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Basal insulin reductions in anticipation of multiple exercise sessions in people with type 1 diabetes – A clinical perspective

Short running title: Basal insulin reductions around exercise in people with type 1 diabetes

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Normal physiology

The islets of Langerhans are regions of the human pancreas that contain endocrine (hormone-producing) cells, constituting 1 to 2% of pancreas volume. There are four main types of endocrine cells within the islets of Langerhans; alpha (α) cells, beta (β) cells, delta (δ) cells and to a lesser degree the pancreatic polypeptide (PP) cells. Of these populations, the β -cells

account for between 65-80% of the pancreatic islets, and whilst predominately responsible for the secretion of the hormone insulin, they also co-secrete C-peptide and amylin. Collectively, the cells in the islets of Langerhans are pivotal in glycaemic regulation and homeostasis.

The determinant of plasma glucose concentration is a function of the rate at which glucose enters the circulation (glucose appearance), balanced by the rate at which glucose is removed (glucose disappearance) ¹. Circulating glucose originates from three sources; post-prandial intestinal absorption, glycogenolysis and gluconeogenesis. The attainment of glucose homeostasis requires a continuous interplay between several glucoregulatory hormones split via their ability to increase (glucagon, adrenaline, cortisol, growth hormone) or decrease (insulin) plasma glucose concentrations.

In regulatory metabolism, insulin is endogenously released in two phases. The first phase release occurs acutely and rapidly (~10minutes) in response to elevated circulating glucose levels. The second phase is independent of circulating glucose concentrations and occurs in a continuous, gradual release from the newly formed vesicles ². Elevations in blood glucose increase the rate of insulin secretion from the β -cells. Once bound to its cell surface receptor, insulin facilitates the entry of extracellular glucose into the intracellular space, thereby lowering circulating levels of blood glucose. However, when glucose levels drop beyond those accepted within physiological norms i.e between 4-7mmol/L⁻¹, insulin release slows or completely stops to avoid hypoglycaemia. A drop beyond this point ($\leq 3.6-3.9$ mmol/L⁻¹) typically triggers the activation of several gluco-regulatory hormones i.e. glucagon and adrenaline which promote hepatic mediated glucose production via the process of glycogenolysis. ^{3 4}.

Type 1 diabetes

Type 1 diabetes mellitus (T1D) is an autoimmune disease characterised by the progressive depletion and destruction of pancreatic β -cells, which results in hyperglycaemia and a

propensity to develop diabetic ketoacidosis (DKA). However, whilst primarily associated with defective insulin secretory capacity, β -cell death also contributes to a progressive loss in α -cell function⁵. As a result, there is often a compromised functionality of glucagon, a peptide hormone which operates to raise glucose concentrations in response to low levels of circulating insulin. An impairment in these processes leads to an increased reliance on the third counter-regulatory mechanism i.e the release of adrenaline. As such attenuation or loss of this response can lead to hypoglycaemia unawareness, a condition which can have serious and sometimes fatal consequences⁶.

Exogenous Insulin Therapy

Clinically, the inability of those with T1D to produce insulin necessitates a lifelong reliance on exogenous insulin therapy, typically administered by subcutaneous (SC) injection. Slight variations of the human insulin molecule are referred to insulin analogues. The term reflects the fact that they are not technically human insulin, rather they are analogues which retain the hormone's glucose management functionality.

When insulin is used in a clinical setting, a volume is injected into a site of subcutaneous tissue. The majority of existing insulin analogues are injected in hexameric form, however, hexamers are too large to readily pass through capillary fenestrae, and thus must first disassociate into either dimers or monomers within the injection depot before entering the circulation. In primary target tissues, the exogenously administered insulin molecules bind to and activate insulin receptors, thereby triggering cellular cascades that promote intracellular glucose uptake and utilisation.

The pharmacological production of insulin has progressed substantially since its discovery in 1921, with significant biochemical adjustments having been made to improve both pharmacokinetic and pharmacodynamic profiles. The progression from purified animal to recombinant human insulin was made by Eli Lilly, who produced insulin Humulin in 1982.

