Keynote lecture: Mediterranean diet and regression of atherosclerosis. Is it possible?

I. Shai (Israel)
Mediterranean diet & regression of atherosclerosis; Is it possible?

Iris Shai
Ben-Gurion University
Israel
Atherosclerosis - a dynamic process

The lipid rich plaque initiates inflammatory processes that include recruitment of circulating macrophages & phagocytosis of the oxidised LDL

Hansson GK. N Engl J Med. 2005
The natural history of atherosclerosis reflects different components of the vessel wall.

**Intima-Media Thickness (IMT):** mainly by hypertensive medial hypertrophy

**Plaque:** lipids, inflammation, oxidative stress, endothelial dysfunction, etc

**Thrombosis:** plaque rupture
Carotid arteries

• Blood vessels that deliver blood through the neck to the brain

• One carotid artery on each side of the neck
What is the average annual progression of atherosclerosis in the CAROTID?

<table>
<thead>
<tr>
<th>Ultrasound Measurement</th>
<th>IMT - 0.015 mm/year</th>
<th>Carotid plaque area - 5 mm²/year</th>
<th>Carotid plaque volume - 50 mm³/year</th>
</tr>
</thead>
</table>

**Case 1**
- IMT = 0.95 mm
- PA = 0.38 cm²
- PV = 297 mm³

Resolution of carotid IMT ultrasound is ~ >0.3mm
Plaque area goes up steeply after age 45

Distribution of carotid plaque area by age groups and sex

Sex

- Male
- Female

Carotid total plaque area (cm²) + SE

Age group

30-35 35-40 40-45 45-50 50-55 60-65 65-70 70-75 75-80 > = 80

men

women

Spence JD. Nature Clinical Practice Neurology 2006
Aggressive risk factor modification & lipid lowering agents, statins in particular, lead to a reduction in the size of the lipid pool, attenuation of the inflammatory process, & reduced thrombogenicity.

Shanmugam N, et al. Cardiovascular Drugs and Therapy 2010
Targeted therapy in plaque regression are **aggressive lipid lowering and anti inflammatory**

### Current markers for prediction of plaque regression

<table>
<thead>
<tr>
<th>Cholesterol markers</th>
<th>Inflammatory markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL:HDLC Ratio</td>
<td>CRP</td>
</tr>
<tr>
<td>Apolipoprotein B: apoprotein A-1 Ratio</td>
<td>Monocyte count</td>
</tr>
</tbody>
</table>

Shanmugam N, et al. Cardiovascular Drugs and Therapy 2010
Medical treatment

• Plaque regression can be achieved by aggressive LDL reduction with high dose statin therapy and HDL elevation.

• Supplemental niacin therapy has been suggested to have additional benefit, particularly through a reduction of the LDL/HDL ratio.
Medical treatment: 50% success in halting or regression of the carotid plaque area

5 years follow-up of 1686 treated patients

Spence JD. Stroke 2002

* increase (or decrease) of $\geq 0.05 \text{ cm}^2$ from baseline
Mediterranean diet
Meta-Analysis Comparing Mediterranean to Low-Fat Diets for Modification of Cardiovascular Risk Factors

Alain J. Nordmann, MD, MSc, a Katja Suter-Zimmermann, PhD,a Heiner C. Bucher, MD, MPH,a Iris Shai, RD, PhD,b Katherine R. Tuttle, MD,c Ramon Estruch, MD, PhD,d Matthias Briel, MD, MSca,e

The American Journal of Medicine (2011)
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Mean change in systolic blood pressure at 2 years (mmHg)

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted Mean Difference (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esposito, 2004</td>
<td>-3.00 (-3.46, -2.54)</td>
<td>24.1</td>
</tr>
<tr>
<td>Shai, 2008</td>
<td>-1.20 (-4.71, 2.31)</td>
<td>11.6</td>
</tr>
<tr>
<td>Esposito, 2009</td>
<td>0.00 (-0.77, 0.77)</td>
<td>23.3</td>
</tr>
<tr>
<td>Predimed, 2010</td>
<td>-1.80 (-3.39, -0.21)</td>
<td>20.0</td>
</tr>
<tr>
<td>Tuttle, 2008</td>
<td>-3.00 (-9.02, 3.02)</td>
<td>5.8</td>
</tr>
<tr>
<td>Esposito, 2003</td>
<td>-2.00 (-4.58, 0.58)</td>
<td>15.3</td>
</tr>
</tbody>
</table>

Overall (95% CI)

-1.70 (-3.35, -0.05)

Favors Mediterranean

Favors Low Fat

Weighted Mean Difference

-3  0  3

Heterogeneity $P < 0.001$

Inconsistency $I^2 = 89\%$
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The American Journal of Medicine (2011)
A few studies reported that lifestyle interventions can *halt the progression* of carotid IMT and others have shown *no effect*.

