Role of diet in prevention and treatment of hypercholesterolaemia/hypertriglyceridaemia in children

C. Hartman (IL)
Nutritional Treatment of Hyperlipidemia in Children

Special Emphasis on Hypercholesterolemia

Corina Hartman
Schneider Children’s Medical Center
Israel
Nutritional Treatment of Hyperlipidemia in Children

Lecture Objectives

- Introduction to the subject
- Screening for hyperlipidemia in childhood
- Diagnosis and evaluation of hyperlipidemia in children
- CHILD1 and CHILD2 nutritional intervention
- Familial hypercholesterolemia (FH)
Why is hyperlipidemia important?  
Noncommunicable disease (NCD)

57 Million Death/ WHO 2008 statistics

Cardiovascular diseases
Cancer
Chronic Pulmonary Disease
Diabetes
Why is hyperlipidemia important? Noncommunicable disease (NCD)

57 Million Death/ WHO 2008 statistics

Cardiovascular disease is the leading cause of death among NCD
Why is hyperlipidemia important? CVD risk assessment

- Framingham risk score: Gender, Age, Diabetes, Smoking, SBP, HDL-C, TC
- New CVD risk assessment: Added, treatment for hypertension, ethnicity

Why is hyperlipidemia important?

CVD risk assessment

Framingham risk score: Gender, Age, Diabetes, Smoking, SBP, HDL-C, TC

New CVD risk assessment: Added, treatment for hypertension, ethnicity

Hypercholesterolemia and the risk of CVD

Atherosclerotic lesions are present in young

- Pathological evidence
  - Korean/Vietnam War
    - Enos WF, et al. JAMA 953;152:10
    - Strong JP. JAMA 1986;256:2863-6
  - PDAY study
    - JAMA 1990;264:3018-24
    - Circulation. 2000;102:374-379
  - Bogalusa Heart Study

CVD risk factors are present in childhood

Risk factors such as hyperlipidemia, hypertension and obesity may be present from childhood

the Bogalusa Heart Study. Circulation. 1988;77:856-64

Atherosclerotic lesions are present in young

- Surrogate markers (CIMT), the evidence

Vijayasarathi A et al. J Lip 2014;1-7

Cholesterol levels track from childhood to adulthood

- Tracking
  - Bogalusa Heart Study
  - Muscatine Study
  - Amsterdam Growth and Health Study

  • 43% remained above the 90th
  • 62% remained above the 75th
  • 81% remained above the 50th
Obesity epidemics, a new CVD risk factor

Metabolic syndrome in adulthood
Metabolic syndrome in childhood
No metabolic syndrome in childhood

Adult type 2 diabetes
Metabolic syndrome in childhood
No metabolic syndrome in childhood

CVD risk in childhood

- Atherosclerosis lesions are present in children
- Hyperlipidemia has been linked to atherosclerosis lesions
- Hyperlipidemia and MeS track from childhood to adulthood
- CV health index is poor in 20-40% of 12 to 19 young Americans
- Very poor diets is reported by 3/4 of American youth
# How to screen for hyperlipidemia in childhood

## Selective Screening

**AAP, AHA (2007)**
- Family with dyslipidemia OR
- Family with premature CHD OR
- Unknown family history OR
- Other CVD risk factors

## Universal Screening

**NHLBI, AAP (2011)**
- Universal screening between 9-11 y and 17-21 y
- Selective screening between 2-8y and 12-16y in selected
  - Weight/Height since 2 y
  - Blood pressure since 3 y
  - BMI

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2007 US Preventive Services Task Force
“The evidence is insufficient at this time to recommend for or against universal screening”
### How to screen for hyperlipidemia in childhood

#### Selective Screening

- **AAP, AHA (2007)**
  - Family with dyslipidemia OR
  - Family with premature CHD OR
  - Unknown family history OR
  - Other CVD risk factors

