

Diabetes - Diagnosis and Treatment in the Primary Care Office

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Madrid I ~ 10:10am - 10:55am

Edward Shahady, MD
86675 N Hampton Club Way
Fernandina Beach, FL 32034
Tel: (850) 443-1230
Email: eshahady@att.net

Objectives

- Contrast A1C and FBS for diagnosing diabetes and pre-diabetes
- Review standards of care for diabetes care
- Discuss therapeutic options for diabetes in light of new studies
- Review cardio metabolic risk in diabetes

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Diabetes – Diagnosis and Treatment in the Primary Care Office

Edward Shahady MD
Medical Director
Diabetes Master Clinician Program
Florida Academy of Family Physicians

Objectives

- Review performance of recent guidelines for diagnosing diabetes and pre-diabetes
- Discuss evidence for life style and or Metformin for diabetes prevention and treatment
- Develop a rational plan for A1C, LDL and B/P goals based on recent and past studies
- Utilize metabolic defects to guide medication choices for treatment
- Understand the importance of inflammation in diabetes

History of Diabetes

- 1921 Insulin discovered Banting and Best
- 1950's Sulfonylureas developed
- 1960's Urine strips developed
- 1969 First glucose meter
- 1979 A1C test devised
- 1993 DCCT study-1996 UKPDS- *value of lower A1C*
- ACCORD (discord), VADT, ADVANCE
- Since 1995 8 new drugs developed-50 new meters-
- Next 5 years-20 new drugs for diabetes

Basic Thinking to guide screening and Rx for Diabetes

- Type 1 (T1) can and does appear in adults but it takes longer for the pancreas to lose its Beta Cell Function
- Type 2 (T2) present in 90-95%-not all are obese and obesity does not always equal diabetes
- Cardiovascular impact of diabetes in T2 present 7 to 10 years before blood sugar rises
- Treatment of T2 is all about Insulin Resistance and its Metabolic defects-not the same in all T2

CASE

- Harry a 42 Year old Hispanic man comes to your office for routine physical. No complaints
- Family Hx of diabetes and Father died of MI age 44
- BMI 28, Waist 42 in, B/P 142/90
- Total Chol (TC)=180, Triglycerides=250, LDL (calculated)=100 HDL=30 and Non-HDL 150
- FBS=132 finger stick- A1C is 6.2

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ARS

What is your Diagnosis for Harry?

- A. Diabetes
- B. Pre-Diabetes or at high risk for Diabetes
- C. Metabolic Syndrome
- D. Not sure

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New ADA Guidelines Dx. Diabetes and Pre-Diabetes

- Diabetes A1C \geq 6.5%-FBG \geq 126 mg/dl 2hr \geq 200 mg/dl
- Pre-Diabetes- A1C 5.7 to 6.4% FBS 100-125, 2hr 141-199
- Point of care A1C for follow up not Dx
- A1c misleading when hemolysis or significant anemia present
- Not recommended for Dx in Type 1 or Gestational Diabetes

– American Diabetes Association Position Statement Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010;33: S62-69 no change 2011

New AACE Guidelines

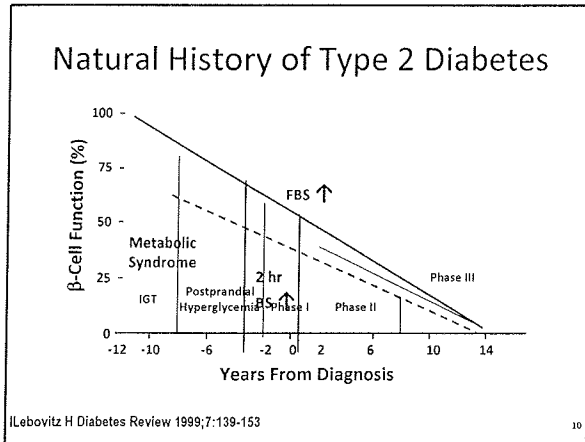
- A1C an optional criterion for Dx diabetes, not primary criterion.
- Use traditional glucose criteria for diagnosis when feasible
- Do not support the use of A1C alone to identify patients with pre-diabetes or high risk for diabetes.
- They do agree that an A1C of 5.7% to 6.4% can be used as a screening test

