



REVIEW ARTICLE

Simple Protocol to Initiate and Intensify Insulin in Primary Care

Faris Matloub*

Dubai Health Authority, United Arab Emirates



*Corresponding author: Faris Matloub, Dubai Health Authority, Dubai, United Arab Emirates, PO Box: 333751

The primary care physician often faced with type 2 diabetes that need insulin, usually when two or more oral hypoglycemic agents were tried and failed to maintain target glycemic control, owing to gradual decline in insulin secretion due to reduction of beta cell function. The likelihood for starting insulin is more the longer duration of diabetes. The United Kingdom Prospective Diabetes Study told us that 53% of patients initially treated with sulphonylureas required insulin therapy at 6 years, reaching up to almost 80% at 9 years.

The healthcare provider needs to inform and explain clearly that a new stage of disease had just started, and that this is not a sign of treatment failure neither to mark the succession of impending complications. After deciding the glycaemic target based on patient age, duration of diabetes, absence/presence of comorbidities and availability of support services, the attending physician and diabetes nurse often need to discuss the insulin option through rapport building relations. They would individualize insulin regimen and targets taking into consideration patients concerns, needs and lifestyle.

In most patient's insulin is started in addition to already given oral agents. Keeping "Metformin" on-board will minimize insulin dose and reduce weight gain plus its favourable cardiovascular effect. Secretagogues like Sulphonylureas or inhibitors of dipeptidyl peptidase 4 "DPP4 inhibitors" might need dose reduction to avoid hypoglycemia.

Usually a single injection of long acting insulin analogue "Glargine" or "Detemir" is started to suppress hepatic glucose production and maintain near normoglycemia in the fasting status. Should the insulin analogues are not affordable an intermediate acting

"Neutral Protamine Hagedorn - NPH" could be used instead as advised by NICE guidelines where a bedtime injection (rather than post dinner dose) is advisable; to let the peak action coincides with early morning hepatic glucose production.

The doses started is often determined by Hb A1C level. I found the AACE Comprehensive Diabetes Management Algorithm 2013 [1] so clear and easy to implement. It divides patients according to their respective Hb A1C level; those below 8% to start with 0.1 - 0.2 IU/kg, above 8% to start with 0.2 - 0.3 IU/kg usually given at bedtime. The patient is advised to monitor his fasting BG level to up-titrate the dose every 3 days: when FBG 110 - 139 mg/dL: to add 1 IU, when FBG 140 - 180 mg/dL: to add 2 IU and if FBG > 180 mg/dL: to add 4 IU.

If hypoglycaemia reported; to reduce insulin dose: when BG < 70 mg/dL: to reduce the dose by 10% - 20% and if BG < 40 mg/dL: to reduce the dose by 20% - 40%.

If glycemic targets are still not achieved, then it is time to intensify the regimen. Prandial insulin injection is usually added to make total daily insulin dose "0.3 - 0.5 IU/kg"; half basal and half prandial before the meals. Usually we start with one prandial bolus insulin before the largest meal, which is the lunch in the Arab Gulf and East Mediterranean region. Assessment in the next visit (usually after 2-3 months) is performed. If target could not be reached then a second prandial injection prior to the second largest meal is introduced. If I was not sure when to place the second dose then the higher glucose change pre and post meal will help. In most times a third one will follow for optimal control of both fasting and postprandial glucose levels. This will eventually end up into basal/bolus regimen.

A less commonly used form of insulin initiation is twice daily premixed insulin. It is combination of short/intermediate acting insulin. The short acting component serve to cover the meal that follows injection, while the intermediate component to cover the next meal (for morning dose) or to control morning FBG (for the evening dose). This approach is practiced more in Europe than in North America and my region of practice. Patients are started with two doses before breakfast and supper. However, some achieve target with single injection.

For example, a starting dose is 6 IU of “Novomix 30” (30% as part, 70% protaminated as part), or “Lispro mix 75/25” (25% lispro, 75% insulin lispro protamine suspension) could be given before breakfast and 6 IU pre dinner. To be up-titrated by INITIATE treat-to-target study algorithm:

FPG or pre-dinner

(mg/ dL) Dose adjustment

- < 80-2 IU
- 80-110 No change
- 111-140 + 2 IU
- 141-180 + 4 IU
- > 180 + 6 IU

Pre-dinner dose is titrated according to fasting plasma glucose whereas pre-breakfast dose titration is based on pre-dinner self-measured plasma glucose values.

Another option is to start prandial insulin prior to meals. Three (or more) injection of short acting human or analogue (Lispro, Aspart, or Glulisine) insulin is given. This could be added to “Metformin” while “SU” or “Acarbose” are usually stopped. It will address postprandial hyperglycaemia and improve the HbA1c level. Though being an option, it is infrequently used regimen in ambulatory care.

The choice of insulin regimen is largely influenced by regional practice and physician preference. The patient profile, lifestyle, how much target to be achieved, levels of FBG and PPG, patient education and; not to forget the monthly cost and insurance coverage.

For the basal insulins, long acting insulin analogues “Glargine” and “Detemir” are considered better options compared to NPH due to longer durations of action and slower absorption rates where it could be given once a day with lower risk for hypoglycemia. “Glargine” offers peakless insulin that extends beyond 24 hours, suitable to be used once daily at bedtime in most occasions. “Detemir” shows less “inter-patient variability” in BG compared with NPH or glargine, which suggests that detemir has a more predictable glucose-lowering effect [2]. We might consider “NPH” if the price of analogues is

not affordable, or not covered by insurance plan.

