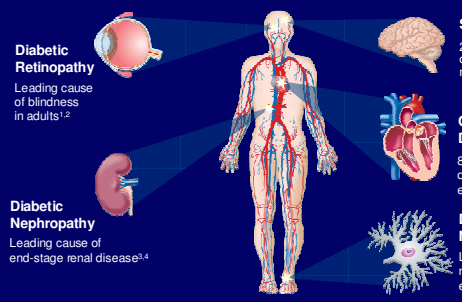
Optimize inpatient hyperglycemia control

中國醫藥大學附設醫院台北分院
新陳代謝科 李國陽醫師

Chronic complication of T2DM



Diabetic Retinopathy
Leading cause of blindness in adults[1,2]

Diabetic Nephropathy
Leading cause of end-stage renal disease[3,4]

Stroke
2- to 4-fold increase in cardiovascular mortality and stroke[5]

Cardiovascular Disease
8/10 individuals with diabetes die from CV events[6]

Diabetic Neuropathy
Leading cause of non-traumatic lower extremity amputations[7,8]

[1]UK Prospective Diabetes Study Group. *Diabetes Res* 1990; 13:1–11. [2]Fong DS, *et al. Diabetes Care* 2003; 26 (Suppl. 1):S99–S102. [3]The Hypertension in Diabetes Study Group. *J Hypertens* 1993; 11:309–317. [4]Molitch ME, *et al. Diabetes Care* 2003; 26 (Suppl. 1):S94–S98. [5]Kannel WB, *et al. Am Heart J* 1990; 120:672–676. [6]Gray RP & Yudkin JS. Cardiovascular disease in diabetes mellitus. In *Textbook of Diabetes* 2nd Edition, 1997. Blackwell Sciences. [7]King's Fund. *Counting the cost. The real impact of non-insulin dependent diabetes.* London: British Diabetic Association, 1996. [8]Mayfield JA, *et al. Diabetes Care* 2003; 26 (Suppl. 1):S78–S79.

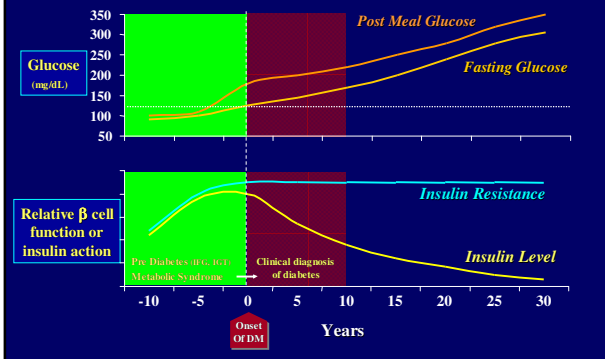
Goal for T2DM management

Glucose control	Healthy	ADA[1]	AACE[2]	IDF[3]
HbA_{1c} (%)	<6	<7	≤6.5	≤6.5
Mean FPG mmol/l (mg/dl)	<5.6 (<100)	5–7.2 (90–130)	<6 (<110)	<6 (<110)
Mean postprandial PG mmol/l (mg/dl)	<7.8 (<140)	<10* (<180)	<7.8** (<140)	<7.5** (<135)

*1–2 hours postprandial; **2 hours postprandial.

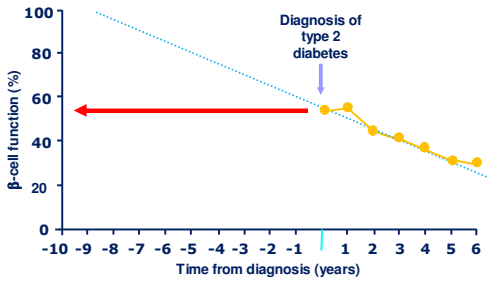
PG=plasma glucose.
1. American Diabetes Association. Diabetes Care 2005;28(suppl 1):S14–36.
2. American Association of Clinical Endocrinologists. Endocr Pract 2002;8(suppl 1):43–84.
3. International Diabetes Federation. Diabet Med 1999;16:716–30.

T2DM Natural Course



Adapted from *Type 2 Diabetes BASICS*. International Diabetes Center (IDC), Minneapolis, 2000.

Up to 50% B-cell function loss at T2DM diagnosis



Holman RR. *Diabetes Res Clin Prac* 1998; 40 (Suppl.):S21–S25.

