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Clinical applications of growth on medical ketogenic diets:

How to best manage pediatric patients

A.G. Christina Bergqvist MD
Professor of Neurology and Pediatrics
The Perelman School of Medicine
Director of the Ketogenic Diet Program
The Children's Hospital of Philadelphia
Philadelphia, PA 19103, USA
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Conflict of interest

I have been provided an honorarium for this presentation by Nutricia North America.

None of the above poses a conflict of interest or influences my presentation.

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Objectives

- Summarize literature related to patient's growth on the medical ketogenic diet
- Define elements of the medical ketogenic diet that affect growth in children
- Construct interventional plans to help manage growth

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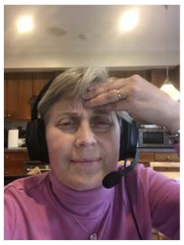
Ketogenic Diet ≠ Medical Ketogenic Diets



TREATMENT RESISTANT EPILEPSY

- IEO carbohydrate metabolism
- GLUT-1+PDH
- > 10 Other medical disorders

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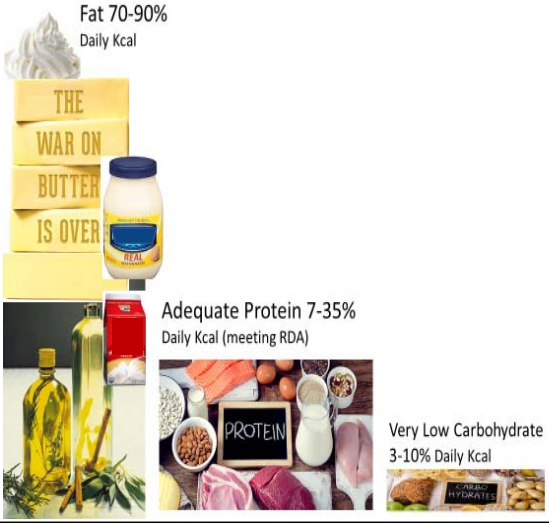
Ketogenic Diets



- Diet types
  - Classic KD
  - Gradual KD
  - MCT KD
  - Modified KD
  - Modified Atkins
  - Low Glycemic Index Diet
  - Prescribed by RD/MD
- Ratio
  - Ketogenic (gr) : Antiketogenic (gr)
  - 0.5-4:1
- Weighed/Measured/Calories restricted or counted
- Supplemented – nutritionally complete
- COMPLIANCE to be effective against seizures

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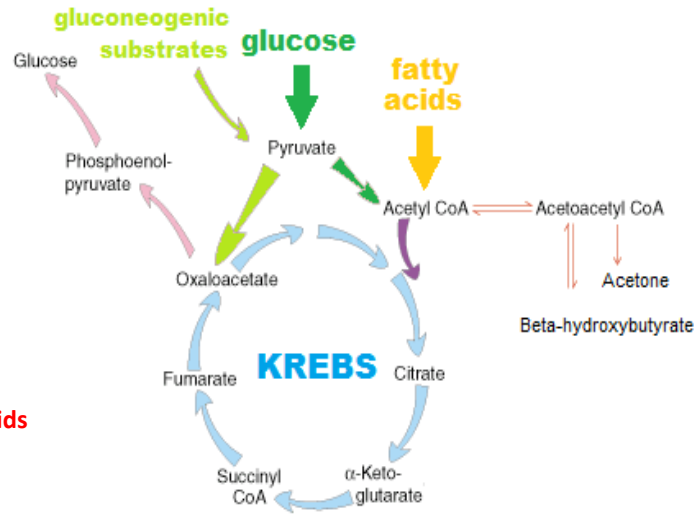
Metabolic changes with fasting and ketogenic diets

- Glucose drops
- Insulin drops
- Glycogen depleted- gluconeogenesis incr
- Fatty Acid oxidation
  - Increased energy production
- Ketone production
  - BHB
  - Acetoacetate
  - acetone

