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Clinical Guidelines

2019

The Use of Antibody Testing in the Management of Diabetes Mellitus

When should the Antibody Test be used?

If a person has clinical symptoms of type 2 diabetes with early manifestation, below the age of 55 years, confirm diagnosis with antibody tests (i.e. If there is any doubt in Type-classification, perform the test).

Latent autoimmune diabetes of adulthood (LADA) classification: If a person with type 2 diabetes is suspected of being LADA, perform the antibody test to detect for an autoimmune response, with impending insulin dependency.

What is the Antibody Test?

Detection of antibodies raised against GAD and IA-2 are both good indicators of an autoimmune response (type 1 diabetes).

Euroimmune Anti-GAD and Anti-IA-2 ELISA kits are run approximately once per week (once sufficient samples have been received) by most commercial labs. The test takes 2 days to complete.

Where do I Send the Samples?

- Contact your local pathology laboratory for further details on the requirements and procedure
- Sample required is usually a 7 ml clotted SST tube.

When should the Antibody Test NOT be used?

Type 1 risk assessment: Do not use as a routine predictive tool of type 1 diabetes in related family members. To date there are no early intervention treatment guidelines available, so there is no clinical relevance. Testing for predictive purposes is considered ethically unacceptable.

People with type 2 diabetes who fail to respond to oral treatment should be placed directly onto insulin, if required, without prior antibody testing.

The Treatment of Patients in Mild to Moderate Diabetic Ketoacidosis

On Admission:

- Assess level of consciousness (Glasgow Coma Scale) and symptoms of nausea / presence of vomiting
- Check
  - BP
  - Pulse
  - Respiratory Rate
  - Temperature
  - Blood glucose (finger prick)
  - Urine for ketones
- Contact the attending doctor and report findings whilst the following is done:
- Start intravenous therapy of Normal Saline, 1 litre to run over 1 hour
- Take venous blood for
  - Urea & Electrolytes
  - Creatinine
- Administer 6 IU **short / rapid acting** (Humulin R / Humalog / NovoRapid / Apidra) insulin as a stat IVI bolus.

Thereafter:

- Monitor Capillary Blood Glucose (finger prick) every 2 hours (continue nursing observations as required)
- Check **ALL** urine passed for ketones
- **Intravenous therapy:** Continue with normal saline
  - Rate to be determined by Doctor
  - KCl replacement to be determined by Doctor
- **Insulin:** 6 IU **short / rapid acting** insulin IVI as bolus hourly

Continue above regimen until blood glucose is below 12 mmol/l on 2-hourly blood glucose testing. As soon as a blood glucose of below 12 mmol/l is documented, change to the following regimen:

Intravenous therapy: 5 % Dextrose Water, 1 litre + 1.5 g (20 mmol) KCl **alternating with** 5 % Dextrose Saline, 1 litre + 1.5 g (20 mmol) KCl, 8 hourly.

Insulin: short / rapid acting insulin to be given as IVI bolus hourly as per 2-hourly capillary blood glucose measurements according to the last measured blood glucose as per the following scale:

Blood Glucose (mmol/l)	No. of Units short / rapid acting Insulin to be given Hourly
< 4	Nil
4.1 – 10.0	5u
10.1 – 16.0	6u
16.1 – 20.0	8u
> 20.0	10u

Note:

- Intravenous Dextrose and hourly insulin to be continued until urine is free of ketones
- Intermediate / Long-acting insulin may be administered **subcutaneously** addition to the IV insulin
- Blood gas estimations are not done routinely – only on instruction from Doctor
- Patients are treated in a Medical Ward unless the Doctor requests transfer to ICU
- **ALL** urines to be tested for ketones

The Perioperative Management of Diabetes Mellitus

Introduction

Many different regimens have been described and used with varying amounts of success in managing diabetes during surgery. The commonest regimen utilizes the continuous intravenous infusion of insulin and glucose. However, this requires very good nursing care, unfortunately seldom found in our hospitals today. It is usually utilized only in the following circumstances:

1. With major surgery, (e.g. coronary artery bypass, vascular surgery etc.)
2. It requires an anaesthetist who fully understands the regimen.
3. Patients are usually nursed in an Intensive Care Environment post-op.

Unless one has fully trained nursing staff and an anaesthetist and surgeon all of whom understand insulin infusion techniques, it is best to use a simpler approach.

