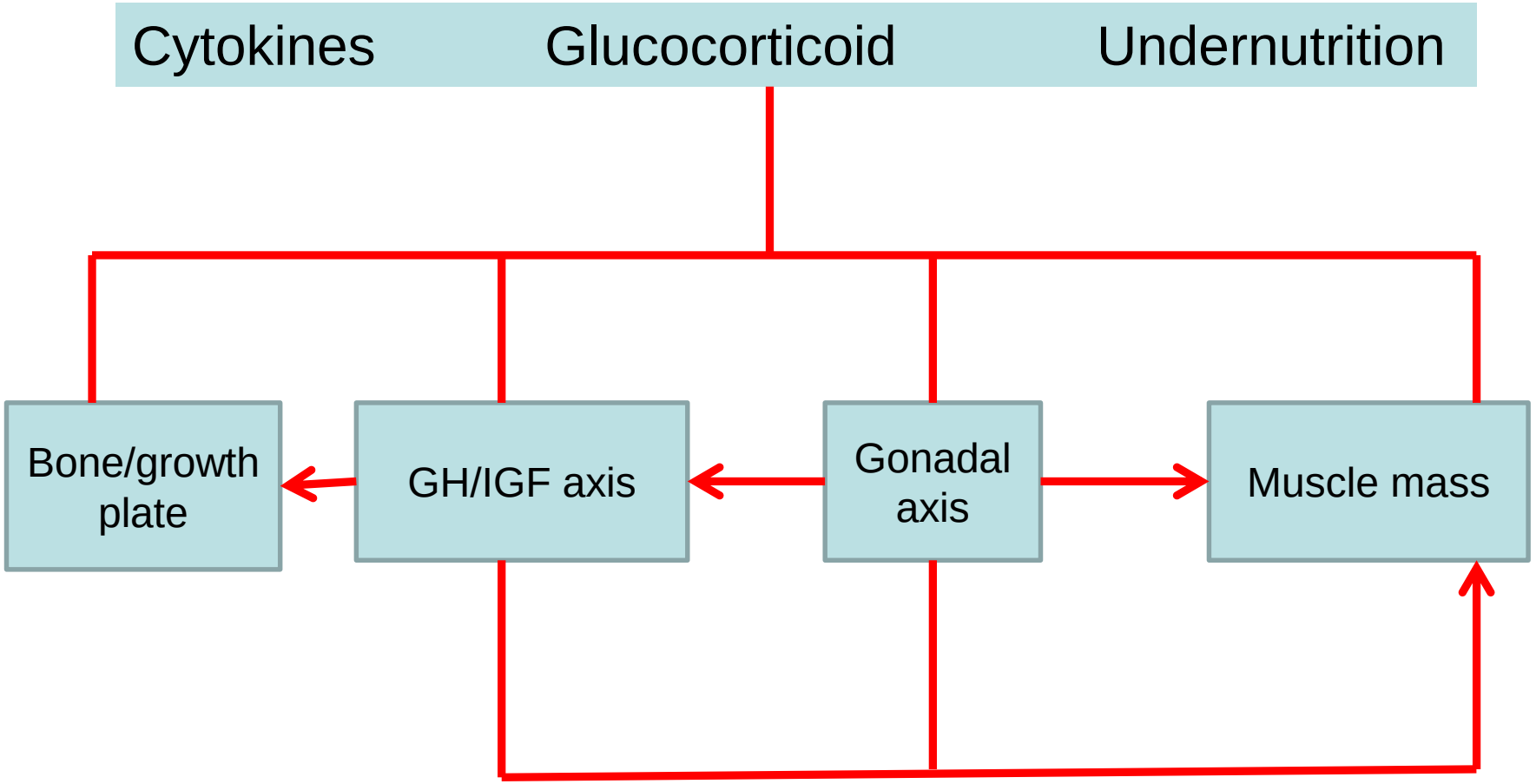
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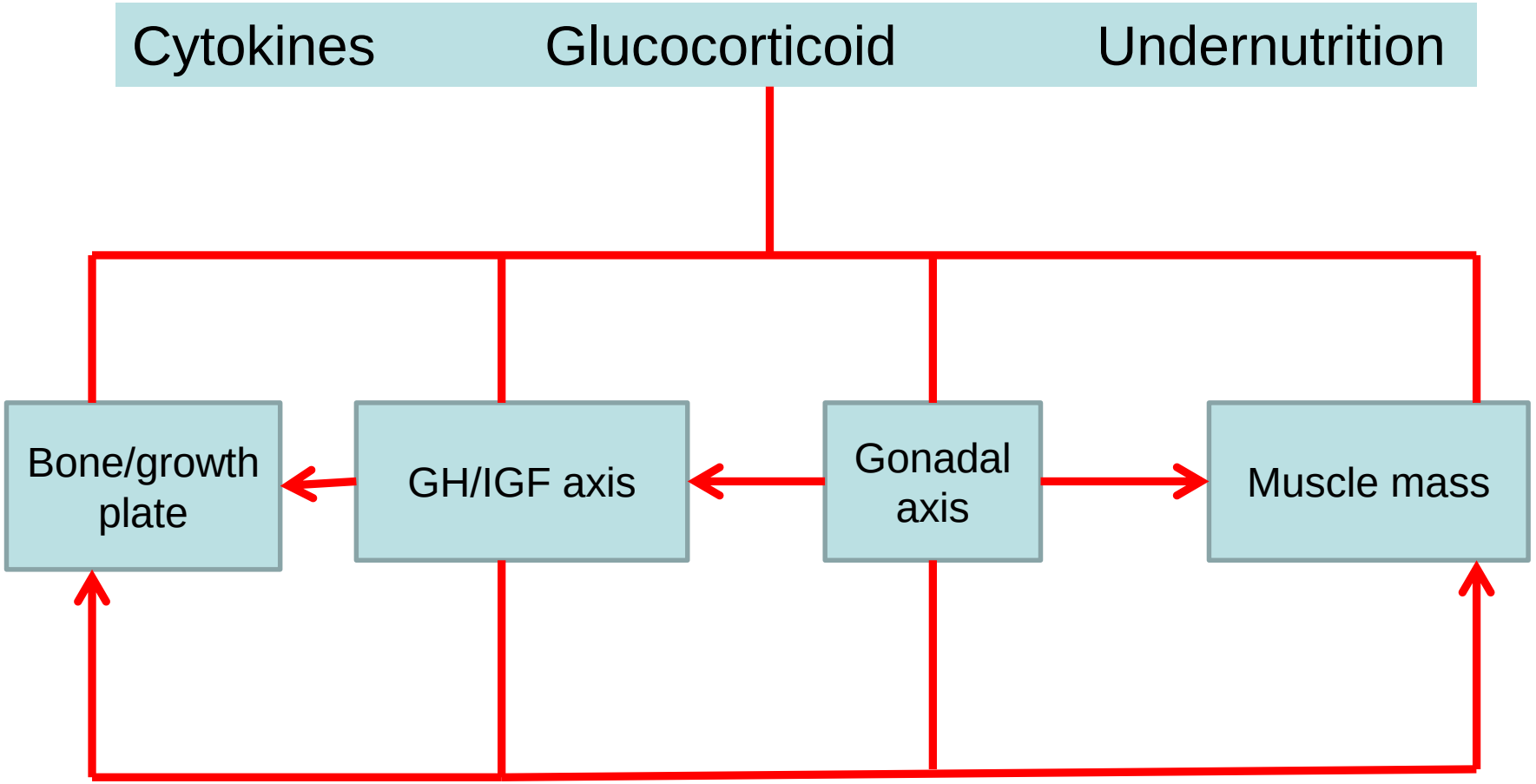
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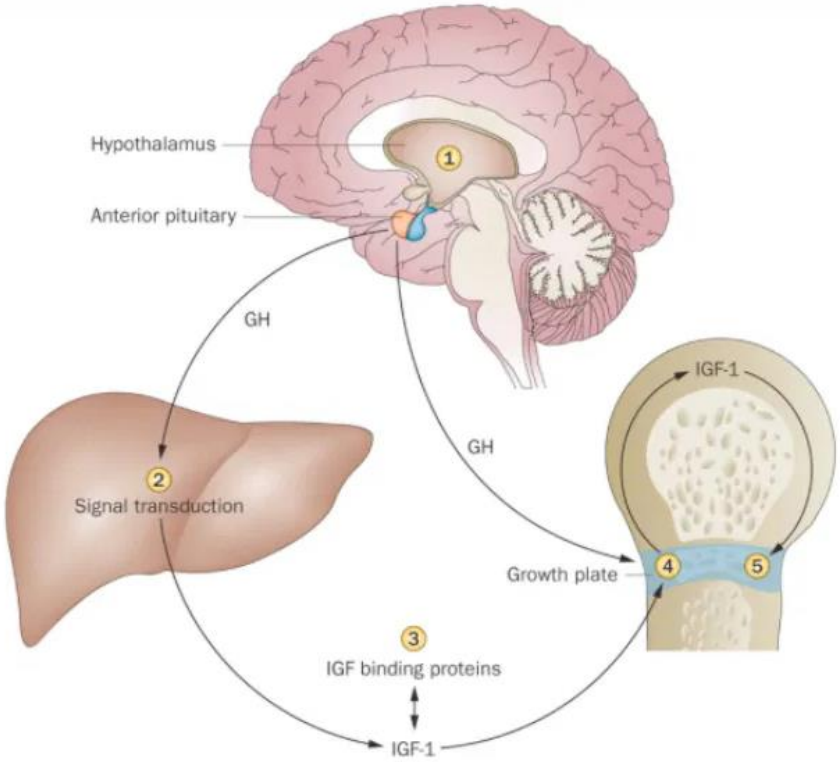
GH / IGF Axis In Chronic Illness



