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REVIEW ARTICLE

Different Insulin Initiation Regimens in Patients with Type 2 Diabetes - A Review Article

Mir Mudassir Ali[1*], Khin Thida Aung[2], Madelein Young[3], VS Eligar[4] and JS Davies[4]

[1]*Department of Acute Medicine, University Hospital Lewisham, UK*

[2]*Department of General Practitioner/Family Physician, Metis Clinic, Tavoy, Myanmar*

[3]*Department of Health Sports and Science, University of South Wales, UK*

[4]*Department of Diabetes and Endocrinology, University of South Wales, UK*

***Corresponding author:** *Mir Mudassir Ali, Department of Acute medicine, University Hospital Lewisham, UK Tel: 447918723005, E-mail: Mudassir.ali@nhs.net; dr.mudassir87@gmail.com*

Introduction

The United Kingdom Prospective Diabetes Study [1] has shown that beta-cell function declines over time, and insulin will be needed to achieve good glycaemic control in type 2 diabetes mellitus (T2DM). Recent studies show that initiating insulin early, especially when HbA1c (Glycated haemoglobin) is > 9% improves glycaemic control and patient outcome [2]. Meta-analysis by Kramer, et al. [3] showed that short term intensive insulin therapy for 2-3 weeks had favourable outcomes on recovery and maintenance of beta-cell function, glycaemic remission besides increment in beta-cell function and decrease insulin resistance.

The decision of health care professional (HCP) to start insulin therapy is precipitated by [4]:

- Worsening symptoms of hyperglycaemia.
- A persistently elevated HbA1c despite maximum tolerated doses of oral hypoglycaemic therapy.
- Inter-current illness or patient started on steroid therapy.

It is imperative to review the patient's diet and compliance with medicine before making a decision to start insulin therapy. National Institute for Health and Care Excellence (NICE) [5] recommends using insulin based therapy when HbA1c remains ≥ 7.5% or 58 mmol/mol after using suitable oral hypoglycemic agents or GLP-1 analogs if appropriate. Combination of most of the oral hypoglycaemic agents (OHAs) with insulin is very effective and safe, provided you consider mechanism of action of different types. Consider the on-going need for the OHAs while patient is on insulin. The Medicines and Healthcare products Regulatory Agency [6] has advised to be careful while using insulin with pioglitazone as it can increase risk of heart failure, especially in patients at risk. Continue metformin if there is no contraindication or intolerance [5]. In patients where metformin can't be used due to renal impairment, dipeptidyl peptidase-4 (DPP-4) inhibitors in dosage based on eGFR (estimated glomerular filtration rate) can be used along with insulin, as they are weight neutral and increases sensitivity of islet cells to glucose, without risk of hypoglycaemia. It would be prudent to continue agents like Sodium glucose co-transporter (SGLT2) inhibitors or Glucagon Like Peptide (GLP-1) RA if required. SGLT2 inhibitors act through insulin independent pathways and reduce the total insulin dose required due to the glycosuria. GLP-1 receptor analogs has been approved by NICE to be used along with basal insulin only. Sulphonylureas or insulin secretagogues should be avoided in combination of insulin in view of increased risk of hypoglycaemia, unless used in reduced doses. The various insulin types available are:

1) **Rapid acting:** Begins to work in 15 minutes, peak around 1 hour and continues to work for about 2-4

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hours.

2) **Ultra fast acting:** Apidra (Fiasp) Which begins to act 4-7 minutes before regular apidra and lasts for around 3 hours.

3) **Short acting:** Reaches systemic circulation in 30 min, peaks after about 2-3 hours and remains active for around 3-6 hours.

4) **Intermediately acting:** Onset of action after 2-4 hours, peaks 4-12 hours later and remains active for about 12-18 hours.

5) **Long acting:** Gradually absorbed from injection site due to unique preparation. Its activity can range from 18-24 hours. The ultra-long acting insulin degludec, has plasma concentrations measurable beyond 24 hours allowing for flexible dosing.

The table, summarises various insulin types and preparations available in market (Table 1).

There are many reasons that patients do not achieve glycaemic targets. These can be patient factors, disease related factors and also clinical inertia, for example, delay in intensification of treatment [7]. (Table 2)

The Evidence Based Use of Various Insulin Types and Regimes are Discussed Below:

Basal insulin and dose titration

Table 1: Various insulin types and preparations available in market.

