A RESEARCH REVIEW™
EDUCATIONAL SERIES

Insulin intensification in type 2 diabetes

Making Education Easy 2019

About the Reviewer

Dr Brandon Orr-Walker
MB ChB Auckland; FRACP

Dr. Brandon Orr-Walker is an Endocrinologist working first at Auckland City Hospital, then at Middlemore Hospital to establish an Endocrinology Department. Initially employed in general endocrinology, he was invited to lead an already well-established and innovative clinical diabetes team in 2004, and from 2005 provided clinical leadership for the Counties Manukau DHB "Let's Beat Diabetes Program", and subsequently was the Minister of Health's Clinical advisor on Diabetes (2010-2012). He is the Immediate Past President of The New Zealand Society for the Study of Diabetes (NZSSD).

Brandon has served on numerous local, regional, and national advisories including the NZ Guidelines Group, and provided clinical advice leading to the development of the Diabetes Care Improvement Packages (DCIP) when the long-established annual "Get Checked" program was scrapped. He remains committed to the promotion and provision of excellent diabetes care regardless of clinical venue, and for differing needs, of patients.

The aim of this review is to encourage primary care practitioners to actively review patients on basal insulin, and add a mealtime insulin if required in order that the risk of diabetes-related complications is reduced. In particular, the reasons for the reluctance to initiate mealtime insulin are examined, including patients' concerns regarding hypoglycaemia. The intended audience for this review is primary healthcare professionals, including general practitioners, practice nurses and diabetes nurse educators. This review is supported by an educational grant from Novo Nordisk.

Type 2 diabetes – a progressive disease

Type 2 diabetes mellitus (T2DM) is a progressive disease in which β-cells increasingly fail, resulting in an impairment of insulin secretion, and frequently occurring on the background of insulin resistance (**Figure 1**).[1] This is manifest clinically by the presence of increased fasting blood glucose levels.[2-4] In addition, the usual mealtime insulin response/secretion is blunted,[2-4] and results in greater post-prandial blood glucose excursions and increased HbA1c levels.[4, 5]

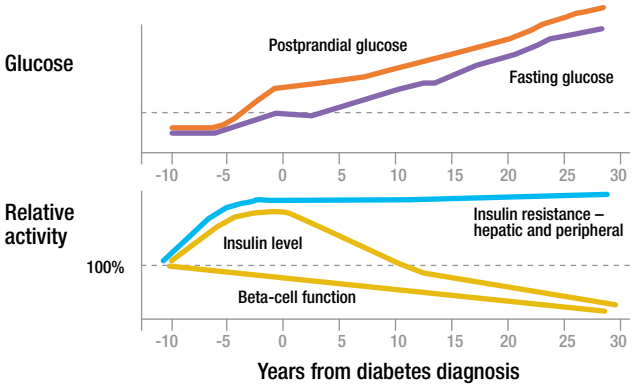

Figure 1. Type 2 diabetes is a chronic progressive disease with increasing impairment of β-cell function resulting in increased fasting glucose and postprandial glucose levels

Given the increased prevalence of T2DM,[6] primary care practitioners are increasingly facing the challenges associated with this progressive disease. In New Zealand, there are fewer funded options for glycaemic management than other OECD countries, yet diabetes prevalence and rates of complications are similar or above that seen in those countries. Increasing numbers of individuals with T2DM will require insulin initiation, as well as its intensification. Consequently, it is vital that all primary care practitioners are aware of the options for intensifying basal insulin regimens with mealtime insulin so that glycaemic targets can be met and diabetes-related complications can be avoided.

Glycaemic targets

The 2011 New Zealand guidelines recommend patients aim for a glycaemic target of an HbA1c of 50–55 mmol/mol, or as individually agreed.[7] In order to achieve these HbA1c targets, stepwise lifestyle interventions (e.g. exercise, dietary changes) and pharmacological therapies are recommended by both international and NZ guidelines.[7-9] Importantly, glycaemic targets need to take into account diabetes duration, the presence of co-morbidities, the person's life expectancy, social circumstances and their personal beliefs and priorities.[7, 9] Less stringent HbA1c goals may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions, and those for whom the target is difficult to attain despite intensive self-management education, repeated counselling, and effective doses of antidiabetic agents, including insulin.[10]

Stepwise treatment of a progressive disease

The progressive nature of T2DM means that modification of the basal insulin regimen and more intensive treatment are likely to be required over time if the target HbA1c is to be achieved.[7, 9, 11] The NZ guidelines recommend metformin as a first-line antidiabetic agent, followed by the addition of a sulfonylurea if required, and then insulin.[2] The NZ guidelines also emphasise that it is important for people with T2DM to be aware at an early stage after the diagnosis of the disease that insulin is likely to be required as their disease progresses.[7, 12]

