Choosing an insulin regime: a developing country perspective

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Insulin is a frequently prescribed drug in diabetes practice. Considered the most effective glucose-lowering intervention, insulin replacement therapy is a key component of effective diabetes management, irrespective of the stage of the condition.[1] Used as monotherapy, in combination with oral anti-diabetic drugs, and with incretin-based therapy, insulin is the most potent glycemia-lowering therapy available.[1]

Insulin is available in a range of preparations and delivery devices, and can be used to craft a variety of combinations and regimes.[2] All these regimes are backed by evidence in the form of randomised controlled trials and observational studies. Published reports often suggest conflicting ways of choosing regimes for insulin initiation and intensification. Well-written reviews do try to provide guidance for decision-making,[3,4] but this is complicated further by differing opinions of various international guidelines.[5–8] Widely used guidelines originate from the developed world,[5,9,10] and are appropriate for the clinical scenario of the country of origin. Understandably, they do not take into account the biopsychosocial realities of developing countries, so markedly different from those seen in developed nations. We review the diabetes scenario in the developing world, and try to address the issue of appropriate choice of insulin regimes in this context.

The developed world – diabetes as a chronic disease

The developed world tends to view diabetes as a chronic disease. Practitioners in optimally resourced healthcare settings may assume that persons with diabetes are screened and diagnosed in the natural course of the condition, and report dutifully for follow-up at regular intervals. This, too, is correct, in the vast majority of their cases. It is also perceived, by authors of various guidelines, that persons with diabetes will present themselves for intensification of therapy if current treatment fails to control glycated haemoglobin (HbA_{1c}).[9] This may be correct in many instances. The American Association of Clinical Endocrinologists guidelines, for example, reinforce the validity of this assumption when they classify persons seeking anti-diabetic therapy in to three categories, based upon their initial HbA_{1c}. The mid-range HbA_{1c} of 7.5% to 9.0% is perhaps thought to be the glycaemic status of the average person presenting for treatment in the United States.[9]

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The developing world: diabetes as an acute or chronic disease

Most of the world's population, however, live in developing countries. So too, do 80% of the world's people with diabetes. Most of the countries in the Top Ten list of persons living with diabetes are middle- and low-income nations.[11] It stands to reason, therefore, that the choice of insulin regime should take socioeconomic and healthcare issues of these people into consideration

For the developing world, diabetes is not only a chronic condition, but an acute disease as well, which can be life threatening. The high incidence of hospitalisations and mortality reported from resource-challenged countries bears testimony to this fact.[11] Complications such as diabetic ketoacidosis and infections including foot infections, tuberculosis, and human immunodeficiency virus (HIV) are not uncommon.[12,13] Healthcare providers in developing countries often encounter the acute face of diabetes, replete with multiple infections and metabolic co-morbidities. For such health professionals, the term 'complications' conjures visions of septicaemias and trauma. This is in contrast to his or her colleague in the developed world, for whom 'complicated conditions' imply chronic abnormalities such as retinopathy, nephropathy, and cardiovascular disease.

The exhortation of Western guidelines, therefore, to adopt less aggressive glycaemic targets in the 'presence of co-morbid conditions' may confuse developing country practitioners.[10] Most infectious or non-infectious acute complications would require an aggressive glycaemic control strategy, using intensive insulin regimes, for the short-term, to control confounding factors. Alleviation of the acute complication, as well as correction of glucotoxicity and lipotoxicity, may allow de-escalation of the prescribed insulin regime. The change in intensiveness of insulin regimes can be measured both in terms of number of doses per day, and total units per day. In other words, the presence of acute metabolic or infectious morbidity may influence the choice of insulin regime in developing countries, in a manner not described fully in Western guidelines.

Pattern of diabetes care-seeking behaviour is not uniform

Kalra et al describe four distinct patterns of diabetes care, based upon healthcare-seeking behaviour as a function of time.[14] The classic picture of gradual up-gradation is seen in patients who need, and are prescribed, gradual intensification of therapy as their disease progresses. This pattern follows suggestions made by guidelines, and reflects not only optimal diabetes care, but also optimal diabetes care-seeking behaviour on the part of patients.

The second scenario is seen in patients who present with acute co-morbidity, or severe hyperglycaemia, receive initial intensive therapy, and then experience a reduction in requirement of drugs, due to correction of glucotoxicity, lipotoxicity, and other factors. Such clinical cases are common in the developing world.

A third situation, known as the 'yo-yo' or 'see-saw' pattern, describes patients who present with high glucose levels, respond to therapy, and then discontinue it for a period of time, for various reasons, before returning to the physician with uncontrolled hyperglycaemia. This situation implies inadequate patient and community education related to diabetes.

