Metabolic Programming and Importance of Optimum Protein Intake for A Child's Long-term Health
Critical Phases of Growth that Promote Development of Obesity: From Intra-uterine Years to Preschool Years

Intra-uterine Life
- Growth patterns modify fat and lean body mass, neuroendocrine appetite control mechanisms, and pancreatic functional capacities\(^1,2\)

Infancy
- Catch-up growth\(^1\)
- Rapid weight gain during infancy (the growth acceleration hypothesis)\(^3\)

Pre-school years
- Early adiposity rebound (by 43 months)\(^2\)

Metabolic Programming/Developmental Plasticity: Origin of Non-Communicable Diseases

Metabolic programming

Induction, deletion, or impaired development of a somatic structure by an early life stimulus\(^1\)

Alterations in nutrient and hormonal milieu during critical periods of growth and development may alter foetal genome expression; this leaves a lasting impact on physiological structures and functions.\(^2\)

Early-life Programming and Implications for Health in Adulthood

Dr. H.T. Wickramasinghe


Thrifty Phenotype Hypothesis
Epigenetic Modifications and Under Nutrition Early in Life: Association with Metabolic Diseases Risk

Epigenetic modifications\(^1,^2\)
DNA methylation and/or nucleoprotein acetylation/methylation

Adequate nutrition

Undernutrition

Involved in normal physiological functions

May lead to increased risk of metabolic diseases

1. De Oliveira JC. NutrMetab. 2012;9(80)
The Mesengenic Process

THE MESENGENIC PROCESS

Mesenchymal Stem Cell (MSC)

Proliferation
- Osteogenesis
- Chondrogenesis
- Myogenesis
- Mast Cell Proliferation
- Tendogenic/Ligamentogenesis
- Adipogenesis
- Other

"Commitment"
- Transitory Osteoblast
- Transitory Chondrocyte
- Transitory Myoblast

Lineage Progression
- Osteoblast
- Chondrocyte
- Myoblast Fusion
- Transitory Stromal Cell
- Transitory Fibroblast
- Preadipocyte
- Early Adipocyte

Differentiation
- Osteocyte
- Hypertrophic Chondrocyte
- Myotube
- Stromal Cells
- T/L Fibroblast
- Adipocyte
- Dermal and Other Cells

Maturation
- Bone
- Cartilage
- Muscle
- Marrow
- Tendon/Ligament
- Adipose Tissue
- Connective Tissue

Mesenchymal Tissue

Bone Marrow/Periosteum

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Methylation Glimpse

- Animal Base Protein
  - Choline
  - B12
- Vegetables & Fruits
- Nuts & Seeds

B6 difficult without grains

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Annu Rev Med. 2009;60:39-54
Epigenetics

- How characteristics are inherited across cell or organism generations without changes in the DNA sequence itself
- Heritable traits of this kind might be influenced by the environment
- Modern version of ‘Nature versus Nuture’

Agouti Mouse

- The new field of epigenetics is showing how your environment and your choices can influence your genetic code — and that of your kids

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ALSPAC study

- The UK Avon Longitudinal Study of Parents and Children (ALSPAC) is a long-term health research project involving more than 14,000 mothers enrolled during pregnancy in 1991 and 1992.

- Analysing data from the study, researchers showed that the sons of fathers who smoked before puberty had a significantly greater body mass index (measure of obesity) at 9 years of age: 18.15 compared with 17.23 in sons of fathers that never smoked [1].

- But there was no effect on the body mass index of the daughters.

ALSPAC--the Avon Longitudinal Study of Parents and Children. I. Study methodology. Golding J1, Pembrey M, Jones R; ALSPAC Study Team.
Overkalix epidemiological study

- Research has shown from the analysis of old records of people born in 1890, 1905, and 1920 from Overkalix, an isolated community in Northern Sweden, that there is an association of ancestral food supply with longevity and death from cardiovascular disease and diabetes.

- The records showed that the paternal grandfathers’ food supply during mid childhood was indeed linked to the risk of death in grandsons, but not in grand-daughters. Poor availability of food was associated with reduced risk of death in grandsons by 35 % while good availability of food was associated with increased risk of death by 67 % compared with controls.

