DIABETES MELLITUS TREATMENT AND COMPLICATIONS

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THIS IS MODERN MEDICINE

Diabetes

- Multisystem Complications of Diabetes
- Describe and explain the macrovascular effects of Diabetes
- Describe and explain the effects of Diabetes on microvasculature
- Outline effects of Diabetes on peripheral nervous system and autonomic nervous system
- Features of Diabetic eye disease
- Describe treatment of Diabetes

Epidemiology

- Global burden of Diabetes
- Epidemic
- Much higher in developing countries

Prevalence USA 2005

Prevalence of Diabetes in USA in 2005	
Diagnosed DM	14.6 million
Undiagnosed DM	6.2 million
Prediabetes	54 million

- Total Diabetes 20.8 million
- 1.5 million new DM diagnosed 2005 in >20 year olds

Global Diabetes Millions

Global Diabetes in Millions			
	1997	2000	2010
Type 1	3.5	4.4	5.4
Type 11	120	146.8	215.3
Total	**123.5**	**151.2**	**220.7**

- Type 1 Increase by approx 3% annually

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2007 Top Ten

Country	Population
India	40.9 million (6% adult population)
China	39.8 million (4.3% adult population)
USA	19.6 million
Russian Fed	9.6 million
Germany	7.4 million
Japan	7 million
Pakistan	6.9 million
Brazil	6.9 million
Mexico	6.1 million
Egypt	4.4 million

Diabetes in Ireland

- **Figures for 2013:**
  - Estimated comparative prevalence of diabetes **5.5%**
  - Estimated comparative prevalence of impaired glucose tolerance **6.6%**
  - **75,900** people with undiagnosed diabetes
  - Mean diabetes-related expenditure per person with diabetes **€4,092**
  - Diabetes related deaths (20-79) **1,568**

- **National prevalence of diabetes estimated to rise from 6.5% in 2013 to 7.9% in 2035.**

Based on UN 2012 (adjusted for 2013) population estimate of 3,209,000.

International Diabetes Federation. IDF Diabetes Atlas, 6th edn. Brussels, Belgium:
International Diabetes Federation, 2013. http://www.idf.org/diabetesatlas. Last accessed March 2014.

Costs

- Individual patient
  - Chronic disease
  - Fear of complications
  - Shorter life expectancy
    - 10-20 yrs Type 1
    - 7-10 yrs Type 11

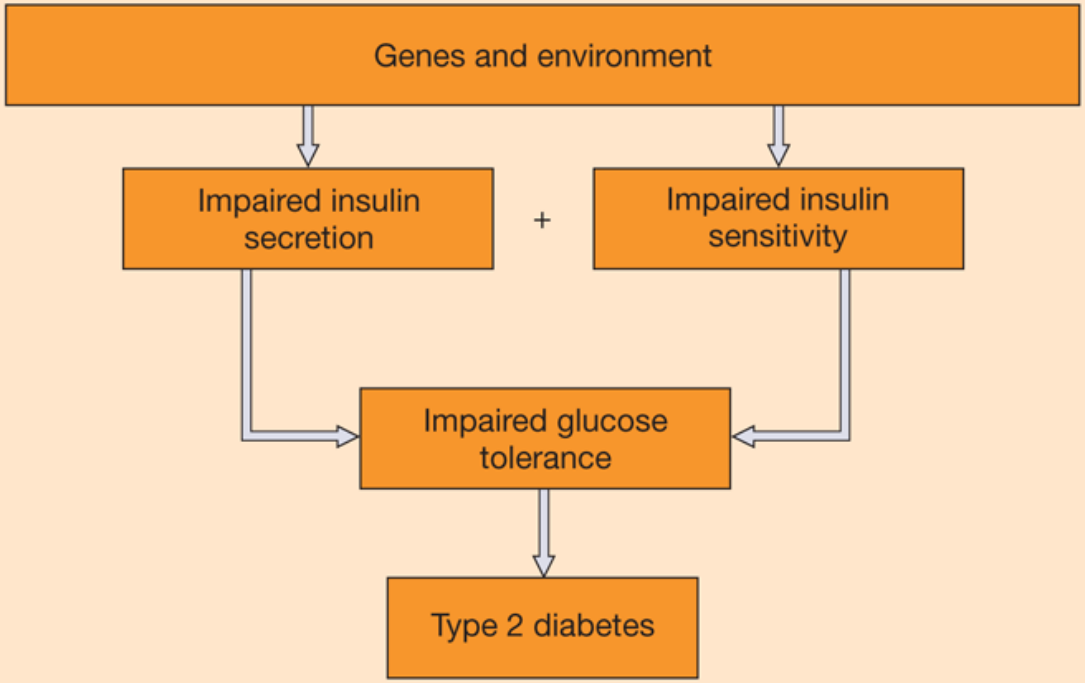
Economic Costs

- Total world expenditure
- USA More than 50%
  - about 150 Billion
- India Spends 2 Billion
- Indirect costs

What is Diabetes

The relative or absolute deficiency of insulin resulting in hyperglycemia

Etiology of Type 2 Diabetes



Gerich JE. *Endocr Rev* 1998;**19**:491-503.

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Diabetes has a Genetic Basis

- High concordance in monozygotic twins (80%)
- Familial clustering
- High prevalence in particular ethnic groups

Barnett AH, Eff C, Leslie RDG, Pyke DA. *Diabetologia* 1981;**20**:87-93.
Mather HM, Keen H. *Br Med J (Clin Res Ed)* 1985;**291**:1081-1084.

Genetic Loci Identified that Confer Type 2 Diabetes Risk

Four susceptibility genes identified that confer type 2 diabetes risk:

- Mutation in *TCF7L2* gene, which is thought to result in reduced insulin secretion
- Mutation in zinc transporter, which is involved in regulating insulin secretion
- 2 mutations in genes potentially involved in beta-cell development or function

Abbreviations: *TCF7L2*, transcription factor-7-like 2.

Sladek R, Rocheleau G, Rung J, *et al*. *Nature* 2007;**445**:881-885.

