Dietary carbohydrates and metabolic outcomes: assessing the totality, consistency and quality of epidemiologic observations and clinical interventions

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Overview

♦ A diet that affects glucose homeostasis may be fundamental to vascular health outcomes
  • Glycemic response, glycemic index, and glycemic load
  • Supports from evolutionary theory, epidemiologic observations, and experimental evidence
    – Functional measures to study diet and disease in human populations
    – Biological intermediaries for diabetes and cardiovascular disease
    – Sex, body weight, and age as important modifiers

♦ Conclusions
  • Integrative framework for research
  • Preventive recommendation
Pathogenesis of DM/CHD Related to Insulin Resistance

Genes → Diabetes mellitus → Obesity → Insulin resistance → Hyperglycemia → Hyperinsulinemia

- Diets (high GL/insulin demand)
- Dyslipidemia (↑TG, ↓HDL)
- Amyloid deposit
- Relative insulin deficiency
- Glycation of LDL (↑)
- Sorbitol (↑)
- NO/vasodilatory response (↓)
- Beta-cell mass (↓)

Hemodynamic changes: inflammation, impaired fibrinolysis and thrombosis

Coronary Heart Disease

Liu, 1998; Liu and Manson, 2001
## Traditional Epidemiology:
### Common Risk Factors for Three Major Metabolic Diseases

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Type 2 DM</th>
<th>CHD</th>
<th>Colon Ca.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>↑↑↑</td>
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<tr>
<td>Tobacco</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Physical inactivity</td>
<td>↑↑</td>
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<tr>
<td>Obesity</td>
<td>↑↑↑↑</td>
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<tr>
<td>Sex??</td>
<td></td>
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<tr>
<td>Excess energy intake</td>
<td>↑?</td>
<td>↑?</td>
<td>↑?</td>
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<tr>
<td>Saturated fat</td>
<td>↑?</td>
<td>↑?</td>
<td>↑?</td>
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<tr>
<td>Red meat</td>
<td>↑?</td>
<td>↑?</td>
<td>↑?</td>
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<tr>
<td>Refined carbohydrates</td>
<td>↑↑?</td>
<td>↑↑?</td>
<td>↑↑?</td>
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<tr>
<td>Dietary fibers</td>
<td>↓↓?</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Fruits &amp; vegetables</td>
<td>↓↓?</td>
<td>↓↓</td>
<td>↓↓</td>
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<tr>
<td>Whole grains</td>
<td>↓↓?</td>
<td>↓↓</td>
<td>↓↓</td>
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<tr>
<td>Nuts/legumes</td>
<td>↓↓?</td>
<td>↓↓</td>
<td>↓↓</td>
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<tr>
<td>Moderate Alcohol</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑</td>
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</table>

Modified from Giovannucci 1995 and Liu 1998
Sex differences related to vascular outcomes in prospective studies

BMI and risk of type 2 diabetes → stronger in women

Diabetes and risk of CVD mortality → stronger in women

Willett NEJM 1999; Huxley BMJ 2005

Fig 2 Overall summary estimates of relative risks and 95% confidence intervals for fatal coronary heart disease in men and women with and without diabetes in 22 studies that reported both age and multiple adjusted coefficients.
Dose-response relation between blood glucose and CHD risk

Plasma glucose (mg/dL)

Log relative risk
The effect of decreasing PPG with acarbose, an -glucosidase inhibitor, on DM development in a multicenter double-blind, placebo-controlled, randomized trial Chiasson et al. Lancet 2002
The effect of decreasing PPG with acarbose, an α-glucosidase inhibitor, on CVD development in a multicenter double-blind, placebo-controlled, randomized trial Chiasson et al. JAMA 2004
GI & Voluntary Food Intake

*Ludwig et al. Pediatrics 1999, 103:e261*

**Kilocalories Consumed**

**Cumulative Voluntary Food Intake**

Legend:
- High GI
- Med GI
- Low GI
Low GI diets improve triglycerides
Low GI diet compared with high GI diet

-25 -20 -15 -10 -5 0 5

Frost et al 1994
Fontvieille et al 1992
Wolever et al 1992
Fontvieille et al 1988
Jenkins et al 1985
Jenkins et al 1987
Jarvi et al 1999
Brand et al 1991

25 type 2, 12 wks
18 type 1 & 2, 5 wks
6 type 2, 6 wks
8 type 1, 3 wks
12 CHD, 4 wks
30 CHD, 4 wks
20 type 2, 24 days

Average change in 8 studies = -12%

*Include extensive data from Prof. Y.X. Yang Chinese CDC
Changes in HbA$_{1c}$ or fructosamine

Low GI diets compared with high GI diets

Frost et al 1994
Fontvieille et al 1992
Brand et al 1991
Wolever et al 1992
Wolever et al 1992
Jenkins et al 1988
Fontvielle 1988
Collier et al 1988
Gilbertson et al 2000

Average difference in HbA$_{1c}$ in 9 studies = -11%

Adapted from Brand-Miller et al. 2001
Change in Glycemic Control
Low vs high GI diets

• Glycemic control -
  10% improvement for a 10 unit decrease in GI

• Comparison with other interventions

  DCCT - 20%
  UKPDS  - 11.5%
  Acarbose - 6.5%
  Insulin analogues - 2.5%

Adapted from Stephen Colagiuri  Aust Nutr Soc 2001
Fasting plasma TG concentrations by GL, GI and carbohydrate intake

