



Understanding the use of insulin in the treatment of diabetes mellitus

Presenter

Title

Affiliation

Date

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Statement of disclosure

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Learning objectives

To identify the indications for insulin use

To understand the criteria required in choosing an insulin for patients with diabetes

To review the evidence that supports the use of human insulin and insulin analogues in patients with type 1 diabetes, type 2 diabetes, and gestational diabetes

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Where did the evidence come from?

Canadian Agency for Drugs and Technologies in Health (CADTH)

CADTH is an independent, not-for-profit agency funded by Canadian federal, provincial, and territorial governments to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision makers.

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Diabetes mellitus

In 2005-2006, ~ 1.9 million Canadians were diagnosed with diabetes

- one in 17 people had been diagnosed with diabetes

Approximately 90% have type 2 diabetes

By 2011, the number of Canadians with diagnosed diabetes is expected to be ~ 2.6 million

PHAC. *The face of diabetes in Canada*; 2008.
CDCP. *National diabetes fact sheet*; 1997.
PHAC. *Report from the national diabetes surveillance system*; 2008.

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Diabetes mellitus (cont'd)

More than \$800 million in direct health care costs for Canada in 2000

- Estimated by 2010, it will cost the health care system \$15.6 billion per year

In 2005-2006, compared to adults without diabetes, adults with diagnosed diabetes were hospitalized:

- 23 times more often for lower limb amputations;
- seven times more often with chronic kidney disease;
- three times more often with all cardiovascular diseases.

PHAC. *Report from the national diabetes surveillance system*; 2008.
McCann J, et al. *Provincial Reimbursement Advisor* 2008;11(3):52-65.
PHAC. *The cost of diabetes*; 2008.

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Diabetes classification

Type 1 diabetes

- Encompasses diabetes that is primarily a result of pancreatic beta cell destruction and is prone to ketoacidosis
- This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown

Type 2 diabetes

- May range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance

Gestational diabetes

- Glucose intolerance, first onset during pregnancy

Other

- Genetic defects, infections, drug or chemical-induced

CDA. *Can J Diabetes* 2008;32(suppl 1):i-S201

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Indications for the use of insulin

Type 1 diabetes

Pregnant or lactating female

Gestational diabetes not controlled with lifestyle changes

Type 2 diabetes not controlled with meal choices, activity and/or use of oral agents

Indications for the use of insulin (cont'd)

Type 2 diabetes with severe infection, undergoing major surgery, or requires corticosteroid therapy

Ketoacidosis or hyperosmolar nonketotic syndrome

Rapid glucose reduction/control desired

A1C \geq 9.0% +/- symptomatic hyperglycemia with metabolic decompensation

Considerations for choosing the most appropriate insulin

Efficacy

- A1C, Fasting plasma glucose, 2-h postprandial glucose
- Prevention of chronic complications
 - Coronary artery disease, peripheral artery disease, cerebrovascular disease
 - Retinopathy, nephropathy and neuropathy
 - Gastroparesis, infections and skin changes

Adverse Effects

- Overall hypoglycemia
- Nocturnal hypoglycemia
- Severe hypoglycemia
- Weight gain

Quality of Life

Cost

- Individual patient
- Society

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Recommended targets for glycemic control

	A1C (%)	FPG (mmol/L)	2hPPG (mmol/L)
T1DM - age > 12 yrs T2DM	7.0	4.0-7.0	5.0-10.0 (5.0-8.0 if A1C targets not being met)
T1DM, age < 6 yrs	< 8.5	6.0-12.0	
T1DM, age 6-12 yrs	< 8.0	4.0-10.0	

A1C=Glycosylated hemoglobin; FPG=Fasting Plasma Glucose; 2hPPG=2-h postprandial plasma glucose; T1DM=Type 1 diabetes mellitus; T2DM=Type 2 diabetes mellitus

Relationship between A1C and Mean plasma glucose (MPG)

$$\text{MPG (mmol/L)} = [1.98 * \text{A1C (\%)}] - 4.29$$

Example: A1C = 7%, MPG (mmol/L) = 1.98 * 7 - 4.29 = 9.57

CDA. *Can J Diabetes* 2008;32(suppl 1):i-S201.
Rohlfing CL, et al. *Diabetes Care* 2002;25(2):275-8.