Rozario, K. S., Lloyd, C., & Ryan, F. (2015, November 20). The regulation of growth by GH and IGF1 axis [Digital image]. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK343487/

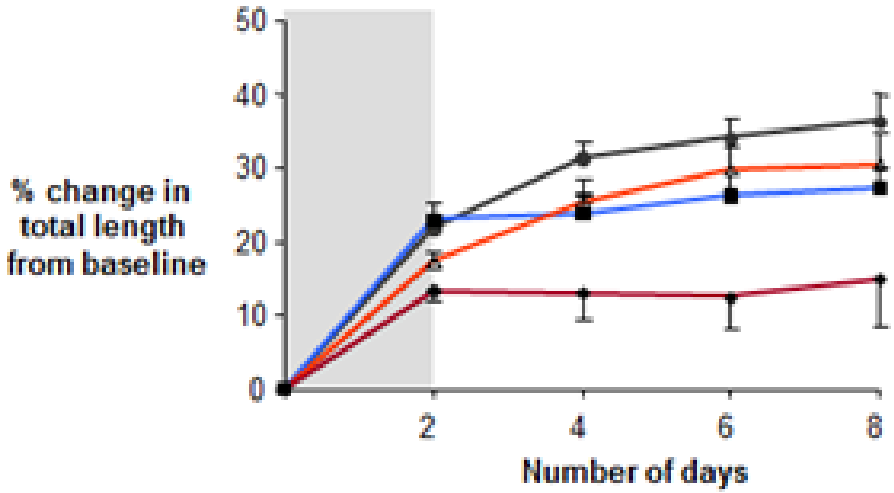
Common to see

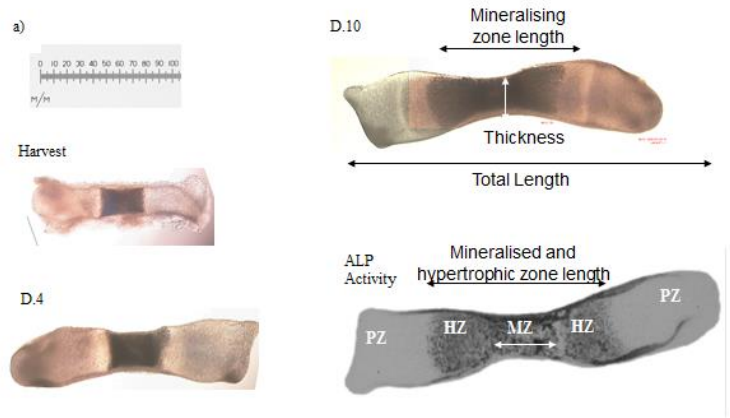
- Hormone insensitivity (esp GH)
- Hormone insufficiency

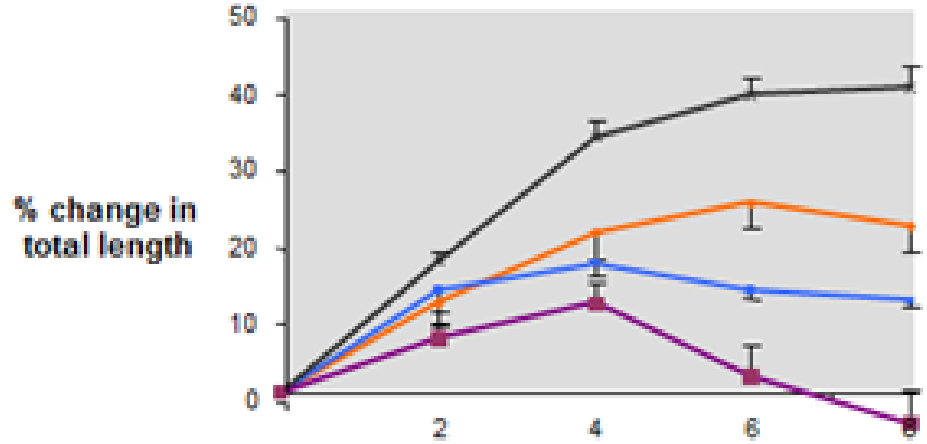
Defect transient and reversible

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

Direct Effect Of Cytokines On Growth Plate





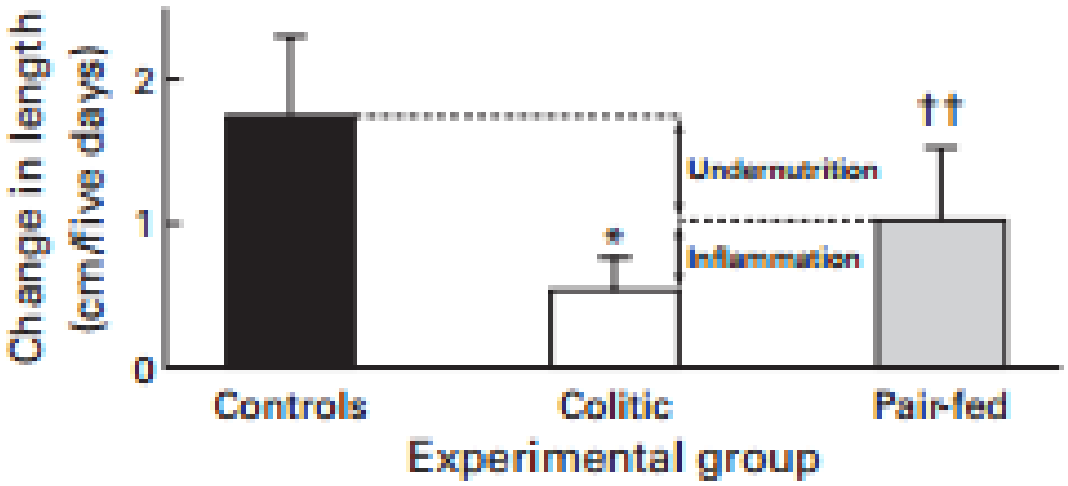


Pivotal role of TNF and IL1 on growth impairment at the level of the growth plate

