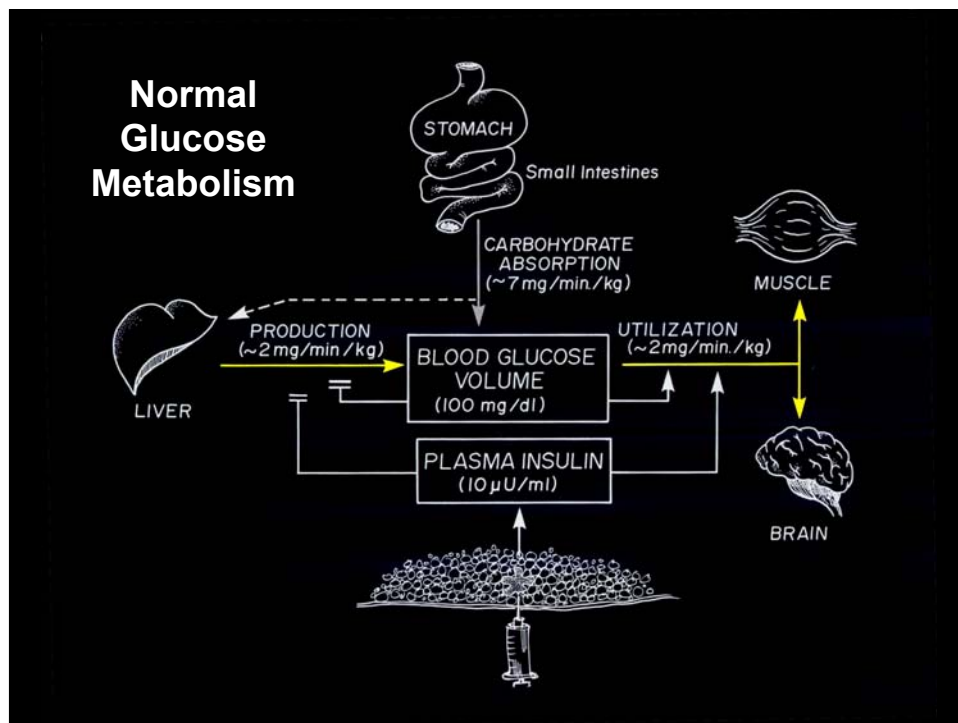
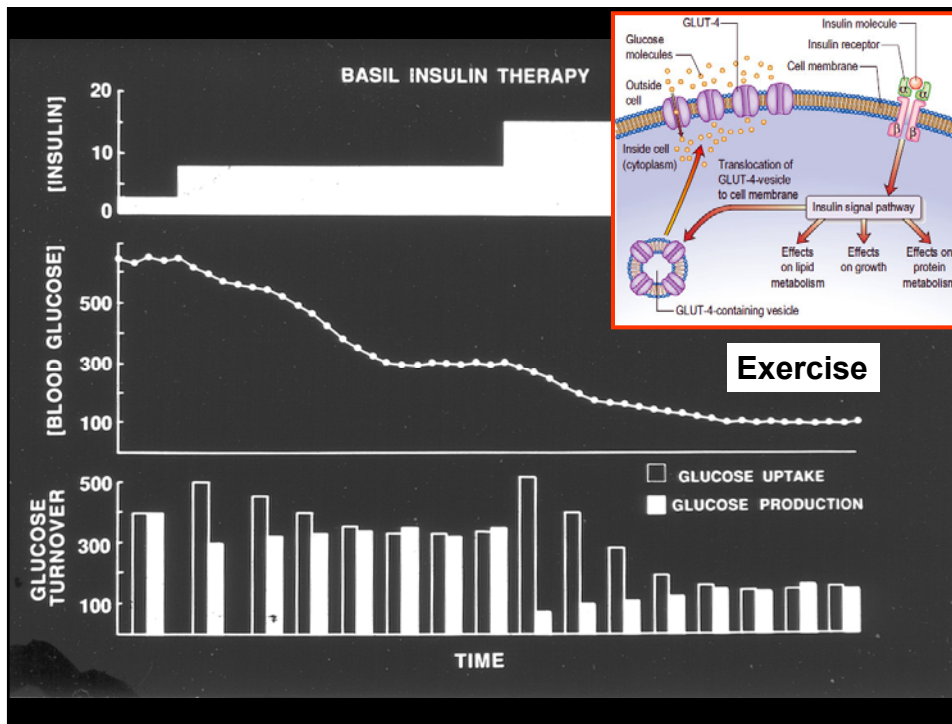


# Basal Insulin Therapy & Glucose Counting

## Providing Stability to an Unstable Disease

Thomas A. Hughes, M.D.  
Professor of Medicine - Retired  
Division of Endocrinology, Metabolism, and Diabetes  
University of Tennessee Health Science Center  
[HughesEndo.com](http://HughesEndo.com)



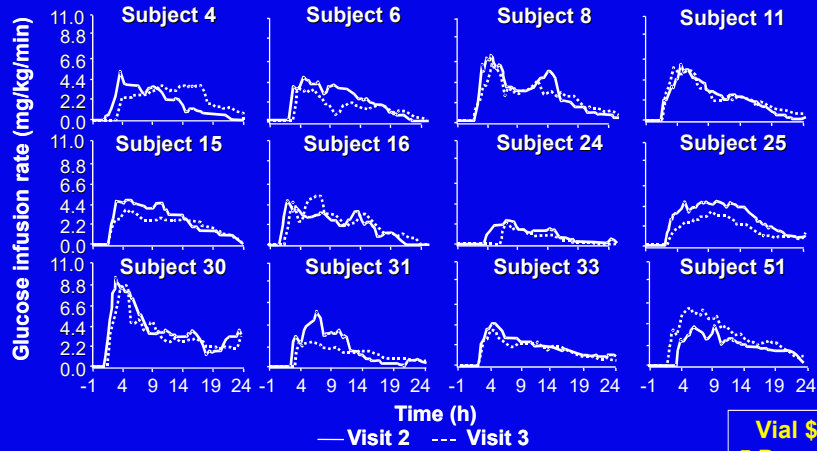


## Exogenous Basal Insulin

### Desirable characteristics for basal insulin

- Single daily injection → 24-hour coverage
- Plasma glucose profiles without peaks
- Consistent absorption profiles

## Intrasubject Variability (GIR) With NPH Insulin

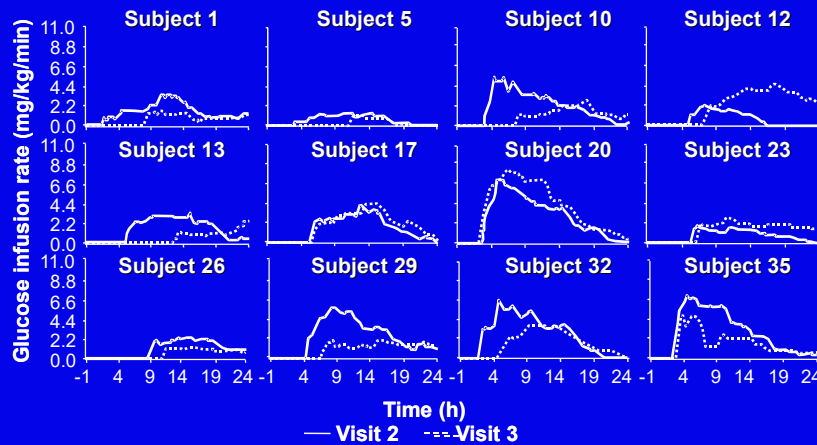


Vial \$37  
5 Pens \$43  
(Walmart)

**Inject Every 8 Hours**

Scholtz et al. *Diabetologia*. 1999;42(suppl 1):A235.