- In contrast, the nutritional status of the paternal grandmother had no influence on the grandsons, but affected the granddaughter in a similar way. Good food availability increased the risk of death for grand-daughters by 113 %, while poor food availability decreased the risk of death by 49 percent.
Early-Life Undernutrition as a Programming Stimulus for Paediatric Obesity

Undernutrition in pregnant women has been linked to low-birth-size infants and increased risk of developing glucose intolerance and obesity later in life.

Disposition to overweight and obesity is not solely determined by genetic make-up.

Protein intake exceeding metabolic requirements, (>15% of energy) may increase weight gain during infancy and the risk of developing obesity in childhood.

**Mechanism of the Early Protein Hypothesis**

- **Protein in excess of metabolic requirements**
  - Enhances secretion of insulin and insulin like-growth factor-1 (IGF-1)
  - Decreases human growth hormone and lipolysis

- **Early growth (first 2 years)**
- **Adipocyte activity (differentiation)**

# Optimal Protein Intake in Infants: Striking A Balance

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Weight (kg)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>WHO/FAO/UNU Recommendation 2007</th>
<th>BOYS</th>
<th>GIRLS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safe level of protein intake (g/kg/day)</td>
<td>Safe level of protein intake (g/day)</td>
<td>Weight (kg)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Safe level of protein intake (g/kg/day)</td>
</tr>
<tr>
<td>0.1</td>
<td>0.177</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>1.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td>1.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td>1.24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>1.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10.2</td>
<td>1.14</td>
<td>11.6</td>
<td>9.5</td>
</tr>
<tr>
<td>1.5</td>
<td>11.5</td>
<td>1.03</td>
<td>11.8</td>
<td>10.8</td>
</tr>
<tr>
<td>2</td>
<td>12.3</td>
<td>0.97</td>
<td>11.9</td>
<td>11.8</td>
</tr>
<tr>
<td>3</td>
<td>14.6</td>
<td>0.90</td>
<td>13.1</td>
<td>14.1</td>
</tr>
<tr>
<td>4–6</td>
<td>19.7</td>
<td>0.87</td>
<td>17.1</td>
<td>18.6</td>
</tr>
<tr>
<td>7–10</td>
<td>28.1</td>
<td>0.92</td>
<td>25.9</td>
<td>28.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>WHO reference values

- Mean safe level of protein intake reduces with age
- Safe intake of protein (PE%) according to WHO requirements
  - **6-month-old:** 7.7 PE%
  - **2.5-year-old:** 5.2 PE%

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Optimal Protein Intake in Infants: Striking A Balance


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Optimal Protein Intake by age in Toddlers: Striking A Balance

Protein intake for infants and children (boys and girls)²


Alternatively, protein intake during the second year of life may impact the development of obesity later in life.

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How an infant is fed is as important as what an infant is fed

Bottle feeding of Formula or Breastmilk and Weight Gain in the First 12 months

Monthly Weight gain (g/month)

<table>
<thead>
<tr>
<th></th>
<th>Monthly Weight Gain (g/month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BREASTFED</td>
<td>2</td>
</tr>
<tr>
<td>HM &amp; FORMULA BY BOTTLE</td>
<td>37 (n=107) P = 0.08</td>
</tr>
<tr>
<td>FORMULA BY BOTTLE</td>
<td>71 (n=2016) P &lt; 0.001</td>
</tr>
<tr>
<td>HM BY BOTTLE</td>
<td>89 (n=34) P = 0.02</td>
</tr>
</tbody>
</table>

Adapted. Li R et al Arch Pediatr Adolesc Med 2012
During complementary feeding

Protein content in the diet of an exclusively breastfed child increases by 3–4 fold.