Insulin is most potent for hyperglycemia control

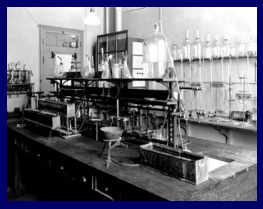
Interventions	Expected decrease in HbA1c
Lifestyle	1 – 2 %
Insulin	1.5 – 3.5 %
Metformin	1 – 2 %
Sulfonylureas	1 – 2 %
Glitazones	0.5 – 1.4 %
α-glucosidase inhibitors	0.5 – 0.8 %
Exenatide	0.5 – 1 %
Glinides	1 – 1.5 %
Pramlintide	0.5 – 1 %
Sitagliptin	0.5 – 0.8 %

Nathan DM,et al. Diabetologia 2008; 51:8-11

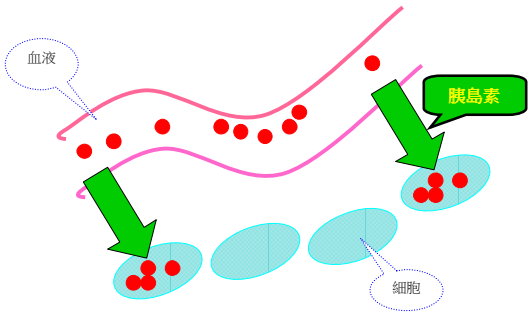
Sir Frederick G. Banting

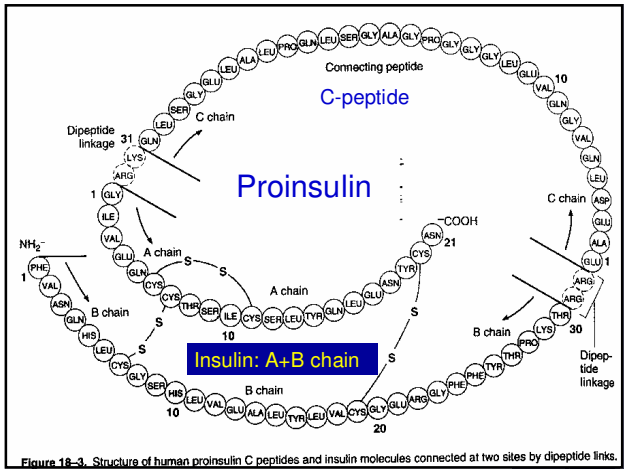
The Nobel Prize of Medicine, 1923

世界糖尿病日: 11/14

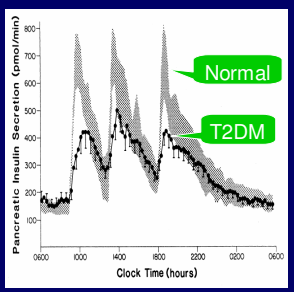


Insulin– bridge between blood and cell





Insulin secretion in normal and T2DM



- Normal
  - Maximal postprandial insulin levels are usually 3-8, and even 10-fold higher than before the meal
  - Reaches peak insulin level in 30-90 minutes, then decline
- DM
  - Lower peak
  - delayed insulin secretion

Insulin Phrarmacokinetics

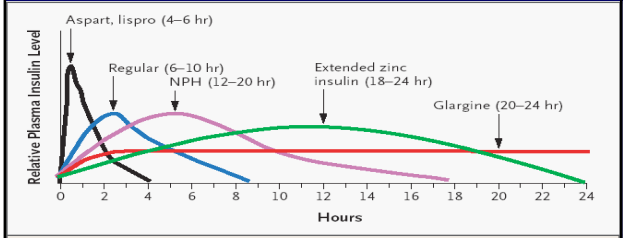


Figure 2. Approximate Pharmacokinetic Profiles of Human Insulin and Insulin Analogues.

The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons.

