Research on Type 2 Diabetes Prevention & Complications
Including DPP, Look AHEAD, RISE and GRADE Studies

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March 21, 2015
Objectives

- What is the challenge in prevention
- What has research shown us works, what does not
- What benefit persists over time
- What complications associated with diabetes are changing
- What are future questions
Projecting the Future Diabetes Population: The Imperative for Change

• 382 million adults (8.3%) worldwide living with diabetes
• Estimated projected rise over 592 million by 2035
• $147 billion spent on diabetes in Europe, 2013
• $263 billion No America and Caribbean, 2013.
• Diabetes has become a major cause of death in younger than 60 yrs.
• Effective diabetes prevention and management necessary to battle this global epidemic
Prevention

**Continuum of Risk & Intervention**

- **200 Million with Obesity Risk Factors?**
- **140 Million Overweight or Obese***
- **85 Million High Risk for Diabetes**
- **Diabetes, Heart Disease, Stroke**

**Population-based Policies** (Social/Cultural Change)  
Long-term Payoff

**Resource Intensive Programs** (Prevent Obesity-Related Risks)  
Shorter-term Payoff

† Using ADA prediabetes definition OR A1c 5.7-6.4%; Source: NHANES 2005-06
No surprises

- Obesity correlates with higher risk for development of diabetes (DM)
- Waist circumference is better correlate with DM risk than BMI
- Weight gain since young adulthood independent predictor of DM risk, even after adjustment for current BMI

Dietary factors for the prevention of diabetes

Figure 1: Changes in global dietary trend over time
A high diet 1 score indicates a high availability of sugars, meat, animal products, animal fats, milk, eggs, and total calories, in addition to low availability of pulses and cereals based on the United Nations Food and Agriculture Organization food balance sheets.⁴

Specific Nutrient Associations

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Number of cohorts</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haeme-iron</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Glycaemic index</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Glycaemic load</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>DHA/EPA</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Vegetable fibre</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Fruit fibre</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Alpha-linolenic acid</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Cereal fibre</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2: Summary of meta-analyses of prospective cohort studies of nutrient intake and glycaemic variables and type 2 diabetes**

DHA = docosahexaenoic acid. EPA = eicosapentaenoic acid. Relative risks are a comparison of extreme categories, except for DHA/EPA (per 250 mg per day increase) and alpha-linolenic acid (per 0.5 g per day). All nutrients and glycaemic variables were assessed from dietary intake, except vitamin D for which blood 25-hydroxyvitamin D was used.

A high dietary fat intake is directly associated with increased risk for the development of DM.

True or False?
Dietary Fats

- Increased risk of DM indirectly by promoting weight gain
- BUT studies in humans do not support high-fat diets have a detrimental effect on insulin sensitivity
- Women’s Health Initiative, incidence of diabetes not reduced in women following low-fat diet compared to control group
- Quality of fat important- diets high in plant-based over animal fats more protective: greater intake of omega-6 polyunsaturated fatty acids (PUFA) associated with lower DM risk
- Nurses’ Health Study: Replacement of saturated fat with PUFA associated with lower risk of developing DM
- However, association between omega-3 PUFA and diabetes risk has been inconsistent
Question 2:

- Higher carbohydrate intake has been associated with decreased risk of development of DM.

True or False?
Dietary Carbohydrate

- Prospective observational evidence suggests that the relative carbohydrate proportion of a diet does not affect DM risk.
- Diet rich in fiber, especially cereal fiber, might reduce the risk of diabetes. Fruit fiber weaker inverse association than cereal fiber.
- Carbohydrate quality can be measured by evaluation of glycemic response to carbohydrate-rich foods, such as glycemic index (GI) and glycemic load (GL, a product of GI and the amount of carbohydrates of a food).
- In meta-analyses of prospective studies, low GI and GL diets were associated with lower risk of diabetes than were diets with a higher GI and GL, independent of amount of cereal fiber.
Increased risk of developing diabetes is associated with:

A- Smoking
B- Coffee
C- Mediterranean Diet
D- Alcohol
The ex- and heavy current smokers -highest incidence of diabetes of 12.5% and 11.1% respectively, compared with never-smokers (7.9%) during 4 years of follow-up.