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## Weight Gain in Infants related to the Nutritional Composition and Volume of the Milk Consumed

<table>
<thead>
<tr>
<th>Volume consumed</th>
<th>On day 1</th>
<th>On day 7</th>
<th>After day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Milk</td>
<td>21.5±4.2 mL/day</td>
<td>495.3±33.4mL/day</td>
<td>673.6 ± 29 mL/day</td>
</tr>
<tr>
<td>Formula Milk</td>
<td>170.5 ± 55.8mL/day</td>
<td>NA</td>
<td>761.8 ± 18 mL/day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average Energy Intake</th>
<th>Breast Milk</th>
<th>12 kcal/day</th>
<th>440 kcal/day (day 14-6 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula Milk</td>
<td>114 kcal/day</td>
<td></td>
<td>513 kcal/day (day 14-6 weeks)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average Protein Intake</th>
<th>Breast Milk</th>
<th>0.5 g</th>
<th>8.8 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula Milk</td>
<td>2.4 g</td>
<td></td>
<td>10.7 g/day</td>
</tr>
</tbody>
</table>

- **Hester SN. J Nutr Metab. 2012;2012:891201**

**Dr. H.T. Wickramasinghe**
The European Childhood Obesity Trial or CHOP study included 1138 healthy, formula-fed infants and 619 exclusively breastfed children

**Lower protein**: 1.77 g protein/100 kcal (7.1 PE%) and 2.2 g protein/100 kcal (8.8 PE%), respectively

OR

**Higher protein**: 2.9 g/100 kcal (11.7PE%) and 4.4 g protein/100 kcal (17.6 PE%), respectively for the first year.

Length, weight, weight-for-length, and BMI increase was lower for breastfed than for higher-protein formula-fed children between baseline and at 12 months of age.

High Protein Intake during Infancy and Early Childhood on Body Composition at 7 Years: The DONALD Study

Findings of the DOortmund Nutritional and Longitudinally Designed (DONALD) Study, which evaluated the impact of high protein intake during infancy and early childhood on body composition at 7 years, indicated that:

| Early protein intake is associated not only with a higher BMI but also with a higher %body fat in mid-childhood. | A high protein intake at 12 months of age may result in later adiposity if high protein intake is maintained throughout the second year of life. |

Optimal Protein Concentration of Formula to Slow Down Fast Growth

Data from 3 pooled studies indicated that

- Children born to overweight or obese mothers had accelerated growth during the first year of life, even when breastfed.

- An increase in the protein content of formulas of 1 g/100 kcal caused an increase in weight gain of 287 g between 3 and 12 months.

- Formulas with a protein content that was just moderately above that of human milk supported normal growth while significantly slowing down fast growth.

Reducing the protein content in infant formulas near to the levels of breast milk for infants beyond 3–4 months of age may slow down fast growth if breastfeeding duration is <3 months.

Low Protein Content and Lower Obesity Risk in School-Aged Children: Childhood Obesity Project

Comparison of formula fed infants (n=1090) who received higher protein or lower protein content formula vs. breastfed infants (n=588)

Infant formula with a lower protein content decreases the risk of obesity at school age

Infant foods that provide excessive protein intake should be avoided to decrease childhood obesity


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Benefits of Early Interventions in Later Health

Optimal protein with right composition, concentration and conformation will have favorable amino acid profile and antigenic signature which may help in healthy metabolic programming, weight gain growth and immunity.


Early dietary interventions and feeding during infancy may carry a window of opportunity to prevent a greater risk of metabolic and related diseases in later life.
Development of obesity begins *in utero* and continues into preschool years.

During the sensitive development stages, nutrition and hormones influence gene expression through **epigenetic processes** that trigger early metabolic programming which can lead to the development of obesity.

Undernutrition during pregnancy has been linked to low-birth-size infants and increased risk of developing glucose intolerance and obesity later in life.

Higher protein content of infant formula is associated with obesity; hence, optimal composition, concentration and conformation near to the level of breast milk may help in healthy metabolic programming, weight gain growth and immunity.
Case Discussion on Obesity
Assessment of Paediatric Obesity

BMI (Kg/m²) is an accepted and the most feasible index to assess obesity in clinical practice.

Internationally established BMI cut-offs are not well defined in children due to significant effects of age, gender, pubertal status, and race/ethnicity on growth.