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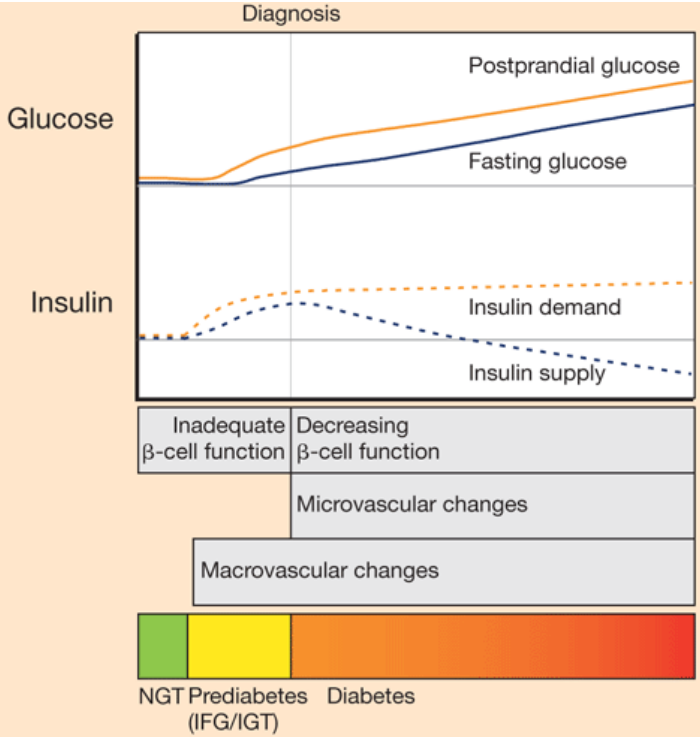
Progression of Type 2 Diabetes Reflects an Increasing Imbalance Between Insulin Supply and Demand



Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

From: Marks JB. In: *Atlas of Diabetes* 3rd Ed, 2006. Skyler JS ed. Philadelphia, PA. Current Medicine Group.

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Recommended Glycemic Targets for the Clinical Management of Diabetes

	ADA/EASD	IDF	Non-diabetic range
FPG (mmol/L mg/dL)	5.0–7.2 (90–130)	<5.5 (100)	<5.5 (100)
PPG (mmol/L mg/dL)	<10.0 (180) (peak)*	<7.8 (140)†	<7.8 (140)
HbA1c (%)	<7.0	<6.5	≤6.0

*1–2 hours after the beginning of the meal
†2 hours after ingestion of a 75 g glucose load

Abbreviations: ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IDF, International Diabetes Federation; PPG, postprandial plasma glucose.

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New ADA EASD Guidelines

Regarding medication management, for patients with clinical cardiovascular disease, a sodium–glucose cotransporter-2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended. Individual agents within these drug classes have been shown to have cardiovascular benefits.

For patients with chronic kidney disease (CKD) or clinical heart failure and atherosclerotic cardiovascular disease, an SGLT2 inhibitor with proven benefit should be considered.

They conclude: "The management of hyperglycaemia in type 2 diabetes has become extraordinarily complex with the number of glucose-lowering medications now available. Patient-centred decision making and support and consistent efforts to improve diet and exercise remain the foundation of all glycaemic management. Initial use of metformin, followed by addition of glucose-lowering medications based on patient comorbidities and concerns is recommended as we await answers to the many questions that remain."

Classification

Type 1	
Type 11	Beta cell dysfunction and insulin resistance, gradual loss of Beta cell
PreDiabetes	Previously IFG IGT
Metabolic Syndrome	
GDM	
Others	Eg MODY

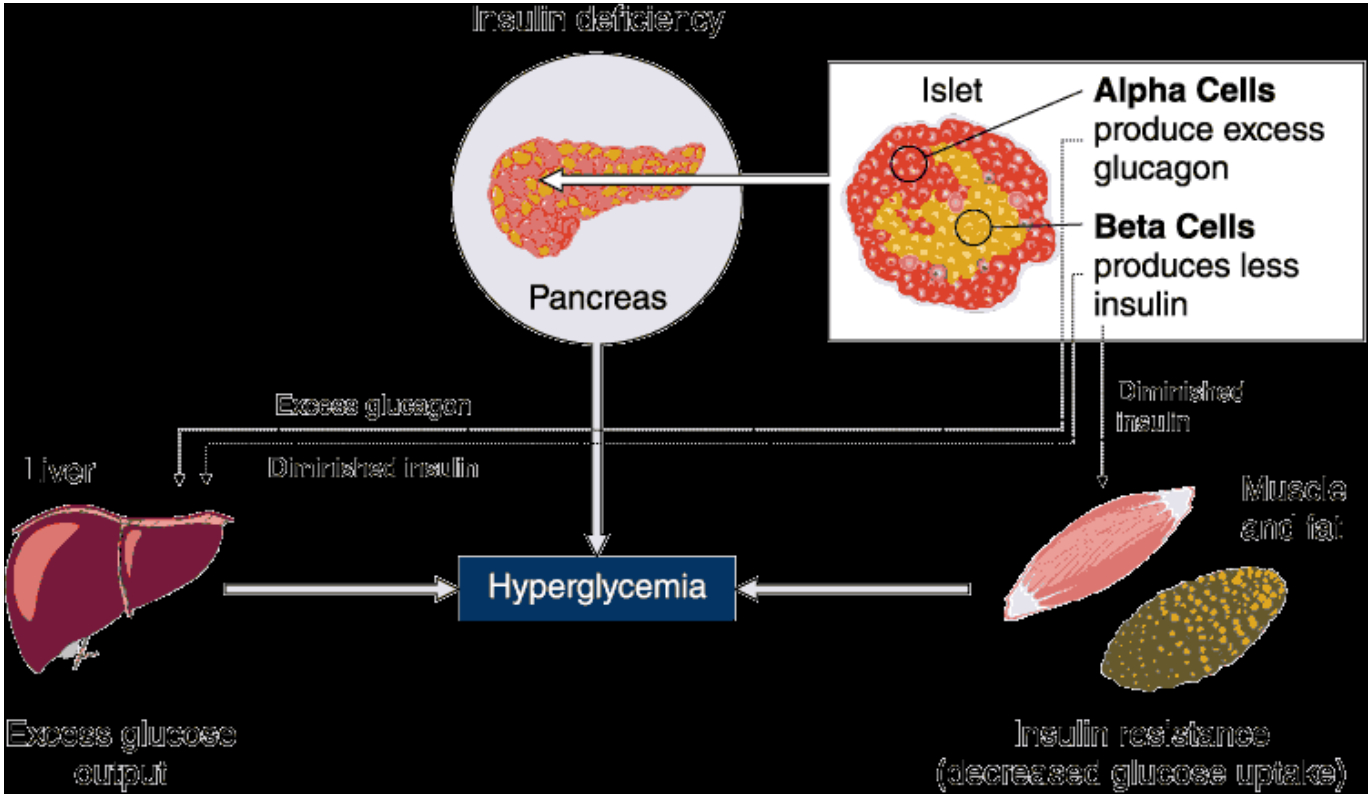
Definition

Diabetes	FBS	>7.1 mmol/l	
	2 Hr	>11.1	
	HbA1c	> 6.5%	(47 IFCC)
PreDiabetes	FBS	5.6-7.1	IDF
		6.1-7.1	ADA
	2 Hr	7.8-11.1	
GDM	FBS	>5.2	IDF/ADA
	1hr	>10	
	2hr	>8.4	

Pathophysiology

- Progression of Insulin Resistance to Diabetes
- 50% Beta cell function lost by Diagnosis

