JCD

ARTICLE

Insulin and OADs: When and How to Combine?

Dr. Sowrabha Bhat[a] and Dr. Rana Bhattacharjee[b]

a MD (Medicine)

b MD (Medicine) DM (Endocrinology) MRCP FICP, Dept. of Endocrinology, IPGME & R and SSKM, Kolkata

INTRODUCTION

Diabetes is a progressive disease. After about 10–15 years of diabetes there is generally an exhaustion of the pancreatic insulin reserve. It is well known that adequate glycemic control reduces both microvascular and macrovascular complications of diabetes. In most diabetics who fail to achieve their glycemic targets with oral antidiabetic medications, shifting completely to insulin may be the only option. But in some patients there may be a role of combining insulin with oral antidiabetic agents as they may work synergistically thus reducing the dose of insulin needed and therefore its metabolic side effects and the cost of medication. This would mostly apply to patients with type 2 diabetes who are obese and have some beta cell reserve and such a subset may account for about 20–40% of all diabetics failing oral antidiabetic medication.[1,2]

Insulin-sulfonylurea Therapy and the Rationale

During the 1990s the BIDS (bedtime insulin daytime sulfonylurea)concept became popular, long before insulin combinations with metformin came into everyday practice.[1,3] Various studies found combining insulin with sulfonylurea to result in better glycemic control and reduce the insulin requirement in diabetics on twice-a-day insulin. Sulfonylureas stimulate endogenous insulin secretion which reaches the liver via the portal vein unlike exogenous insulin which bypasses the liver and reaches the peripheral circulation. This insulin reaching the liver has direct effects on hepatic glucose production. Also sulfonylureas have several extrapancreatic actions potentiating that of insulin such as reduction of hepatic gluconeogenesis, increase in hepatic glycolysis, and increase in skeletal muscle glucose uptake thereby decreasing insulin resistance.[2] Thus,sulfonylurea and insulin have a distinct synergistic effect and seem to have an advantage over insulin alone atleast in the subset of diabetics with good pancreatic beta cell reserve. The decrease in insulin dose requirement reduces the side effects caused by large doses of insulin such as weight gain, sodium retention, hypertension, and dyslipidemia.[2,3] With the development of various oral antidiabetic agents in recent years, option of combining with insulin has become more flexible.

INDICATIONS FOR INITIATING INSULIN ON ORAL ANTIDIABETICS: THE CURRENT SCENARIO

As per the American Diabetes Association (ADA) 2018, insulin may be added to a diabetic patient taking oral antidiabetic drugs (OADs) in the following situations:

1. Basal Insulin

i. In a diabetic not achieving glycemic targets despite being on monotherapy with metformin for more

than three months, adding a basal insulin may be an option.

ii. In a diabetic not achieving glycemic targets on dual therapy with metformin and another OAD for 3 months or more, basal insulin may be added.[4]

2. Combination Injectable Therapy

i. In a diabetic already on triple drug therapy for more than 3–6 months but not able to achieve glycemic targets.

ii. At diagnosis if the glycated hemoglobin is greater than or equal to 10%, blood glucose is more than or equal to 300 mg/dl or patient is symptomatic.[4]

HOW TO INITIATE INSULIN IN A PATIENT ON OAD?

Once Daily Basal Insulin

Basal insulin provides the baseline constant level of insulin in the body and prevents fasting hyperglycemia. It is often initiated failing adequate blood glucose control with OADs. As shown by the APOLLO trial and the 4T trial, basal insulin combined with oral hypoglycemic agents was non inferior to prandial insulin in terms of A1C reduction. Although it had lower risks of hypoglycaemia it provided better patient satisfaction probably due to fewer number of daily injections.[5,6] The choice of insulin may be an intermediate acting one such as neutral protamine Hagedorn (NPH) or a long-acting insulin such as U-100 glargine, U-200 glargine, Detemir, or Degludec. Although the chances of nocturnal hypoglycemia are lower with the latter they substantially increase the cost of medication which needs to be considered in some patients.[7]