Surgery is divided into *major* and *minor* and for the purposes of this approach, they are defined as follows:

- *Major surgery*: patient unable to eat post-op
- *Minor surgery*: patient able to eat post-op

All surgery in patients with diabetes should be scheduled for first thing in morning if possible!

There are thus four possible scenarios -

1. Minor Surgery in a patient on Oral Agents:

- This should be scheduled for first thing in the morning.
- Patient omits Oral Agents in the morning. Takes them with a light meal as soon as he / she recovers from anaesthetic.
- NO Intravenous glucose to be given
- If patient requires IV therapy, it should be Normal Saline.

2. Major Surgery in a patient on Oral Agents:

Before theatre:

- Check blood glucose (finger prick)
- Start IV 5 % Dextrose-Water alternating with 5 % Dextrose-Saline 8 hourly
- Add KCl as necessary (Usually 1 amp / 1.5 g per litre).
- Give empirical dose of 30 IU of a basal insulin (Protaphane, Humulin N, Lantus or Levemir) sub cut.
- Repeat this daily until IV therapy discontinued. (Dose can be adjusted depending on response).
- Use additional **short / rapid acting** insulin (Actrapid / Humulin R / Humalog / NovoRapid / Apidra etc.) subcutaneously 6 hourly according to 6 hourly finger prick blood glucose - see scale of 'top-up' insulin doses below.
- Today many units have developed their own algorithms for IV insulin infusions and these are now considered the 'gold standard' of care, provided they are understood and implemented by trained staff.

Post-Op:

Continue as above. As soon as patient off IV therapy, stop insulin and resume OHAs.

3. Minor surgery in patients on insulin:

- This must be done first in morning if problems are to be avoided.
- Give normal insulin dose the day and night before surgery.
- Omit insulin on morning of surgery

Before theatre:

- Check blood glucose
- If over 10 mmol/l, give decreased dose of normal morning insulin.
- If <10 mmol/l, no insulin.
- If IV therapy necessary, use Normal Saline only NOT Dextrose.

Post-Op:

- As soon as patient awake, give normal morning insulin dose and follow with Breakfast.

4. Major Surgery in patients on Insulin:

Before theatre:

- Give normal insulin dose the day or night before surgery.
- On the morning of surgery check finger prick blood glucose
- Commence 5 % Dextrose-Water + 1.5 g (1 amp) KCl and alternate this with 5 % Dextrose-Saline + 1.5 g KCl 8 hourly.

Post-Op: Three options depending on extent / seriousness of surgery and patients general condition:

1. Today many units have developed their own algorithms for IV insulin infusions and these are now considered the 'gold standard' of care, provided they are understood and implemented by trained staff.

2. Give decreased amount of patient's TOTAL insulin dose (Add total 24-hour insulin doses together and divide by 3) as NPH (Protaphane or Humulin N) when IV therapy commenced and give second equivalent dose as NPH in evening before bed. **Or** give $^{2}/_{3}$ the total dose as once daily insulin glargine (Lantus, Optisulin, Basaglar) or insulin detemir (Levemir). To this, add 6 hourly **short / rapid acting** insulin according to 6 hourly finger prick blood glucose as per 'top-up' scale below. Continue this until patient able to discontinue IV and eat.

3. Give **short / rapid acting** insulin 6 IU IVI hourly and monitor finger-prick blood glucose hourly. Titrate dose of insulin up or down by 2 IU to 'clamp' blood glucose between 6-8 mmol/l. This is the preferred regimen for unstable patients, more major surgery, and delivery / Caesarean for pregnant women. However, it requires trustworthy nursing and proper instruction of nursing staff.

Suggested 'Top-up' Scale (as per 2. & 4.)

