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Starting Insulin in General Practice Workshop - Pre-Conference Workshop
Thursday, 09 June 2011  
Start 2:00pm  
Duration: 4 hours  
Works
Starting Insulin Sooner Rather Than Later

Rotorua GP CME June 2011

Kingsley Nirmalaraj FRACP
Endocrinologist and Physician
BOPDHB
Agenda

• Size of the problem
• What is T2DM anyway?
• Natural History of Type 2 diabetes
• Does management of glycaemia matter?
• Self-monitoring of blood glucose (SMBG)
• ADA/EASD Guidelines for the treatment of hyperglycaemia in type 2 diabetes (DM2)
• Treatment targets
Global projections for the diabetes epidemic: 2003–2025 (millions)

## Update: NZHS Findings

**Diagnosed diabetes** for adults, by DHB area (unadjusted)

<table>
<thead>
<tr>
<th>DHB area</th>
<th>Prevalence (95% CI)</th>
<th>Number of adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northland / Tairawhiti / Hawke’s Bay / Lakes / Whanganui</td>
<td>4.5 (3.4–5.7)</td>
<td>17000</td>
</tr>
<tr>
<td>Waitemata</td>
<td>4.0 (2.8–5.2)</td>
<td>15200</td>
</tr>
<tr>
<td>Auckland</td>
<td>4.9 (3.4–6.3)</td>
<td>15600</td>
</tr>
<tr>
<td>Counties Manukau</td>
<td>8.2 (6.4–9.9) +</td>
<td>26400</td>
</tr>
<tr>
<td>Waikato</td>
<td>5.6 (4.2–7.0)</td>
<td>14400</td>
</tr>
<tr>
<td>Bay of Plenty / Taranaki / MidCentral</td>
<td>4.8 (3.5–6.1)</td>
<td>16900</td>
</tr>
<tr>
<td>Wairarapa / Hutt Valley / Capital and Coast</td>
<td>5.1 (3.6–6.7)</td>
<td>17700</td>
</tr>
<tr>
<td>Canterbury</td>
<td>4.4 (2.7–6.1)</td>
<td>16500</td>
</tr>
<tr>
<td>Nelson Marlborough / West Coast / South Canterbury / Otago / Southland</td>
<td>4.4 (3.0–5.8)</td>
<td>17400</td>
</tr>
<tr>
<td>New Zealand total</td>
<td>5.0 (4.6–5.5)</td>
<td>157100</td>
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</tbody>
</table>
Undiagnosed rate ratios
Auckland Heart and Health Survey (2007)
Numbers

• People in NZ with known diabetes 190,000
• Number with undiagnosed diabetes
• Practices ~1100 (173/Practice)
• GPs ~3500 (54/GP)
• Your practice?
People with diabetes are over represented as hospital inpatients.
Diabetes Management Remains Suboptimal

- Over 40% of individuals with Type 2 had an HbA1c over 7%
- Over 90% of individuals with Type 1 had an HbA1c over 7%

NZ Get Checked data

Bar chart showing:
- % of subjects
  - <7%: 60
  - 7%-9%: 30
  - >9%: 10

Saydah SH et al. JAMA. 2004;291:335-342
What is Type 2 Diabetes (DM2)?

• **DM2**
  - FPG $\geq$ 7.0 mmol/L or
  - 2 hr GTT $\geq$ 11.1 mmol/L
  - HBA1c $\geq$ 6.5% (new)
  - Symptomatic + random glucose $\geq$ 11.1

• **Impaired fasting glucose or impaired glucose tolerance**
  - FPG of 6.1 (5.6 in ADA guidelines) to 6.9
  - 2 hr GTT of 7.8 to 11.0
  - HBA1c of 5.7-6.4% (66% sensitivity & 88% specificity for 6Y incidence of DM - Diabetes Care. 2011. 34:S62.)
  - HBA1c of 6-6.4% imparts a $> 10$ X greater risk DM.
Natural History of T2DM

- Years from diagnosis:
  - -10
  - -5
  - 0 (Onset)
  - 5
  - 10
  - 15

- Beta-cell function
- Insulin secretion
- Insulin resistance
- Postprandial glucose
- Fasting glucose

- Microvascular complications
- Macrovacular complications

Data extrapolated.
β-Cell Function & Glycaemic Control in DM2

As β-cell function declines …

…hyperglycemia increases over time

UKPDS=United Kingdom Prospective Diabetes Study; SU=sulfonylurea.
β-cell glucose & insulin sensitivity vs. 2-h plasma glucose concentration in obese NGT, IGT, & DM2

**Type 1 Diabetes** reflects an absolute lack of insulin and requires insulin replacement.

**Type 2 Diabetes** is a progressive condition...and changes with time.

The mechanisms of T2DM is multifactorial including:

- Pancreatic islet cell dysfunction
  - Deficient insulin response by b-cells
  - Excessive production of glucagon by α-cells
- Excessive hepatic output of endogenous glucose
  - From diminished insulin & insulin sensitivity and excess glucagon
- Impaired uptake of glucose in the peripheral tissues
  - A consequence of insulin resistance

*With progressive worsening over time*
But, does glucose control prevent CVD?

