The 5th IAS-OSLA Course on “Lipid Metabolism and Cardiovascular Risk”
Muscat, Oman, February 8-11, 2019

Effect of diet and exercise on dyslipidaemia and CVD

Khalid Al-Rasadi, BSc, MD, FRCPC
Head of Biochemistry Department, SQU
Head of Lipid and LDL-Apheresis Unit, SQUH
President of Oman society of Lipid & Atherosclerosis (OSLA)
**Relationship Between Diet and CV Disease**

*Diet* → **Intermediary Biological Mechanisms*** → **Risk of Coronary Heart Disease**

*Includes lipid levels [LDL-C, HDL-C, triglycerides, Lp(a), blood pressure, thrombotic tendency, cardiac rhythm, endothelial function, systemic inflammation, insulin sensitivity, oxidative stress, homocysteine level*

Total Fat – Ecological Data

Seven Countries Study
The PREDIMED trial (Prevencion con Dieta Mediterranea)

A multicenter trial in Spain

7447 participants at high CVD risk but no prior CVD events

three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet

Lyon Diet Heart Study

605 patients following a myocardial infarction randomized to a Mediterranean* or Western** diet for 4 years

A Mediterranean diet reduces cardiovascular events

65% lower CHD death rate in the treatment group

*High in polyunsaturated fat and fiber,
**High in saturated fat and low in fiber

Recommendations for Cardiovascular Disease Risk Reduction

• Balance calorie intake and physical activity to achieve or maintain a healthy body weight
• Consume a diet rich in fruits and vegetables
• Consume whole-grain, high-fiber foods
• Consume fish, especially oily fish, at least twice a week
• Limit intake of saturated fat to <7%, trans fat to <1% of energy, and cholesterol <300 mg/day by:
  – Choosing lean mean and vegetable alternatives
  – Choosing fat free (skim), 1% fat, and low-fat dairy products,
  – Minimizing intake of partially hydrogenated fats
• Minimize intake of beverages and foods with added sugar
• Choose and prepare foods with little or no salt
• If alcohol is consumed, do so in moderation

AHA=American Heart Association

Source: AHA Nutrition Committee. Circulation 2006;114:82-96
Effects of dietary fat and carbohydrates on LDL-C
A systematic review and meta-regression analysis evaluated 84 randomized controlled trials including 2353 participants

<table>
<thead>
<tr>
<th></th>
<th>Carbohydrates</th>
<th>MUFA</th>
<th>PUFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>↓1.2</td>
<td>↓1.3</td>
<td>↓1.8</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>↓0.4</td>
<td>↓1.2</td>
<td>↓0.2</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>↑1.9</td>
<td>↑0.2</td>
<td>↓0.4</td>
</tr>
</tbody>
</table>

Trans Fat

In controlled feeding trials among adults, for every 1% of energy from *trans* MUFA replaced with 1% of energy from:

- MUFA or PUFA
  - \(\downarrow\) LDL-C by 1.5 and 2.0 mg/dL, respectively.

- SFA, MUFA, or PUFA
  - \(\uparrow\) HDL-C by 0.5, 0.4 and 0.5 mg/dL, respectively.