Blood Glucose (mmol/l)	Short / rapid acting Insulin Dose (IU)
<6	Nil
6.1 – 8	4
8.1 – 10	6
10.1 – 15	8
15.1 – 20	10
>20	12

This scale can be adjusted up or down by 2 IU across the board depending on patient response

Protocol for the Treatment of Type 1 Diabetes in Members of the CDE Diabetes Management Programme

The treatment of type 1 diabetes is highly individualised and the treatment regimens used depend on many factors, including the patients age, level of literacy, work situation, family support systems and the presence or absence of both microvascular and macrovascular complications. As such, a detailed protocol for the treatment of type 1 diabetes is neither possible nor desirable. However, certain key management procedures are specified and need to be adhered to:

1. **Patient Education:** Every person with type 1 diabetes must undergo adequate diabetes education. The amount of education provided will depend upon the individual's needs and requirements, but will be not less than:
   i. detailed training in the causes, management and prevention of hypoglycaemia / ketonuria / ketoacidosis, insulin action and insulin adjustment,
   ii. the performance of home blood glucose monitoring and the interpretation of results, and
   iii. The importance of and means of attaining and maintaining diabetes control.

   Thereafter, patients will be expected to attend a session with the diabetes educator at least twice a year. More intensive education programmes will be provided for patients who request or are deemed suitable for this.

2. **Emergency Care:** Every accredited CDE Preferred Provider (Diabetes Centre) is contractually obliged to provide a 24-hour emergency telephone contact number ('Hotline') so that all patients have emergency access when and if needed. Every patient must be given a Glucagon Hypo kit and ketone testing strips to enable community management of acute diabetes complications.

3. **Other Health Care professionals:** All patients must have access to and consult with a dietician, podiatrist and ophthalmologist as per the CDE 'Minimum Care Guidelines'.

4. **Insulin Regimens:** Type 1 diabetes is a condition that results in a total lack of endogenous insulin. For survival, insulin replacement therapy must be given. Any insulin regimen used must consider prandial as well as basal insulin requirements and must be administered at least twice daily. The insulin to be used is not circumscribed as there are numerous options available. The selection of an appropriate regimen must be individualised, dependant on several factors and should be a joint decision of the doctor, diabetes educator and the patient. As a general principle, a multiple injection regimen is preferred, using human or analogue insulins and dependent upon the patient's individual requirements.

   Insulin infusion pump therapy can be considered when indicated (as per 'Continuous subcutaneous insulin infusion therapy in type 1 diabetes: 2013 clinical guidelines and recommendations from the Association of Clinical Endocrinologists of South Africa (ACE-SA)).

5. **Home Glucose Monitoring:** every patient will be supplied with a blood glucose monitoring meter and sufficient testing strips for their needs. Patients should be expected to test at least 3 times a day and should receive between 100 and 150 testing strips per month. More will be supplied in specific instances when required, such as pregnancy, adolescence, patients on insulin pumps or in the context of intercurrent illness.

6. **Continuous Glucose monitoring (CGM):** Several devices are now available for CGM and new ones are being introduced on a regular basis. CGM had generally been recommended as an adjunct to pump therapy, but recently is being adopted by patients on multiple injection regimens. As a general principle, CGM should be commenced by Diabetologists or CDE Centres of Excellence who have the expertise to counsel, support and guide patients in its use.

7. **Doctor's Responsibilities:** These are outlined in the CDE 'Minimum Care Guidelines'. Every patient will see the doctor at least once every 6 months. However, when deemed necessary, such as unstable or uncontrolled patients, children and adolescents, and in pregnancy, visits that are more frequent are expected, as often as the individual situation requires. The patient's doctor also shares risk, being responsible for hospital costs for any acute diabetes admission, as outlined in the CDE 'Minimum Care Guidelines'.

Treatment Targets: The following are recommended, according to individual patient circumstances

	Adults	Hypo unawareness	16-18 years	6-16 years	2-5 years	<2 years
HbA1c	<7.5 %	<8.5 %	<7.5 %	7.5-8.5 %	7.5-9 %	7.5-9 %
Fasting Glucose	4-6.7 mmol/l	4-8 mmol/l	4.4-6.7 mmol/l	4.4-10 mmol/l	5.5-12 mmol/l	5.5-14 mmol/l

Protocol for the Treatment of Type 2 Diabetes in Members of the CDE Diabetes Management Programme

Objectives of the CDE Diabetes Management Programme

A. **To Promote a sense of Well-being in Patients who have Diabetes**

- Comprehensive education to permit patients to understand their condition, the importance of maintaining adequate glycaemic control and the means of achieving it.
- Promote patient self-empowerment in the management of their condition,
- Provide a sense of security for members of the Programme via constant availability and a 24-hour 'Hotline' facility.
- Provide psychological support to patients in both coming to terms with a chronic condition and managing the necessary life-style changes. This may be achieved through rapport with the help of a psychologist if needed, but is supported by the dietician and rapport with the diabetes educator.
- Achieve satisfactory glycaemic control, not only rendering the patient asymptomatic, but also controlling blood glucose levels to an individualised target range that provides the optimum balance between the reduction in risk of microvascular complications of uncontrolled diabetes and the cardiovascular and other risks of hypoglycaemia.
- Avoid hospitalisation and reduce work / school absenteeism.
- Encourage healthy lifestyle, exercise and sport.