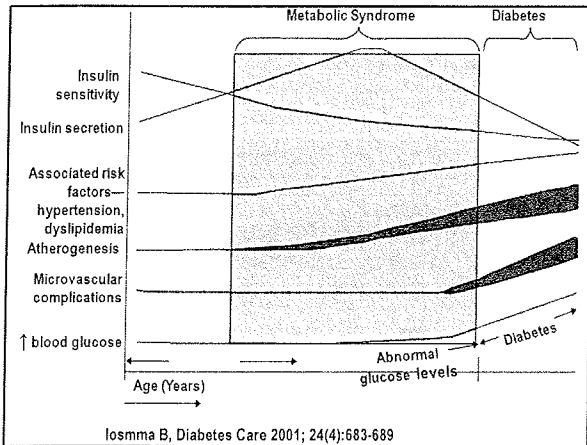
– American Association of Clinical Endocrinologists accessed on line
www.aace.com/pub/pdf/guidelines/A1cPositionStatement.pdf

ARS

How long has he had abnormal blood sugar, hypertension and dyslipidemia?

- A. Abnormal blood sugar for 1 to 2 years
- B. Abnormal blood pressure and lipids for 8 to 10 years
- C. Increased arterial plaque and atherogenesis for 8 to 10 years
- D. A and B
- E. A B and C *





Fasting Plasma Glucose and A1C for identifying and predicting Diabetes

- 2849 American Indians ages 45-74 screened and followed for 4+ years
- Of those that developed diabetes A1C ≥ 6.5 identified 57%
- FPG ≥ 126 identified 94%

Adapted from Diabetes Care 2011;34:363-68

**Odds Ration for predicting Diabetes
 in 4 years from Pre-Diabetes**

	A1C alone	FBS alone	Both
A1C 6 to 6.4	5.9		3.4
FBS 120-125		3.1	2.3
BMI >30	2.6	3.7	3.0
Parental Hx Diabetes	1.6	1.2	1.3
Sibling Hx Diabetes	1.6	1.6	1.4

Adapted from Diabetes Care 2011;34:363-68

**Odds Ration for predicting Diabetes
 in 4 years from Pre-Diabetes**

	A1C alone	FBS alone	Both
Micro Albuminuria	2.0	2.7	2.4
Hypertension	1.6	1.7	1.6
↑ Triglycerides	1.5	1.6	1.5
↓ HDL	1.5	1.6	1.6
↑Waist Size	2.6	3.9	2.4

Adapted from Diabetes Care 2011;34:363-68

ARS

How would you Rx the dysglycemia in Harry-remember
 Family Hx positive, A1C 6.2, FBS 132, HDL 30,
 Triglycerides 250,

- A. Life style changes only
- B. Life style plus Metformin*
- C. Life style plus Pioglitazone
- D. None of the above

Pre-Diabetes Treatment With Metformin (Level E)

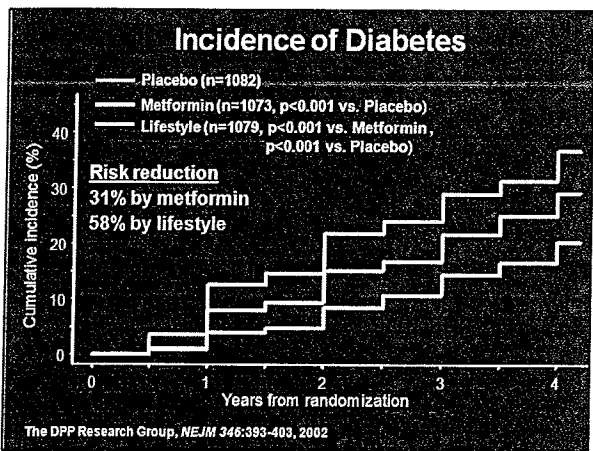
- ADA Panel recommends lifestyle modification and metformin (850 mg twice per day) if patient has IFG (FPG ≥ 100 and < 126 mg/dL) or IGT 2-hour post prandial (≥ 140 and < 200 mg/dL) and any 1 of the following:
 - < 60 years of age*
 - BMI ≥ 35 kg/m²
 - Family history of diabetes in first-degree relatives*
 - Elevated triglycerides*
 - Reduced high-density lipoprotein*
 - Hypertension*
 - A1C $> 6.0\%$ *