How long does the investment take to pay the dividend?
Lessons from UKPDS: Better Control Means Fewer Complications

Every 1% reduction in HbA1c

- Deaths from diabetes: 21%
- Heart attacks: 14%
- Microvascular complications: 37%
- Peripheral vascular disorders*: 43%

HbA1c: Glycosylated haemoglobin; UKPDS: UK Prospective Diabetes Study.
*p<0.0001; †Lower extremity amputation or fatal peripheral vascular disease.
**DCCT-EDIC: Long-term Risk of Macrovascular Complications**

*Diabetes Control and Complications Trial (DCCT) ended and Epidemiology of Diabetes Interventions and Complications (EDIC) began in year 10 (1993). Mean follow-up: 17 years.**

**There is a metabolic “memory” of good glucose control.**

Recent Trials of Glycaemic Control

- Both DCCT and UKPDS intensive treated arm were able to reach an average HBA1c average of 7.0%.
- UKPDS took newly diagnosed patients with DM2.
- Rates of DM complications were log linear and extended down to HBA1c of 6.0% begging the question of whether lower HBA1c target would lead to better outcomes.

- ADVANCE (3.5Y) & ACCORD (5Y) tested this hypothesis
  - Patients:
    - Established DM2 (average duration 8-10 years of disease)
    - CV disease or CV risk factors already present
ACCORD & ADVANCE

• Decreased microvascular complications in intensive Rx.

• Lower rates of CV event than predicted studies. (Secondary to high levels of statins use, BP control, ASA usage, smoking cessation?)

• No statistical difference in composite CV outcome
  – Trend towards decreased CV events in intensive arm
  – But, increased mortality in intensive arm of ACCORD only-Why?
  – ACCORD vs. ADVANCE patients
    • Longer duration of diabetes (by 2 yrs) in ACCORD
    • Worse DM (more patients already on insulin & with higher HBA1c @ baseline)
    • More obese with greater weight gain through the study
    • Higher usage of TZDs and insulin
    • HBA1c was lowered more rapidly in ACCORD vs. ADVANCE (<1yr vs >1 yr)
    • Much higher rate of severe hypoglycaemia**
## Primary & Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive N (%)</th>
<th>Standard N (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
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<tr>
<td>Primary</td>
<td>352 (6.86)</td>
<td>371 (7.23)</td>
<td>0.90 (0.78-1.04)</td>
<td>0.16</td>
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<tr>
<td><strong>Secondary</strong></td>
<td></td>
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</tr>
<tr>
<td>Mortality</td>
<td>257 (5.01)</td>
<td>203 (3.96)</td>
<td>1.22 (1.01-1.46)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>186 (3.63)</td>
<td>235 (4.59)</td>
<td>0.76 (0.62-0.92)</td>
<td>0.004</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>67 (1.31)</td>
<td>61 (1.19)</td>
<td>1.06 (0.75-1.50)</td>
<td>0.74</td>
</tr>
<tr>
<td>CVD Death</td>
<td>135 (2.63)</td>
<td>94 (1.83)</td>
<td>1.35 (1.04-1.76)</td>
<td>0.02</td>
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<tr>
<td>CHF</td>
<td>152 (2.96)</td>
<td>124 (2.42)</td>
<td>1.18 (0.93-1.49)</td>
<td>0.17</td>
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</table>
Subset Analysis

• Significant decrease in CV events in those with:
  – Shorter duration of DM
  – Absence of known CV disease

• Higher risk of mortality in those with:
  – Severe hypoglycaemia (& higher HBA1c?)
  – (Hypoglycaemia unawareness is associated with cardiovascular autonomic neuropathy which is a strong risk factor for sudden death)
Steno-2 Post Trial: Any CVD events

Cumulative incidence of patients with a major CVD event during follow-up

**Cumulative incidence of CVD events (%)**

HR 0.41, P=0.0002

**Years of follow-up**

**Cumulative incidence of CVD events (%)**

**Numbers at risk**

<table>
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<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
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<tbody>
<tr>
<td>Conventional</td>
<td>80</td>
<td>70</td>
<td>60</td>
<td>46</td>
<td>38</td>
<td>29</td>
<td>25</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Intensive</td>
<td>80</td>
<td>72</td>
<td>65</td>
<td>61</td>
<td>56</td>
<td>50</td>
<td>47</td>
<td>31</td>
<td></td>
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Gaede et al. NEJM 2008
Diabetes Treatment = “PLAGUE-F”

Pressure
Lipids
Aspirin
Glucose
Urine albumin/creatinine ratio
Eye exam yearly
Foot exam each visit

Barnes, The Diab Educ 2004; 30: 126
Glycaemic control

Reach “individual” HbA1c target WITH SAFETY
i.e. with reduced risk of hypos

FPG
4-6mmol/L

HbA$_{1c}$
<7%

Individual Treatment GOAL

Normoglycaemia

International Diabetes Federation (Europe). A desktop guide to Type 2 diabetes mellitus.
Most of Our Lives are Spent in the Postprandial State

FPG, 2-Hour Postchallenge Glucose, and Mortality in Individuals Not Known as Diabetic: DECODE Study

* Adjusted for age, gender, and study center.