Regular review of the person with T2DM is essential if they are to reach their glycaemic targets.[12] Treatment intensification should occur in people who are adherent with their current antidiabetic agent(s), but who are unable to meet targets. Guidelines suggest that intensification should occur if HbA_{1c} levels do not meet, or closely approach, an agreed target within three months.[7, 10, 13]

Failure to intensify insulin treatment

Many people with T2DM do not meet their glycaemic targets and do not receive timely treatment intensification when it is needed.[14-17] Resistance to initiating or intensify therapy has been reported at each step;[7, 10] not only when intensifying oral agents, but particularly when initiating or intensifying insulin therapy.[18-22] The failure to intensify therapy when treatment targets are not met has been termed 'clinical inertia'.[9]

In particular, international data indicate that many people with T2DM treated with basal insulin (ranging from around 30% to approximately 80%) fail to reach their glycaemic targets,[17, 23-25] suggesting that these individuals would benefit from intensification of this treatment regimen.

In primary care, there are often delays in intensifying therapy for those on basal insulin. For example, a retrospective analysis of data from UK primary care patients (n=11,696) treated with basal insulin indicated that among patients eligible for treatment intensification (HbA1c ≥58 mmol/mol [7.5%]), only 31% had their treatment regimen intensified.[11] Of this group, a median 3.7 years was spent on basal insulin before intensification to bolus or premixed insulin (or glucagon-like peptide-1 receptor agonists) occurred.[11] Similar delays in insulin intensification have been reported in other studies from primary care settings.[26, 27]

In the real world, analysis of a large US electronic medical record data-base indicated that, in people initiating basal insulin, the likelihood of achieving glycaemic targets diminished considerably within the first 12 months (**Figure 2**) and patients who had not achieved their HbA1c goal by 12 months, were unlikely to do so.[28] This outcome suggests that treatment intensification of a basal insulin regimen should not be delayed beyond a year, ideally within 3-9 months, if treatment goals are to be reached.[28]

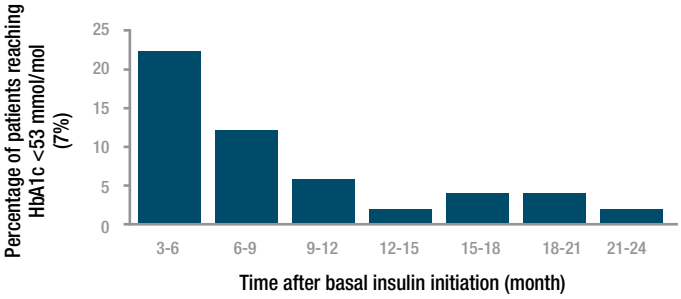

Figure 2. Percentage of patients with T2DM who reached their first HbA1c <53 mmol/mol (7%) after basal insulin initiation[28]

A recent meta-analysis of three clinical trials involving people with T2DM (n=458) treated with basal insulin (insulin glargine) found that increasing the basal insulin dose from >0.3 to 0.5 IU/kg/day had a diminishing effect on glycaemic outcomes, with only small reductions in fasting plasma glucose and HbA1c occurring.[29] Moreover, once insulin was increased beyond 0.5 IU/kg/day, there was a plateauing effect with no further glycaemic improvement, but an associated increase in weight. These outcomes prompted the researchers to recommend intensification of therapy with additional agents to cover postprandial glucose excursions when HbA1c remains above target and the insulin dose starts to approach 0.5 IU/kg/day.

Conversely, studies reporting excellent achievement of glycaemic control with insulin in addition to metformin and sulphonylureas reveal that, irrespective of the starting insulin type selected, intensification to an additional insulin type beyond dose titration alone is needed to maintain excellent control.[25, 30]

Reasons for clinical inertia when intensifying an insulin regimen

The reasons for the slowness to intensify antidiabetic therapy when glycaemic targets are not being met are multifactorial, with physician-, patient-, and healthcare system-related factors all contributing.[13, 19, 20, 31, 32] Patient-related factors contributing to delays in insulin initiation or intensification include a fear of injection-related pain, and concerns about weight gain, hypoglycaemia, increased regimen complexity (especially multiple daily injections), and perceived stigma.[11, 16, 19, 33, 34] People with T2DM may also feel that the need to intensify insulin treatment is a result of their failure to control the disease, instead of understanding that it reflects the progressive nature of their disease. Anticipatory guidance early in the course of the disease may help mitigate these fears.