The Pathophysiology of Type 2 Diabetes includes Three Main Defects



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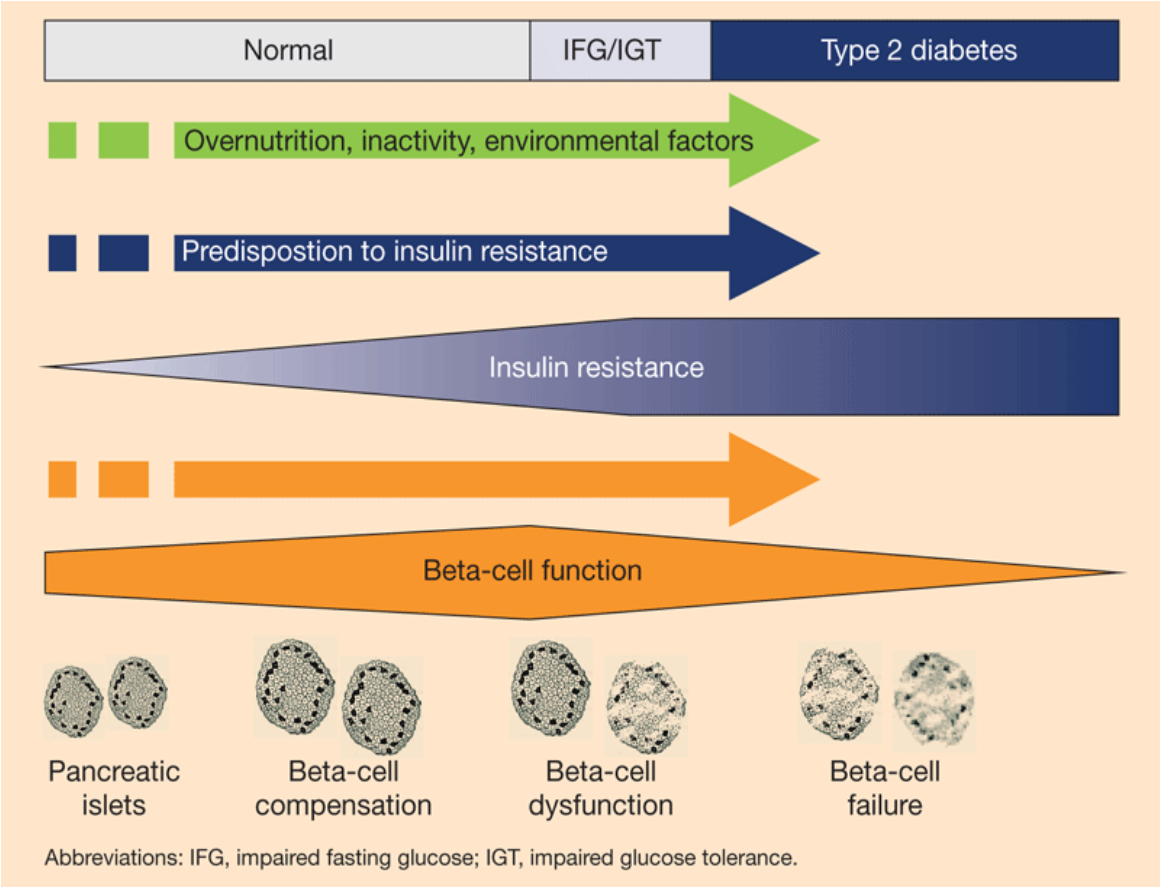
As Diabetes Progresses, Beta Cells Fail To Compensate For Insulin Demand



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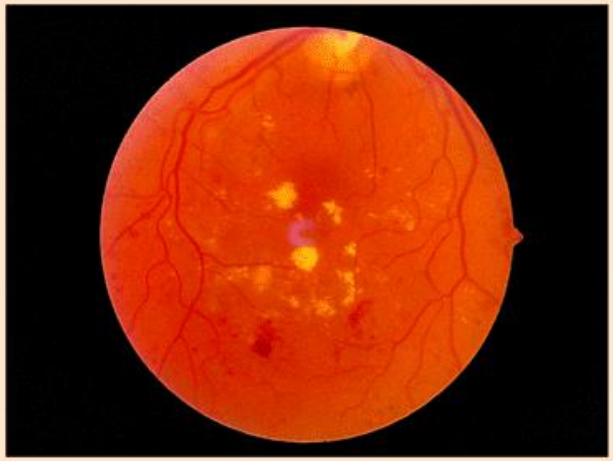
Goals of Treatment

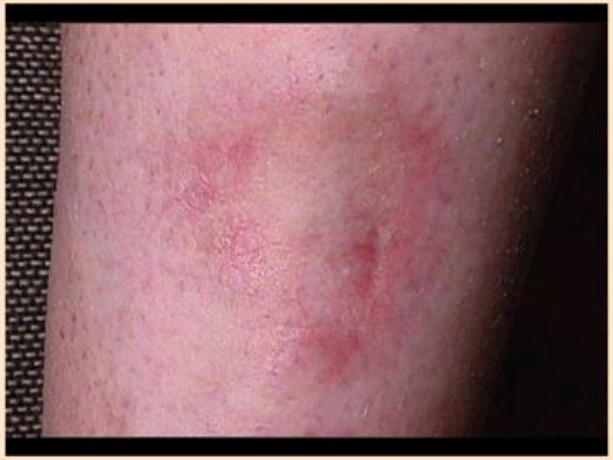
UKPDS
DCCT

Complications

- Microvascular Neuropathy - Amputation significantly increases the risk of death in next two years
- Retinopathy
- Nephropathy - Diabetes is the commonest cause of ESRF
- Autonomic
- Macrovascular Cardiovascular
  Cerebrovascular
  Peripheral vascular

Tissue Changes Associated with Hyperglycemic Damage





From: Fondo de diapositivas de la Spanish Endocrinology and Nutrition Association, 2005.