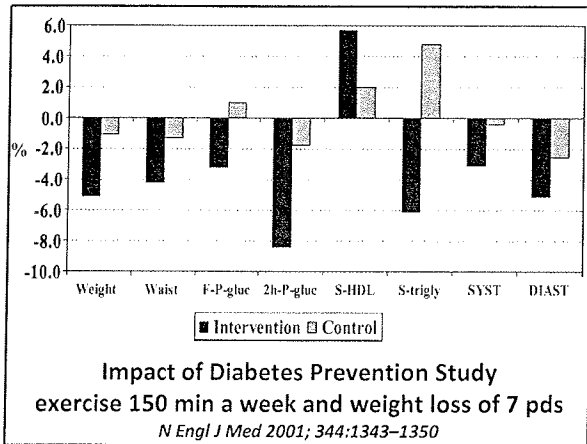
Nathan DM et al. (2007), Diabetes Care 30(3):753-759 continues to be recommended in 2011 ADA guidelines diabetes.org

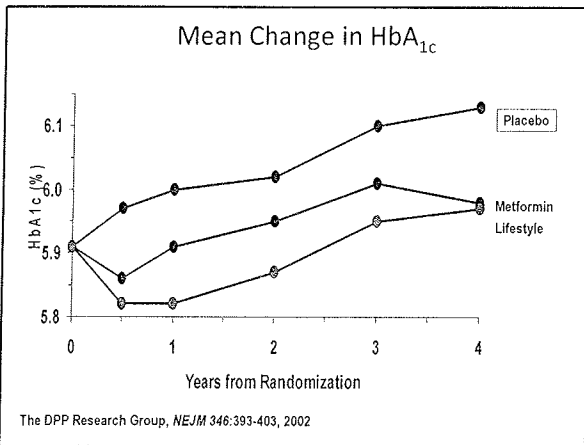
Why Early Identification of risk for diabetes?

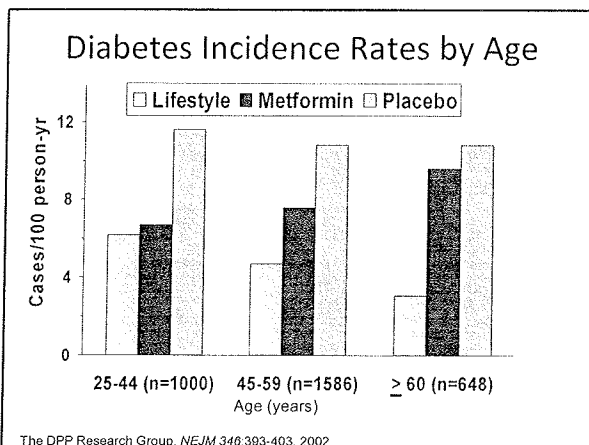
- Patients with A1C levels of 6.0 to 6.5% are 10 times more likely to develop diabetes. Some patients at risk are not always identified at this level and levels of 5.5 to 6% are needed.^{1,2}
- Most of the enthusiasm for identifying patients at risk for diabetes result of the Diabetes Prevention Program (DPP). Lifestyle and Metformin delayed onset of diabetes.