IL6 impact on bone

MacRae et al J Endocrinol 2006

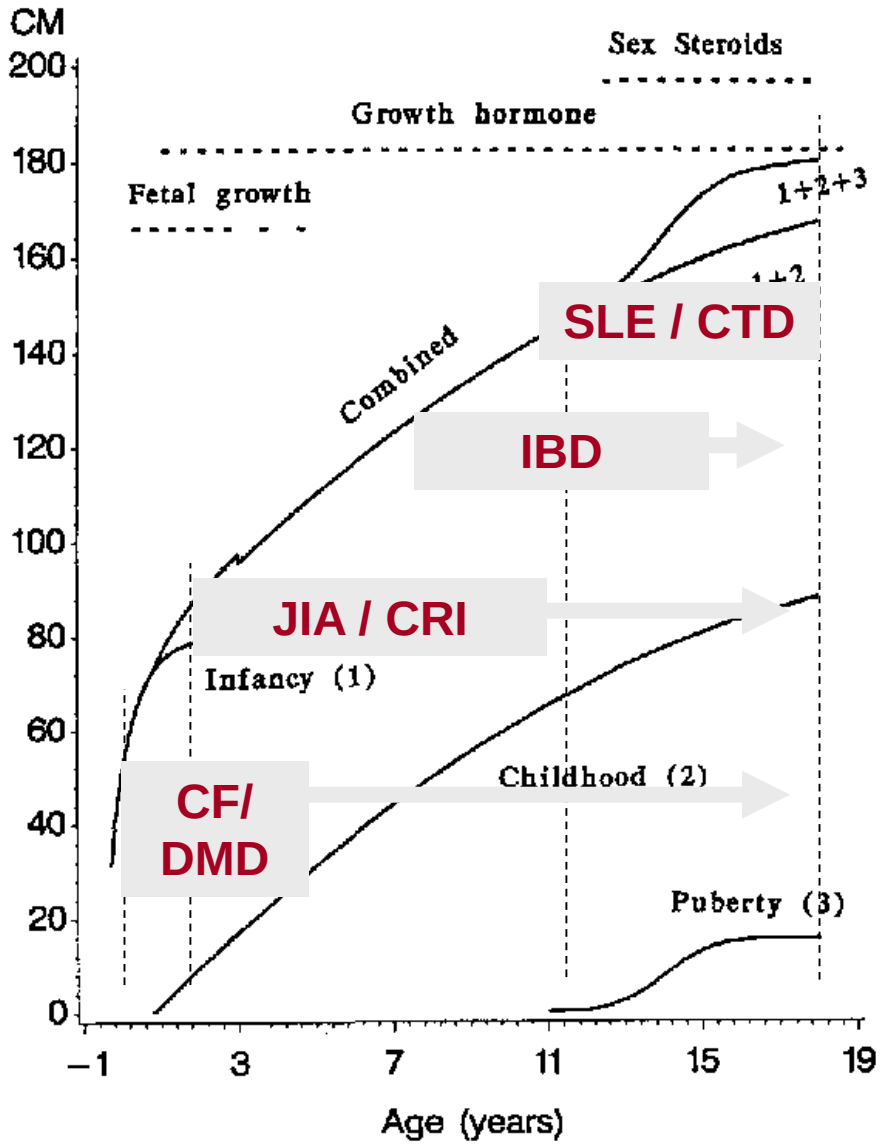
Inflammation And Nutrition In IBD Growth Failure



Balinger AB et al Gut 2000

Clinical evidence of poor growth in chronic illness

Chronic Diseases In Childhood

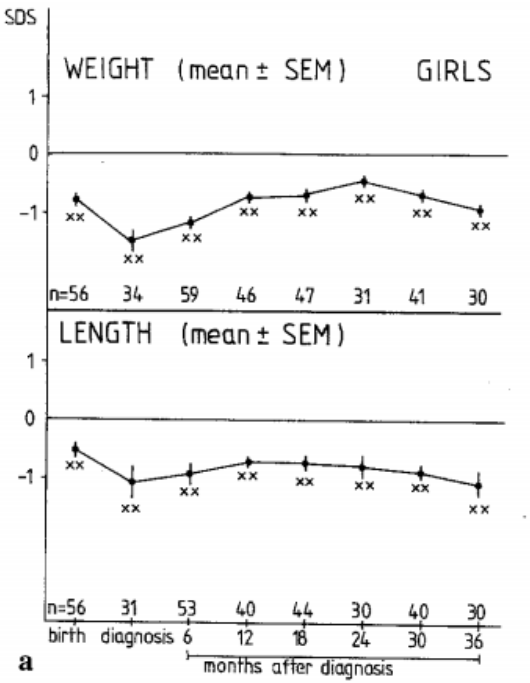


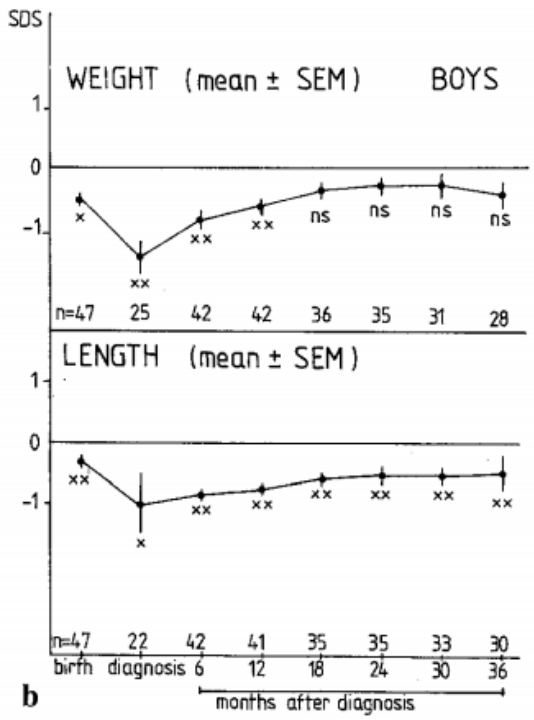
Effect on growth

- Disease specific aspects
  - Drugs
  - Nutrition
  - Metabolic state
  - Hypogonadism
- Common aspect
  - Inflammation