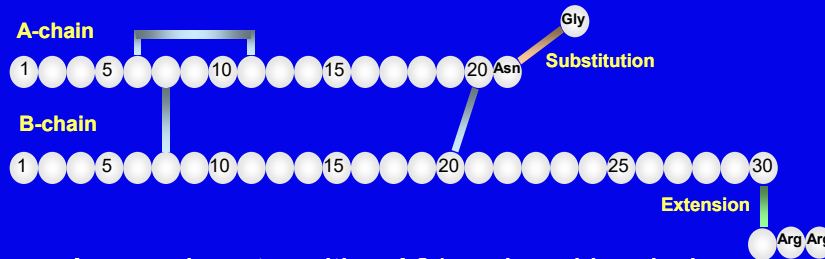
## Intrasubject Variability (GIR) With Ultralente<sup>®</sup> Insulin



Scholtz et al. *Diabetologia*. 1999;42(suppl 1):A235. Ultralente<sup>®</sup> is a trademark of Eli Lilly and Company.

# Lantus<sup>®</sup> Insulin (glargine [rDNA origin])

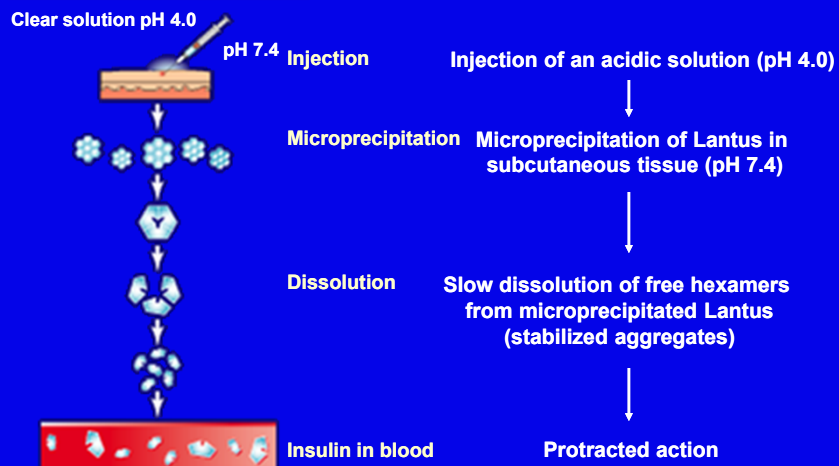
Vial \$57  
5 Pens \$81  
(Walgreens)



- < Asparagine at position A21 replaced by glycine
  - Provides stability
- < Addition of two arginines at the C-terminus of the B-chain
  - More soluble at slightly acidic pH and less soluble at physiologic pH of subcutaneous tissue

Seipke et al. *Diabetologia*. 1992;35(suppl 1):A4. Lantus package insert.

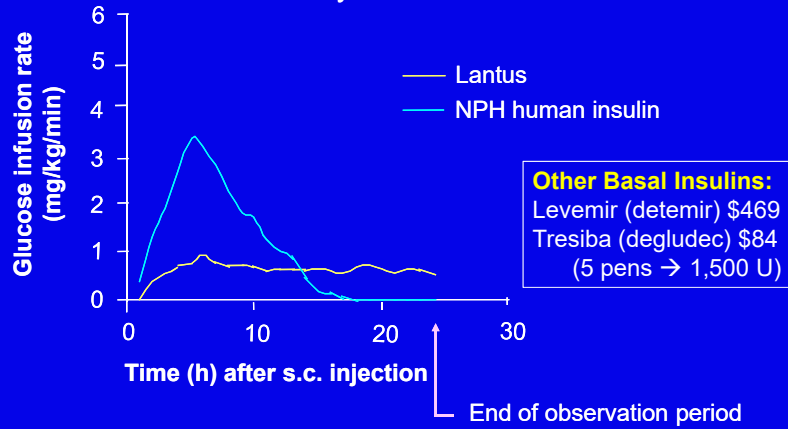
## Mechanism of Action of Lantus<sup>®</sup>



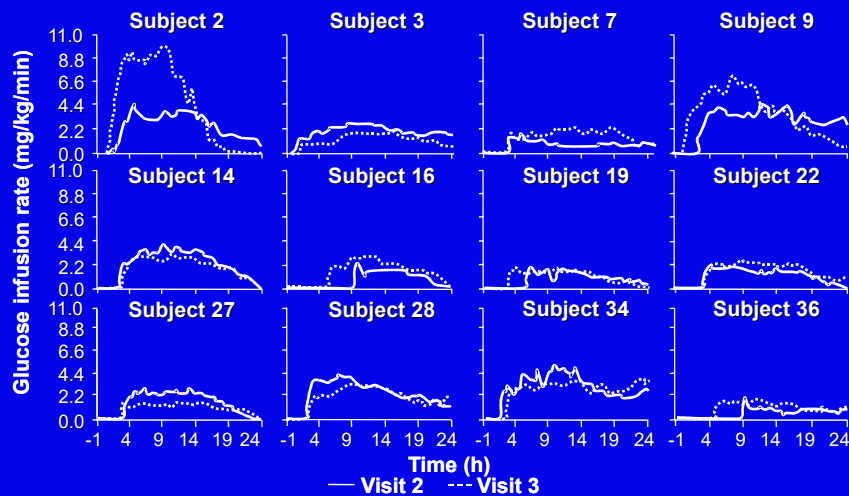
Seipke et al. *Diabetologia*. 1992;35(suppl 1):A4. Hilgenfeld et al. *Diabetologia*. 1992;35(suppl 1):A193.

## Pharmacokinetics of Lantus® Insulin (glargine [rDNA origin]):

Hourly mean values



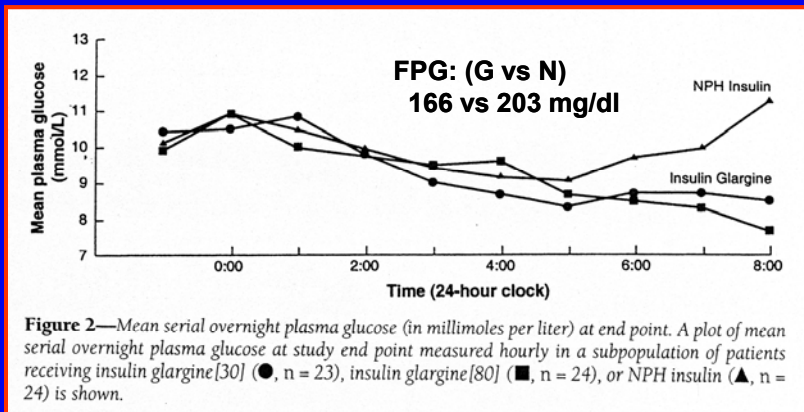
## Intrasubject Variability (GIR) with Lantus® Insulin (glargine)



Scholtz et al. *Diabetologia*. 1999;42(suppl 1):A235.