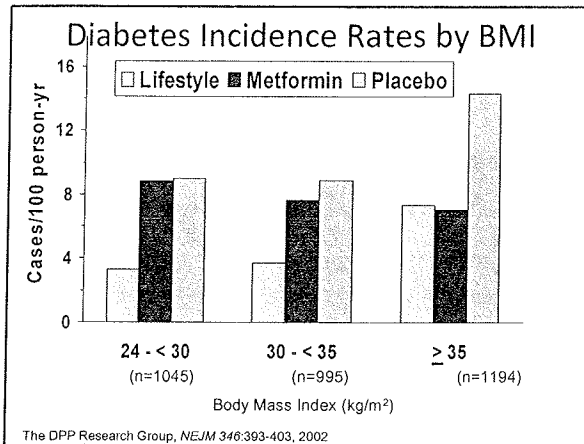
¹ J Gen Intern Med 2004;19:1175-2. Diabetes Care 2009;32: 644-646 ³. N Engl J Med 2002;346:393-403

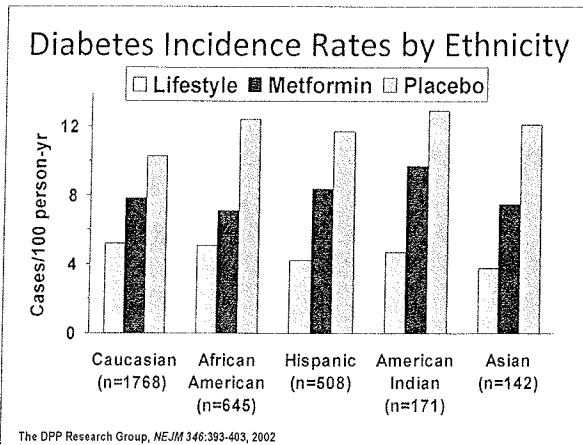


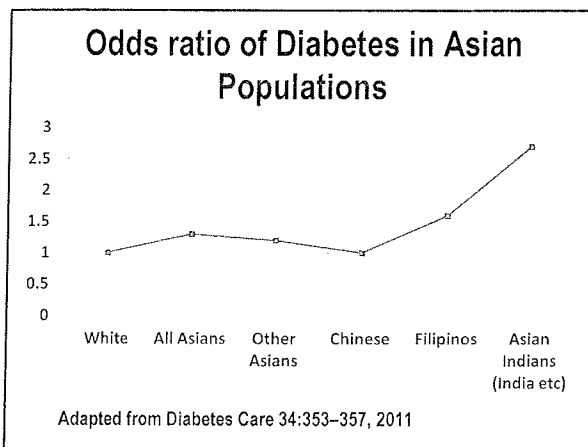












Pre-Diabetes

Treatment With Metformin (Level E)

- ADA Panel recommends lifestyle modification and metformin (850 mg twice per day) if patient has IFG (FPG \geq 100 and <126 mg/dL) or IGT 2-hour post prandial (\geq 140 and <200 mg/dL) and any 1 of the following:
 - <60 years of age *
 - BMI \geq 35 kg/m²
 - Family history of diabetes in first-degree relatives*
 - Elevated triglycerides*
 - Reduced high-density lipoprotein*
 - Hypertension
 - A1C >6.0%

Nathan DM et al. (2007), Diabetes Care 30(3):753-759 continues to be recommended in 2011 ADA guidelines diabetes.org 25

Metformin, HDL and Cancer Risk

- Patients with Diabetes have an increased risk for cancer of all types
- High HDL protective against cancer--HDL of 47 optimal
- Diabetic patients taking Metformin have a 54% decreased incidence of cancer
- If HDL is less than 40- Metformin provides a 72% lower risk
- Both Metformin and HDL stimulate the AMP-activated protein kinase (AMPK) pathway-this inhibits cancer growth-

Diabetes Care 2011;34:375-80
Diabetes Care 2009;32:1620-25

Recommendation:

- For patients that the clinician believes are at risk for diabetes, obtain an A1C level and a FBS
- If the level is 5.7–6.4%, or FBS 100 to 125 inform the patient of their increased risk for diabetes and all of its complications.
- Counsel them about strategies for weight loss and increased physical activity. Consider the addition of Metformin as an adjunct to the life style changes if obese, HDL ↓, Triglycerides ↑ or Fam Hx positive

