Protein and Obesity

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Outlines

- Overview of Childhood Obesity Epidemic in Malaysia
  - Young children and Adolescents
  - Morbidity

- Metabolic Programming of Obesity

- Protein Intake in Early Infancy: Long-term Effects
  - Obesity
  - Visceral Adiposity
  - Carotid Intima Media Thickness
  - Growth
  - Brain development

- Early Protein Intake: Mechanism of Action

- Early Protein Intake: Other Studies
Prevalence of Overweight in Adults

Malaysia is leading in the prevalence of obesity among Southeast Asian countries.

Adult prevalence in some Asian Countries
(overweight + obesity)

Malaysia
Thailand
Singapore
Taiwan
Japan
Philippines
Indonesia
Vietnam

WHO collaborating centre for obesity prevention- Deakin Uni. Australia
5.4% or over 477,000 children below the age of 18 years were obese in Malaysia (NHMS 2011).
Nationwide Nutrition Survey (N=3542); aged 6 months to 12 years

Fig 1: Prevalence of Childhood Overweight and Obesity Status in Children (6 months–12 years)

- Overweight: 9.8%
- Obesity: 11.8%

Fig 2: Gender and Regional Comparisons of Childhood Obesity

- Boys:
  - Rural: 9.9%
  - Urban: 15.1%
- Girls:
  - Rural: 6.5%
  - Urban: 10.2%

1 in 5 children in Malaysia is overweight or obese.

*Distribution of schoolchildren by BMI-for-age

*Data from Global School-based Student Health Survey, 2012 Fact Sheet; overweight = >+1SD, obese = >+2SD from median for BMI by age
Prevalence of Childhood Obesity (NHMS)

National Health and Morbidity Survey

Percentage (%)

2006
2011
2015
Children who remained obese beyond the first decade of life, **80%** went on to become overweight adults.


Obese children become obese adults

- An obese 7 year old has 40% chance
- An obese teenager has 70% chance
Waist circumference for Malaysian children (age 6-16 years) at 90\textsuperscript{th} percentile

The IDF Definition
(for age 10 to <16 years old)

Metabolic syndrome: presence of **abdominal obesity** and 2 or more of these criterias:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (WC)</td>
<td>≥90th percentile</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>≥1.7 mmol/L</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>&lt;1.03 mmol/L</td>
</tr>
</tbody>
</table>
| Blood Pressure                  | Systolic ≥130 mmHg OR
|                                 | Diastolic ≥85 mmHg |
| Glucose                         | ≥5.6 mmol/L    |
|                                 | (If ≥5.6mmol/L [or known T2DM]) |

The IDF Consensus Definition of Met Synd in Children and Adolescents, Pediatric Diabetes 2007
Obesity: Why the concern?

- No 5 of 10 leading risk factors causes of death
- No 4 in middle income countries → Malaysia

Global Health Risks WHO 2009

- Obesity
- Metabolic Risk
- Metabolic Syndrome
- CVD T2DM

Hypertension
Dyslipidaemia
Insulin Resistance
Health Implications of Childhood Obesity

**Long-term impacts**
- Psychological problems\(^4\)
- Cardiovascular disease\(^3\)
- Type 2 diabetes\(^5\)
- NASH, Cirrhosis, HCC
- Infertility
- Increased mechanical load\(^5\)
- Sleep apnoea, orthopaedic pain\(^5\)

**Short-term impacts**
- Low self esteem\(^4\)
- Hypertension, Dyslipidaemia\(^1\)
- Insulin resistance\(^1\)
- NAFLD
- Timing of thelarche, menarche\(^3\), PCOS

**Adult Obesity\(^5\)**
Typical phenotype of T2DM
Metabolic Programming of Obesity
Early nutrition and late outcome

Early nutrition

Dietary habits

Infancy? Early childhood?