B. **Prevent or Delay Complications:**

- Discourage Smoking
- Define and treat additional risk factors (Lipids; Blood Pressure; Obesity etc. as laid out in 'Therapeutic Goals' - next page).
- Attain and maintain optimal glycaemic control

C. **Detect, Manage or Refer for Management any Complications that might arise:**

- Ophthalmologist
- Cardiologist
- Vascular Surgeon
- Neurologist, Etc.

The CDE Diabetes Management Programme is only contracted to manage Diabetes. Some of the patients joining the Programme are already under the management of their current Family Practitioner or Specialist Physician and wish to remain under their own doctors for non-diabetes care. It is therefore sometimes necessary to refer these patients back to their own doctors for management of these co-morbidities. Wherever feasible, however, CDE doctors should attempt to provide total care to their patients under the Programme.

Therapeutic Goals

1. Glycaemic Control:

Glycaemic targets need to be **individualized**. Generally, the following HbA1c targets apply:

- <6.5 % Ideal for a newly diagnosed, younger and / or otherwise healthy individual
- <7.0 % Recommended target for the majority of patients
- <7.5 % Acceptable for elderly, high-risk individuals and those who are hypoglycaemia unaware
- <8.0 % May be acceptable in some patients (E.g. The elderly, those with multiple comorbidities etc.)
- >8.0 % terminal illness and the very elderly - those with a short-expected lifespan where glycaemic control is less important and the major goal of therapy is to keep these individuals free of osmotic symptoms.

Recommended Blood Glucose Profiles on Home Monitoring		
	Ideal	Acceptable
Fasting	4.0-7.0 mmol/l	6.5-8.0 mmol/l
Random	4.0-7.0 mmol/l	5.0-10 mmol/l

Blood Glucose (Home monitoring) is recommended as following:

For patients on OHAs: 3-5 times a week

- 3 times weekly fasting
- 1-2 times weekly random, preferably before supper or 2 hours post-prandial

Patients **on Insulin**: At least 1-2 times daily, but more if control unstable.
Home glucose monitoring is only useful in patient on OHAs

- If it is used in conjunction with patient education
- The patient knows his/her glycaemic targets
- As an educational tool to assess the effects of lifestyle and medical nutritional therapy.
- After intensification of therapy to monitor response.

2. Attainment of Acceptable Body Weight:

Do not set unrealistic targets.

- If overweight (BMI >25 kg/m^2 [23 kg/m^2 in Asians]) - Aim for 5-10 % reduction in mass. More, only if possible.
- If normal weight (BMI 18.5 – 25/23 kg/m^2) - Maintain adequate nutrition.

3. Achieve optimal blood lipid concentrations:

- Initially by dietary manipulation
- Most patients with type 2 diabetes will require statin therapy to attain lipid goals.

Aim for

- Total Cholesterol <4.5 mmol/l
- LDL-cholesterol <1.8 mmol/l
- Triglycerides (TG) <1.7 mmol/l
- HDL- cholesterol >1.0 mmol/l (men), >1.2 mmol/l (women)

4. Adequate blood Pressure control:

Aim for <140/90 mmHg

In view of the CDE contractual obligations to the relevant Medical Aid and Medical Aid Administrators, the following treatment protocols concentrate solely on the treatment of the diabetes / glycaemia. However, it is inherent in our obligation to our patients that all other aspects of care, in particular those outlined above (e.g. Lipids, hypertension etc.), will be appropriately and adequately assessed and treated according to accepted treatment guidelines and protocols.

All aspects of diabetes care and treatment will be funded from the Capitation fee (see CDE 'Minimum Care Guidelines' in CDE Association Contract). Additional therapies will be prescribed and administered according to the requirements, rules and drug formularies of the patients Medical Aid. As a gesture of good faith for those Medical Aids that have joined the CDE Programme, CDE doctors will at all times attempt to attain the best possible treatment outcomes in a cost-effective manner for treatments not included in the Diabetes Programme package. However, the patient's best interests must be given priority at all times.