A fourth pattern known as the linear pattern, describes a situation where the patient continues to be prescribed almost the same drugs, irrespective of glycaemic levels or other co-morbid developments, over a long period of time. This indicates lack of pro-activism on the part of the diabetes care provider.

'Doctor shopping' may also occur during the course of the condition. It is not uncommon to have patients request deintensification of insulin regimes, after having been cured of significant acute illness with intensive glucose-lowering strategies. An understanding of these patterns helps choose an appropriate regime of insulin. Paraphrasing this statement, healthcare-seeking behaviours of the person with diabetes, and the stage of natural history of diabetes at which he or she presents, influence the choice of an insulin regime. Adherence and persistence to prescribed insulin regimes are also influenced by the nature of diabetes care being followed by the majority of the community.

Human resources are limited

Prescribing insulin is not a simple or quick task. While writing a prescription of tablets or of insulin takes perhaps the same amount of time and energy, the pre-prescription and post-prescription work involved in insulin therapy is significant. To be effective and safe, an insulin prescription should be accompanied by an explanation of why it is necessary, motivation to accept it, demonstration of insulin technique, education regarding hypoglycaemia and its management, information about self-monitoring, and empowerment related to self-adjustment of dosage.[15] Carried out diligently and carefully, this consumes a disproportionate amount of both time and energy. Many healthcare practices are unable to afford the human resources required for this.[16] It thus becomes imperative to choose simple insulin regimes, preparations, and devices, which require less time to explain, and which are easier to use for the person with diabetes.

While circumstances will vary for each individual patient, they will also change for each healthcare setting. Appropriate choices should be made to ensure cost-effectiveness in each situation. In particular, the availability and cost of qualified, trained manpower, the ability to prevent iatrogenic hypoglycaemia by detailed education, and the cost of managing hypoglycaemia if it occurs, should be weighed against the advantages of achieving glycaemic control with intensive regimes.

Choosing a regime

Insulin regimes are traditionally classified as basal (conventional insulin such as neutral protamine Hagedorn [NPH] or analogues like insulin glargine, detemir, and degludec), premixed (conventional insulin combinations such as 30/70 – 30% regular insulin, 70% NPH insulin; or analogue combinations such as 25/75 – 25% lispro, 75% protaminated lispro; 30/70 – 30% aspart, 70% protaminated aspart; 50/50 – 50% lispro, and 50% protaminated lispro; 50/50 – 50% aspart, 50% protaminated aspart), and basal-bolus or intensive (multiple-component insulin regimen consisting of basal insulin given once daily, usually at bedtime and prandial insulin (regular insulin; or a rapid-acting analogue such as aspart, lispro, and glulisine) given three times, one each before breakfast, lunch, and supper). However, with newer evidence supporting the use of once-daily premixed insulin, classification can also be done in terms of number of doses per day (once daily, twice daily, and so on). Novel thrice-daily regimes such as prandial insulin thrice daily; premixed-prandial-premixed; and prandial-prandial-premixed are also used in specific clinical situations.[17]

In Tables 1 and 2, we offer a pragmatic way of choosing an initial insulin regime, based upon a few simple clinical, biochemical, and practical factors. The insulin regime is a dynamic choice, which can be changed as per need. Correction of acute toxicity allows one to downgrade the regime, i.e. reduce the number of injections, while inability to achieve glycaemic targets without significant hypoglycaemia suggests a need to intensify the regime.

Clinical factors strongly influence the choice of initial regime. Presence of significant illness such as trauma, fracture, planned elective surgery, acute infection, or necessity for steroid therapy, should encourage use of intensive regimes. These may be de-intensified once control of glycemia, and of the comorbid state, is achieved.

Persons with concomitant illness which puts them at high risk of hypoglycaemia should preferably receive premixed or basal insulin. The safest insulin currently available, with respect to hypoglycaemia, is insulin degludec.[18]

Clinical factor/choice of regime	Basal[1]	Premixed[2]	Intensive[3]
Fasting hyperglycaemia alone	++	+	++
Postprandial hyperglycaemia alone	–	+	++
Both fasting and postprandial hyperglycaemia	–	++	++
High HbA_{1c} at presentation (>8.5%)	–	++	++
Low HbA_{1c} at presentation (<8.5%)	+	++	–
Acute comorbidity requiring euglycaemia for management, e.g. infection, trauma	–	+	++
High risk of hypoglycaemia	+	+	–

Notes:
1. Basal insulin includes conventional insulin (e.g. NPH) or analogues (e.g. glargine, detemir, and insulin degludec).
2. Premixed insulin includes conventional insulin combinations such as 30/70 – 30% regular insulin,70% NPH insulin; 50/50 – 50% regular insulin, 50% NPH insulin; or analogue combinations such as 25/75 – 25% lispro, 75% protaminated lispro; 30/70 – 30% aspart, 70% protaminated aspart; 50/50 – 50% lispro, 50% protaminated lispro; 50/50 – 50% aspart, 50% protaminated aspart.
3. Intensive insulin means a multiple-component insulin regimen consisting of basal insulin given once daily (usually at bedtime) and prandial insulin (regular or an analogue such as aspart, lispro, and glulisine) given three times a day – one each before breakfast, lunch, and supper.