Since then, the variety of insulin analogues has expanded considerably, encompassing a range of products that differ in their duration of action, time of onset and peak effect. The type of insulin analogue largely reflects its absorption rate, thus insulins are classified in relation to their duration of action i.e ultra-fast acting, fast-acting, short-acting, intermediate-acting, long-acting, ultra-long acting, and combination products (Table 1).

Table 1. Synopsis of currently available insulin analogues for individuals with type 1 diabetes

Insulin Type	Insulin Name	Pharmaceutical Manufacturer	Duration of Action	
			Duration	Onset
ULTRA-FAST ACTING	Flasp	Novo-Nordisk	3-5 hours	3-5minutes
FAST	Humalog (lispro)	Lilly	3-5 hours	5-20 min
	Apidra (Glulisine)	Sanofi Aventis	3-5 hours	10 min
	Novorapid (Aspart)	Novo-Nordisk	3-5 hours	10 min
SHORT	Humulin R	Lilly	6-8 hours	0.5-1 hours
	Actrapid	Novo-Nordisk	8 hours	0.5 hours
INTERMEDIATE	Humulin N	Lilly	18-24 hours	1-2 hours
	Novo NPH	Novo-Nordisk	24 hours	1.5 hours
	Humulin L	Lilly	18-24 hours	1-3 hours
	Novolin Lente	Novo-Nordisk	22 hours	2.5 hours
COMBINATION	Humalog Mix (25% Lispo & 75% protamine suspension)	Lilly	18-24 hours	30-45 min
	Humulin 20/80 Humulin 30/70	Lilly	18-24 hours	30 min
LONG	Humulin U	Lilly	24-28 hours	4-6 hours
	Novolin Ultralente	Novo-Nordisk	28 hours	4 hours
	Lantus (Glargine)	Lantus	20-24 hours	1.5 hours
	Levemir (Detemir)	Novo-Nordisk	20-24 hours	2.5 hours
ULTRA LONG	Degludec (Tresiba)	Novo-Nordisk	42 hours	30-90 min
	U300 Glargine	Toujeo	>30 hours	30-90min

Developments in Basal insulin analogues

In the case of basal insulin development, the challenge has been to retard absorption to a greater extent than occurs with human insulin – ideally to produce a constant, peak-less kinetic profile that more mimics normal basal insulin secretion ¹⁶.

Unlike endogenous insulin production (which is secreted in a glucose-dependent manner), the dose of exogenous insulin must be manually titrated to maintain euglycemia ¹⁷. As such, correctly identifying a dosing strategy across a 24hour time span is an important feature for minimising within-patient variability ¹⁷. However, basal analogues have presented a number of flaws which compromise the attainment of this goal. Produced back in the 1950's, the original human insulin-based products, such as NPH insulin, had suboptimal pharmacokinetic (PK) profiles, characterised by inappropriate peaks of action coupled with high variability from injection to injection. Combined, these attributes not only accentuated the risk of hypoglycaemia but also necessitated the need for twice daily dosing.

In the early 2000's, insulins detemir (TM Levemir) and glargine (TM Lantus) were created in an attempt to overcome some of the PK issues of their preceding analogues.

However, in comparison to regular human insulin, neither provide an ideal absorption profile that closely mimics normal physiology ¹⁶. Thus, the development of ultra-long acting insulins that achieves steady state PK with a low peak: trough ratio should be of clinical and patient advantage.

Insulin Glargine 300units/mL

Insulin Glargine (IGlar) substitutes the amino group 21^A-Asn for Gly thereby forming its unique chemical structure (21^A-Gly-31^B-Arg-32^B-Arg-human insulin)¹⁵. Following subcutaneous injection, IGLar precipitates at physiological pH to form a depot from which insulin glargine is slowly released ¹⁸. In 2015, a more concentrated form of IGLar [insulin

glargine 300 units/mL (IGlar U300)] was released. IGLar U300 has a reduced redissolution rate, longer duration of action and lower fluctuation rate following subcutaneous injection compared to glargine 100 units/mL (U100)¹⁹. However, whilst its PK and pharmacodynamic profile is improved, ultrastructural three-dimensional research has observed the formation of larger microprecipitates in the tissues following IGLar U300 injection. Physiologically, this may cause a disproportionate release and delayed absorption rate of insulin into the blood stream (Seested et al, 2016)²⁰

