UNIT NO. 4

ISSUES IN PHARMACOTHERAPY

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ABSTRACT

Conventionally, management of Type 2 diabetes starts with a trial of dietary and lifestyle modification before initiating pharmacotherapy. There is a role for early initiation of drug therapy. Use of combination pharmaco-therapy for Type 2 diabetes stems from UKPDS data, which showed that monotherapy with either sulphonylureas or metformin was unable to maintain glycemic control over the 10 years of the UKPDS and this deteriorated over time. Previously, glycemic targets have been centered around fasting plasma glucose and glycated hemoglobin (Hba1c) levels. Over the past decade, post meal glucose or post-prandial hyperglycemia has gain importance as an independent and strong predictor of cardiovascular risk in addition to microvascular risk. Currently, in both the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (ACE) guidelines, equal emphasis is placed on glycemic targets for fasting, post-prandial glucose as well as Hba1c levels. Glycemic targets are also now stricter and lower in an effort to reduce cardiovascular mortality.

INITIATING TREATMENT

Conventionally, management of Type 2 diabetes starts with a trial of dietary and lifestyle modification before initiating pharmacotherapy. The duration of medical nutrition therapy (MNT) cum exercise varies between 3 – 6 months, depending on the patient's symptoms of hyperglycemia which is in turn related to the 'severity' of diabetes at diagnosis. The UKPDS (UK Prospective Diabetes Study) showed the benefit that can be obtained with this approach. During the 3-month dietary run-in at the beginning of the study, Hba1c fell from 9% to 7% in the 5,000 odd newly diagnosed diabetic patients.

The one critical exception is of course the diagnosis of insulin-requiring diabetes (Type 1 diabetes or diabetes secondary to pancreatic endocrine damage), where insulin has to be started at the same time as MNT/exercise.

Increasingly, however, the move is towards early initiation of pharmacotherapy for all but the least hyperglycemic of patients eg Hba1c < 8% at diagnosis. Some of the reasons put forward for this concept include the need to reverse glucose-toxicity allowing some recovery of pancreas function, which may not be possible with just MNT alone; the urgency to attain and the lower target set for glycemic control.

Whatever the belief, lifestyle modification involving MNT and exercise and weight reduction if overweight remains central to diabetes counseling, education and management.

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COMBINATION THERAPY

Use of combination pharmaco-therapy for Type 2 diabetes stems again from UKPDS data, which showed that monotherapy with either sulphonylureas or metformin was unable to maintain glycemic control over the 10 years of the UKPDS and this deteriorated over time. Conversely, more and more patients needed combination therapy to maintain the required glycemic control over the course of study – this rose to 50% at 3 years, 70% at 6 years and 85 % at 9 years. Combination use of different pharmacologic agents also allowed stricter glycemic targets to be reached.

The second reason for combining therapeutic agents is to deal with the "dual-defect" present in Type 2 diabetes – insulin resistance or reduced insulin sensitivity, and pancreas dysfunction causing disordered insulin secretory action. Combine agents that address both defects – insulin secretagogues (sulphonylureas and prandial glucose regulators) to improve insulin secretion and insulin sensitizers (biguanides and thiazolidenediones) to improve insulin action.

A third reason for combination drug therapy is that lower doses of individual agents may be used with a lower potential of adverse side-effects. Common drug regimes in local use involve any 2 or 3 drug combination of insulin secretagogues (sulphonylureas or prandial glucose regulators), metformin, TZD or acarbose. It has been said that when 3 drugs are being considered, discussion with the patient should be initiated regarding the cost-effectiveness of this versus use of insulin instead. The entry into the market of fixed drug combinations e.g. avandamet (avandia + metformin), glucovance (glibenclamide + metformin) and glucotrol (glipizide + metformin) has allowed combination pharmaco-therapy to progress to 4 drug combinations. The issue of multiple drug combination is not only that of cost and side effects, but also of compliance.

Combination therapy in diabetes should not forget combinations of insulin with oral agents. Any of the 4 classes of oral agents can be, in practice, combined with insulin. Insulin use in such cases can either be 'partial' (commonly a night dose of insulin added to an existing oral regimen) or 'full' (twice daily or more insulin doses). In both, hypoglycemia is an ever-present concern and should be considered and watched out for. This can be averted by:

a. reducing the dose of oral agents when insulin is added
b. starting with a lower dose of insulin
c. caution over use of insulin on top of insulin secretagogues.

The combination of insulin and the TZD avandia, should also be used with caution due to a higher reported incidence of edema.

EARLY AGGRESSIVE TREATMENT

From the Singapore data of the DIABCARE-Asia Study, only 33% of the diabetic patients we treat achieve an Hba1c goal of less than 7%. This is by no means exceptional as similar percentages of poor control are seen in other countries as well. Rather, there is an urgent need to improve the overall control of diabetes. It is postulated that part of the reason for poor control is the lack of early aggressive treatment to lower Hba1c to target levels, soon after diagnosis of diabetes.