**Regression** of carotid atherosclerosis by dietary intervention has not been well evident.
The DIRECT study

- **322 moderately obese; BMI = 31 kg/m²; age = 52 yrs; 86% men**
- **Most procedures done within the workplace; exclusive, regulated, cafeteria**
- **Tight follow-up; Spouse support program**
- **Equal intensity**
- **One-phase design**

**Adherence**: 95% after 1 yr; 85% after 2 yrs
Adherence evaluation
FFQ, times 0, 6, 12, 24 months

- The Mediterranean diet-group consumed the highest dietary fiber and monounsaturated/saturated fat ratio ($P<0.05$)

- The low-carb diet-group consumed the fewest carbs, highest fat, protein and cholesterol, and had higher urinary ketones ($P<0.05$)

- Common to the three diets:
  - i. less calories;
  - ii. less junk food (salt, trans-fat) & cakes;
  - iii. More vegetables
2-year weight loss was more successful in Low-carb and Med diets

The Dietary Intervention Randomized Controlled Trial- DIRECT
ITT analysis

Shai I et al.
New Eng J Med 2008
Med & Low-carb diets → more favorable in lipid profile

Circulation 2010

New Eng J Med 2008
Dietary Intervention to Reverse Carotid Atherosclerosis

Iris Shai, RD, PhD*; J. David Spence, MD*; Dan Schwarzfuchs, MD; Yaakov Henkin, MD; Grace Parraga, PhD; Assaf Rudich, MD, PhD; Aaron Fenster, PhD; Christiane Mallett, MSc; Noah Liel-Cohen, MD; Amir Tirosh, MD, PhD; Arkady Bolotin, PhD; Joachim Thiery, MD; Georg Martin Fiedler, MD; Matthias Blüher, MD; Michael Stumvoll, MD; Meir J. Stampfer, MD, DrPH; for the DIRECT Group

Can dietary intervention affect the carotid atherosclerosis?

• 3D US Images (common & internal carotid; R, L)
• Sensitive
• analyzed simultaneously; blind to time point & dietary group
• Randomized by duration of statin use (%20)
Higher baseline carotid VWV was associated with increased IMT, age, male sex, baseline weight, blood pressure, and insulin levels
NO association with LDL-c w/wo statins

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Tertiles of baseline carotid vessel wall volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid vessel wall volume, mm$^3$</td>
<td>Lowest 685.39</td>
</tr>
<tr>
<td>Intima-media thickness (IMT), mm</td>
<td>0.777</td>
</tr>
<tr>
<td>mean=0.817 mm</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>49.10</td>
</tr>
<tr>
<td>Men, %</td>
<td>74</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86.07</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>126.45</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>77.43</td>
</tr>
<tr>
<td>Fasting insulin, µU/MI</td>
<td>12.98</td>
</tr>
</tbody>
</table>

‡ p<0.05 ‡p<0.01 for age-adjusted P of trend (except of age) across tertiles LDL-c: 115;123;117 mg/ dL
AFTER 2 YEARS OF DIETARY INTERVENTION?

Significant 5% *regression* in Carotid Vessel Wall Volume 
[-58.1mm³ (95%CI;-35.1,-81.0; p<0.001)]
Similar across the diet groups

change in IMT = -1.1% (p=0.18)
2-year diet effect on carotid atherosclerosis; representative sample images
2/3 exhibited *regression* (-128.0mm³)

1/3 exhibited *progression* (+89.6mm³)

What were the differences between those participants?

after excluding ptc with +/- 2% of VWV
A. The regression group had greater weight loss after excluding ptc with +/- 2% of VWV.
B. The regression group had greater decrease of systolic blood pressure after excluding ptc with +/- 2% of VWV

* p<0.001
Regression vs. progression

A. Greater **weight loss** (-5.3kg vs. -3.2kg; p=0.03)

B. Greater decrease of **systolic blood pressure** (-6.8mmHg vs. -1.1mmHg; p=0.009)

C. Decrease of **total-homocysteine** (-0.06µmol/L vs. +1.44µmol/L; p=0.04)

D. Tendency toward **increase of apoA1** (+0.05g/L vs. -0.001g/L; p=0.06)
In MV model, only the decrease in **systolic blood pressure** remained a significant independent modifiable predictor of greater regression in both carotid vessel wall volume and intima-media thickness.