Coffee Consumption

• Meta-analysis (15 epidemiological studies, 9 prospective and 6 case-control, involving 200,000 participants): Compared with no consumption, four or more cups of coffee/day resulted in 35% reduced risk of DM2.

• 2\textsuperscript{nd} meta-analysis (20 prospective studies total of 500,000 people with follow-up 2-20 yrs) inverse association between coffee consumption and risk of DM2 and dose dependent.

• Risk reduced 7% per cup of coffee/day. Decaffeinated or caffeinated
• Analysis 6 studies, total of 225,000 individuals showed risk of developing DM2 about one-third lower in people who drink 3-4 cups of decaffeinated coffee per day than in people who do not drink coffee.
Alcohol

Figure 1. Relationship between alcohol intake and relative risk (RR) of type 2 diabetes in women (A) and men (B). Pooled and fitted RR estimates with 95% CI presented. Adapted from Ballenas et al. [4].

A. Pietraszek, S. Gregersen, K. Hermansen

Alcohol and type 2 diabetes. A review

Nutrition, Metabolism and Cardiovascular Diseases, Volume 20, Issue 5, 2010, 366 - 375
Dietary Changes
The “Toxic Environment”

High-Calorie Food is...
- Highly palatable
- Heavily advertised
- Inexpensive
- Near-ubiquitous
- Supersized

Sedentary Lifestyles
Feasibility of Preventing Type 2 Diabetes

- There is a long period of glucose intolerance that precedes the development of diabetes
- Screening tests can identify persons at high risk
- There are safe, potentially effective interventions that can address modifiable risk factors:
  - Obesity
  - Body fat distribution
  - Physical inactivity
  - High blood glucose
Interventions To Reduce the Risks Associated with Prediabetes

• Intensive lifestyle management is the cornerstone of all prevention efforts

• No pharmacologic agents are currently approved for the management of prediabetes
  – Pharmacotherapy targeted at glucose may be considered in high-risk patients after individual risk:benefit analysis
Is it Possible to Delay the Onset of T2DM?


Incidence of Diabetes
Diabetes Prevention Program (DPP)

Figure 2. Cumulative Incidence of Diabetes According to Study Group.

The diagnosis of diabetes was based on the criteria of the American Diabetes Association.10 The incidence of diabetes differed significantly among the three groups (P<0.001 for each group).

Risk reduction
31% by metformin
58% by lifestyle

(n=1079, p<0.001 vs. Metformin
p<0.001 vs. Placebo)

(n=1073, p<0.001 vs. Placebo)
Diabetes Prevention Program
Conclusions

- **Lifestyle modification** was most effective for individuals ≥60 years of age and for those with lower baseline BMI

- **Metformin** reduced the risk of developing type 2 diabetes most effectively in patients <60 years of age, and in those with a baseline BMI >35 kg/m²

- **Early intervention** resulted in the greatest rate of diabetes prevention/delay in all groups
Intensive Lifestyle Intervention Prevents Progression From IGT to T2DM

Diabetes Prevention Program (n=3234)

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence per 100 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive lifestyle intervention*</td>
<td>4.8</td>
</tr>
<tr>
<td>Metformin 850mg BID</td>
<td>7.8 (31%)</td>
</tr>
<tr>
<td>Placebo (n=1082)</td>
<td>11</td>
</tr>
</tbody>
</table>

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat meal plan and ≥150 min/week moderate intensity physical activity.
Diabetes Prevention Program: Weight loss for reduced diabetes incidence

- Recent analysis of 2-year outcomes from the Diabetes Prevention Program (DPP) showed the importance of weight loss.
- Weight loss over 2 years is strongest predictor of:
  - Reduced diabetes incidence (HR 0.90 per kg, 95% CI 0.87, 0.93; P < 0.01)
  - Improved fasting glucose (β = -0.57 mg/dL per kg, 95% CI -0.66, -0.48; P < 0.01)
- Weight cycling (repeated weight loss and gain) was associated with increased diabetes incidence.