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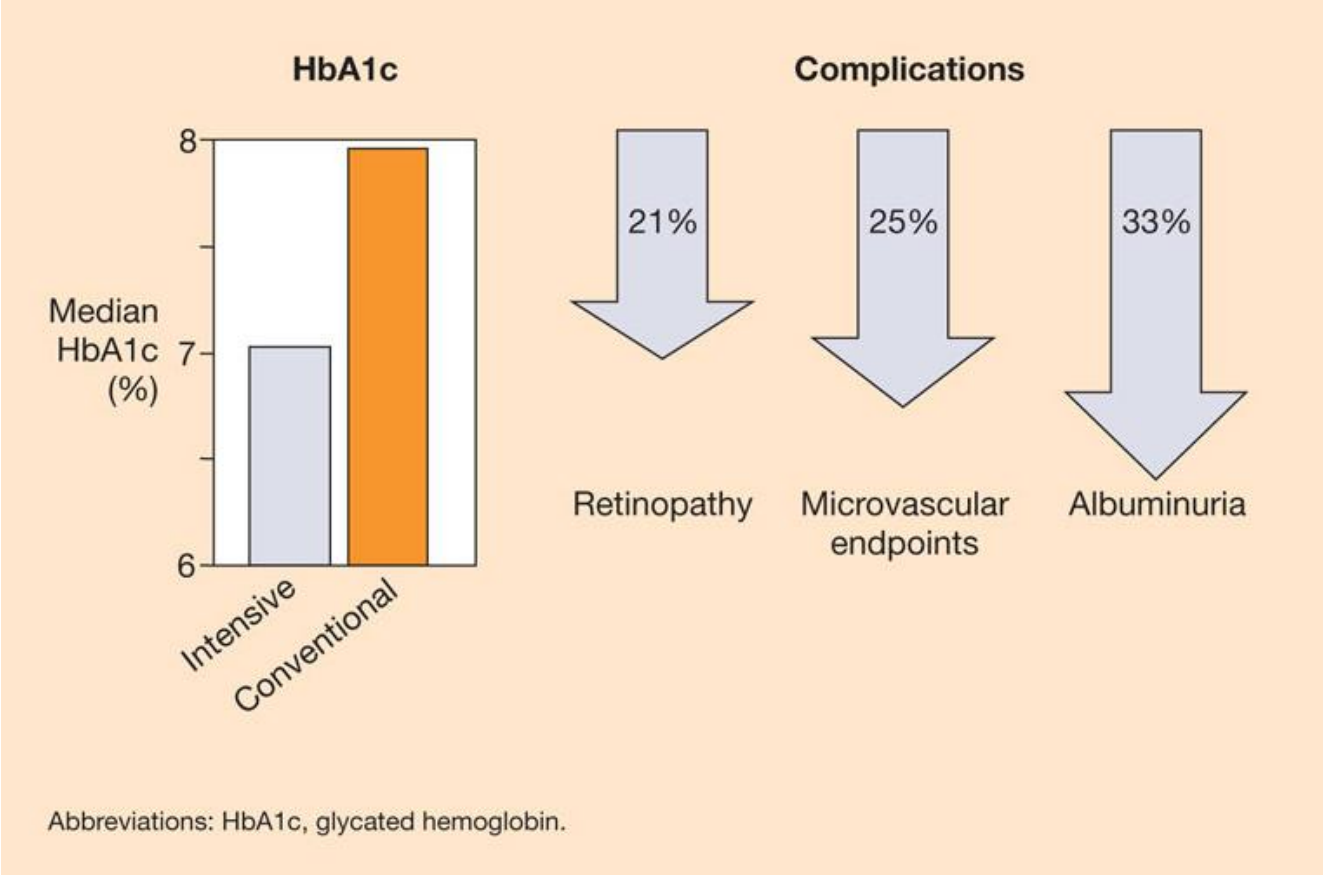
Primary Objectives of Effective Disease Management

Risk factors	Targets
Hyperglycemia	Reduce hyperglycemia (HbA1c <7%*)
Hypertension	Lower systolic blood pressure (<130 mm Hg)
Dyslipidemia	Decrease LDL-C levels (<100 mg/dL or 2.6 mmol/L) Raise HDL-C levels (>46 mg/dL or 1.2 mmol/L) Lower triglycerides (<150 mg/dL or 1.7 mmol/L)

*For 'the individual patient', HbA1c levels should be 'as close to normal (<6%) as possible without significant hypoglycemia'.

Abbreviations: HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

A Multidisciplinary Team Can Provide Better Glycemic Control and Treatment Outcomes



Abbreviations: HbA1c, glycated hemoglobin.

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Measures of Hyperglycemia

Random plasma glucose
- Without regard to time of last meal

Fasting plasma glucose
- Before breakfast

Oral glucose tolerance test
- 2 hours after a 75-g oral glucose drink

Postprandial plasma glucose
- 2 hours after a meal

Hemoglobin A1c
- Reflects mean glucose over 2–3 months

American Diabetes Association. *Diabetes Care* 2000;**23**:S20-S23.

ACCORD

- INCREASED MORTALITY IN INTENSIVE GROUP
- HbAIC 6% VS 7%
- Severe hypo increased risk of death
- Xs mortality in intensive group mostly in patients who failed to reach target aic

HYPO

- AUTONOMIC
- NEUROGLYCOPENIC

- Severe – need assistance of another person

Hypo Unaware Predictors

- High HbA1c
- Duration of insulin treatment
- Autonomic impairment
- Peripheral sensory impairment
- CKD
- Education level

DKA

- Medical emergency
- Need hydration, control of infection, potassium replacement and insulin
- Non Ketotic hyperosmolar coma occurs in NIDDM.