ADA 2018 recommends initiating basal insulin at a dose of 10 units per day or 0.1–0.2 units/kg/day. It can be an add-on to either metformin alone or one additional oral antidiabetic medication. The dose is subsequently adjusted by 10–15% or 2–4 units once or twice weekly to achieve the target fasting blood glucose. In case of hypoglycemia unexplained by any specific cause and thus assumed to be due to an inappropriately higher insulin dose, the dose must be down titrated by 10–20% or 4 units.[4]

Combination Insulin Therapy

If glycemic targets are not achieved despite up titration of basal insulin to a dose of more than 0.5 units/kg/day or A1C remains above target even if fasting blood glucose is reasonably controlled, shifting to a combination insulin therapy is to be considered. These can be started while continuing metformin but GLP-1 receptor analogues, DPP4 inhibitors, and sulfonyl ureas are typically dropped.[4,7]

1. Basal-Plus Insulin Regime

If the patient fails to achieve A1C targets on basal insulin plus metformin,ADA 2018 recommends addition of a rapid acting insulin injection before the largest meal as one of the next options.[4]

The recommended starting dose for the bolus insulin is 0.1 units/kg or 4 units or 10% of the basal insulin dose. The dose is then adjusted once or twice weekly by 10–15% or 1–2 units to reach the target self-monitoring of blood glucose (SMBG). Hypoglycemia needs to be addressed by decreasing the corresponding insulin dose by 10–20% or 2–4 units.[4] Pre meal oral secretagogues may need to be decreased in dose or stopped.[7]

On this regimen if A1C remains above target value after 3 months, proceeding to a basal plus 2 (two rapid acting insulin before meals) or basal-bolus regimen (three rapid acting insulin injections before meals) may be considered.[4]

2. Once Daily Premix/Co-formulation Insulin

This regimen may be more suitable in the Asian ethnic group in achieving glycemic control as suggested by various studies. Also it has certain advantages like simplicity for initiating insulin, addressing both fasting and post meal glycemia, and ease of up titration to twice or thrice daily injections if needed.[7]

Premixed human insulin(30/70), (25/75), or (50/50) or premixed analogues such as BIAsp (30/70), Lispromix (25/75) may be used. Newer analogue formulations include insulin degludec/ insulin aspart.

These can be used either before breakfast to control pre-dinner and post-breakfast hyperglycemia or before dinner in order to prevent early morning

fasting hyperglycemia. The recommended starting dose is 0.2–0.3 units/kg/day or 10–12 units per day, while the pre-meal secretagogue has to be dropped. The dose is then titrated weekly to target pre meal blood glucose to 80–130 mg/dl. If more than 30 units (or 40–50 units as per other studies) is needed the dose is to be divided.[4,5,7]

3. Premixed Insulin Twice or Thrice Daily

If the patient fails to achieve glycemic targets with basal insulin, a second option as per the ADA 2018 recommendations is to change to a twice daily premixed insulin regime. In this case, it is recommended that the basal dose is divided into half each in the morning and evening or two-thirds in the morning and one-third at night. The usual starting dose would be around 6 units each before breakfast and before dinner. The dose is then adjusted by 10–20% or 1–2 units once or twice weekly until the target blood glucose is reached. In case of with no obvious cause, the corresponding insulin dose is reduced by 10–20% or 2–4 units.[4]

If the A1C target is not achieved with twice a day premixed insulin,that is, if the post lunch blood glucose is more than 180 mg/dl or A1C >7%, it is recommended to advance to the thrice daily regimen, the third dose being added pre lunch. The pre breakfast insulin dose may need to be reduced by 2–4 units once the pre-lunch dose has been added to avoid hypoglycemia. Dose titration is done as in case of twice daily regimen based on the lowest/mean value of the three most recent pre-breakfast/pre-dinner values but also keeping in mind the post lunch blood glucose.[7] It must be remembered that ADA recommendation for use of thrice-a-day premixed insulin is applicable to biphasic analogs only.