#### Universal Screening

- **NHLBI, AAP (2011)**
  - Universal screening between 9-11 y and 17-21 y
  - Selective screening between 2-8y and 12-16y in selected
  - Weight/Height since 2 y
  - Blood pressure since 3 y
  - BMI

#### Genetic screening

- Netherland, Norway, Wales
How to screen for hyperlipidemia in childhood (2011)

<table>
<thead>
<tr>
<th>Age</th>
<th>Who</th>
<th>How</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth -2 years</td>
<td>No screening</td>
<td>-</td>
</tr>
<tr>
<td>2–8 years</td>
<td>Target groups</td>
<td>Two fasting lipid panels and average the values</td>
</tr>
<tr>
<td>9-11 years</td>
<td>Universal screening</td>
<td>Non fasting lipid profile Calculate non-HDL-C: If non-HDL-C &gt;145 mg/dl, obtain two fasting lipid panels and average the values</td>
</tr>
<tr>
<td>12-16 years</td>
<td>Target groups</td>
<td>Two fasting lipid panels and average the values</td>
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<tr>
<td>17-21 years</td>
<td>Universal screening</td>
<td>Non fasting lipid profile Calculate non-HDL-C: If non-HDL-C &gt;145 mg/dl, obtain two fasting lipid panels and average the values</td>
</tr>
</tbody>
</table>

Target groups: Positive family history, presence of risk factors or condition

How to screen for hyperlipidemia in childhood

**ProScreening**
- Atherosclerosis begins in childhood
- Lipids levels track from childhood to adulthood
- Intervention in children changed surrogate markers as CIMT
- Lifestyle changes are easier in childhood

**ConsScreening**
- No direct evidence that help outcome of CVD in adults
- May improperly label children as sick
- Promotes use of drugs instead of healthy lifestyle
- Harmful effects of restrictive diets and drugs
- Expensive
What is elevated cholesterol?

- **NCEP guidelines are based on cholesterol distribution among American children in the Lipid Research Clinics Prevalence study**
  - For TC and non-LDL-C
    - 75th percentile was set as borderline and
    - 95th percentile as high
  - For triglycerides:
    - 75th percentile was set as borderline and
    - 90th percentile as high
Cut Points for Lipid and Lipoprotein Levels in Young Adults

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentile</th>
<th>Total C mg/dl</th>
<th>LDL-C mg/dl</th>
<th>HDL-C mg/dl</th>
<th>Trigl mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptable</td>
<td>&lt;75th</td>
<td>&lt;170</td>
<td>&lt;110</td>
<td>&gt;45</td>
<td>&lt;115</td>
</tr>
<tr>
<td>Borderline</td>
<td>75&lt;sup&gt;th&lt;/sup&gt;-95&lt;sup&gt;th&lt;/sup&gt;</td>
<td>170-199</td>
<td>110-129</td>
<td>40-44</td>
<td>115-149</td>
</tr>
<tr>
<td>Elevated/low</td>
<td>&gt;95th</td>
<td>&gt;200</td>
<td>&gt;130</td>
<td>&lt;40</td>
<td>&gt;150</td>
</tr>
</tbody>
</table>

Cut Points for Total Cholesterol and LDL Concentrations in Children and Adolescents. Adapted from NCEP guidelines for children and adolescents.
Distribution of Lipoproteins by Age and Gender in Adolescents

Courtney J. Jolliffe, MSc; Ian Janssen, PhD

Males 12-20 years

Prevalence of hyperlipidemia in childhood

NHANES 2007-2010

Hyperlipidemia, diagnosis and differential diagnosis

- Primary Hyperlipidemia
- Secondary Hyperlipidemia
## Primary Hyperlipidemia, genetic defects

