PRACTICAL MANAGEMENT OF DIABETES MELLITUS: WHAT’S WRONG WITH US?

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7th October, 2017 (Lashio)
- Wrong diagnosis
- Wrong concepts in the control of diabetes
- Wrong management concepts
- Wrong choice of patients
- Wrong dosage
- Wrong combination of OHAs
- Wrong information/beliefs – metformin and renal damage

- End stage of DM
- No other treatment options that lower the damage to eyes, kidneys, etc
- Barriers like unaffordable, no refrigeration, painful and no capacity for injection
- Hypoglycemia
- Hyperinsulinaemia
SELECTION OF PATIENT

- Type 1 DM patients
- Type 2 DM patients
- MODY
- LADA
- GDM
- SECONDARY DIABETES
**DIAGNOSIS OF DM (WHO CRITERIA)**

- **Symptoms of hyperglycaemia** (eg polyuria, polydipsia, unexplained weight loss, visual blurring, genital thrush, lethargy) AND raised venous glucose detected once—fasting ≥7mmol/L or random ≥11.1mmol/L OR

- **Raised venous glucose on 2 separate occasions**—
  - fasting ≥7mmol/L,
  - random ≥11.1mmol/L or
  - oral glucose tolerance test (OGTT)—2h value ≥11.1mmol/L

- **HbA1c ≥48mmol/L (6.5%)**, but below doesn’t exclude DM. Avoid in pregnancy, children and type 1 DM.

- Whenever you have a needle in a vein, do a blood glucose (unless recently done); note if fasting or after food. Non-systematic, but better than urine tests (too many false negatives). In one UK GP trial, 5% of those screened aged 40–69 had new DM.
SMBG (SELF MONITORING BLOOD GLUCOSE)

For Out Patients:
- FBS: 80-120 mg/dl
- 2HPPL / 2HPPD: <180 mg/dl

For Inpatients
- FBS:
- 2HPPL / 2HPPD:
## Spectrum of DM Type I and Type II

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Younger (usually &lt;30)</td>
<td>Older (usually &gt;30)</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Lean</td>
<td>Overweight</td>
</tr>
<tr>
<td><strong>Symptom duration</strong></td>
<td>Weeks</td>
<td>Months/years</td>
</tr>
<tr>
<td><strong>Higher risk ethnicity</strong></td>
<td>Northern European</td>
<td>Asian, African, Polynesian and American-Indian</td>
</tr>
<tr>
<td><strong>Seasonal onset</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Heredity</strong></td>
<td>HLA-DR3 or DR4 in &gt;90%</td>
<td>No HLA links</td>
</tr>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Autoimmune disease</td>
<td>No immune disturbance</td>
</tr>
<tr>
<td><strong>Ketonuria</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Insulin deficiency</td>
<td>Partial insulin deficiency initially</td>
</tr>
<tr>
<td></td>
<td>± ketoacidosis</td>
<td>± hyperosmolar state</td>
</tr>
<tr>
<td></td>
<td>Always need insulin</td>
<td>Need insulin when beta cells fail over time</td>
</tr>
<tr>
<td><strong>Biochemical</strong></td>
<td>C-peptide disappears</td>
<td>C-peptide persists</td>
</tr>
</tbody>
</table>
MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

- Maturity-onset diabetes of the Young (MODY) is a genetically and clinically heterogeneous group of disorders.
- Characterized by nonketotic diabetes mellitus.
- Autosomal dominant – (+) Family history.
- Onset usually before 25 years of age.
- Resulting from a primary defect in pancreatic beta-cell function (6 causative gene mutations in insulin and glucose regulation).
- Account for 1-5% of all cases of diabetes.
- Most common clinical presentation is a mild, asymptomatic increase in blood glucose in a child, adolescent, or young adult with a prominent family history of diabetes.
- Resembles with Type 2 DM and relatively mild but the patient are not obese and not insulin resistant.
### GENETIC DEFECTS OF BETA-CELL FUNCTION

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene mutated</th>
<th>Chromosome no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODY 1</td>
<td>Hepatocyte nuclear factor 4A (HNF4A)</td>
<td>20</td>
</tr>
<tr>
<td>MODY 2</td>
<td>Glucokinase (GCK)</td>
<td>7</td>
</tr>
<tr>
<td>MODY 3</td>
<td>Hepatocyte nuclear factor 1A (HNF1A)</td>
<td>12</td>
</tr>
<tr>
<td>MODY 4</td>
<td>Insulin promoter factor 1 (ING1)</td>
<td>13</td>
</tr>
<tr>
<td>MODY 5</td>
<td>Hepatocyte nuclear factor 1B(HNF 1B)</td>
<td>17</td>
</tr>
<tr>
<td>MODY 6</td>
<td>Neuro 1/ BETA2</td>
<td>2</td>
</tr>
</tbody>
</table>
Model of a Pancreatic Beta Cell and the Proteins Implicated in Maturity-Onset Diabetes of the Young (MODY).
LADA: Latent autoimmune diabetes of adults
A form of type 1 DM, with slower progression to insulin dependence in later life.

GDM: Gestational DM

The aim is to normalise the maternal blood glucose and thereby reduce excessive fetal growth.
- Dietary modification
- Regular pre- and post-prandial self-monitoring of blood glucose, aiming for pre-meal blood glucose levels of <5.5 mmol/L (100 mg/dL) or post-meal blood glucose levels of <7.0 mmol/L (125 mg/dL)
- Metformin or Glibenclamide is considered safe to use in pregnancy.
- Insulin may be required, especially in the later stages of pregnancy.
- After delivery, maternal glucose usually rapidly returns to pre-pregnancy levels.

Woman should be tested at least 6 weeks post-partum with an oral glucose tolerance test.