- MUFA or PUFA
  - \(\downarrow\) TG by 1.2 and 1.3 mg/dL.
Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shekelle et al(17)</td>
<td>1.11 [0.91, 1.36]</td>
<td>1981</td>
</tr>
<tr>
<td>Mc Gee et al(9)</td>
<td>0.86 [0.67, 1.12]</td>
<td>1984</td>
</tr>
<tr>
<td>Kushi et al(13)</td>
<td>1.33 [0.95, 1.87]</td>
<td>1985</td>
</tr>
<tr>
<td>Posner et al(16)</td>
<td>0.92 [0.68, 1.24]</td>
<td>1991</td>
</tr>
<tr>
<td>Goldbourn et al(35)</td>
<td>0.86 [0.66, 1.35]</td>
<td>1993</td>
</tr>
<tr>
<td>Fehily et al(28)</td>
<td>1.57 [0.56, 4.42]</td>
<td>1994</td>
</tr>
<tr>
<td>Ascherio et al(4)</td>
<td>1.11 [0.87, 1.42]</td>
<td>1996</td>
</tr>
<tr>
<td>Esrey et al(6)</td>
<td>0.97 [0.80, 1.18]</td>
<td>1996</td>
</tr>
<tr>
<td>Pietinen et al(15)</td>
<td>0.93 [0.60, 1.44]</td>
<td>1997</td>
</tr>
<tr>
<td>Boniface et al(5)</td>
<td>1.37 [1.17, 1.60]</td>
<td>2002</td>
</tr>
<tr>
<td>Jakobsen et al(8)</td>
<td>1.03 [0.66, 1.60]</td>
<td>2004</td>
</tr>
<tr>
<td>Oh et al(33)</td>
<td>0.97 [0.74, 1.27]</td>
<td>2005</td>
</tr>
<tr>
<td>Tucker et al(18)</td>
<td>1.22 [0.31, 4.77]</td>
<td>2005</td>
</tr>
<tr>
<td>Xu et al(10)</td>
<td>1.91 [0.31, 11.84]</td>
<td>2006</td>
</tr>
<tr>
<td>Leosdottir et al(14)</td>
<td>0.95 [0.74, 1.21]</td>
<td>2007</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1.07 [0.96, 1.19]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02; Chi² = 25.54, df = 15 (P = 0.04); I² = 41%
Test for overall effect: Z = 1.22 (P = 0.22)

<table>
<thead>
<tr>
<th>Stroke</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mc Gee et al(9)</td>
<td>1.04 [0.72, 1.50]</td>
<td>1984</td>
</tr>
<tr>
<td>Goldbourn et al(35)</td>
<td>0.92 [0.56, 1.51]</td>
<td>1993</td>
</tr>
<tr>
<td>Gillman et al(11)</td>
<td>0.64 [0.49, 0.84]</td>
<td>1997</td>
</tr>
<tr>
<td>Iso et al(31)</td>
<td>1.05 [0.33, 3.39]</td>
<td>2001</td>
</tr>
<tr>
<td>He et al(29)</td>
<td>0.79 [0.52, 1.19]</td>
<td>2003</td>
</tr>
<tr>
<td>Iso et al(30)</td>
<td>0.30 [0.13, 0.71]</td>
<td>2003</td>
</tr>
<tr>
<td>Sauvaget et al(34)</td>
<td>0.58 [0.28, 1.20]</td>
<td>2004</td>
</tr>
<tr>
<td>Leosdottir et al(14)</td>
<td>1.22 [0.91, 1.64]</td>
<td>2007</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0.81 [0.62, 1.05]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.08; Chi² = 18.03, df = 7 (P = 0.01); I² = 61%
Test for overall effect: Z = 1.58 (P = 0.11)

Total (95% CI) 1.00 [0.89, 1.11]

Heterogeneity: Tau² = 0.03; Chi² = 52.63, df = 23 (P = 0.0004); I² = 56%
Test for overall effect: Z = 0.06 (P = 0.95)

Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies$^1$–$^3$

Marianne U Jakobsen, Eilis J O’Reilly, Berit L Heitmann, Mark A Pereira, Katarina Bälter, Gary E Fraser, Uri Goldbourt, Göran Hallmans, Paul Knekt, Simin Liu, Pirjo Pietinen, Donna Spiegelman, June Stevens, Jarmo Virtamo, Walter C Willett, and Alberto Ascherio

Design: a follow-up study of 11 pooled American and European cohort studies including 344,696 persons; outcome CHD over a 4–10 yr FU, 5249 coronary events and 2155 coronary deaths occurred

Results: For a 5% lower energy intake from SFAs and a concomitant higher energy intake from PUFAs risk of coronary events HR: 0.87 (95% CI: 0.77-0.97); HR for coronary deaths 0.74 (0.61-0.89).