<table>
<thead>
<tr>
<th>Disease</th>
<th>Lipid profile,</th>
<th>Molecular defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCH, familial combined</td>
<td>TC, TG, CM</td>
<td>LPL, lipoprotein lipase; APOC2, apolipoprotein C2</td>
</tr>
<tr>
<td>hyperlipidaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH, familial hypercholesterolaemia</td>
<td>TC, LDL-C</td>
<td>LDLR, LDL receptor; APO, apolipoprotein B; PCSK9, proprotein convertase subtilisin/kexin type 9; LDLRAP1, low-density lipoprotein receptor adaptor protein 1</td>
</tr>
<tr>
<td>FHC, familial hyperchylomicronaemia</td>
<td>TC, TG, LDL-C</td>
<td>APOA5, apolipoprotein A5 common SNPs</td>
</tr>
<tr>
<td>DBL, dysbetalipoproteinaemia</td>
<td>TC, TG, IDL-C</td>
<td>APOA5, apolipoprotein A5 common SNPs</td>
</tr>
<tr>
<td>FHTG, familial hypertriglyceridaemia</td>
<td>TC, TG, CM</td>
<td>APOE, apolipoprotein E common SNPs</td>
</tr>
<tr>
<td>MHL, mixed hyperlipidaemia</td>
<td>TC, TG, CM</td>
<td>LPL, lipoprotein lipase; APOC2, apolipoprotein C2; APOA5, apolipoprotein A5 common SNPs; APOE, apolipoprotein E common SNPs</td>
</tr>
<tr>
<td>TD, Tangier disease</td>
<td>TG, low TC, LDL-C, HDL-C</td>
<td>ABCA1, ATP-binding cassette A1</td>
</tr>
<tr>
<td>LCAT deficiency</td>
<td>TG, low TC, LDL-C, HDL-C</td>
<td>LCAT, lecithin cholesterol acyltransferase</td>
</tr>
<tr>
<td>HLD, hepatic lipase deficiency</td>
<td>TC, TG, LDL-C, HDL-C, IDL-C</td>
<td>LIPC, hepatic lipase</td>
</tr>
<tr>
<td>CETPD, CETP deficiency</td>
<td>TC, TG, HDL-C</td>
<td>CETP, cholesteryl ester transfer protein</td>
</tr>
<tr>
<td>SITO sitosterolemia</td>
<td>TC, LDL-C low HDL-C</td>
<td>ABCG5/G8, ATP-binding cassette transporter G5/G8</td>
</tr>
</tbody>
</table>
# Secondary Hyperlipidemia, etiology

<table>
<thead>
<tr>
<th>Classification</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Diabetes mellitus, hypothyroidism, hypopituitarism, insulin resistance</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Obesity, lipodystrophy, alcohol, anorexia, bulimia, porphiria</td>
</tr>
<tr>
<td>Storage Diseases</td>
<td>Glycogen storage disease, Niemann-Pick, Tay-Sachs</td>
</tr>
<tr>
<td>Hepatic Diseases</td>
<td>Cholestatic liver disorders</td>
</tr>
<tr>
<td>Renal Diseases</td>
<td>Chronic renal failure, nephrotic syndrome, hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Chronic Inflammatory Disorders</td>
<td>Systemic lupus erythematous, juvenile rheumathoid arthritis</td>
</tr>
<tr>
<td>Drugs</td>
<td>Androgens, glucocorticoids, calcineurin inhibitors, retinoids, oral contraceptives</td>
</tr>
<tr>
<td>Other</td>
<td>Pregnancy, Klinefelter syndrome, idiopathic hypercalcemia, hemophagocytic syndrome</td>
</tr>
</tbody>
</table>
Familial Hypercholesterolemia (FH)

- AD disorder
- Affects 1 in 500 people worldwide
- The genetic defect: mutations that affect the production and function of cell-surface LDL-R
- Consequence: Impaired hepatic clearance of circulating LDL particles, and their accumulation in the bloodstream
- Approximately 1600 mutations have been identified to date
- By 60 years, 50% males and 30% women have significant CVD and 5% by 30 years
Clinical Diagnosis of Familial Hypercholesterolaemia

Simon Broome Register Group (1991)
Dutch Lipid Clinic Network (1999)