Description	Insulin and insulin analogue preparation
Rapid acting insulin	Lispro
	Aspart
	Glulisine
Short acting insulin	Regular/soluble insulin
Ultra-fast acting insulin	Aspart (Fiasp)
Intermediate acting insulin	NPH or Isophane insulin
Long acting insulin	Glargine
	Detemir
	Degludec (Ultra-long acting)
	Toujeo (Glargine-high strength insulin)
Biosimilar insulin	Abasaglar (Glargine)
Premixed insulin (Human)	70% NPH 30% Regular
	50% NPH 50% Regular
Premixed insulin (Analogues)	75% NPL 25% Lispro
	50% NLP 50% Lispro
	70% Protamine aspart 30% Aspart

NPL: Neutral Protamine Lispro; NPH: Neutral Protamine Hagedorn.

When initiating insulin in T2DM, NPH insulin is the preferred option either once or twice daily, according to the need, unless:

- Individual's lifestyle is affected by symptomatic hypoglycaemia, or
- Twice daily insulin injection is deemed inappropriate due to other reasons.

In such situations a long-acting insulin analogue, detemir or glargine, should be considered [5]. The newer insulins like degludec, toujeo (high strength insulin) and biosimilars (example: Abasaglar) can also be used.

It can be initiated as 10 U/day or 0.1-0.2 U/kg/day. To reach the target fasting plasma glucose (FPG) level, titration of insulin is done by 10-15% or 2-4 units (U) once or twice weekly [8].

The duration of action of lantus and NPH is around 24 hours and 14 hours or more respectively. The effectiveness of basal insulin is estimated by FPG levels and titrated accordingly. The best time to dose basal insulin is either with evening meal or before bedtime [8] (Table 3).

The benefit of long-acting analogue insulins over NPH insulin, appears to be in the lower incidence of nocturnal hypoglycaemia, which must be a consideration when determining insulin choice. Due to its lesser day-to-day variability, degludec has the potential to further reduce the risk of hypoglycaemia than other long-acting basal insulins [9]. The DEVOTE study showed that degludec was non-inferior to glargine with respect to incidence of cardiovascular events with significant reductions in severe hypoglycaemia, especially nocturnal [10].

High-strength insulin products such as insulin glargine 300 units/ml (Toujeo) have been developed for people with type 1 or type 2 diabetes who have large daily insulin requirements to reduce the number and volume of injections. In 3 randomised controlled trials (RCTs) in 2496 adults with type 2 diabetes, Toujeo had similar efficacy to insulin glargine 100 units/ml (Lantus) in terms of HbA1c reduction [11].

Toujeo is not bioequivalent to insulin glargine 100 units/ml (Lantus) and dose adjustment is needed when patients are switched from Lantus or other basal insulins to Toujeo or vice versa.

Premixed insulin and dose titration

Premixed insulin therapy is suitable for patients who cannot count carbohydrates or those who have consistent

Table 2: The causes of secondary drug failure to Oral hypoglycemic agents [31].

The patient factors	Disease related factors
• An improper diet • Obesity • Lack of exercise • Lack of knowledge of diabetes and stress	• An impaired C-peptide response to a meal • An enhanced basal rate of hepatic glucose production which is insufficiently suppressed by insulin • Impaired storage of glucose as glycogen

Table 3: Evidence of analogue insulin used in the treatment of T2DM.