**Table 2. Predictors of 2-Year Change in Carotid VWV and IMT: Multivariate Regression Model**

<table>
<thead>
<tr>
<th>Variable in the Models</th>
<th>Change in Carotid VWV: Multivariate Model 1</th>
<th>Change in Carotid IMT: Multivariate Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline level, time 0 (carotid VMV, mm³ in model 1; and carotid IMT, mm in model 2)</td>
<td>-0.319 (0.001)</td>
<td>-0.335 (0.002)</td>
</tr>
<tr>
<td>Change in systolic blood pressure, mm Hg</td>
<td>0.232 (0.01)</td>
<td>0.275 (0.008)</td>
</tr>
<tr>
<td>Change in weight, kg</td>
<td>0.013 (0.32)</td>
<td>-0.063 (0.52)</td>
</tr>
<tr>
<td>Change in total homocystine, μmol/L</td>
<td>0.028 (0.75)</td>
<td>-0.054 (0.57)</td>
</tr>
<tr>
<td>Change in apoA1, g/L</td>
<td>-0.072 (0.43)</td>
<td>-0.009 (0.93)</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.064 (0.48)</td>
<td>-0.058 (0.56)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.019 (0.83)</td>
<td>-0.020 (0.83)</td>
</tr>
<tr>
<td>Mediterranean vs low-fat assigned diet</td>
<td>0.092 (0.35)</td>
<td>-0.020 (0.85)</td>
</tr>
<tr>
<td>Low-carbohydrate vs low-fat assigned diet</td>
<td>-0.046 (0.64)</td>
<td>0.074 (0.50)</td>
</tr>
</tbody>
</table>

*Circulation 2010*
Results from the PREDIMED trial
Med Diets enhanced with virgin olive oil or nuts were not effective in inducing regression of carotid atherosclerosis after 1 year intervention. However, they were effective among subjects with elevated baseline IMT, suggesting that subclinical atherosclerosis may respond to dietary intervention within a relatively short time frame only among subjects with a high initial atherosclerotic burden.

Does the nutritional effect last?
How do traditional biomarkers and novel adipokines change during “weight loss” and “regain” phases?

- Progranulin
- MCP-1
- Leptin
- Adiponectin
- Vaspin
- Chemerin
- RBP4
- HDL-c
- TG
- CRP
- Fetuin-A
Two Patterns of Adipokine and Other Biomarker Dynamics in a Long-Term Weight Loss Intervention

**Pattern A** biomarkers whose dynamics correspond to weight-loss phases (sig diff of direction between phases, <0.05)

- Keeping healthy diet is beyond weight loss and can gradually halt the progression or regress your atherosclerosis

**Diabetes Care 2012**
Can alcohol regress atherosclerosis, beyond the effect of Med diet?
The 2-year CArdiovasCulaR Diabetes and Ethanol (CASCADE) Randomized Controlled Trial

BGU/NRCN/Soroka, Israel

Collaborators:
Robarts Institute, Canada
Harvard U, USA
Leipzig U, Germany
Karolinska Institute, Sweden

Funded by

ClinicalTrials.gov Identifier: NCT00784433
Mineral water (150cc / day at dinner) + Mediterranean diet

White wine (150cc / day at dinner) + Mediterranean diet

Red wine (150cc / day at dinner) + Mediterranean diet

The 2-year CASCADE trial

• All beverages provided
• Dietary sessions

Picture source: The Nutrition Source, Department of Nutrition, Harvard School of Public Health
Mediterranean diet & regression of atherosclerosis; Is it possible?

- Healthy DIET IS EFFECTIVE for inducing a significant regression of carotid atherosclerosis.

- Regression is more apparent with diet who maintained at 2 years greater declines in weight (5.5 Kg, 11 lbs) & blood pressure (~6-7 mmHg) and increase in apoA.

- Med diet as a perfect strategy