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Glycemic control in people with diabetes mellitus

1 Introduction

Diabetes mellitus is classified as a chronic metabolic disease sharing common metabolic dysfunctions with cardiometabolic syndrome, which has now been recognised as a disease entity by the World Health Organisation **[1]**.

There are mainly two types of diabetes mellitus, namely type 1 (T1DM) and type 2 (T2DM). T1DM is an autoimmune disease whereby pancreatic cells are destroyed and is commonly diagnosed in adolescents. T2DM on the other hand, occurs when the pancreas does not produce enough insulin and the relevant insulin sensitive cell receptors are rendered unresponsive.

Screening, diagnosis, and management of both types of diabetes lie at the forefront of current efforts to combat the prevalence and effects of the chronic disease on global mortality rate. Studies so far have shown that, screening compared to no screening for diabetes mellitus does not affect all-cause mortality **[2, 3]**. Regarding diagnosis, most studies indicate that it is possible to accurately diagnose people with either T2DM or prediabetes (impaired glucose tolerance) **[4]**.

As far as management of diabetes mellitus is concerned, the most important factors are, control of blood glucose levels and healthy diet regimes. Optimal management of the condition is greatly dependent on the balance between insulin replacement administration and the ability of people with diabetes mellitus to adhere to healthy diet regimes.

There are numerous insulin analogues and biosimilars as well as insulin delivery pathways, and these are critical factors in achieving glycemic control and minimising the occurrence of events such as hypoglycaemia (below threshold blood glucose levels) and hyperglycaemia (above threshold blood glucose levels). The risk of complications in people with diabetes mellitus is minimal if blood glucose levels are strictly monitored and controlled quickly.

In the remainder of this report, the types of insulin analogues and their activity, toxicological and glycemic control efficacy profiling are discussed. Moreover, the different pathways for exogenous insulin administration into the human body are discussed and critically compared. Finally, where possible, conclusions are drawn, taking also into account the importance of patient adherence to healthy diet regimes.

2 Insulin analogues

2.1 Development of insulin analogues

Nowadays, insulin analogues are grown in bio-fermenters using suitable microorganisms and recombinant DNA technology, prior to being purified **[5]**. In the past, exogenous insulin was usually extracted from the pancreas of animals such as pigs.

Currently, a lot of studies are being conducted to assess the advantages of adding more insulin purification stages in the form of High-Performance-Liquid-Chromatography. Despite these

efforts, it has not yet been proven whether purified insulin analogues resembling native human insulin the most, provide optimal insulin therapy. In addition, insulin analogues derived from recombinant DNA technology are far more costly to produce than animal insulins **[6, 7]**.

The production of insulin analogues in bio-fermenters can be more easily tuned to assist in avoiding systemic allergic complications in people with T1DM and T2DM **[7]**. Their purification remains important since, they may be used in T1DM and T2DM combination therapies. which involve taking both insulin and non-insulin oral medications. The non-insulin ones are usually substances which handle the metabolic assimilation of ingested carbohydrates **[8, 9]**.

2.2 Types of Insulin analogues

There are several types of insulin analogues and these are characterised based on their onset of action, peak-action time, and duration of action, following administration in the bloodstream **[10]**.

The most common regimen of insulin therapy is the standard basal-bolus regimen. Basal (background) insulin is administered during periods of fasting whereas bolus insulin is taken after meals. Basal insulin is long or intermediate-acting whereas bolus insulin is short or rapid-acting. Another common regimen prescribed nowadays is that of administering intermediate-acting insulin twice per day **[11]**.

When developing new insulin analogues, the starting point for comparing their efficiency is usually based on these two regimens. For example, *degludec* (*IDeg*), a new generation long-acting insulin analogue, was compared in terms of its ability to reduce the frequency of nocturnal hypoglycaemia events in T1DM patients while being administered only once per day. The basis for comparison in this case, was that of intermediate-acting insulin being administered twice per day **[12]**.