## Basal Insulin in Type 1 Diabetes

256 Patients, FPG = 202 mg/dl, HgbA1c = 7.9% 4 weeks (NPH bid or HS)

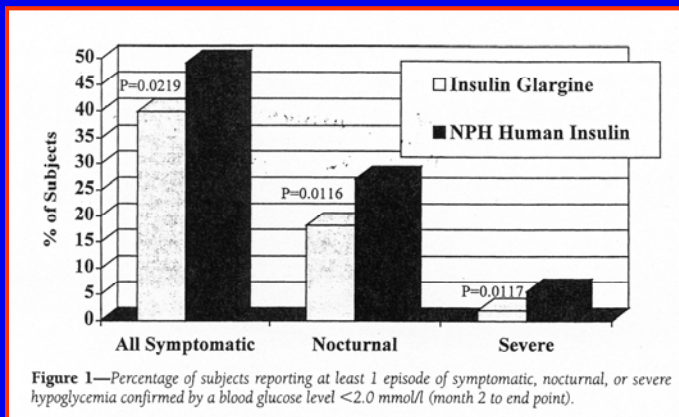


Rosenstock et al., Diabetes Care 23:1137-1142, 2000

## Hypoglycemia in Type 1 Diabetes

534 Patients  
FPG = 202 mg/dl  
HgbA1c = 7.7%  
Goal FPG -->  
80-120 mg/dl  
28 weeks  
(NPH bid or HS)

FPG: (G vs N)  
-30 vs -6 mg/dl  
HgbA1c:  
-0.16 vs -0.21



Ratner et al., Diabetes Care 23:639-643, 2000

## Basal Insulin in Type 2 Diabetes

518 Patients  
 Age ~ 59.4 yrs  
 BMI ~ 30.5  
 White ~ 80%  
 No oral agents  
 FPG = 191, 200 mg/dl  
 HgbA1c ~ 8.6%  
 C-peptide = 0.6 mmol/l  
 NPH bid ~ 80%

Goal FPG < 120 mg/dl  
 28 weeks (NPH bid or HS)

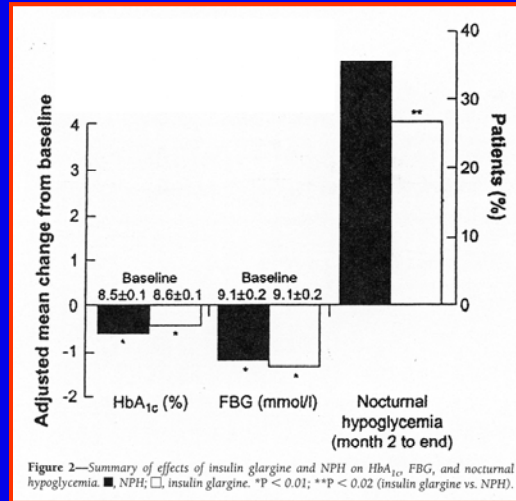


Figure 2—Summary of effects of insulin glargine and NPH on HbA<sub>1c</sub>, FBG, and nocturnal hypoglycemia. ■, NPH; □, insulin glargine. \*P < 0.01; \*\*P < 0.02 (insulin glargine vs. NPH).

Rosenstock et al., Diabetes Care 23:631-636, 2000

## Hypoglycemia in Type 2 Diabetes

426 Patients  
 Age ~ 59 yrs  
 BMI: 28.9  
 SU ± Met, Acar > 1 yr  
 (continued)  
 FPG ~ 190 mg/dl  
 HgbA1c ~ 9.0%  
 C-peptide = 0.95 mmol/l

Bedtime insulin only  
 Goal FPG < 117 mg/dl  
 52 weeks

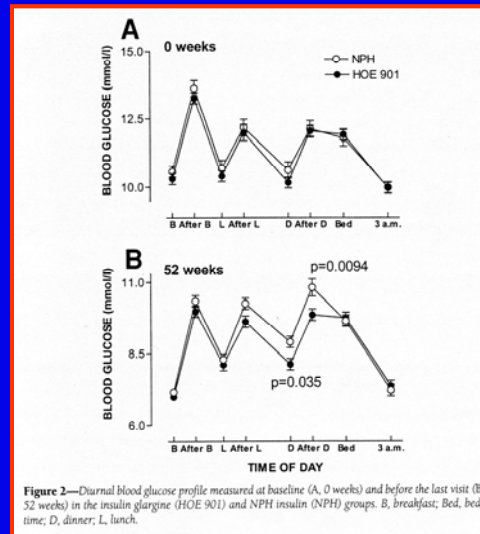


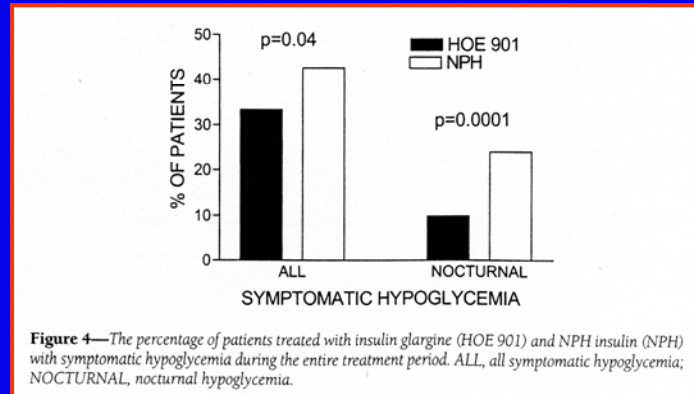
Figure 2—Diurnal blood glucose profile measured at baseline (A, 0 weeks) and before the last visit (B, 52 weeks) in the insulin glargine (HOE 901) and NPH insulin (NPH) groups. B, breakfast; Bed, bedtime; D, dinner; L, lunch.