For a 5% lower energy intake from SFAs and a concomitant higher energy intake from CHO there was a significant association with coronary events (HR 1.07; (CI: 1.01- 1.14); for coronary deaths 0.96 (0.82- 1.13).

MUFA intake was not associated with CHD. Jakobsen et al Am J Clin Nutr 89:1–8 2009
coronary events

A

PUFAs for SFAs (per 5 E% increments)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHS (7), F</td>
<td>0.87</td>
<td>(0.77-0.97)</td>
</tr>
<tr>
<td>AHS (7), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC (8), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC (8), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATBC (9), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMC (10), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMC (10), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPS (5), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPS (5), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPFS (11), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHSa (4), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHSb (4), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIP (14), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIP (14), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHS (15), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>0.87</td>
<td>(0.77-0.97)</td>
</tr>
</tbody>
</table>

coronary deaths

B

PUFAs for SFAs (per 5 E% increments)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHS (7), F</td>
<td>0.74</td>
<td>(0.61-0.89)</td>
</tr>
<tr>
<td>AHS (7), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC (8), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATBC (9), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMC (10), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMC (10), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPS (5), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPS (5), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPFS (11), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHSa (4), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHSb (4), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIP (14), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIP (14), M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHS (15), F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>0.74</td>
<td>(0.61-0.89)</td>
</tr>
</tbody>
</table>
CHs for SFAs (per 5 E% increments)

**coronary events**

- AHS (7), F
- AHS (7), M
- ARIC (8), F
- ARIC (8), M
- ATBC (9), M
- FMC (10), M
- GPS (5), M
- GPS (5), F
- HPFS (11), M
- NHSa (4), F
- NHSb (4), F
- VIP (14), F
- VIP (14), M
- WHS (15), F

Combined: 1.07 (1.01-1.14)

**coronary deaths**

- AHS (7), F
- AHS (7), M
- ARIC (8), F
- ARIC (8), M
- ATBC (9), M
- FMC (10), M
- GPS (5), M
- GPS (5), F
- HPFS (11), M
- IIHD (12), M
- IWHS (13), F
- NHSa (4), F
- NHSb (4), F
- VIP (14), M
- WHS (15), F

Combined: 0.96 (0.82-1.13)

Jakobsen et al Am J Clin Nutr 89:1–8, 2009
Aim: to investigate the risk of myocardial infarction (MI) associated with a higher energy intake from carbohydrates and a concomitant lower energy intake from SFAs. Carbohydrates with different glycemic index (GI) values were also investigated.

Design: Our prospective cohort study included 53,644 women and men free of MI at baseline with median of 12 years follow up.

Conclusion: This study suggests that replacing SFAs with carbohydrates with low-GI values is associated with a lower risk of MI, whereas replacing SFAs with carbohydrates with high-GI values is associated with a higher risk of MI.
Risk of CHD among 53,644 adults followed for 12 years. *p<0.05
Reduction in the Consumption of Trans Fatty Acids and the Risk of CHD in The Netherlands-Zutphen

↓TFA 2.4%

↓CHD 23%
Benefits of fish oil supplementation

• In the Diet and Reinfarction Trial (DART) in 2033 men with CHD increased intake of fish or use of 2 fish oil caps/day reduced CHD mortality 29% over 2 years

• In GISSI 11324 men and woman with CHD use of 1 gr. of n-3 PUFA decreased CVD events including mortality 15%

Nuts, Soy, Phytosterols, Garlic

• Nurses’ Health Study: five 1oz servings of nuts per week associated with 40% lower risk of CHD events

• Metaanalysis of 38 trials of soy protein showed 47g intake lowered total, LDL-C, and trigs 9%, 13%, and 11%

• Phytosterol-supplemented foods (e.g., stanol ester margarine) lowers LDL-C avg. 10%

• Meta-analysis of garlic studies showed 9% total cholesterol reduction (1/2-1 clove daily for 6 months).
Dietary fat and cardiovascular risk in children

- Evidence for dietary fat and cardiovascular risk in children is limited.