Figure 1 depicts typical glucose and endogenous insulin blood concentration profiles for healthy individuals, and clearly shows that insulin secretion from the pancreas closely follows the natural dynamic cycle of blood glucose. Any exogenous insulin analogue aims to mimic this behaviour closely.

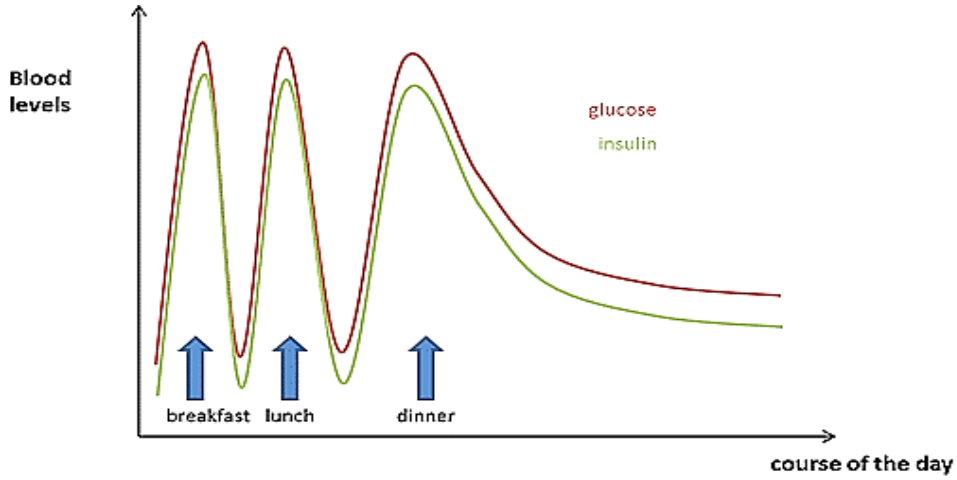

Figure 1: Circadian dynamic of blood glucose and insulin in blood following secretion from the pancreas. Food intake and postprandial blood glucose peaks are managed by synchronous endogenous insulin release **[13]**.

In addition, figure 2 depicts activity against duration of action, for different types of insulin analogues. Table 1 describes the characteristics of these types of insulin analogues.

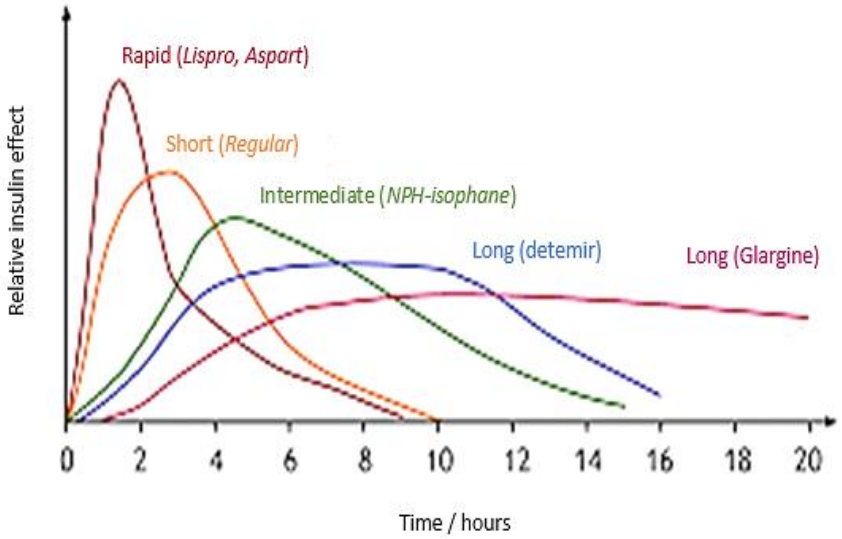

Figure 2: Relative insulin effect against time since injection into a patient for different types of insulin analogues **[14, 15]**.

Table 1: List of characteristics and common examples of insulin analogues used in treatment therapies for T1DM and T2DM **[15]**.