Acids



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Side Effects of Ketogenic Diet(s)

Short Term

- Metabolic shift into ketosis
- Tolerance of a fat diet
- Initiation practices

Long Term

- Chronic effects on the body by the metabolic/hormonal changes required to maintain ketosis
- Maintenance practices
  - Ratio (macronutrients, protein)
  - Calorie, fluid restriction
- Duration of KD
- Supplementation
  - Adequate
  - Compliance
  - Malabsorption

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Growth

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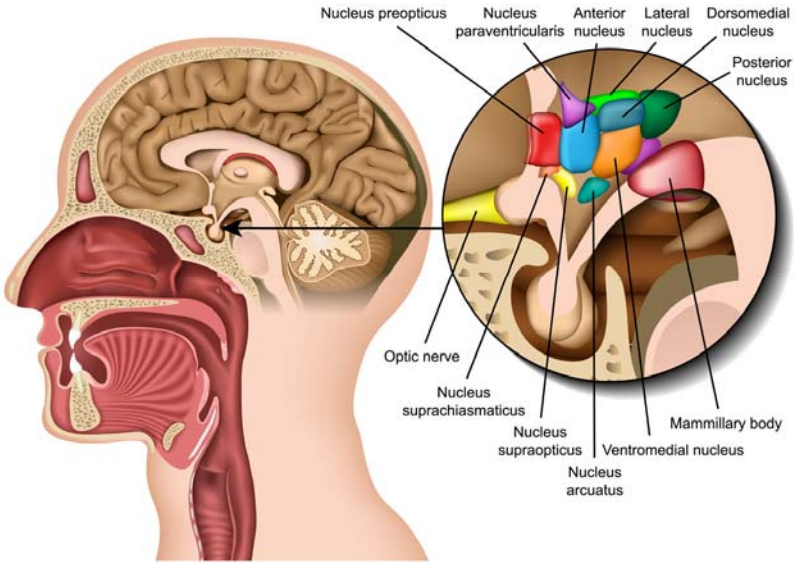
Hypothalamus

Greek *ὑπό* = *under* and *θάλαμος* = *room, chamber*



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Hypothalamic Function

Links the CNS to endocrine system
- (releasing hormones) to the pituitary

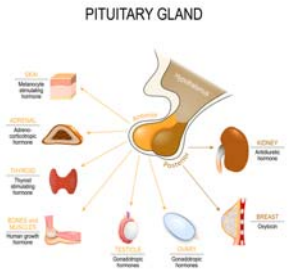
Growth

Homeostasis
- Body temperature, BP
- Food, water intake
- Hunger, thirst
- Metabolic rate

Emotion- fear

Sexual behavior, reproduction

Circadian Rhythm



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GH axis

Hypothalamus
- Arcuate nucleus releases GH releasing hormone

Pituitary

GH released pulsitile 2-3 AM
- Slow wave sleep, NREM 3
- Target cells in body, muscle, bone, tissue
- Feed back

IGF-1
- Major hormone related to linear growth in children together with GH. Made by liver bound to 6 different BP that regulates its availability to cells.
- Systemic organ growth including nerve growth

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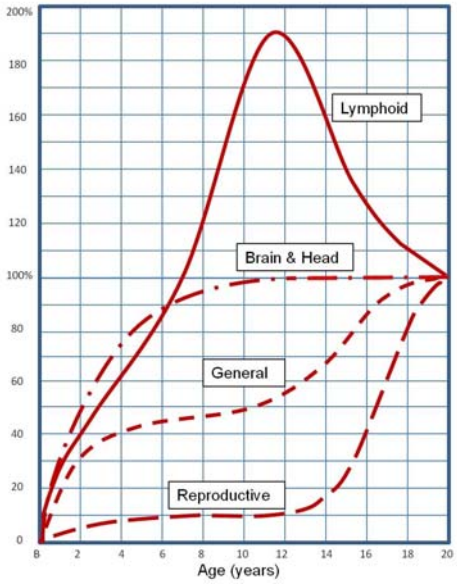
Post Natal Growth