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Hypoglycemia

Fear of hypoglycemia

Hypoglycemia has been defined as:

- Development of autonomic or neuroglycopenic symptoms
- Low plasma glucose level (<4.0 mmol/L for patients treated with insulin or an insulin secretagogue)
- Symptoms responding to the administration of carbohydrate

Hypoglycemia (cont'd)

Hypoglycemia can further be defined by the severity of the event

Mild

- Autonomic symptoms (trembling, palpitations, sweating, anxiety, hunger, nausea, tingling) are present; able to self-treat

Moderate

- Autonomic and neuroglycopenic symptoms (difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, dizziness); able to self-treat

Severe

- Unresponsiveness, unconsciousness, seizures or coma; unable to self-treat, requires assistance; plasma glucose < 2.8mmol/L

Hypoglycemia (cont'd)

Trial definitions: Overall, Severe, or Nocturnal

Overall: most often defined as any signs or symptoms of hypoglycemia and/ or blood glucose <4mmol/L

Severe: usually defined as an event with characteristic hypoglycemic symptoms requiring the assistance of another person

Nocturnal hypoglycemia

- **Hypoglycemia that occur at night (2400 to 0600)**
- **Approximately 50% symptomatic**
 - Some symptoms include: sweating, headache, hunger, nightmares
- **Autonomic and neuroglycopenic warning signals of hypoglycemia are inhibited**

Nocturnal hypoglycemia (cont'd)

- **Effects of nocturnal hypoglycemia**
 - Memory impairment
 - Deterioration of mood
 - Increase of total sleep time
 - Prolong QT interval
- **Poorly defined in most trials**

CDA. *Building competency in diabetes education: the essentials*; 2004.
Banarer S, et al. *Diabetes* 2003;52(5):1195-203.
Jones TW, et al. *N Engl J Med* 1998;338(23):1657-62.
Cryer PE. *N Engl J Med* 2004;350(22):2272-9.
Jauch-Chara K, et al. *Diabetes Care* 2007;30(8):2040-5.
Robinson RT, et al. *Diabetologia* 2004;47(2):312-5.
Matyka KA, et al. *Arch Dis Child* 1999;81(2):138-42.
Pillar G, et al. *J Pediatr* 2003;142(2):163-8.
CADTH. *Optimal Therapy Report* 2008;2(1).

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Types of Insulin

Prandial (Bolus) Insulins (*trade name*)

Human insulin
Short-acting insulin
Insulin regular (<i>Humulin®-R, Novolin® ge Toronto</i>)
Rapid-acting insulin analogues
Insulin aspart (<i>NovoRapid®</i>)
Insulin lispro (<i>Humalog®</i>)

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Types of Insulin (cont'd)

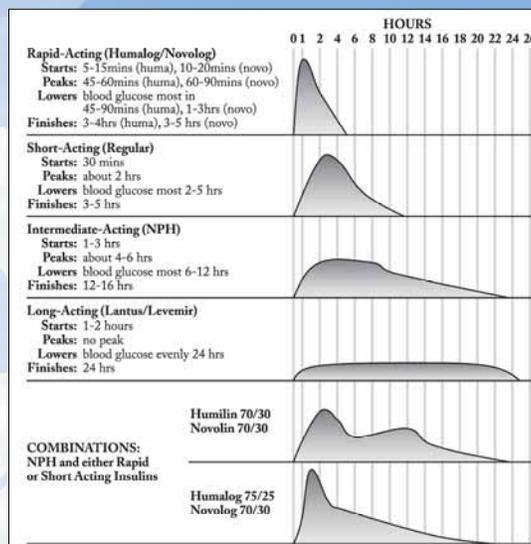
Basal Insulins (*trade name*)

Human Insulin
Intermediate-acting insulin
Insulin NPH (<i>Humulin®-N, Novolin® ge NPH</i>)
Long-acting insulin analogues
Insulin detemir (<i>Levemir®</i>)
Insulin glargine (<i>Lantus®</i>)

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Types of insulin (cont'd)