Insulin analogue type	**Blood activity characteristics (time following subcutaneous injection)**	**Examples**
Rapid acting	• Onset of action: ~ 15 min. • Peak action time: ~ 2 hr. • Duration of action: ~ 2-4 hr.	• *Humalog* • *Admelog*
Regular short acting	• Onset of action: ~30 min. • Peak action time: ~ 3-4 hr. • Duration of action: ~ 3-6 hr.	• *Humulin R* • *Novolin R* • *Velosulin R*
Intermediate acting	• Onset of action: ~ 2-4 hr. • Peak action time: ~ 6-8 hr. • Duration of action: ~ 12-18 hr.	• *Humulin N* • *Novolin N* • *ReliOn*

Long acting	• Onset of action: ~ 7 hr. • Peak action time: ~ 12 hr. • Duration of action: ~ 24 hr.	• *Degludec (IDeg)* • *Detemir* • *glargine*

Insulin activity profiles are essential, regarding the correct classification of each type of analogue for use in treatment of T1DM and T2DM. They form the basis for insulin treatment regimens.

A far as glycemic control is concerned, the toxicological profile of each type of insulin plays an important role in its approval for T1DM and T2DM treatment by authorities such as the Food and Drug Administration (FDA) in the United States **[16]**.

Moreover, when characterising the glycemic control efficacy of insulin, tests are conducted in clinical settings against different pharmacokinetic (PK) and pharmacodynamic (PD) variables **[17]**.

PK variables assess the effects the body has on a drug whereas, PD variables assess the effects a drug has on the body.

PK and PD parameters cannot be generalised. They vary depending on the clinical setting of any experiment. For example, studies were conducted on insulin analogues to quantify their glycemic control efficacy by measuring variables such as plasma glucose concentrations and glucose infusion rates (mg glucose per kg of body weight per minute). To determine the pharmacokinetics of the insulin analogues in these studies, blood samples were tested prior to the start of each treatment and 120 hr after the final dose of insulin in each treatment **[18]**.

On the contrary, to quantify the pharmacodynamics of the insulin analogues, a hyper insulinemic clamp was used. This device maintains normal blood glucose levels and then acutely raises blood plasma glucose concentrations to 125 mg/l above basal glucose concentrations. Continuous infusion of glucose assisted in analysing the PD response of the insulin analogues, which was examined after the final dose of each treatment in each experiment **[18]**.

2.3 Toxicological and glycemic control efficacy profiling of insulin analogues

In the case an insulin analogue is intended for use in both T1DM and T2DM patients, independent clinical toxicological assessments targeting specifically either T1DM or T2DM patients must be conducted.

This approach is also employed when assessing the glycemic control efficacy of insulin analogues. For example, studies designed to assess the PK and PD properties of insulin analogues in T1DM patients, cannot be used to support robust conclusions about the clinical utility and clinical risk/benefit analyses of insulin analogue formulations used in T2DM patients. There is extensive supporting evidence of conflicting conclusions from studies that investigated the same insulin analogues using different study design features and analytical approaches. However, frequent clinical pharmacological studies and PK and PD profiling of

insulin analogues intended for use in either T1DM or T2DM patients can provide valuable insights to better design and conduct large scale future clinical studies **[19, 20]**.

For toxicological profiling in general, the key features that need to be examined are the metabolic and mitogenic properties of insulin analogues. Mitogenic potential refers to the ability of the insulin analogues to induce the cells located in their immediate surroundings to begin cell division. Studies show that there is not yet clear clinical or in vivo evidence for carcinogenic effects of commercially available insulin analogues at therapeutic doses. There is, however, evidence of mitogenic potency in non-commercial insulin analogues from in vitro studies in cancer cell lines. The metabolic activity is commonly assessed in vitro studies using glucose uptake and stimulation of lipogenesis **[21]**.

