Diabetes Mellitus Type 2: An Update, Diagnosis And Treatment Considerations

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KFC: support diabetes research by buying an 800 calorie, 56 spoonful of sugar "Mega Jug"

Cory Doctorow at 11:11 AM Sat via SUBMITTERATOR

Mitch sez, "A KFC franchise in Utah is asking customers to help fight diabetes -- by purchasing an 800-calorie Mega Jug of sugary soda to wash down their meals."

The reaction: It's hard to imagine what KFC was thinking, says Joe Waters at Selfish Giving. Although after "the dreadful Double Down," it's no surprise these folks have "deep fried their reputation again." Give this franchise owner credit for wanting to do some good, says Jenn Savedge at Mother Nature Network. But why not tie the promotion to something healthier like, say, grilled chicken? Trying to link a drink with 56 spoonfuls of sugar to a health cause has to qualify as one of the biggest PR misfires ever.

Irony alert: Buy KFC's 800-calorie soda to support diabetes research (Thanks, Mitch!)

(Image: Ridiculous drink size, a Creative Commons Attribution (2.0) image from wyscan's photostream)
Diabetes risk gene 'from Neanderthals'

By Paul Rincon
Science editor, BBC News website

A gene variant that seems to increase the risk of diabetes in Latin Americans appears to have been inherited from Neanderthals, a study suggests.

We now know that modern humans interbred with a population of Neanderthals shortly after leaving Africa 60,000-70,000 years ago.

This means that Neanderthal genes are now scattered across the genomes of all non-Africans living today.

Details of the study appear in the journal Nature.

The gene variant was detected in a large genome-wide association study (GWAS) of more than 8,000 Mexicans and other Latin Americans. The GWAS approach looks at many genes in different individuals, to see whether they are linked with a particular trait.

People who carry the higher risk version of the gene are 25% more likely to have diabetes than those who do not, and people who inherited copies from both parents are 90% more likely to have diabetes.

The higher risk form of the gene - named SLC16A11 - has been found in up to half of people with recent Native American ancestry, including Latin Americans.
Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2014

Percentage with Diabetes
Number with Diabetes

Year

Number with Diabetes ( Millions )

Percentage with Diabetes

Diabetes/Pre-Diabetes Prevalence

- 29 Million Have DM/ 86 Million Pre-DM
- 21M Diagnosed/27.8% Are Undiagnosed
- 37% of Age 20 years and + Have Pre-DM
- 51% of Age 65 years and + Have Pre-DM!
- Direct Cost 176B (Medical Expenditures)
- Indirect Cost 69B (Disability/Work Loss/Premature Death)
- Total Cost 245 Billion

Millions of Cases of Diabetes in 2000 and Projections for 2030, with Projected Percent Changes

Diabetes Mellitus in the U.S.: Health Impact of the Disease

6th leading cause of death

- Life expectancy ↓ 5 to 10 yr
- Cardiovascular disease ↑ 2X to 4X
- Nerve damage in 60% to 70% of patients
- Renal failure*
- Blindness*
- Amputation*

*Diabetes is the no. 1 cause of renal failure, new cases of blindness, and nontraumatic amputations.

Hazard Ratios for Death from Cancer and from Noncancer, Nonvascular Causes among Participants with Diabetes as Compared with Those without Diabetes at Baseline.

### A. Cancer Death

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Deaths</th>
<th>Hazard Ratio with Diabetes (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>535</td>
<td>2.16 (1.62–2.88)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2189</td>
<td>1.53 (1.24–1.83)</td>
</tr>
<tr>
<td>Ovary</td>
<td>1149</td>
<td>1.45 (1.03–2.07)</td>
</tr>
<tr>
<td>Colon rectum</td>
<td>3876</td>
<td>1.40 (1.20–1.63)</td>
</tr>
<tr>
<td>Bladder</td>
<td>834</td>
<td>1.40 (1.01–1.96)</td>
</tr>
<tr>
<td>Oral</td>
<td>473</td>
<td>1.38 (0.90–2.12)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>547</td>
<td>1.36 (0.83–2.23)</td>
</tr>
<tr>
<td>Kidney</td>
<td>815</td>
<td>1.28 (0.89–1.83)</td>
</tr>
<tr>
<td>Lung</td>
<td>7823</td>
<td>1.27 (1.13–1.43)</td>
</tr>
<tr>
<td>Breast</td>
<td>3338</td>
<td>1.25 (1.02–1.52)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>795</td>
<td>1.21 (0.86–1.69)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1531</td>
<td>1.16 (0.92–1.46)</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>310</td>
<td>1.11 (0.58–2.11)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>3425</td>
<td>0.93 (0.77–1.13)</td>
</tr>
<tr>
<td>Prostate</td>
<td>2217</td>
<td>0.89 (0.71–1.19)</td>
</tr>
<tr>
<td>Endocrine and nervous</td>
<td>1299</td>
<td>0.88 (0.60–1.27)</td>
</tr>
<tr>
<td>Site unspecified or other</td>
<td>8680</td>
<td>1.17 (1.07–1.27)</td>
</tr>
</tbody>
</table>