ARS

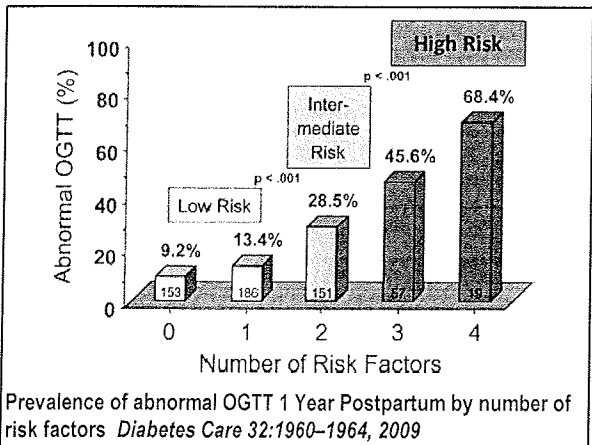
Choose one of the following as most likely to predict which women will develop diabetes following gestational diabetes.

- A. Required Insulin during pregnancy*
- B. Pre-pregnancy BMI ≥ 25
- C. Gestational Age at Dx ≤ 14 weeks
- D. All the above

Risk factors that predict developing Type 2 diabetes 1 year post partum

Factor	Odds Ratio	P Value
OGTT 1 hr >200 mg/dl	2.73	0.001
Insulin Therapy	2.12	0.001
Pre-Pregnancy BMI ≥ 30	2.12	0.002
Gestational age at Dx ≤ 24 wks	1.81	0.010

Adapted from Diabetes Care 32:1960–1964, 2009



Only 20% of the obstetricians, even in an academic medical center, ordered postpartum diabetes screening tests for their patients (1).

Most studies reported a patient return rate less than 50% (2,3)

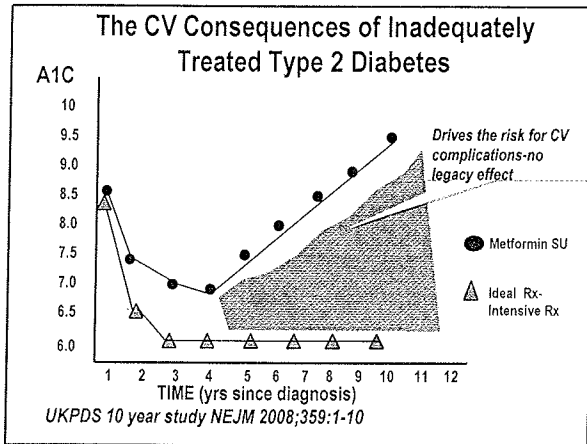
1. Almaro C, Ecker T, Moroz L, Bucovetsky L, Berghella V, Baxter J. Obstetricians seldom provide postpartum diabetes screening for women with gestational diabetes. *Am J Obstet Gynecol* 2008;198:528.
2. Smirnakis K, Chasan-Taber L, Wolf M, Markenson G, Ecker J, Thadhani R. Postpartum diabetes screening in women with history of gestational diabetes. *Obstet Gynecol* 2005;106:1297-1303
3. Hunt K, Conway D. Who returns for postpartum glucose screening following gestational diabetes mellitus? *Am J Obstet Gynecol* 2008;198:404

What are your treatment goals for A1C?

- Recent studies ACCORD, ADVANCE, VADT have challenged the ADA treatment goals for A1C.
- Two landmark studies, the Diabetes Control and Complications Trial (DCCT/EDIC), and the United Kingdom Prospective Diabetes Study (UKPDS), provide excellent evidence that lowering HbA1c levels to 7% or less reduces the incidence of CVD 42% and 33%

Value of Early Aggressive Rx

- UKPDS 10 year study "Legacy Effect" those who were treated aggressively vs. those who were not had fewer macrovascular complications after 10 plus years. *UKPDS 10 year study NEJM* 2008;359:1-10
- DCCT-EDIC Study "Metabolic Memory" those who were treated aggressively vs. those who were not had fewer macrovascular complications after 10 plus years. *DCCT-EDIC NEJM* 2005;353:2643-53.