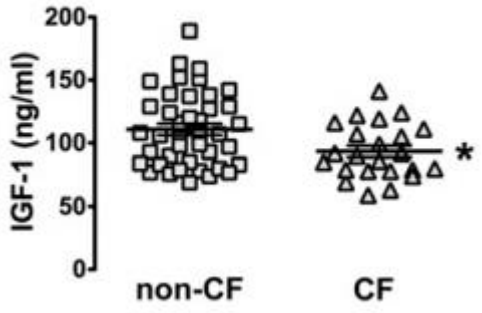
Karlberg et al, Eur J Clin Nutr, 1994

Growth in cystic fibrosis



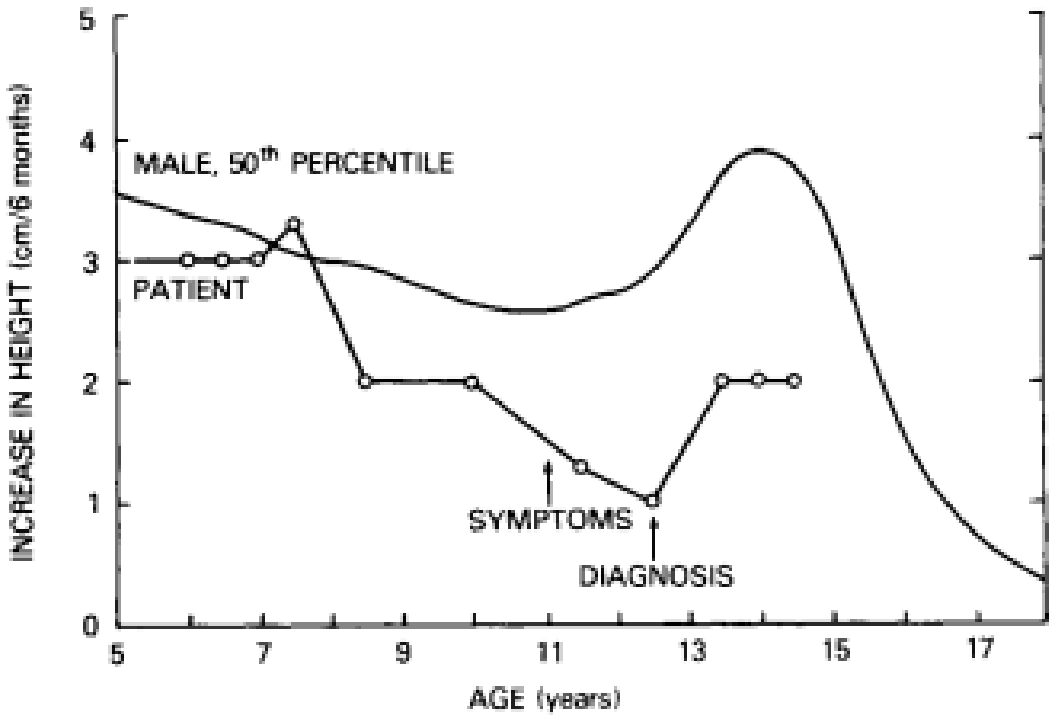


Hauesler G et al Eur J Pediatr 1994



Rogan MP et al Proc Natl Acad Sci U S A. 2010

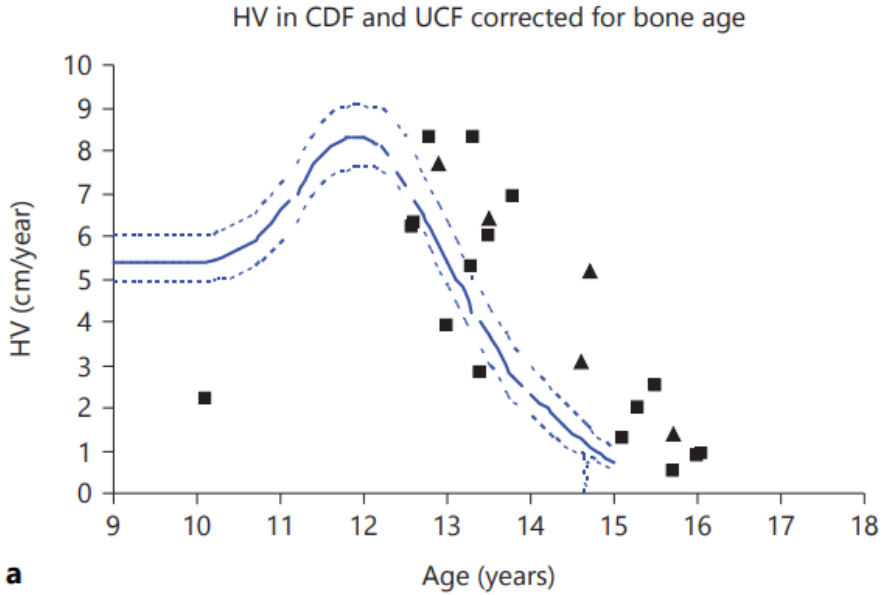
Growth failure prior to symptoms in CD

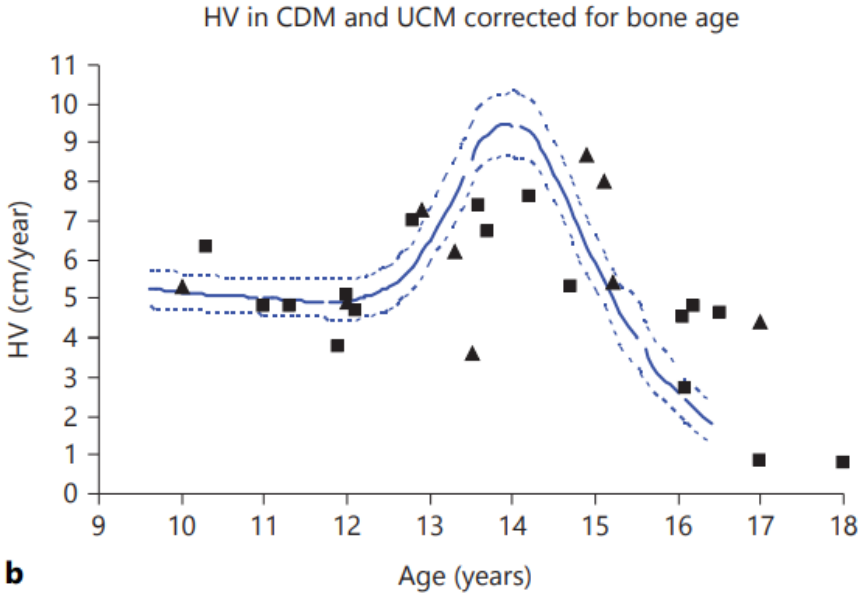