4. Basal-bolus Insulin Regimen

This regimen is considered the "gold standard" for the management of patients with type 1 diabetes. In patients with type 2 diabetes if A1C targets is not achieved with basal-plus regimens, it is recommended to proceed to three pre meal rapid acting insulin injections along with basal insulin. The starting dose is 0.1 units/kg or 4 units or 10% basal dose before each meal. The dose of the basal insulin needs to be decreased by the same amount if the A1C is less than 8%. The doses of pre meal insulins are adjusted by 10–15% or 1–2 units weekly or twice weekly to achieve target SMBG values and hypoglycemia requires dose reduction of corresponding insulin as in case of basal-plus regimens.[4,7]

CHANGING FROM INSULIN TO ORAL ANTIDIABETIC MEDICATION

There are fewer indications and lesser evidence for shifting from insulin to oral antidiabetic medication.

Neonatal Diabetes

In most forms of diabetics, caused due to KATP mutations, it is possible to change from insulin to sulfonylurea successfully. Hence genetic testing is considered mandatory as early as possible.[8] However since this is difficult in resource poor settings, some authors suggest a trial of empiric sulfonylurea therapy.[9]

Those cases caused by mutations of insulin gene, pancreatic agenesis are unlikely to respond to sulfonylurea. Certain clues that may preclude a trial with sulfonylurea are a clear history of consanguinity, unremitting diarrhoea, cerebellar agenesis/hypoplasia, gastrointestinal and cardiac malformations.[9] While on insulin, glyburide may be started at a dose of 0.1 mg/kg twice a day and increased daily to reach a dose of 1 mg/kg/day within 5–6 days, while the insulin is gradually tapered carefully monitoring the blood glucose levels.[8,9] Other sulfonylureas like gliclazide, glimepiride, and glipizide have been used successfully in this situation.

MODY-Maturity Onset Diabetes of the Young

Diabetes in young patients with at least a two-generation family history of diabetes, a negative insulin antibody screen, and a good insulin reserve suggested by C-peptide levels suggest a diagnosis is MODY. Type 2 MODY (GCK7 mutation) may not need treatment whereas patients with type 1 MODY (HNF4 alfa) and type 3 MODY (HNF1 alfa) may atleast in earlier stages respond well to sulfonylurea therapy. Glipizide, glyburide, glimepiride, or

gliclazide have been successfully used to treat these transcription factor MODY subtypes. Early sulfonylurea therapy in these patients has been suggested to slow down in the rate of beta cell decline but needs further studies for clarification.[10]

Diabetes in Lactation

Many women who are shifted from OADs to insulin during pregnancy are anxious when suggested to restart it. Although insulin is the safe choice,studies on glyburide 5–10 mg/ day and glipizide 5 mg/day have proven to be safe in lactation.[11] The theoretical infant dose of these drug were found to be less than 1.5% of weight adjusted maternal dose which is much less than the acceptable limit of 10%.[12] Also studies on metformin use in lactation found minimal levels in breast milk. No difference in weight, height, motor, or social milestones were found between infants on formula feeds and those breastfed by mothers taking metformin.[11,12] However, long-term data is absent.

Type 2 Diabetic at Discharge from Hospital

For hospitalized patients who were on insulin therapy for glycemic control, there are no well-defined guidelines for transitioning to outpatient management at discharge. If the blood glucose levels are within target patients may be allowed to go back to pre admission insulin doses. However, it is generally agreed that they need to be shifted to simpler insulin regimens or if possible oral antidiabetic with basal insulin. It is important to ensure that the patients are aware of insulin administration techniques as many of them may have been on insulin for the first time during the hospital stay. Hypoglycemia may be a concern with the use of secretagogues if the patient has not resumed normal diet post discharge. If the patient was well controlled with OADs before discharge he/she may be shifted back to the same regimen provided there is no contradiction. Counselling at the time of discharge may be seen as an opportunity to review and revise the antidiabetic medications of the patient.[13]