Another fundamental feature in toxicological profiling is the ability of the insulin formulation to rapidly convert into its pharmacologically active metabolites. This minimises the in vivo exposure of cells to the insulin analogue. Long-acting *glargine* for example, is rapidly converted into its pharmacologically active metabolites in the bloodstream **[22]**.

As far as glycemic control efficacy is concerned, there are many biomarkers and glycemic variables that are measured continuously or on average temporally. Examples include glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG), portal vein glucose/insulin concentrations and plasma glucose/insulin concentrations among others **[23, 24]**. It has not yet been established, which combination of glycemic parameters gives the best means by which to compare the glycemic control efficacy of various insulin analogues. There are, however, many statistical models that are currently being employed in Machine Learning algorithms to identify the optimal bundle of determinant parameters for glycemic control in T1DM and T2DM patients **[25, 26]**.

3 Exogenous insulin delivery pathways

3.1 Available routes for exogenous insulin administration

Common routes for insulin administration in people with T1DM and T2DM include oral insulin (ingestion), inhalation of insulin in aerosol spray or powder form and subcutaneous insulin injection in the upper arm or abdomen. There are other modes of insulin delivery such as, intraperitoneal through a thin membrane beneath the surface of the abdomen, but these will not be discussed. The main ones widely used or studied are the oral, subcutaneous, and inhaled insulin pathways **[27]**.

As far as the inhaled insulin delivery pathway is concerned, nebulisers were initially used. This pathway offers the advantage of increased insulin absorption into the bloodstream through large perfusive areas in the alveoli of the lungs. However, the exact mechanism of insulin absorption through the pulmonary epithelium remains unclear. The first products used insulin in dry powder form but led to increased risk of hypoglycaemia in smokers due to increased absorption. They were withdrawn from the market due to their high cost and bulkiness. Nowadays, new inhalation devices are being investigated such as AERx, Aerodose, proMaxx and Afrezza. These are close to FDA approval **[28]**.

In general, the inhaled insulin route is associated with technical and long-term safety issues. Currently there is much more investment in the oral and subcutaneous insulin delivery modes for commercial applications **[28]**.

3.2 Comparisons between oral and subcutaneous insulin delivery pathways

Oral insulin delivery involves absorption of insulin tablets through the gastrointestinal (GI) tract into the portal vein leading to the liver **[29]**. It more closely mimics physiological basal insulin concentrations. On the contrary, subcutaneous insulin delivery involves injection of insulin via insulin smart pens or insulin pumps into the interstitial fluid under the skin **[30]**.

Table 2 lists the benefits and disadvantages of the oral and subcutaneous insulin delivery pathways.

Table 2: List of advantages and disadvantages of oral and subcutaneous insulin administration routes.

Insulin delivery mode	Advantages	Disadvantages
Subcutaneous injection	• Combines insulin pump and glucose monitoring technologies **[31]**. • Integration with digital diabetes apps and clinics for sharing real time meta-data on glycemic variables [**32]**. • Employs sensor augmented pump therapy (SAP) which replaces multiple daily injections (MDI) of insulin, cost effectively **[33]**.	• Psychological factor of needle phobia and physical injection pain **[34]**. • May result in peripheral vein hyperinsulinemia **[35]**.
Oral	• More closely mimics physiological insulin delivery through the portal vein **[36]**. • Less intrusive than subcutaneous with higher patient compliance **[37]**.	• Limited insulin absorption through GI tract **[38]**. • Potential of altered gut microbiome in host and extraintestinal organ insulin accumulation **[39]**. • More demanding toxicological profiling of insulin conjugates and coated insulin nanoparticles **[40]**.

As far as the oral insulin delivery pathway is concerned, the large size and hydrophobicity of insulin result in low permeability through the GI tract. Numerous efforts are underway to develop insulin tablets coated with pH adjusters, insulin solubilisers and absorption enhancers which promote sustained and targeted release of insulin through the GI tract. Enteric coatings and methacrylic acid copolymers which are pH activated are widely used in this domain. These substances should ideally be insoluble in media with pH of less than 6. Figure 3 depicts a common enteric coating drug release profile **[41, 42]**.