Simon Broome and Dutch Lipid Criteria

1. Elevated cholesterol level (TC or LDL-C), AND
2. Presence of tendon xanthomata in the patient or first degree relative, AND
3. Family history of elevated cholesterol or premature coronary heart disease OR
4. Genetic diagnosis plus one of the above

US MedPeded Criteria

• Use cut-off age specific and relative specific criteria for total cholesterol only

Simon Broome Register Group. BMJ. 1991;303(6807):893-6
Evaluation of hyperlipidemia

- Comprehensive family pedigree and risk factors’
- Lipoprotein profile of all immediate family members
- Physical examination, BP measurement
- Nutritional evaluation: diet, anthropometry
- Blood chemistry, according to history and PE
- Baseline non-invasive assessment of vascular changes
- **Planning of treatment and its goals**
- Follow up
# Treatment Goals

## Cardiovascular risk stratification

<table>
<thead>
<tr>
<th>Tier/ Risk classification</th>
<th>Medical conditions</th>
<th>Tier specific cutpoints/ treatment goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manifest CVD &lt; 30 years</td>
<td>Homozygous FH</td>
<td>BMI ≤ 85% for age and gender BP ≤ 90% for age and gender LDL-C ≤100 mg/Dl FG &lt; 100 mg/dL; HbA1C &lt; 7%</td>
</tr>
<tr>
<td>Clinical evidence</td>
<td>Diabetes mellitus, type 1 Chronic kidney disease/end stage renal disease Post heart transplantation Kawasaki disease with CA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate risk</strong></td>
<td>Heterozygous FH</td>
<td>BMI ≤ 90% for age and gender BP ≤ 95% for age and gender LDL-C ≤130 mg/Dl FG &lt; 100 mg/dL; HbA1C &lt; 7%</td>
</tr>
<tr>
<td>Accelerated atherosclerosis</td>
<td>Kawasaki disease with regressed coronary aneurysms Diabetes mellitus, type 2 Chronic inflammatory disease</td>
<td></td>
</tr>
<tr>
<td>Pathophysiological evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At risk</strong></td>
<td>Post–cancer-treatment survivors Congenital heart disease Kawasaki disease without coronary involvement</td>
<td>BMI ≤ 95% for age and gender BP ≤ 95% +5mmHg for age and gender LDL-C ≤160 mg/Dl FG &lt; 100 mg/dL; HbA1C &lt; 7%</td>
</tr>
<tr>
<td>High risk setting for accelerated atherosclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidemiological evidence</td>
<td></td>
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## Treatment Goals

Risk factors and conditions to consider

<table>
<thead>
<tr>
<th>Family History</th>
<th>High risk factors</th>
<th>Moderate risk factors</th>
</tr>
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<tbody>
<tr>
<td>Parent, grandparent, uncle/ aunt (male&lt; 55, female &lt;65)</td>
<td><strong>High risk conditions</strong>&lt;br&gt;Manifest CVD &lt; 30 years&lt;br&gt;Clinical evidence</td>
<td><strong>Moderate risk conditions</strong>&lt;br&gt;Accelerated atherosclerosis&lt;br&gt;Pathophysiological evidence</td>
</tr>
<tr>
<td>Myocardial infarction&lt;br&gt;CABG/ stent/ angioplasty&lt;br&gt;Sudden cardiac death</td>
<td><strong>HT</strong> requiring drug therapy&lt;br&gt;BMI&gt; 97%&lt;br&gt;Current smoker</td>
<td><strong>HT</strong> not requiring therapy&lt;br&gt;BMI 95%- 97%&lt;br&gt;HDL-V &lt; 40 mg/dl</td>
</tr>
<tr>
<td>Homozygous FH&lt;br&gt;Diabetes mellitus, type 1/2&lt;br&gt;Chronic kidney disease/&lt;br&gt;ESRD/ post transplant&lt;br&gt;Post heart transplantation&lt;br&gt;Kawasaki disease with CA aneurysms</td>
<td></td>
<td><strong>Heterozygous FH</strong>&lt;br&gt;Kawasaki disease with regressed coronary aneurysms&lt;br&gt;Chronic inflammatory disease&lt;br&gt;Nephrotic syndrome&lt;br&gt;HIV</td>
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## Treatment Goals