Average BMI value varies with age from 13 kg/m² at birth to 17 kg/m² at the age of 1 year, 15.5 kg/m² at 6 years, and then increases to 21 kg/m² at 20 years.¹

BMI: Body mass index

¹ IAP. Indian Pediatrics. 2004;41:559–575.
**Cut-offs for Assessing Paediatric Obesity**

WHO growth standards are commonly used for assessing paediatric obesity

<table>
<thead>
<tr>
<th>Z-score (percentile)</th>
<th>BMI category for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 (99)</td>
<td>Obese</td>
</tr>
<tr>
<td>&gt;2 (97)</td>
<td>Overweight</td>
</tr>
<tr>
<td>&gt;1 (85)</td>
<td>Risk of overweight</td>
</tr>
<tr>
<td>0 (50)</td>
<td>Normal</td>
</tr>
<tr>
<td>&lt;-1 (15)</td>
<td>Normal</td>
</tr>
<tr>
<td>&lt;-2 (3)</td>
<td>Wasted</td>
</tr>
<tr>
<td>&lt;-3 (1)</td>
<td>Severely wasted</td>
</tr>
</tbody>
</table>

Based on the height and weight of the child, the **BMI was found to be 22.2**, placing the BMI-for-age **above the 99th percentile** for boys age of 4 years.

BMI: Body mass index

Khadilkar V. *Indian J Endocrinol Metab.* 2011;15 Suppl 3:S166–

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Role of Maternal Obesity and Gestational Diabetes on Child’s Weight Gain

There is extensive evidence to confirm the association between maternal factors (including increased BMI and gestational diabetes) with paediatric obesity.¹

Maternal adiposity and its effects: developmental programming on the child¹

Role of Parental Feeding Practices and Diet in Determining Obesity in Children

Parental attention to hunger and satiety cues

1. Parental inattention to a child’s hunger or satiety cues has been positively associated with overfeeding or overweight in infants.

Parental attention to hunger and satiety cues

- Total energy intake is positively linked with risk of paediatric obesity.1
- Substituting carbohydrate-rich foods (fruit and vegetables, which are low in protein and calories) with other energy-dense foods will impact diet quality.
- Consumption of sweetened sugar beverages increases the risk of obesity by 2.57 times compared to normal children.2

Role of Protein Intake in Early Years

Alterations in the quality and quantity of nutrients consumed by infants during the first year of life may affect developing tissues\(^1\)

Mechanism of the Early Protein Hypothesis\(^3\)

Protein in excess of metabolic requirements

Enhances secretion of insulin and insulin like-growth factor-1 (IGF-1)

Decreeses human growth hormone and lipolysis

- Early growth (first 2 years)
- Adipocyte activity (differentiation)

Role of Sedentary Behavior in Paediatric Obesity

- Sedentary behaviors such as television viewing, use of cellular phones, playing video games and browsing the internet should be limited.\(^1,2\)

- More than 2 hours per day of TV viewing has been significantly associated with increased BMI and adiposity in young children.\(^3\)

Parents should be advised to avoid punishing children for being physically active and withholding physical activity as a punishment.\(^3\)

References:
Weight Loss Goals for Children

- To reduce BMI until it is <85th percentile\(^1,2\)
  - Long-term monitoring of BMI
  - Short-term (<3 months) monitoring of weight changes
- Resolution of comorbidities associated with obesity

<table>
<thead>
<tr>
<th>Age group</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>No defined targets</td>
<td>No defined targets</td>
</tr>
<tr>
<td>2–5 years</td>
<td>Weight maintenance</td>
<td>Maximum weight loss of 1 lb/month</td>
</tr>
<tr>
<td>6–11 years</td>
<td>Weight maintenance</td>
<td>≥ 99th percentile: Maximum weight loss of 1 lb/month  &gt;99th percentile: Maximum weight loss of 2 lb/week</td>
</tr>
<tr>
<td>12–18 years</td>
<td>Weight maintenance</td>
<td>Maximum weight loss of 2 lb/week</td>
</tr>
</tbody>
</table>

1 lb: 0.5 kg; 2 lb: 1 kg

Dietary and Lifestyle Interventions

Weight loss goal
• Moderate weight loss (≤1 kg/week)

Dietary and Behavioral Intervention
• Regular family meal with fruits and vegetables
• No sugar-sweetened foods and eating out
• ≥1 h of physical activity
• ≤2 h of screen time daily
• Monthly follow-up

After 3 months of lifestyle intervention, the patient reported a weight loss of 4.0 kg.

BMI: Body mass index; LDL: Low-density lipoprotein.