- Brain matures fastest- continued pruning plasticity during life
- Somatic growth stepwise childhood adolescence
- Reproductive entering of puberty
- Lymphoid prepubertal



Harris et al; the measurement of man, Minneapolis, University of Minnesota Press 1930

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Growth Data – Study Design

Retrospective

- Charts, Email/Mail/ Phone
- Self reported
  - under report wt (f), over report ht(m)
- Cheaper, larger sample size, less-accurate

Prospective

- Clinic(s) Average Medical Assistant
- Supervised nurses
- Trained RD, Anthropometrist
- Expensive, Higher Quality Data, accurate

Difference: "2 inches"

Bridges et al, Ped Endocrinology 2010
O'Conner et al, J of Pediatrics 2009

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Weight

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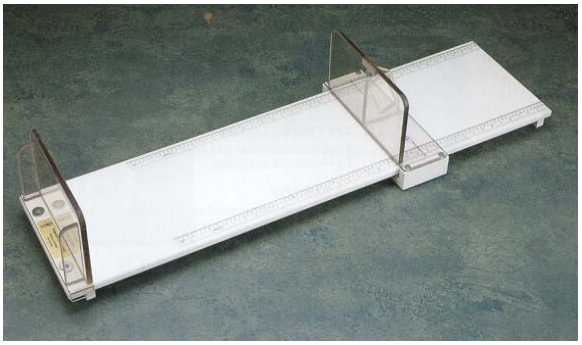
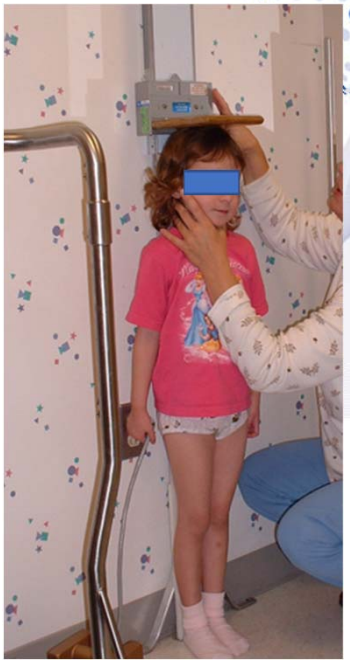
Length