National Treatment protocol for People with Type 2 Diabetes

The CDE follows the 2017 South African guidelines published by The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA):

The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The SEMDSA 2017. Guidelines for the Management of Type 2 diabetes mellitus. *Journal of Endocrinology, Metabolism and Diabetes of South Africa*. Vol 22(1): 1-189.

These guidelines are extremely comprehensive and current and should be read carefully and fully.

ANNEXURE 1

Protocol for use of Oral Hypoglycaemic Agents in Type 2 Diabetes

In all patients, Metformin should be started on diagnosis and continued unless not tolerated.

NOTE: *It is the expressed intention of the Diabetes Management Programme that CDE does not dictate to CDE Centres as to which drugs to use and which sulphonylureas to select. The servicing doctor must decide this, based on his/ her own clinical experience. Since individual doctors are directly responsible for their own patient's well-being and control, they must be comfortable with the agents they elect to use. The details below are thus only recommendations and a guide to correct practice.*

A. **INSULIN SENSITIZERS**

Recent recommendations suggest that sensitizers should probably be prescribed de novo (On diagnosis)

Biguanides - Metformin

a) ***Glucophage –*** recommended

b) ***Generics*** – Many available. In our experience, those that are not enteric coated tend to have more gastrointestinal (GIT) side effects. Therefore, if generics are used the enteric coated generics are suggested.

Recommended starting dose: 500 mg bd. Optimal dose is 1 g bd. - a dose of up to 3 grams daily may occasionally be tried in very obese patients.

If excessive gastrointestinal effects occur, try taking after meals. With slow titration upwards, patients may be able to adapt to side effects.

Comment: Theoretically can precipitate lactic acidosis and should not be used in the very elderly or those with significant renal or hepatic impairment.

c) ***Glucophage XR 500 mg and 1000 mg- Slow-release format. Equipotent with standard metformin. Better intestinal absorption and less GIT side effects. Can be given once daily in a dose up to tablets (2 g) daily.***

Thiazolidinediones (TZDs) - Pioglitazone

Have different site and mode of action to metformin and work on both peripheral and hepatic insulin resistance.

a) **Actos (15 mg and 30 mg)** has been associated with increased fracture risk in women and small increased incidence of bladder cancer. Pioglitazone been reintroduced in the South African Guidelines as an alternative insulin sensitising agent to metformin. Generics now only versions available.

B. **INSULIN SECRETAGOGUES**

Sulphonylureas

Glibenclamide

a) **Daonil; Euglucon**

b) **Glycomin; Glyben; numerous other generics.** Glibenclamide has fallen into disrepute because of tendency to cause severe hypoglycaemia. Better sulphonylureas are available.

Comment: Considered the most potent of the sulphonylureas and the most likely to cause hypoglycaemia, which may then be severe and protracted. Should no longer be used and has been removed as a sulphonylurea option in the SA Guidelines.

Gliclazide

a) **Diamicron**

b) ***Ziclin; Glucomed; Rolab-Gliclazide; Diaglucide (Biogaran) & other generics*** - Our experience suggests that all these available generics are acceptable and seem to have a similar efficacy profile to the original. Can be used.

Recommended starting dose 40 mg (½ tablet) bd.

The maximum effective dose is probably not more than 80 mg bd. Higher doses are not recommended.

Comment: As with all sulphonylureas, can cause hypoglycaemia.

c) ***Diamicron MR 30 mg*** and ***60 mg tablets*** and several generics: a modified release formulation of gliclazide in which gliclazide released from the tablet better matches the circadian variation in glycaemia of the person with type 2 diabetes. This modified release formulation also allows for once daily dosing leading to improved medication adherence. Patients changed from twice-daily gliclazide to once daily Modified Release had lower HbA1c levels after the switch. Diamicron MR does not interfere with the protective effects of ischaemic preconditioning and is associated with a low risk of hypoglycaemia. It is available in 30 mg and 60 mg tablets and is always given *once daily*. Diamicron 80 mg may be changed to Diamicron MR on a tablet for tablet basis i.e.: 1 x 80 mg tablet Diamicron = 1 x 30 mg Diamicron MR. The dose can be increased to 120 mg daily.