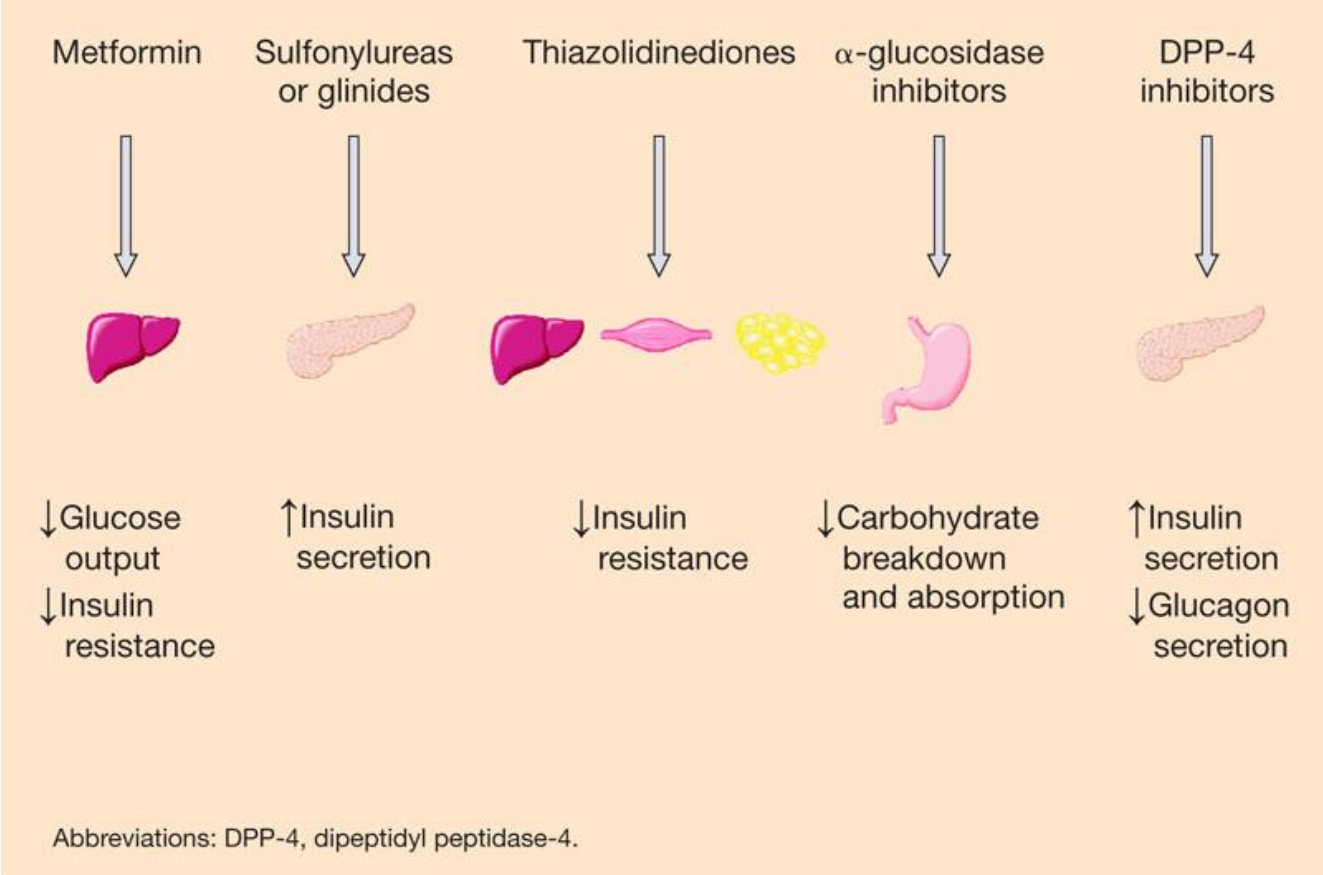
Monitoring

- HbA1c 6-7%
- Lipids TC <4, TG <1.5, LDL<2, HDL>1.2
- Renal function
- Blood pressure <130/80, <125/75
- Feet
- Eyes

Treatment

- Lifestyle - Diet and weight loss
- Metformin
- Sulfonylureas
- TZD
- DPP4 inhibitors
- Incretin mimetic, GLP analogues
- Insulin

Currently Available Oral Antidiabetics and Their Primary Sites Of Action



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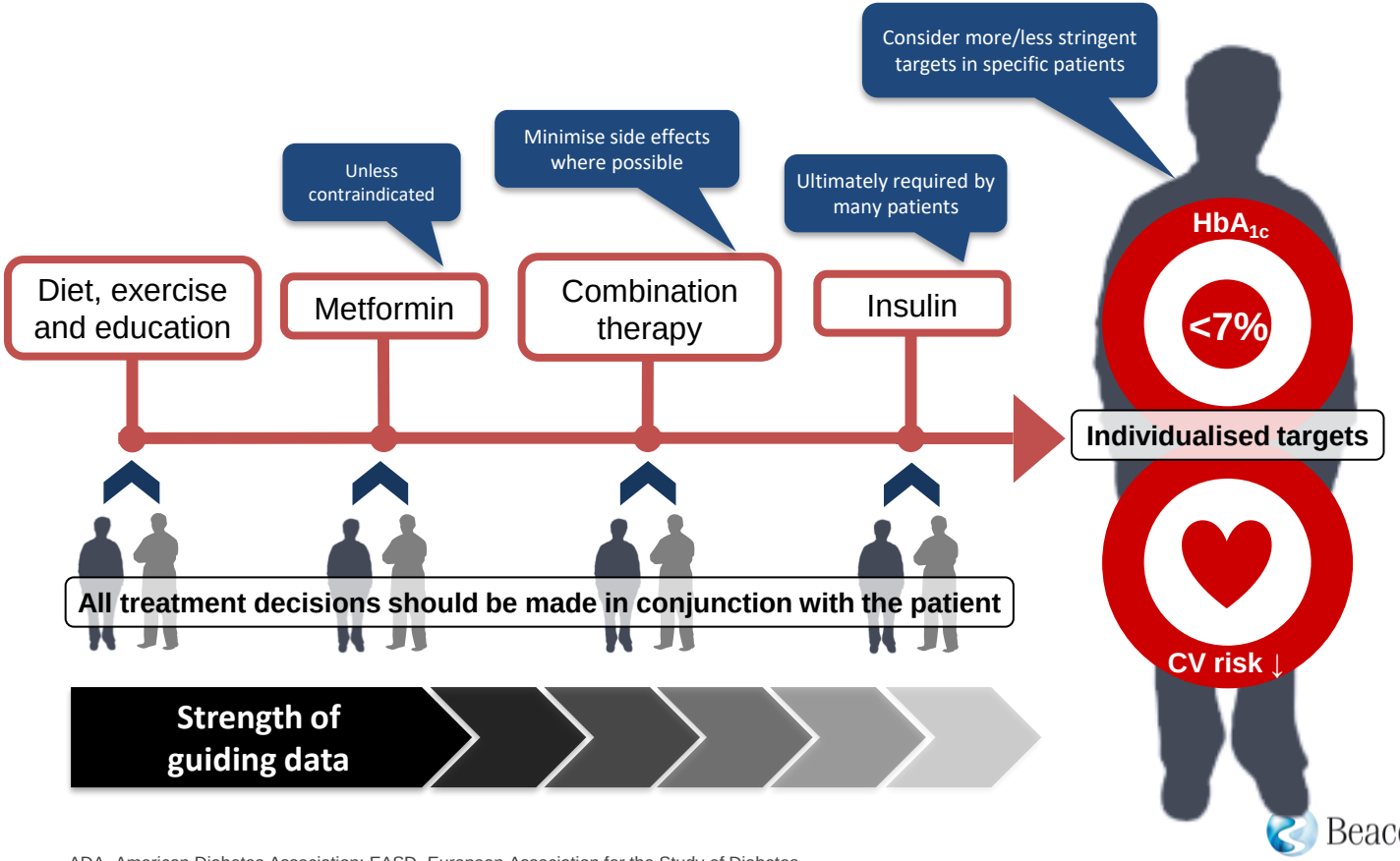
ADA/EASD 2012 Position Statement on the Management of Type 2 Diabetes



ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.
Adapted from: Inzucchi SE, *et al. Diabetes Care* 2012;**35**:1364–79.