Delahanty LM. Diabetes Care. 2014. [Epub ahead of print].
Intensive Lifestyle Intervention Effectively Prevents T2DM as Populations Age

Diabetes Prevention Program (DPP)
(n=3234)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-44</td>
<td>11.6</td>
<td>6.7</td>
<td>6.2</td>
</tr>
<tr>
<td>45-59</td>
<td>10.8</td>
<td>4.7</td>
<td>7.6</td>
</tr>
<tr>
<td>≥60</td>
<td>10.8</td>
<td>9.6</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Diabetes Incidence per 100 Person-Years

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat meal plan and ≥150 min/week moderate intensity physical activity

DPP Research Group. NEJM 2002;346:393-403
Lifestyle Change and Weight Loss Reduces Long-term Incidence of T2DM Finnish Diabetes Prevention Study (n=522)

Kaplan-Meier estimate of probability of remaining free of diabetes

Follow-up Time (Years)

Log-rank test P=0.0001
Hazard ratio: 0.57 (95% CI 0.43-0.76)

Intensive lifestyle intervention goal: 5% reduction in body weight with moderate-intensity physical activity for ≥30 minutes/day plus meal plan consisting of <30% calories from fat, <10% calories from saturated fat, and ≥15 mg fiber.

Lifestyle Long-term Effects
Cumulative 20-Year Incidence of T2DM

Da Qing Diabetes Prevention Study

6-year intervention hazard rate ratio 0.49 (95% CI 0.33-0.73)
20-year follow-up hazard rate ratio 0.57 (95% CI 0.41-0.81)

Number at risk
Control 135 105 69 48 40 37 34 27 27 23 14
Intervention 428 387 314 250 230 206 192 161 147 136 114

Intensive Lifestyle Intervention Reduces Blood Pressure

Diabetes Prevention Program (N=3234)

Blood Pressure Change

- Placebo
- Metformin
- Intensive lifestyle intervention

Hypertension Prevalence

- Placebo
- Metformin
- Intensive lifestyle intervention

Systolic blood pressure (mmHg)

P<0.001

Intensive Lifestyle Intervention Reduces Dyslipidemia

Diabetes Prevention Program
(N=3234)

Look AHEAD (Action for HEAlth in Diabetes) Study

- Any type of glucose-lowering medication allowable
- No more than 30% of enrolled participants could be receiving insulin
- Included patients with and without a history of cardiovascular disease
- Two groups of patients (N=5145; mean age 59 years) were randomly assigned:
  - 1. Intensive Lifestyle Intervention (ILI)
    - Goal = attain weight loss of 7% and maintain it
    - Lowering caloric intake and increase physical activity
  - 2. Control Group
    - Diabetes support and education only
- Any medication changes were made by patients’ own care providers

Effects of Weight Loss on CV Outcomes: Look AHEAD

• **Purpose:** To study long-term cardiovascular effects of weight loss; 16 clinical sites in the U.S.

• **Inclusion Criteria:**
  - Age 45-75 years
  - T2DM Self-reported
  - BMI ≥ 25 kg/m² (≥ 27 kg/m² for patients on insulin)
  - A1C ≤ 11.0%
  - SBP < 160 mm Hg
  - DBP < 100 mm Hg
  - Tg < 600 mg/dL
  - Ability to complete an exercise test
  - Managed by a PCP

V= cardiovascular; A1C=glycated hemoglobin; BMI=body mass index; DBP=diastolic blood pressure; PCP=primary care provider; BP=systolic blood pressure; T2DM=type 2 diabetes mellitus; Tg=triglycerides

Look AHEAD Study

• **Primary Endpoint**
  - First occurrence of a cardiovascular (CV) outcome
    • Death from CV cause
    • Nonfatal myocardial infarction (MI)
    • Nonfatal stroke
    • Hospitalization for angina