Gliclazide MR is the preferred sulphonylurea in the 2017 SEMDSA Guidelines.

Glipizide

a) ***Minidiab*** - No generic equivalent available

Recommended starting dose 2.5 mg (1/2 tab) bd.

Maximum effective dose is probably not more than 5 mg (1 tab) bd. Doses higher than 7.5 mg bd. or 5 mg t.d.s not recommended.

Comment: Shortest acting of all the sulphonylureas and may have a place in treating the very elderly because of potentially reduced duration of hypoglycaemia, if it occurs. Because of the short half-life, it should be taken at least 2 or 3 times daily, which may be a disadvantage. Not often used.

Glimepiride

a) ***Amaryl;***

b) ***Glamaryl & other generics***

Recommended starting dose 1 mg daily

Maximum effective dose probably 4 mg daily and dose above 6 mg daily not recommended.

Comment: True once-a-day dosage schedule, less hyperinsulinaemia and weight gain and lower incidence of hypoglycaemia. Glimepiride can be taken before, during or after meals unlike the other sulphonylureas, which need to be taken before meals. Therefore, could be indicated in elderly patients and those who are obese but need the addition of a sulphonylurea.

C. **NON-SULPHONYLUREA INSULIN SECRETAGOGUES**

Repaglinide

a) ***NovoNorm*** - No generic available. Ultra-short acting and taken with meals as often per day as the patient eats. Works on the sulphonylurea receptor and promotes acute phase insulin release***.***

Comment: A relatively weak hypoglycaemic agent, not convincingly better than available sulphonylureas. Requires multiple daily doses (before all meals). May promote bad eating habits, but equally may be useful for occasional patients who are unable to eat regularly. Very expensive option.

D. **DPP-4-INHIBITORS**

- Do not cause weight gain and do not cause hypoglycaemia if used without a sulphonylurea or insulin.
- Correct place in therapeutic protocol would be second-line as an alternative to sulphonylurea, particularly in the very overweight patient.
- An expensive alternative to sulphonylureas.
- Can be tried as triple oral therapy before starting insulin.

Vildagliptin

a) ***Galvus: (generic: Jalra)*** Starting dose 50 mg daily to be increased to 50 mg bd.

(Requires monitoring of hepatic enzymes before starting therapy and regularly thereafter - see package insert).

Saxagliptin

a) ***Onglyza:*** Only one dose of 5 mg daily

(Liver function test monitoring not required.)

Sitagliptin

a) ***Januvia***: Dose 100 mg daily. 25 and 50 mg doses are available for use with reduced renal function.

Comment: All three agents very similar in efficacy and price. Both Galvus (GalvusMet) and Januvia (Janumet) are available in combination with metformin (see Section G).

E. **GLP-1 Agonists**

- Injectable agents that have the advantage of causing weight loss together with a reduction in HbA1c.
- Do not cause hypoglycaemia.
- High incidence of GIT side effects, particularly nausea and vomiting.
- Extremely expensive.
- Recommended place is in patients with BMI >35 kg/m2 on maximum effective doses of oral agents.
- Unfortunately, being used widely by the general public as a weight-reducing drug.

Exenatide

a) ***Byetta:*** Dose 5 µg bd by subcutaneous injection for 1 month, then 10 µg bd.

Liraglutide

b) ***Victoza:*** Dose 0.6 mg daily by subcutaneous injection for 1 week, then 1.2 mg daily.

Can go up to1.8 mg daily in selected individuals.

Has become an option as 3rd line therapy in patients who are progressing to insulin deficiency.

Recommended in ADA Guidelines as second-lone therapy in those with established CVD

F. **OTHER AGENTS**

Alpha-glucosidase inhibitors, Acarbose:

a) ***Glucobay*** **-** no generic available

Recommended starting dose 25 mg (½ tablet) daily or bd., taken with meals and increasing slowly over several weeks to 50-100 mg t.d.s. Maximum dose usually 100 mg t.d.s., but very few patients can tolerate this dosage.

Comment: Works primarily by reducing post-prandial hyperglycaemia and has a fairly 'weak' effect on overall blood glucose control. Cost / benefit ratio is dubious. It has a high incidence of gastrointestinal side effects, which many patients find unacceptable. Indication for use probably confined to patients with slight hyperglycaemia confined mostly to post-prandial glucose peaks. Does not add much to patients already approaching secondary failure and therefore of doubtful use as an 'add-on' agent in patients already on optimal doses of other agents and inadequately controlled.