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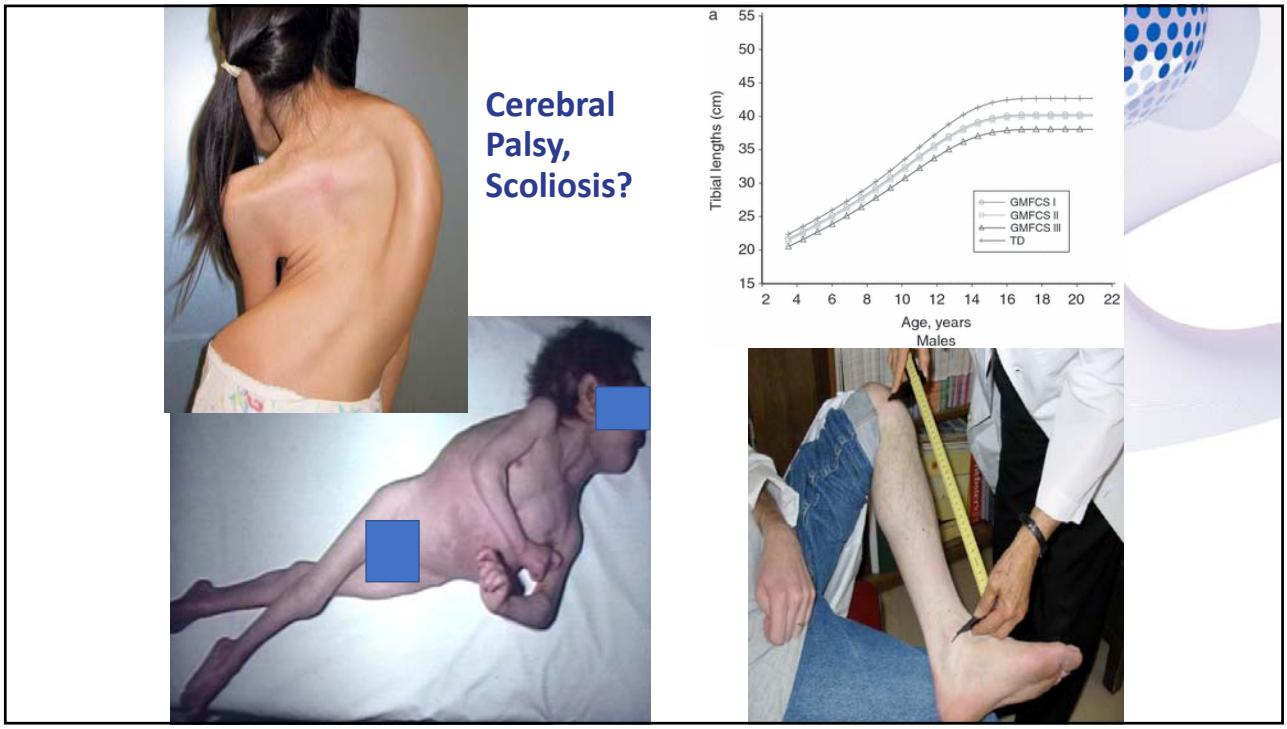

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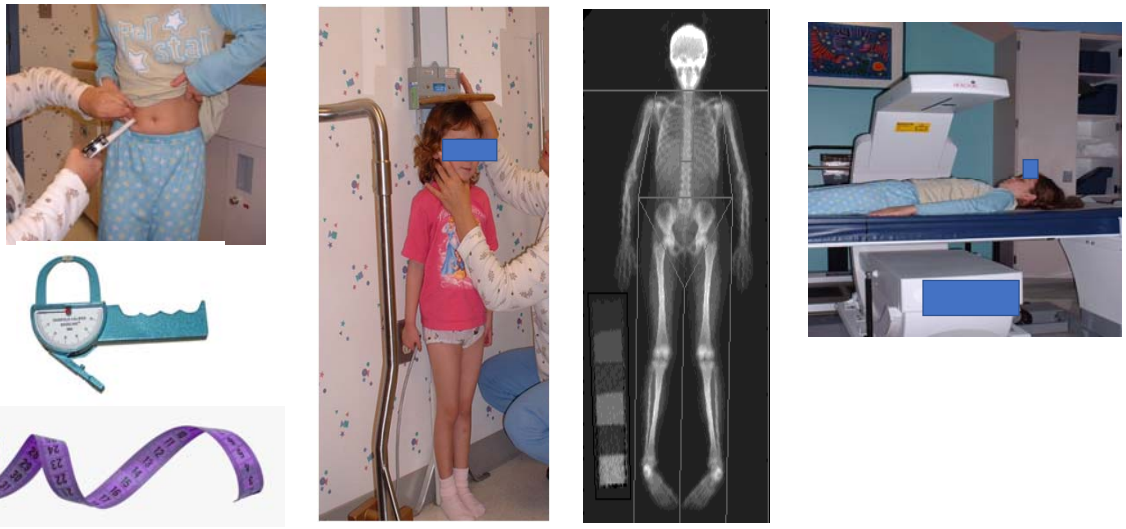
Growth Assessment Tools



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Z-scores

- Measurements have to be age and gender normalized to **Z-scores** for comparisons
- BMI = Wt (kg)/ Ht (m^2)
- Approximation for body composition
  - Does not tell you localized changes in body composition
  - Unchanged BMI-Z does not mean child is growing normally.
  - If both wt and ht velocity decrease, then BMI will be unchanged.
- Use with other measures of body composition
- Skinfolds, DXA, Bod Pod®, underwater weighing, etc.