Kanof ME et al Gastroenterology 1988

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

Puberty & pubertal growth in IBD





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

Mason et al Horm Res Paediatr 2015

Enteral Nutrition And Impact On IGF Axis

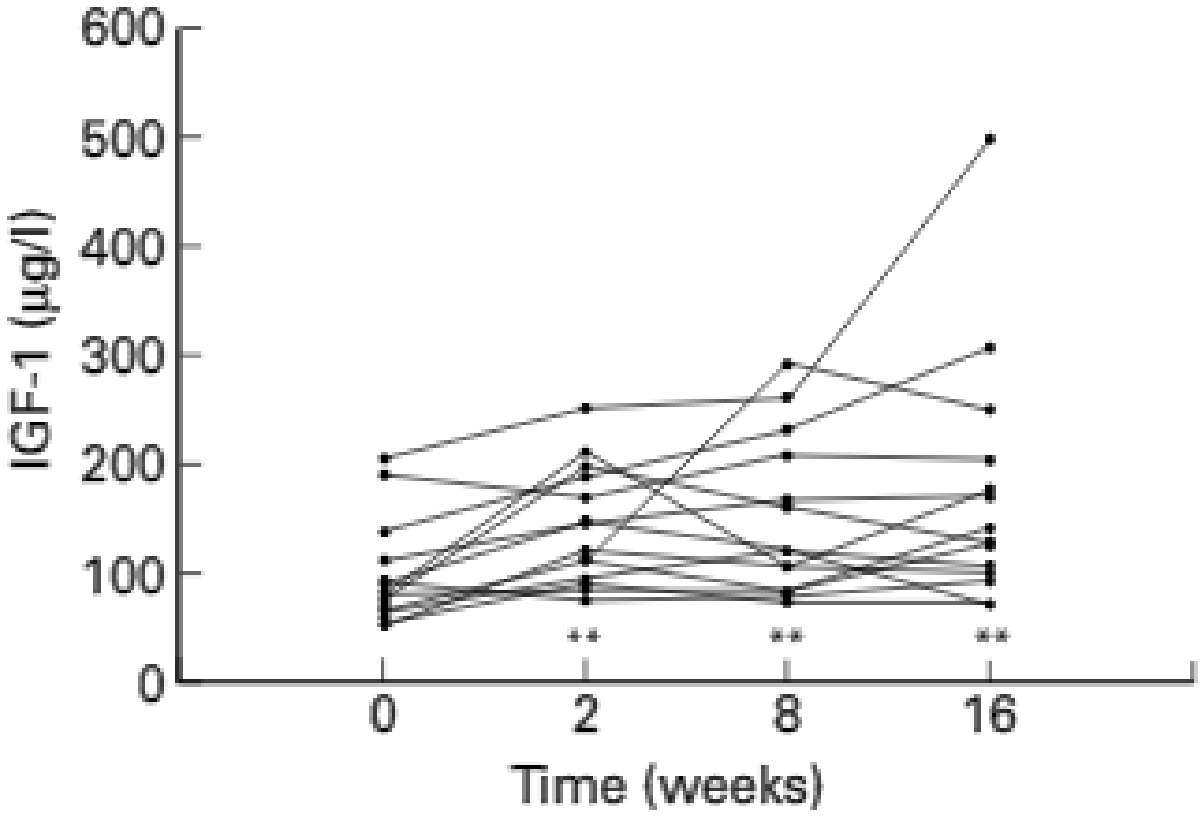
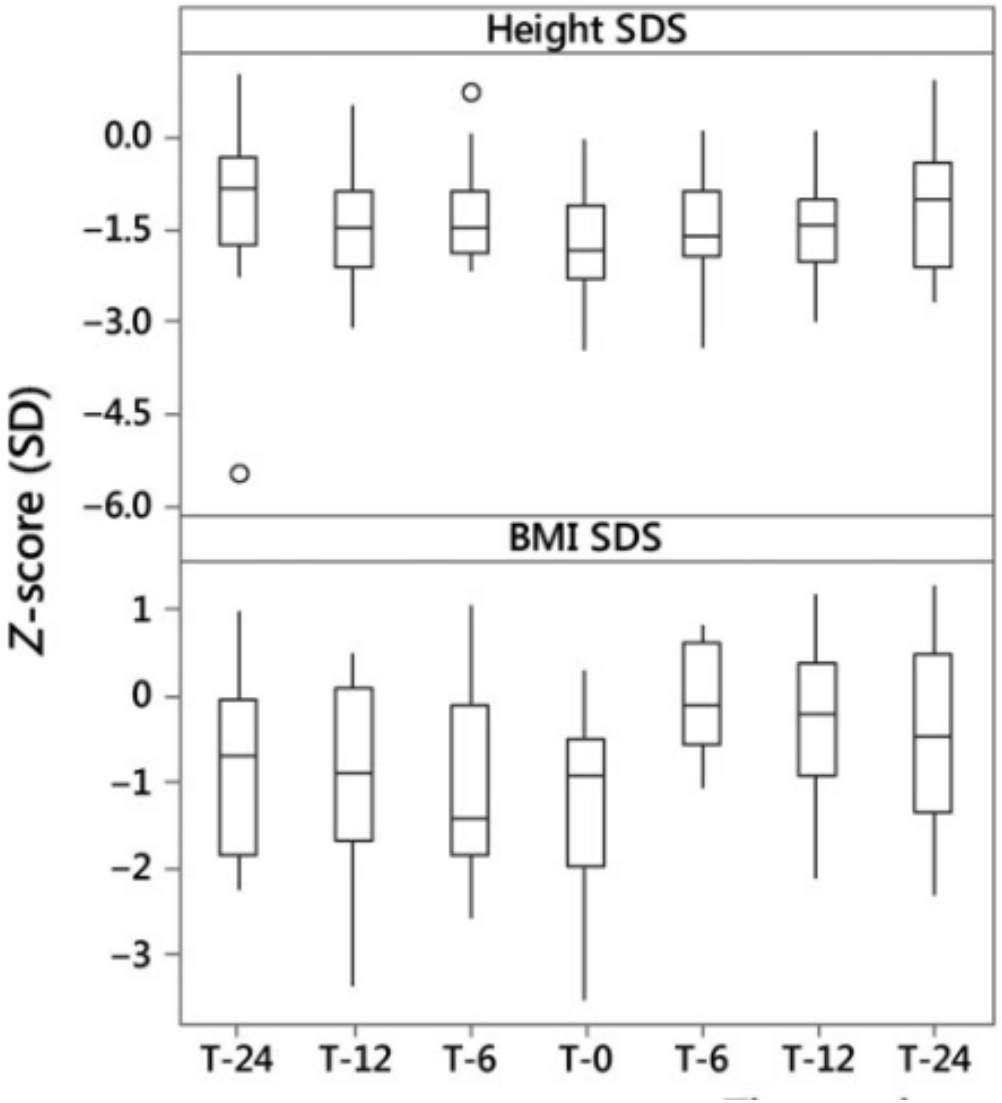