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METFORMIN

- Insulin sensitiser
- Can use with insulin
- No Hypos
- Weight negative
- Improve other vascular risk factors
- Decreased cancer
- Side effects, nausea and lactic acidosis
- Avoid in renal impairment

Secretagogues

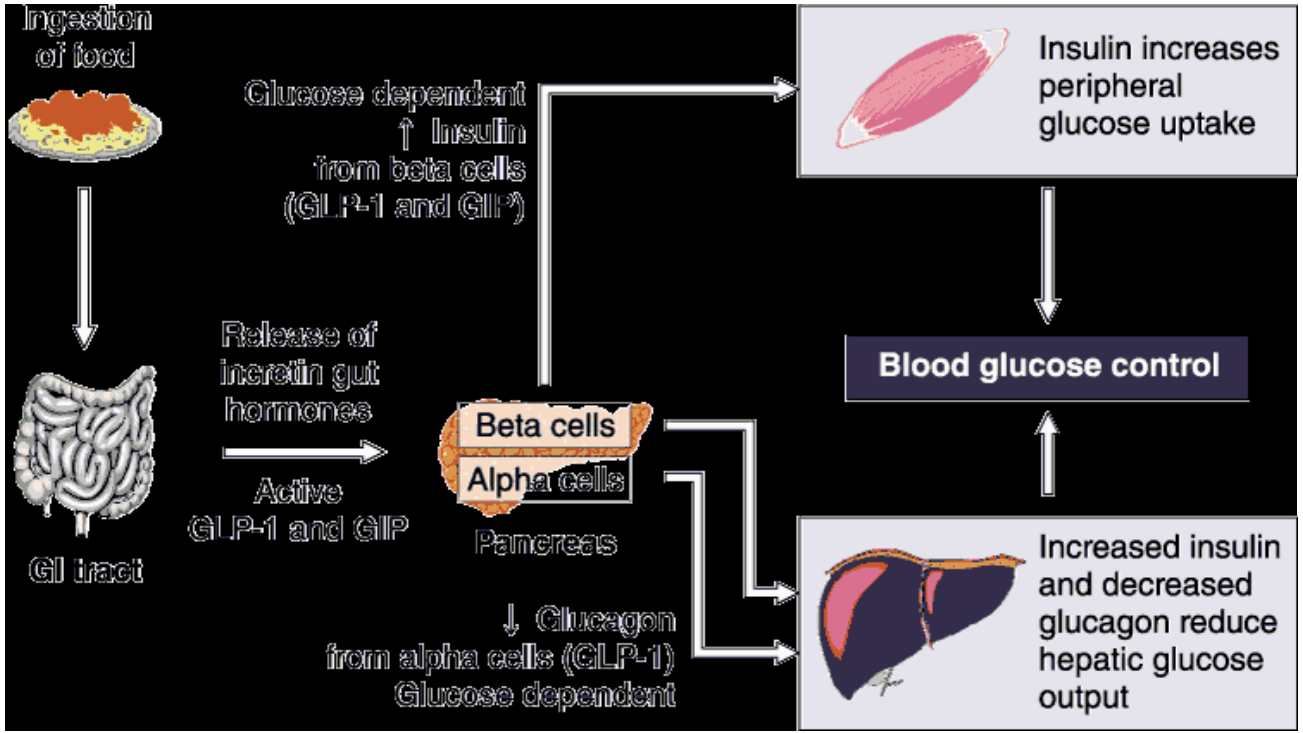
- Sulfonylureas and Glinides

- Hypos
- Weight positive
- ?effect on Beta cell mass
- Drug interactions

TZDs

- Rosiglitazone
- Pioglitazone
- Side effects are weight gain and they can cause heart failure

The Role of Incretins in Glucose Homeostasis



Abbreviations: GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

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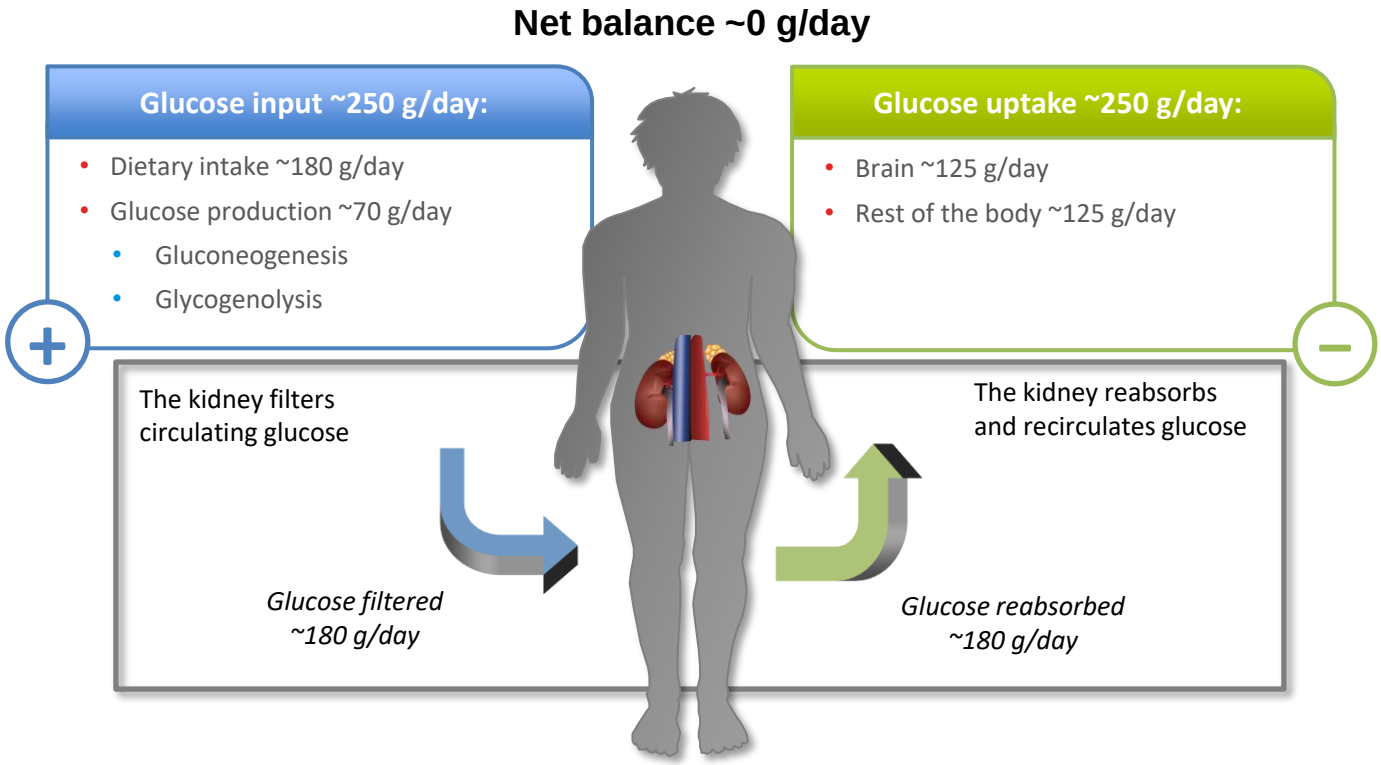
Incretin Type Drugs

- DPP4 Inhibitors
- Incretin mimetics

Normal glucose homeostasis[1,2]