Study	Intervention	Outcomes	Statistical significance
Swinnen, et al. [32] (24 week randomised trial)	Once daily glargine versus twice daily detemir	27.5% glargine and 25.6% detemir achieved HbA1c < 7%	P = 0.254
		Greater proportion detemir patients < 6.5% Weight gain higher for glargine	P = 0.017
		Lower doses of glargine for equivalent glycaemic control	P < 0.001
		Hypoglycaemia similar	P < 0.001
Meneghini, et al. [33] (26 week randomised trial)	Detemir versus glargine	38% detemir and 53% glargine achieved HbA1c < 7% Weight loss with detemir (- 0.49 kg) versus weight gain with glargine (+ 1.0)	P = 0.026
		Lower doses of glargine for equivalent glycaemic control	P = 0.0208
		Reduced incidence of hypoglycaemia for detemir	P = 0.034
Waugh, et al. [34]. Systematic review of long-acting insulin analogues	Glargine versus NPH	Similar improvements to HbA1c	Not Significant (NS)
		Hypoglycaemia, symptomatic, nocturnal and severe	Mixed results some significant reduction for glargine, some NS
		Weight gain for both glargine and NPH	NS Mixed results
	Detemir versus NPH	Similar improvements in HbA1c	P < 0.05
		Symptomatic and severe hypoglycaemia	P < 0.00001 [34]
		Less nocturnal hypoglycaemia for detemir	P < 0.05
		Less weight gain for detemir than NPH	
Zinman, et al. [35] (1 year trial)	Degludec versus glargine	Reduction in HbA1c similar in both groups Insulin doses similar Confirmed hypoglycaemia similar	P = 0.40
		Confirmed nocturnal hypoglycaemia less for degludec	P = 0.106
		Less severe hypoglycaemia for degludec	P = 0.004
		Similar weight gain in both groups	P = 1.017
Marso SP, et al. [10] (DEVOTE, 3 Year trial)	Degludec versus Glargine (Cardiovascular safety)	Primary outcome	Hazard ratio 0.91, 95% CI 0.78-1.06 P < 0.001 for non-inferiority Rate ratio 0.6, P < 0.001 for superiority
		Severe hypoglycaemia incidence	Odds ratio 0.73, P < 0.001 for superiority

eating patterns and routine lifestyle. Initiating insulin therapy with premixed insulin once daily, opens the possibility of a stepwise approach to intensify therapy to twice or thrice daily to achieve target HbA1c levels [12]. NICE [5] recommends to start premixed insulin if HbA1c > 9.0%.

A twice daily dose has been recommended for initiation of premix insulin but a once daily dose has been found to be effective for patients who are reluctant to start insulin and require < 20 units/day [13]. Kilo, et al. [14] evaluated the effectiveness of initiating patients on a simple once daily regimen with insulin aspart 30/70, NPH insulin and biphasic human insulin 30/70, in combination with metformin. The results showed a 1.1%-1.3% reduction of Hba1c for all groups with FPG reductions of 31% for aspart 30/70, 37% for NPH and 28% for biphasic human insulin, concluding that each one could safely be added to metformin.

Premixed insulin can be initiated according to the following common standards [15]:

- 10 U/day once daily either in the morning or evening or 0.3-0.5 U/kg/day, depending on glucose level.
- 0.2 U/kg/day for Hba1c < 9% and 0.4 U/kg/day for Hba1c > 9%. Patients with Hba1c > 9% are at increased risk of complications, hence optimal glycaemic control is required.
- Twice a day premixed insulin if total daily dose of insulin (TDD) is more than 20 U, dosed along with breakfast and evening meal based upon carbohydrate content in meal and daily activity.
- The 50:50 ratio can be considered for premix analogues, if a single dose exceeds 30 U.

Tanaka and Ishii [16] found lispro mix 50/50 insulin, which is high proportion insulin containing 50% rapid and 50% intermediate acting insulin, controlled the post-prandial glucose (PPG) and stabilised the diurnal blood glucose variations in patients who had poor control on insulin 70/30 or 75/25. Lispro 50/50 had more rapid onset of action with lower risk of nocturnal hypoglycaemia.

The initial dose can be titrated once or twice weekly for 12 weeks and every two weeks thereafter, according to the FPG targets as per algorithm below [15] (Table 4).

Basal-plus insulin

The addition of a single prandial insulin injection to the already existing basal regimen before the main meal or the meal consistent with highest PPG, is referred to as a "basal-plus" strategy [17,18]. This has been an effective method when intensifying insulin therapy, before a full basal-bolus regimen is to be implemented [19]. Careful patient evaluation and timing are necessary due to the complex nature of this regimen and the need for multiple daily injections and multiple daily glucose monitoring. Therefore younger, highly motivated, active individuals with variable eating habits with both type 1 and T2DM will be best suited for such a regimen (Table 5).

