Brief Communication

Flexibility in insulin prescription

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ABSTRACT

This communication explores the concept of flexibility, a propos insulin preparations and insulin regimes used in the management of type 2 diabetes. The flexibility of an insulin regime or preparation is defined as their ability to be injected at variable times, with variable injection-meal time gaps, in a dose frequency and quantum determined by shared decision making, with a minimal requirement of glucose monitoring and health professional consultation, with no compromise on safety, efficiency and tolerability. The relative flexibility of various basal, prandial and dual action insulins, as well as intensive regimes, is compared. The biopsychosocial model of health is used to assess the utility of different insulins while encouraging a philosophy of flexible insulin usage.

Key words: Biphasic aspart, biphasic lispro, degludec, degludec aspart, detemir, glargine, glulisine, hypoglycemia, insulin aspart, lispro, neutral protamine Hagedorn, type 2 diabetes

Introduction

"*DO NOT match lifestyle to the insulin regimens. RATHER, match the regimen to the lifestyle*" Easier said than done, this statement reflects the core philosophy of person-centered care. Keeping the person with diabetes at center stage of treatment, one should try to provide effective, safe glycemic control, with minimal intrusion into his or her lifestyle. Traditional insulin regimes, such as human insulin based protocols, and basal-bolus therapy may demand strict observation of 3 + 3 meal patterns, and require insulin administration at specified times of the day. The rigidity which characterizes these treatments prevents the practice of person-centered care in the true sense.

Development of newer insulins and insulin co-formulations has introduced the concept of flexibility in diabetes care.

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Flexibility is an adjective which describes the capability of a material, schedule, or personality to bend, adapt or yield.[1] A flexible ruler, for example, can easily be bent without breaking. A flexible agenda is one which can be modified or adapted while a flexible person demonstrates pliability or is agreeable to change. In medicine, flexibility may be taken to mean the absolute range of movement at a joint(s).[2] This concept also incorporates the change in muscle length.

In diabetes care, the word flexibility can be used to qualify treatment targets, treatment regimes, and specific drugs. Flexibility (or the lack thereof) is also an important attribute of persons with diabetes, their caregivers, and diabetes care professionals (DCPs)!

Because of the versatility of this word, it can be used in multiple ways. At the same time, this property makes it susceptible to misuse and confusion. We try to bring clarity to this field by focusing on the flexibility of various insulin regimes and preparations.

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Flexibility of an insulin regime and of preparations includes various domains under its umbrella. There include the ability to change time of administration, injection-meal time gaps, site of administration, the number of doses, and quantity of doses from a patient-centre perspective. It also encompasses the intrusion index of insulin therapy, i.e., the need to adhere to strict dietary and physical activity plan, the recommendation frequency of self-monitoring of blood glucose, and the the requirement for other investigation/concomitant treatment modalities. Within particular insulin regimes, flexibility also means the ability to modify specific doses of prandial and basal components.

These domains, though usually concordant with each other, sometimes pose a dilemma for the DCP. What may seem flexibility to the person with diabetes, e.g., the ability to take two premixed instead of four basal-bolus injections, may be thought of as inflexibility by the DCP, who is unable to titrate the ratio of prandial and bolus insulin. Keeping this in mind, a comprehensive definition of flexibility should be aimed at.

We suggest that "flexibility of an insulin regime or preparation is defined as their ability to be injected at variable times, with variable injection-meal time gaps, in a dose frequency and quantum determined by shared decision making, with minimal requirement of glucose monitoring and health professional consultation, with no compromise on safety, efficiency and tolerability."

The following sections describe various regimes and preparations, focusing on their flexibility, as defined above.

Insulin Regimes

Conventionally, insulin regimes are classified as basal, premixed, and intensive.[3] An intensive regime is one which includes 3 or more injections per day. Thus, prandial, basal plus (≥3 doses), and basal-bolus regimes are included in the intensive category. Basal plus (2 doses), split-mix, and coformulations are other types of insulin regimes and preparations. Recently, a number-based taxonomy approach has been used to provide a framework which can include both traditional as well as newly developed insulin regimes.[4]

Basal Insulins

Basal insulin regimes are considered to be simple, less intrusive and flexible, as they involve only one injection per day, do not require adherence to a strict meal pattern, and allow relative freedom of lifestyle.[5] Though neutral protamine Hagedorn insulin should preferably be taken with a snack, basal analogues can be injected without regards to meal timings.

Within the basal insulins, detemir has to be prescribed in the evening or at bedtime, at the same time.[6] Glargine can be injected at any time of the day, at the same time each day.[7] Insulin degludec can be injected at any time of the day, without regards to the previous injection timing, provided an 8 h gap is maintained.[8] Thus, of the basal preparations, glargine and degludec appear the most flexible [Table 1].