### B. Noncancer, Nonvascular Death

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Deaths</th>
<th>Hazard Ratio with Diabetes (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>686</td>
<td>3.02 (2.19–3.82)</td>
</tr>
<tr>
<td>Infection (excluding pneumonia)</td>
<td>1081</td>
<td>2.39 (1.95–2.93)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1429</td>
<td>2.28 (1.90–2.74)</td>
</tr>
<tr>
<td>Digestive system disorder (excluding liver)</td>
<td>2034</td>
<td>1.70 (1.43–2.04)</td>
</tr>
<tr>
<td>Falls</td>
<td>642</td>
<td>1.70 (1.11–2.60)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2893</td>
<td>1.67 (1.45–1.92)</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>1948</td>
<td>1.64 (1.32–2.02)</td>
</tr>
<tr>
<td>Intentional self-harm</td>
<td>963</td>
<td>1.58 (1.16–2.15)</td>
</tr>
<tr>
<td>Endocrine, metabolic, or nutritional disorders</td>
<td>299</td>
<td>1.49 (0.88–2.52)</td>
</tr>
<tr>
<td>All external causes</td>
<td>4181</td>
<td>1.36 (1.19–1.56)</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>3133</td>
<td>1.28 (1.07–1.53)</td>
</tr>
<tr>
<td>COPD and related conditions</td>
<td>3197</td>
<td>1.27 (1.07–1.50)</td>
</tr>
<tr>
<td>Alzheimer's disease or related conditions</td>
<td>1273</td>
<td>1.21 (0.92–1.59)</td>
</tr>
<tr>
<td>Other noncancer, nonvascular deaths</td>
<td>2412</td>
<td>1.72 (1.53–1.93)</td>
</tr>
</tbody>
</table>

Nurses Health Study

• Five Keys For Women To Reduce Their Risk Of Diabetes By 91%
  – Maintain BMI <25
  – Eat a Diet High in Cereal Fiber and Polyunsaturated Fat and Low in Saturated and Trans Fats and Glycemic Load
  – Exercise Regularly
  – Quit Smoking
  – ½ Drink of Alcohol Per Day

Diabetes Prevention Program

• Randomized:
  – Standard lifestyle recommendations plus metformin 850 mg BID,
  – Standard lifestyle recommendations
    • Food Pyramid/NECP Step 1, Exercise
  – Intensive program of lifestyle modifications:
    • weight loss >7 % by diet + exercise 150 min./week
Diabetes Prevention Program

• Participants:
  – BMI 24 + (22+ Asians)
  – Age: 25 years +
  – Fasting Plasma glucose: Between 95 to 125 mg/dl (125 mg/dl American Indian clinics)
  – Two-hour 75g glucose load: Between 140 to 199 mg/dl
• Half were from racial or ethnic minority groups.
• 3234 followed for average of 2.8 years
Changes in Body Weight (Panel A) and Leisure Physical Activity (Panel B) and Adherence to Medication Regimen (Panel C) According to Study Group. Changes in weight and leisure physical activity over time differed significantly among the treatment groups (P<0.001 for each comparison).
Cumulative Incidence of Diabetes According to Study Group. The incidence of diabetes differed significantly among the three groups (P<0.001 for each comparison).
Hazard Ratios for Major Causes of Death, According to Baseline Levels of Fasting Glucose.

Criteria for the diagnosis of diabetes

FPG $\geq 126$ mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.\(^*\)

OR

2-h PG $\geq 200$ mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.\(^*\)

OR

A1C $\geq 6.5\%$ (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.\(^*\)

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose $\geq 200$ mg/dL (11.1 mmol/L).