• **Secondary Endpoints**
  - Death from: CV cause, nonfatal MI, or nonfatal stroke
  - Death from: Any cause, MI, stroke
  - Hospitalization for: Angina, coronary artery bypass surgery, percutaneous coronary intervention, heart failure, or peripheral vascular disease

Look AHEAD Study

- **Outcomes** in intensive lifestyle intervention (ILI) group:
  - Weight Loss
    - First year: Lost 8.6% of body weight
    - Average weight loss at end of trial, 6%
  - Improved A1C
  - CKD risk decreased by 31%
  - Over 9.6 years of follow up, there was **no significant difference** between the intensive ILI group and the control group in terms of **CV morbidity and mortality**
Look AHEAD Study
Change in Weight and Fitness: 10 Years of Follow Up

Look AHEAD Study

Change in Waist Circumference and A1C Levels: 10 Years of Follow Up

# Look AHEAD Study

## Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients with Event</th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td>no.</td>
<td>no. of events (rate/100 person-yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina</td>
<td>821</td>
<td>418 (1.92)</td>
<td>403 (1.83)</td>
<td>0.95 (0.83–1.09)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td>no.</td>
<td>no. of events (rate/100 person-yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>550</td>
<td>283 (1.25)</td>
<td>267 (1.17)</td>
<td>0.93 (0.79–1.10)</td>
<td>0.42</td>
</tr>
<tr>
<td>Death from any cause, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>1025</td>
<td>529 (2.43)</td>
<td>496 (2.25)</td>
<td>0.93 (0.82–1.05)</td>
<td>0.23</td>
</tr>
<tr>
<td>Death from any cause, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, CABG, PCI, hospitalization for heart failure, carotid endarterectomy, or peripheral vascular disease</td>
<td>1177</td>
<td>600 (2.81)</td>
<td>577 (2.67)</td>
<td>0.94 (0.84–1.05)</td>
<td>0.29</td>
</tr>
</tbody>
</table>
Look AHEAD Study

Conclusions:

• Look AHEAD found no significant difference in CV outcomes between the ILI and control groups.

• However, the ILI intervention group had greater reductions in weight, A1C, and greater initial improvements multiple other domains:
  – Reductions in rates of urinary incontinence, sleep apnea and depression
  – Improvements in quality of life, physical functioning, and mobility

# Nutrition

## Reduced Calorie Diet

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General eating habits</td>
<td></td>
</tr>
<tr>
<td>- Regular meals and snacks; avoid fasting to lose weight</td>
<td></td>
</tr>
<tr>
<td>- Plant-based diet (high in fiber, low calories, low glycemic index, high in phytochemicals/antioxidants)</td>
<td></td>
</tr>
<tr>
<td>- Understand Nutrition Facts Label information</td>
<td></td>
</tr>
<tr>
<td>- Incorporate beliefs and culture into discussions</td>
<td></td>
</tr>
<tr>
<td>- Informal clinician-patient discussions</td>
<td></td>
</tr>
<tr>
<td>- Use mild cooking techniques instead of high-heat cooking</td>
<td></td>
</tr>
</tbody>
</table>

A negative energy balance is necessary to achieve weight loss.

# Nutrition

## Nutritional Components

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Carbohydrate | - Understand health effects of the 3 types of carbohydrates: sugars, starch, and fiber  
|            | - Target 7-10 servings per day of healthful carbohydrates (fresh fruits and vegetables, pulses, whole grains)  
|            | - Lower-glycemic index foods may facilitate glycemic control:* multigrain bread, pumpernickel bread, whole oats, legumes, apple, lentils, chickpeas, mango, yams, brown rice  |
| Fat        | - Eat healthful fats: low-mercury/low-contaminant-containing nuts, avocado, certain plant oils, fish  
|            | - Limit saturated fats (butter, fatty red meats, tropical plant oils, fast foods) and trans fats  
|            | - Use no- or low-fat dairy products  |
| Protein    | - Consume protein from foods low in saturated fats (fish, egg whites, beans)  
|            | - Avoid or limit processed meats  |
| Micronutrients | - Routine supplementation not necessary except for patients at risk of insufficiency or deficiency  
|            | - Chromium; vanadium; magnesium; vitamins A, C, and E; and CoQ10 not recommended for glycemic control  |

*Insufficient evidence to support a formal recommendation to educate patients that sugars have both positive and negative health effects.*

Adherence Is More Important Than Diet Type for Weight Loss Success

How Much Exercise Is Enough?