The fear of hypoglycaemia, a commonly reported concern for both patients and primary care practitioners, contributes to the clinical inertia surrounding insulin intensification.[33] Hypoglycaemia is an acknowledged risk with all insulin-based therapies.[33] However, careful titration of insulin therapy can achieve good glycaemic control without significant risk for hypoglycaemia.[33] Data from a meta-analysis of studies involving patients whose insulin treatment had been intensified with either a basal-bolus and or a premixed insulin regimen reported a low overall hypoglycaemia event rate (0.16 episode/patient/year), with no significant difference between the two regimens.[35]

Both the perceived and actual risk of hypoglycaemia can be managed through effective anticipatory guidance and education on the likely incidence of hypoglycaemia associated with the individual's treatment regimen.[33, 34] Patients should be educated how to recognise signs of hypoglycaemia, how to treat it, and that, if it occurs, they should discuss insulin adjustments with their primary care practitioner. Additionally, patients should be reminded that factors apart from their insulin regimen may be contributing to an increased risk for hypoglycaemia. Examples of contributing factors include missing or delaying meals or ingesting smaller meals than planned, a change in the normal level of exercise, other medications, other comorbid conditions (such as renal failure), unexpected illness or concomitant drug or alcohol consumption.[33, 34, 36] Insulin injection techniques including agitation of insulins are also important and require the education of patients by suitably trained healthcare professionals (HCPs).

It is also important that the right HbA1c target is selected for each individual patient in the light of their risk of hypoglycaemia, especially for older patients.[36, 37] If the individual's glycaemic target is set too low in the light of their associated risk factors, patients may omit insulin to avoid hypoglycaemia, at the expense of achieving glycaemic control. Over titration of the basal insulin may result in hypoglycaemia as patients attempt to reach their glycaemic target.[38] Earlier initiation of prandial insulin therapy may enable patients to reach their glycaemic target and potentially avoid this issue.

EXPERT COMMENT

HCP familiarity and confidence with insulin management is important to maximise acceptance, adherence and effectiveness of therapy. This is important for both patient perception (how well we can inform patients, hear their concerns and answer their questions) and experience (how well we can achieve improvements in glycaemic management, and problem solve and reduce adverse experiences). In my experience, a patient who a year after commencing insulin has no improvement in glycaemic control (e.g. due to lack of intensification) is not going to be convinced of the value of being on such treatment. Additionally, a patient who, for example, becomes hypoglycaemic because they were not taught to agitate a mixed insulin, or take it with meals (for the rapid component and postprandial improvement) may become frustrated and lose confidence in their HCP.

Importance of achieving glycaemic targets

The achievement of glycaemic targets is important given the association between the failure to control the disease and the increased risk of complications.[39, 40] The impact of glycaemic control on microvascular complications is apparent,[39, 40] and it has also been demonstrated that T2DM confers a substantial independent risk of the individual having atherosclerotic cardiovascular disease.[9] HbA1c levels outside targets have been shown to be predictors of acute myocardial infarction and stroke.[41] Delays to the intensification of therapy increase the risk of adverse cardiovascular outcomes as demonstrated in a retrospective cohort study, which indicated that a 1-year delay in treatment intensification in people with uncontrolled T2DM significantly increased the risk of myocardial infarction, heart failure, stroke and a composite endpoint of cardiovascular events.[15]

EXPERT COMMENT

Improved glycaemic control (targeting and achieving lower HbA1c) reduces complications. There is a latency to see all of the benefits of this, but the value has lasting "legacy" effects. A failure to achieve this early results in clinical outcomes that are worse and cannot be "caught up" by later better control. At the extreme, super-intensive efforts of control after significant delay, and the development of complications may even be counterproductive or harmful.

Insulin – has the most potential to lower to HbA1c targets

Insulin, compared with other antihyperglycaemic agents, if given in adequate doses, has the most potential to lower HbA1c levels, doing so in a dose-dependent manner.[9] NZ guidelines recommend that insulin therapy should be considered if the individual with T2DM has unsatisfactory glycaemic control (measured HbA1c does not meet or closely approach agreed target) or there are signs and symptoms of hyperglycaemia despite lifestyle interventions, a review of medication adherence and dose optimisation of oral hypoglycaemic agents.[7]

Various formulations of insulin are available with differing durations of action (**Figure 3**). Basal insulin refers to intermediate- or long-acting insulin which aims to cover the body's basal metabolic insulin requirement (including regulating hepatic glucose production).[9] In contrast, bolus or prandial insulin aims to reduce glycaemic excursions after meals. These short- and rapid-acting insulin formulations, which are administered at mealtime, are generally used to intensify basal insulin therapy in patients not meeting glycaemic targets.[9] Premixed formulations contain mixtures of a fixed ratio of short-acting and intermediate-acting forms of insulin, and are designed to be given either once or twice daily.