* In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.\(^*\)

American Diabetes Association, *Diabetes Care*. 2017 (suppl 1)
Using the A1c For Diagnosis

• A1c ≥6.5% on two separate tests (Unless symptoms and glucose >200 mg/dl): DM DX
• A1c ≥ 5.7-, but <6.5%: Increased Risk/Pre-DM
• Caveats:
  – In acute onset DM, A1c may be normal (esp. with Pediatric Type 1 DM)
  – Underestimates glycemic control in shortened RBC survival and overestimates in iron deficiency anemia
  – Possible racial differences
  – Not for use in pregnancy/Unknown for Children
  – May not correlate with OGTT or FPG

American Diabetes Association, *Diabetes Care*. 2017 (suppl 1)
Who Should Be Screened?

• Age 45 years and above: Repeat every 3 years

• Screen if:
  – BMI ≥ 25 kg/m² (≥ 23 kg/m² in Asian Americans)
  – Adults: At least one additional risk factor for diabetes
  – Children: Overweight + Two additional risk factors at age 10 or puberty onset (if occurs earlier)

– American Diabetes Association, Diabetes Care. 2017 (suppl 1)
Risk Factors For Type 2 Diabetes

• Prediabetes or History of GDM
• Family History Of Diabetes in First Degree Relative
• Physical Inactivity
• Race/Ethnicity (e.g. Asian, African, Hispanic, And Native-Americans, Pacific Islanders)
Risk Factors For Type 2 Diabetes

- Hypertension ($\geq 140/90$ mm/Hg in adults)
- HDL $\leq 35$ mg/dl and/or TG $\geq 250$ mg/dl
- History of GDM or delivery of a newborn weighing $>9$ lbs
- Polycystic Ovarian Syndrome
- Insulin resistance (e.g. Acanthosis Nigricans, severe obesity)
- History of CVD
Prevention of Diabetes In Prediabetes

Definition:
A1c 5.7-6.4%, FPG 100-125 or OGTT 140-199

Prevention:
• Refer to program that adheres to the DPP
  • 150 min/week of exercise/7% weight loss
• Consider Metformin If: BMI >35, <60 years, GDM History, Rising A1c
• A1c at least yearly
• Screen/Treat Modifiable CV Risk Factors

American Diabetes Association, Diabetes Care. 2017 (suppl 1)
## Prevalence of Complications at Time of Diagnosis: UKPDS

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any complication</td>
<td>50</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>21</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>18</td>
</tr>
<tr>
<td>Absent foot pulses ($\geq 2$) and/or ischemic feet</td>
<td>14</td>
</tr>
<tr>
<td>Impaired reflexes and/or decreased vibration sense</td>
<td>7</td>
</tr>
<tr>
<td>Myocardial infarction/angina/claudication</td>
<td>$\sim 2-3$</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>$\sim 1$</td>
</tr>
</tbody>
</table>

UKPDS = United Kingdom Prospective Diabetes Study.
*Some patients had more than one complication at diagnosis.
Adapted from Holman RR. *Consultant.* 1997;37(suppl):S30-S36.
Accord Trial

- 10,251 adults aged 40-79 years with type 2 diabetes with CVD or 55-79 with risks of CVD
- A1c ≥7.5%
- Randomized to A1c < 6% vs. 7-7.9%
- Combos of metformin, TZDs, (primarily rosiglitazone), insulins, sulfonylureas, exenatide, and acarbose.
- Primary Outcome: CV death, nonfatal MI or nonfatal CVA
- The intensive glucose-lowering arm was terminated at 3.5 years due to excess mortality

Median Glycated Hemoglobin Levels at Each Study Visit
Kaplan-Meier Curves for the Primary Outcome and Death from Any Cause

**A Primary Outcome**

- Standard therapy
- Intensive therapy

**B Death from Any Cause**

- Standard therapy
- Intensive therapy

**HRs and P-values**

- **Primary Outcome (HR 0.9, P=0.16)**
- **Death from Any Cause (HR 1.22, P=0.04)**
Accord Trial: Mortality

![Bar chart showing mortality rates for intensive and standard treatment groups.]

Intensive treatment (n=5,128; HbA1c goal <6%) had 257 deaths.

Standard treatment (n=5,123; HbA1c goal 7% to 7.9%) had 203 deaths.