NEJM 2005; 352: 2

Action data of insulin

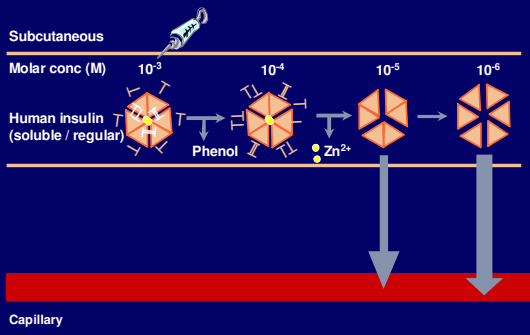
Table 1. Duration of Action of Standard Insulins and Insulin Analogues.*

Insulin	Onset of Action	Peak Action	Effective Duration
Standard			
Regular	30–60 min	2–3 hr	8–10 hr
NPH	2–4 hr	4–10 hr	12–18 hr
Zinc insulin (Lente)	2–4 hr	4–12 hr	12–20 hr
Extended zinc insulin (Ultralente)	6–10 hr	10–16 hr	18–24 hr
Analogues			
Lispro	5–15 min	30–90 min	4–6 hr
Aspart	5–15 min	30–90 min	4–6 hr
Glargine	2–4 hr	None	20–24 hr

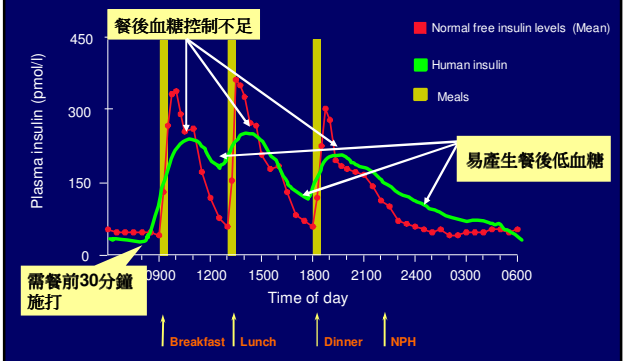
* Serum insulin profiles are based on a subcutaneous injection of 0.1 to 0.2 unit per kilogram of body weight; large variation within and between persons may be noted. Data are from DeWitt and Hirsch.[6]

NEJM 2005; 352: 2

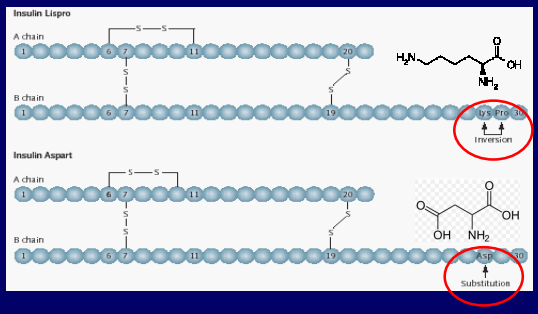
Regular Insulin



Human insulin disadvantage

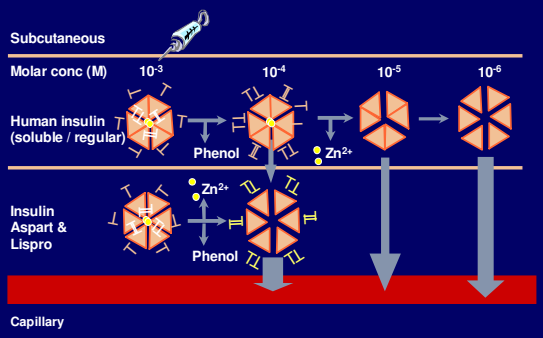


Meal time insulin analogues: Insulin Lispro and Insulin Aspart



NEJM 2005; 352: 2

Rapid acting insulin analogues: Insulin Aspart and Insulin Lispro



Insulin Pharmacokinetics

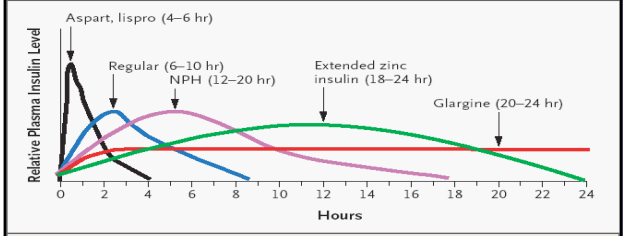
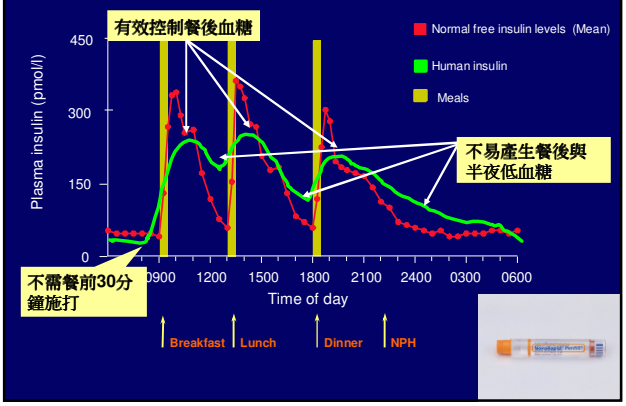


Figure 2. Approximate Pharmacokinetic Profiles of Human Insulin and Insulin Analogues.
The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons.