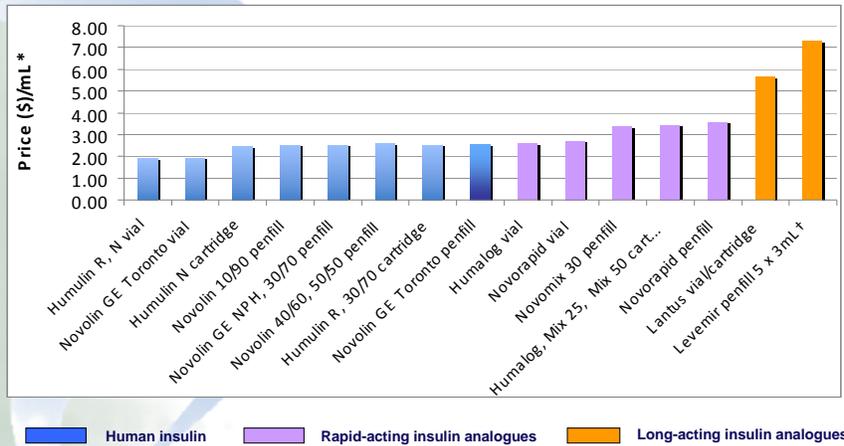


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American Diabetes Association. The term "Novolog®" is the international name for what is called "NovoRapid ®" in Canada. Used with permission. Developed by University of Michigan Health System from original material - American Diabetes Association, October 2008.



Insulin price comparison



*Ontario Drug Benefits Formulary/Comparative Drug Index [database on the Internet]; 2008 Dec 3.

† D. Groleau, NovoNordisk Canada, Mississauga, ON: personal communication, 2008 Dec 9.

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Considering the evidence

COMPUS Expert Review Committee

Studies first analyzed for evidence of clinical benefit and harm

- Safety, effectiveness and clinically-important differences (if any)

Results then analyzed on the basis of cost for clinical benefit

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Considering the evidence (cont'd)

Recommendations formulated

- based on efficacy, safety and pharmacoeconomic data
- “GRADE” process ranks the quality of evidence and the strength of each recommendation

Feedback sought from advocacy groups and industry

Definitions

Confidence interval

- The probable range in which a population parameter lies based on a random sample of the population

Relative risk

- The ratio of the absolute risk of an event among the exposed group to the absolute risk of an event among the unexposed group in an epidemiological study

Rate ratio

- The ratio of the person-time incidence rate in the exposed group to the person-time incidence rate in the unexposed group in an epidemiological study

Definitions (cont'd)

Weighted mean difference

- A method of meta-analysis used to combine measures on continuous scales, where the mean, standard deviation and sample size in each group are known. The weight given to each study is determined by the precision of its estimate of effect and is equal to the inverse of variance. This method assumes that all the trials have measured the outcome on the same scale

No significant difference

- No statistically significant difference between the two measured outcomes

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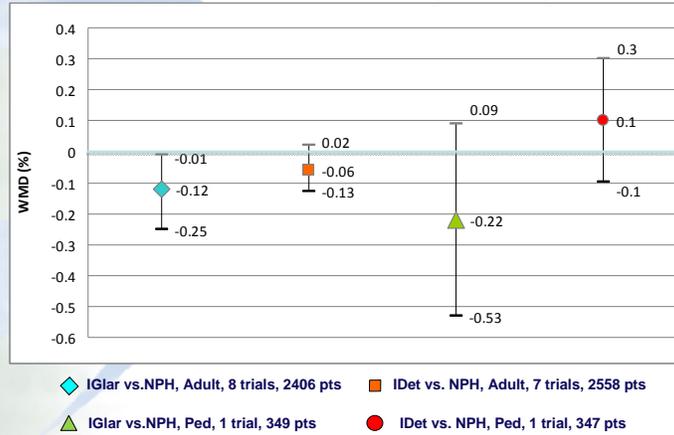
Type 1 Diabetes Mellitus

Basal Insulin

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Long-acting insulin analogues vs. NPH in type 1 diabetes

Pooled A1C values in comparisons of long-acting insulin analogues vs. NPH in adult and pediatric patients



A1C=Glycosylated hemoglobin; IDet=Insulin detemir; IGlar=Insulin glargine; NPH=Neural protamine Hagedorn; WMD=weighted mean difference

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Bugden S, et al. *Academic detailing upskilling document insulin analogues*; 2009.



Type 1 diabetes – adult Basal insulins

Insulin glargine vs. NPH (common pre-meal bolus insulin in both arms)

- A1C favours insulin glargine:
 - WMD (95%CI) = -0.12% (-0.25, -0.01)
- Mean body weight significantly lower for insulin glargine:
 - WMD (95%CI) = -0.40 kg (-0.76, -0.03)
- Severe, nocturnal and overall hypoglycemia = no significant difference

CADTH. *Optimal Therapy Report 2008;2(7)*.
 CADTH. *Optimal Therapy Report 2008;2(1)*.