Source: [www.nhlbi.nih.gov/health/prof/heart/other/acord/](www.nhlbi.nih.gov/health/prof/heart/other/acord/)

Endocrine Today. March 10, 2008
Advance Trial

- 11,140 “High Risk” Patients Type 2 DM
- DM2 diagnosed at age 30
- Age ≥55 years, + major micro or macrovascular disease or vascular disease risk factor
- Randomized to gliclazide plus other agents
- Intensive arm goal: A1c<6.5%
- Five year study

Glucose Control at Baseline and during Follow-up, According to Glucose-Control Strategy

A

Mean Glycated Hemoglobin (%)

P<0.001

Standard control

intensive control

Value

Standard

7.32

7.01

7.30

6.93

24 36 48 60 66

Months of Follow-up

Intensive

7.29

6.70

7.29

6.53

7.31

6.50

7.33

6.52

7.29

6.53

B

Mean Fasting Blood Glucose (mmol/liter)

P<0.001

Standard control

intensive control

Level

Standard

8.15

7.17

7.84

6.47

7.92

6.51

7.74

6.55

Months of Follow-up

Intensive
Cumulative Incidences of Events, According to Glucose-Control Strategy

**A** Combined Major Macrovascular and Microvascular Events

- **HR 0.9**

**B** Major Macrovascular Events

- **HR 0.86**

**C** Major Microvascular Events

- **HR 0.9**

**D** Death from Any Cause

- **HR 0.86**

Glycemic Effects On CV Disease

Conclusions

• Glycemic control may reduce: Non-fatal MI, albuminuria, retinopathy, brain shrinkage
• Glycemic control may not protect CV or renal function, vision or cognition in first 3-5 years
• Highest Risk: Intensive therapy, but A1c still >7%
• Avoid Hypoglycemia-Possible Increase Death
• Metabolic Memory

Diabetes Care Vol 35, Oct 2012, 2100-2107
Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus: ACCORD

4733 Pts assigned to (non-blinded):
SBP <120 or <140
Primary composite outcome: Nonfatal MI, nonfatal CVA, or death from CV causes
Follow-up was 4.7 years
Same inclusion criteria as the glycemic portion of the Accord Study
# Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (N = 2363)</th>
<th>Standard Therapy (N = 2371)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events</td>
<td>%/yr</td>
<td>no. of events</td>
<td>%/yr</td>
</tr>
<tr>
<td>Primary outcome*</td>
<td>208</td>
<td>1.87</td>
<td>237</td>
<td>2.09</td>
</tr>
<tr>
<td>Prespecified secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>126</td>
<td>1.13</td>
<td>146</td>
<td>1.28</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>36</td>
<td>0.32</td>
<td>62</td>
<td>0.53</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>34</td>
<td>0.30</td>
<td>55</td>
<td>0.47</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>150</td>
<td>1.28</td>
<td>144</td>
<td>1.19</td>
</tr>
<tr>
<td>From cardiovascular cause</td>
<td>60</td>
<td>0.52</td>
<td>58</td>
<td>0.49</td>
</tr>
<tr>
<td>Primary outcome plus revascularization or nonfatal heart failure</td>
<td>521</td>
<td>5.10</td>
<td>551</td>
<td>5.31</td>
</tr>
<tr>
<td>Major coronary disease event†</td>
<td>253</td>
<td>2.31</td>
<td>270</td>
<td>2.41</td>
</tr>
<tr>
<td>Fatal or nonfatal heart failure</td>
<td>83</td>
<td>0.73</td>
<td>90</td>
<td>0.78</td>
</tr>
</tbody>
</table>

* The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.
† Major coronary disease events, as defined in the protocol, included fatal coronary events, nonfatal myocardial infarction, and unstable angina.

Hypertension Treatment

- LSM: Weight Loss/DASH/PE/Lower ETOH and Na (<1500 mg/day), increase K
- BP >120/80: LSM, BP ≥140/90: Meds + LSM
- Goals: <140/90 or <130/80 if younger, albuminuria, or CV Risk, and safe
- Meds: ACE or ARB then diazide or amlodipine
- Administer at least one med at bedtime
- Monitor serum creatinine/GFR and potassium

American Diabetes Association, Diabetes Care. 2017 (suppl 1)
Microalbuminuria: Not A Benign Finding

- Associated with cardiovascular morbidity and mortality
- **Screen Yearly**: Urine microalbumin/Cr
  - At diagnosis in Type 2
  - 5 years after diagnosis of Type 1
- Retest annually along with GFR estimate
- **Rx**: BP Meds/A1c reduction/Tobacco cess.
- Refer if: heavy proteinuria/no retinopathy/rapid GFR decline/advanced renal insufficiency, GFR <30