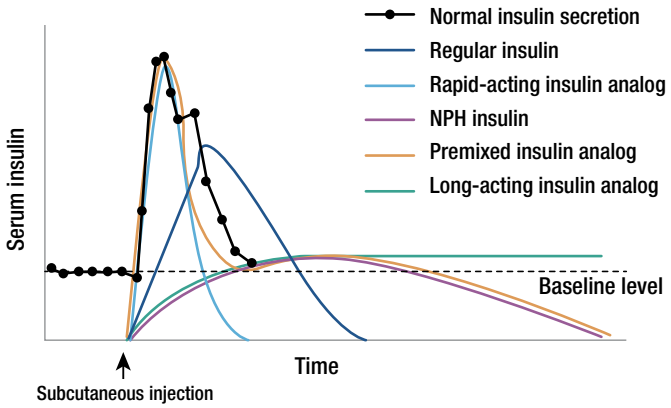

Figure 3. Schematic representation of insulin time-action profiles (refer to full product information for accurate pharmacokinetic profiles of each individual agent)

Basal insulin is often a preferred option in primary care when insulin is needed to meet glycaemic targets, due to its relative ease of use and relative low risk of hypoglycaemia.[9, 25, 42, 43] NZ guidelines,[7] as well as the NZ primary care handbook,[44] recommend basal insulin as initial insulin therapy in addition to metformin and other oral agents. NZ guidelines recommend isophane insulin as the basal insulin,[7] but recognise that other regimens may be considered. Alternative regimens include basal insulin analogues (if there are concerns regarding hypoglycaemia), or premixed insulin (if post-prandial levels are elevated and the HbA1c target has not been met).[7]

EXPERT COMMENT

Insulin is insulin! However, there are important characteristics that separate the different classes in terms of time of onset of action, and duration (profile) and variability of dose-to-dose effect. The hypoglycaemic effect of insulin is dependent on dose. The ability to vary dose is a key attribute of its therapeutic value, but also of its risk in use. HCPs who effectively manage patients on insulin need to be expert in their knowledge of available insulin options and proficient with the practical aspects of insulin administration.

Rational for intensifying basal insulin regimens

In people with T2DM, basal insulin secretion is impaired, but an injection of a basal insulin will provide a steady level of insulin that suppresses hepatic glucose production by acting directly on the liver and thus controlling fasting plasma glucose levels.[2-4] In addition, the usual rapid and marked increase in insulin that occurs in response to a meal does not occur (**Figure 4**).[4, 45] In individuals with T2DM, peak levels of insulin are lower than normal and occur 90–120 minutes after the meal begins rather than in the first 30 minutes.[4] This results in greater post-prandial glucose excursions and consequently increases in HbA1c levels.[5]

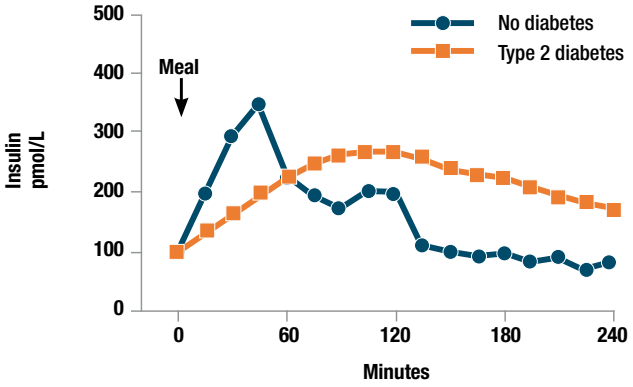

Figure 4. Post-prandial insulin profile. Plasma insulin concentrations observed in people with, and without, type 2 diabetes following ingestion of a meal

Treatment guidelines and insulin intensification

Basal insulin has no direct effect on post-prandial blood glucose levels. Consequently, international guidelines,[9, 36, 46] have provided recommendations for the intensification of therapy with the use of mealtime insulin in patients inadequately controlled on basal insulin.[9] Such clear directions for insulin intensification are not available in NZ guidelines,[7] nor in the NZ primary care handbook,[44] both of which are overdue for redrafting.

The 2018 American Diabetic Association/European Association for the Study of Diabetes guidelines have recommended two alternative approaches for the control of mealtime excursions in blood glucose.[9]

- One approach is to administer mealtime insulin in addition to basal insulin, with the mealtime insulin being given first as an initial dose with the largest meal or the meal with the largest post-prandial blood glucose excursion. Then, if glycaemic targets have not been met with one dose of prandial insulin daily, additional prandial injections can be added to other meals in a step-wise manner.[9, 47] The stepwise addition of prandial insulin to bolus insulin has also been termed a basal–plus regimen.
- An alternative intensification approach is to switch from basal insulin to one- to three-daily administrations of a fixed combination of short- and long-acting insulin (termed premixed insulins).[9, 48, 49]

An algorithm for intensifying basal insulin that includes these two alternative approaches is presented in **Figure 5**.