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Type 1 diabetes – adult Basal insulins (cont'd)

Insulin detemir vs. NPH (common pre-meal bolus insulin in both arms)

- A1C – No significant difference
- Mean body weight significantly lower for insulin detemir:
 - WMD (95%CI) = -0.73 kg (-1.42, -0.03)
- Favours insulin detemir:
 - Nocturnal hypoglycemia:
 - Rate ratio (95% CI) = 0.66 (0.60, 0.73)
 - Relative risk (95% CI) = 0.92 (0.85, 0.98)
 - Overall hypoglycemia
 - Rate ratio (95% CI) = 0.84 (0.74, 0.97)
 - Severe hypoglycemia
 - Relative risk (95% CI) = 0.74 (0.58, 0.96)

Type 1 diabetes – adult Basal insulins (cont'd)

Insulin detemir vs. insulin glargine

(common pre-meal bolus insulin in both arms)

- A1C, overall hypoglycemia (rate ratio and relative risk), nocturnal hypoglycemia (relative risk) and mean body weight – no significant difference
- Favours insulin detemir:
 - Severe hypoglycemia
 - Relative risk (95% CI) = 0.25 (0.07, 0.86)
 - Rate ratio (95% CI) = 0.41 (0.2, 0.86)
 - Nocturnal hypoglycemia
 - Ratio ratio (95% CI) = 0.66 (0.58, 0.76)

Type 1 diabetes – children

Basal insulins

Insulin glargine vs. NPH (common pre-meal bolus insulin in both arms)

- No significant difference: A1C, severe, nocturnal, or overall hypoglycemia

Insulin detemir vs. NPH (common pre-meal bolus insulin in both arms)

- No significant difference: A1C, severe hypoglycemia
- Favours insulin detemir in nocturnal hypoglycemia
 - Relative risk (95% CI) = 0.85 (0.77, 0.94)
 - Rate ratio (95% CI) = 0.77 (0.70, 0.84)
- Favours insulin detemir in rate ratio for overall hypoglycemia
 - Rate ratio (95% CI) = 0.89 (0.86, 0.93)
 - **Relative risk showed no significant difference**

Recommendation:

Basal insulin in type 1 diabetes

When a basal insulin is required, insulin NPH is recommended[†] over long-acting insulin analogues, such as glargine or detemir, in most patients with type 1 diabetes.

If a long-acting insulin analogue is used, there is no preference between the available agents.

[†]For most children with type 1 diabetes, it is suggested that insulin NPH be used in preference to long-acting insulin analogues.

Type 1 Diabetes Mellitus

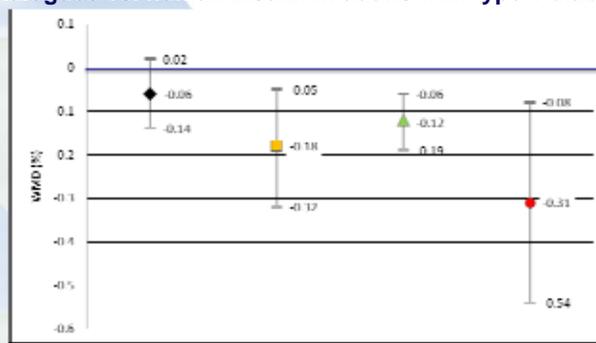
Bolus Insulin

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Rapid-acting insulin analogues vs. Human insulin in type 1 diabetes

Pooled A1C values in comparisons of rapid-acting insulin analogues vs. human insulin in adults with type 1 diabetes



- ◆ ILis vs. HI (MDI), 16 trials, 5426 pts
- ILis vs. HI (CSII), 6 trials, 595 pts
- ▲ IAsp vs. HI (MDI), 5 trials, 2888 pts
- IAsp vs. HI (CSII), 2 trials, 147 pts

A1C=Glycosylated hemoglobin; CSII=continuous subcutaneous insulin infusion; HI=Human insulin; IAsp=Insulin aspart; ILis=Insulin lispro; MDI=multiple daily injection; WMD=weighted mean difference

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Type 1 diabetes – adult – Bolus insulins Insulin lispro vs. human insulin