NEJM 2005; 352: 2

Aspart (NovoRapid)



Pharmacokinetics of Insulin

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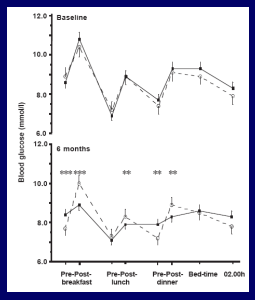
Lispro	5–15 min	30–90 min	4–6 hr
Aspart NovoRapid	5–15 min	30–90 min	4–6 hr
Glargine	2–4 hr	None	20–24 hr

* Serum insulin profiles are based on a subcutaneous injection of 0.1 to 0.2 unit per kilogram of body weight; large variation within and between persons may be noted. Data are from DeWitt and Hirsch.[6]

NEJM 2005; 352: 2

NovoRapid lowers post-meal sugar than RI



- RI tid + NPH hs (white) vs. aspart tid + NPH hs (black)
- Those who received aspart as meal insulin had significantly lower post-meal glucose levels
- Hypoglycemia risk is similar (aspart vs. RI)
  - Minor: 7.64 vs. 7.54 /patient-year
  - Major: 0.81 vs. 0.97 /patient-year

Home et al. Diabetic Med 2000; 17:762-70

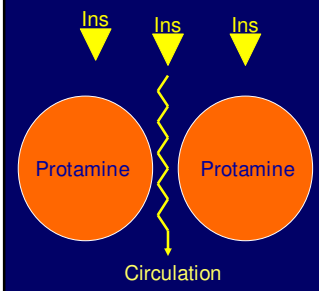
NovoRapid causes less hypoglycemia than RI

	Insulin aspart Events		Human insulin Events			
	n	Pt-year^{-1}	*n*	Pt-year^{-1}	RR (95% CI)*	*P*-value†
Exposed						
Minor	1590	35.8	1752	38.2	0.93 (0.87–1.00)	0.048
Major all	38	0.85	51	1.12	0.72 (0.47–1.09)	0.13
Major night	9	0.80	31	2.70	0.28 (0.13–0.59)	0.001
Major daytime	29	0.86	20	0.58	1.38 (0.78–2.45)	0.27
Grade A all‡	28	0.64	40	0.88	0.67 (0.41–1.08)	0.10
Grade A night	6	0.54	24	2.1	0.24 (0.10–0.59)	0.002
Grade A daytime	22	0.66	16	0.47	1.30 (0.68–2.48)	0.42
Grade B all§	10	0.23	11	0.24	0.89 (0.38–2.10)	0.79
Grade B night	3	0.26	7	0.61	0.42 (0.11–1.63)	0.21
Grade B daytime	7	0.20	4	0.12	1.71 (0.50–5.88)	0.39

*The estimated relative risk is based on a statistical model conditioning on the total number of events per subject and correcting for relative exposure time on IAsp and HI.
†The *P*-values are based on the Wald test.
‡Grade A: the patients received oral glucose.
§Grade B: the patients required intravenous glucose or glucagon treatment.

Heller SR et al., Diabetic Med 2004

NPH (Neutral Protamine Hedgedorn)



- Mr. Hedgedorn發展出來的
- Protamine: 魚精蛋白
- Prolong action by mixture -> mix before use