From the results obtained in table, not all differences observed were statistically significant when comparing them in the use of this strategy to basal-bolus and premixed regimens.

Table 4: Premixed insulin dose titration.

Pre-meal plasma glucose level	Dose titration units (U)
≤ 100 mg/dl (≤ 5.6 mmol/l)	- 2U
100-110 mg/dl (5.7-6.1 mmol/l)	No change
110-140 mg/dl (6.2-7.8 mmol/l)	+ 2U
140-180 mg/dl (7.9-10 mmol/l)	+ 4U
≥ 180 mg/dl (≥ 10 mmol/l)	+ 6U

Basal-bolus regimen and dose titration

Basal-bolus regimen is an intensified insulin therapy when target glycaemic control is not achieved with basal insulin. This regimen mimics the physiological insulin secretion from the pancreas. The intermediate or long acting insulin is given as basal insulin. The rapid or short-acting insulin is given as bolus insulin before meal. This regimen needs frequent and active self-monitoring, knowledge on insulin-carbohydrate ratio and correction factors (CF), and titration of insulin dose to achieve target glycaemic control [20].

The basal-bolus insulin regimen can be initiated by intensifying the basal or basal plus regimen. To initiate, the TDD (0.6-1.0 units/kg) is first calculated. Then 50% of TTD is given as basal insulin which is administered at bedtime. The remaining 50% is divided between bolus doses for breakfast, lunch and dinner [21].

There are different methods of dose titration, adjusting 2-3 units in appropriate dose every 3-7 days to achieve the target. Generally, titration of basal insulin is based on FPG, while bolus insulin is based on pre prandial or PPG levels at mentioned in table 6 [21].

- Increase or decrease insulin by 10% depending on blood glucose reading shown in Table 6 [21].

Table 5: Evidence for the use of the basal-plus strategy.

Trial	Duration & Population Size	Intervention	Target HbA1c	Results
1.2.3 study [36]	24 weeks 115 subjects vs. 113 subjects	Insulin glargine + OHA's + once daily insulin glulisine vs. insulin glargine + OHA's + twice daily insulin glulisine	< 7%	• Proportion achieving target HbA1c: 30% vs. 33% • Severe hypoglycaemia 0.28 vs. 0.89 events/ patient year • Weight change + 3.8 vs. + 4.1 kg
Stepwise [18]	48 weeks 150 subjects vs. 146 subjects	Insulin detemir + OHA's + stepwise aspart to largest meal (based on premeal glucose): Simple STEP vs. Insulin detemir + OHA's + stepwise aspart to largest meal (based on post-meal glucose) Extra STEP	< 7%	• Proportion achieving target HbA1c: 31% vs. 27% • Severe hypoglycaemia 0.04 vs. 0.01 events/ patient year • Weight change + 2.7 vs. + 2.0 kg
All to target [37]	60 weeks 192 subjects vs. 189 subjects vs. 191 subjects	Twice daily premixed insulin + 2-3 OHA's vs. insulin glargine + once daily glulisine + 2-3 OHA's vs. insulin glargine + stepwise addition of insulin glulisine + 2-3 OHA's	< 7%	• Proportion achieving target HbA1c: 39% vs. 49% vs. 45% • Severe hypoglycaemia 0.02 vs. 0.1 vs. 0.2 events/patient year

Table 6: Insulin dose optimisation according to blood glucose readings.

Basal/bolus insulin	Time of self-monitoring blood glucose
Basal insulin	Fasting pre-breakfast blood glucose
Pre-breakfast bolus insulin	2-hours post-breakfast or pre-lunch blood glucose
Pre-lunch bolus insulin	2-hours post-lunch or pre-dinner blood glucose
Pre-dinner bolus insulin	post-dinner or bedtime blood glucose

- To titrate the bolus dose, add or deduct the correction dose to or from the bolus dose.

  Correction dose = Excess or deficit blood glucose × CF.

  CF = 1500/TDD (will give the value in mg/dl, used when patient is on rapidly acting insulin)

- To titrate the basal dose, some use Treat-to-Target Trial's titration schedule as per table [22] (Table 7).

