Insulin Therapy in Diabetes Mellitus – Part 1

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Objectives – Part 1

- Background: Brief review of epidemiology, diagnosis, classification and pathophysiology of diabetes mellistus.

- Discuss clinical scenarios where insulin is the treatment of choice for diabetes mellitus.

Epidemiology of Diabetes
(US data released 1/26/2011)

- **Affects 25.8 million children and adults**
  - 8.3% of the population

- **13 million men (11.8%) and 12.6 million women (10.8%) have DM**

http://www.diabetes.org/diabetes-basics/diabetes-statistics

Worldwide statistics

In 2010, an estimated 285 million adults worldwide have diabetes, nearly 7% of the adult population.

- **Conservative estimates predict that by 2030, 438 million people will have diabetes, almost 8% of the adult population**

- **The greatest increases will occur in Africa and the Middle East and North Africa, followed by South-East Asia and South and Central America.**

IDF Diabetes Atlas, 4th ed. International Diabetes Federation, 2009.

Epidemiology of Diabetes
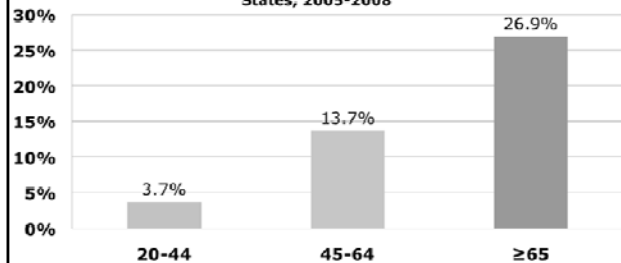**(US data released 1/26/2011)**

- **Prevalence by Race (2007-2009)**

12.6% of non-Hispanic blacks
11.8% of Hispanics
8.4% of Asian Americans
7.1% of non-Hispanic whites

http://www.diabetes.org/diabetes-basics/diabetes-statistics

Diagnosed and Undiagnosed Diabetes

Estimated percentage of people ages ≥20 years with diagnosed and undiagnosed diabetes, by age group, United States, 2005-2008

Age group	Percentage
20-44	3.7%
45-64	13.7%
≥65	26.9%

National Diabetes Information Clearinghouse. National Diabetes Statistics, 2011.
Available at: National Health and Nutrition Examination Survey
http://diabetes.niddk.nih.gov/dm/pubs/statistics/

Epidemiology of Diabetes
(US data released 1/26/2011)

- **DM contributed to 231,404 deaths in 2007**

- **DM carries significant morbidity**
  - **Leading cause of blindness, renal failure and non-traumatic amputations**
  - **2-4 x higher risk of heart disease death and stroke risk**
  - **60-70% have Neuropathy**

- **Total cost of DM was $174 billion in 2007**
  - **DM patient cost is 2.3 x higher than same person without DM**

http://www.diabetes.org/diabetes-basics/diabetes-statistics

Criteria for the Diagnosis of Diabetes

A1C ≥6.5%
OR
Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)
OR
2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT
OR
A random plasma glucose ≥200 mg/dL (11.1 mmol/L)

Classification and Diagnosis. Diabetes Care 2014;37(suppl 1):S15; Table 2.

Classification of Diabetes

Type 1 Diabetes (5-10%): beta-cell destruction often with absolute insulin deficiency

A. Immune mediated (5-10%) (includes LADA)

- Auto-antigens: glutamic acid decarboxylase-65 (GAD65), protein tyrosine phosphatase Ia-2 (IA-2), islet cell autoantibody (ICA) and insulin autoantibody (IAA)

B. Idiopathic (more rare)

Classification of Diabetes

Type 2 Diabetes (90-95%)

Insulin resistance with relative insulin deficiency

Classification of Diabetes - Other

- Genetic defects of beta cell function. (MODY)
- Genetic defects in insulin action.
- Diseases of the exocrine pancreas.
- Endocrinopathies.
- Drug- or chemical-induced. (eg. Steroids)
- Infections.
- Other forms of immune-mediated diabetes.
- Genetic syndromes sometimes associated with diabetes. (Down's syndrome)
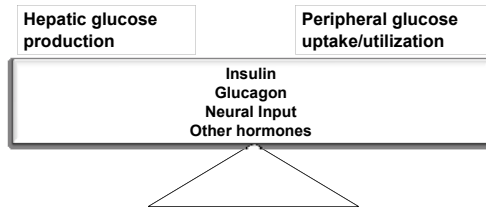- Gestational diabetes.