Prandial Insulins

Human regular insulin should be administered 30 min before a meal, while rapid-acting insulin analogues such as aspart, glulisine and aspart offer the advantage of a shorter injection-meal gap. These analogues can be injected 5 min before, or after, a meal, with no negative impact on efficacy.[3]

Dual Action Insulins

While human premixed insulins (biphasic human insulin) need to be injected 30 min before a meal, premixed insulin analogs (biphasic aspart, biphasic lispro) can be taken 5 min before a meal, or immediately after it.[9] The injections have to be taken with the same meal (s) every day, whether in a once daily, twice daily or thrice daily dose.[4] Insulin co-formulations such as I Deg Asp (insulin degludec aspart) offer the flexibility of change in timing of administration. For example, a person on a once daily regime of I Deg Asp, to be taken with the major meal, may choose to have his injection at breakfast on one day, and at lunch or dinner on the next. A minimum inter-dose gap of 8 h, required, however.[10]

Dual action insulins, including premixed insulins, are relatively less complex as compared to basal-bolus regimes. However, they are limited in flexibility in terms of dose titration, especially self-titration.[11] As with basic algorithms, however, one can easily master the simple skills required to use premixed insulins in a flexible manner.

The Biopsychosocial Perspective

Flexibility is much more than a semantic term, a pharmacological attribute or a biomedical benchmark. Flexibility is a concept which encompasses the biological, psychological, and social aspects of diabetes care [Box 1]. The unique pharmacological properties of insulin analogues allow subtle differentiation in terms of flexibility and facilitate appropriate choice based on biomedical factors. Personal preferences regarding frequency and timing of administration, as well as the frequency of glucose monitoring, which also play a role in the choice of insulin, are guided by flexibility as well. Social environmental

Table 1: Domains of flexibility of various insulins

Insulin regime	Insulin preparation	Flexibility domain			
		Flexibility in timing of administration	Flexibility in meal-injection time gap	Flexibility in dose adjustment	Perceived burden/intrusion
Basal	NPH	+	NA	+	Low
	Detemir	++ (at bed time)	NA	+ (dose self-titration algorithms are available)	Low
	Glargine	++ (at the same time every day, any time of the day)	NA	+ (dose self-titration algorithms are available)	Low
	Degludec	+++ (at any time of the day)	NA	+ (dose self-titration algorithms are available)	Low
Dual action	Biphasic human	+ (twice a day, with antipodal meals)	− (30 min before a meal)	+	Medium
	Biphasic aspart/ lispro	++ (once, twice or thrice (BI Asp) daily. Twice daily dose must be administered with antipodal meals)	+ (5 min before, to 5 min after, a meal)	+ (dose self-titration algorithms are available)	Low-medium
	Insulin degludec aspart (I Deg Asp)	+++− (with the major meal(s) of the day, which need not necessarily be the same meal(s) every day. Twice daily dose need not necessarily be administered with antipodal meals)	+ (5 min before, to 5 min after, a meal)	+ (dose self-titration algorithms are available)	Low-medium
Basal plus	One basal injection with one or two prandial doses	+ (the bolus dose is given with the major meal of the day, which need not be the same meal everyday)	Depends on choice of rapid acting insulin (regular insulin, aspart, glulisine, lispro)	+ (5 min before, to 5 min after, a meal)	High
Basal-bolus	One or two basal injections with 3 prandial doses	None	Depends on choice of rapid acting insulin	+	Highest
Intensive	One I Deg Asp dose with two I Asp doses	+ (the I Deg Asp dose is given with the major meal of the day, which need not be the same meal every day)	+ (5 min before, to 5 min after, a meal)	+	High

I Deg Asp: Insulin degludec aspart, BI Asp: Biphasic aspart, NA: Not available, NPH: Neutral protamine Hagedorn

Box 1: Biopsychosocial aspects of flexibility

- Biomedical aspects
  - Pharmacokinetics of insulin preparations
  - Pharmacodynamics of insulin preparations and regimes
  - Meal patterns and quantity
- Psychological aspects
  - Preference related to frequency of injection
  - Preference related to timing of injection
  - Need/ability to self-monitor glucose
- Social aspects
  - Job profile: Regularity of lifestyle
  - Privacy for injection
  - Financial impact

factors, such as nature of the job (involving shift work), availability of privacy for monitoring and injection at specific times, and financial issues, also revolve around flexibility.

Thus, flexibility of insulin straddles the biopsychosocial model of health care. Flexibility is a person-centred concept as well, as it keeps the person's preferences, wishes and needs at centre stage. In large studies, people living with diabetes have highlighted various limiting factors in their management of diabetes, and the need for greater self-involvement. Similar feelings are echoed by their family members and health care professionals. As flexibility responds to patient needs and convenience, it is concordant with the tenants of person-centred care.

Summary

Discussion and debate around the flexibility of insulin preparations, and insulin regimes, is an important facet of enhancing person-centeredness. The practice of "flexible" treatment regimes, to the extent possible, without harming patient well-being, is a philosophy which mirrors those of person-centred care and the biopsychosocial model. Prescription of drugs which allow flexibility in their use will help achieve the aims of these useful management frameworks.

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Conflicts of interest

There are no conflicts of interest.

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