SGLT2-Inhibitors:

Two are currently available:

a) ***Forxiga****: 10 mg once daily*

b) ***Jardiance****: 10 or 20 mg once daily*

Recommended as alternatives for second or third line therapy.

Recommended in ADA guidelines as first or second line therapy for patients with heart failure or those with early diabetic kidney disease.

Comment: These agents are the only agents available for treating diabetes that do not directly or indirectly act on insulin secretion or sensitivity. They exert their effect by promoting glucosuria.

They are largely ineffective if eGFR is below 60 mL/min/1.73 m^2;

Effective in reducing HbA1c by up to 1.5% but have significant side effects. Can cause hypotension, dehydration, acute kidney shutdown and very occasionally euglycaemic ketoacidosis. Should be used with caution.

G. **FIXED COMBINATION AGENTS**

To reduce the tablet load in patients on polypharmacy, several combination tablets are now available

a) ***Glucovance***

This is the first fixed combination oral agent to enter the South African market. It is a complimentary combination of the biguanide, metformin and the sulphonylurea, glibenclamide. It addresses the two core defects of type 2 diabetes (Insulin resistance and β-Cell dysfunction) and comes in the following strengths:

- 250 mg / 1.25 mg
- 500 mg / 2.5 mg
- 500 mg / 5 mg

Because the drug has a dual mode of action, lower dosing of the individual components is possible. This tends to improve tolerability. Improved compliance is expected with simplification of the treatment regimen. Good cost / efficacy ratio. If used, the prescribed strength must be stated carefully. The fact that it utilizes glibenclamide as the sulphonylurea is a disadvantage (see above).

b) ***Janumet***

A combination of Januvia and metformin. Available in three strengths:

- 50/500 mg
- 50/850 mg
- 50/1000 mg

To be taken twice daily. If used, the prescribed strength must be stated carefully

c) ***Galvus Met***

A combination of Galvus and Metformin. Available in two strengths, 50/850 and 50/1000. To be taken twice daily. If used, the prescribed strength must be stated carefully

d) **Amaryl Combi**

A combination of Amaryl and metformin. Available in two strengths, 1/250 and 2/500. To be taken twice daily. If used, the prescribed strength must be stated carefully

GENERAL COMMENTS

1. All patients will eventually require dual therapy with an insulin sensitizer and a secretagogue.
2. A DPP4-Inhibitor, GLP-1 agonist or SGLT-2 Inhibitor may be tried as a third-line oral agent before commencing insulin therapy.
3. It is generally better to use lower doses of each agent in combination than increasing one agent to maximum effective dose before adding the second. An exception to this may be the massively obese patient where higher doses of metformin may be preferable to adding a sulphonylurea.
4. There is no purpose in combining two sulphonylureas in one patient.
5. If adequate glycaemic control is NOT being achieved on optimal doses of combination OHAs, it is better to accept the need for insulin therapy rather than use excessive doses of OHAs.

ANNEXURE 2

Insulin Therapy in Patients with Type 2 Diabetes

Criteria for commencing Insulin Therapy in a Patient on Optimal OHA Therapy

Generally, insulin should be commenced in any patient who has an HbA1c >7 % and / or Fasting Blood Glucose on Home Monitoring averaging >6.5 mmol/l (*and no remediable dietary or other confounders are present*). These targets should be individually adjusted if a patient:

- Is very elderly and asymptomatic
- has another terminal disease.
- lives alone and is incapable of self-management and/or is unable to recognize hypoglycaemia.

In all cases, insulin therapy in people with type 2 diabetes can and should be commenced on an outpatient basis facilitated by a Diabetes Educator. Adequate education into insulin therapy, injection technique and hypoglycaemia detection and management is essential. All patients should be supplied with Glucagon and a member of the family taught how to use it.

Suggested Insulin Regimens

a) **Combination therapy with Nocté NPH + OHA**

Useful in patients as a starting regimen. Therefore, this regimen works best when instituted fairly early.

Also, useful as a 'halfway' negotiation to wean resistant patients on to Insulin therapy - i.e. use this form of combination therapy for a few weeks before converting patients onto a more conventional b.d. regimen.