Table 1 Pragmatic way of choosing an initial insulin regime on the basis of clinical factors

Clinical factor/choice of regime	Basal[1]	Premixed[2]	Intensive[3]
Inability to have regular meals	+	+	–
Inability to self-monitor	+	+	–
Inability to self-adjust doses	+	+	–
Inability to remain in regular touch with diabetes care team	+	+	–
Inability to self-inject	+	+	–
Psycho-social factors	+	+	–
Poor family support and acceptance	+	+	–
Low personal acceptance of insulin	+	+	–

Notes:
1: Basal insulin includes conventional insulin (e.g. NPH) or analogues (e.g. glargine, detemir, and insulin degludec).
2: Premixed insulin includes conventional insulin combinations such as 30/70 – 30% regular insulin,70% NPH insulin; 50/50– 50% regular insulin, 50% NPH insulin; or analogue combinations such as 25/75 – 25% lispro, 75% protaminated lispro; 30/70 – 30% aspart, 70% protaminated aspart; 50/50 – 50% lispro, and 50% protaminated lispro; 50/50– 50% aspart, and 50% protaminated aspart.
3: Intensive insulin means a multiple-component insulin regimen consisting of basal insulin given once daily (usually at bedtime) and prandial insulin (regular or an analogue such as aspart, lispro, and glulisine) given three times a day – one each before breakfast, lunch and supper.

Table 2 Pragmatic way of choosing an initial insulin regime on basis of practical factors

Biochemical factors also inform the choice of treatment. Fasting glycaemia is best controlled by basal insulin, and postprandial by premixed or intensive regimes. The presence of both fasting and postprandial hyperglycaemia implies the need for premixed or intensive regimes. The excursion between postprandial and fasting glucose values can be used to estimate the need for such insulin. Another formula suggests measuring the ratio of fasting glucose (in mmol/l) to HbA_{1c}: a ratio>1.3 implies the necessity for basal insulin.[19]

The above listed biological factors, however, may have to be modulated according to practical and psychosocial factors. The ability to take regular meals, self-inject, adjust doses, and consult the diabetes care team may change the prescription of insulin. Psychosocial issues including personal and family attitudes may also influence choice of management. Premixed insulin is characterised by efficacy, along with safety and convenience. Relative glycaemic excursions after each meal can help decide the timing of administration of premixed insulin, if it is prescribed in a once-daily dose.

Diabetes care professionals working in developing countries are familiar with unwelcome situations such as limited supply of insulin, or inadequate facilities for self-monitoring of blood glucose, or inability of patients to return for regular follow-up because of sociopolitical or geographical reasons. In these cases, the primary aim of aggressive glycaemic control for most infectious or non-infectious acute complications should remain the same. The approach or strategy for achieving such an aim, however, may be modified as per local factors. The dosage of oral anti-diabetic agents (OADs) should be optimised, and insulin added as per availability and need. Basal insulin for example, NPH, can be prescribed once daily to control elevated fasting glucose levels, and twice daily to manage generalised hyperglycaemia. Regular insulin may be added where inappropriate postprandial excursions are present even after OAD optimisation. Where glucose monitoring at multiple time points is not feasible, we suggest monitoring therapy with fasting blood glucose and keeping it as a primary target for control. Once fasting euglycaemia has been achieved, dosage of prandial insulin can be adjusted by testing paired blood glucose values. For example: to decide the need for, and dose of, regular insulin before breakfast, a blood sample before breakfast and 2 hours after breakfast can be taken. If the excursion is unacceptable, regular insulin can be added and titrated appropriately. The decisions for lunch- and supper-time insulin can be similarly taken.

Conclusions

This developing world perspective should be read in conjunction with existing guidelines on diabetes management. This viewpoint adds to, rather than negates, the collective evidence discussed in various guidelines.

It suggests a fresh way of approaching a common clinical situation, i.e. the choice of an insulin regime. This should help not only practitioners in the developing world, but in advanced countries as well. It highlights the need to consider severity of diabetes, presence of acute infectious and non-infectious comorbidity, and availability of resources, while choosing appropriate insulin therapy. Blanket recommendations by various guideline-issuing authorities may not be entirely appropriate. Adequate use should be made of all available insulin regimes, to ensure appropriate control for all.

It is hoped that this perspective may allow readers to practice 'glocal' diabetology, i.e. following global guidelines, in concordance with local pragmatism.

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