Source: American Diabetes Association, 2011.
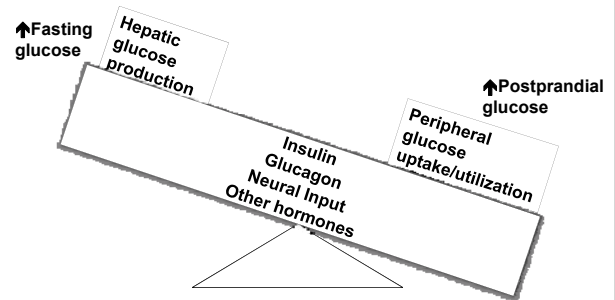
Important note:

- Classification of the type of diabetes is helpful in determining treatment options BUT any classification may require treatment with insulin.

- Type 1 Diabetes without fail requires insulin therapy but it is not uncommon that the many other forms will also as the diseases progresses or during exacerbations.

Review of normal physiology

- **Normal glucose homeostasis relies on a delicate balance between glucose production and utilization.**

| Hepatic glucose production | Peripheral glucose uptake/utilization |

Insulin
Glucagon
Neural Input
Other hormones

Diabetes mellitus – balance is disturbed

↑Fasting glucose

Hepatic glucose production

↑Postprandial glucose

Peripheral glucose uptake/utilization

Insulin
Glucagon
Neural Input
Other hormones

What makes diabetes mellitus insulin requiring?

- **Beta cell failure/loss:**
  - Antibody mediated beta cell destruction (T1DM)
  - Glucotoxicity and lipotoxicity (T2DM)
  - Chemical or drug induced, inflammatory (pancreatitis)
  - Post-pancreatectomy
- **Consider co-morbidities and cause:**
  - Heart failure, liver failure, kidney failure, steroid therapy, post-transplant
- **Clinical presentation:**
  - New onset, degree of hyperglycemia, ketosis, inpatient status.

Case Example

- **34 year old white male presents to the clinic with 3 weeks of polyuria, polydipsia, weight loss and fatigue.**

- **No PMH/PSH. Nonsmoker, denies tobacco, social EtOH (none recently). On no medications.**

- **Exam: Afebrile, HR 98, other vitals unremarkable. BMI 28. No acute distress and exam is unremarkable otherwise.**

Case Example - continued

- Finger stick blood glucose in clinic = "HI"
- Sent to ER for hyperglycemia. Labs with blood glucose of 684, trace ketones, unremarkable electrolytes and renal/liver function.
- Treated with IVF and IV insulin with improvement of blood glucose to 150 and resolution of ketosis.
- Hgb A1c = 11.8.
- What is the best discharge treatment regimen for him?

Case Example- Management

- Younger mildly overweight adult patient with new diagnosis of diabetes mellitus.
- Significant hyperglycemia as demonstrated by Hgb A1c.
- T2DM vs T1DM?
- Either way, insulin therapy is recommended with multiple daily doses.
- Future treatment (outpatient) may depend on antibody testing, c-peptide evalution, and glucose control.

ADA Recommendations: Insulin Therapy for Type 1 Diabetes

Most people with type 1 diabetes should:

- Be treated with MDI injections (3–4 injections per day with basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII).
- Be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity.
- Use insulin analogs to reduce hypoglycemia risk.

ADA Recommendations: Therapy for Type 2 Diabetes

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes.

- In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset.

- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.

Insulin Therapy in Diabetes Mellitus – Part 2

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Objectives – Part 2

- **Review different types of insulin.**
- **Understand how to start insulin.**
- **Introduce how to adjust insulin.**
- **Review treatment goals.**
- **Discuss complications of insulin therapy.**
- **Introduce Insulin pump therapy: selection of appropriate patients and contraindications.**

Different Types of Insulin preparation.

| Insulin Preparations	Onset of Action	Peak Action	Duration of Action
BOLUS INSULIN			
Regular	30 minutes	2-4 hours	6-10 hours
*Lispro (*Humalog*) *Aspart (*Novolog*) *Glulisine (*Apidra*)	5-15 minutes	1-2 hours	4-6 hours
BASAL INSULIN			
NPH	1-2 hours	4-8 hours	10-20 hours
*Glargine (*Lantus*)	1-2 hours	Flat	~ 24 hours
*Detemir (*Levemir*)	1-2 hours	Flat	~ 24 hours ^