Yki-Jarvinen et al., Diabetes Care 23:1130-1136, 2000

## Hypoglycemia in Type 2 Diabetes

426 Patients  
 Age ~ 59 yrs  
 BMI = 28.9  
 SU ± Met, Acar  
 (continued)  
 FPG ~ 190 mg/dl  
 HgbA1c ~ 9.0%  
 C-peptide = 0.95

Bedtime insulin  
 Goal FPG < 117  
 52 weeks

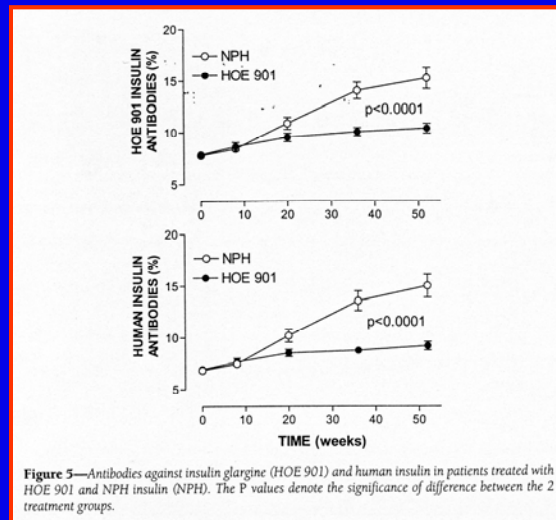


Yki-Jarvinen et al., Diabetes Care 23:1130-1136, 2000

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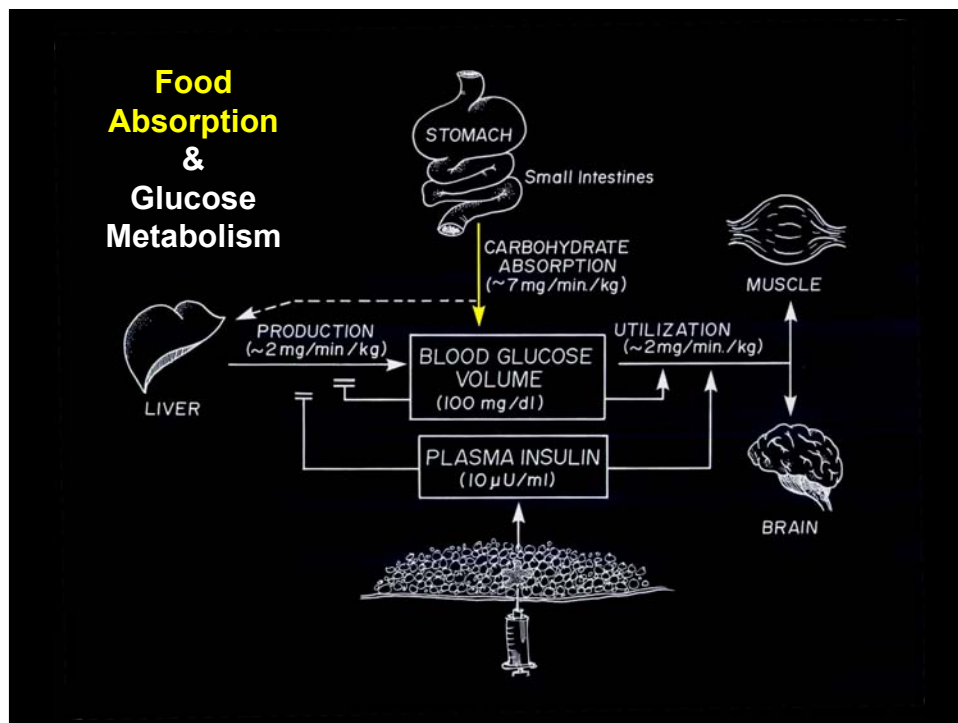


Yki-Jarvinen et al., Diabetes Care 23:1130-1136, 2000

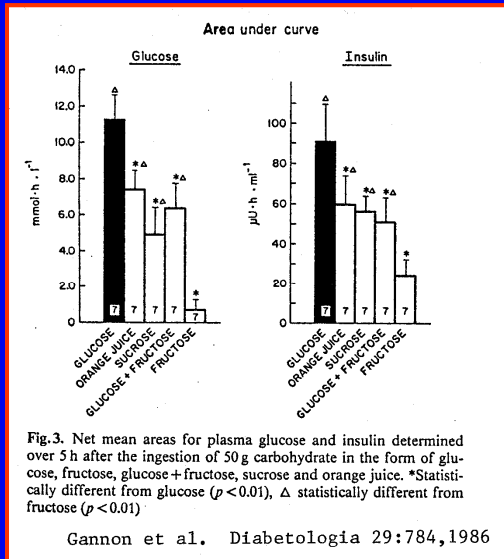


## Adverse Events Associated With Lantus® Insulin (glargine [rDNA origin])

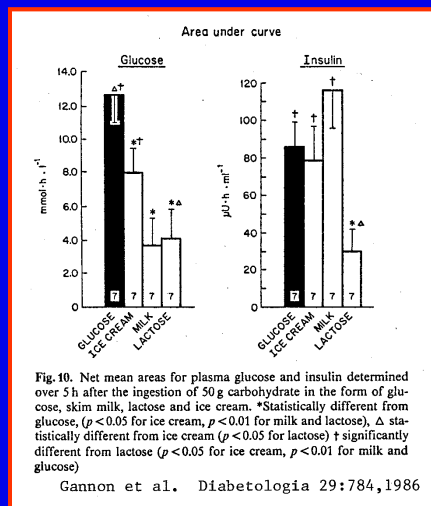
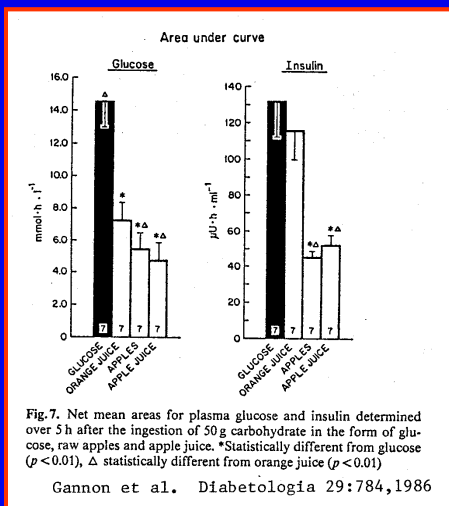
- < Allergic reactions
  - Immediate-type allergic reactions are rare
- < Injection site reactions
  - 1 in 37 Lantus-treated patients reported at least one incident of injection site pain throughout the course of treatment (Lantus 2.7% vs 0.7% NPH)
  - Reports of pain at the injection site were usually mild and did not result in discontinuation of therapy
- < Lipodystrophy
- < Sodium retention and edema
  - May also occur with the use of any human insulin therapy



# Glucose Response to Food



# Glucose Response to Food



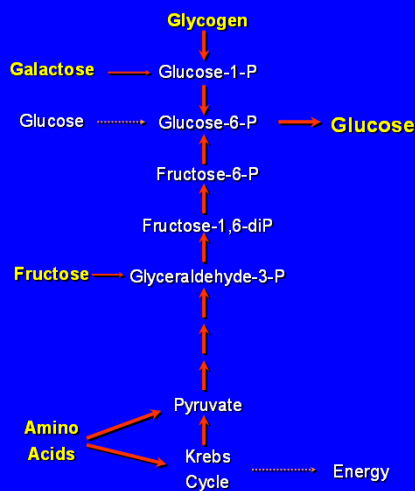
# Glucose Response to Food

Table 1. Glycaemic index: the area under the blood glucose response curve for each food expressed as a percentage of the area after taking the same amount of carbohydrate as glucose. Data from normal individuals [95]