Metabolic programming

Late health outcome

Which nutrients?
Which hormones?
Which life period?
Adipogenesis

In humans adipogenesis is observed in fetal and early postnatal life

Granado M, Obesity Facts 2012
IGF-1 and Growth

- Insulin like growth factor -1 (IGF-1) is structurally and functionally similar to insulin

- IGF-1 plays a role in:
  - regulation of postnatal human growth*
  - regulation of intrauterine growth: IGF-1 levels in cord blood correlate with birth weight **

- **IGF-1 mediates proliferation and differentiation of preadipocytes to mature adipocytes***

High Protein Intake in Infancy: Long-term Effects
Comparison of protein fractions from human and cow’s milk

Total proteins:
- Human milk: 0.89 g/dl
- Cow milk: 3.30 g/dl

- It is virtually impossible to obtain an amino acid profile that is similar to human milk with the usual ingredients (skim milk and whey)
- Necessity to give more protein to have enough of the limiting amino acids
Protective effect of breast milk in later obesity

**Fig. 2.** Effect of breastfeeding vs. formula feeding on childhood obesity: covariate-adjusted odds ratios of 9 studies and pooled adjusted odds ratio (AOR). Adapted from Owen et al. [30].
Rapid weight gain in infancy or first 2 years of life*
Increased obesity risk to adulthood

*16 studies

Nettleton et al, Ann Nutr Metab 2014
<table>
<thead>
<tr>
<th>Age interval (months)</th>
<th>Growth</th>
<th>Losses</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>0-1</td>
<td>1.03</td>
<td>0.95</td>
<td>1.98</td>
</tr>
<tr>
<td>1-2</td>
<td>0.78</td>
<td>0.93</td>
<td>1.71</td>
</tr>
<tr>
<td>2-3</td>
<td>0.56</td>
<td>0.90</td>
<td>1.46</td>
</tr>
<tr>
<td>3-4</td>
<td>0.38</td>
<td>0.89</td>
<td>1.27</td>
</tr>
<tr>
<td>4-12</td>
<td>0.24</td>
<td>0.92</td>
<td>1.16</td>
</tr>
</tbody>
</table>
High protein supply compared to infant needs
FAO/WHO/UNU recommended protein intake: does it matter?
Formula fed infants compared to breast fed infants

• ↑protein intake → ↑ serum AA
• ↑serum IGF-1 levels*
• Accelerated growth from 4-6 months of life**

...but multifactorial influence in observational studies does not prove cause-effect relationship

*Hoppe C, Am J Clin Nutr 2004
### Childhood Obesity Project (CHOP): RCT

<table>
<thead>
<tr>
<th></th>
<th>Infant formula</th>
<th>Follow on formula</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower protein</td>
<td>Higher Protein</td>
</tr>
<tr>
<td>N=540 infants</td>
<td>N=550 infants</td>
<td>Lower protein</td>
</tr>
<tr>
<td>N=550 infants</td>
<td>Higher protein</td>
<td>Higher protein</td>
</tr>
<tr>
<td>Energy</td>
<td>g/100ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>69.9</td>
<td>69.8</td>
</tr>
<tr>
<td></td>
<td>72.7</td>
<td>72.5</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>g/100ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>7.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Proteins</td>
<td>g/100ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.25</td>
<td>2.05</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Proteins % energy</td>
<td>g/100ml</td>
<td></td>
</tr>
<tr>
<td>Proteins</td>
<td>% energy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.1</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>8.8</td>
<td>17.6</td>
</tr>
<tr>
<td>Lipids</td>
<td>g/100ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Koletzko B, AJCN 2009
European Childhood Obesity Project Study (CHOP)

Healthy newborns (n=1138)

- Breastfed Approx. 4mo (n=298)
- Bottlefed from 1st mo (approx. N=700)
  - Low protein
    - 1.77g/100kcal
    - 2.2g/100Kcal (n=313)
  - High protein
    - 2.9g/100kcal
    - 4.4g/100Kcal (n=323)

Regular follow-up visit (3, 6, 12, 24mo, every 6mo up to 6years)
Growth, markers of obesity, feeding, behavior, health, biochemical markers
CHOP Trial

Weight-for-length

Increased BMI at 2y

No difference in length-for-age

**Long-term follow up of CHOP Trial**

RCT, childhood obesity project (CHOP study), 1678 healthy term infants enrolled in 5 European countries