Recommended Protocol: Start with 0.2 IU/kg body weight and increase by 4 IU every 3-4 days (under the guidance of the Diabetes Educator) until the fasting glucose is generally below 6.5 mmol/l. This can sometimes require a large dose of insulin to achieve and doses as high as 100+ IU NPH Insulin nocté have been recorded, without untoward effects. Patients should be advised to check their blood glucose overnight (~3 AM) once every 10 days until a stable dose has been established.

b) **Combination therapy with once-daily insulin glargine (Lantus/Optisulin/Basaglar) or insulin detemir (Levemir) + OHA**

This is an alternative first-line insulin therapy for people with type 2 diabetes. Glargine can be given at any consistent time of the day, as convenient for patient, but is usually instituted at night. Levemir, however, should be given at bedtime. Recommended as the first-choice insulin for failed OHA patients, provided cost is not an issue. Should be used if patients experience nocturnal hypoglycaemia on NPH insulin.

Recommended Protocol: Add glargine / detemir to current OHA regimen, using same dose schedule as for NPH above).

c) Combination therapy with once-daily insulin glargine U-300 (Toujeo) + OHA

This is another alternative first-line insulin therapy for people with type 2 diabetes. Can be given at any consistent time of the day, as convenient for patient, but is usually instituted at night. Duration of action up to 30 hours. Ideal for patients using large doses of insulin such as the very obese, and for those who inject an inconsistent times.

d) **'Basal Plus' Regimen**

If target Fasting Glucose levels are being achieved on a basal insulin regimen but, the HbA1c remains above the person's target level the implication is that the post-prandial glucose levels are elevated. Start a rapid-acting insulin analogue before the biggest meal of the day, titrating the dose to achieve a post-prandial glucose of <7.8 mmol/l. If target HbA1c is still not achieved, introduce a second dose of rapid-acting analogue before the second largest meal of the day etc.

e) **Multiple Injection Regimens:**

In some young and non-obese people with type 2 diabetes, a multiple injection regimen may be more acceptable to their lifestyle.

Recommended Protocol: Patients should be treated as for type 1 diabetes in all respects.

f) **Combination therapy using before-supper pre-mixed insulin + OHA.**

Occasionally used in patients who have large suppers and in whom the bedtime glucose level is too high, but with adequate glycaemic control during the day. This regimen is used often in the USA instead of nocté basal insulin.

g) **Twice-daily Premixed Insulin**

Probably the commonest, but not necessarily the best, insulin regimen used in type 2 diabetes. With the Pen-injectors it is easy to administer and simple to use. Good glycaemic control can be achieved with this in most patients with type 2 diabetes. A 30/70 Mix is usually employed (Humulin 30/70, Humalog Mix25 / NovoMix 30 are also effective for this regimen and may be more convenient for some patients as they are able to inject at the time of the meal (and not 30-45 minutes before). Humalog Mix25 / NovoMix 30 may also control post-breakfast and post-supper hyperglycaemia better than the other premixed insulin's. Humalog Mix50 can be used three times a day in appropriate patients.

Recommended Protocol: Start with 0.3 IU/Kg body weight and with $^{2}/_{3}$ before breakfast and $^{1}/_{3}$ before supper (if patient follows a European pattern of eating, or a 50:50 split for patients following a traditional South African meal pattern, where supper is the largest meal). Increase by 2-4 IU every 3-4 days according to the results of twice-daily (fasting and pre-supper) home glucose monitoring. NOTE: Due to the pathophysiology of type 2 diabetes and the tendency in this country for a large supper, morning glucose levels are often higher than evening levels and it is not unusual for patients to eventually require more insulin in the evening than in the morning

If adequate glycaemic control or a satisfactory quality of life is not being achieved on a twice-daily regimen, conversion to a multiple injection regimen should be considered.

In some patients in whom 2 injections of pre-mix are not achieving the required result, but who are resistant to a formal 4-injection per day basal-bolus regimen, Humalog Mix 50 given 3 times a day pre-meal may be an alternative.

Note: Once pre-prandial insulin (in the form of either a rapid-acting analogue or premixed insulin) is instituted, there is no longer any place for the ongoing use of sulphonylureas and they should be stopped. Metformin, however, should be continued indefinitely.