Insulin Degludec

Recently, the development of insulin Degludec (IDeg); a new ultra-long acting insulin analogue with a duration of action that comfortably exceeds 24hours, has been achieved¹⁷. The name ‘***De-gluc-dec***’ originates from its unique structural profile which acylates ***DesB30*** at the ϵ -amino group of LysB29 with a ***glutamic acid*** ligand at position 29. The opposing end of this glutamic acid ‘spacer’ is then attached to a hexadecandioyl 16 fatty diacid side chain, completing the biochemical structure of IDeg.

Pharmacological profile

The impressive pharmacological profile of IDeg derives from its specifically engineered molecular structure which encourages multi-hexamer formation via a prolonged depot release¹⁷. To date, IDeg is the only insulin analogue to self-associate into multi-hexamers upon SC injection. In the pharmaceutical formulation i.e in the presence of phenyl and zinc, the IDeg hexamers adopt a formation from which only one hexameric end can interact with the side chain of another¹⁷. After injection, the phenol is lost and the dihexamer poles open at both ends thereby enabling the formation of long soluble multihexamer chains²¹. The loss of zinc allows the monomers to be slowly released which adeptly creates a soluble depot from which IDeg is gradually absorbed into the circulation on a continuous basis.

Pharmacokinetic profile

The ultra-long profile of IDeg brings with it several clinically relevant glycaemic outcomes. Firstly, research has shown that steady state (SS) concentrations of IDeg are reached within 3 days of once-daily dosing with no risk of insulin ‘stacking’²². Moreover, concentration-time curves and glucose infusion rate (GIR) profiles obtained during a one-dosing interval at SS conditions have highlighted the consistent distribution of IDeg formulations over a typical 24 hr treatment interval²³.

The flat shape of the pharmacodynamic profile of IDeg is supported by parameters such as distribution of the glucose lowering effect and relative fluctuation¹⁷. Importantly, these characteristics support a glucose lowering effect across a range of clinically relevant dose levels (0.4, 0.6 or 0.8 u/kg)²⁴. Moreover, recent comparative research investigating glycaemic outcomes associated with IDeg versus IGLar U300, found IDeg produced a lower day-to-day and within-day variability than that of IGLar U300 in patients with T1D.²⁰ Finally, the peak-less, extended and highly predictable glucose lowering profile of IDeg allows for variation in the once-daily-dosing strategy of up to 8 hours^{25 26} which has important social and practical patient appeals²⁷.

Clinical questions and concerns

The new generation of ultra-long basal insulins provide improved therapeutic care for patients with T1D. However, although progressive, the introduction of any new product demands careful consideration of important clinical outcomes. Similar to that of its preceding analogues, the efficacy of IDeg in minimising the occurrence and magnitude of hypoglycaemia requires thorough investigation. Unsurprisingly, both iatrogenic and exercise induced hypoglycaemia represent major concerns in this patient population. Thus, considering the heightened risk of developing hypoglycaemia both during and as long as 24 hours after exercise participation,²⁸
²⁹ insulin management must be carefully considered.

During exercise, the increased skeletal muscle contraction rates, heightened insulin sensitivity and inability to regulate circulating insulin concentration result in an augmented skeletal muscle uptake but decreased appearance of circulating blood glucose. These physiological responses, coupled with the more rapid appearance of exogenous insulin due to elevations in both thermo-and-hemodynamics as well as an inability to effectively counteract the drop-in glucose concentrations, exacerbate the likelihood of hypoglycaemia in individuals with T1D. Therefore, although the importance of regular physical exercise in glucose management for individuals with T1D is magnified by its acknowledgement as a key adjunct to insulin therapy by several governmental, charitable and healthcare organisations - exercise participation rates remain low, with fears around loss of glycaemic control during and after exercise reported as one of the major barriers to regular engagement ³⁰.

These fears are perhaps exacerbated by uncertainty in how to appropriately adjust exogenous insulins around exercise to best preserve blood glucose concentrations.

Whilst research has highlighted improved post exercise glycaemia when bolus insulin is reduced in the pre-and-post-exercise period ³¹, adjustments have mostly been done against a background of the basal insulins IGLar, NPH or IDet ^{32 33, 34, 35, 36, 37, 38 39} with less work investigating IDeg.

For the majority of patients, basal insulins are not normally adjusted in anticipation of exercise. However, complete suspension of basal insulin administration in pump users during exercise has been found to decrease exercise-induced hypoglycaemia by ~30% in children and adolescents ⁴⁰. Although an effective strategy for pump users, complete basal omission in those using multiple daily injections (MDIs) is difficult and potentially dangerous. Encouragingly, recent work reported complete protection from exercise-induced and nocturnal episodes of hypoglycaemia when patients on MDI reduced basal insulin IGLar and IDet by 20% the

morning of an anticipated exercise session in combination with a 75% reduction in rapid-acting insulin (100% dose = 9, 80% dose = 0) ⁴¹.

Whilst still in its infancy, research has started to explore glycaemic outcomes associated with exercise and/or bolus insulin manipulations on a background of IDeg in patients with T1D. Initial work by Moser and colleagues reported no hypoglycaemic episodes both during and after high intensity interval-and-continuous-exercise when multiple adjustments in bolus insulin were made on a background of stable IDeg dosing ⁴². More recently, comparative work has highlighted the low and similar risk of exercise-induced hypoglycaemia on a background of IDeg and IGLar. ⁴³. However, whilst IDeg has been used as the basal insulin, these studies have only involved acute manipulations to pre-exercise bolus insulin with no basal adjustments being made. Addressing this gap, Moser et al. was the first to experiment with IDeg adjustments around exercise in individuals with T1D ⁴⁴.

Description of Othmar paper

Nine T1D individuals on a background of IDeg were recruited into the study. The authors set out to assess the effects of a reduction in IDeg around multiple aerobic exercise sessions at a moderate intensity ($63 \pm 7\% \text{ VO}_2 \text{ max}$). Basal insulin dose reductions were introduced 3 days before the first exercise session, with 5 consecutive days of exercise being performed under either a 100% or 75% individualised IDeg dose. Trials were separated by a four-week wash out period and acutely standardised with participants consuming a comparable ~63g CHO at least two hours before the start of exercise combined with an individualised bolus insulin dose. This minimised the possible contributions of opposing basal and acute bolus insulin manipulations on exercise performance and glycaemia.

The two main variables assessed were (1) time spent in specific glycaemic ranges and (2) number of hypoglycaemic events over the five days of consecutive exercise. The study concluded that a 25% reduction of basal IDeg around exercise has the potential to increase time

spent in euglycaemia, though had no influence on time spent in hyper- or hypoglycaemia or the number of hypoglycaemic episodes.

Critique

This study provided an excellent insight into acute glycaemic outcomes associated with IDeg manipulations around exercise. However, subject numbers were small and included a relatively homogenous group with good glycaemic control. This not only makes wider generalisation difficult, but also overlooks important diabetes related variables. Moreover, the dose reduction was made three days prior to the initial exercise session. Outside of elite or specifically structure sports programming, this degree of forewarning is largely unrealistic for the majority of recreationally active individuals. Thus, given the ultra-long duration of IDeg, questions remain as to whether a reduction in the basal insulin dose on the day of, or evening before the anticipated exercise provides protection against the risk of hypoglycaemia.

Finally, although overall time spent in glycaemic ranges provides valuable metrics, a further breakdown focusing on specific time frames i.e acutely post exercise and nocturnal periods, would be of much clinical and practical relevance.

Further research going forward

With new insulin analogues that differ in their pharmacokinetic and pharmacodynamic profile being made available, exploring the interaction of modern insulin analogues and exercise is crucial in our understanding of how we can encourage patients with type 1 diabetes to maintain a physically active lifestyle. The results of this study have set a premise for future research which should continue to investigate the effect of IDeg manipulations around exercise, carbohydrate feeding and rapid acting insulin adjustments. From a clinical perspective the inclusion of patients with varying degrees of glycaemic control and physical fitness would provide invaluable information that assists the development of exercise guidelines.

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