Outcome	Effect estimate (95% CI) CSII	Effect estimate (95% CI) MDI
A1C (%)	WMD -0.18 (-0.32, -0.05)	No significant difference
Mean 2-hour postprandial plasma glucose (mmol/L)	WMD -2.89 (-4.48, -1.3)	WMD -0.99 (-1.54, -0.45)
Severe hypoglycemia	Relative Risk: no significant difference	Relative Risk 0.78 (0.65, 0.94)
Nocturnal hypoglycemia	Rate Ratio 0.67 (0.51, 0.88)	Rate Ratio 0.58 (0.35, 0.98)
Overall hypoglycemia	Rate Ratio: no significant difference	Rate Ratio: no significant difference
Weight gain	No significant difference	No significant difference

A1C=Glycosylated hemoglobin; CI=Confidence interval; CSII=Continuous subcutaneous insulin infusion; MDI=Multiple daily injection; WMD=Weighted mean difference

Type 1 diabetes – adult – Bolus insulins (cont'd) Insulin aspart vs. human insulin

Outcome	Effect estimate (95% CI) CSII	Effect estimate (95% CI) MDI
A1C (%)	WMD -0.31 (-0.54, -0.08)	WMD -0.12 (-0.19, -0.06)
Severe hypoglycemia	Relative Risk: no significant difference	Relative Risk: no significant difference
Nocturnal hypoglycemia	Rate Ratio 0.55 (0.43, 0.70)	No data
Overall hypoglycemia	Rate Ratio 0.58 (0.40, 0.85)	Rate Ratio: No significant difference
BMI	No data	No significant difference

A1C=Glycosylated hemoglobin; BMI=Body mass index; CI=Confidence interval; CSII=Continuous subcutaneous insulin infusion; MDI=Multiple daily injection; WMD=Weighted mean difference

Type 1 diabetes – adult – Bolus insulins (cont'd) Insulin lispro vs. insulin aspart

Outcome	*Effect estimate (95% CI) CSII
A1C (%)	No significant difference
Nocturnal hypoglycemia	Rate ratio: no significant difference
Overall hypoglycemia	Rate ratio 1.49 (1.37, 1.63)

A1C=Glycosylated hemoglobin; CI=Confidence interval; CSII=Continuous subcutaneous insulin infusion

*Based on information from 1 RCT (total sample size = 87)

Type 1 diabetes – children Bolus insulins

Insulin lispro vs. human insulin:

- No significant difference = A1C, severe hypoglycemia
- Families of pre-adolescent patients reported an increased willingness to continue with insulin lispro
- In adolescents using multiple daily injections, rate ratios for nocturnal and overall hypoglycemia favour insulin lispro
 - Nocturnal hypoglycemia
 - Rate ratio = 0.61 (95% CI: 0.57,0.64)
 - Overall hypoglycemia
 - Rate ratio = 0.90 (95% CI: 0.88, 0.93)

Type 1 diabetes – children

Bolus insulins (cont'd)

Insulin aspart vs. human insulin: in preadolescents using multiple daily injections:

- No significant difference in A1C, overall hypoglycemia, patient satisfaction with diabetes treatment

Insulin lispro vs. insulin aspart: in children with type 1 diabetes using continuous subcutaneous insulin infusion:

- No significant difference in A1C and hypoglycemia

Recommendations:

Bolus insulins in type 1 diabetes

When a bolus insulin is required, either regular human insulin or rapid-acting insulin analogues (aspart or lispro) are recommended[§] in most patients with type 1 diabetes, with the exception of adolescents.

If a rapid-acting insulin analogue is used, there is no preference between the available agents.

In adolescents with type 1 diabetes, a rapid-acting insulin analogue (i.e., lispro or aspart) is suggested over regular human insulin.

[§]For most preadolescents it is suggested that either regular human insulin or the rapid-acting insulin analogues can be used.