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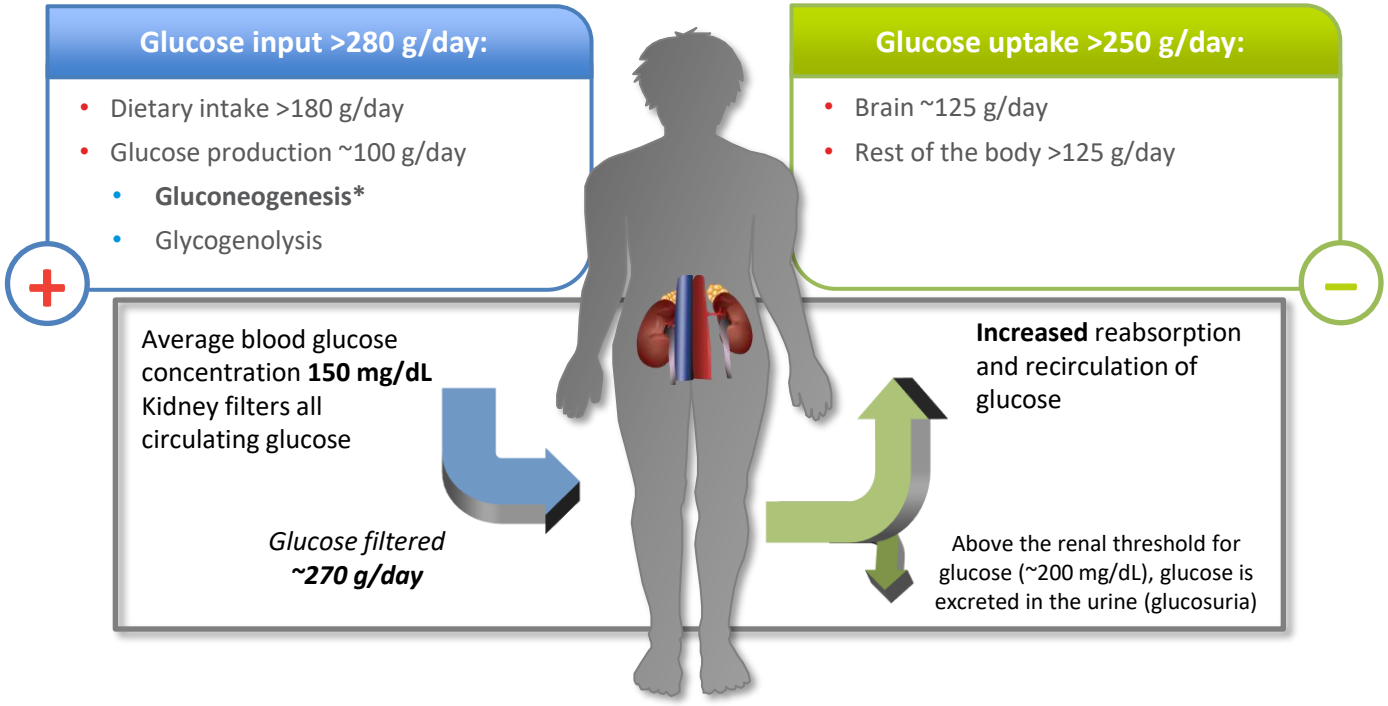
Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Gerich, JE. *Diabetes Obes Metab* 2000;**2**:345–50.

Glucose Handling In Type 2 Diabetes[1,2]



*Elevated glucose production in patients with Type 2 diabetes attributed to hepatic and renal gluconeogenesis.[2]

1. Gerich JE. *Diabet Med* 2010;**27**:136–42; 2. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract* 2008;**14**:782–90.

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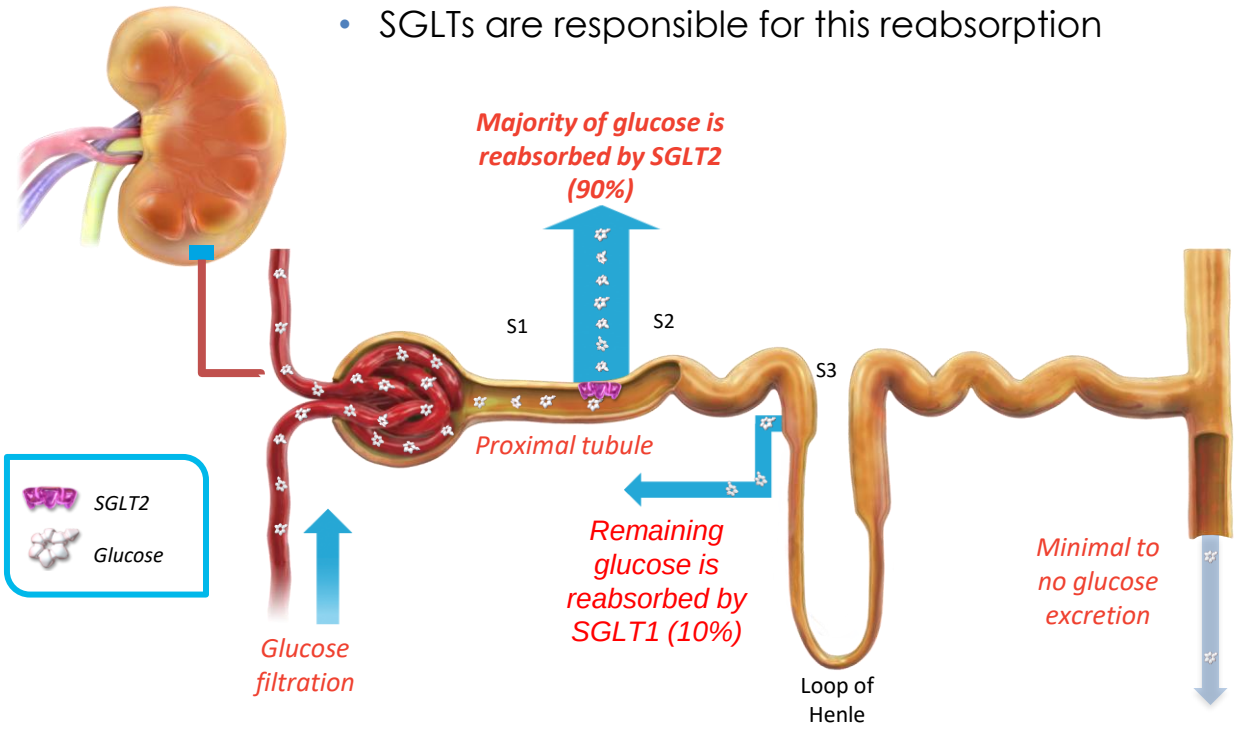
Normal Renal Glucose Handling[1–3]

- The kidneys filter and reabsorb 180 g of glucose per day
- SGLTs are responsible for this reabsorption



SGLT, sodium-glucose co-transporter.

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21.