Fig. 2 Serum IGF-I-values during enteral nutrition (**$P = 0{\cdot}005$ compared with 0 weeks).

Beattie RM et al Clin Endocrino 1998

Long term gastrostomy feeding in CD



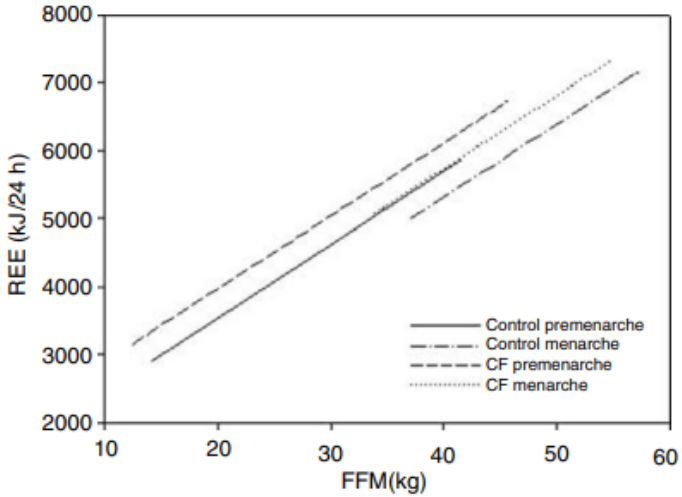
Duncan et al Acta Paediatr 2018

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[a]

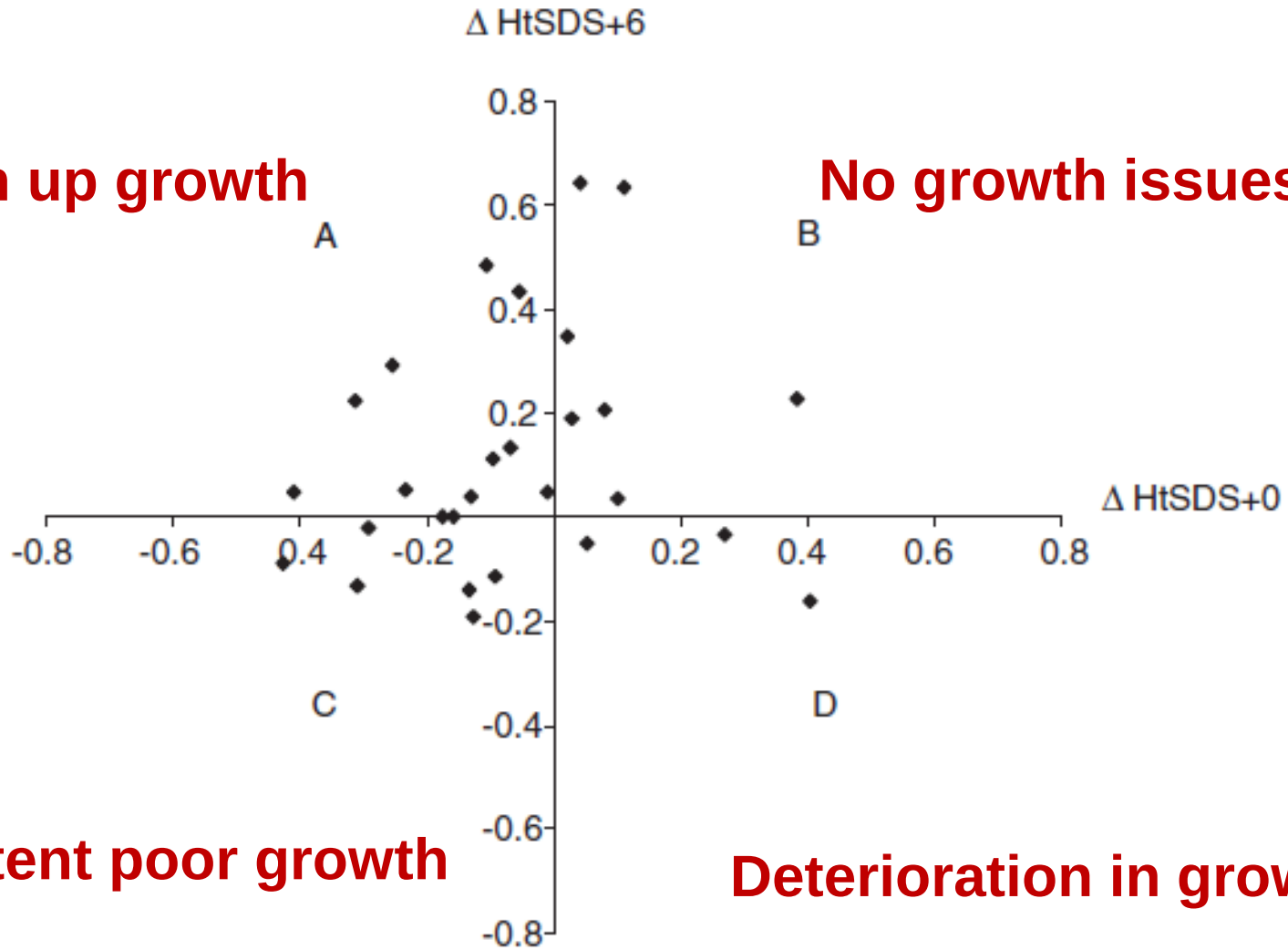
	No. of years before gastrostomy		6 to 18 mo after gastrostomy		18 to 30 mo after gastrostomy	
	Percentile	Range	Percentile	Range	Percentile	Range
Weight	2	1,6	12	1,28[b]	12	1,29[b]
Height	5	1,34	6	1,48[c]	10	2,34[c]
	%	*range*	%	*range*	%	*range*
Weight as % of ideal	88	80,92	90	85,99[b]	93	86,98[b]