Type 2 Diabetes Mellitus

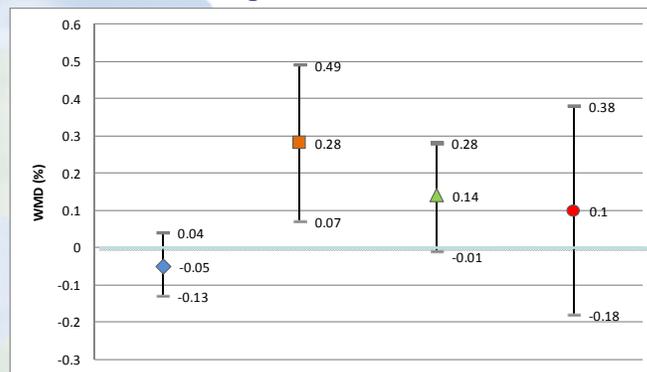
Basal Insulin

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Long-acting insulin analogues vs. NPH in type 2 diabetes

Pooled differences in A1C in comparisons of long-acting insulin analogues vs. NPH in adults



- ◆ IGlar vs. NPH (w/OAD), 9 trials, 3397 pts
- IGlar vs. NPH (w/o OADs), 1 trial, 518 pts
- ▲ IDet vs. NPH (w/OAD), 2 trials, 796 pts
- IDet vs. NPH (w/IAsp), 1 trial, 505 pts

A1C=Glycosylated hemoglobin; IAsp=Insulin aspart; IDet=Insulin detemir; IGlar=Insulin glargine; NPH=Neural protamine Hagedorn; OAD=oral antidiabetes agent; WMD=weighted mean difference

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Bugden S, et al. Academic detailing upskilling document insulin analogues; 2009.

Type 2 diabetes

Basal insulins

Insulin glargine (+ oral antidiabetes agent) vs. NPH (+ oral antidiabetes agent)

- No significant difference: A1C, fasting plasma glucose
- Weight Gain: No significant difference
- Severe hypoglycemia: No significant difference
- Favours insulin glargine:
 - Nocturnal hypoglycemia
 - Relative Risk (95% CI) = 0.56 (0.47, 0.68)
 - Rate ratio (95% CI) = 0.41 (0.29, 0.59)
 - Overall hypoglycemia
 - Relative Risk (95%CI) = 0.87 (0.81, 0.93)

Type 2 diabetes

Basal insulins (cont'd)

Insulin glargine (+ human insulin) vs. NPH (+ human insulin) [no oral antidiabetes agent]

- A1C favours NPH
 - WMD (95% CI) = 0.28 (0.07, 0.49)
- Body Weight and % that reached target A1C ($\leq 7\%$) : No significant difference
- Nocturnal hypoglycemia favours insulin glargine
 - Relative Risk (95% CI) = 0.78 (0.62, 0.98)
- Overall hypoglycemia: No significant difference

Type 2 diabetes Basal insulins (cont'd)

Insulin detemir (+ oral antidiabetes agent) vs. NPH (+ oral antidiabetes agent)

Outcome	Effect estimate (95% CI)
A1C	No significant difference
Fasting plasma glucose	No significant difference
Severe hypoglycemia	Rate ratio (95%CI) = 0.13 (0.02, 0.91) Relative Risk showed no significant difference
Nocturnal hypoglycemia	Rate Ratio (95% CI) = 0.45 (0.38, 0.54) Relative Risk (95% CI) = 0.53 (0.31, 0.91)
Overall hypoglycemia	Rate ratio (95%CI) = 0.54 (0.50, 0.58) Relative Risk showed no significant difference
Mean Difference in Body Weight	WMD (95%CI) = -1.27kg (-1.95, -0.58)

A1C=Glycosylated hemoglobin; CI=Confidence interval; NPH=Neutral protamine Hagedom; WMD=Weighted mean difference

Type 2 diabetes Basal insulins (cont'd)

Insulin detemir (+ insulin aspart) vs. NPH (+ insulin aspart) [no oral antidiabetes agent]

- A1C, fasting plasma glucose, overall hypoglycemia (relative risk) – no significant difference
- Nocturnal hypoglycemia favours insulin detemir
 - Relative Risk (95% CI) = 0.66 (0.45, 0.96)
- Weight favours insulin detemir
 - WMD (95%CI) = -0.80kg (-1.46, -0.14)

Type 2 diabetes

Basal insulins (cont'd)

Insulin detemir (+ insulin aspart) vs. insulin glargine (+ insulin aspart)

- A1C favours insulin glargine
 - WMD (95%CI) = 0.20 (0.10, 0.30)
- Fasting plasma glucose: No significant difference
- Weight favours insulin detemir
 - WMD (95%CI) = -1.50kg (-2.47, -0.53)

Insulin detemir (+ oral antidiabetes agents) vs. insulin glargine (+ oral antidiabetes agents):

- A1C, hypoglycemia, and body weight: No significant difference

Recommendations

Basal insulin in Type 2 diabetes

When a basal insulin is required, insulin NPH is recommended over a long-acting insulin analogue (glargine or detemir), in most adults with type 2 diabetes.