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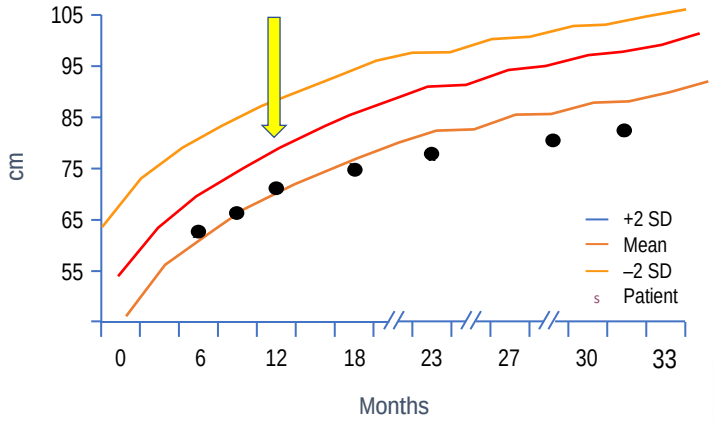
Height deceleration 6 mo on KD



*KD initiated at 12 months.

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Current growth studies on KD

1999- 2021, longer studies; Goal to measure growth

- Sample range 21-237 pts
- 5 retrospective, 7 prospective
- Quality of Data Collected
  - Anthopometrist
  - Mixed in other included Clinic Chart Data
  - Trained Nurse/RD for most
  - Parent recall, questionnaires

Short term studies – 3 to 6-month duration

- Couch et al 1999, Liu et al 2003 and Numis et al 2011
- Mixed results
- Design study too brief to show change,

General Design – Growth studies min 12 months

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Longer Term Studies

- 12 longer term prospective studies: Vining et al 2002, Williams et al 2002, Petersen et al 2005, Neal et al 2008, Spulber et al 2009, Bergqvist et al 2008, Groulau 2014, Lambrechts 2015, Svedlund 2019, Armeno 2019, Herrero 2020, and Liu 2021
- Children with drug resistant epilepsy (DRE) suboptimal growth at baseline. WAZ HAZ (-WAZ, -HAZ)
- All – deceleration of weight and height z-score over 12 months.
- HT velocity(cm/year) measured before and after KD.
  - -1 Z to to -3.5 Z-scores - Spulber et al
- Higher ketosis (blood and urine worse HAZ)
  - Peterson et al and Spulber et al
- Cerebral palsy did worse – Vining, Bergqvist,
- Young age worse – Vining, Bergqvist, Neil
- Ambulation – mixed results?

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Protein and growth on KD

KD prescription practices

- **Protein intake should meet RDA for age on all forms of KD**
- Classical KD may still be inadequate
- Gluconeogenesis – protein turned into glucose
- **Who is at Risk ?**
  - Calories restricted (classical KD) - very low kcal requirements
    - Prescribed <RDA protein
  - No show-failure to follow up
  - Doing well from sz stand point not coming for nutritional follow up

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CKD MCT KD Protein

MCT-KD vs KD – Neil et al 2008

- Prospective n=75 baseline, 3, 6, 12 mo (40 pt)
- **Protein (prt): 1.13 vs 1.67 g/kg/d**
- No difference both showed deceleration HAZ and WAZ group as a whole over time

CKD Protein to energy ratio – Nation et al 2014

- Retrospective n=35
- Min 6mo
- Poor growth - protein or cal < 80% RDA prt
- prt-energy ratio < 1.4g/prt/100kcal
- Recommended: Protein >1.5 g/100 kcal of KD

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MAD – Protein

Chen *et al, 2012*

- >3-4g/kg/day-protein
- N=54 children, >6 mo exposure.
- Growth data ? first 6 mo - ? weight loss
  - 15% < 10% HT at 6 mo – no discussion of change in ht.