	Glycaemic index (%)		Glycaemic index (%)		Glycaemic index (%)
<i>Grain, cereal products</i>					
Bread (white)	69	<i>Fresh Legumes</i>		<i>Fruit</i>	
Bread (wholemeal)	72	Broad beans*	79	Apples (Golden Delicious)	39
Buckwheat	51	Frozen peas	51	Bananas	62
Millet	71	<i>Root Vegetables</i>			
Pastry	59	Beetroot*	64	Oranges	40
Rice (brown)	66	Carrots*	92	Orange juice	46
Rice (white)	72	Parsnips*	97	Raisins	64
Spaghetti (wholemeal)	42	Potato (instant)	80	<i>Sugars</i>	
Spaghetti (white)	50	Potato (new)	70	Fructose	20
Sponge cake	46	Potato (sweet)	48	Glucose	100
Sweetcorn	59	Swede*	72	Maltose	105
		Yam	51	Sucrose	59
<i>Breakfast cereals</i>					
'All-bran'	51	<i>Dried and Tinned Legumes</i>			
Cornflakes	80	Beans (tinned, baked)	40	<i>Dairy Products</i>	
Muesli	66	Beans (butter)	36	Ice cream	36
Porridge Oats	49	Beans (haricot)	31	Milk (skimmed)	32
'Shredded Wheat'	67	Beans (kidney)	29	Milk (whole)	34
'Weetabix'	75	Beans (soya)	15	Yoghurt	36
<i>Biscuits</i>					
Digestive	59	Beans (tinned soya)	14	<i>Miscellaneous</i>	
Oatmeal	54	Peas (blackeye)	33	Fish fingers	38
'Rich Tea'	55	Peas (chick)	36	Honey	87
'Ryvita'	69	Peas (marrowfat)	47	'Lucozade'	95
Water	63	Lentils	29	'Mars bar'	68
				Peanuts*	13
				Potato crisps	51
				Sausages	28
				Tomato soup	38

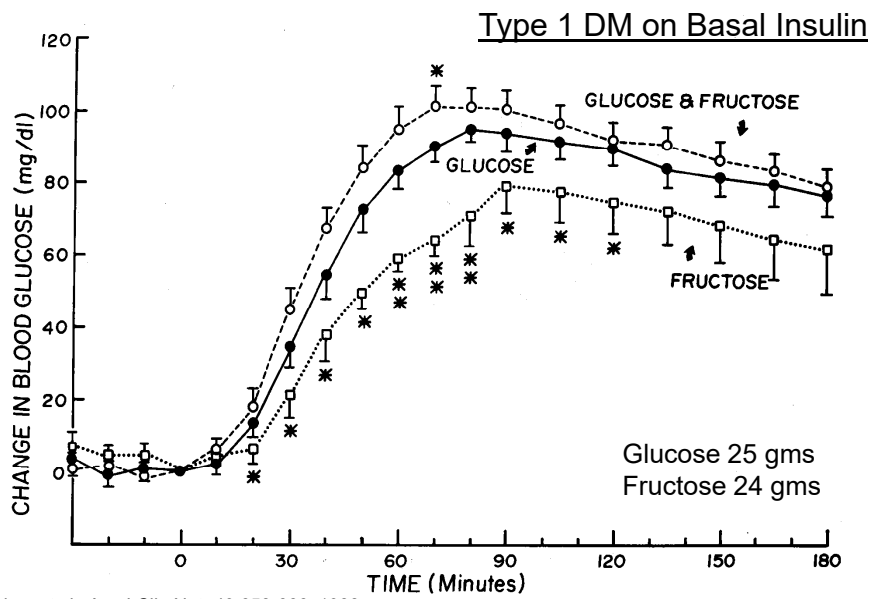
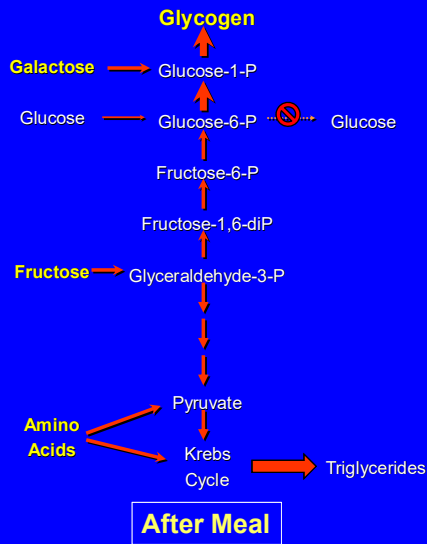
\* Only 25 g carbohydrate portion given.