**Lower protein content in IF reduces BMI and obesity risk at school age**

**Infant diet and BMI until early school age**


Cochrane Review, 55 studies on obesity prevention in children: mean BMI effect -0.15 kg/m² (95% CI -0.21 to -0.08)

Low protein intake in infants: BMI -0.51 kg/m²
Lower protein content in IF reduces BMI and obesity risk at school age.
Visceral fat - CHOP Trial

- age 5 years
- 275 children
  - subcutaneous fat (SC)
  - pre-peritoneal fat (PP)
- PP - marker of visceral fat

Gruszfeld D, Nutr Metabol Cardiovasc Dis 2016
<table>
<thead>
<tr>
<th></th>
<th>Intervention formula</th>
<th>Comparison of HP vs. LP</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Lower Protein N = 97</td>
<td>Higher Protein N = 86</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple linear regression</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Median [IQR]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>minimally adjusted estimated difference (95% CI)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-value</td>
<td>fully adjusted estimated difference 95% CI *</td>
</tr>
<tr>
<td>SC fat layer (cm)</td>
<td>0.258 [0.148; 0.397]</td>
<td>0.245 [0.177; 0.410]</td>
<td>0.036</td>
</tr>
<tr>
<td>PP fat layer (cm)</td>
<td>0.432 [0.330; 0.553]</td>
<td>0.501 [0.377; 0.637]</td>
<td>0.052</td>
</tr>
<tr>
<td>SC fat area (cm²)</td>
<td>0.242 [0.144; 0.373]</td>
<td>0.244 [0.166; 0.396]</td>
<td>0.037 (-0.031; 0.104)</td>
</tr>
<tr>
<td>PP fat area (cm²)</td>
<td>0.360 [0.273; 0.470]</td>
<td>0.427 [0.322; 0.540]</td>
<td>0.052 (0.002; 0.102)</td>
</tr>
<tr>
<td>SC/PP fat area</td>
<td>0.692 [0.397; 1.080]</td>
<td>0.665 [0.416; 1.000]</td>
<td>-0.018 (-0.159; 0.124)</td>
</tr>
</tbody>
</table>

Visceral adiposity at 5y of age is increased with high protein intake in infancy
• Carotid intima-media thickness (cIMT) measured at 5 years

• Measurement of carotid artery IMT is recommended for cardiovascular risk assessment in asymptomatic adults
### IMT- CHOP Trial

- **cIMT was associated with ApoA1**

<table>
<thead>
<tr>
<th></th>
<th>Higher protein (HP)</th>
<th>Lower protein (LP)</th>
<th>p value HP vs. LP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>cIMT (mm) Median [IQR]</td>
<td>N</td>
</tr>
<tr>
<td>All</td>
<td>125</td>
<td>0.38 [0.32;0.45]</td>
<td>133</td>
</tr>
<tr>
<td>Boys</td>
<td>72</td>
<td>0.38 [0.32;0.45]</td>
<td>61</td>
</tr>
<tr>
<td>Girls</td>
<td>53</td>
<td>0.37 [0.32;0.45]</td>
<td>72</td>
</tr>
</tbody>
</table>

Cardiovascular risk at 5y of age is not increased with high protein intake in infancy

Gruszfeld D, Ann Nutr Metab 2015
Safety of less protein: normal length growth

<table>
<thead>
<tr>
<th></th>
<th>Convent. Protein</th>
<th>Reduced protein</th>
<th>Breast fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (cm)</td>
<td>51.89±3.03</td>
<td>51.96±2.92</td>
<td>51.65±2.45</td>
</tr>
<tr>
<td>6 yrs. (cm)</td>
<td>116.86±4.74</td>
<td>117.25±4.52</td>
<td>116.78±5.26</td>
</tr>
<tr>
<td>Baseline (SDS)</td>
<td>-0.22±1.00</td>
<td>-0.24±1.02</td>
<td>-0.01±1.05</td>
</tr>
<tr>
<td>6 yrs. (SDS)</td>
<td>0.23±0.94</td>
<td>0.30±0.88</td>
<td>0.22±1.03</td>
</tr>
</tbody>
</table>