To normalise BG both FPG & PPG need to be controlled

Most insulin is initiated when HbA$_{1c}$ > 8.5%

Adapted from Monnier L et al. Diabetes Care 2003;26:881–5
HbA1c’s are not created equal

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Supper</th>
<th>Over Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c mmol/L</td>
<td>11.1</td>
<td>8.3</td>
<td>5.6</td>
<td>2.8</td>
</tr>
</tbody>
</table>

HbA1c = 7.8%
HbA1c’s are **not** created equal

Example of someone on **too much** long/intermediate acting insulin & not enough prandial insulin who will need to snack in between meals & at bedtime to avoid hypoglycaemia.
Self Monitoring of Blood Glucose (SMBG)

- HBA1c only provides information on average blood sugar.

- It will not tell you the range of blood sugars.

- SMBG is essential in treatment of DM.
  - Analogy: It is hard to drive safely if you can’t see where you are going.
SMBG

• On lifestyle alone/Metformin
  – Useful intermittently to establish effect of food/exercise on glucose (consecutive measurements are most helpful)
    – Allows direct feedback to the patients & contributes to patient knowledge
    – Hopefully helps modify behaviour (if patients are educated)
  – Useful to examine pattern of glucose elevation to help assess adequacy of Rx (ex: 2-3 days of 6 X day testing just prior to seeing physician)

• Type 2 DM on oral hypoglycaemic agents or insulin
  – As above, plus
  – Monitoring for hypoglycaemia (recommend a day of 6X day testing after commencing Rx or dose change).
Glucose Focused Testing Examples
Actionable information for informed decision-making

Pattern Testing …
Multi-point BG profiles for a specific duration to use pattern analysis to identify problem areas for remediation.

Paired Testing …
Testing to explore cause and effect BG variance related to life events or activities, such as food, lifestyle, and current medication. Supports patient self-learning and engagement.

Adjustment Testing …
BG testing to support activities to determine dose adjustment.
ADA & EASD Consensus Statement (2006 & revised in 2009)

• Management of hyperglycaemia in DM2 Algorithm.

• Goal HBA1c is < 7.0 (IDF rec. < 6.5)

• Basis for anti-hyperglycaemic agent choice:
  – Effectiveness in lowering glucose
  – Effectiveness in decreasing complications
  – Safety profile
  – Ease of use & expense.
Tier 1: Well-validated core therapies

At diagnosis:
Lifestyle + Metformin

STEP 1

STEP 2
Lifestyle + Metformin
+ Basal insulin
Lifestyle + Metformin
+ Sulfonylurea

STEP 3
Lifestyle + Metformin
+ Intensive insulin

Tier 2: Less well-validated therapies

Lifestyle + Metformin
+ Pioglitazone
No hypoglycaemia
Oedema/CHF
Bone loss

Lifestyle + Metformin
+ GLP-1 agonist
No hypoglycaemia
Weight loss
Nausea/vomiting

Lifestyle + Metformin
+ Pioglitazone
+ Sulfonylurea

Lifestyle + Metformin
+ Basal insulin

Fig. 2 Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle interventions at every visit. Check HbA₁c every 3 months until HbA₁c is <7%, and then at least every 6 months. The interventions should be changed if HbA₁c is ≥7%. aSulfonylureas other than glybenclamide (glyburide) or chlorpropamide. bInsufficient clinical use to be confident regarding safety. See text box: Titration of metformin. See Fig. 1 for initiation and adjustment of insulin. CHF, congestive heart failure.
Treatment Targets

HBA1c       < 7.0 (< 6.5 if it can be done safely)

Pre-meal BS  < 6.0

2 hr pp BS   < 8.0

LDL         < 2.5
            < 2.0 (current NZ CV guidelines)
            < 1.8 for those with pre-existing CVD

BP          < 130/80 (if no renal impairment)
            < 125/75-80 (with renal impairment)
“Clinical inertia is due to at least three problems:

1. overestimation of care provided
2. use of “soft” reasons to avoid intensification of therapy
3. lack of education, training, and practice organization aimed at achieving therapeutic goals

Physicians will need to build into their practice a system of reminders and performance feedback to ensure necessary care.”

Phillips et al, Annals of Internal Medicine, 2001

Work to meet Targets
Key Points

• Diabetes is a major health problem with multiple complications (esp. Maori/Pacific and Asian populations)

• Set the patient up realistically for the future
  – DM is a disease of insulin deficiency (& resistance in DM2) that naturally progresses with time

• Education on lifestyle/meds & their effects on BSLs so that glucose readings are interpretable to the patient.

• Don’t delay in advancing treatment to reach glucose targets (to get rid of highs & lows)
  – Metformin
  – SU or Insulin

• Reach non-glycaemic targets
  – BP & Lipids
  – ASA & Smoking Cessation
Early insulin can never be too early!

EARLY INSULIN SAVES HEALTH; SAVES WEALTH

Fight clinical inertia