NPH shortage

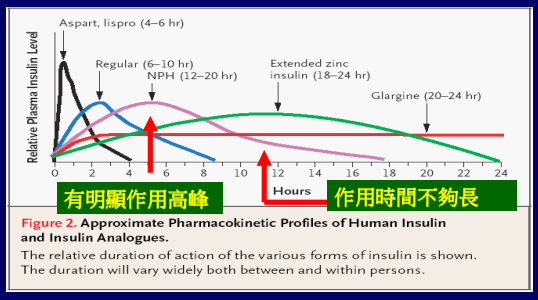


Figure 2. Approximate Pharmacokinetic Profiles of Human Insulin and Insulin Analogues.
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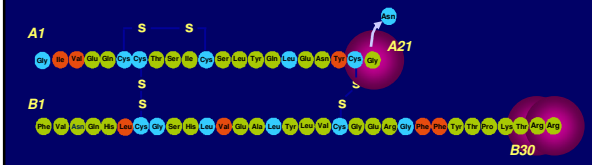
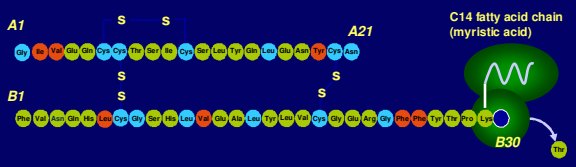
NEJM 2005; 352: 2

Insulin Glargine (Lantus) Precipitate for Protracted Action



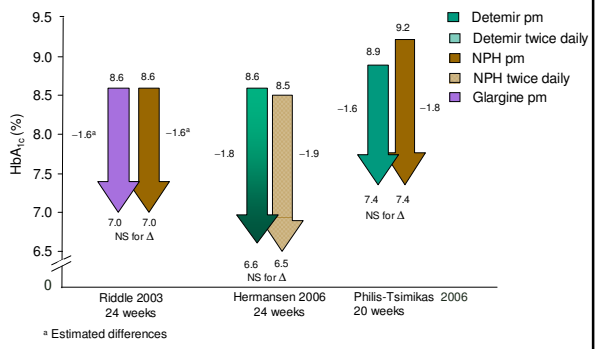
- A21: Gly for Asn, B31B32: add Arg -> Gl argine
- Modify isoelectric point: precipitate in pH 7
- Peakless, qd use

Insulin Detemir (Levemir) Protract Action by Albumin Binding



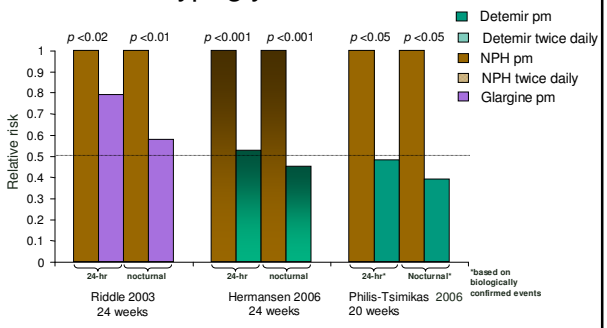
- B29: add myristic acid, B30: delete
- Acylation with a fatty acid side chain: albumin binding
- Steadily release, qd or bid use

Long acting insulin analogues VS. NPH

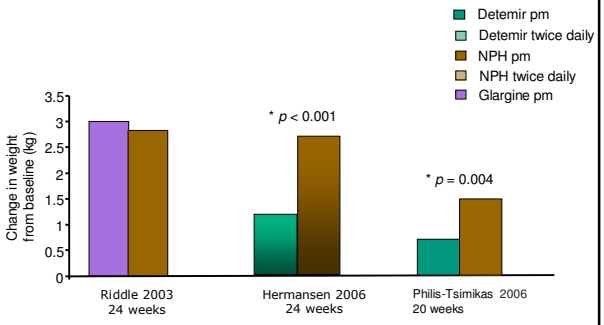


[a] Estimated differences

Long acting insulin analogues cause less hypoglycemia than NPH



Levemir/ Lantus cause less weight gain than NPH



Levemir has less mitogenic potency than Lantus

	IR affinity	IGF-1R affinity	IR off rate	Metabolic potency	Mitogenic potency
Human insulin	=100	=100	=100	=100	=100
X10	205	587	14	207	975
Insulin aspart	92	81	81	101	58
Insulin lispro	84	156	100	82	66
Insulin glargine	86	641	152	60	783
Insulin detemir	18	16	204	27	11

Kurtzhals *et al. Diabetes* 2000;49:999

Insulin use timing

- Type 1 DM
- T2DM, sugar not well controlled under OADs
- GDM
- Stress, Illness, Infection, Surgery
- Hyperglycemic emergency (DKA, HHS)
- OAD contraindication (Allergy, liver or renal impairment)