The stepwise addition of a bolus prandial insulin offers the benefits of a relatively simple, gradual, and structured titration, which may improve the person's confidence as they increasingly require multiple daily injections.[38] The stepwise addition of bolus injections has also been associated with a reduced incidence of hypoglycaemia compared with going straight to a regimen with basal insulin and bolus injections with each meal.[38]

In terms of achieving glycaemic targets, there appears to be no difference in efficacy between basal plus regimens versus premixed insulin regimens, and generally there appears to be a similar overall annual rate of hypoglycaemic events per patient.[35,37,50-52] A meta-analysis of 13 randomised trials in 5,255 people with T2DM, found no significant difference in the HbA1c reduction between intensification with a basal bolus regimen versus a premix regimen,[35] as well as no significant differences in overall hypoglycaemia, weight gain, and insulin dose.

Since improved glycaemic control can be expected with either of these alternative regimens, individual patient factors and preferences become more important.[37, 50, 51] The patient's desire for convenience and willingness to adhere to a treatment regimen should be taken into consideration (**Table 1**).[37, 50]

In general, premixed insulin may be a more favourable option when patients are unwilling or unable to cope with the increased injections, complexity and testing that is required with a basal–plus regimen. Premixed regimens are generally simpler than basal–bolus regimens, as the individual only requires one type of injection device.[53] Conversely, basal–bolus regimens offer greater flexibility than premixed regimens.

Algorithm for intensifying basal insulin

Patient not at target* on basal insulin after 3-6 months

INTENSIFICATION

Initiation

- 4 IU/day or 10% of basal dose

Titration

- Increase rapid-acting (prandial) insulin dose by 2U every three days to achieve target

2-hour PPBG levels (mmol/L)	Rapid-acting (prandial) insulin dosage adjustment
≥8 (for three consecutive days)	No change or ↑ by 2 IU
6.0–7.9	No change
4.0–5.9	↓ by 2 IU
<4.0 on any day	↓ by 2–4 IU

Prandial (rapid-acting) insulin

- One dose of prandial insulin with largest meal
- Continue basal insulin at current dose
- Continue metformin and consider tapering sulphonylureas
- Monitor 2 hour PPBG levels
- If not at target**, progress to injections before 2 or 3 meals

Premix insulin

- Replace basal insulin with:
  - OD dose of premixed insulin (before or soon after the start of the largest meal if total insulin dose <30 IU)
  - BID dose (pre breakfast and largest meal) if total insulin dose >30 IU
- Continue metformin and consider tapering sulphonylureas
- Monitor PPBG and FBG
- If not at target**, increase number of daily injections of premixed insulin (to a maximum three-times daily)

Initiation

- Unit to unit conversion of basal to premix insulin

Titration

- Adjust the evening premixed insulin dose once or twice a week

Lowest reading (mmol/L) of the previous 3 days (fasting or pre-prandial) (FBG or PPBG)	Insulin dosage adjustment
>10	↑ by 4 IU
8–10	↑ by 2 IU
7–7.9	No change or ↑ 2 IU
6–6.9	No change
4–5.9	↓ by 2 IU
<4.0 or severe hypoglycaemia	↓ by 4 IU

BID = twice-daily; FBG = fasting blood glucose; OD = once-daily; PPBG = postprandial blood glucose.

*HbA1c target is 50–55 mmol/mol (or as individually agreed).[13] Measure every 3-6 months according to individual needs.
**Advise 6–8 mmol/L FBG and 8–10 mmol/L PPBG (or as individually agreed).[36]

Figure 5. Algorithm for intensifying basal insulin

Table 1. Patient factors to consider when intensifying basal insulin[37, 50, 53]

Patient factor	Basal bolus regimen	Premixed insulin regimen
Patient prefers fewer injections or a single injection device	↓	↑
Patient prefers less frequent monitoring of blood glucose levels	↓	↓
Patient able to easily inject (e.g. cognitive ability, manual dexterity, no need for carer)	↑↑	↑
Patient has difficulty adhering to a complex regimen	↓	↑
Patient prefers a flexible regimen due to inconsistent timing and content of meals	↑↑	↓

EXPERT COMMENT

Patient characteristics, lifestyles and preferences are the key determinants when choosing an insulin treatment strategy for intensification. HCPs should be proficient with both approaches suggested.