## Carbohydrate Metabolism Liver: Glucose Production



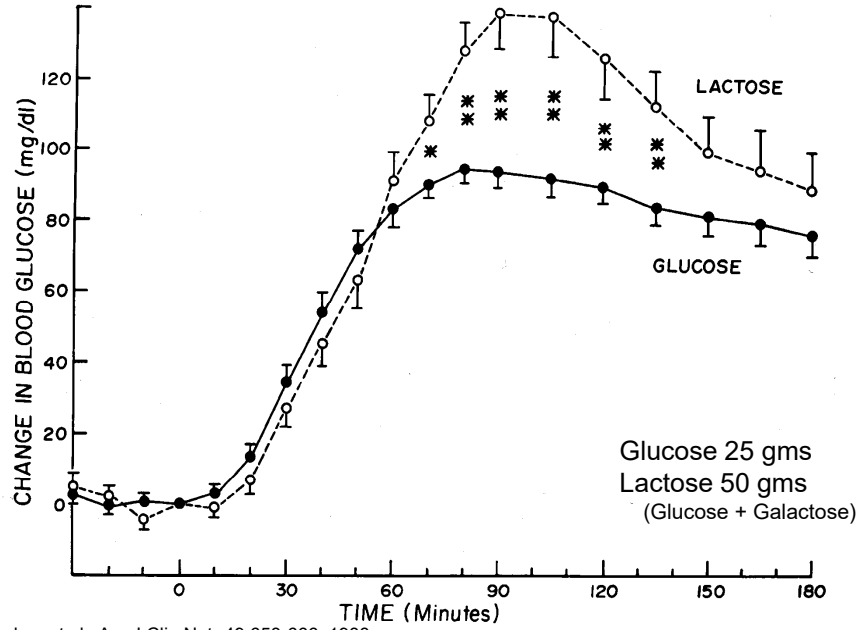
**Fasting**

## Carbohydrate Metabolism Postprandial Liver Storage

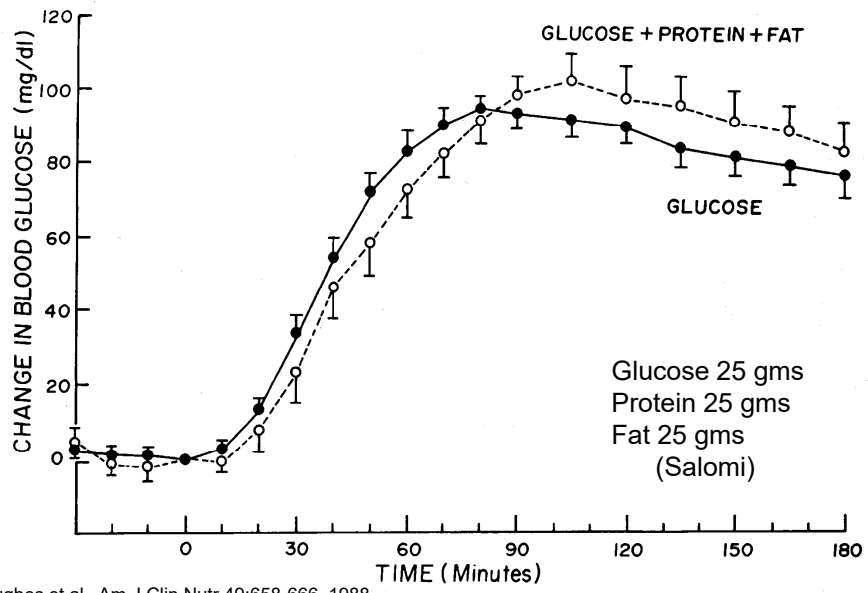


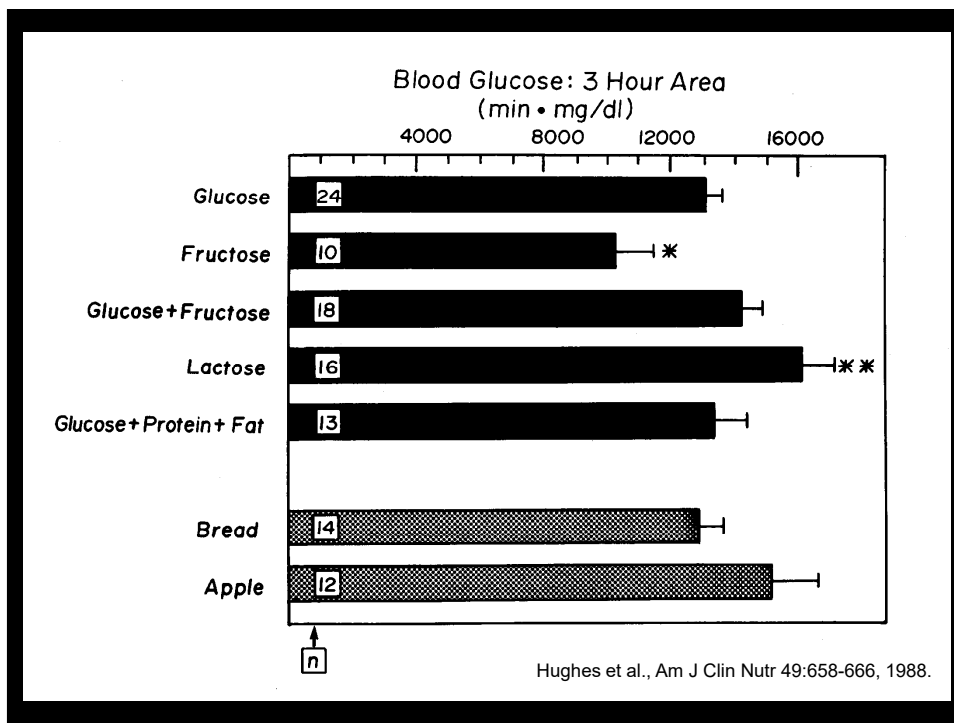
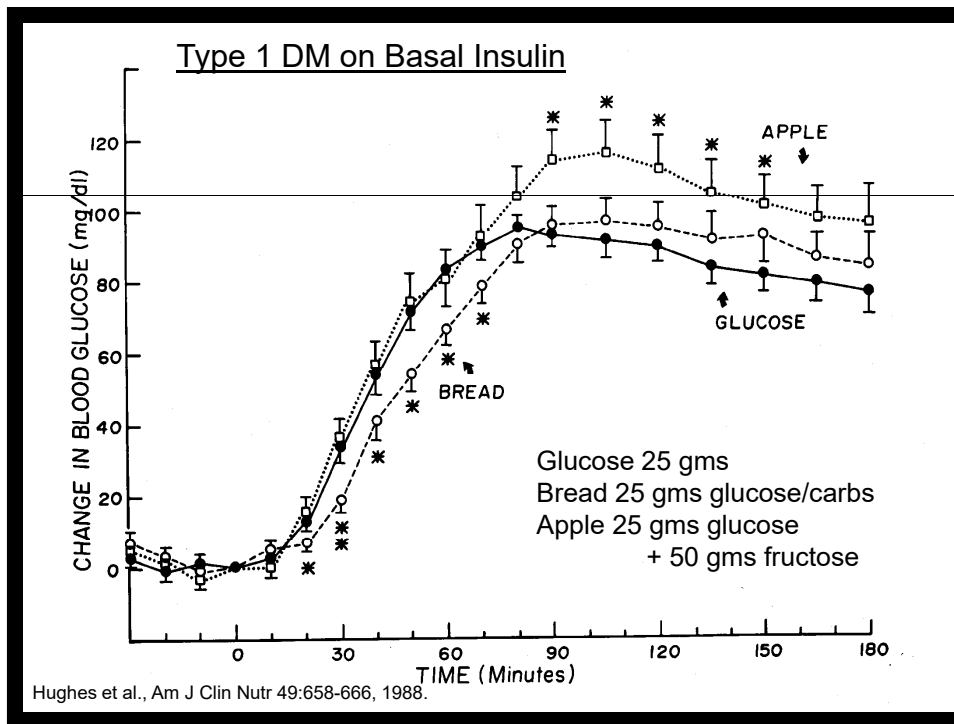
Hughes et al., Am J Clin Nutr 49:658-666, 1988.

### Type 1 DM on Basal Insulin



### Type 1 DM on Basal Insulin





## Glucose Response to Food

---

- Conclusions:
  - Only the **glucose** component of food impacts the blood glucose level
  - **Fructose** and **galactose** are only converted to glucose when given alone
  - **Fat** and **protein** probably slow the absorption of glucose
  - **Protein alone** does increase blood glucose a small amount

## Glucose Response to Food

---

- Food Calculations:
  - Starches are 100% glucose
  - “Sugars” are ~50% glucose
    - Sucrose, Lactose, Fruit (depends)
  - Fiber is non-absorbed carbohydrate
  - Therefore:
    - **Glucose = total carb – half sugars – fiber**
    - Add up the number of servings
    - Initially take one unit of short-acting insulin per 10 grams of glucose and then adjust depending on blood glucose response

## Glucose Response to Food

---

<b>Practice:</b>					
Time 7:40 AM					
Blood Glucose: 186 mg/dl					
<b>Breakfast:</b>					
<b>Food:</b>	<b>per serving:</b>				
	<u>Carbs</u>	<u>Sugars</u>	<u>Fiber</u>	<u>Glucose</u>	<u>Servings</u>
One cup of Del Monte Lite fruit cocktail	_____	_____	_____	_____	_____
8 oz skim milk	_____	_____	_____	_____	_____
½ cup Quaker Oats	_____	_____	_____	_____	_____
3 strips of bacon	_____	_____	_____	_____	_____
2 egg beaters	_____	_____	_____	_____	_____
<b>Total Glucose for meal:</b> _____					
Insulin for Food:	_____	Units			
Insulin supplement:	_____	Units			

## Glucose Response to Food

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- Information Sources:
  - Food Labels
  - <http://www.fatsecret.com/calories-nutrition/usda/white-bread>
  - USDA web site: [www.nal.usda.gov/fnic/](http://www.nal.usda.gov/fnic/)
  - Restaurants must provide this information



## Glucose Response to Food

### Understanding the nutrition label

The "Nutrition Facts" label found on most food products gives you key information to help you follow your diet plan. The following is based on the American Diabetes Association (ADA) recommendations.