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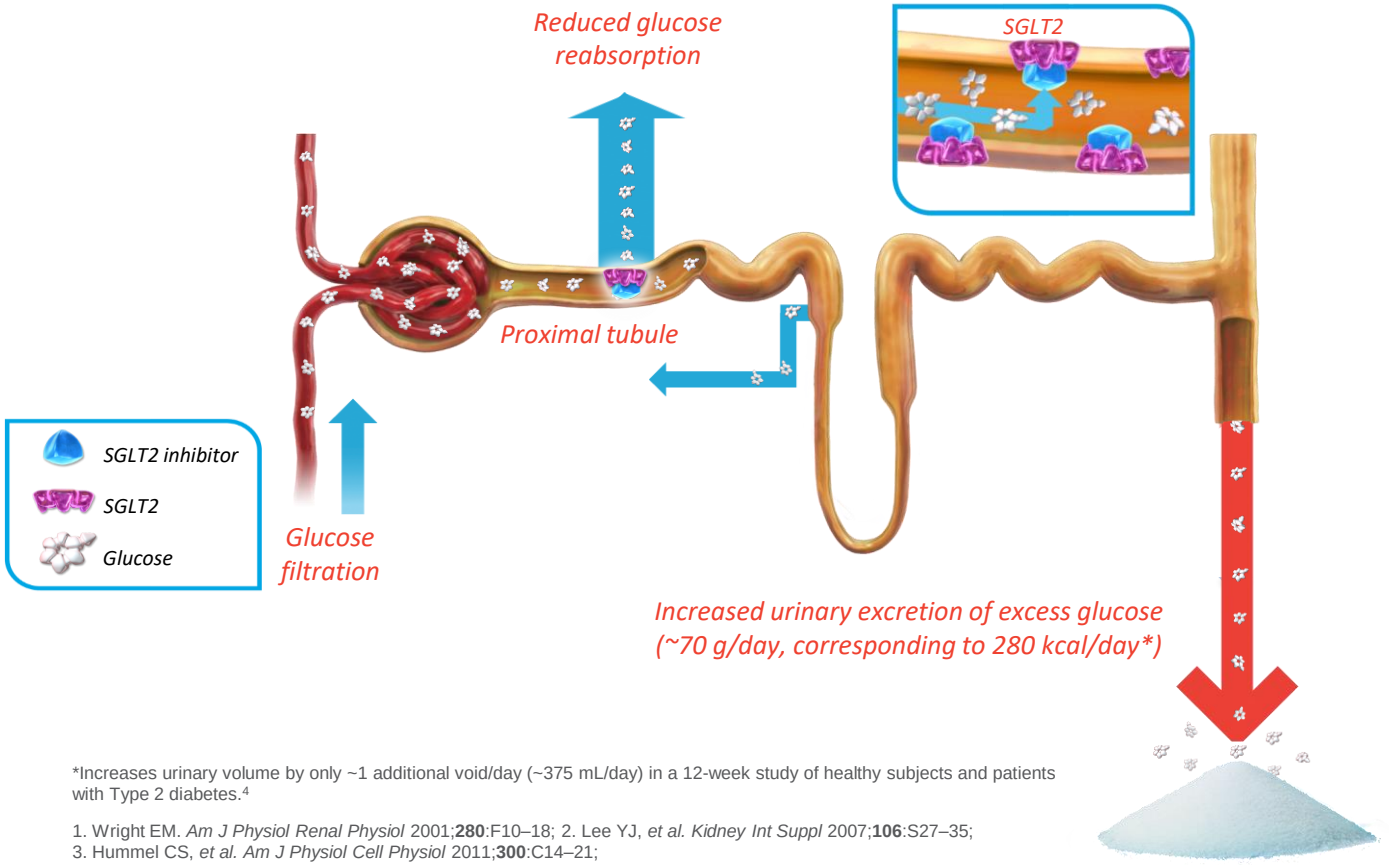
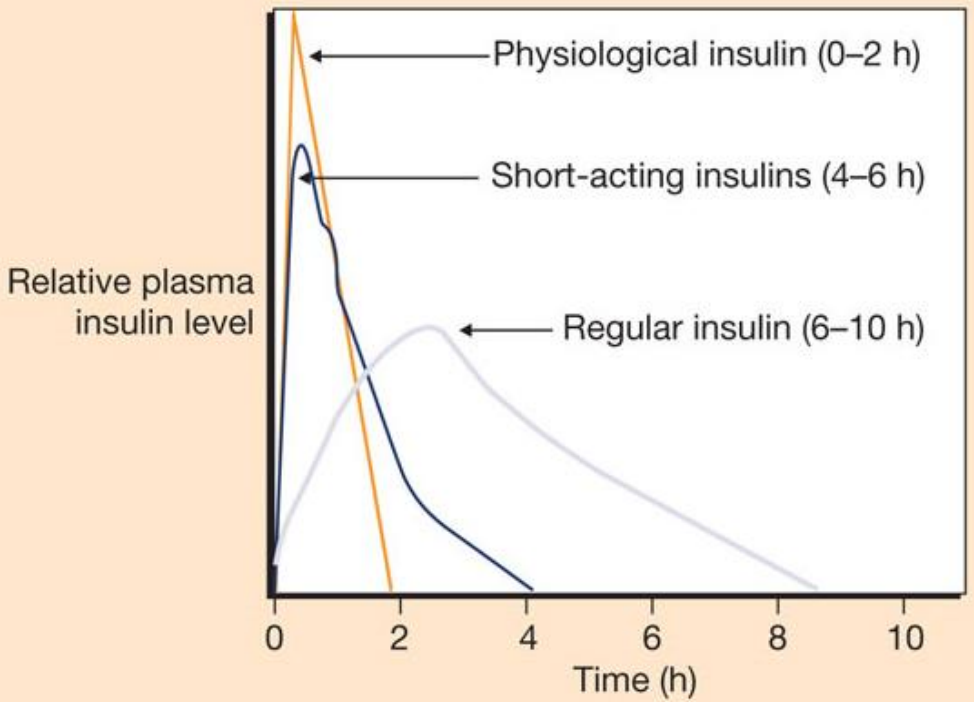
SGLT2 is a New Target that Can Help Lower Blood Glucose Levels by Acting on the Kidney[1–3]



*Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.[4]

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21;
3. Forxiga®. Summary of product characteristics. AstraZeneca, Available on www.medicines.ie Last accessed March 2014.

Differences Between Rapid-acting Insulin Analogs



From: Hirsch IB. *N Engl J Med* 2005 **352**:174-183.

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The Basal-Bolus Insulin Concept

The basal–bolus insulin concept aims to mimic as closely as possible the complex physiological daily pattern of insulin secretion in healthy individuals

Basal insulin

- Near-constant insulin levels throughout the day
- Suppresses hepatic glucose production and lipolysis overnight and during prolonged periods between meals
- Covers ~50% of daily insulin needs

Bolus insulin (meal-time or prandial)

- Immediate rise and sharp peak at 1 hour post-meal
- Limits hyperglycemia after meals
- Covers 10–20% of total daily insulin requirement at each meal

Basal Acting insulin

- 24 hr basal, Levemir, Lantus
- Mimic physiology of pancreas
- Side effects hypo's, lipohypertrophy

Diabetes

- Multisystem Complications of Diabetes
- Describe and explain the macrovascular effects of Diabetes
- Describe and explain the effects of Diabetes on microvasculature
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Thank you

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