Diabetes Care 2003;26: S121-125; *JAMA 2003; 289: 2254-2264 ; 2010 中華民國糖尿病臨床照護指引*

Acute illness and hyperglycemia

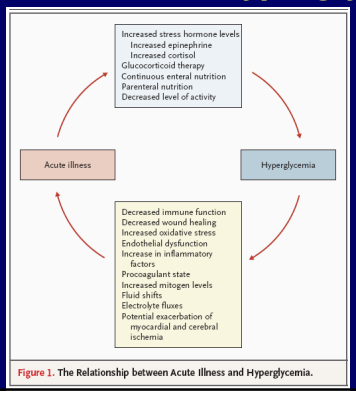


Figure 1. The Relationship between Acute Illness and Hyperglycemia.

N Engl J Med 355:18 1903-11; 2006

Inpatient sugar level and prognosis

Table 1. Summary Data from Randomized Clinical Trials of Intensive Insulin Therapy in Critically Ill Patients.*

Trial Name (Source)†	No. of Patients	Type of ICU	Blood Glucose Level Targeted		Blood Glucose Level Achieved‡		Primary Outcome	Rate of Outcome		Odds Ratio (95% CI)
			Intensive Glucose Control	Conventional Glucose Control	Intensive Glucose Control	Conventional Glucose Control		Intensive Glucose Control	Conventional Glucose Control	
			milligrams per deciliter					percent		
Leuven 1 (Van den Berghe et al.[3])	1548	Surgical	80–110	180–200	103	153	Death in ICU	4.6	8.0	0.58 (0.38–0.78)
Leuven 2 (Van den Berghe et al.[4])	1200	Medical	80–110	180–200	111	153	Death in hospital	37.3	40.0	0.94 (0.84–1.06)
Glucontrol (Devos et al.,[5] Preiser J.C.: personal communication)	1101	General	80–110	140–180	118	144	Death in ICU	16.7	15.2	1.10 (0.84–1.44)
VISEP (Brunkhorst et al.[6])§	537	General	80–110	180–200	112	151	Death at 28 days	24.7	26.0	Not reported
NICE-SUGAR[7]	6104	General	81–108	144–180	118	145	Death at 90 days	27.5	24.9	1.14 (1.02–1.28)

N Engl J Med 360:13 1346-49; 2009

Glycemic goal in impatient

Table 1. Glycemic targets in hospitalized patients.

All Critically Ill Patients
- BG between 140 and 180 mg/dL
- IV insulin preferred

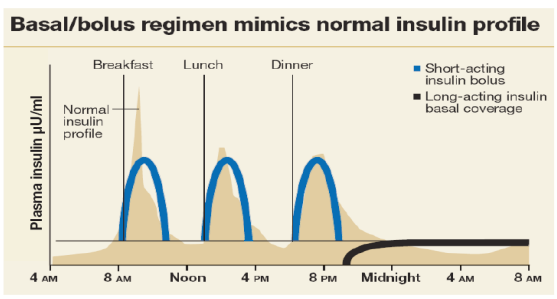
Non-Critically Ill Patients
- Pre-meal < 140
- Random < 180
- Scheduled SC dosing preferred

Hypoglycemia*
- Reassess regimen if BG < 100 mg/dL
- Modify regimen if BG < 70 mg/dL

Sliding-Scale Insulin
- Discouraged

Curr Med Res Opini 26:589-98; 2010

Basal-Bolus regimen



Clinical Diabetes 29:1 1-9; 2011

Calculate Total Daily Dose (TDD)

Table 1. Determining a TDD for Insulin-Naive Patients

TDD Estimation	Patient Characteristics
0.3 units/kg body weight	• Underweight • Older age • Hemodialysis
0.4 units/kg body weight	• Normal weight
0.5 units/kg body weight	• Overweight
≥ 0.6 units/kg body weight	• Obese • Insulin resistant • Glucocorticoids

Clinical Diabetes 29:1 1-9; 2011

Divide TDD to meal time and basal insulin

- ◆ 睡前 Basal Insulin (**Levemir**) = TDD X 50%
- ◆ 三餐前 Bolus Insulin (**NovoRapid**) = (TDD X 50%) / 3
- ◆ 根據測得指間血糖與目標值調整劑量; 進食量少亦需調整餐前劑量

Clinical Diabetes 29:1 1-9; 2011

How much 1U Insulin will lower glucose

" 1700" Rule (for analogue)