- The Bogalusa Heart Study found that in children intake of animal fat, the major source of dietary saturated fat, was associated with higher body weight.

- The Cardiovascular Risk in Young Finns study (Young Finns) was a multicenter longitudinal cohort study of 3956 individuals 3 to 18 years of age in 1980 who had ongoing follow-up assessment of diet and blood lipids over 21 years. At the end of follow up those who were on traditional dietary pattern had a higher LDL-C and increased CIMT compared to those on health-conscious pattern diet.

- The STRIP trial is a randomized study with >20 years of follow-up compared the effects of reduction in saturated fat starting in infancy compared with usual dietary intake and lifestyle among normal children from infancy through adolescence. LDL-C cholesterol levels were lower in the intervention compared with the control group.
Key Recommendations:

Consume a healthy eating pattern that accounts for all foods and beverages within an appropriate calorie level.

A healthy eating pattern includes:\[1\]
- A variety of vegetables from all of the subgroups—dark green, red and orange, legumes (beans and peas), starchy, and other
- Fruits, especially whole fruits
- Grains, at least half of which are whole grains
- Fat-free or low-fat dairy, including milk, yogurt, cheese, and/or fortified soy beverages
- A variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), and nuts, seeds, and soy products
- Oils

A healthy eating pattern limits:
- Saturated fats and trans fats, added sugars, and sodium

Key Recommendations that are quantitative are provided for several components of the diet that should be limited. These components are of particular public health concern in the United States, and the specified limits can help individuals achieve healthy eating patterns within calorie limits:
- Consume less than 10 percent of calories per day from added sugars\[2\]
- Consume less than 10 percent of calories per day from saturated fats\[3\]
- Consume less than 2,300 milligrams (mg) per day of sodium\[6\]
- If alcohol is consumed, it should be consumed in moderation—up to one drink per day for women and up to two drinks per day for men—and only by adults of legal drinking age.\[8\]

In tandem with the recommendations above, Americans of all ages—children, adolescents, adults, and older adults—should meet the Physical Activity Guidelines for Americans to help promote health and reduce the risk of chronic disease. Americans should aim to achieve and maintain a healthy body weight. The relationship between diet and physical activity contributes to calorie balance and managing body weight. As such, the Dietary Guidelines includes a Key Recommendation to:
- Meet the Physical Activity Guidelines for Americans.\[6\]
<table>
<thead>
<tr>
<th>LDL–C - Advise adults who would benefit from LDL–C lowering* to:</th>
<th>Strength</th>
<th>Evidence</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| 1. Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages and red meats.  
   a. Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus).  
   b. Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet. | A (Strong) | CQ1: ES4 (high), ES6 (low), ES8 (moderate), ES9 (moderate) | I  
A  
A |
| 2. Aim for a dietary pattern that achieves 5% to 6% of calories from saturated fat. | A (Strong) | CQ1: ES11 (high) | I  
A  
A |
| 3. Reduce percent of calories from saturated fat. | A (Strong) | CQ1: ES11 (high), ES12 (moderate), ES13 (moderate) | I  
A  
A |
| 4. Reduce percent of calories from trans fat. | A (Strong) | CQ1: ES14 (moderate), ES15 (moderate) | I  
A  
A |
2013 AHA/American College of Cardiology lifestyle guidelines

There is insufficient evidence to determine whether lowering dietary cholesterol reduces LDL–C

Physical Activity Evidence and Guidelines
Adverse Effects of Physical Inactivity

Physical Inactivity

- Inflammation
- Dyslipidemia

- Age
- Diabetes Mellitus
- Obesity
- Genetics

- Hypertension
- Smoking
- Hypercoagulability
- Novel Risk Factors

Atherosclerosis
Pre-diabetic Conditions: Benefit of Lifestyle Modification

Diabetes Prevention Program (DPP)

3,234 patients with elevated fasting and post-load glucose levels randomized to placebo, metformin (850 mg bid), or lifestyle modification* for 3 years