⇒ Reduced infant formula protein is safe for longitudinal growth

Weber etal, *AJCN 2014*
Protein intake and growth velocity

- **RCT** (194 infants)
  - EXPL 1.61 g/100 kcal
  - CTRL 2.15 g/100 kcal

- **1.61 g/100 kcal formula supports normal growth**

Ziegler E, JPGN 2015
Growth studies with formula containing 1.8g protein/100 kcal show growth close to the WHO standard

- Result of a meta-analysis of 5 studies with reduced protein formula (1.8g/100kcal) with modified whey

Safety of less protein: neuropsychological development

- Neuropsychological test battery, 8yrs
  Visual, selective, focused & sustained attention, visual-perceptual integration, processing speed, visual-motor coordination, verbal fluency & comprehension, impulsivity/ inhibition, flexibility/ shifting, working memory, reasoning, visual-spatial skills & decision making, internalizing, externalizing & total behaviour problems

- No group differences, also when adjusted for confounders

⇒ Reduced infant formula protein is safe for brain development


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Hauner Children’s Hospital, Univ. Munich
Early Protein Intake: Mechanism of Action
The “Early Protein Hypothesis”

Excessive protein intake in early infancy

↑ Insulin-releasing amino acids

↑ Insulin, ↑ IGF-1

Early growth (first 2 years)

↑ Weight gain & ↑ Risk of obesity

Valine, Leucine, Isoleucine

Adipogenic activity (Adipocyte differentiation)

Serum AA concentrations at 6m

Socha P. AJCN 2011
IGF-1 at 6 month

P<0.001

IGF1-total

P<0.001

IGF1-free

IGF-1 and body weight:
- Correlated with weight/height at 12 m of age
- Correlated with weight/height increase during first 6m

Socha P. AJCN 2011
IGF-BP2 and IGF-BP3 at 6 month

Socha P. AJCN 2011
Urinary C-peptide/creatinine and serum glucose

Socha P. AJCN 2011
IGF-1 regulation: genetic only 3.8%, nutritional 15.1%
Protein intake and renal size

- Kidney volume related to protein intake and IGF-1
- IGF-1 has an independent direct effect on kidney volume
  - Direct effect of protein on kidney: 0.12
  - Effect through IGF-1: 0.23

Lugue V, Pediatric Research 2013
Early Protein Intake: Other Studies
Infants of overweight mothers

3 times more likely to be overweight if born to overweight mothers as compared to those born to mothers of a healthy weight.¹

1. J Obesity 2012; 1-18
Infants born to overweight or obese mothers.

Inostroza J et al JPN 2014; 59:70-77
Weight corrected for differences at 3 months

Longitudinal analysis: Time trends of predicted means and 95% CI estimated by the mixed model.
IGF-1 levels

![Graph showing IGF-1 levels over time for different groups.](image)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Month</th>
<th>Δ</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPL-CTRL</td>
<td>6</td>
<td>-18.29%</td>
<td>-32.08% to -4.49%</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-18.98%</td>
<td>-37.92% to 0.04%</td>
<td>0.050</td>
</tr>
<tr>
<td>BF-CTRL</td>
<td>6</td>
<td>-20.95%</td>
<td>-35.35% to -6.54%</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-14.50%</td>
<td>-33.33% to 4.34%</td>
<td>0.130</td>
</tr>
<tr>
<td>EXPL-BF</td>
<td>6</td>
<td>2.66%</td>
<td>-12.44% to 17.76%</td>
<td>0.728</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-4.48%</td>
<td>-24.40% to 15.43%</td>
<td>0.657</td>
</tr>
</tbody>
</table>
Protein intake and growth/obesity: systematic review

• RCT: 12 studies
  • Except for CHOP - all small studies
  • Early outcomes for most of the studies (4-7 m)
  • Different outcomes
    • BMI reported only for CHOP
  • Different protein intakes compared

• Conclusion
  • More studies are needed
  • Limited evidence

Patro-Golab B, J Nutr 2016
Conclusions

- Childhood obesity prevalence is at an alarming rate in Malaysia
- High protein intake in infancy is related to later obesity and visceral adiposity risk
- IGF-1 axis and insulin response are influenced by protein intake during early infancy
- Reducing protein intake in infancy can be used for early obesity prophylaxis