Make sure you look at the serving size or you may be getting more fat, calories, and cholesterol than you think!

Cholesterol should be limited to 300 mg or less daily.

Carbohydrates can affect blood sugar levels, so make sure you monitor your levels and adjust your carbohydrate intake accordingly.

Carbohydrates that are high in fiber are often better choices than low-fiber carbohydrates.

Make sure you get a variety of vitamins and minerals for a balanced diet.

#### Nutrition Facts

Serving Size 1 cup (30g)  
Servings Per Container About 14

Amount Per Serving	Daily Value*	% Daily Value**
<b>Calories</b> 110	150	
Calories from Fat 15	20	
<b>Total Fat</b> 2g	4%	2%
Saturated Fat 0g	0%	0%
Polyunsaturated Fat 0.5g		
Monounsaturated Fat 0.5g		
<b>Cholesterol</b> 0mg	0%	0%
<b>Sodium</b> 280mg	10%	12%
<b>Total Carbohydrate</b> 22g	4%	7%
Dietary Fiber 3g	9%	9%
Soluble Fiber 1g		
Sugars 1g		
Other Carbohydrate 18g		
<b>Protein</b> 5g		
Vitamin A	1%	5%
Vitamin C	1%	50%
Calcium	4%	2%
Iron	35%	35%
Vitamin D	1%	15%
Thiamin	15%	20%

Information on the front of the box such as "lite," "low-fat," "cholesterol-free," "good source of fiber," and "sugar-free" are regulated by the government and can be useful in helping you pick out healthy foods.

Ask your doctor or nutritionist about how many calories you should be eating per day.

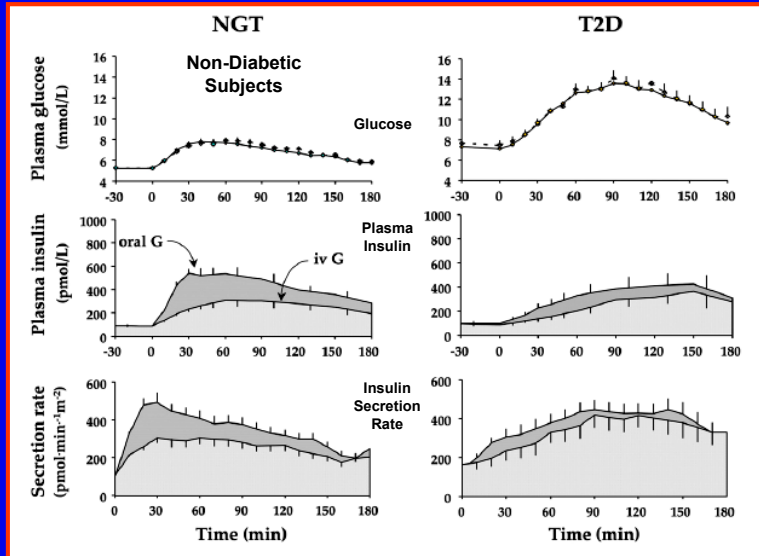
Fat should be limited to 30% or less of daily calories. **Saturated fat** should be limited to less than 10% of daily calories.

Protein should be limited to 10% to 20% of daily calories. If you have signs of diabetes-related kidney disease, your doctor may recommend a lower-protein diet.

## Insulin Bolus to Cover Ingested Glucose & Corrections

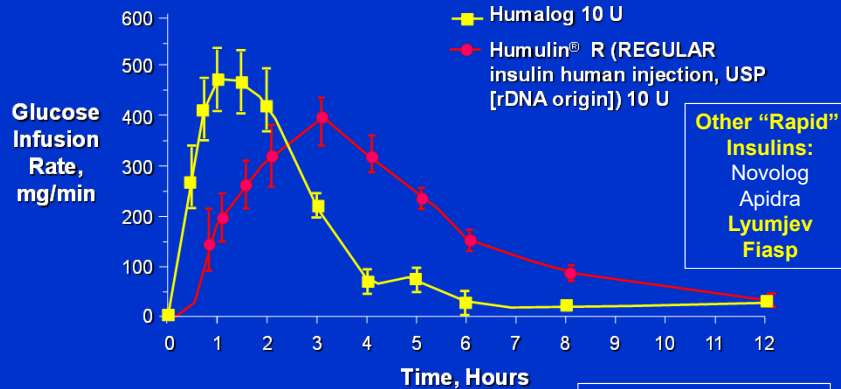
- Fast onset of action (<15 minutes)
- Short duration to match food (<3 hours)
- Easy to make small increments in dosage
- Accurate delivery (reproducible)
- Painless
- Convenient storage and delivery
- Inexpensive

## Insulin Secretion



Ferrannini & Mari: Metabolism 63:1217-1227, 2014

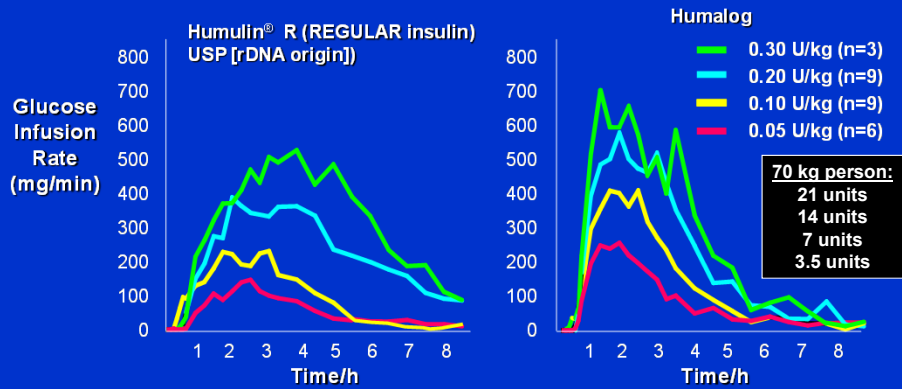
## Biological Action of Humalog vs. Regular Insulin: Glucose Clamp Study in Healthy Subjects



Data from Howey DC, et al. *Diabetes*. 1994;43:396-402.  
Humulin is a registered trademark of Eli Lilly and Company.