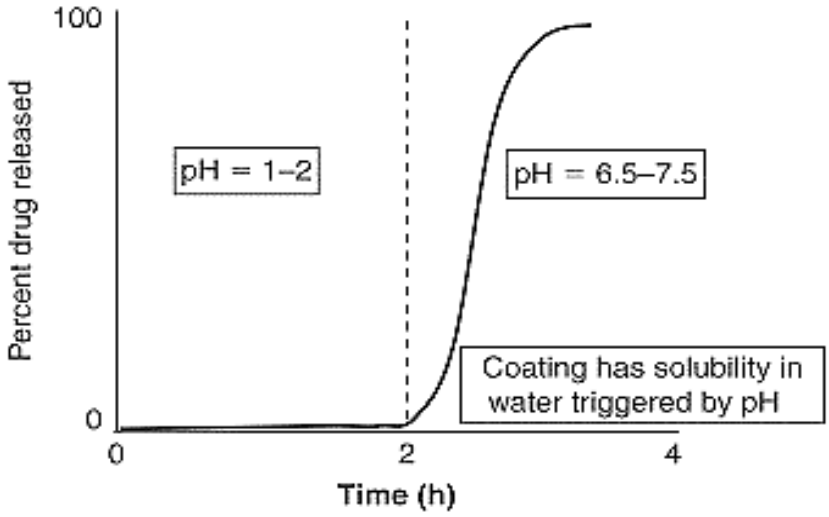

Figure 3: Typical enteric coating drug release profile. The profile should ideally exhibit inhibition of drug release in stomach acid conditions **[42]**.

Many oral insulin conjugates undergoing clinical trials are enteric coated, but no oral delivery system developed thus far has demonstrated a clear clinical advantage over the subcutaneous route **[43]**. In addition, toxicological profiling of these substances proves to be a burden since, experimental exposures to large short-term doses are unable to mimic the realistic outcome of long-term minimal dose exposure in people **[44]**.

The subcutaneous route does not offer these drawbacks. It also allows use of Sensor Augmented Pump therapy (SAP) which combines glucose monitoring sensor technology with pump injection technology. Medtronic's MiniMed system is an example of a commercially available sensor-pump integrated device **[45]**. These devices have Threshold Suspend (TS) automated systems which minimise the likelihood of nocturnal hypoglycaemia events, mainly in people with T1DM. These automated systems work by suspending insulin delivery for up to 2 hr when plasma glucose concentrations are at low thresholds of 60-70 mg/dl. The TS system was approved by the FDA to reduce the severity and duration of hypoglycaemia events **[46]**. However, there are still risks associated with the technologies used in the subcutaneous delivery pathway. These include the risk of excessive correction of high/low glucose, alert fatigue of TS system leading to alert silencing or glucose monitoring termination and allergic reactions to the adhesives keeping the subcutaneous insulin sensors in place **[47]**.

Each insulin delivery route has its advantages and disadvantages. The one employed widely commercially though, is the subcutaneous route which permits integration with glucose monitoring devices.

4 Conclusions

Overall, glycemic control in people with diabetes mellitus is a multistage process and more importantly, varies from patient to patient. Development of insulin analogues and the optimisation of their activity profiles is one piece of the puzzle. Insulin treatment regimens usually combine at least two types of insulin and the delivery of these analogues to patients with either T1DM or T2DM is an equally important stage in the process.

The subcutaneous delivery mode is widely used because it combines technologies such as glucose monitoring systems which can be deployed and integrated with digital environments. Information gathered using glucose monitors can be readily transmitted to medical doctors, and glycemic control can become more interactive and personalised in this manner.

Adherence of people with diabetes mellitus to healthy diet and exercise regimes is also a critical factor. The subcutaneous insulin delivery route and the technologies it combines are means by which patient compliance to healthy diet and exercise can be encouraged.

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