Intensive Glucose Lowering and Cardiovascular Disease Prevention in Diabetes: Reconciling the Recent Clinical Trial Data

Circulation 2010;122:2201-2211

Study: all meta-analysis of several studies including recent trials like ACCORD	Number of Patients	Reduced CVD
Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. <i>Lancet. 2009;373:1765-1772</i>	33,040	Reduction in nonfatal MI (17%) Reduced coronary heart disease (15%)
Systematic review: glucose control and cardiovascular disease in type 2 diabetes. <i>Ann Intern Med. 2009; 151:394-403.</i>	27,802	Reduced CVD events (10%)
Intensive glucose control and macrovascular outcomes in type 2 diabetes. <i>Diabetologia. 2009;52:2288-2298.</i>	27,049	Reduced MI (15%)

What are your treatment goals for A1C?

- 2009 a meta-analysis reviewed 5 prospective, randomized, controlled trials (33,040 patients) to assess the effect of an intensive glucose-lowering regimen included the UKPDS, ACCORD, ADVANCE, and VADT studies.
- "Intensive compared with standard glycemic control significantly reduces coronary events without an increased risk of death. However, the optimum mechanism, speed, and extent of A1c reduction might be different in differing populations."
 - Ray et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. *Lancet. 2009;373:1765-1772.*

What are your treatment goals for A1C?

- At the ADA meeting June 2009 the lead authors of the ACCORD and VADT concluded that intensive glycemic control does not account for the increase in cardiovascular deaths.
- Rapid changes in glycemia, older age, and co-morbidities accounted for the increased cardiovascular mortality in intensively treated patients.
- In the ACCORD trial, "Patients with the lowest A1c levels had the lowest risk. The excess mortality risk was in those patients who failed to achieve and sustain A1c levels between 6% and 7%."

Riddle et al Diabetes Care 33:983-990, 2010

Recommendations Treatment goals for A1C?

- Recently diagnosed diabetes, aggressive treatment (A1C goal of <6%) will lower cardiovascular risk in addition to significantly reducing risk for retinopathy, neuropathy and nephropathy. (preserves pancreas)
- If diabetic for 15+ years, older (frail), history of cardiovascular events; less aggressive treatment indicated (A1C goal of 7 to 7.5 %).
- Do not reduce A1C rapidly with medications especially insulin. Gradual lowering over 6 months to a year is advised.

What have we learned from ACCORD and VADT

- One size does not fit all i.e. A1C <7
- A1C >7 if older, had prior CV event, longer duration of diabetes, started with higher A1C
- Early aggressive Rx to A1C ≤ 6 if
 - Less than 15 years duration
 - A1C started 8 or less
 - No prior CV event
 - Younger

Guide for determining A1C Goal for individual patient

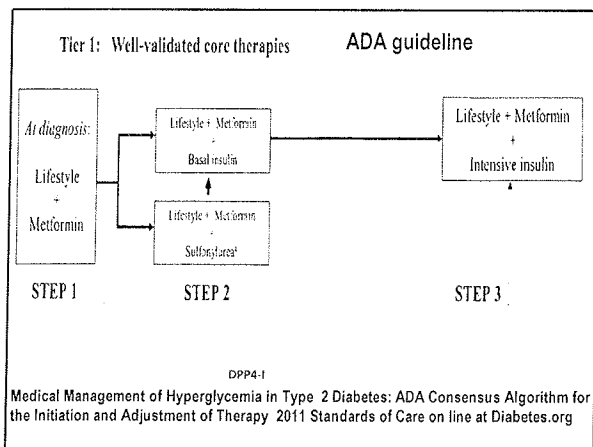
Intensive	Less Intensive	Least Intensive
A1C GOAL 6 → 7 → 8		
Psychosocial		
Less depression and distress, good support motivated, more resources, self confident		Depression, Distress, few resources, not confident, poor support
Hypoglycemia Risk		
Low		High
Older/Frail		
Younger/active		Older/less active/frail
Co Morbidities		
None		Multiple severe
Cardiovascular Complications		
None		Advanced Cardiovascular Disease Advanced Microvascular Disease

Adapted from Ann Intern Med 2011;154:554-559

ARS
 What does the American Diabetes Association recommend as first line Rx for a newly diagnosed patient with Diabetes?