Giugliano, et al. [23] concluded it to be the best regimen to attain the target glycaemic control. The patients treated with basal-bolus regimen had statistically significant achievement of HbA1c target of < 7% compared to biphasic insulin, 63.5% vs. 50.8% (odd ratio 0.57 [95% CI 0.36-0.90]) (p = 0.034). No difference was seen in terms of incidence of hypoglycaemia or weight gain between the two regimens.

In Treating to Target in Type 2 Diabetes (4-T) study, 67.7% of the patients in biphasic group, 73.6% in the prandial group and 81.6% in the basal group were later intensified to basal-bolus regimen, and two-third of them reached the glycaemic target [24].

Premix human insulin vs. Premix analogue insulin

Insulin analogues closely mimic physiological endogenous insulin secretion. Compared to human insulin formulations, they have a more predictable onset and duration of action, along with increased flexibility for dose administration and meal times [25].

A comparative analysis of various studies comparing premix human insulin vs. premix insulin analogues is given in the Table 8.

In conclusion, premix analogues are similar to human insulin but some trials have shown better HbA1c reduction. The main advantage is better post-prandial glucose control and less delayed hypoglycaemia.

Table 7: Treat-to-Target trial's titration schedule for basal insulin.

Fasting blood glucose	To increase in basal insulin
120-140 mg/dl (6.7-7.8 mmol/l)	2 units
141-160 mg/dl (7.9-8.9 mmol/l)	4 units
161-180 mg/dl (9.0-10 mmol/l)	6 units
> 180 mg/dl (> 10 mmol/l)	8 units

Premixed versus basal insulin

When initiating insulin, the HCP could consider premixed or basal insulin, depending on clinical situation (Table 9).

These studies show that glycaemic control can be better with pre-mixed rather than basal insulin, but with higher risk of hypoglycaemic episodes and weight gain.

Fasting glucose levels contribute to HbA1c at all levels of glycaemia, but when HbA1c is less than 9%, prandial glucose levels become more important. However, further analysis of DURABLE trial showed that only premixed lispro insulin decreased prandial glucose. Where initial HbA1c was less than 9%, there is greater improvement in HbA1c with pre-mixed insulin rather than basal [26].

Thus for the following patients, pre-mixed insulin may provide better glycaemic control [27]:

- HbA1C > 8.5%.
- Poor patient compliance with high demands of basal bolus regimen.

Table 8: Comparing premix human insulin vs. premix insulin analogues.

Glycaemic control					
Name of study	**Study population size (n)**	**Patients included**	**Drugs compared**	**Inference**	**p Value**
Matto, et al. [38]	n = 151	Type 2 diabetes	Insulin lispro 75/25 vs. Human insulin 70/30	Reduction in mean 4 point blood glucose profile: Insulin lispro > Human insulin	p = 0.004
Malone, et al. [39]	n = 84	Type 2 diabetes	Insulin lispro 75/25 vs. Human insulin 70/30	PP blood glucose excursion: Lower with insulin lispro than human insulin	p < 0.001
				AUC in glucose concentration - time curve: Less in insulin lispro than human insulin	----
Christiansen, et al. [40]	n = 403	Type 2 diabetes	BI Asp 30 vs. NPH (BD)	Comparable reduction in HbA1c with both (0.67% with BI Asp 30 0.61% with NPH)	----
				PP increment over 3 meals: Lower with BI Asp 30 than NPH	p < 0.0001
Boehm, et al. [41]	n = 294	Type 1 diabetes and Type 2 diabetes	BI Asp 70/30 vs. Human insulin 70/30	Reduction in HbA1c: Similar with both	----
				PP blood glucose control: BI Asp > Human Insulin	----
PP: Post Prandial; AUC: Area Under Curve; BI Asp: Biphasic Insulin Aspart.					

Table 9: Comparing pre-mixed and basal insulin initiation regimens in T2DM.