*Analogues
^Duration is slightly shorter than **G**largine

Mooradian, A. D. et. al. Ann Intern Med 2006;145:125-134

Duration and onset of action
Source: ADA-EASD Position Statement: Management of Hyperglycemia in T2DM
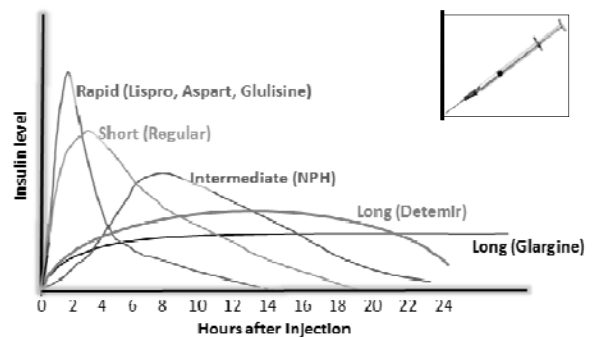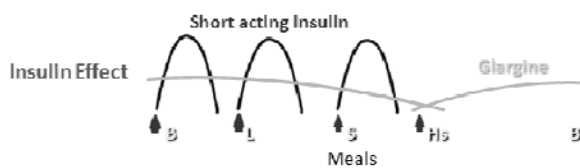
Insulin Pen

Image: CDC Amanda Mills

Images courtesy of Wellcome Images

Insulin Rx options:

- **Using regular insulin "sliding scale" alone should be avoided.**
- **2nd choice insulin: avoid if possible.**
  - **Regular insulin alone.**
  - **NPH insulin alone.**
  - **Pre-Mixed insulin. (e.g 70/30, 25/75 or 50/50)**
- **Basal/bolus insulin: 4 injections per day is the first and best choice.**
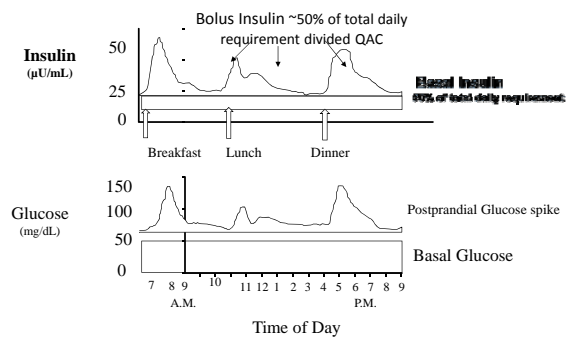
Basal-bolus insulin

Pros
- **Physiological insulin delivery**
- **Improve prandial and fasting BG without hypoglycemia**
- **Stable basal insulin coverage throughout the day.**

Cons:
- **Inconvenient, multiple dosing.**
- **Cannot mix.**

Physiologic Insulin Secretion
24-Hour Profile

Why not mixed insulin and NPH?

- **NPH has peak insulin action→ hypoglycemia.**
- **Patient has to eat 3 meals at regular times.**
- **Prone to hypoglycemia especially with irregular eating habit or if skipping meals.**
- **Mixed insulin: fixed dose of short acting insulin (Aspart , Lispro, Regular) and NPH.**
- **Hard to make adjustments → labile control depending upon BG level and carb intake.**

Why not sliding scale?

"Typical sliding scale"

| Blood sugar before lunch 280 |
⇩
| Receives 6 U insulin sliding scale |

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| 75 g of carb for lunch |
⇩
| Blood sugar before dinner 245!! |

Why not sliding scale?

"Typical sliding scale"

| Blood sugar before lunch 280 |
⇩
| Receives 6 U insulin sliding scale |
⇩   ⇩
| 75 g of carb for lunch | 15 g of carb for lunch |
⇩   ⇩
| Blood sugar before dinner 245!! | Blood sugar before dinner 60!! |

Why not sliding scale?

"Typical sliding scale"

Blood sugar before lunch 280
⇩
Receives 6 U insulin sliding scale
⇩   ⇩
75 g of carb for lunch   15 g of carb for lunch
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Blood sugar before dinner 245!!   Blood sugar before dinner 60!!

"The better way"

Blood sugar before lunch 280

Why not sliding scale?

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Blood sugar before dinner 245!!   Blood sugar before dinner 60!!

"The better way"

Blood sugar before lunch 280
⇩
6 U insulin sliding scale (correction factor) for hyperglycemia of 280 , PLUS 5 U insulin for 75 g carb lunch

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Why not sliding scale?