- A. Life style changes only
- B. Life style plus Metformin *
- C. Life style plus Pioglitazone
- D. Life style plus Sulfonourea

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Insulin Resistance and Metabolic defects in T2 Diabetes



Liver keeps producing glucose –should turn off with hyperglycemia-main cause of elevated fasting blood sugar **Metformin**



Skeletal Muscle glucose transport is defective- post prandial glucose uptake decreased leading to post prandial hyperglycemia- muscle is glucose (energy) deficient **Pioglitazone Metformin**



Visceral Fat cells depend on insulin to drive Free Fatty Acids (FFA) in to the cell. This function defective in T2D. Excessive FFA in circulation is toxic (lipotoxicity) ↑ insulin resistance-elevated triglycerides the cue to lipotoxicity -inflammation **Pioglitazone**

Adapted from DeFronzo RA. Diabetes 2009 (58). 773-795

Insulin Resistance and Metabolic defects in T2 Diabetes



Pancreas-initially produces increased amounts of insulin to overcome Resistance-with decreased beta cell function, glucotoxicity and lipotoxicity hyperglycemia follows **Sulfonoureas**



GI tract-Incretin effect (GLP-1) response to a meal decreased 50%-GLP-1 stimulates pancreatic insulin release so less insulin released-Alpha cell produces more glucagon (thinks more glucose is needed) **GLP1 agonists DPP4 Inhibitors**



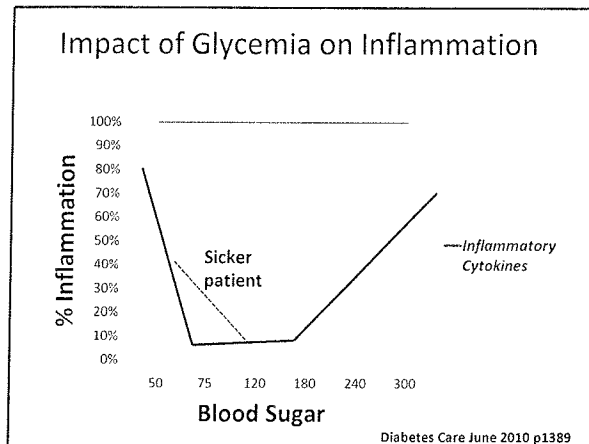
Kidney-is very efficient at reabsorbing glucose-SGLT 2 system facilitates this-body (brain, CV system) is glucose deficient so renal response is to increase SGLT 2 levels and increase renal reabsorption of glucose **New Drugs-SGLT2 Inhibitors**

Adapted from DeFronzo RA. Diabetes 2009 (58). 773-795

Inflammation the driving force behind diabetes complications

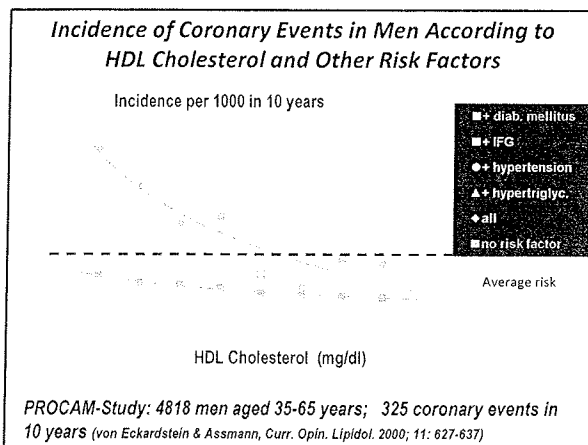
- Insulin resistance, diabetes, hypertension and dyslipidemia create inflammation and lead to endothelial dysfunction.
- Rx the above with lifestyle and medication protects the endothelium-we are endotheliologists