American Diabetes Association, *Diabetes Care*. 2017 (suppl 1)
Incidences of Myocardial Infarction in Type 2 Diabetes

Heart Protection Study: Diabetes Sub-study

- 5963 UK adults (aged 40–80 years) known to have diabetes
- No History of CHD in 49%
- Mean total cholesterol of 220, LDL of 124, HDL of 41, and TG of 204.
- Randomized: 40 mg simvastatin vs. placebo
- Study Length: 5 years

### HPS: Major Vascular Events by Prior Diabetes

<table>
<thead>
<tr>
<th>Vascular Events</th>
<th>Simvastatin (10,296)</th>
<th>Placebo (10,267)</th>
<th>STATIN Better</th>
<th>Placebo Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>898 (8.7%)</td>
<td>1212 (11.8%)</td>
<td></td>
<td>27% reduction (15–38) p&lt;0.0001</td>
</tr>
<tr>
<td>No diabetes</td>
<td>619 (8.5%)</td>
<td>835 (11.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strokes</td>
<td>444 (4.3%)</td>
<td>585 (5.7%)</td>
<td></td>
<td>24% reduction (6–39) p=0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>149 (5.0%)</td>
<td>193 (6.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>295 (4.0%)</td>
<td>392 (5.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularizations</td>
<td>939 (9.1%)</td>
<td>1205 (11.7%)</td>
<td></td>
<td>17% reduction (3–30) p=0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>260 (8.7%)</td>
<td>309 (10.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>679 (9.3%)</td>
<td>896 (12.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major vascular events</td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td></td>
<td>22% reduction (13–30) p&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>601 (20.2%)</td>
<td>748 (25.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>1432 (19.6%)</td>
<td>1837 (25.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Does Everyone With Diabetes Need A Statin?

- Anyone with LDL > 100 or multiple risk factors
- Age > 40 with one or more CVD risk factors
- Anyone With Overt Cardiovascular Disease
- Goals:
  - LDL Goal < 70 with overt CVD
  - LDL Goal < 100 otherwise
  - If on max statin and not in goal- Aim for LDL 30-40% of baseline
  - Triglycerides < 150
  - HDL > 40 (men), > 50 (women)

American Diabetes Association, *Diabetes Care*. 2014 (suppl 1)
<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended statin intensity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factor(s)**</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or</td>
<td>Moderate plus ezetimibe</td>
</tr>
<tr>
<td></td>
<td>in patients with a history of ASCVD who cannot tolerate high-dose statins</td>
<td></td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
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</tr>
</tbody>
</table>

American Diabetes Association, Diabetes Care. 2017 (suppl 1)
# High- and Moderate-Intensity Statin Therapy

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowers LDL-C by (~\geq50%)</td>
<td>Lowers LDL-C by (~30%) to &lt;50%</td>
</tr>
<tr>
<td>Atorvastatin 40*-80 mg</td>
<td>Atorvastatin 10 mg (20 mg)</td>
</tr>
<tr>
<td>Rosuvastatin 20 mg (40 mg)</td>
<td>Rosuvastatin (5 mg) 10 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg†</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 mg (80 mg)</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
</tr>
</tbody>
</table>

*Down titrate if unable to tolerate atorvastatin 80 mg; 
Initiation of or titration to simvastatin is not recommended by the FDA due to increased myopathy risk 
Italics denotes FDA-approved doses that were not tested in trials reviewed for guideline development 
Once-daily doses unless otherwise specified. Avg LDL-C-lowering potential listed expected to vary in clinical practice.
Recommendations For Aspirin (75-162 mg) Therapy in the Diabetes

• Secondary Prevention
• Primary Prevention *With no increased risk of bleeding and:
  – 10 Year CV risk > 10% - Includes most men and women > 50 low bleeding risk with at least one of the following:
    • Family History of Premature CHD
    • Smoker
    • Hypertension
    • Albuminuria (Micro or Macro)
    • Dyslipidemia

• Not for use under 21 years

Clopidogrel For Aspirin Intolerance

American Diabetes Association, *Diabetes Care*. 2017 (suppl 1)
Retinopathy Screening

• Type 1: Annually Starting at Age 10/puberty or Within 5 Years After Onset, then annually
• Type 2: Starting At Diagnosis
• Repeat Every 2 Years if No RN
• Pregnancy: Before Conception, During The First Trimester With Close Follow-up
• GDM: Not At Increased Risk