CASE STUDIES

Case I: goes to basal-bolus at one meal

Sarah, a 59-year-old female with a BMI of 35 kg/m^2 and a 5-year T2DM history. Her HbA1C had risen steadily to 72.7 mmol/mol, despite metformin treatment. Sarah had been reluctant to start injecting herself with insulin, but her GP had reassured her it would not be as difficult or as painful as she expected. After a discussion with her GP, treatment with isophane insulin 10 U/day was initiated in addition to her metformin. Sarah was provided with information on how to titrate her insulin dose based on her self-monitored blood glucose levels and was asked to return to her GP for a check-up in a few months. Seven months later, Sarah reported she was now taking 19 U/day of insulin isophane, and this was not controlling her glucose levels. There was no real change in either her HbA1C or fasting glucose levels. Sarah did not report any symptoms of hypoglycaemia. She maintained that she was taking her medication as prescribed, but admitted to having stopped increasing her insulin dose because she thought an increase would not help. She was annoyed that she was not seeing any improvement in her glucose levels or HbA1c despite almost doubling the dose she was initially prescribed. She asked if there was any other medication that she could take.

Recommendation: Sarah would have benefitted from further education and follow-up about the progressive nature of diabetes. She should have been advised that her initial dose of isophane insulin was low for safety reasons and it was expected that she would have to increase this dose. Guidance regarding the frequency of titration would have helped Sarah to continue with the titration. Phone calls from her medical centre between visits would have helped Sarah with the appropriate titration and given her reassurance that her prescribed treatment was working. She could also be advised as to when it might be appropriate to intensifying her insulin therapy beyond basal insulin only. The confidence and skills Sarah has gained through monitoring her glucose levels and titrating her basal insulin will help to reassure her that she will be able to manage a bolus dose of prandial insulin when Sarah and her primary HCP decide it is time to intensify her treatment regimen.

Case II: switches to premix

Colin is a 65-year-old male, with a BMI of 28 kg/m^2 (77 kg) and a 6-year history of T2DM. He has been managing well on metformin and insulin glargine for several years but has found that his HbA1C level had risen above 63.9 mmol/mol over the past 6 months despite regularly increasing his insulin dose. He is currently taking 35 IU of insulin glargine once daily. His latest HbA1C was 77.0 mmol/mol, and although his fasting glucose levels were 5.9 mmol/L, examination of his self-monitoring glucose log indicated several post-prandial glucose excursions of up to 13.0 mmol/L. He claims not to have experienced any symptoms of hypoglycaemia. He is very keen to stay on his current familiar regimen of a once-daily injection of insulin. He has recently retired and he and his wife have settled into a routine that includes regularly timed meals.

Recommendation: Colin's HbA1C and self-monitoring glucose levels suggest he might be receiving too much basal insulin and would benefit from prandial insulin. His strong reluctance to change his daily regimen might have been mitigated by earlier anticipatory guidance regarding the progressive nature of T2DM and the eventual need for additional therapies. Given his reluctance to add further injections to his daily regimen, the use of a once-daily dose of premixed insulin might be a suitable choice for him. Since Colin's fasting glucose is well controlled, switching to premixed insulin that has a prandial insulin component that manages the post-meal excursions could allow him to keep his familiar daily regimen of once-daily injections, despite the need to intensify therapy. Further education about the progressive nature of T2DM may prepare him should a twice-daily injection of the premixed insulin be require in the future. Colin should be reminded about the symptoms of hypoglycaemia and encouraged to maintain his regular routine of meals.

CONCLUSIONS

- **The progressive nature of T2DM means that treatment with basal insulin will become necessary for many patients if their individual glycaemic targets are to be met and diabetes complications are to be prevented.**
- **For patients treated with basal insulin, mealtime insulin may be necessary to control post-prandial glucose excursions and enable the attainment of glycaemic targets.**
- **Patients treated with basal insulin who do not achieve their HbA1C goals within 12 months have a very low probability of doing so thereafter, highlighting the importance of timely intensification.**
- **The reluctance to intensify insulin therapy may be multifactorial and may include a variety of patient-related factors, including the fear of hypoglycaemia.**
- **Both the perceived and actual risk of hypoglycaemia can be managed through effective anticipatory education and guidance. HCPs must be proficient in the theoretical and practical management of glycaemic treatments, including insulin.**
- **Patients should be educated how to recognise signs of hypoglycaemia, how to treat it, and that, if it occurs, they should be encouraged to discuss insulin adjustments with their primary care practitioner.**
- **International guidelines recommend two basic approaches for intensifying basal insulin: the use of rapid-acting insulin as additional prandial injections or the use of rapid acting insulin part of a premix insulin formulation.**