Early aggressive treatment does not only refer to starting drug therapy early in the course of diabetes. It is also the mindset of both physician and patient to settle for nothing less than guidelines-directed glycemic targets.

TREATING TO TARGET

Previously, glycemic targets have been centered around fasting plasma glucose and glycated hemoglobin (Hba1c) levels. Over the past decade, post meal glucose or post-prandial hyperglycemia has gain importance as an independent and strong predictor of cardiovascular risk in addition to microvascular risk.

Currently, in both the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (ACE) guidelines, equal emphasis is placed on glycemic targets for fasting, post-prandial glucose as well as Hba1c levels.

Glycemic targets are also now stricter and lower. The concern is again macrovascular risk. However, aiming for lower plasma glucose thresholds are only one facet of the problem. Data from the Steno 2 Study suggests that a multifactorial risk intervention targeting blood glucose, dyslipidemia, hypertension, smoking, microalbuminuria, ACE-inhibitors or Angiotensin Receptor Antagonists, use of aspirin are all necessary to bring down cardiovascular-related mortality.

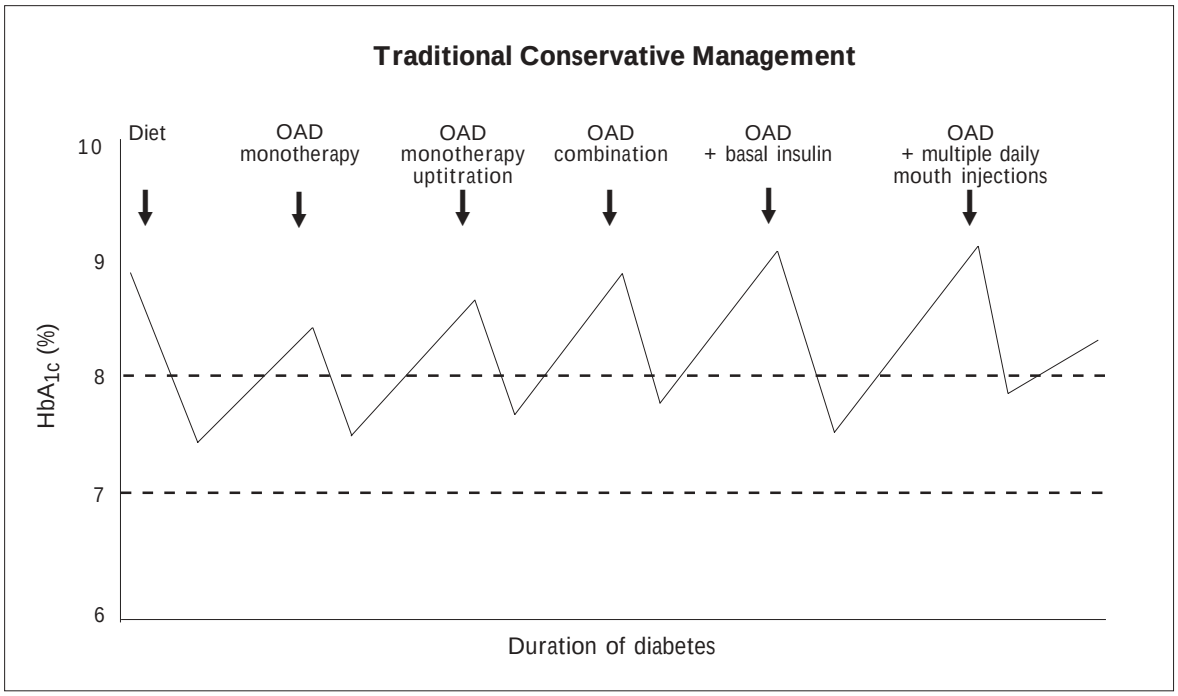
ASSESSMENT OF CONTROL

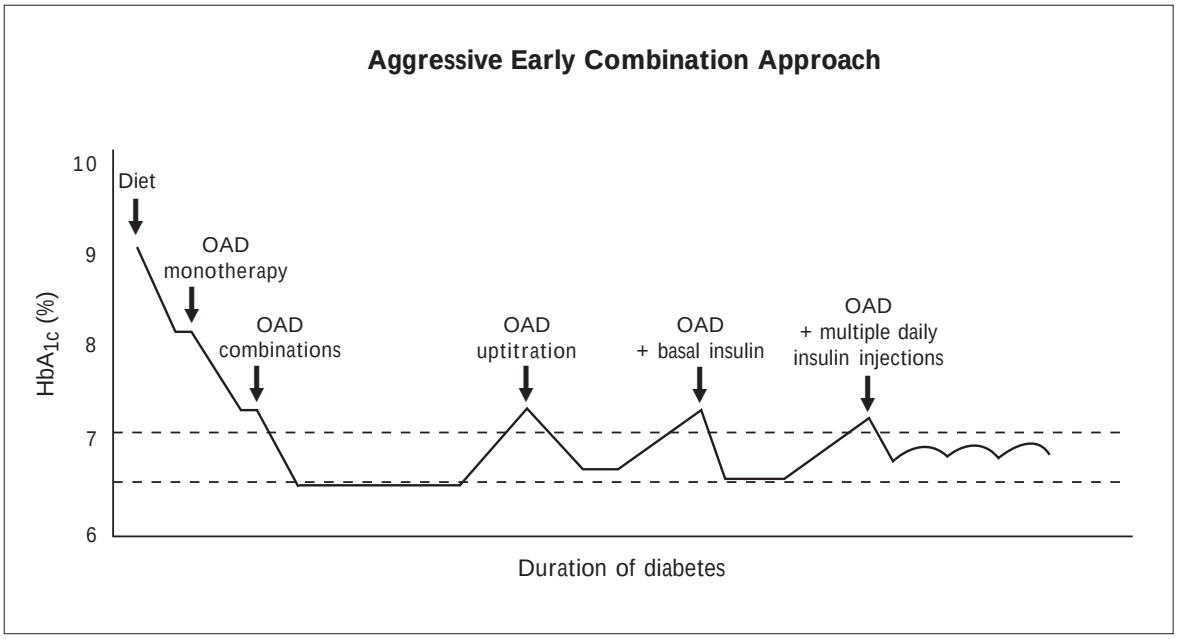
At doctor visits, a mix of fasting and post meal plasma or capillary glucose measurements, together with 3-monthly Hba1c measurements would give an indication of glycemic control. The patient's own self-monitored capillary glucose records, done daily or a few times a week add supplementary data. Not only is this a reflection of day-day glucose excursions, but it yields valuable data that would help both patient and doctor correlate symptoms to glucose levels and glucose levels to medication dose and food intake. Self-monitoring of blood glucose is necessary for all those on insulin, whether Type 1 or insulin-requiring Type 2 as it allows the individual insulin doses to be titrated.

'Assessment of control' in diabetes extends to monitoring blood pressure and lipid profile, as well as weight and body fat control.

COMPLIANCE