"Typical sliding scale"

Blood sugar before lunch 280
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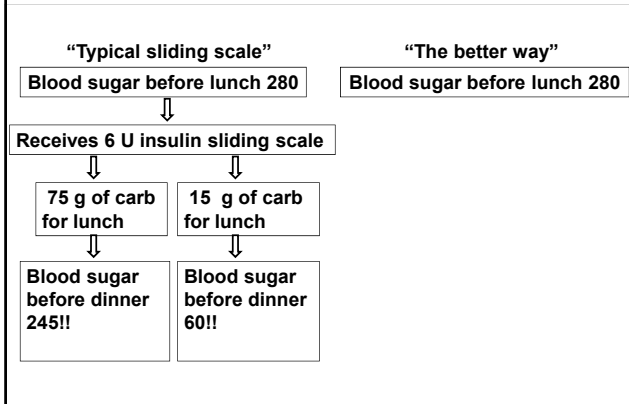75 g of carb for lunch   15 g of carb for lunch
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"The better way"

Blood sugar before lunch 280
⇩
6 U insulin sliding scale (correction factor) for hyperglycemia of 280 , PLUS 5 U insulin for 75 g carb lunch
⇩
Blood sugar before dinner 124!!

What is a sliding scale?
Measure FSG → give insulin
(usually qac+hs)

Low Dose Algorithm		Individualized Dose Algorithm	
Premeal BG	**Additional Insulin**	**Premeal BG**	**Additional Insulin**
150-199	1 unit	150-199	___ units
200-249	2 units	200-249	___ units
250-299	3 units	250-299	___ units
300-349	4 units	300-349	___ units
>349	5 units	> 349	___ units

9

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300-349	4 units	300-349	___ units
>349	5 units	> 349	___ units

Steps to initiating SQ insulin

1. Total daily insulin dose= 0.4-0.5 unit/kg

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2. Basal = 50% of total daily dose
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3. Prandial dose 50% of total daily dose divided over meals
a) insulin to carb ratio
High=1u/5gm, Standard =1 u/10 gm, Low=1 u/20 gm
b) Fixed dose insulin

Steps to initiating SQ insulin

1. Total daily insulin dose= 0.4-0.5 unit/kg

⇩

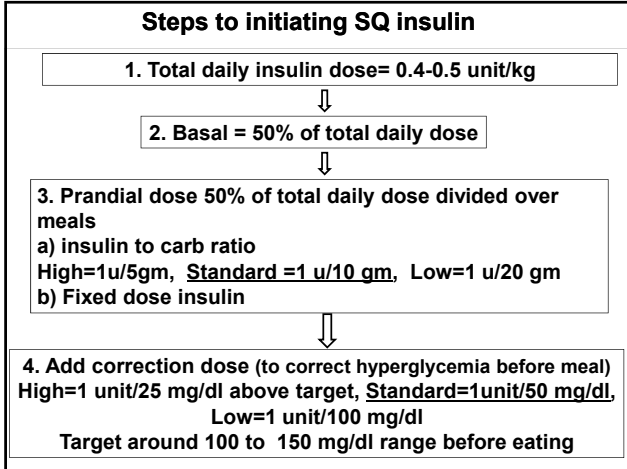| 2. Basal = 50% of total daily dose |
| --- |

⇩

3. Prandial dose 50% of total daily dose divided over meals
a) insulin to carb ratio
High=1u/5gm, Standard =1 u/10 gm, Low=1 u/20 gm
b) Fixed dose insulin

⇩

4. Add correction dose (to correct hyperglycemia before meal)
High=1 unit/25 mg/dl above target, Standard=1unit/50 mg/dl,
Low=1 unit/100 mg/dl
Target around 100 to 150 mg/dl range before eating

MDI vs. CSII

MDI (Multiple Daily Injections)

- Several shots per day
- Two different types of insulin: long acting and short acting
- Challenging to cover shifts in insulin sensitivity, day/night schedule changes.

"Pool""

CSII (Continuous Subcutaneous Insulin Infusion)

- Programmable basal delivery
  - Dawn phenomenon
  - Multiple patterns
  - Temp basals
- Accurate dosing
- More flexible
- Safety features to avoid overdose

"Dribble"

Problems with insulin pump

- **Allergic reaction: much rarer now with recombinant human insulin (< 1-3%).**
- **Technical problems: pump failure, battery problems, memory loss, tubing problems, leakage at infusion site.**
- **Infusion site problems: Erythema, subcutaneous nodule or abscess, cellulitis.**
  - **major reason for discontinuation.**

Patient characteristics for successful insulin pump use:

- **Motivation.**
- **Realistic expectations.**
- **Uses carbohydrate counting effectively.**
- **Checking BG 4+ times per day.**
- **Dedicated team (CDE , physician and patient).**

Selection of the appropriate patient is the most important step.