Lifestyle modification reduces the risk of developing DM by 39% compared to Metformin

*Includes 7% weight loss and at least 150 minutes of physical activity per week

Knowler WC et al. NEJM 2002;346:393-403.
173 sedentary, overweight (body mass index >24 kg/m2) post-menopausal women randomized to moderate intensity exercise vs. stretching for 1 year

**Exercise Evidence:**

**Effect on Body Composition**

Moderate exercise reduces total and intra-abdominal fat

Note: Minutes per week spent in moderate-intensity sports activity (low-active, 135 min/wk; intermediately active, 136-195 min/wk; and highly active, >195 min/wk)

Nurse’s Health Study

Exercise reduces the incidence of obesity and DM

Source: Hu FB et al. JAMA 2003;289:1785-1791
Exercise Evidence: Effect on Coronary Heart Disease Risk

Women’s Health Initiative Observational Study

Vigorous exercise*

Relative Risk of CHD

P=0.008

Walking

Relative Risk of CHD

P=0.004

Quintiles of activity (MET-hour/week**)

*Includes aerobics, aerobic dancing, jogging, tennis, and swimming laps

**Average active hours per week × energy expenditure per activity

CHD=Coronary heart disease

Source: Manson JE et al. *NEJM* 2002;347:716-725
Effect of cardiac rehabilitation in randomized controlled trials following a MI

Cardiac rehabilitation reduces CV events after a MI

* p<0.0125

CV=Cardiovascular, MI=Myocardial infarction

Source: Oldridge NB et al. JAMA 1988;260:945-950
**Exercise Evidence: Effect on Lipid Parameters**

**Look AHEAD Trial**

5,145 patients aged 45-74 years with type 2 DM and BMI of 25 kg/m² (27 kg/m² if taking insulin) randomized to an intensive lifestyle intervention (ILI) involving group and individual meetings to achieve and maintain weight loss through decreased caloric intake and increased physical activity versus diabetes support and education (DSE)

<table>
<thead>
<tr>
<th></th>
<th>ILI</th>
<th>DSE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dL)</td>
<td>-5.2 ± 0.6</td>
<td>-5.7 ± 0.6</td>
<td>0.49</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>3.4 ± 0.2</td>
<td>1.4 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-30.3 ± 2.0</td>
<td>-14.6 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Metabolic Syndrome</td>
<td>-14.7 ± 0.8</td>
<td>-7.1 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Intensive lifestyle intervention results in greater improvement in lipid parameters

BMI=Body mass index, DM=Diabetes mellitus, DSE=Diabetes support and education, ILI=Intensive lifestyle intervention

Box 1.2 The ACSM-AHA Primary Physical Activity Recommendations (23)

- All healthy adults aged 18–65 yr should participate in moderate intensity, aerobic physical activity for a minimum of 30 min on 5 d · wk\(^{-1}\) or vigorous intensity, aerobic activity for a minimum of 20 min on 3 d · wk\(^{-1}\).

- Combinations of moderate and vigorous intensity exercise can be performed to meet this recommendation.

- Moderate intensity, aerobic activity can be accumulated to total the 30 min minimum by performing bouts each lasting ≥10 min.

- Every adult should perform activities that maintain or increase muscular strength and endurance for a minimum of 2 d · wk\(^{-1}\).
Conclusion

- Saturated fat increases LDL-C, a major cause of atherosclerosis and CVD, and replacing it with polyunsaturated or monounsaturated fat decreases LDL-C.

- Randomized clinical trials showed that polyunsaturated fat from vegetable oils replacing saturated fats from dairy and meat lowers CVD.

- Prospective observational studies in many populations showed that lower intake of saturated fat coupled with higher intake of polyunsaturated and monounsaturated fat is associated with lower rates of CVD and all-cause mortality.

- There is a need for current policy actions of many local and national jurisdictions to reduce industrial trans fatty acids in the food.

- Regular exercise can reduces the incidence of obesity, DM and CAD.