Svedlund et al, 2019

- Protein intake not reported
- n= 38 Baseline - 2 yrs
- Growth – no change in WAZ 2 yrs
- HAZ baseline -0.4 no change over 2 yrs
- BMI baseline - 2 yrs increased

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Insulin like growth factor 1 (IGF-1)

- IGF-1 + GH important GF for linear growth in children
- Spulber et al found deceleration of IGF-1 Z-score from -1 to -3 Z-score over one year.
- Bergqvist found decreased in Z-score from 0 to -2.25 in 3 months then remained suppressed.
- Decline of BMC Z-score measured by DEXA in 2 measurements "whole body and AP spine" by > -0.5 Z score/year

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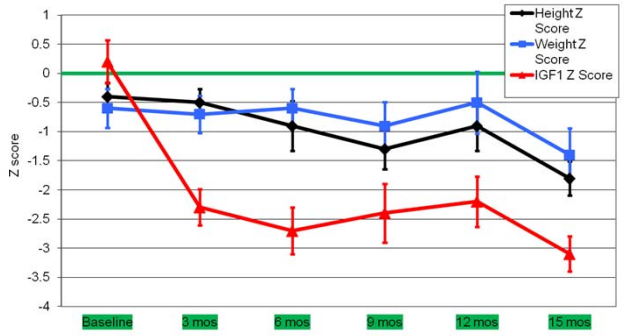
IGF-I, Height, and Weight Status in Children with IE over 15 Months of KD Therapy



Bergqvist et al, 2009

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Summary Growth Studies

- Short term studies unlikely to show change, growth studies, minimal study length12 month
- Deceleration of Height velocity, HAZ, WAZ
- Protein (small changes) intake no effect
- Lower ratio KD protective
- Young children at higher risk
- Cerebral palsy higher risk
- Caloric restriction higher risk
- Ambulation may be protective?
- Mediated via the GH and IGF-1 axis

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Management Options

- Growth hormone deficient
- rGH, 1985 available
- Benefits: Accelerated height velocity, adult heights, improved body composition, more FFM (muscle and bone).
- Side Effects: pain and/or redness injection site, transient fever, gynecomastia, arthralgia, edema, pseudotumor, insulin resistance, progressive scoliosis, slipped femoral epiphysis

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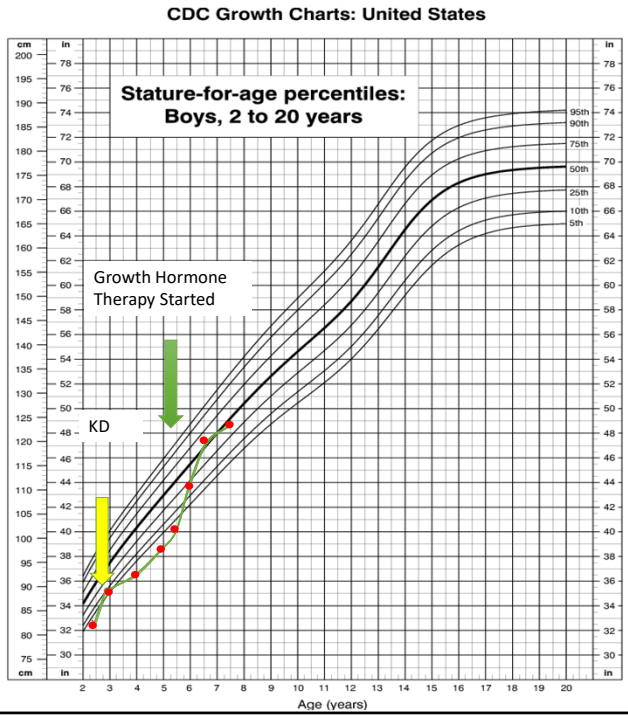

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Catch up growth?