Contraindications

- Poor compliance.
- Unwillingness/inability to calculate meal doses or check at least 4 blood glucose tests daily.
- Psychiatric conditions (severe recurrent or unresolved depression, and severe eating disorders).
- Dementia.
- Retinopathy (requiring laser Rx especially if starting A1c is very high), significant vision impairment.

Pumps are not the easy way out to replace multiple insulin injections.

What is the target for my patient?

- Goal should be individualized.
- Not one size fit all.
- Can relax control in following patients. (Target HgbA1c 7 to 8 range)
1. Limited life expectancy.
2. Elderly with multiple co-morbidities such as CVD , poor PO intake and poor mental status.
3. Patients with high risk for hypoglycemia such as ESRD on HD.
4. History of recurrent hypoglycemia.
5. Severe hypoglycemia unawareness.

Target Hgb A1c less than 6.5%.

- Relatively young patients without end organ damages (eg. neuropathy, CVD)
- Tight control in those patients can prevent future complications.
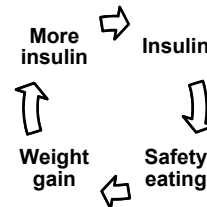
Monitoring

- HgbA1c alone does not tell you the full story.
- Highly labile glucose can still result in HgbA1c less than 7%.
- HgbA1 is not reliable in
  - Severe anemia
  - Recent blood loss or blood transfusion.
  - Hemoglobinopathy (sickle cell, congenital spherocytosis)
- Regular monitoring of BG can lead to better control.
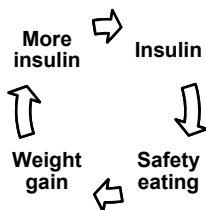- Encourage home BG monitoring.

Hypoglycemia

- **Important complication.**
- **Can be fatal.**
- **Always ask about hypoglycemia symptoms at every visit.**
- **Recommend checking BG first before eating a snack if patient feels hungry.**
- **Feeling hungry may not be real hypoglycemia.**
- **Patients with high BG (above 200) may still feel symptoms of a "low" at normal BG (around 100).**

Over-insulinization

More insulin → Insulin → Safety eating → Weight gain → (cycle)

Over-insulinization

More insulin → Insulin → Safety eating → Weight gain → (cycle)

- Suspect in patients taking high dose of insulin with frequent snacking all day.
- ↓insulin →↓ snack and carb intake →cut the vicious cycle.

Adjustment of insulin

- **Ongoing process.**
- **No need to get perfect number/dose immediately.**
- **Gradual titration (20-30% adjustment).**
- **Need to know BG pattern.**
- **Presence of hypoglycemia.**
- **Always ask about eating/drinking habits (such as regular soda, snacks) which can affect BG significantly.**

John Smith

Morning fasting	Before lunch	Before dinner
120	200	280
150	250	300
100	180	250
Lantus -40 units	Novolog 5 units before each meal	

John Smith

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- **Higher BG values after meal indicate inadequate meal coverage insulin.**
- **Common in steroid induced hyperglycemia and high carb intake with meal.**
- **Would need to increase meal time insulin .**

Martha

Morning fasting	Before lunch	Before dinner
80	120	135
60	100	125
55	90	115

Martha

Morning fasting	Before lunch	Before dinner
80	120	135
60	100	125
55	90	115

- **Low fasting sugar indicates high basal insulin rate .**
- **Long acting insulin needs to be reduced.**

Sara

Morning fasting	Before lunch	Before dinner	Bedtime
190	120	135	90
180	100	125	70
200	90	115	88

Sara

Morning fasting	Before lunch	Before dinner	Bedtime
190	120	135	90
180	100	125	70
200	90	115	88

- ⬆fasting sugar due to rebound effect of nocturnal hypoglycemia around midnight .
- Long acting insulin needs to be reduced.

Sara

Morning fasting	Before lunch	Before dinner	Bedtime	midnight
190	120	135	90	60
180	100	125	70	48
200	90	115	88	55

- ⬆fasting sugar due to rebound effect of nocturnal hypoglycemia around midnight .
- Long acting insulin needs to be reduced.

Should oral agents be stopped for initiation of insulin ?

- **No need to stop all oral agents (TZD, metformin or Sitagliptin) when insulin is added.**
- **If basal/bolus insulin is added, SU may be stopped for risk of hypoglycemia.**
- **Benefits of oral agents such as metformin and pioglitazone.**
  - **β cell preservation.**
  - **Lipid profile.**
  - **Fatty liver.**

Lifestyle modification and education

- Diabetes education is vital.
- Must know survival skill such as DKA and hypoglycemia.
- Encourage to eat balance diet, regular eating habit.
- Reduce ready sugar and high carb diet.(such as regular soda)