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

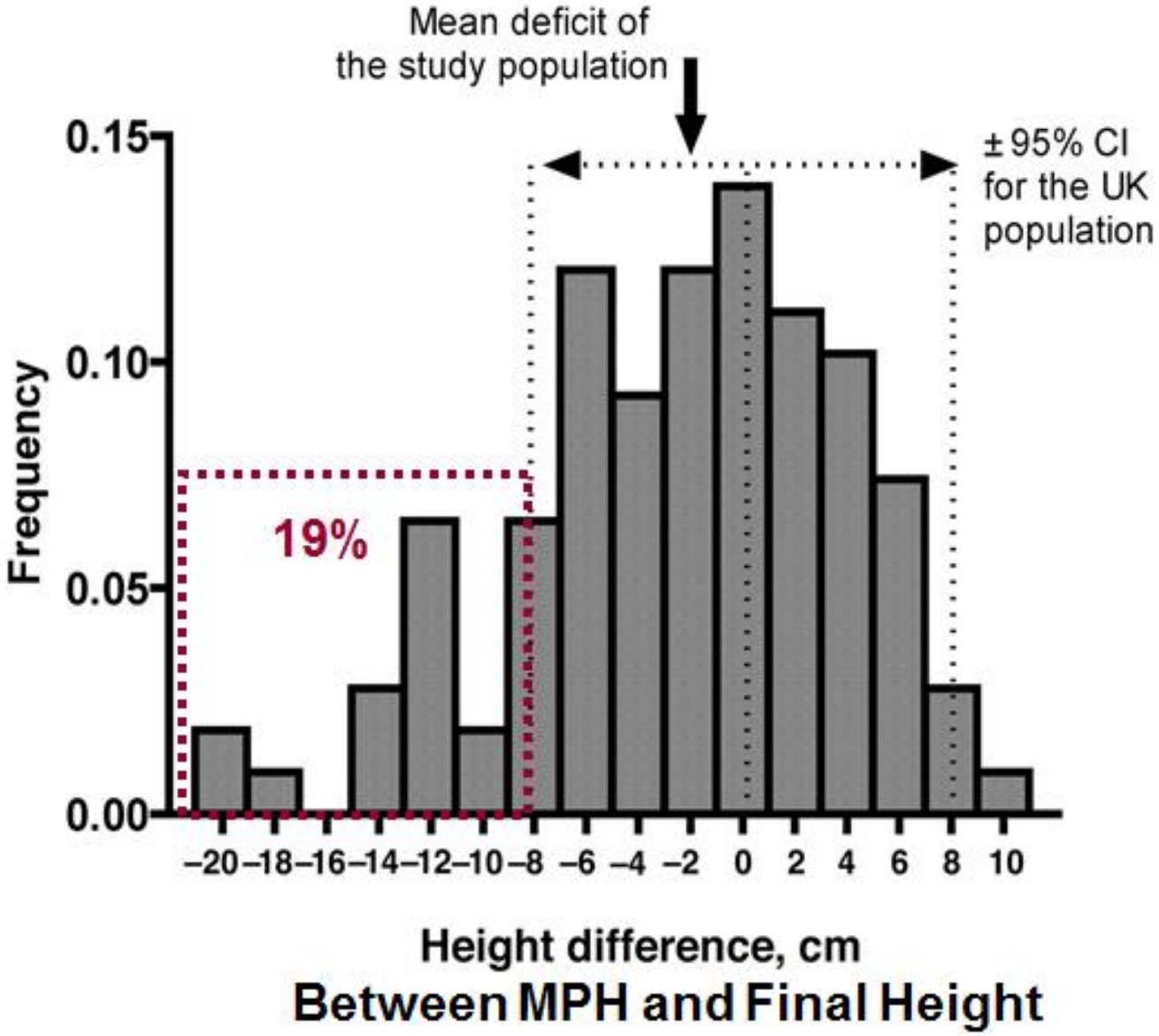
No growth issues

Persistent poor growth

Deterioration in growth

Malik et al J Pediatr Gastroenterol Nutr 2011

Adult height in childhood onset CD



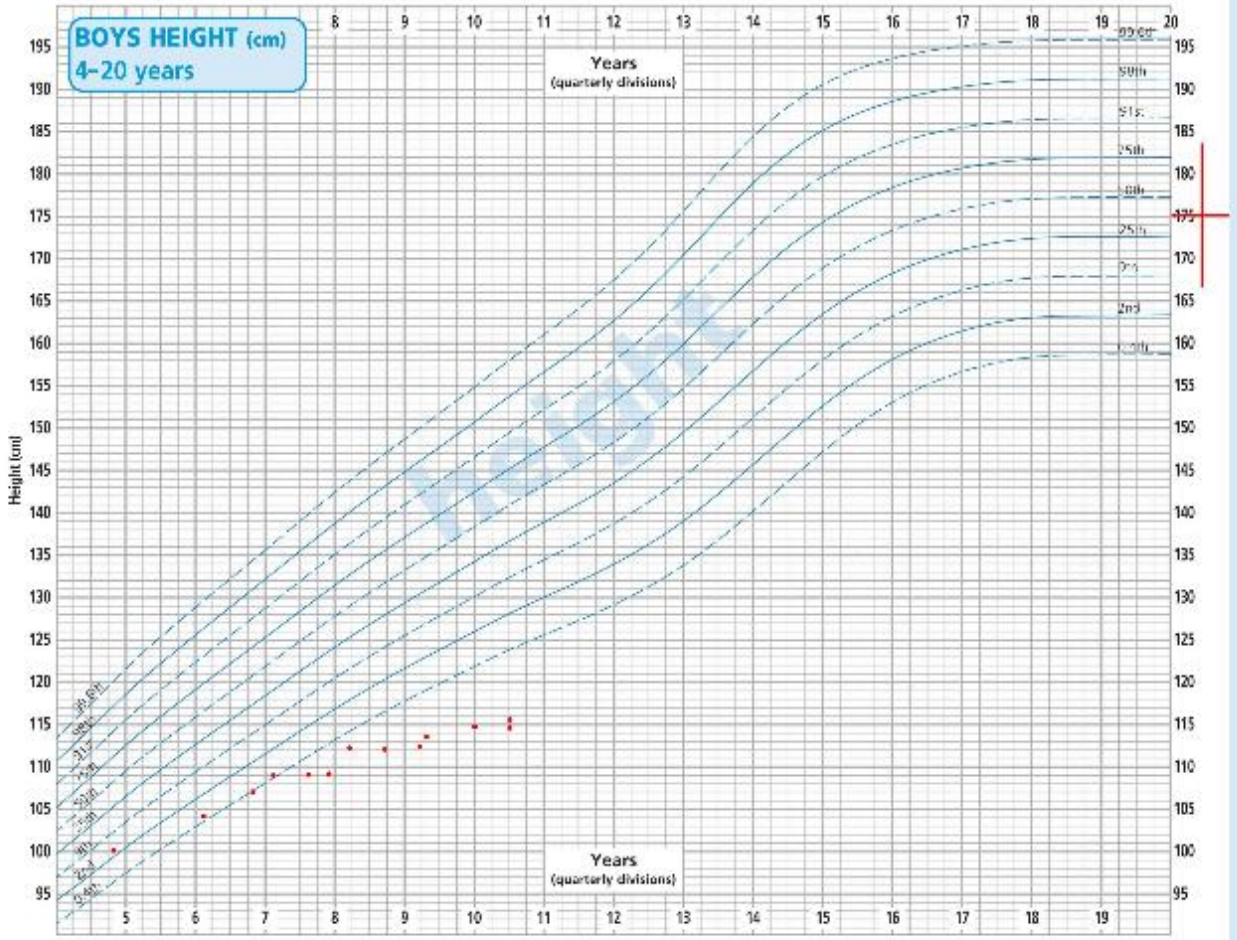
Sawczenko, A. et al. Pediatrics 2006

Growth and childhood asthma

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

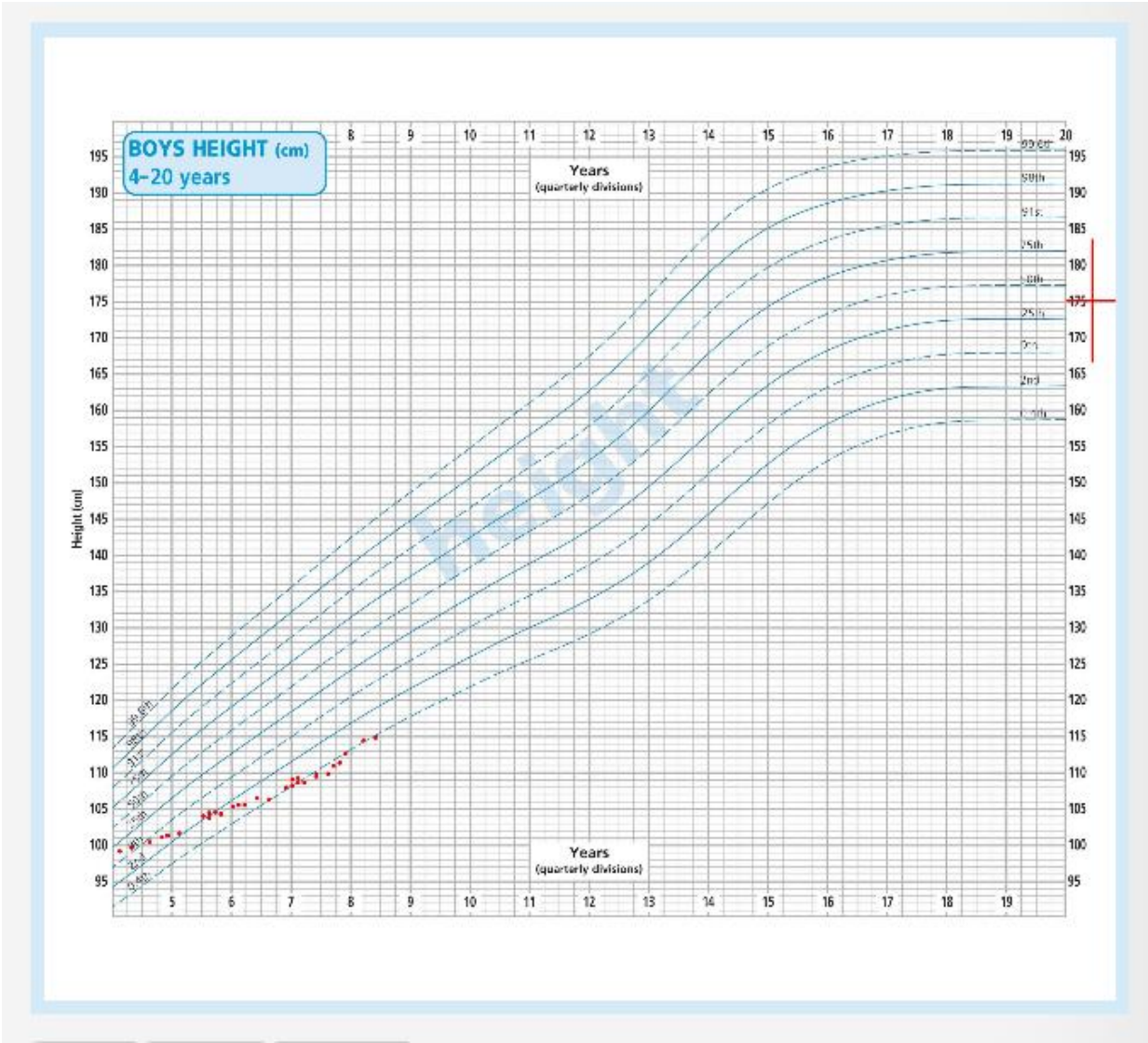
Zhang L et al Cochrane Database Syst Rev 2014

Growth with long term oral GC



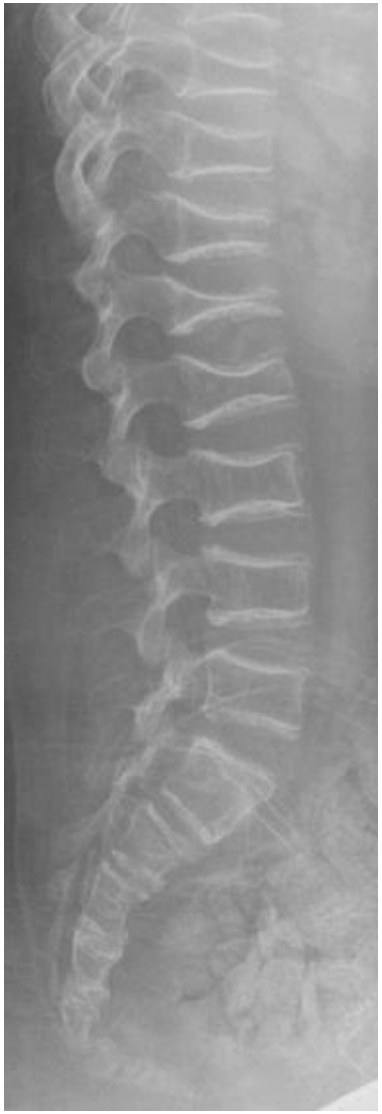
10 year old boy with DMD on daily oral GC since age 6 years