Nurses’ Health Study

- Glycemic Index (p=0.03)
- Carbohydrate (p=0.005)
- Glycemic Load (p<0.001)

Liu et al. AJCN 2001
Fasting Plasma TG Levels by Dietary Glycemic Load
Postmenopausal Women with Different BMI’s

Liu et al. AJCN, 2001
Adjusted geometric mean plasma concentrations of high-sensitivity C-reactive protein (hs-CRP) by quintiles (Q1–Q5) of energy-adjusted dietary glycemic load in 244 women in 2 BMI categories


Subsequently confirmed by Rhodes et al in a randomized trial of overweight pregnant women AJCN 2010
Geometric mean high density lipoprotein cholesterol and triglyceride levels*

*Adjusted for age, smoking (current, past, never), exercise (4 category), hormone replacement therapy use (current, past, never), family history of MI, history of diabetes, body mass index (4 category), and intakes of total energy, alcohol intake (4 category), and quintile of total fat, protein, cholesterol, folate, and magnesium intake. Dietary glycemic load additionally adjusted for quintile of fiber intake.
Relation between HDL-cholesterol concentration and glycemic index in men and women (Frost et al, 1999)
Mean concentrations of HDL by glycemic index among men and women aged 20+ years, NHANES III, 1988-1994 (Ford and Liu, Arch Int Med 2000)

Adjusted for age, race or ethnicity, education, smoking status, body mass index, alcohol intake, physical activity, percent kilocalories from protein (quintiles), percent kilocalories from fat (quintiles), total energy intake (quintiles).
Results: Diet-by-sex interaction

% Total Adipose Growth (0 to 8 Weeks)

- Male
- Female

Slide courtesy of Drs Tom Drake & Jake Lusis
Mean concentrations of Carotenoids by glycemic index among 15270 US adults, NHANES III

Quintile of dietary glycemic index

- Lycopene
- Lutein/zeaxanthin
- Beta-carotene
- Crptoxanthin
- Alpha-carotene

Liu and Ford, 2002
Mean concentrations of serum Vitamin E and Vitamin C by glycemic index among 15270 US adults, NHANES III

Liu and Ford, 2002
Potential biochemical mechanisms

High GI/GL feeding causes:

♦ Postprandial hyperglycemia & hyperinsulinemia - *(immediate responses)*

♦ Counterregulatory hormonal responses which stimulate appetite, FFA production, and possibly protein breakdown – *(late responses)*

♦ Shifts in substrate utilization away from fat towards carbohydrates

♦ Increased enzymatic capacities for carbohydrate oxidation and lipogenesis, and decreased enzymatic capacity of fat oxidation
Adjusted estimates of relative risk of type 2 diabetes according to GL by sex from a meta-analysis of all prospective cohorts with 7.5 million years of followup (up to August 2012)

Livesay et al. Am J Clin Nutr 2013
Multivariate relative risk of CHD by body mass index and glycemic load

Test for interaction, P < 0.01

<table>
<thead>
<tr>
<th>BMI</th>
<th>RR</th>
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<tbody>
<tr>
<td>&lt; 23</td>
<td>1.00</td>
</tr>
<tr>
<td>23-29</td>
<td>1.05</td>
</tr>
<tr>
<td>&gt;29</td>
<td>1.42</td>
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</table>

<table>
<thead>
<tr>
<th>GL</th>
<th>RR</th>
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<tr>
<td>&lt; 23</td>
<td>0.94</td>
</tr>
<tr>
<td>23-29</td>
<td>1.11</td>
</tr>
<tr>
<td>&gt;29</td>
<td>1.20</td>
</tr>
</tbody>
</table>

Liu et al 2000
Different constituents of a low GI/GL diet

♦ Fruits and vegetables
♦ Whole grains
♦ Nuts
♦ Legumes (peas, beans, soybeans)
♦ Fish
♦ Dairy foods
Conclusion

Due to our genetic mal-adaptation to westernized lifestyle/environment, we are increasingly becoming a metabolically efficient population.

Substantial evidence indicates significant biological importance and clinical utilities of the GI/GL concepts, in that:

1) Carbohydrate-containing foods differ in their abilities to raise plasma glucose and insulin (Level A),
2) Diets characterized by high GL adversely affect metabolic intermediates (Level B),
3) May increase risk of vascular outcomes (diabetes and cardiovascular diseases) especially among those who are prone to insulin resistance (Level B and C).

Can we conclusively demonstrate the efficacy of glucose homeostasis diet on vascular health in randomized trials:

- Not feasible
- Not ethical
- Not necessary
Conclusion

- When thinking about diet, which is only one aspect of our westernized environment, we need to keep in mind what kind of people we have become metabolically.

  - Consider sex, body weight, and age as important modifiers when assessing diet-disease relation and making dietary recommendation
    - Reduce heterogeneity and improve biological understanding of the “glucose homeostasis” diet

  - Regarding the clinical utility of the GI concept,
    - It is better than the “simple/complex” in classifying carbohydrates
    - Does go beyond individual food-based guidelines, even in the context of caloric density and nutrient composition
    - GI is most useful for ranking high/dense-carbohydrate foods