• Intensity
  – Moderate, “conversational” exercise (: should be able to talk comfortably )
  – Heart rate at 70% of maximum (max HR = 220 – age)

• Frequency
  – 3-4 times per week
  – Maintain regular schedule with realistic goals

• Motivation
  – Cross-train (ie, walk, ride, swim)
  – Use exercise partner or professional trainer or attend organized programs
  – Reward self

• Health care professional team must exude positive attitude regarding importance of exercise
"But Doc, I Can’t Walk Too Far"

<table>
<thead>
<tr>
<th><strong>All patients</strong></th>
<th>Recommend low-impact exercise: stationary bicycle, swimming, elliptical machine, stairstepper, treadmill, low-impact aerobics, weight-lifting machine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot disease, peripheral vascular disease, arthritis</td>
<td>Swimming, water aerobics, upper body resistance training</td>
</tr>
<tr>
<td>Orthostatic conditions</td>
<td>Semi-recumbent chair and weight lifting, semi-recumbent cycling, water exercise</td>
</tr>
<tr>
<td>Elderly</td>
<td>Stretching while sitting, movement exercise (eg, tai chi, hatha yoga)</td>
</tr>
</tbody>
</table>
What’s New in the Research Pipeline?

• GRADE
  The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study
• RISE
  Restoring Insulin Secretion study
• PERL
  Preventing Early Renal Loss in Diabetes (Type 1)
Guidelines:

**Glycemic Control Algorithm**

**Lifestyle Modification**
(Including Medically Assisted Weight Loss)

**Entry A1c < 7.5%**
- **Monotherapy**
  - Metformin
  - GLP-1 RA
  - DPP4-i
  - AG-i
  - SGLT-2
  - TZD
  - SU/GLN

  If A1c > 6.5% in 3 months add second drug (Dual Therapy)

**Entry A1c ≥ 7.5%**
- **Dual Therapy**
  - GLP-1 RA
  - DPP4-i
  - TZD
  - SGLT-2
  - Basal insulin
  - Colesevelam
  - Bromocriptine QR
  - AG-i
  - SU/GLN

  If not at goal in 3 months proceed to Triple Therapy

**Entry A1c > 9.0%**
- **No Symptoms**
  - Dual Therapy
  - Triple Therapy
  - Insulin or Other Agents

- **Symptoms**
  - Add or Intensify Insulin

**Legend**
- = Few adverse events or possible benefits
- = Use with caution

*Order of medications listed are a suggested hierarchy of usage
**Based upon phase 3 clinical trials data*
GRADE Study:

• 7 year long comparator trial in early DM 2 of metformin vs metformin plus either:
  GLP-1 agonist or Sulfonylurea or DPP-4 inhibitor or basal Insulin

• Designed to answer whether dual therapy in early diabetes better preserves beta-cell function (in contrast to current early monotherapy)

• Drugs, lab, exams provided at no cost to participant, plus $25 to patient per study visit after enrollment

• Call 206-598-4978 for additional information
RISE Study

- Prediabetes or diagnosed with type 2 diabetes within past year. Two trials will examine adults; the other will look at youth. Metformin alone;
- Metformin alone, metformin plus liraglutide, and glargine, a long-acting insulin that would be used for three months before switching to metformin (additional arm is bariatric surgery)
- The trial aims to enroll 255 people among several UW sites
- Call 206-598-4978 for additional information
• Type 1 diabetes and known renal disease
• Allopurinol versus placebo
• Will last 3 years, kidney function will be measured periodically to see if this treatment is effective
• Call 206-598-4882 (option 8)
Thank you!!