Diabetes mortality driven by B/P

- Diabetes mellitus is associated with increased risks of death and cardiovascular events in Framingham subjects, much of this excess risk is attributable to coexistent hypertension.
- Hypertension is associated with a 72% increase in the risk of all-cause death and a 57% increase in the risk of any cardiovascular event in individuals with diabetes mellitus.
- *Hypertension. 2011;57:891-897.*



ARS

Which of the following is associated with endothelial dysfunction and cardio-metabolic risk?

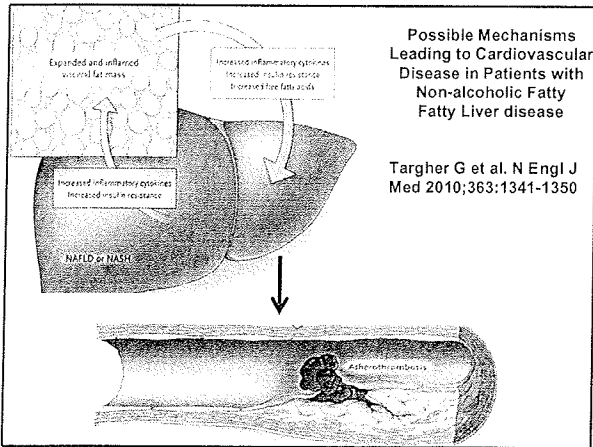
- A. Increased Urine micro-albumin
- B. Increased AST and ALT
- C. A and B *
- D. None of the above

Elevated Urine Microalbumin

- Several studies have shown that micro-albuminuria is associated with low-grade systemic inflammation and endothelial dysfunction.
- Even low-grade albuminuria, is an important marker of future CVD events even in individuals free of diabetes and hypertension.

– Stuveling EM, Bakker SJ, Hillege HL, Burgerhof JG, de Jong PE, Gans RO, de Zeeuw D. C-reactive protein modifies the relationship between blood pressure and microalbuminuria. *Hypertension*. 2004;43:791-796.

– Clausen et al Endothelial haemostatic factors are associated with progression of urinary albumin excretion in clinically healthy subjects: a 4-year prospective study. *Clin Sci (Lond)*. 1999;97:37- 43.



What are some easily available risk markers of endothelial dysfunction-inflammation in Diabetes?

- High LDL levels
- Low HDL levels
- Non-HDL (Total Cholesterol-HDL)
- ↑ ↑ AST and ALT
- ↑ ↑ Urinary Microalbumin
- Hypertension
- Hyperglycemia and Hypoglycemia

ACCORD LIPID Trial

- Compared the combination of fenofibrate and simvastatin, to simvastatin alone. decreased triglycerides and increased HDL, no reduction of cardiovascular events in patients with Type 2 diabetes at high risk for cardiovascular disease.
- Recommendation: Continue to use statins in diabetic patients. If triglycerides are elevated and or HDL is low consider using niacin (has evidence benefits CVD. If triglycerides remain over 500 would add fibrates and fish oil to decrease chance of pancreatitis.

– The ACCORD Study Group, *Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus* N Engl J Med 2010 362: 1563-1574

ACCORD B/P Trial

- In the ACCORD BP arm T2 diabetes patients at high risk for CVD compared at two systolic BP targets (140 mm Hg and 120 mm Hg). Reaching the target of 120 did not reduce the rate of fatal and nonfatal major cardiovascular events. The interpretation of the ACCORD BP results is complicated by the fact that the event rate observed in the standard-therapy group was almost 50% lower than the expected rate.
- Recommendation: It is still reasonable to attempt achieving a goal of 130/80 in all patients with diabetes. There are enough other good studies indicated the value of this goal. As always we need to monitor our older patients for undesirable side effects

– The ACCORD Study Group, *Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus* N Engl J Med 2010 362: 1575-1585