Kim et al, 2013

- Retrospective, n=40 pt
- Deceleration HAZ during KD
- Catch up 1 year post KD
- Still suboptimal WAZ HAZ

For children in developing countries who have been malnourished, catch up growth is associated with early puberty, shorter final adult height.

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Soo What????

- Want a normal growth pattern for our children with DRE “if possible”.
- Abnormal body composition
  - Thin bones
  - Short statue
- Increased morbidities – fractures, lower QOL, increased cost
- Understanding growth may help us understand the mechanism(s) of the KD.
  - Abnormal IGF-1 associated with neurodegenerative disorders, autism etc.
  - IGF-1 “neurotrophic” growth hormone, via BDNF may affect synaptogenesis, linked to anti-epileptogenic effects of the KD?
  - Expanded use of KD cancer, GF affect tumor growth

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Macronutrient Composition of Current Dietary Therapies KD, Modified KD, LGIT

Macronutrient % daily cal	Fat %	Carb %	Protein %	Reduce sz	Side effects
American Diet	20-30	**55**	15-20	?	?
Ketogenic Diet 4:1	90	**3**	7	↑	↑
Modified KD <2:1 (MAD)	60-80	**3-10**	20-40		
LGIT < 1:1	60-70	**10 GI<50**	20-30		

- Weigh risk/benefit of KD with your current ratio and treatment at each visit
- Challenge: Recognize new side effects

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Bone Health and Epilepsy and AED

- Increased Risk of Fractures
  - Incidence of fractures 2-6x general population
  - Fractures with seizures and falls 30-60%
- AED direct effect
  - Increase turnover, osteoblast, clast
- AED indirect effect
  - Vitamin D shorten t1/2, inactive form
  - Acidosis steal from BMC, loss urine

Vestergaard, *Acta Neurol Scand, 2005*

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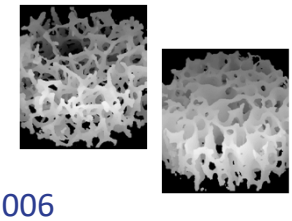
Children with epilepsy on KD are they at risk for osteopenia fractures?



- Hahn et al 1972
  - 5 pt, 2.5 year on KD vs. control vs. AED only
  - Reduced BMD in KD
- Bertoli et al 2002
  - 7 children, 6 mo KD
  - No change in BMC
  - Too short of a study
- Kang et al 2004
  - 19/129 pt osteopenia,
  - 4 by X-ray
  - 1 pathological fracture
- Grossbeck et al 2006
  - 28 children on KD >6 yrs
  - 21% fracture,
  - Time first fracture 1.5 yrs of KD therapy
  - 14% multiple fractures
- Bertoli et al 2014
  - 3 adult Glut-1 > 5y KD
  - Normal BMD before KD, normal BMD after KD

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Progressive BMC loss in Children with IE treated with the KD

25 pre-pubertal children >5yrs with TRE
- Normal control 847 children sex, age, race match

Age= 7.3 yr +1.9
- Race aa/w= 4/21

CP= 32%, Ambulating= 84%

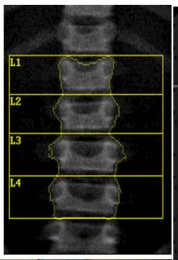
Intellectual disability= 68%

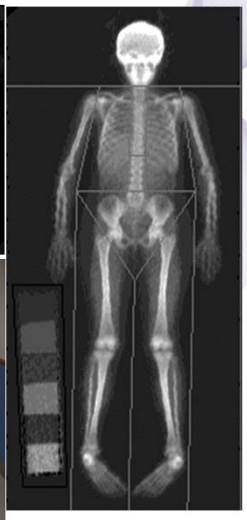
Failed average 8 AED

AED
- Baseline = 2.4±0.7
- 15 mo = 1.0 ±0.94
- 36% on KD only

Methods: WB & AP DXA

q 3 mo for 15 mo KD





Bergqvist et al, AJCN, 2008

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Bergqvist et al 2008 *AJ Clin Nutrition*