Walgreens: Vial \$21  
5 Pens \$76

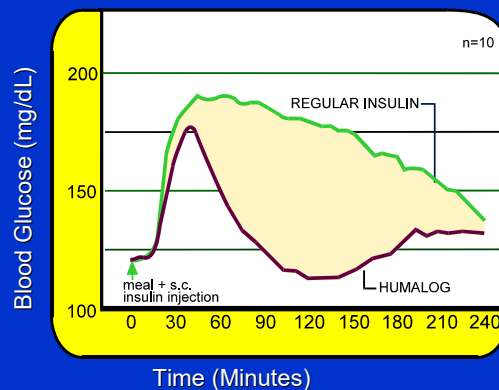
## Effect of Dose (sc) of Humulin R and Humalog on Time-Action Profile in Healthy Volunteers



sc, subcutaneous.  
Data from Woodworth JR, et al. *Diabetes*. 1993;42(suppl 1):54A.

18

## Glucose Response to a High Caloric Meal in Patients with Type 1 Diabetes

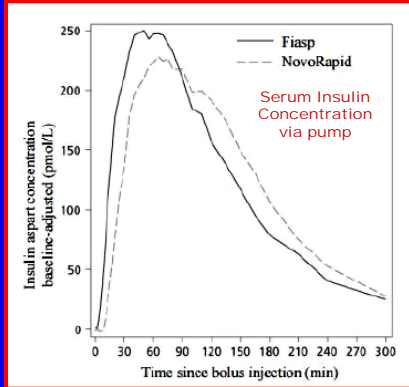
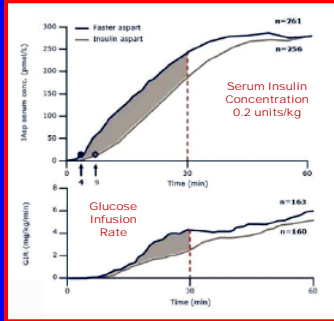


Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

Humalog prescribing information, © 2000.

19

# Fiasp - "fast Novolog"



Onset of action: 5 minutes earlier

Time to maximum glucose infusion rate: 11 minutes earlier

Maximum glucose-lowering effect : 1 & 3 hours

Glucose-lowering effect during the first 30 minutes (AUC-GIR, 0-30 min) 51 mg/kg vs 29 mg/kg (ratio: 1.74 [1.47;2.10] 95% CI)

Total glucose-lowering effect & maximum (GIRmax) glucose-lowering effect were comparable between Fiasp & NovoRapid

Fiasp has not been shown to lower A1c better in clinical trials → do not use if more expensive!

Company Data

# Fiasp - "fast Novolog"

Parameter for Insulin Effect	70 Kg Person Units:		
	7	14	28
	FIASP 0.1 units/kg	FIASP 0.2 units/kg	FIASP 0.4 units/kg
Time to first measurable effect	-20 minutes	-17 minutes	-16 minutes
Time to peak effect	-91 minutes	-122 minutes	-133 minutes
Time for effect to return to baseline	-5 hours	-6 hours	-7 hours

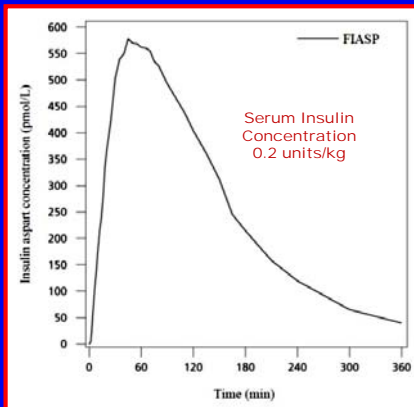
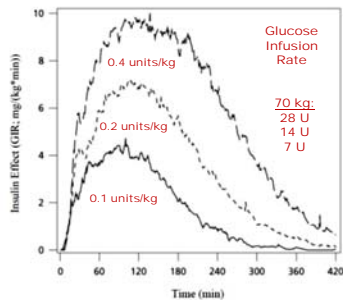


Figure 2. Mean insulin effect (i.e., mean pharmacodynamic effect) over time after SQ injection of 0.1, 0.2 and 0.4 unit/kg of FIASP in patients (N=46) with Type 1 diabetes

Pharmacokinetic results from a euglycemic clamp study in adult patients with type 1 diabetes (N=51) showed that insulin aspart appeared in the circulation ~2.5 minutes after administration of FIASP (Figure3).

Time to maximum Insulin concentrations was achieved ~63 minutes after administration of FIASP

Package Insert - 2022

# Management of Type 1 Diabetes

---

- Use a stable **basal** insulin to control the fasting glucose level
- Adjust **boluses** to cover different meal compositions (“glucose counting”)
- Use “**supplemental**” insulin at breakfast and supper to correct miscalculations or uncontrolled factors (typically one unit for every 25 mg/dl above 100)
- Reduce both basal and boluses for **exercise**

# Typical Supplemental Insulin Regimen

---

<u>Blood Glucose:</u>	<u>Adjustment:</u>
<50	Eat a carbohydrate snack immediately (15-30 grams). Take the full meal insulin dose <u>after</u> eating the whole meal.
50-70	Subtract 2 units from the meal insulin and take after eating the meal. If no meal is planned, eat a small snack (15 grams carbohydrate).
71-125	No Adjustment is needed.
126-150	Add 1 U short-acting insulin
151-175	Add 2 U short-acting insulin
176-200	Add 3 U short-acting insulin
201-250	Add 4 U short-acting insulin
251-300	Add 6 U short-acting insulin
301-350	Add 8 U short-acting insulin
351-400	Add 10 U short-acting insulin
>400	Add 12 U short-acting insulin, check urine ketones

Use only if it has been 5 hours since last bolus

## Diabetes Mellitus in the US: Overview

### Prevalence

Approximately 15 million Americans

- 1 in every 17 people
- half do not know they have it

### Incidence

625,000 new cases diagnosed yearly

### Impact

Leading cause of

- blindness in adults
- renal failure
- nontraumatic amputations

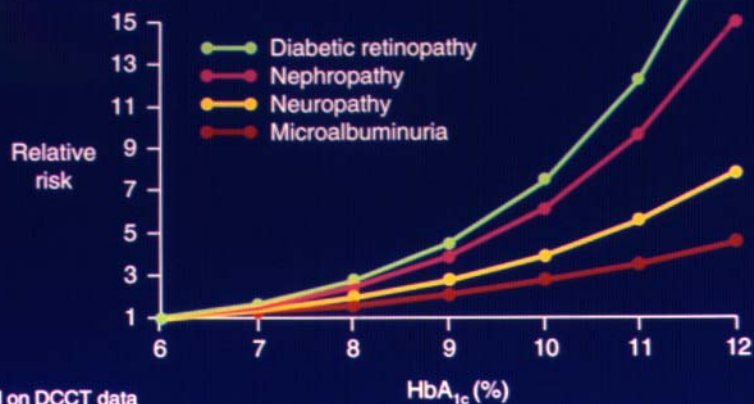
15% of total healthcare costs (\$105 billion annually)

**More than 90% of cases are type 2 diabetes**

Harris M. In: *Diabetes in America*. 2nd ed. 1995;chap 1.  
Rubin RJ et al. *J Clin Endocrinol Metab*. 1994;78:809A-809F.

## DCCT

Relative risk of progression of diabetic complications  
by mean HbA<sub>1c</sub>\*



\*Based on DCCT data

Skyler JS. *Endocrinol Metab Clin North Am*. 1996;25:243-254.