Identifying patients with gestational diabetes

sma glucose (after glucose load) ≥ 8 mmol/L (144 mg/dL)
- Consider testing high-risk women at first booking visit with an HbA1c or fasting blood glucose
Secondary Diabetes Mellitus

- Pancreatic disease (e.g. pancreatitis, pancreatectomy, neoplastic disease, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy)

- Excess endogenous production of hormonal antagonists to insulin, e.g.
  - Growth hormone – acromegaly
  - Glucocorticoids – Cushing’s syndrome
  - Glucagon – glucagonoma
  - Catecholamines – phaeochromocytoma
  - Thyroid hormones – thyrotoxicosis

- Drug-induced (e.g. corticosteroids, thiazide diuretics, phenytoin)

- Uncommon forms of immune-mediated diabetes (e.g. IPEX (immunodysregulation polyendocrinopathy X) syndrome)

- Associated with genetic syndromes (e.g. Down’s syndrome; Klinefelter’s syndrome; Turner’s syndrome; DIDMOAD (Wolfram’s syndrome) – diabetes insipidus, diabetes mellitus, optic atrophy, nerve deafness; Friedreich’s ataxia; myotonic dystrophy)
# Glycemic Target for Out-Patients

## HbA1c Goals

<table>
<thead>
<tr>
<th>Nonpregnant adult</th>
<th>&lt;7% (53mmol/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease</td>
<td>&lt;6.5 (48mmol/mol)</td>
</tr>
<tr>
<td>Patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-lasting diabetes</td>
<td>&lt;8% (64mmol/mol)</td>
</tr>
</tbody>
</table>
GLYCEMIC TARGETS IN HOSPITALIZED PATIENTS

<table>
<thead>
<tr>
<th>Standard definition of glucose abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperglycemia</strong></td>
</tr>
<tr>
<td>- &gt;140mg/dl (7.8mmol/L)</td>
</tr>
<tr>
<td><strong>Admission HbA1c value</strong></td>
</tr>
<tr>
<td>- ≥6.5% (suggests that diabetes preceded hospitalization)</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
</tr>
<tr>
<td>- previously defined as blood glucose &lt;70mg/dl (3.9mg/L), and now define clinically significant hypoglycemia as blood glucose &lt;54mg/dl (3.0mg/L)</td>
</tr>
<tr>
<td><strong>Severe hypoglycemia</strong></td>
</tr>
<tr>
<td>- previously &lt;40mg/dl (2.2mmol/L), and now it is defined as that associated with severe cognitive impairment regardless of blood glucose level</td>
</tr>
</tbody>
</table>
GLYCEMIC TARGET IN PREGNANCY

Glucose monitoring
- Fasting ≤95mg/dl (5.3mmol/L) and either
- One-hour postprandial ≤140mg/dl (7.8mmol/L) or
- Two-hour postprandial ≤120mg/dl (6.7mmol/L)
In the patients with regular meal, glucose monitoring should be performed **before meal**.

In the patients with enteral/parenteral nutrition, glucose monitoring is advised every 4-6 hours.

More frequent blood glucose testing will range from every 30 minutes to 2 hours in the patient with IV insulin infusion.
# INSULIN THERAPY IN HOSPITALIZED PATIENTS

<table>
<thead>
<tr>
<th>Type of patients</th>
<th>Insulin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical care setting</td>
<td>Continuous IV insulin infusion</td>
</tr>
<tr>
<td>Outside of critical care units</td>
<td>Scheduled insulin regimens (regimens using insulin analogue and human insulin result in similar glycemic control)</td>
</tr>
<tr>
<td>With no meal or continuous enteral/parenteral nutrition</td>
<td>Rapid- or short-acting insulin before meals or every 4-6 hours</td>
</tr>
<tr>
<td>Noncritically ill patients with poor oral intake or those who are taking nothing by mouth</td>
<td>Basal insulin or a basal plus bolus correction insulin regimen</td>
</tr>
<tr>
<td>Noncritically ill patients with good nutritional intake</td>
<td>An insulin regimen with basal, nutritional, and correction components</td>
</tr>
</tbody>
</table>
MODERATE VERSUS TIGHT GLYCEMIC CONTROL

- Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold $\geq 180\text{mg/dl} (10.0\text{mmol/L})$.
- Once insulin therapy is started, a target glucose range of 140-180\text{mg/dl} (7.8-10.0\text{mmol/L}) is recommended for the majority of critically ill and noncritically ill patients.
- More significant goals, such as $<140\text{mg/dl} (7.8\text{mmol/L})$, may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia.
- Conversely, higher glucose ranges may be acceptable in terminally ill patients, those with severe comorbidities, and in inpatient care setting where frequent glucose monitoring or close nursing supervisions not feasible.
ANTIHYPERGLYCEMIC AGENTS IN HOSPITALIZED PATIENTS

- In most instances in the hospital setting, insulin is the preferred treatment for glycemic control.
- However, in certain circumstances, it may be appropriate to continue home regimens including oral antihyperglycemic medications.
- If oral medications are held in the hospital, there should be a protocol for resuming them 1-2 days before discharge.
CHOICE OF TYPE OF INSULIN

Types of Insulin

Classified on the basis of

- Species - Bovine/Porcine/Human
- Purity – Human Monocomponent
- Action Profile - short, intermediate & long acting
- Strength - 100 i.u/ml & 300 i.u/ml

Species and purity - the most important determinants of antigenicity
Types of Insulin

- Short-acting – Regular (Actrapid)
- Intermediate – NPH
- Premixed – Mixtard 30
- Rapid-acting - Humalog®, NovoRapid®, Apidra
- Long-acting - Glargine (Lantus), Detemir (Levemir)
- Premixed Analogue – NovoMix 30
SO.....WHAT ARE INSULIN ANALOGUES??

Molecules produced by genetic engineering wherein the amino acid sequence in human insulin is changed to alter its pharmacokinetics. However, they bind to insulin receptors in the same way as human insulin and produce similar effects.

Also termed as:

*Designer Insulins*
*Insulin receptor ligands*
*Democratic insulins*
ARTS OF INSULIN ANALOGUE

Human Insulin
MW 5808

Insulin glargine
(Lantus®)
Avg MW 6063

Insulin aspart
(NovoRapid)
Avg MW 5826

Insulin detemir
(Levemir®)
Avg MW 5917

Insulin glulisine
(Apidra®)
Avg MW 5823
PK/PD OF ANALOGUE INSULIN

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset Time (min)</th>
<th>Duration of Action (h)</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin lispro</td>
<td>10-15</td>
<td>4-6</td>
<td>B</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>10-15</td>
<td>4-6</td>
<td>B</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>10-15</td>
<td>4-6</td>
<td>C</td>
</tr>
<tr>
<td><strong>Rapid-Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>30-90</td>
<td>24-26</td>
<td>C</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>30-90</td>
<td>Up to 24</td>
<td>B</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>60</td>
<td>&gt;42</td>
<td>C</td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Source: References 9, 12-17.*
INSULIN DEFICIENCY & DIABETES

- Type 1 - absolute deficiency - insulin therapy essential to survive
- Type 2 DM - relative deficiency
  - loss of first phase
  - sluggish second phase
ABSOLUTE INDICATIONS FOR INSULIN

Regular or continuous Use
* Type 1 Diabetes
* Type 2 Diabetes with OAD failure
  - Primary
  - Secondary

Intermittent Use
* Type 2 diabetes during
  - major surgery
  - pregnancy, labour and delivery
  - myocardial infarction
  - acute infections
  - acute metabolic crisis like hyperosmolar coma and lactic acidosis
* Gestational diabetes mellitus

Life-saving in T1DM
Essential in T2DM
## Pharmacological Profile of Different Basal Insulins

<table>
<thead>
<tr>
<th>Basal insulin classification</th>
<th>Insulin preparation</th>
<th>Onset (hours)*</th>
<th>Peak (hours)</th>
<th>Duration (hours)</th>
<th>Within subject variability (CV%)</th>
<th>Timing of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate or long-acting</td>
<td>NPH</td>
<td>1-3</td>
<td>4-6</td>
<td>12-16</td>
<td>68</td>
<td>Usually taken once or twice daily</td>
</tr>
<tr>
<td>Long-acting analog</td>
<td>Glargine</td>
<td>0.5-2</td>
<td>Flat, no peak</td>
<td>~24</td>
<td>32-82</td>
<td>Usually taken once-daily at the same time every day</td>
</tr>
<tr>
<td></td>
<td>Detemir</td>
<td>0.5-2</td>
<td>Flat, no peak</td>
<td>~20</td>
<td>27</td>
<td>Usually taken once or twice daily</td>
</tr>
<tr>
<td></td>
<td>Degludec</td>
<td>NR</td>
<td>Flat, no peak</td>
<td>&gt;42</td>
<td>20</td>
<td>Once-daily, any time of the daily</td>
</tr>
<tr>
<td></td>
<td>LY2605541</td>
<td>NR</td>
<td>Flat, no peak</td>
<td>&gt;36</td>
<td>&lt;18</td>
<td>Once-daily</td>
</tr>
<tr>
<td></td>
<td>U300</td>
<td>NR</td>
<td>Flat, no peak</td>
<td>&gt;36</td>
<td>NR</td>
<td>Once-daily</td>
</tr>
</tbody>
</table>

*Onset and peak times vary based on individual metabolic responses and are subject to within-subject variability (CV%).

 timings are usually taken once or twice daily.
## Basal insulin regimen

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>10 Units or 0.2 U/kg/day at bed time</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Fasting Plasma Glucose (FPG/FBS)</td>
</tr>
<tr>
<td>Optimization</td>
<td>Adjust insulin dose after 3 consecutive FBS (every 3-7 days)</td>
</tr>
<tr>
<td></td>
<td>&lt;80 mg% → reduce dose by 2 unit</td>
</tr>
<tr>
<td></td>
<td>80-110 mg% → maintain current dose</td>
</tr>
<tr>
<td></td>
<td>&gt;110 mg% → increase dose by 2 units</td>
</tr>
</tbody>
</table>
TIMING OF INJECTION IN ONCE DAILY BASAL INSULIN REGIMEN

- Administration of NPH in the evening appears to be superior to morning injection.(1,2)
- Studies examining the injection time of the long-acting insulin analogs showed conflicting results.
- One study conducted with insulin glargine found greater reductions in A1C and nocturnal hypoglycemia with morning compared with evening injection.(3)
- whereas a larger comparison of morning versus evening glargine with an identical study design did not find any difference (both studies investigated this issue against a background of glimepiride once daily).(4)
- A morning administration of insulin detemir was associated with lower glucose levels during the day and a trend toward a reduced risk of nocturnal hypoglycemia compared with evening injection.(5)

OTHER OPTIONS FOR THE INITIATION OF INSULIN THERAPY

Treating to Targets in Type 2 diabetes (4-T) study

- The **biphasic** and **prandial insulin** regimens provided better glycemic control than **once-daily basal insulin** (escalated to twice daily in 34% of patients) but at the expense of increased risks of hypoglycemia and weight gain.

- **Biphasic** insulin reduced A1C levels to the same extent as **prandial** insulin, the latter regimen was associated with the most hypoglycemic episodes and the highest weight gain (1).

INITIATION WITH PRANDIAL INSULIN IS GENERALLY NOT A FIRST-CHOICE APPROACH WHEN STARTING INSULIN IN TYPE 2 DIABETIC PATIENTS.

- To date there is no clinical trial evidence supporting the specific lowering of postprandial glucose levels when aiming to lower cardiovascular risk in type 2 diabetes. (1)

- A therapeutic regimen involving the addition of either basal or prandial insulin analogue is equally effective in lowering haemoglobin A1C. (2)

1. DIABETES CARE, VOLUME 32, SUPPLEMENT 2, NOVEMBER 2009.
The lower A1C levels reached with biphasic insulin comes at the expense of increased risks of hypoglycemia and weight gain. (1, 2)

Trials with systematic dose titration demonstrated that once-daily basal insulin achieves the currently recommended glycemic levels in many patients with type 2 diabetes. (3)

LANMET study proved that A1C levels decreased from 9.1% at baseline to 7.1% with combination therapy of bedtime insulin glargine or NPH insulin and metformin. (4)

Finally, it seems likely that insulin initiation by means of one (basal) injection may also facilitate patients’ acceptance of insulin initiation. (5)

3. Diabetes Care 2003;26:3080–3086
5. DIABETES CARE, VOLUME 32, SUPPLEMENT 2, NOVEMBER 2009.
• Consider initiating combination insulin injectable therapy when blood glucose is \( \geq 300 \text{ mg/dL (16.7 mmol/L)} \) or A1C is \( \geq 10\% (86 \text{ mmol/mol}) \) or if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia).

• As the patient’s glucose toxicity resolves, the regimen may, potentially, be simplified.
When BG≥300mg/dL (86 mmol/mol or HbA1c ≥10%) or patient with symptoms of hyperglycemia

**Initiate Basal Insulin**
Usually with metformin +/- other noninsulin agent

- **Start:** 10 U/day or 0.1-0.2 U/kg/day
- **Adjust:** 10-15% or 2-4 units once or twice weekly to reach FBG target
- **For hypo:** Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10-20%

If A1C not controlled, **consider combination injectable therapy**

**Add 1 rapid-acting insulin injection before largest meal**

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount
- **Adjust:** ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

If A1C not controlled, **advance to basal-bolus**

**Add ≥2 rapid-acting insulin injections before meals (‘basal-bolus’)**

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount
- **Adjust:** ↑ dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

**Change to premixed insulin twice daily (before breakfast and supper)**

- **Start:** Divide current basal dose into ½ AM, ½ PM or ⅓ AM, ⅔ PM
- **Adjust:** ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

If A1C not controlled, **advance to 3rd injection**

**Add GLP-1 RA**

- If not tolerated or A1C target not reached, change to 2 injection insulin regimen

If goals not met, **consider changing to alternative insulin regimen**

**Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)**

- **Start:** Add additional injection before lunch
- **Adjust:** ↑ doses by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- **For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%
BOLUS INSULIN REGIMEN

- Short-acting: prandial blood glucose control
- Profile depends on insulin used
BASAL–BOLUS REGIMEN

- Short- and long- (intermediate-) acting components to control prandial and between-meal blood glucose
- Four or five daily injections
  - Short-acting: one at each of three mealtimes
  - Long-acting: one or two for control between meals
- Used by few type 2 patients, mostly those with severe $\beta$-cell failure
- Typical regimen for type 1 patients
### Basal-Bolus insulin regimen

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>60% of TDD is Regular and 40% of TDD is Basal</td>
</tr>
<tr>
<td></td>
<td>20% of TDD for each meal and 40% at Pre-Dinner or Bed-time</td>
</tr>
<tr>
<td>Monitoring</td>
<td>4-5 times Self Monitoring of Blood Glucose (SMBG)</td>
</tr>
<tr>
<td>Optimization</td>
<td>Depends on SMBG and dose adjustment should be individualized</td>
</tr>
<tr>
<td>Intensification</td>
<td>Basal-Bolus regimen</td>
</tr>
</tbody>
</table>
A mix of short- and long- (intermediate-) acting insulins: control prandial and between-meal blood glucose

Profile depends on insulins used and the proportions
## Premixed insulin regimen

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiation</strong></td>
<td>10 Units or 0.2 U/kg/day at pre-dinner (OD) and divide the total daily dose 2/3 in the morning and 1/3 in the evening for human insulin and 50:50 of the dose for modern insulin</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Fasting Plasma Glucose (FPG/FBS) (OD) Pre-Breakfast &amp; Pre-Dinner glucose (BD)</td>
</tr>
<tr>
<td><strong>Optimization</strong></td>
<td>Adjust insulin dose after 3 consecutive Pre-Breakfast glucose (OD) Adjust morning dose with Pre-Dinner glucose and evening dose with Pre-Breakfast glucose &lt;80 mg% → reduce dose by 2 unit 80-130 mg% → maintain current dose &gt;130 mg% → increase dose by 2 units</td>
</tr>
<tr>
<td><strong>Intensification</strong></td>
<td>Basal-Bolus regimen</td>
</tr>
</tbody>
</table>
PATIENT CONCERNS ABOUT INSULIN

- Fear of injections
- Perceived significance of need for insulin
- Worries that insulin could worsen diabetes
- Concerns about hypoglycemia
- Complexity of regimens
DRAWWBACKS OF INSULIN

1. Hypoglycaemia
2. Weight gain
3. Allergic Reactions –
   - Local redness, itching – self limiting, disappears with continuation of therapy
   - Systemic allergy – angioedema, anaphylaxis-rare, requires desensitization
4. Insulin lipoatrophy
5. Insulin Edema
BARRIERS

- Unaffordable
- Painful
- No capacity for injection
- No refrigerator
COMBINATION WITH ORAL ANTI-DIABETES
GOALS FOR GLYCEMIC CONTROL

INDIVIDUALIZE GOALS

A1C ≤ 6.5%
For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5%
For patients with concurrent serious illness and at risk for hypoglycemia
<p>| | |</p>
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<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong></td>
<td>Lifestyle therapy, including medically supervised weight loss, is key to managing type 2 diabetes.</td>
</tr>
<tr>
<td><strong>2.</strong></td>
<td>The A1C target must be individualized.</td>
</tr>
<tr>
<td><strong>3.</strong></td>
<td>Glycemic control targets include fasting and postprandial glucoses.</td>
</tr>
<tr>
<td><strong>4.</strong></td>
<td>The choice of therapies must be individualized on basis of patient characteristics, impact of net cost to patient, formulary restrictions, personal preferences, etc.</td>
</tr>
<tr>
<td><strong>5.</strong></td>
<td>Minimizing risk of hypoglycemia is a priority.</td>
</tr>
<tr>
<td><strong>6.</strong></td>
<td>Minimizing risk of weight gain is a priority.</td>
</tr>
<tr>
<td><strong>7.</strong></td>
<td>Initial acquisition cost of medications is only a part of the total cost of care which includes monitoring requirements, risk of hypoglycemia, weight gain, safety, etc.</td>
</tr>
<tr>
<td><strong>8.</strong></td>
<td>This algorithm stratifies choice of therapies based on initial A1C.</td>
</tr>
<tr>
<td><strong>9.</strong></td>
<td>Combination therapy is usually required and should involve agents with complementary actions.</td>
</tr>
<tr>
<td><strong>10.</strong></td>
<td>Comprehensive management includes lipid and blood pressure therapies and related comorbidities.</td>
</tr>
<tr>
<td><strong>11.</strong></td>
<td>Therapy must be evaluated frequently until stable (e.g., every 3 months) and then less often.</td>
</tr>
<tr>
<td><strong>12.</strong></td>
<td>The therapeutic regimen should be as simple as possible to optimize adherence.</td>
</tr>
<tr>
<td><strong>13.</strong></td>
<td>This algorithm includes every FDA-approved class of medications for diabetes.</td>
</tr>
</tbody>
</table>
# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPO</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
<td>Moderate/Severe</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
</tr>
<tr>
<td><strong>RENAL/GU</strong></td>
<td>Contraindicated CKD Stage 3B, 4, 5</td>
<td>Exenatide Not Effective with eGFR &lt; 45 Genital Mycotic Infections</td>
<td>Not Effective with Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td><strong>GI Sx</strong></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
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<tr>
<td><strong>CHF</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Possible Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Possible Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Safe</td>
<td>Neutral</td>
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<tr>
<td><strong>ASCVD</strong></td>
<td>Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>?</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td><strong>BONE</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
</tbody>
</table>

### Legend

- **Green**: Few adverse events or possible benefits
- **Yellow**: Use with caution
- **Orange**: Likelihood of adverse effects
- **Question Mark**: Uncertain effect

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**Algorithm for Adding/Intensifying Insulin**

**Start Basal** (Long-Acting Insulin)
- **A1C < 8%**
  - TDD: 0.1–0.2 U/kg
- **A1C > 8%**
  - TDD: 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:
- **Fixed regimen**: Increase TDD by 2 U
- **Adjustable regimen**:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10%–20%
  - BG < 40 mg/dL: 20%–40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

*Glycemic Goal:*
- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

**Intensify** (Prandial Control)
- **Add GLP-1 RA**
  - Or SGLT-2i
  - Or DPP-4i
- **Add Prandial Insulin**
  - **Basal Plus 1, Plus 2, Plus 3**
    - Begin prandial insulin before largest meal
    - If not at goal, progress to injections before 2 or 3 meals
    - Start: 10% of basal dose or 5 units
  - **Basal Bolus**
    - Begin prandial insulin before each meal
    - 50% Basal / 50% Prandial
    - TDD 0.3–0.5 U/kg
    - Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:
- Increase prandial dose by 10% or 1–2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10%–20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20%–40%
Managing **Type 2 diabetes** in adults

**Adult with type 2 diabetes**

**Lifestyle interventions**

**Dietary control**

**Metformin tolerated**

- Offer standard release initially
- Consider modified release if not tolerated

**Metformin contraindicated**

- If HbA1c rises to 48 mmol/mol:
  - Consider monotherapy
    - DPP or PIO or SU

- If HbA1c rises to 58 mmol/mol:
  - Consider dual therapy
    - DPP + PIO or DPP + SU or PIO + SU

If patient is hyperglycaemic, consider:

- **SU** or Short acting insulin

Review treatment when blood glucose has been controlled.
# Glycemic Management (Initial)

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or no symptoms</td>
<td>Hyperglycemia (FPG &gt; 150, RPG &gt; 250mg/dl)</td>
<td>Marked hyperglycemia (FPG &gt; 250, RPG &gt; 350mg/dl)</td>
</tr>
<tr>
<td>Negative ketones AND</td>
<td>HbA1c &gt; 7.0%</td>
<td>Significant weight loss</td>
</tr>
<tr>
<td>No acute concurrent illness AND</td>
<td>Does not meet criteria for mild or severe</td>
<td>Severe/significant symptoms</td>
</tr>
<tr>
<td>HbA1c &lt; 7.0%</td>
<td>DKA or Hyperosmolar state</td>
<td>Severe intercurrent illness or surgery</td>
</tr>
<tr>
<td>Diet + PA</td>
<td>Metformin or other OHA</td>
<td>Insulin</td>
</tr>
</tbody>
</table>
Figure — Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. (53).
Figure — Antihyperglycemic therapy in type 2 diabetes: general recommendations.
**Basal insulin** (usually with metformin +/- other noninsulin agent)

- **Start:** 10 U/day or 0.1/0.2 U/kg/day
- **Adjust:** 10-15% or 2-4 U once-twice weekly to reach FBG target.
- **For hypo:** Determine and address cause; ↓ dose by 4U or 10-20%.

**Add 1 rapid insulin injection before largest meal**

- **Start:** 4 U, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

If not controlled after FBG target is reached (or if dose >0.5U/kg/day), treat PPG excursions with Mealtime insulin. (Consider initial GLP-1-RA Trial)

**Add ≥ 2 rapid insulin injections before meal (“basal-bolus”)**

- **Start:** 4 U, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

**Change to premixed insulin twice daily**

- **Start:** divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

**If not controlled, consider basal-bolus**

**Flexibility**

- **More Flexible**
- **Less Flexible**

**Figure. Approach to starting and adjusting insulin in type 2 diabetes**
Initial Treatment Strategy

Mild
- Start NT and PA +/- MFM

Intermediate
- If after 6-8 weeks, target not met
- Start metformin
- Choose alternate drug if metformin C/I

Severe
- Start insulin immediately
- Initiate or Add Insulin

Titrate dose over 1-3 months.
- If patient reaching goals, periodically reassess medication use and effectiveness
- If discharged from hospital on new DM medications, re-assess medication dosing
INITIAL TREATMENT STRATEGY

Nutrition therapy (NT), physical activity, blood glucose monitoring and patient education are the cornerstones of diabetes management for all patients. Pharmacological management should be used in combination with nutrition therapy and physical activity. Current weight status and lifestyle should be considered when choosing initial pharmacological therapy.

Initial Presentation (Based on characteristics listed within each box)

Mild
- Mild or no symptoms AND
- Negative ketones AND
- No acute concurrent illness AND
- A1C ≤ 7.0%

Intermediate
- Hyperglycemia (e.g. FPG > 150 mg/dl\(^2\) or elevated random glucose > 250 mg/dl\(^2\) AND/OR
- A1C > 7.0\(^%\)
- Does not meet criteria for mild or severe

Severe
- Marked hyperglycemia (e.g. if FPG > 250 mg/dl, A1C > 10\%, random glucose > 350 mg/dl) OR
- Significant weight loss OR
- Severe/significant symptoms OR
- 2+ or greater ketonuria OR
- DKA/ hyperosmolar state OR
- Severe intercurrent illness or surgery

Start NT and physical activity and consider addition of metformin

If after 6-8 weeks, target not met

Start metformin. Choose alternate drug if metformin is contraindicated

Start insulin immediately

Titrate dose over 1-3 months. Reinforce NT and physical activity
- If initial therapy results in the patient reaching goals, periodically reassess medication use and effectiveness
- If patient discharged from hospital on new diabetes medications, re-assess medication choices and dosing

See page 3 section on “INITIATE OR ADD INSULIN”
ADVANCED ANTIDIABETES MEDICATION THERAPY

ADVANCING ANTIDIABETES MEDICATION THERAPY

If A1C >7% or not at individualized goals within 1-3 months:

- INITIATE ORAL ANTIDIABETES MEDICATION OR ADD ADDITIONAL ORAL DIABETES MEDICATION OF A DIFFERENT CLASS

- INITIATE OR ADD INSULIN $^{4,5,6}$
  - Consider starting with:
    - Long-acting insulin detemir or insulin glargine U-100 once or twice daily or once daily degludec or insulin glargine U-300 for basal therapy
    - Intermediate-acting insulin (NPH) once or twice daily, as part of a conventional program
    - Premixed insulin: 75/25 NPH/lispro, 50/50 NPH/lispro, 70/30 NPH/aspart, 70/30 NPH/regular insulin or 70/30 degludec/aspart once or twice daily
  - Suggested starting dose for insulin: 0.1-0.2 units/kg body weight/day
  - Titrate/adjust insulin dosage to achieve glucose goals

- ADD GLP-1 RECEPTOR AGONIST OR INSULIN TO ORAL ANTIDIABETES MEDICATION $^{4,5,6}$

IF 2 - 3 MONTHS AFTER ADDITION OF ORAL ANTIDIABETES MEDICATION, INSULIN OR GLP-1 AGONIST, A1C > 7% OR NOT AT INDIVIDUALIZED GOALS, CONSIDER: $^{4,5,6}$
- Combining GLP-1 with basal insulin
- Adding pre-meal rapid or short-acting insulin (e.g. aspart, glulisine, lispro, regular or human insulin inhalation) to intermediate or long-acting insulin
- Adding or switch to a premixed rapid acting and long acting insulin
- Adding basal insulin and adjusting the rapid or short-acting insulin
- Changing to multidose insulin therapy using combination of rapid, short, intermediate, or long-acting insulin
- Adding oral antidiabetes medication to improve glycemic control if already on insulin (metformin, sulfonylureas, meglitinide, D-phenylalanine, DPP-4 inhibitors, GLP-1 agonist, α-glucosidase inhibitors, SGLT-2 inhibitors, TZDs and colesevelam are approved for use in combination with insulin)
- If post-prandial excursions predominate, refer to endocrinologist for reassessment of therapy or for consideration of pramlintide use.
ADVANCED ANTIDIABETES MEDICATION THERAPY

ADVANCING ANTIDIABETES MEDICATION THERAPY

If A1C >7% or not at individualized goals within 1-3 months:

- INITIATE ORAL ANTIDIABETES MEDICATION OR ADD ADDITIONAL ORAL DIABETES MEDICATION OF A DIFFERENT CLASS
- INITIATE OR ADD INSULIN
  - Consider starting with:
    - Long-acting insulin detemir or insulin glargine U-100 once or twice daily or once daily degludec or insulin glargine U-300 for basal therapy
    - Intermediate-acting insulin (NPH) once or twice daily, as part of a conventional program
    - Premixed insulin: 75/25 NPH/lispro, 50/50 NPH/lispro, 70/30 NPH/aspart, 70/30 NPH/reg insulin or 70/30 degludec/aspart once or twice daily
  - Suggested starting dose for insulin: 0.1-0.2 units/kg body weight/day
  - Titrate/adjust insulin dosage to achieve glucose goals
- ADD GLP-1 RECEPTOR AGONIST OR INSULIN TO ORAL ANTIDIABETES MEDICATION

IF 2 - 3 MONTHS AFTER ADDITION OF ORAL ANTIDIABETES MEDICATION, INSULIN OR GLP-1 AGONIST, A1C > 7% OR NOT AT INDIVIDUALIZED GOALS, CONSIDER:

- Combining GLP-1 with basal insulin
- Adding pre-meal rapid or short-acting insulin (e.g. aspart, glulisine, lispro, regular or human insulin inhalation) to intermediate or long-acting insulin
- Adding or switch to a premixed rapid acting and long acting insulin
- Adding basal insulin and adjusting the rapid or short-acting insulin
- Changing to multidose insulin therapy using combination of rapid, short, intermediate, or long-acting insulin
- Adding oral antidiabetes medication to improve glycemic control if already on insulin (metformin, sulfonylureas, meglitinide, D-phenylalanine, DPP-4 inhibitors, GLP-1 agonist, α-glucosidase inhibitors, SGLT-2 inhibitors, TZDs and colesvelelam are approved for use in combination with insulin)
- If post-prandial excursions predominate, refer to endocrinologist for reassessment of therapy or for consideration of pralminite use.
WRONG COMBINATION OF OHAS

- Same mechanism of action
- Same receptors
- More than one agent from the same class of drugs
- More than three agents simultaneously
Figure — Antihyperglycemic therapy in type 2 diabetes: general recommendations.
WRONG INFORMATION OR BELIEFS

- Wrong belief about metformin
- Wrong belief about renal damage

THE HIGHER THE DOSAGE THE MORE EFFECTIVE THE TREATMENT
With long-term use, fear of metformin-associated lactic acidosis initially blighted the use of metformin in some countries.

However, a recent systematic review of prospective comparator trials and observational cohorts suggests that lactic acidosis is extremely rare, with a similar incidence in people with diabetes taking metformin or other glucose-lowering agents.
Indeed, many people have suggested that the contraindication of metformin use in chronic kidney disease stage 3 and beyond (estimated GFR [eGFR] <60 ml min$^{-1}$ [1.73 m$^{-2}$]) is too restrictive.

A further meta-analysis, however, supports the cautious use of metformin in individuals with chronic kidney disease with an eGFR as low as 30 ml min$^{-1}$ [1.73 m$^{-2}$], with appropriate dose reductions and meticulous ongoing measurement of renal function.
END STAGE OF DIABETES

Complications:
- DKA
- HONK

- Microvascular:
  - Retinopathy, cataract
  - Nephropathy
  - Peripheral neuropathy
  - Autonomic neuropathy
  - Foot disease

- Macrovascular:
  - Coronary circulation
  - Cerebral circulation
  - Peripheral circulation

No other treatment options that lower the damage to eye, kidney, etc.
Renal disease: End-stage renal failure (ESRF): GFR <15 mL/min/1.73m² or need for renal replacement therapy (RRT—dialysis or transplant)

Liver Diseases: Liver Transplant is required for
- Acute fulminant hepatic failure of any cause, including acute viral hepatitis.
- Chronic liver disease: usually for complications of cirrhosis, no longer responsive to therapy.
- Primary biliary cirrhosis: Need transplant when serum bilirubin is persistently >100 μmol/L or symptoms such as itching are intolerable.
- Chronic hepatitis B if HBV DNA negative or levels falling under therapy
- Chronic hepatitis C
- **Heart disease**: Cardiac transplant for Stage D heart failure (Refractory symptoms requiring special intervention)

- **Lung disease**: *Single lung transplantation* is used for end-stage emphysema, Pulmonary fibrosis, Primary pulmonary hypertension, Cystic fibrosis, Bronchiectasis, Emphysema – particularly α1-antitrypsin inhibitor deficiency, Eisenmenger’s syndrome.
Pancreas disease:

- **Type 1 diabetes** is a T cell-mediated autoimmune disease involving destruction of the insulin-secreting β cells in the pancreatic islets. Progressive loss of β cell function takes place over a prolonged period (months to years), but marked hyperglycaemia, accompanied by the classical symptoms of diabetes, occurs only when **80–90% of the functional capacity of β cells has been lost.**

- Insulin treatment
- No need to do pancreas transplant
HYPOGLYCEMIA

- Plasma glucose ≤3mmol/L.

- Threshold for symptoms varies.

**Symptoms:**
- *Autonomic*—Sweating, anxiety, hunger, tremor, palpitations, dizziness.
- *Neuroglycopenic*—Confusion, drowsiness, visual trouble, seizures, coma. Rarely focal symptoms, eg transient hemiplegia. Mutism, personality change, restlessness and incoherence may lead to misdiagnosis of alcohol intoxication or even psychosis.
Fasting Hypoglycemia

- **Exogenous drugs**, eg *insulin*, oral hypoglycaemics. Does she have access to these (diabetic in the family)? Body-builders may misuse insulin to help stamina. Also: *alcohol*, eg a binge with no food; *aspirin poisoning*; ACE-i; β-blockers; *pentamidine*; quinine sulfate; aminoglutethamide; insulin-like growth factor.

- Pituitary insuiciency.
- Liver failure, plus some rare inherited enzyme defects.
- Addison’s disease. Islet cell tumours (insulinoma) and immune hypoglycaemia (eg anti-insulin receptor antibodies in Hodgkin’s disease).
- Non-pancreatic neoplasms, eg fibrosarcomas and haemangiopericytomas.

Post-prandial Hypoglycemia

- after gastric/bariatric surgery (‘dumping’), and
- in type 2 DM

Insulinoma:

Often benign (90–95%) pancreatic islet cell tumour is sporadic or seen with **MEN-1**. It presents as fasting hypoglycaemia, with Whipple’s triad: **1** Symptoms associated with fasting or exercise **2** Recorded hypoglycaemia with symptoms **3** Symptoms relieved with glucose.
Other causes of hypoglycemia:

- Hypoglycaemia with other tumours
- Hepatic and renal causes of hypoglycaemia
- Endocrine causes of hypoglycaemia
- Drug-induced hypoglycaemia
- Alcohol-induced hypoglycaemia
- Factitious hypoglycaemia
HYPERINSULINAEMIA

- Due to insulin resistance associated with obesity, PCOS and the metabolic syndrome

- One of the diabetic risk factors for macrovascular complications
The Somogyi effect (first discovered by Dr. Michael Somogyi) is caused by nighttime hypoglycemia, which leads to a rebound hyperglycemia in the early morning hours.

When blood glucose drops during the night, hormones are released which trigger the liver to release stored glucose. This normally results in a high-fasting glucose reading the next morning.

The Somogyi effect is a result of having extra insulin the body before bedtime, either from not having a bedtime snack, or from having your long-acting insulin not at the proper dose.

The Somogyi effect occurs mainly with type 1 diabetics.
SOMOGYI PHENOMONON

Normal glucose at night

High Insulin given at 9pm

Leads to hypoglycemia
At around 2-3pm

Due to hypoglycemic stress

Glucagon and other stress hormones are released

Leads to hyperglycemia
In morning

SOMOgyi = SO MOch insulin

Dawn = Down insulin
It is similar to the dawn phenomenon in that both lead to high morning blood glucose readings as a result of a hormone release that causes the liver to release glucose into the blood.

The difference is that dawn phenomenon is not caused by hypoglycemia, but by a random release of the triggering hormones.

-Early morning (3-4am) hypoglycemia due to excess administration of Insulin at night but again at morning around 6-7am there will be hyperglycemia.

Explanation of 6am hyperglycemia is given below

When the blood glucose level falls below normal, the body responds by releasing the endocrine hormone glucagon as well as the stress hormones epinephrine, cortisol and growth hormone.
- Glucagon facilitates release of glucose from the liver that raises the blood glucose immediately, and
- the stress hormones cause insulin resistance for several hours, sustaining the elevated blood sugar.
TREATMENT OF SOMOGYI OR DAWN PHENOMENON

- Check blood glucose level at 2-3 am to identify whether it is Somogyi or Dawn effect (hypoglycemia in Somogyi and hyperglycemia in Dawn)

- Time for taking long-acting insulin is changed

- Consume extra dosage of insulin if there is a symptom of Dawn phenomenon
CONSIDERATION TO LIFE STYLE MODIFICATION
CONSIDERATION TO QUALITY OF LIFE AND DDS17
DIABETES DISTRESS SCALE (DDS17)

- Living with diabetes can sometimes be tough.
- There may be many problems and hassles concerning diabetes and they can vary greatly in severity.
- Problems may range from minor hassles to major life difficulties.
- Listed below are 17 potential problem areas that people with diabetes may experience.
- Consider the degree to which each of the 17 items may have distressed or bothered **DURING THE PAST MONTH** and circle the appropriate number.

---

<table>
<thead>
<tr>
<th></th>
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<th>Not a Problem</th>
<th>A Slight Problem</th>
<th>A Moderate Problem</th>
<th>Somewhat Serious Problem</th>
<th>A Serious Problem</th>
<th>A Very Serious Problem</th>
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<td>Feeling that my doctor doesn't know enough about diabetes and</td>
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<td>Feeling that diabetes is taking up too much of my mental and</td>
<td>1</td>
<td>2</td>
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</tr>
<tr>
<td>5</td>
<td>Feeling that my doctor doesn't give me clear enough directions</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>on how to manage my diabetes.</td>
<td></td>
<td></td>
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<td>6</td>
<td>Feeling that I am not testing my blood sugars frequently enough.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
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<tr>
<td>7</td>
<td>Feeling that I will end up with serious long-term complications,</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
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<tr>
<td></td>
<td>no matter what I do.</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>8</td>
<td>Feeling that I am often failing with my diabetes routine.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<td>6</td>
</tr>
<tr>
<td></td>
<td>Not a Problem</td>
<td>A Slight Problem</td>
<td>A Moderate Problem</td>
<td>Somewhat Serious Problem</td>
<td>A Serious Problem</td>
<td>A Very Serious Problem</td>
<td></td>
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<td>---</td>
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<td></td>
</tr>
<tr>
<td>9. Feeling that friends or family are not supportive enough of self-care efforts (e.g. planning activities that conflict with my schedule, encouraging me to eat the &quot;wrong&quot; foods).</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>10. Feeling that diabetes controls my life.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>11. Feeling that my doctor doesn't take my concerns seriously enough.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>12. Feeling that I am not sticking closely enough to a good meal plan.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>13. Feeling that friends or family don't appreciate how difficult living with diabetes can be.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>14. Feeling overwhelmed by the demands of living with diabetes.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
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<tr>
<td>15. Feeling that I don't have a doctor who I can see regularly enough about my diabetes.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>16. Not feeling motivated to keep up my diabetes self management.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>17. Feeling that friends or family don't give me the emotional support that I would like.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
The DDS17 yields a **total diabetes distress score plus 4 subscale scores**, each addressing a different kind of distress. To score, simply sum the patient’s responses to the appropriate items and divide by the number of items in that scale.

Current research suggests that

- a mean item score 2.0 – 2.9 should be considered ‘moderate distress,’
- a mean item score > 3.0 should be considered ‘high distress.’
- Current research also indicates that associations between DDS scores and behavioral management and biological variables (e.g., A1C) occur with DDS scores of > 2.0.
- Clinicians may consider moderate or high distress worthy of **clinical attention**, depending on the clinical context.

---

<table>
<thead>
<tr>
<th>Section</th>
<th>Formula</th>
<th>Mean Item Score</th>
<th>Moderate Distress or Greater? (mean item score &gt; 2)</th>
</tr>
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<tbody>
<tr>
<td><strong>Total DDS Score</strong></td>
<td>a. Sum of 17 item scores.</td>
<td></td>
<td>yes__ no__</td>
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<tr>
<td></td>
<td>b. Divide by:</td>
<td>17</td>
<td></td>
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<tr>
<td></td>
<td>c. Mean item score:</td>
<td></td>
<td></td>
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<tr>
<td><strong>A. Emotional Burden</strong></td>
<td>a. Sum of 5 items (2, 4, 7, 10, 14)</td>
<td></td>
<td>yes__ no__</td>
</tr>
<tr>
<td></td>
<td>b. Divide by:</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. Mean item score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate distress or greater? (mean item score &gt; 2)</td>
<td>yes__ no__</td>
<td></td>
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<tr>
<td><strong>B. Physician Distress</strong></td>
<td>a. Sum of 4 items (1, 5, 11, 15)</td>
<td></td>
<td>yes__ no__</td>
</tr>
<tr>
<td></td>
<td>b. Divide by:</td>
<td>4</td>
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<td></td>
<td>c. Mean item score:</td>
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<td>Moderate distress or greater? (mean item score &gt; 2)</td>
<td>yes__ no__</td>
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<tr>
<td><strong>C. Regimen Distress</strong></td>
<td>a. Sum of 5 items (6, 8, 3, 12, 16)</td>
<td></td>
<td>yes__ no__</td>
</tr>
<tr>
<td></td>
<td>b. Divide by:</td>
<td>5</td>
<td></td>
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<tr>
<td></td>
<td>c. Mean item score:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Moderate distress or greater? (mean item score &gt; 2)</td>
<td>yes__ no__</td>
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<tr>
<td><strong>D. Interpersonal Distress</strong></td>
<td>a. Sum of 3 items (9, 13, 17)</td>
<td></td>
<td>yes__ no__</td>
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<td></td>
<td>b. Divide by:</td>
<td>3</td>
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<tr>
<td></td>
<td>c. Mean item score:</td>
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<td></td>
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<tr>
<td></td>
<td>Moderate distress or greater? (mean item score &gt; 2)</td>
<td>yes__ no__</td>
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</tbody>
</table>
ASSOCIATIONS BETWEEN DDS17 SCORES AND KEY DIABETES VARIABLES

A

B

C

D

Source: Diabetes Care © 2012 American Diabetes Association, Inc.
Quality of life

Let’s find out more about the well-being of diabetic patients!
8+1 DIMENSION OF QUALITY OF LIFE

- Material living conditions
- Productive or main activity
- Health
- Education
- Leisure and social interaction
- Economic and physical safety
- Governance and basic rights
- Natural and living environment
- Overall experience of life
Fig (5): Other secondary end points favoring surgery over medical treatment.
DIABETES-RELATED DISTRESS
HOW TO TREAT THE DAWN EFFECT

- Take long-acting insulin in the evening so its peak action happens when the blood sugars start rising.
- Change the type of insulin taken in the evening.
- Start incorporating a continuous glucose monitor (CGM) to avoid the dawn phenomenon.
- Take a small amount of insulin overnight if blood sugar goes up during the night.
- Switch to an insulin pump, which can be programmed to automatically increase basal rates in the morning.
<table>
<thead>
<tr>
<th>States and regions</th>
<th>Male</th>
<th>Female</th>
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<td>3,769,778</td>
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<td>Mandalay</td>
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<td>Ayeyarwaddy</td>
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<td>3,226,030</td>
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<td>Shan</td>
<td>3,087,257</td>
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<td>Sagai</td>
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<td>Magway</td>
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<td>Rakhine</td>
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<td>Mon</td>
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<td>Kachin</td>
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<td>878,611</td>
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<td>Taninthayi</td>
<td>724,536</td>
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<tr>
<td>Nay-pyi-daw</td>
<td>601,072</td>
<td>636,966</td>
<td>1,2388,038</td>
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<td>Chin</td>
<td>243,326</td>
<td>265,033</td>
<td>508,359</td>
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<td>Kayar</td>
<td>154,330</td>
<td>155,883</td>
<td>310,213</td>
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<td><strong>Total</strong></td>
<td><strong>25,647,847</strong></td>
<td><strong>27,740,101</strong></td>
<td><strong>53,387,948</strong></td>
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