Compliance is affected by dosing of medication, polypharmacy and adverse effects of the tablets. Some of these have been circumvented by availability of combination drugs like avandamet (avandia + metformin) and glucovance (glibenclamide + metformin) as well as once daily medication (glibenclamide, glimepiride (amaryl), avandia (rosiglitazone)) or new formulations like diamicron MR. Peculiar to diabetes





is that sometimes, once-daily dosing convenience of tablets like glimepiride has to be sacrificed for the sake of more frequent pre-meal dosing of tablets like repaglinide or acarbose for the sake of less beta-cell stimulation and therefore less hunger, hypoglycemia or weight gain.

ADA, ACE and IDF glycemic goals

Biochemical index	ADA[1,2]		ACE[3]		IDF[4] (Europe)	
HbA_{1c} (%)	<7		≤6.5		≤6.5	
	mg/dl	mmol/l	mg/dl	mmol/l	mg/dl	mmol/l
Fasting/preprandial plasma glucose	90-130	5.0-7.2	<110	<6.0	≤110	≤6.0
Postprandial plasma glucose	<180	<10.0	≤140	≤7.8	NA	NA
Bedtime plasma glucose	110-150	6.0-8.3	NA	NA	NA	NA

[1] American Diabetes Association. *Diabetes Care 2003; S33-S50.*
[2] American Diabetes Association. *Diabetes Care 2002; S35-S49.*
[3] American Association of Clinical Endocrinologists. *Endocrine Pract 2002; 8(Suppl 1): 40-82.*
[4] European Diabetes Policy Group. *Diabetes Med 1999:716-730.*

Still, compliance issues sometimes govern the need to keep the dosing of diabetic medication simple at twice daily regimens, for example, using metformin at 850 mg twice daily instead of 500 mg thrice daily.

TREATMENT FAILURE

Treatment failure or the inability to reach glycemic targets is easy to define, but the cause may be harder to elucidate. Non-compliance to medication and/or MNT/exercise advice, secondary sulphonylurea failure, and pancreatic beta-cell failure may all be responsible.

The first step is to exclude dietary non-compliance as a cause. Next is whether drug-compliance is an issue. Once excluded, then hyperglycemia in the presence of combination therapy with insulin secretagogues and sensitisers, suggests the need for insulin therapy. From the UKPDS, up to a third of diabetics required insulin at the end of 9 years of follow-up, highlighting the progressive nature of the condition.

LEARNING POINTS

- **There is a role for early initiation of drug therapy in the management of Type 2 diabetes**
- **Combine drugs from different classes to address the primary defects present in Type 2 diabetes**
- **Glycemic targets are now stricter in an effort to reduce cardiovascular mortality.**