American Diabetes Association, *Diabetes Care*. 2017 (suppl 1)
Foot Care

• Yearly:
  • 10 g Monofilament plus one of the following: 128-Hz tuning fork, pinprick, ankle DTRs, vibration threshold
  • Pulses, visual exam, symptoms
• At Each Visit: Visual Exam, Symptoms
• Refer: Smokers, lack of protective sensation, structural abnormalities, LE complications, PVD

American Diabetes Association, *Diabetes Care*. 2017 (suppl 1)
Diabetes Care In The Hospital: Summary

• Initiate Insulin for Persistent Hyperglycemia >180
• Goals: All 140-180, Selected ICU: 110-140
• Check A1c on Admission
• Monitor non-DM patients on high risk therapy
  • Glucorticoids, TPN, octreotide, etc.
• Avoid sliding scales alone: Use Basal + Bolus
• Basal Insulin and Carbs 24/7 in Type 1 DM
• Consult Diabetes Educator and Dietitian

American Diabetes Association, *Diabetes Care*. 2017 (suppl 1)
Depicted are patient and disease factors used to determine optimal A1C targets.

### Approach to the Management of Hyperglycemia

<table>
<thead>
<tr>
<th>Patient / Disease Features</th>
<th>More stringent</th>
<th>A1C 7%</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other drug adverse effects</td>
<td>low</td>
<td></td>
<td>high</td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td></td>
<td>short</td>
</tr>
<tr>
<td>Relevant comorbidities</td>
<td>absent</td>
<td>few / mild</td>
<td>severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>few / mild</td>
<td>severe</td>
</tr>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td>highly motivated, adherent, excellent self-care capabilities</td>
<td>less motivated, nonadherent, poor self-care capabilities</td>
<td></td>
</tr>
<tr>
<td>Resources and support system</td>
<td>readily available</td>
<td>limited</td>
<td></td>
</tr>
</tbody>
</table>

American Diabetes Association Dia Care 2017;40:S48-S56
Pathophysiology of Type 2 Diabetes

Figure 1 Multiorgan and tissue pathophysiology of type 2 diabetes.
Abbreviations: FFA, free fatty acids; GLP-1, glucagon-like peptide-1.
Earlier and More Aggressive Intervention May Improve Patients’ Chances of Reaching Goal

Published Conceptual Approach

- Diet and exercise
- OAD monotherapy
- OAD up-titration
- OAD combination
- OAD + basal insulin
- OAD + multiple daily insulin injections

A1C, %

Mean A1C of patients

Duration of Diabetes

Antihyperglycemic therapy in type 2 diabetes: general recommendations.

**Start with Monotherapy unless:**
- AIC is greater than or equal to 9%, consider Dual Therapy.
- AIC is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

**Monotherapy**

<table>
<thead>
<tr>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
</tr>
<tr>
<td><strong>COSTS</strong></td>
</tr>
</tbody>
</table>

If AIC target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

**Dual Therapy**

<table>
<thead>
<tr>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
</tr>
<tr>
<td><strong>COSTS</strong></td>
</tr>
</tbody>
</table>

If AIC target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

**Triple Therapy**

<table>
<thead>
<tr>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SU</strong></td>
</tr>
<tr>
<td><strong>DPP-4 I</strong></td>
</tr>
<tr>
<td><strong>SGLT2 I</strong></td>
</tr>
<tr>
<td><strong>GLP-1 RA</strong></td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
</tr>
</tbody>
</table>

If AIC target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

**Combination Injectable Therapy** (See Figure 8.2)

American Diabetes Association Dia Care 2017;40:S64-S74

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Major Targets of Oral Drug Classes

Pancreatic Islet Cells
- Sulfonylureas
- Meglitinides
- DPP-4 inhibitors/Incretins

Liver
- Biguanides
- TZDs
- DPP-4 inhibitors/Incretins

Muscle and Fat
- TZDs
- Biguanides

Gut
- alpha-Glucosidase inhibitors

Renal
- SGLT2 inhibitors

↓Glucose level

DPP-4=dipeptidyl peptidase-4; TZD=thiazolidinediones.
Physiological Serum Insulin Secretion Profile

Plasma insulin (µU/ml)

Breakfast  Lunch  Dinner

Time

4:00  8:00  12:00  16:00  20:00  24:00  4:00  8:00
Combination injectable therapy for type 2 diabetes.
Effects of Metformin on FPG in Glyburide-Treated Patients

Mean Change from Baseline FPG (mg/dL)