### Risk factors and conditions to consider

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<td>BMI $\leq 85%$ for age and gender</td>
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<tr>
<td><strong>LDL-C $\leq 100$ mg/dL</strong></td>
<td></td>
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<td>FG $&lt; 100$ mg/dL; HbA1C $&lt; 7%$</td>
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<td>BP $\leq 95%$ for age and gender</td>
<td></td>
</tr>
<tr>
<td><strong>LDL-C $\leq 130$ mg/dL</strong></td>
<td></td>
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<tr>
<td>FG $&lt; 100$ mg/dL; HbA1C $&lt; 7%$</td>
<td></td>
</tr>
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</table>
Treatment plan for dyslipidemia in children

- Dietary intervention is the primary approach to treating children and adolescents with elevated blood cholesterol or other dyslipidemia or conditions associated with increased CVD risk
  - Population / preventive approach/ DGA recommendations (TLS)
  - CHILD1/2 (individualized approach for groups at risk/ dyslipidemia)

- ESPGHAN recommendations (JPGN 1994)
- NCEP guidelines (Pediatrics 1992)
- AAP guidelines (2006)
- AAP guidelines (2011)
New Healthy Food Pyramid

Nutritional Guidelines

Encourage water intake
Primary beverage: fat-free milk
Avoid sugar-sweetened beverages
Limit naturally sweetened juice
Encourage high dietary fiber intake
Limit sodium intake
Teach portions based on EER for age/sex/activity
Limit fat intake to 25 to 40% according to age/EER
Limit TFA/ SFA/ cholesterol
Limit simple CHO intake/ promote complex CHO consumption

Prevalence of CVD risk factors in childhood

Ideal Cardiovascular Health Index

Hyperlipidemia, treatment plan

**Phase 1 – three to 6 months trial period**
- The Cardiovascular Health Integrated Lifestyle Diet (CHILD 1)
- CHILD 2-LDL Diet for Elevated LDL-C
- CHILD 2-Triglyceride Diet for Elevated Triglyceride or Non-HDL-C

**Phase 2 – Reevaluation**
- Have the treatment goals been achieved?
- Decide of further step (nutrition or adding drugs)

**Phase 3 – Follow up**
- Growth and maturation
- Lipids levels and Surrogate markers FU
Nutritional intervention in children

<table>
<thead>
<tr>
<th>CHILD 1</th>
<th>CHILD2 (LDL-C, TG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Total fat 25-30% / REE</td>
<td>• Total fat 25-30% / REE</td>
</tr>
<tr>
<td>• <strong>Saturated fats 8-10 % / REE</strong></td>
<td>• <strong>Saturated fats &lt;7% / REE</strong></td>
</tr>
<tr>
<td>• Mono unsaturated fats: &lt; 20% / REE</td>
<td>• Mono unsaturated fats: &lt; 20% / REE</td>
</tr>
<tr>
<td>• Polyunsaturated: up to 10% of total calories</td>
<td>• Polyunsaturated: up to 10% of total calories</td>
</tr>
<tr>
<td>• Carbohydrates: 50-60% of total calories</td>
<td>• Carbohydrates: 50-60% of total calories</td>
</tr>
<tr>
<td>• Protein: 10-20% of total calories</td>
<td>• Protein: 10-20% of total calories</td>
</tr>
<tr>
<td><strong>Cholesterol &lt;300 mg per day</strong></td>
<td><strong>Cholesterol &lt;200 mg per day</strong></td>
</tr>
<tr>
<td>• Total calories: maintain proper growth and development</td>
<td>• Total calories: maintain proper growth and development</td>
</tr>
<tr>
<td></td>
<td>• <strong>Plant stanol/sterol esters 2g/day</strong></td>
</tr>
<tr>
<td></td>
<td>• Increase fish consumption (TG)</td>
</tr>
<tr>
<td></td>
<td>• Replace simple CHO with complex (TG)</td>
</tr>
</tbody>
</table>
Dietary intervention for hypercholesterolemia