- **Divide 1700 by the TDD**

eg. 80 kg insulin resistant patient

TDD = 80 X 0.6 = 48

1700/ 48 = 35

" 1500" rule for Human insulin

Diabetes Technol Ther 5:237 , 2003
Davidson PC et al. Endocr Pract 14:1095-1101, 2008

Correctional insulin

** Low Dose Scale is recommended for lean or elderly patients or low basal or meal insulin doses.*
** Moderate dose Scale is recommended for patients acutely ill or febrile or moderate basal or meal insulin doses.*
** High Dose Scale is recommended for patients on steroids, TPN or tube feedings, or high basal or meal insulin doses*

Capillary Blood Glucose	□ Low Dose	□ Moderate Dose	□ High Dose	□ Individualized Dose
<70 mg/dL	Implement hypoglycemia policy	Implement hypoglycemia policy	Implement hypoglycemia policy	Implement hypoglycemia policy
140 mg/dL or less	0 units	0 units	0 units	
141-180 mg/dL	1 units	2 units	3 units	
181-220 mg/dL	2 units	4 units	6 units	
221-260 mg/dL	3 units	6 units	9 units	
261-300 mg/dL	4 units	8 units	12 units	
301-340 mg/dL	5 units	10 units	15 units	
> 340 mg/dL	6 units	12 units	18 units	

TDD 20-40 1U ~ 40 *TDD 40-80 1U ~ 20* *TDD 80-120 1U ~ 10* *Clinical Diabetes 29:1 1-9; 2011*

Hyperglycemia protocol

Follow Hypoglycemia Protocol (Policy No. 3.20). For BGM < 70 mg/dL: If ALERT/RESPONSIVE, give 6 oz. regular soda, recheck BGM in 15 minutes IF UNRESPONSIVE/NPO, WITH IV ACCESS give 25 mL D50 IV, recheck BGM in 15 minutes, WITH NO IV ACCESS, give 1 mg Glucagon IM, position on side, recheck BGM in 15 minutes. NOTIFY physician.

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Case

- 55 y/o woman, DM, HTN
  Metformin(500) 1# tid, Amaryl (2) 1#qd
  BH 155, BW 80
  admitted for fever for 3 days and flank pain r/o APN, on CMZ
  one touch AC 224

➡ St Novorapid (224-140)/20 U
HbA1C
Shift OHAs to Insulin

Divide TDD to Meal time and basal insulin

- ◆ 睡前 Basal Insulin (**Levemir**) = (80X 0.6) X 50% = 24 U
- ◆ 三餐前 Bolus Insulin (**NovoRapid**) = (80 X 0.6X 50%) / 3 = 8 U

NovoRapid 8U-8U-8U tid AC
Levemir 24 U hs

Dose correction

- NovoRapid 8U-8U-8U tid AC, Levemir 24 U hs
- One touch sugar 142, 168, 185, 225
- Increase dinner NovoRapid (225-140)/20 = 4U

NovoRapid 8U-8U-12U tid AC
Levemir 24 U hs

Dose correction

- NovoRapid 12U-10U-12U tid AC, Levemir 24 U hs
- One touch sugar 142, 78, 134, 156
- Decrease breakfast NovoRapid (140-78)/20 = 4U

NovoRapid 8U-10U-12U tid AC
Levemir 24 U hs

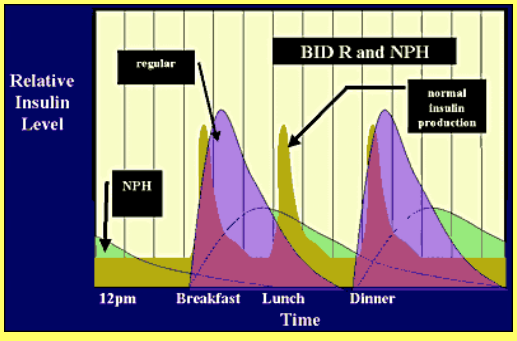
From admission to discharge

- NovoRapid 8U-10U-12U tid AC, Levemir 26 U hs
- TDD = 8+ 10+12+26 = 56
- Novomix (56X 2/3) before breakfast
  Novomix (56X 1/3) before dinner
  corrected by one touch sugar bid ac