RESOURCES FOR PRIMARY CARE

NZ Primary Care Handbook 2012 https://www.health.govt.nz/system/files/documents/publications/nz-primary-care-handbook-2012.pdf

Guidance on the Management of Type 2 Diabetes 2011
http://www.moh.govt.nz/notebook/nbbooks.nsf/0/60306295DECB0BC6CC257A4F000FC0CB/$file/NZGG-management-of-type-2-diabetes-web.pdf

Living well with diabetes: a plan for people at high risk of or living with diabetes 2015–2020. https://www.health.govt.nz/system/files/documents/publications/living-well-with-diabetes-oct15.pdf

Quality Standards for Diabetes Care Toolkit 2014. https://www.health.govt.nz/publication/quality-standards-diabetes-care-toolkit-2014

Diabetes New Zealand website http://www.diabetes.org.nz

REFERENCES

1. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. Diabetes Care. 2019;42:S13-s28.
2. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care. 2003;26:881-5.
3. Monnier L, Colette C. Contributions of fasting and postprandial glucose to hemoglobin A1c. Endocr Pract. 2006;12 Suppl 1:42-6.
4. Riddle MC. Basal glucose can be controlled, but the prandial problem persists-it's the next target! Diabetes Care. 2017;40:291-300.
5. LaSalle JR, Berria R. Insulin therapy in type 2 diabetes mellitus: a practical approach for primary care physicians and other health care professionals. J Am Osteopath Assoc. 2013;113:152-62.
6. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40-50.
7. New Zealand Guidelines Group. Guidance on the management of type 2 diabetes 2011 Wellington New Zealand Guidelines Group; 2011.
8. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. Diabetes Care. 2019;42:S90-s102.
9. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41:2669-701.
10. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38:140-9.
11. Khunti K, Nikolajsen A, Thorsted BL, et al. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. Diabetes Obes Metab. 2016;18:401-9.
12. Best Practice Advocacy Center New Zealand. Managing patients with type 2 diabetes: from lifestyle to insulin. 2015. https://bpac.org.nz/bpj/2015/december/diabetes.aspx. Accessed March 18, 2019.
13. New Zealand Guidelines Group. New Zealand Primary Care Handbook 2012. https://www.health.govt.nz/system/files/documents/publications/nz-primary-care-handbook-2012.pdf's. Accessed 1 March, 2018.
14. Zafar A, Stone MA, Davies MJ, et al. Acknowledging and allocating responsibility for clinical inertia in the management of Type 2 diabetes in primary care: a qualitative study. Diabet Med. 2015;32:407-13.
15. Paul SK, Klein K, Thorsted BL, et al. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol. 2015;14:100.
16. Peyrot M, Barnett AH, Meneghini LF, et al. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. Diabet Med. 2012;29:682-9.
17. Fulcher G, Roberts A, Sinha A, et al. What happens when patients require intensification from basal insulin? A retrospective audit of clinical practice for the treatment of type 2 diabetes from four Australian centres. Diabetes Res Clin Pract. 2015;108:405-13.
18. Marrett E, Zhang Q, Kanitscheider C, et al. Physician reasons for nonpharmacologic treatment of hyperglycemia in older patients newly diagnosed with type 2 diabetes mellitus. Diabetes Ther. 2012;3:5.
19. Khunti K, Millar-Jones D. Clinical inertia to insulin initiation and intensification in the UK: a focused literature review. Prim Care Diabetes. 2017;11:3-12.
20. Reach G, Pechtner V, Gentilella R, et al. Clinical inertia and its impact on treatment intensification in people with type 2 diabetes mellitus. Diabetes Metab. 2017;43:501-11.
21. Khunti K, Wolden ML, Thorsted BL, et al. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care. 2013;36:3411-7.
22. Russell-Jones D, Pouwer F, Khunti K. Identification of barriers to insulin therapy and approaches to overcoming them. Diabetes Obes Metab. 2018;20:488-96.
23. Esposito K, Chiodini P, Bellastella G, et al. Proportion of patients at HbA1c target <7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients. Diabetes Obes Metab. 2012;14:228-33.
24. Hermansen K, Davies M, Derezinski T, et al. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care. 2006;29:1269-74.
25. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med. 2007;357:1716-30.
26. Calvert MJ, McManus RJ, Freemantle N. Management of type 2 diabetes with multiple oral hypoglycaemic agents or insulin in primary care: retrospective cohort study. Br J Gen Pract. 2007;57:455-60.
27. Harris SB, Kapor J, Lank CN, et al. Clinical inertia in patients with T2DM requiring insulin in family practice. Can Fam Physician. 2010;56:e418-24.