Newly Diagnosed Diabetics

Newly diagnosed diabetics who present with osmotic symptoms due to profound hyperglycemia may have pancreatic beta cell dysfunction due to glucotoxicity. Hence, insulin therapy is recommended initially. After a few weeks of insulin therapy, once reasonable glycemic control is achieved the patient may be able to be shifted to oral agents provided he/she is suffering from type 2 diabetes. The transition should be gradual by tapering the insulin doses and close monitoring of blood glucose levels. Some disruption in the glycemic status could be anticipated during the transition. The choice of oral agents would depend on the presence of renal or liver disease, cardiovascular disease status, presence of obesity, risk of hypoglycemia,and age. Although oral therapy may be convenient, some patients may prefer to continue on insulin or advised to do so due to presence of co-morbid conditions.[14]

CONCLUSION

As diabetes is a progressive disease no fixed therapeutic regimen is adequate. Switching from oral to injectable therapy and vice versa needs to be done based on the type of diabetes, stage and duration of disease, age of the patient, glycemic status, presence of comorbidities, and patient preferences. A “one regime fits all”strategy is unlikely to work. Communication and discussion with patient about the pros and cons of various therapeutic options would go a long way in improving patient compliance and success of the therapy. Careful monitoring of blood glucose is needed during the transition from one regime to another.

References

1. Holt RI, Cockram C, Flyvbjerg A, Goldstein BJ, editors. Textbook of Diabetes. John Wiley & Sons; 2017 Mar 6, pp. 487–9.
2. Lebovitz HE, Pasmantier R. Combination insulin-sulfonylurea therapy. Diabetes Care. 1990 Jun 1;13(6):667–75.
3. Shank ML, Del Prato S, De Fronzo RA. Bedtime insulin/daytime glipizide: Effective therapy for sulfonylurea failures in NIDDM. Diabetes. 1995 Feb 1;44(2):165–72.
4. American Diabetes Association. Pharmacologic approaches to glycemic treatment. Diabetes Care. 2018 Jan 1;41 (Supplement 1): S76–83.
5. Bretzel RG, Eckhard M, Landgraf W, et al. Initiating insulin therapy in type 2 diabetic patients failing on oral hypoglycemic agents: Basal or prandial insulin? The APOLLO trial and beyond. Diabetes Care. 2009 Nov 1;32 (Suppl 2): S260–5.
6. Gram J, Henriksen JE, Grodum E, et al. Pharmacological

treatment of the pathogenetic defects in type 2 diabetes: The randomized multicenter South Danish Diabetes Study. Diabetes Care. 2011 Jan 1;34(1):27–33.
7. Kovil R, Chawla M, Rajput R, et al. Consensus on insulin dose and titration algorithms in ambulatory care of type 2 diabetes in India. J Assoc Physicians India. 2017 Feb; 65:17.
8. Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonyl ureas in patients with diabetes due to Kir 6. 2 mutations. N Engl J Med. 2006 Aug 3;355(5):467–77.
9. Carmody D, Bell CD, Hwang JL, et al. Sulfonylurea treatment before genetic testing in neonatal diabetes: pros and cons. J Clin Endocrinol Metab. 2014 Dec 1;99(12):E2709–14.
10. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. Diabetes Care. 2011 Aug 1;34(8):1878–84.
11. Kalra S, Bahendeka S, Sahay R, et al. Consensus recommendations on sulfonylurea and sulfonylurea combinations in the management of Type 2 diabetes mellitus – International task force. Indian J Endocr Metab. 2018; 22:132–57.
12. Feig DS, Briggs GG, Koren G. Oral antidiabetic agents in pregnancy and lactation: Aparadigm shift? Ann Pharmacother. 2007 Jul; 41(7–8):1174–80.
13. Wang CC, Draznin B. Insulin use in hospitalized patients with diabetes: Navigate with care. Diabetes Spectrum. 2013 May 1;26(2):124–30.
14. Lingvay I, Legendre JL, Kaloyanova PF, et al. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: Which is better? Diabetes Care. 2009 Oct 1;32(10):1789–95.