If a long-acting insulin analogue is used, there is no preference between the available agents.

Type 2 Diabetes Mellitus

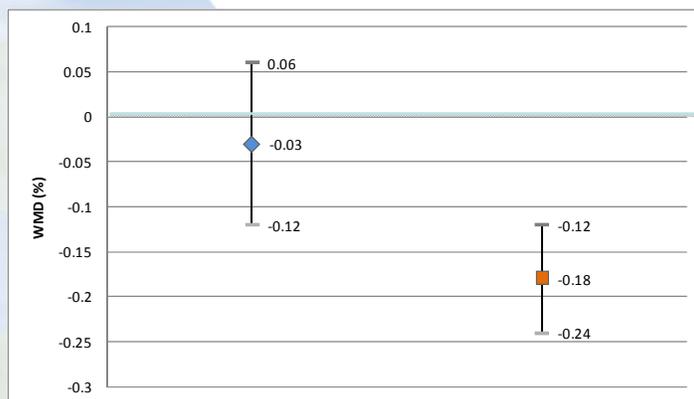
Bolus Insulin

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Rapid-acting insulin analogues vs. human insulin in type 2 diabetes

Pooled A1C differences in comparisons of rapid-acting insulin analogues vs. human insulin in adults with type 2 diabetes



◆ ILis or premixed ILis vs. HI, 11 trials, 3093 pts ■ IAsp or premixed IAsp vs. HI, 4 trials, 421 pts

A1C=Glycosylated hemoglobin; HI=Human insulin; IAsp=Insulin aspart; ILis=Insulin lispro;
WMD=weighted mean difference

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Bugden S, et al. *Academic detailing upskilling document insulin analogues*; 2009.



Type 2 diabetes – adults

Bolus insulins

No significant differences between rapid-acting insulin analogues and human insulin in the following:

- Fasting plasma glucose
- 2-hour postprandial plasma glucose
- Body weight or Body mass index
- Cholesterol levels
- All-cause mortality

A1C: insulin lispro vs. human insulin: No significant difference

- Insulin aspart vs. human insulin: WMD (95%CI): -0.18 (-0.24 to -0.12)

Type 2 diabetes

Bolus insulins (cont'd)

No significant differences in relative risk of nocturnal, overall and severe hypoglycemia between rapid-acting insulin analogues and human insulin

Rate ratio of overall hypoglycemia

- Insulin lispro vs. human insulin: No significant difference
- Insulin aspart vs. human insulin - favours insulin aspart
 - Rate ratio (95%CI) = 0.72 (0.64,0.80)
- Insulin lispro vs. insulin aspart: No significant difference

Rate ratio of nocturnal hypoglycemia

- Insulin lispro vs. human insulin-favours insulin lispro
 - Rate ratio (95%CI) = 0.58 (0.48, 070)

Recommendations

Bolus insulin in type 2 diabetes

When a bolus insulin is required for patients with type 2 diabetes, regular human insulin is suggested over the rapid-acting insulin analogue.

If a rapid-acting insulin analogue is used, there is no preference between the available agents.

Pre-existing diabetes during pregnancy and gestational diabetes

Recommended glycemic targets preconception and during pregnancy

	Glycemic targets
Pre-pregnancy: A1C (%)	7.0 (6.0 if possible)
Once pregnant:	
FPG & preprandial PG (mmol/L)	3.8-5.2
1-hour postprandial PG (mmol/L)	5.5-7.7
2-hour postprandial PG (mmol/L)	5.0-6.6
A1C (%)	6.0 (normal)

A1C=Glycosylated hemoglobin; FPG=Fasting plasma glucose; PG=Plasma glucose

Pharmacotherapy in pregnancy

Discontinue oral antihyperglycemic agents prior to conception, except in patients with polycystic ovary syndrome, where metformin can be safely used for ovulation induction.

Intensive insulin therapy using multiple daily injections or continuous subcutaneous insulin infusion for pre-existing type 1 diabetes during pregnancy.

Self-monitoring blood glucose preprandial and postprandial at least four times per day.