*P=0.001
N=632

Metformin: Conditions That Predispose To Lactic Acidosis

- eGFR 30-45 mL/min/1.73m²: half max dose, <30: D/C
- ALT Or AST: >2-3 Times Normal
- Unstable CHF
- Acute MI/Cardiovascular Collapse
- Severe Infection
- Major Surgical Procedure
- ETOH Abuse Or Binge Drinking
- Metabolic Acidosis
- Contrast Study

Monitor for B12 Deficiency
Thiazolidinediones

Structurally Diverse PPAR\(\gamma\) Agonists

- Rosiglitazone
  - SmithKline Beecham

- Troglitazone
  - Sankyo/Parke Davis

- Pioglitazone
  - Takeda/Lilly
Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Monotherapy Failure at 5 Years.

Treatment was considered to have failed if a patient had a confirmed or adjudicated level of fasting plasma glucose of more than 180 mg per deciliter. Risk reduction is listed for comparisons of pairwise groups from a baseline covariate-adjusted Cox proportional-hazards model. Gray’s estimates of cumulative incidence adjusted for all deaths were smaller than Kaplan–Meier estimates of treatment failure: 10% in the rosiglitazone group, 15% in the metformin group, and 25% in the glyburide group. Bars indicate 95% CIs.
The Incretin Effect in Subjects Without and With Type 2 Diabetes

Control Subjects (n=8)

Patients With Type 2 Diabetes (n=14)

The incretin effect is diminished in type 2 diabetes.

Beta-Cell Workload and Response Are Balanced in Healthy Subjects

Beta-Cell Workload Outpaces Response in Type 2 Diabetes

- Insulin (µU/mL)
- Glucagon (pg/mL)
- Glucose (mg/dL)

N = 26; Mean (SE)
Role of Incretins in Glucose Homeostasis

Ingestion of food

GI tract

Release of gut hormones — Incretins

Pancreas

Glucose-dependent

↑ Insulin from beta cells (GLP-1 and GIP)

Beta cells

Alpha cells

Glucose dependent

↓ Glucagon from alpha cells (GLP-1)

Blood

Glucose uptake by muscles

↓ Glucose production by liver

DPP-4 = dipeptidyl-peptidase 4
Exenatide /Liraglutide/Albiglutide/Dulaglutide/Lixisenatide

- Natural GLP Analogue or GLP Modification
- All: highly resistant to DP-4 and greater potency for the GLP-1 receptor
- LA Forms: Not recommended for first line therapy
- BID vs QW/QD/QW/QW/QD
- Lira. and Lixi. are available with Insulin Combo.
- All: common se: Transient nausea and vomiting
- All: Caution with a history of pancreatitis, renal impairment
Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies.

Liraglutide is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
Exenatide Sustained A1C Reductions at 2.5 Years

Open-label Extension

BYETTA 10 mcg BID (n = 241) Baseline A1C = 8.3%

2.5-y completers; Mean ± SE
Data on file, Amylin Pharmaceuticals, Inc.
See accompanying Prescribing Information and safety information included in this presentation
Exenatide Continued to Reduce Weight at 2.5 Years

Open-label Extension

BYETTA 10 mcg BID (n = 241)

Δ Weight (lbs)

0 10 20 30 40 50 60 70 80 90 100 110 120 130

Time (wk)

-11.2 ± 0.8 lbs

2.5-y completers; Mean ± SE; Weight was a secondary endpoint
Data on file, Amylin Pharmaceuticals, Inc.
See accompanying Prescribing Information and safety information included in this presentation
Sitagliptin, Saxagliptin, Linagliptin, and Alogliptin

- DP4 Inhibitors
- Sita, Saxa and Alo: renal dose adjustment
- All: Rare Arthralgias
- All: Observe for pancreatitis/Alo: Check LFTs
- All: Indicated in monotherapy, and in combo with metformin, SU, Insulin, or TZD.
- Saxa and Alo: Caution in CHF
- All: available in Combo with met, Alo also with pioglitazone, Lina with empagliflozin
Initial Combination Therapy With Sitagliptin Plus Metformin Study: A1C Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LSM A1C Change From Baseline, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
</tr>
<tr>
<td>Sitagliptin 100 mg qd</td>
<td>-0.5</td>
</tr>
<tr>
<td>Metformin 500 mg bid</td>
<td>-1.0</td>
</tr>
<tr>
<td>Sitagliptin 50 mg bid + metformin 500 mg bid</td>
<td>-1.5</td>
</tr>
<tr>
<td>Sitagliptin 50 mg bid + metformin 1,000 mg bid</td>
<td>-2.0</td>
</tr>
<tr>
<td>Metformin 1,000 mg bid</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

qd=once a day; bid=twice a day.
Initial Combination Therapy With Sitagliptin Plus Metformin Study: Change in Body Weight and Incidence of Hypoglycemia