- **The Special Turku Risk Intervention Program (STRIP)**
  - Cohort of **healthy infants aged 7 months to 1 year** of age (540 children, 520 controls), given dietary counseling of a low fat diet (<30% of energy)

- **The Dietary Intervention Study in Children (DISC)**
  - Randomized over 600 children with **elevated LDL-C, aged 8-11 years** at baseline, to a 3 and ultimately 7 year program of diet vs. conventional treatment
14 years of dietary counseling in the STRIP study

DISC STUDY

JAMA 1995;273:1429-35
Pediatrics 1997;100:51-9
Pediatrics 2001;107:256-64

Randomized over 600 children with elevated LDL-C, aged 8-11 at baseline, to a 3 year program of diet vs. conventional treatment
Dietary Adjuvants

- Vitamin E
- Folic acid
- Plant sterols and stanols
- Soluble fiber
- Soy proteins (isoflavones)
- Fish oils (omega-3)
- Garlic extract
- Flaxseed
- Glucomannan
Hyperlipidemia, treatment plan

• Phase 1 – six to 12 months trial period
  – The Cardiovascular Health Integrated Lifestyle Diet (CHILD1)
  – Dietary counseling and follow up

• Phase 2 – Reevaluation
  – Have the treatment goals been achieved?
  – Decide of further step (nutrition or adding drugs)

• Phase 3 – Follow up
  – Growth and maturation
  – Lipids levels and Surrogate markers FU
Hyperlipidemia, treatment plan

• Phase 2 – reevaluation
  – Consider pharmacologic treatment in case of failure to achieve the planned LDL reduction?
    • HMG-CoA reductase inhibitors, statins
    • Cholesterol absorption inhibitors
    • Bile-acid sequestrants
  – Continue dietary counseling and healthy lifestyle promotion
Hyperlipidemia, treatment plan

- Phase 1 – six to 12 months trial period
  - Therapeutic Life-Style Changes (TLC)
  - Dietary counseling and follow up
- Phase 2 – Reevaluation
  - Have the treatment goals been achieved?
  - Decide of further step (nutrition or adding drugs)

- Phase 3 – Follow up
  - Follow up for drugs adverse effects and efficacy
  - Lipids levels and Surrogate markers FU
  - Continue dietary counseling and healthy lifestyle
  - Growth and maturation
Treatment Recommendations for Children with FH

• Heterozygous FH – Therapy goal: reduce LDL < 130mg/Dl
  – CHILD 1/2 dietary intervention
  – Identification and treatment of comorbidities
  – Drug therapy instituted to low LDL-C < 130mg/dl: statins
  – Dietary supplementations: plant sterols
  – Other dietary adjuvants:?

• Homozygous FH
  – Complete CV assessment at diagnosis
  – Treatment instituted ASAP
  – The treatment usually combine plasmapheresis/ LDL apheresis, statins and cholesterol absorption inhibitors
  – Ongoing surveillance for cardiovascular disease
Conclusions

- Atherogenesis early in life is associated with the traditional risk factors for CAD and that these risk factors are present in childhood and tend to track into adulthood.
- While lifestyle modification/dietary intervention is the mainstay of treatment, sometimes it is not sufficient to achieve the desired cholesterol levels and drug therapy may be warranted.
- With the increasing use of drugs in the treatment of children with hypercholesterolemia, it must be emphasized that dietary and drug treatments are synergistic and dietary and life style modifications must not be abandoned after the initiation of drug therapy.
Thank you for your attention and participation