Insulin in pregnancy

Insulin	Pregnancy
Regular, Toronto	B
Aspart	B
Lispro	B
NPH	B
Glargine	C
Detemir	C

B = Likely safe
C = Caution

Briggs GG, et al. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*; 2005.
Micromedex [database on the Internet]; 2008.



Type 1 diabetes – pregnancy Bolus insulins

No significant differences in A1C, severe hypoglycemia, nocturnal hypoglycemia, or overall hypoglycemia between rapid-acting insulin analogues and human insulin.

Suggestion:

- Either regular human insulin or a rapid-acting insulin analogue (i.e., insulin aspart or insulin lispro) can be used in most pregnant women who have type 1 diabetes.



Gestational diabetes

Abnormal glucose tolerance that is first diagnosed during pregnancy

3.7% non-Aboriginal; 8-18% in Aboriginal

Insulin requirements rise at 24-28 weeks

Second trimester: human placental lactogen, cortisol and prolactin increase leads to insulin resistance

Gestational diabetes leads to insulin resistance + beta cell defects

Postpartum – normal glucose tolerance

CDA. *Can J Diabetes* 2008;32(suppl 1):i-S201.
CDA. *Building competency in diabetes education: advancing practice*; 2003.
Dyck R, et al. *Diabetes Care* 2002;25(3):487-93.
Godwin M, et al. *CMAJ* 1999;160(9):1299-302.
Harris SB, et al. *Diabetes Care* 1997;20(9):1422-5.

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Pharmacological interventions

If women with gestational diabetes do not achieve glycemic targets within two weeks with nutrition therapy alone, insulin therapy should be initiated (with up to four injections per day).

Target plasma glucose:

- Fasting plasma glucose/preprandial: 3.8 - 5.2 mmol/L
- 1-h postprandial plasma glucose: 5.5 - 7.7 mmol/L
- 2-h postprandial plasma glucose: 5.0 – 6.6 mmol/L

CDA. *Can J Diabetes* 2008;32(suppl 1):i-S201.

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Gestational diabetes

Bolus insulins

No significant differences in A1C levels or overall hypoglycemia rates with insulin lispro vs. human insulin.

No significant differences in A1C and hypoglycemia (severe, nocturnal, and overall) measures with insulin aspart vs. human insulin.

Recommendations:

- Either regular human insulin or rapid-acting insulin analogues (i.e., insulin lispro or insulin aspart) can be used in most women who develop gestational diabetes.

Insulin dose

Type 2 diabetes

Start with 10 units of NPH or 0.1-0.2 unit/kg of total body weight at bedtime

Do not need to stop oral meds unless otherwise indicated

Thiazolidinediones + insulin is not approved in Canada

Type 1 diabetes

Adult

- 0.5 unit/kg of body weight
- Not acutely ill or ketotic – 0.5 unit/kg may be too high: start with four units before meals and at bedtime

Adolescent

- 0.5 unit/kg of body weight, but expect to increase to 1 unit/kg of body weight

Tips for adjusting insulin

Fix the lows first and the highs later.

Correct breakfast blood glucose first, then correct the next meal of the day.

Adjust insulin by 5-10% per week, or one or two units.

Make an adjustment to only one insulin at a time.

Tips for adjusting insulin (cont'd)

It is important to get the right basal dose. The correct dose will keep blood glucose between four and eight from bedtime to morning without causing a low and usually without requiring a bedtime snack.

To assess for Somogyi (nocturnal hypoglycemia with rebound hyperglycemia in the morning) or overnight control, check blood glucose at 0300 or 0400.

Postprandial targets are helpful when assessing the meal insulin.

Summary

Bolus Insulin Therapy:

- In patients with type 1 diabetes, either regular human insulin or rapid-acting insulin analogues can be considered as first-line therapy (except in adolescent patients).
 - In adolescent patients with type 1 diabetes, rapid-acting insulin analogues may be considered as first-line therapy.
- In patients with type 2 diabetes requiring bolus insulin, regular human insulin may be considered first.*

**Although the evidence is limited and inconsistent, patients who are experiencing significant hypoglycemia while taking human insulin may benefit from rapid-acting insulin analogues.*

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Summary (cont'd)

Basal Insulin Therapy:

- In patients with type 1 or type 2 diabetes requiring basal insulin, insulin NPH should be considered first.*

**Although the evidence is limited and inconsistent, patients who are experiencing significant hypoglycemia while taking insulin NPH may benefit from long-acting insulin analogues.*

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