28. Blonde L, Meneghini L, Peng XV, et al. Probability of achieving glycemic control with basal insulin in patients with type 2 diabetes in real-world practice in the USA. Diabetes Ther. 2018;9:1347-58.
29. Umpierrez GE, Skolnik N, Dex T, et al. When basal insulin is not enough: a dose-response relationship between insulin glargine 100 units/mL and glycaemic control. Diabetes Obes Metab. 2019.
30. McMahon GT, Dluhy RG. Intention to treat - initiating insulin and the 4-T study. N Engl J Med. 2007;357:1759-61.
31. Strain WD, Bluher M, Paldanius P. Clinical inertia in individualising care for diabetes: is there time to do more in type 2 diabetes? Diabetes Ther. 2014;5:347-54.
32. Bailey CJ. Under-treatment of type 2 diabetes: causes and outcomes of clinical inertia. Int J Clin Pract. 2016;70:988-95.
33. Ahren B. Avoiding hypoglycemia: a key to success for glucose-lowering therapy in type 2 diabetes. Vasc Health Risk Manag. 2013;9:155-63.
34. Johnson EL, Frias JP, Trujillo JM. Anticipatory guidance in type 2 diabetes to improve disease management; next steps after basal insulin. Postgrad Med. 2018;130:365-74.
35. Giugliano D, Chiodini P, Maiorino MI, et al. Intensification of insulin therapy with basal-bolus or premixed insulin regimens in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Endocrine. 2016;51:417-28.
36. The Royal Australian College of General Practitioners. General practice management of type 2 diabetes: 2016–18. East Melbourne, Vic: RACGP; 2016.
37. Wu T, Betty B, Downie M, et al. Practical guidance on the use of premix insulin analogs in initiating, intensifying, or switching insulin regimens in type 2 diabetes. Diabetes Therapy. 2015;6:273-87.
38. Meece J. Basal insulin intensification in patients with type 2 diabetes: a review. Diabetes Ther. 2018;9:877-90.
39. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-53.
40. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-89.
41. Rawshani A, Rawshani A, Franzen S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2018;379:633-44.
42. Mosenzon O, Raz I. Intensification of insulin therapy for type 2 diabetic patients in primary care: basal-bolus regimen versus premix insulin analogs: when and for whom? Diabetes Care. 2013;36 Suppl 2:S212-8.
43. Lavernia F. What options are available when considering starting insulin: premix or basal? Diabetes Technol Ther. 2011;13 Suppl 1:S85-92.
44. Ministry of Health. New Zealand Primary Care Handbook 2012. 2012. https://www.health.govt.nz/system/files/documents/publications/nz-primary-care_handbook_2012.pdf. Accessed March 18, 2019.
45. Rizza RA. Pathogenesis of fasting and postprandial hyperglycemia in type 2 diabetes: implications for therapy. Diabetes. 2010;59:2697-707.
46. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2018 executive summary. Endocr Pract. 2018;24:91-120.
47. Raccah D, Huet D, Dib A, et al. Review of basal-plus insulin regimen options for simpler insulin intensification in people with Type 2 diabetes mellitus. Diabet Med. 2017;34:1193-204.
48. Garber AJ, Wahlen J, Wahl T, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). Diabetes Obes Metab. 2006;8:58-66.
49. Linjawi S, Lee BW, Tabak O, et al. A 32-week randomized comparison of stepwise insulin intensification of biphasic insulin aspart (BIAsp 30) versus basal-bolus therapy in insulin-naive patients with type 2 diabetes. Diabetes Ther. 2018;9:1-11.
50. Wu T. Premixed insulin analogues: a new look at an established option. Diabetes and Primary Care Australia. 2016;1:129-33.
51. Kalra S, Czupryniak L, Kilov G, et al. Expert opinion: patient selection for premixed insulin formulations in diabetes care. Diabetes Therapy. 2018;9:2185-99.
52. Vora J, Cohen N, Evans M, et al. Intensifying insulin regimen after basal insulin optimization in adults with type 2 diabetes: a 24-week, randomized, open-label trial comparing insulin glargine plus insulin glulisine with biphasic insulin aspart (LanScape). Diabetes Obes Metab. 2015;17:1133-41.
53. Deed G, Kilov G, Dunning T, et al. Use of 50/50 premixed insulin analogs in type 2 diabetes: systematic review and clinical recommendations. Diabetes Ther. 2017;8:1265-96.

novo nordisk®

This publication has been created with an educational grant from Novo Nordisk. The content is entirely independent and based on published studies and the author's opinions. It may not reflect the views of Novo Nordisk. Please consult the full Data Sheets at www.medsafe.govt.nz before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician.