Achieving glycaemic control

Diabetes is SA’s second biggest killer but there is a critical lack of consensus among experts and policymakers about how this growing epidemic should be tackled.

**Background**

According to Distiller et al, who focusses on the SA cohort that forms part of the International Diabetes Management Practice Study (IDMPS) that aims to describe the characteristics of management and achievement of therapeutic targets in patients with diabetes mellitus (DM), “The incidence of diabetes mellitus, particularly type 2 diabetes is increasing dramatically across the world because of increasing obesity, sedentary lifestyle and population ageing, and is the cause of substantial morbidity and mortality.

“This alarming rate of increase in incidence together with the potential complications of disease renders this disease to be a great challenge facing the healthcare system. The major goal of treatment of diabetic patients is to achieve good (near normal) metabolic control, thus preventing long term complications. Despite all recommendations, a large number of patients are not well-controlled, and do not reach the target of HbA1C value below 7%, indicating a need to better assess the current practices in diabetes management.”

The SEMDSA Expert Committee, is in agreement that the standard of treatment for type 2 diabetes in SA at all levels are not adequate, and that the majority of patients are managed at primary healthcare facilities.

“Type 2 diabetes is a heterogeneous disease, with the underlying mechanism ranging from predominantly insulin resistance with relative insulin deficiency, to predominantly an insulin secretory defect with lesser degrees of insulin resistance. The relative contribution of each abnormality varies between individuals, as well as within the same individual at different stages of the disease. People with type 2 diabetes are heterogeneous; diabetes is prevalent across all socio-economic strata, ethnic groups, age groups and weight categories, in individuals with highly variable nutrient intakes and levels of physical activity”, said Dr Aslam Amod, Durban-based endocrinologist who is also the Chairperson for the country’s 2017 Guidelines for the Management of Type 2 diabetes mellitus. *Journal of Endocrinology, Metabolism and Diabetes of South Africa*, that was launched in May 2017.

The guidelines are developed every few years by the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), in consultation with officials in the Department of Health (DoH) and other experts, and are meant to guide the treatment and prevention of diabetes in both the public and private sector and ‘reflect the best available evidence at the time’.

Due to the heterogeneous nature of the disease, the response to treatment needs to reflect this diversification.

“Type 1 diabetes, which accounts for only 5-10% of cases, results from pancreatic beta-cell destruction leading to absolute insulin deficiency. These patients are prone to ketoacidosis, coma and death. Type 1 diabetes

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**Atheological classification of DM**

The American Diabetes Society, the World Health Organisation and the Canadian Diabetes Association, use the atheological classification for diabetes mellitus, and it is endorsed by JEMDSA.

I. Type 1 diabetes (β cell destruction, usually leading to absolute insulin deficiency)

A. Immune mediated

B. Idiopathic

II. Type 2 diabetes

May range from predominantly insulin resistance with relative insulin deficiency, to a predominantly secretory defect with insulin resistance. Also includes a subset that have ketosis-prone diabetes.

III. Other specific types

A. Genetic defects of β cell function

Maturity onset diabetes of the young (MODY) – currently 11 subtypes, neonatal diabetes mellitus, mitochondrial DNAs

B. Genetic defects in insulin action

Type A insulin resistance, Donahue syndrome (Leprechaunism), Rabson Mendenhall syndrome, lipoatrophic diabetes others

C. Diseases of the exocrine pancreas

Pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, haemochromatosis, fibrocalkulous pancreatopathy, others

D. Endocrinopathies

Acromegaly, Cushings syndrome, glucagonoma, phaeochromocytoma, hyperthyroidism, others

E. Drug or chemical induced

Glucocorticoids, nicotinic acid, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, interferon, pentamidine, diazoxide, atypical antipsychotics, highly active antiretroviral therapy (HAART)

F. Infections

Congenital rubella, cytomegalovirus others

G. Uncommon forms of immune-mediated diabetes

‘Stiff-man’ syndrome, anti-insulin receptor antibodies, others

H. Other genetic syndromes sometimes associated with diabetes

Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreich ataxia, Huntington chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome, others

IV. Hyperglycaemia first detected in pregnancy

A. Gestational diabetes

B. Diabetes mellitus in pregnancy

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The Specialist Forum | Vol. 17 No. 5
The concept of patient-centred care incorporates patients as partners in their healthcare.

Achieving optimal pharmacological approaches

“The optimal pharmacological approach to glucose control for any individual patient varies, which is why many international guidelines have endorsed individualised management, with no restriction on the choice of glucose lowering drug after initial metformin therapy. The concept of patient-centred care integrates patients as partners in their healthcare. In practice, this means providing care that is “respectful of and responsive to individual patient preferences, needs and values, and ensures that patient values guide all clinical decisions”, states the authors of the guideline.

“The SEMDSA approach to glycaemic control does not lose focus of patient-centred care but attempts to provide guidance about appropriate therapeutic choices for primary healthcare practitioners managing patients at different stages of type 2 diabetes. This is done by attempting to match the therapeutic options with the diverse clinical profiles encountered in patients, while still offering a rational approach to drug management.”

Within the context of the South African healthcare system, this approach remains critical, because nurses at primary healthcare clinics need to have access to medicines that promotes the lowest probability of harm.

“The purpose of the algorithm, consequently, is to improve glycaemic control by attempting to give primary healthcare practitioners the tools to achieve this in a way that is both safe and effective,” state the authors.

2017 SEMDSA algorithm for the management of type 2 diabetes in non-pregnant adults without metabolic decompensation or cardiovascular disease

<table>
<thead>
<tr>
<th>Intensify lifestyle interventions throughout</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complex therapy</strong></td>
</tr>
<tr>
<td>Metformin</td>
</tr>
<tr>
<td><strong>Combination insulin</strong></td>
</tr>
<tr>
<td>Premix insulin</td>
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<tr>
<td>Basal-plus prandial insulin</td>
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<tr>
<td><strong>Combination injectable</strong></td>
</tr>
<tr>
<td>Oral agent/s + Basal insulin</td>
</tr>
<tr>
<td>+ GLP-1RA</td>
</tr>
<tr>
<td>Insulin (basal, premix or basal-bolus)</td>
</tr>
<tr>
<td>+ DPP-4i / SGLT2 / GLP-1RA</td>
</tr>
<tr>
<td>[Specialist led team]</td>
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</tbody>
</table>

Legend

- Preferred options
- Alternative options (without motivation)
- Not recommended if HbA1c target is attainable with other agents

Provisions of the algorithm

A patient managed at specialist care level often has comorbidities and more severe disease requiring more complex therapies, states guidelines.

The algorithm applies to the stable type 2 diabetes patients who have suboptimal glycaemic control; it does not apply to the metabolically decompensated patient with severe symptomatic hyperglycaemia; those patients usually need referral for intensive management.

It does not apply to patients with severe microvascular or macrovascular complications; these patients should also be managed under specialist supervision, and the optimal treatment options differ from this algorithm.

This can only serve as a guideline and cannot, and should not be applied rigidly to the very heterogeneous type 2 diabetes population.

Monotherapy

In newly diagnosed patients the target HbA1C should be <6.5% unless there are factors that preclude this. Metformin remains the drug of first choice at diagnosis, and if tolerated, should be continued until contraindicated. If tolerability is poor, consider switching to the extended release formulation.

If metformin is contraindicated or not tolerated consider gliclazide MR if the HbA1C target is <7%, or...
Basal plus therapy: adding a DPP-4 inhibitor, pioglitazone or an SGLT2 inhibitor based on the patient profile.

Fixed dose combinations of a DPP-4 inhibitor + metformin may have compliance and cost advantages. GLP-1RA and insulin offer no compelling advantages at this stage for the added cost/complexity, provided the HbA1C target is still attainable.

**Triple therapy**

If the HbA1C is above the individualised target (which should still be <7% for most patients) with two oral agents, consider adding either a third oral agent or an injectable agent (GLP-1RA or basal insulin).

Consider patient preference, comorbidities, and ability to access medicines as well as the properties of each drug (Figure I and text recommendations) in selecting an appropriate option.

Do not combine a GLP-1RA with either a DPP-4 inhibitor or an SGLT2 inhibitor, and do not combine pioglitazone with insulin. Expected HbA1C reductions are similar when adding a GLP-1RA or titrated basal insulin, and both are slightly superior to triple oral therapy. Insulin initiation must be accompanied by ongoing patient education, appropriate SMBG, self-titration of insulin doses, frequent review (initially) and counselling regarding hypoglycaemia.

Use basal insulin with the lowest acquisition cost. Switch NPH to a basal analogue insulin if nocturnal hypoglycaemia is problematic.

**Complex therapy**

When triple therapy is inadequate at maintaining or achieving glycaemic targets, combination injectable (complex) therapy will become necessary.

The options are:

- `Basal plus` therapy: adding one or more prandial doses of insulin to basal insulin
- Premix insulin: using fixed ratios of pre-mixed insulins
- Combination basal insulin and GLP-1RA therapy.

Each of these options has advantages and disadvantages that will need to be discussed with the patient. For all these options metformin should be retained; other oral agents should be stopped to reduce the cost and complexity of the regimen,” states the authors.

**References:**


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**Figure I: Some of the factors to consider when choosing glucose lowering drug therapy at various stages of type 2 diabetes. Information represents a synthesis of data from various sources.**

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Mean HbA1C lowering</th>
<th>Hypoglycaemia</th>
<th>Weight</th>
<th>Side effects*</th>
<th>Rare serious adverse events</th>
<th>Treatment complexity</th>
<th>Cost (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliclazide MR</td>
<td>-1%</td>
<td>Yes</td>
<td>+0 to 1.5kg</td>
<td>None</td>
<td>None</td>
<td>Simple</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>-1%</td>
<td>Rare</td>
<td>+3 to 5kg</td>
<td>Oedema, CHF</td>
<td>Fractures, bladder cancer</td>
<td>Complex</td>
<td>100-200</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>-0.7%</td>
<td>Rare</td>
<td>Neutral</td>
<td>None</td>
<td>Pancreatitis, tumours</td>
<td>Simple</td>
<td>200-300</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>-1.2%</td>
<td>Rare</td>
<td>-3.0kg</td>
<td>Common: GI</td>
<td>Pancreatitis, tumours</td>
<td>Intermediate</td>
<td>650-2100</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>-1%</td>
<td>Rare</td>
<td>-3.0kg</td>
<td>Common: Dehydration</td>
<td>Fractures, Amputation DKA</td>
<td>Complex</td>
<td>Unknown</td>
</tr>
<tr>
<td>Basal insulin</td>
<td>-1.2%</td>
<td>Yes</td>
<td>+3 to 5kg</td>
<td>None</td>
<td>None</td>
<td>Complex</td>
<td>200-1000$</td>
</tr>
</tbody>
</table>

*Side effects other than weigh gain and hypoglycaemia; GI=gastrointestinal; GU= genitourinary

SAE= serious adverse events; these are rare but still need to be considered; Cost is based on single exit price in the private health sector; figures may differ in the public health sector. *Cost of insulin depends on dose. In the 4T study basal insulin dose ranged from 0.5 u/kg to 1.0 u/kg from year 1 to year 3. This translates to 40 to 80u/day for intensive basal insulin therapy in an 80 kg person. Adverse events refer to common adverse events that impact tolerability and drug discontinuation rates. Treatment complexity considers the ease with which the drug can be prescribed; higher complexity may involve greater resources (consulting time or other resources) in screening for contraindications, educating the patient about the treatment, the patient’s required investment in complying with the treatment (e.g. injecting, SMBG and dose titration) as well as resources to monitor and treat adverse effects.*
The incidence of diabetes mellitus, particularly type 2 diabetes is increasing dramatically across the world because of:

a. increasing obesity, sedentary lifestyle and population not ageing.
b. increasing obesity, active lifestyle and population ageing.
c. decreasing obesity, sedentary lifestyle and population ageing.
d. increasing obesity, sedentary lifestyle and population ageing.

The major goal of treatment of diabetic patients is to achieve good (near normal) metabolic control.

a. True
b. False

despite all recommendations, a large number of patients are not well-controlled, and do not reach the target of HbA1C value below ______%.

a. 10%
b. 7%
c. 3%
d. 12%

Type 2 diabetes is a heterogeneous disease, with the underlying mechanism ranging from predominantly insulin resistance with relative insulin efficiency, to predominantly an insulin secretory defect with lesser degrees of insulin resistance.

a. True
b. False

Due to the nature of the disease, the response to treatment needs to reflect this diversification.

a. Unique
b. Heterogeneous
c. Similar
d. Homogeneous

Consider initial dual therapy with + gliclazide MR if the patient has symptomatic hyperglycaemia and HbA1C is >9% at diagnosis.

a. Metformin
b. DPP-4 inhibitor
c. Pioglitazone
d. SGLT2 inhibitor

If the HbA1C target is not achieved after _____ months of metformin or subsequently rises, consider adding gliclazide

a. A third oral agent
b. An injectable agent
c. A third oral agent or an injectable agent
d. A fourth oral agent or an injectable agent

When triple therapy is inadequate at maintaining or achieving glycaemic targets, combination injectable (complex) therapy will become necessary.

a. True
b. False

Fixed dose combinations of a DPP-4 inhibitor + metformin may have compliance and cost disadvantages.

a. Four
b. Six
c. Five
d. Three

This is to state that I have participated in the CPD-approved programme and that these are my own answers.