Growth with long term oral GC

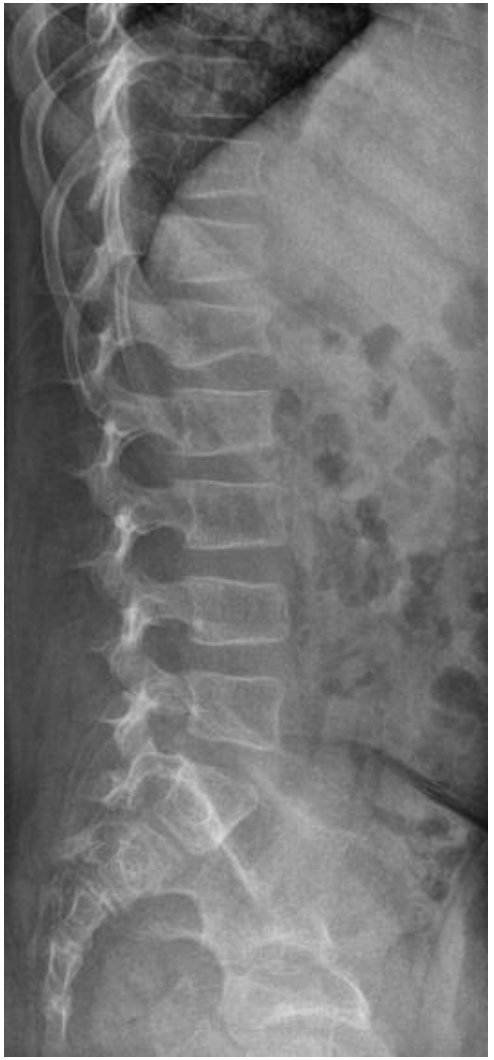


8 year old boy with undiagnosed chronic lung condition on GC since age 2 years

Bone morbidity with long term GC therapy

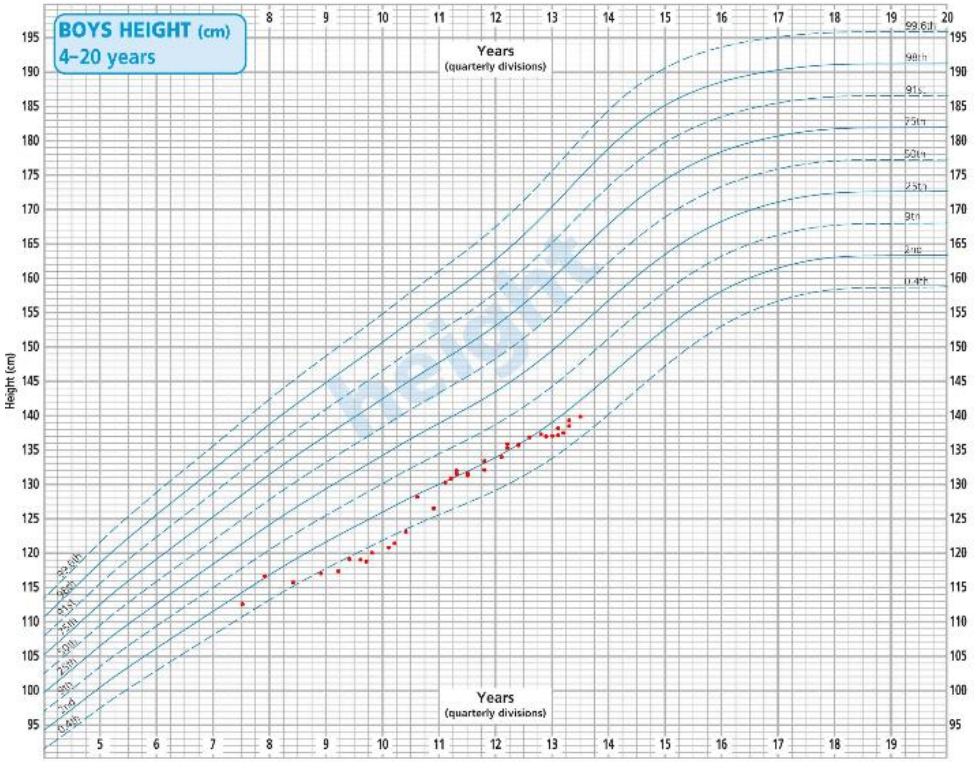


Multiple VF with severe back pain



VF identified from screening x rays, no pain

Delayed puberty in chronic illness



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)

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

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Pubertal abnormalities in adolescents with chronic disease

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Secondary adrenal insufficiency from long term use of GC

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

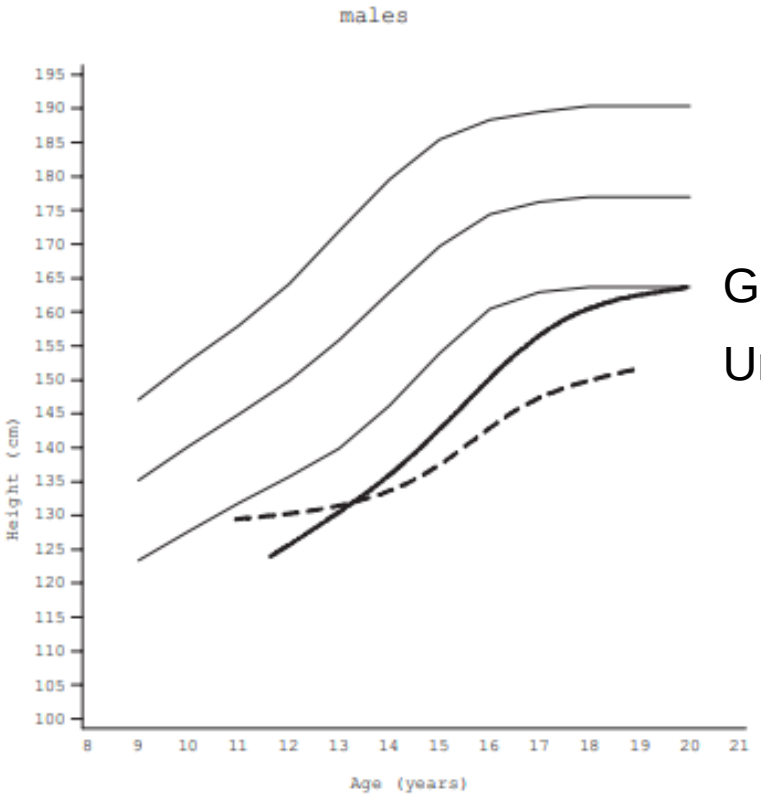
- Pred 1 mg equivalent to Hydrocortisone 4 mg
- Dexamethasone 1 mg equivalent to 20 mg Hydrocortisone

Need sick day steroid plan

Weaning plan if planning to discontinue and testing adrenal axis

Long term GH use in JIA

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



GH therapy

Untreated

Bechtold S et al J Clin Endocrinol Metab 2007

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%

Summary

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

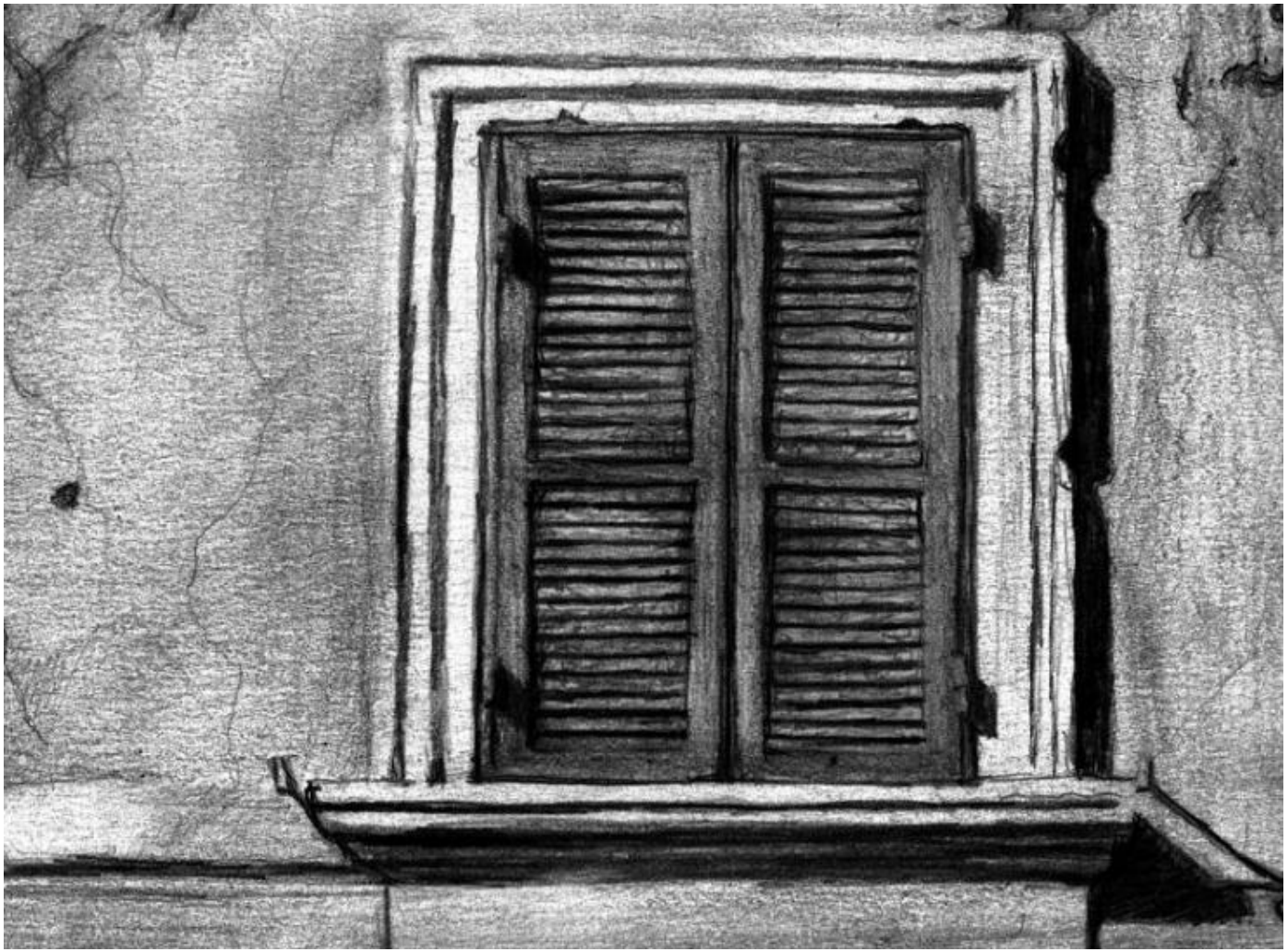
Regular height and weight monitoring (at least 6 monthly)

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.



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QUESTIONS

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