Study	Population criteria	Types of insulin used	Effect on HbA1c	Adverse effects
Giugliano, et al. [23] Meta-analysis of 16 RCTs	7759 patients with T2DM where RCTs were for at least 12 weeks	Biphasic premixed insulins, short-acting prandial insulins and basal insulin	Premixed insulin lead to OR 1.88 to achieve HbA1c < 7% compared with basal insulin	Premixed insulin was associated with 0.34 more hypoglycaemic events/ patient/30 days than basal insulin 1 kg more weight gain was seen with premixed insulins
Janka, et al. [42] Multinational, multicentre, open parallel group study	371 insulin naïve individuals with T2DM and HbA1c between 7.5-10%	Once daily morning insulin glargine and OHAs compared with 30% regular/70% human NPH insulin twice daily alone	Reduction of 1.64% with glargine compared to reduction of 1.31% premixed insulin (p = 0.0003) Glargine led to 45.5% of patients with HbA1c ≤ 7.0% compared to 28.6% without confirmed nocturnal hypoglycaemia (p = 0.0013)	4.07 hypoglycaemic events/ patient year with glargine 9.87 hypoglycaemic events/ patient year with premixed insulin (p < 0.0001)
Initiate study [43] 28 week parallel-group study	233 insulin naïve patients with HbA1c ≥ 8.0% on OHAs Metformin was titrated to 2550 mg/day before insulin initiation	Premixed 70/30% twice daily insulin compared with glargine at bedtime	Mean HbA1c was 6.91% with premixed versus 7.41% with basal insulin (p < 0.01) HbA1c reduced by 2.79% with premixed compared to 2.36% reduction with basal insulin (p < 0.01) especially if HbA1c was > 8.5% HbA1c target of ≤ 6.5% was achieved in 14% more patients with pre-mixed (p < 0.05)	2.7 more hypoglycaemic episodes/year seen with premixed versus basal insulin (p < 0.05) 1.9 kg more weight gain with premixed versus basal insulin (p < 0.01)
Durable trial [44] 24 week randomised, multicentre, multinational, open parallel trial	2091 insulin naïve adults patients with T2DM with HbA1c > 7% on at least 2 OHAs for 90 days	Twice daily premixed lispro protamine suspension 75% and 25% lispro or daily glargine with continuation of OHAs in both groups	7.2% people achieved HbA1c target < 7% with premixed (p < 0.001) Premixed insulin showed 1.8% reduction compared to 1.7% seen with glargine (p = 0.005)	1.1 kg more weight gain seen with premixed rather than basal insulin (p < 0.0001) 4.9 more hypoglycaemic episodes/patient/year with premixed compared to basal insulin (p = 0.007) but fewer nocturnal hypoglycaemia (p = 0.007)

- Low (< 150 mg/dl) fasting or pre-prandial glucose but high HbA1c.

Therefore, despite ADA [8] advising to start patients on basal insulin, there may be situations where premixed insulin maybe more suitable.

Biosimilar insulin

A biosimilar medicine is a biological medicine that is developed to be very closely similar to an existing biological medicine (the reference medicine). The active substance of both is essentially the same biological substance but, just like the reference medicine, the biosimilar has some element of natural variability. Biosimilars undergo a regulatory process which demands extensive comparability studies that demonstrate similarity to the reference medicine. Biosimilars have the potential to offer considerable cost savings [28].

Insulin glargine biosimilar (Abasaglar) is licensed for the treatment of diabetes mellitus both type 1 and type 2. Abasaglar is a basal insulin for once daily use and is bioequivalent to insulin glargine (Lantus). Abasaglar is available as cartridges of 100 units/ml for use in the reusable pen or as a pre filled Abasaglar pen 100 units/ml [28].

The efficacy and safety of Abasaglar is non-inferior to Lantus and this evidence is based on the 2 phase III studies of insulin glargine biosimilar (Abasaglar) in people with type 1 and type 2 diabetes, ELEMENT 1 [29] and ELEMENT 2 [30], respectively.

Conclusion

HCPs should individualise the treatment and discuss with patients, regarding various options and educate them on insulin therapy. Basal insulin is preferred as an augmentation therapy when adding on to the oral hypoglycaemic agents. Replacement therapy includes basal-bolus regimen with correction dose or consider premixed insulin if appropriate [21].

Glucose control, adverse effects, cost, adherence and quality of life should be considered while choosing therapy. Titration of insulin over time is critical for glycaemic control and to prevent diabetes related complications [21]. Though basal-bolus resembles physiological insulin secretion, premixed analogues are good option with less demanding glucose monitoring and injection schedule. The rule should be tailoring the insulin treatment to suit patient and not the other way around [27].

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