- Bone health in children with IE was **suboptimal**
- Progressive decline in BMC during the KD -0.4 to-0.7- Z score/yr, despite;
  - Improving Vitamin D
  - Adequate supplementation calcium
  - Reduced # AED
- The decline in BMC with deceleration in height velocities
- BMI z-score, age, and ambulation were positive predictors of BMC, which declined sharply over 15 months of KD treatment

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The effect of the KD on the developing skeleton

Methods

- KD prospective longitudinal n=63
- DXA baseline, 6 mo intervals (n=29)
- Blood: 25-OH Vitamin D, BsAlk phos, osteocalcin, urine ca/cr
- GMFCS- gross motor functional classification

Results: mixed effects models

- Baseline BMD -0.99 median – less mobile lower BMD
- Decrease of -0.16 BMD/year compared to age matched children similar decreased ht adjusted decreased BMAD 0.19/yr.
- Baseline better BMD larger negative change than those with lower baseline BMD
- Fractures 2/63 = 3% normal (12-36 fractures/1000 children year)
- Markers of Bone turn over not helpful

Simm et al 2017 Epilepsy Research

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The KD and its effects on BMD: A retrospective observational cohort.

- Retrospective observational cohort on KD >6 mo
- 68 patients, 20 had 2 DXA included
- Initial DXA BMD -1.32 ± 1.74
- Follow up DXA 20/68 – BMD 0.22 z-score/yr
- 6 fractures long bones
  - Improvements with bisphophonates

Draaisma et al 2019, Neuropediatrics

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Ketogenic Diet and Osteopenia

Ketosis

- Ketone bodies acids
- Acid load on skeleton, BMC used to buffer PH blood
- Changes in osteoblasts, osteoclast activity, not laying down BMC
- Changed renal conversion of vitamin-D
- Hormonal changes IGF-1 / binding protein

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Prospective study of growth and bone mass in Swedish children treated with the MAD.

- 38 children DRE and Glut -1/PDH Modified Atkins no control group
- Baseline, 1, 2 years
- 50% response rate
- WAZ, HAZ BMIZ suboptimal but stable over 2-year treatment, BMI increases x time
- IGF-1 dropped Bsln-1year then normalized, HAZ dropped 1 yr then improved
- 22/38 due to age - no negative BMC BMD over time
- Why Difference in two studies?
  - MAD isocaloric
  - More protein
  - Less acidosis average bhb 2 mmol/L (treatment citrate)
  - More physical activity
  - Higher baseline vitamin D levels food in Sweden supplemented, supplementation?

Svedlund et al 2019 J of Euro Pead Neuro Society

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Prevention – Treatment Low BMC

Screening with DXA yearly (>3 yrs)

- Pediatric reference data Z-scores
- ISCD 2013 Guidelines
- *Use Screening DXA primary or secondary disease, if results influence management, and there is treatment*

25-OH D in plasma – supplement

- Maximizing Calcium, Vitamin D, Magnesium supplementation and follow blood levels
- Maximizing exercise
- Weight-bearing use of standers or gait trainers for non-ambulating individuals

Endocrinology, nutrition, orthopedic colleagues

Severe osteoporosis and serial fractures

- Bisphosphonates

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CHOP's Dietary Treatments of Epilepsy Team

Medical Director
- Christina Bergqvist

Nurses
- Sarah Tefft
- Meghan Walker

Dietitians
- Cagla Fenton
- Sue Groveman
- Sarah Moran

Medical Chef
- Paige Vondran

Social Worker
- Alex Bullock

Clinical Pharmacologist
- Krishna Patel

Work Study Student
- Olivia Robinson

Coordinator
- Tiffany Molina

Collaborators
- Virginia Stallings, MD
- Babette Zemmel, PhD
- Adda Grimberg, MD
- Joan Schall, PhD
- Paul Gallagher, PhD

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