NG Feeding

Table 4. Sample Insulin Requirement Calculation for a Patient on Enteral Feedings	
Sample: Insulin dose calculation for 80 kg patient with a BMI of 24 kg/m^2 on continuous enteral feeding	
Step 1	**TDD calculation.** TDD: 0.4 units/kg × 80 = 32 units
Step 2	**Insulin dosing based on type of insulin.** Glargine insulin dose: 32 units subcutaneously daily or NPH insulin dose: 16 units subcutaneously twice daily
Step 3	**Correctional scale estimation.** Low correctional scale insulin is most appropriate for patient requiring an estimated TDD of 32 units. Order correctional scale every 4 hours with rapid-acting analogs and every 6 hours with regular insulin

Clinical Diabetes 29:1 1-9; 2011



NPO with IVF, TPN

Guideline algorithm for initiation of total parenteral nutrition in hospitalized patients, emphasizin avoidance and treatment of hyperglycemia (*continued*)

Consider starting separate insulin infusion to treat glucose higher than target
If not feasible- use insulin in TPN bag in any patient at risk of hyperglycemia

On IV insulin infusion*

Monitor fingerstick glucose every 1-2 hours until stable, then every 4 hours

Put 50% of the prior 24 hour insulin into next TPN bag to reduce need for drip, assuming no change in clinical status

IV insulin infusion not feasible

Euglycemic → 15 units insulin/ 100g dextrose

Hyperglycemic → 20 units insulin/ 100g dextrose

>300 mg/dl → normalize before TPN

Monitor fingerstick every 4-6 hours, and supplement with rapid acting insulin given subcutaneously as needed to maintain goal glucose values

Put ~75% of the subcutaneous insulin dose into the next TPN bag, assuming no change in clinical status

Joslin Diabetes Center and Joslin Clinic; 2007

IV Insulin to Sub. Insulin

Table 3. Sample Conversion From IV to Basal/Bolus Insulin	
Sample: Basal/bolus insulin dose calculation for a patient started on diet who required 2 units/hour of insulin overnight while NPO	
Step 1	**Basal dose calculation** Patient's hourly insulin infusion rate while NPO = 2 units/hour 24-hour basal insulin dose during stress = 24 × hourly infusion rate = 24 × 2 = 48 units Adjusted basal dose accounting for stress reduction = 2/3 × 24-hour basal rate = 2/3 × 48 = 32 units of glargine
Step 2	**TDD calculation** TDD = dose is 2 × adjusted basal dose = 2 × 32 = 64 units
Step 3	**Mealtime bolus dose calculation** Patient just started to eat, so 10% of basal dose can be started with each meal = 0.1 × 32 = 3 units with each meal
Step 4	**Correctional scale estimation** A moderate-level correctional scale is most appropriate for an estimated TDD of 64 units

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胰島素的使用

- RI 飯前 30 min 施打
- NovoRapid, Novomix 飯前立即施打
- NPH, Lantus, Levemir 睡前施打
- 若有要吃飯, RI 跟 NovoRapid 一定要打, 除非飯前血糖測得很低 (< 70), 若擔心低血糖,可考慮減 4U打 或 打 ½ dose
- 睡前 NPH, Lantus, Levemir 一定要打, 除非睡前測得血糖很低 (<70)
- 前幾天打過相同劑量發生過低血糖事件, 則需向下調整劑量

胰島素的使用（續)

- 利用 1700/1500 rule 或 Correctional scale 計算需增加胰島素量
- 當下血糖高可打st 速效胰島素 (NovoRapid)
- 飯前血糖高, 調整睡前長效胰島素劑量
- 飯後血糖高, 調整"前一餐"餐前胰島素劑量

胰島素的使用（續)

- 一天所需之總胰島素起始劑量可以體重（kg）X 0.3~0.6 計算, 三餐前打 NovoRapid, 睡前打 Levemir
- 四段打針的病患出院前調整用藥 （換回口服藥, 打一次, 打兩次), 門診回診

應小心使用胰島素的狀況

- 意識不清的病患
- 急性腦中風或急性心肌梗塞之病患
- 有腦中風或心臟病病史
- 過去無糖尿病史病患
- 年紀過大之老人
- 對於低血糖無自覺的病患

以上均是胰島素使用, 若發生低血糖之高風險群, 血糖控制應較保守 (< 180)

THANKS FOR YOUR ATTENTION