**LSM Change From Baseline, kg**

- Sitagliptin 50 mg + metformin 1,000 mg bid
- Sitagliptin 50 mg + metformin 500 mg bid
- Metformin 1,000 mg bid
- Metformin 500 mg bid
- Placebo

**Rates of Hypoglycemia in Combination With Sitagliptin**

- Placebo
- Sitagliptin 100 mg qd
- Metformin 1,000 mg bid
- Metformin 500 mg bid
- Sitagliptin 100 mg qd

**Hypoglycemia n/N (%)**

- Placebo: 1/176 (0.6)
- Sita 100: 1/179 (0.6)
- MF 500 bid: 1/182 (0.5)
- MF 1,000 bid: 2/182 (1.1)
- Sita 50 + MF 500 bid: 2/190 (1.1)
- Sita 50 + MF 1,000 bid: 4/182 (2.2)

Sita=sitagliptin; MF=metformin.

# GLP-Agonists vs DPP-4 Inhibitors: Summary

<table>
<thead>
<tr>
<th>Comparison</th>
<th>GLP Agonists</th>
<th>DDP-4 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admin Route</td>
<td>Injection</td>
<td>Oral</td>
</tr>
<tr>
<td>Insulin/Glucagon</td>
<td>↑↓</td>
<td>↑↓</td>
</tr>
<tr>
<td>Beta Cell Preservation</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Fasting vs Premeal</td>
<td>↓ ♦️ vs ♦️</td>
<td>♦️ vs ♦️</td>
</tr>
<tr>
<td>Weight</td>
<td>↓</td>
<td>↔️</td>
</tr>
<tr>
<td>GI Effects</td>
<td>↑</td>
<td>↔️</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>↔️</td>
<td>↔️</td>
</tr>
</tbody>
</table>
Figure 1 Schematic representation of the distribution of sodium–glucose cotransporters along an unrolled nephron

Canagliflozin/Dapagliflozin/Empagliflozin

- SGLT2 Inhibitor
- Each Before First Meal
- Cana: 100 mg if eGFR 45-59, D/C if <45
- Dapa/Empa: D/C if eGFR is <60/<45
- Genital/Mycotic Infections, UTIs, Volume Depletion, DKA
- Cana: Inc: Mg/K/Phos/Cr Dapa Inc: Phos
- Dapa: Bladder Cancer?/Cana: Amputations?
Canaglifozin vs. Sitagliptin

Package Insert: Combo w/ metformin and Su
Final Thoughts
# Sample Diabetes Flow Sheet

<table>
<thead>
<tr>
<th>Date</th>
<th>Wt</th>
<th>BP</th>
<th>Glucometer</th>
<th>HbA1c</th>
<th>FPG</th>
<th>Chol</th>
<th>LDL</th>
<th>TG</th>
<th>HDL</th>
<th>Cr</th>
<th>TSH</th>
<th>Micro-Alb</th>
<th>Health Main</th>
<th>Full Foot</th>
<th>Ophthalmol.</th>
<th>Nutr</th>
<th>Counsel</th>
<th>DiabetesEd</th>
<th>Cigg</th>
<th>Aspirin</th>
<th>EKG</th>
<th>Dental</th>
</tr>
</thead>
</table>


Achieving Diabetes Management Goals

Person with Diabetes Mellitus

- Family
- Primary Care Physician
- Community
- Employer
- Insurer
- Exercise Physiologist*
- Diabetologist/Endocrinologist
- Other Medical Specialists
- RD*
- RN*
- Pharmacist*
- Certified Diabetes Educator
- Behavioral Specialist*

*May be a certified diabetes educator.
Don’t Forget……..

• To Prevent DM
• Diabetes Education and Dietitian Consults
• To Tritrate Meds and/or Insulin Quickly to Achieve Goals: ABC
• To Screen and Treat for Microalbuminuria
• To Screen For Peripheral Neuropathy/Remove Shoes
• Aspirin/Statins
• Basal-Bolus Insulin in the Hospital
• Basal Insulin and Carbs 24/7 in Type 1 DM