This step of adding basal insulin is more frequently used in daily practice. Most Type 2 diabetics are overweight/obese with feature of abdominal obesity and insulin resistance and using single injection of basal insulin yield modest weight gain. It is good for those reluctant to start insulin (needle phobia), for whom optimizing control is not vital (elder person) and when the risk of hypoglycemia is unacceptable.

For many patients, a basal supplement is adequate to control BG as endogenous insulin will cover the postprandial hyperglycemia. Adding prandial insulin will help to reach the desirable HbA1C target. In this respect, insulin analogues “Lispro”, “Aspart” and “Glulisine” offer advantage of less hypoglycemia compared to “Human” insulin as well as more flexibility in injecting shortly before or immediately after the meal.

In primary care practice we often go with “static” doses. However, “dynamic” doses using calorie counting and dose correction will fine tune PPG levels. This therapy may be a good choice for patients who need flexibility because of inconsistent lifestyle, shift work, regular travelling or sport activities. It will be best to optimize blood glucose control and getting closer to target.

If it was agreed to initiate premixed (Biphasic) insulin, then insulin analogue containing preparations are preferred to human insulin as time-activity profiles of the insulin analogue premixes resemble that of endogenous insulin more closely than human formulations.

Twice-daily pre-mixed insulin provides a simple mode to lower BG with fewer injections. The patient might see it more convenient especially those not doing carbohydrate count. The patient needs to have regular lifestyles, eating equivalent amounts at similar times each day. It needs rigid meal timing and minimum flexibility which often mean more events of nocturnal hypoglycemia; some might end up with three injections a day.

Three-daily mealtime rapid acting insulin necessitate more extensive sessions of patient education and obligation to provide proper doses that address the postprandial hyperglycemia.

Beginning with basal insulin treatment is fairly safe and simple choice from the physician perspective and is frequently more acceptable to patients. This option provides control to a significant portion without frequent bouts of hypoglycaemia. The data suggest that basal analogues may offer advantages according the results of the Treat to Target Trial [3], where a single bedtime injection (NPH or glargine) was added to existing oral agents, and insulin doses were titrated against a fasting glucose of 5.6 mmol/l. There was less hypoglycaemia (especially nocturnal) in the glargine group. This modest improvement of Hb A1C favours “glargine” with add-

ed benefit of less weight gain but with disadvantage of higher cost.

Which analogue; “Glargine” or “Detemir”? We have more experience with “Glargine” insulin. Again, the data showed comparable glycemic effects as shown in a direct comparison in patients with T2DM. HbA1c decreased by 1.5% with both insulins, and 52% of participants achieved HbA1c of < 7%. Weight gain was lower with once-daily detemir but was comparable to glargine once a day when detemir twice a day is given. Hypoglycaemic events were similar; however, higher insulin doses and more injections were needed with detemir to achieve targets in the detemir arm required twice daily dosing [4].

The option of “Premixed” insulin might be attractive for some patients for convenience since they will do less injection and less frequent glucose checking compared to full basal-bolus regimen. It is an example of what is known as “Conventional insulin therapy” which is less likely to achieve target glycemic control. Sometimes Prandial insulin is added before midday meal to improve glycemic control. These insulin regimens need patients with fixed meals regarding timing, composition, calorie contents since the amount of short and intermediate insulin is constant. These insulins were never recommended by the ADA.

Compared with long-acting or NPH, premixed rapid-acting insulin preparations are more effective in reducing postprandial blood glucose levels but less effective in reducing fasting blood glucose. Premixed rapid-acting preparations were more often associated with minor hypoglycemia and weight gain than long-acting insulin or oral agents [5]. Premixed preparations offer little glycemic advantage compared with adequately titrated basal and bolus insulin.

The least clinically used option is premeal prandial insulin shots. This multidose insulin regimen needs a highly motivated patient. However, in the view of limited available data and the disadvantage of weight gain with prandial insulin therapy make it a less encouraging choice in practice.

The delivery device needs to be dealt with. In majority of cases, using “Pen-type” insulin delivery provides a more convenient, less painful, patient-friendly tool with

audible click for visually disturbed fellows have more satisfaction score compared to the traditional insulin syringe, again if the cost is not a matter. But still we find some patients who prefer the traditional “vial and syringe” over the more “cumbersome” newer devices.

Basal-bolus insulin regimen (once-daily insulin Glargine or Detemir plus a rapid-acting insulin analogue: Lispro, Aspart, or Glulisine) mimics the physiologic action of endogenous insulin secretion. Introducing one injection at a time, with each visit might help in individuals reluctant to initiate multiple daily injections allowing patient to experience and adjust insulin doses and intensify therapy which proved to be cost-effective with a marked decrease in health care costs, due to diminished use of OADs, and with significantly fewer inpatient hospitalizations [6].

Supporting services as diabetes health educators, certified nurse when available could help a lot in this respect. At each consultation that follows initiation few educational tips are passed to ensure safety of insulin dosage and stating simple goals that improve patient trust and adherence to therapy.

References

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