

## Early insulin therapy in patients with type 2 diabetes mellitus

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Type 2 diabetes mellitus (T2DM) is a progressive disease characterised by beta cell dysfunction and insulin resistance. Beta cell dysfunction progresses to beta cell failure. Many patients with T2DM are managed with oral agents until complications develop. 'Clinical inertia' in T2DM, defined as lack of initiation or intensification of therapy when clinically indicated, is common among clinicians. Patients are exposed to hyperglycaemia for a long time resulting in glucotoxicity to beta cells, leading to further beta cell deterioration. The traditional approach to the management of T2DM is lifestyle change, diet, exercise, weight loss, oral agents and, lastly, insulin. This traditional approach is usually carried out step-by-step and at a slow pace, with insulin offered as a last option. By the time insulin therapy is initiated, complications have already developed. It is, therefore, important for clinicians to be aware of the importance of initiating insulin therapy early to prevent poor glycaemic control and the development of diabetes-related complications.

### Introduction

Type 2 diabetes mellitus (T2DM) is an insulin-insufficient disease characterised pathophysiologically by beta cell dysfunction and insulin resistance.<sup>1</sup> Glycaemic control is important in the management of T2DM to prevent diabetes-related complications.<sup>1–4</sup> Early in the onset of T2DM there is development of relative insulin deficiency and, later, absolute insulin deficiency.<sup>1</sup> Therefore, when a patient is diagnosed with T2DM, the degree of deficiency depends on the stage of the disease at which the diagnosis has been made.<sup>1</sup> Early in the natural course of T2DM, patients develop insulin resistance, hyperglycaemia and hyperinsulinemia.<sup>3,5</sup> As the disease progresses, patients develop beta cell failure with hyperglycaemia and hypoinsulinemia.<sup>3,5</sup> Most of the patients are diagnosed at the late stage where there is hyperglycaemia and hypoinsulinemia, usually with beta cell function declined by 50%.<sup>5–8</sup> It can be extrapolated from the United Kingdom Prospective Diabetes Study (UKPDS) that beta cell dysfunction could commence 15 years before diagnosis.<sup>9</sup> At this late stage, most patients require exogenous insulin therapy for optimal glycaemic control.<sup>5</sup> Management of T2DM involves addressing the pathophysiology of the disease.<sup>1,10</sup> The following drug classes are important in its management: sulfonylureas, biguanides, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, insulin, dipeptidyl peptidase 4 (DPP IV) inhibitors, glucagon-like peptide-1 (GLP-I) analogues and sodium-glucose cotransporter 2 inhibitors.<sup>1,11</sup> Despite the availability of these drug classes, few patients attain glycaemic control.<sup>2,3,7</sup> This is due to the progressive nature of the disease. Most patients with T2DM will eventually need insulin therapy for glycaemic control.<sup>8,12,13</sup> Insulin is the only drug with an unlimited percentage of HbA1c reduction.<sup>4</sup> Doses of insulin can be titrated until an individualised glycaemic target is reached.<sup>4</sup>

It is, therefore, important for clinicians to understand the importance of early insulin initiation so that glycaemic control can be achieved early and consequently prevent diabetes-related complications.

### Rationale for the use of early insulin therapy in T2DM

Physiologically, fasting glucose is controlled by endogenous basal

insulin secretion, whereas postprandial glucose is controlled by both endogenous basal and bolus insulin secretions.<sup>14</sup> The management of T2DM is to try to simulate the normal physiology of insulin secretion. Insulin therapy in T2DM results in beta cell rest and prevents toxic effects of hyperglycaemia on beta cells.<sup>15,16</sup> Insulin reduces excessive secretory demands on beta cells, is anti-inflammatory, has anti-apoptosis effects and thus results in beta cell recovery.<sup>14,15</sup> The anti-inflammatory effect of insulin benefits vascular endothelium, reducing cardiovascular risk.<sup>14,15</sup> Insulin has been proved to preserve beta cells and improve beta cell function.<sup>15</sup> When insulin therapy in newly diagnosed T2DM was compared with oral agents in terms of beta cell preservation and glycaemic remissions,<sup>8,15,17</sup> insulin showed favourable results in terms of recovery and maintenance of beta cell function, and glycaemic remissions.<sup>8,15,17</sup> The United Kingdom Prospective Diabetes Study (UKPDS) showed that if a patient is diagnosed with T2DM and is managed with oral agents only, in six years he or she will need insulin therapy for glycaemic control.<sup>9</sup> When the insulin and metformin regimen was compared with triple oral hypoglycaemic agents, the insulin and metformin regimen showed better glycaemic control than triple therapy, with less hypoglycaemia and weight gain.<sup>16</sup> A study was conducted where short-term insulin therapy was evaluated in terms of beta cell preservation and beta cell function in patients newly diagnosed with T2DM. After multiple insulin injections over two to three weeks, euglycemia was achieved in 90% of subjects who completed the study. Insulin was withdrawn and patients were managed with diet and exercise only.<sup>8,18</sup> Most of the patients maintained euglycemia for more than 12 months.<sup>18</sup> This study showed that insulin preserved and improved beta cell function and resulted in improvement of endogenous insulin secretion.<sup>18</sup> A study was conducted where insulin monotherapy and metformin monotherapy were individually compared with an insulin and metformin regimen.<sup>19</sup> It was shown that the insulin and metformin regimen achieved better glycaemic control as compared with both drugs used individually.<sup>19</sup>

### Indications for early insulin therapy in T2DM

Insulin therapy is considered as initial therapy in the management of T2DM when the disease is diagnosed in a patient with clinical features of catabolism such as weight loss, in patients with

fasting glucose of more than 14 mmol/l, ketonuria or ketoacidosis, HbA1c of more than 10%, random glucose of more than 16.7 mmol/l, women with gestational T2DM not controlled through diet alone, and in patients who, after discussion of options of therapy, wish to start insulin as initial therapy.<sup>4,9,10,20–22</sup> Insulin is also considered in patients on maximum oral hypoglycaemic agents with individualised glycaemic target unmet.<sup>10–12,20–22</sup>

### Barriers to early insulin initiation in T2DM

Clinicians at times are reluctant to initiate insulin therapy in patients with T2DM despite poor glycaemic control. The common clinician-related barriers are fear of hypoglycaemia, weight gain and misconception that insulin causes cardiovascular disease. The patient-related barriers are fear of needles, fear of disease progression and the misconception that injection is a sign of failure with treatment or a sign that the disease is more severe than that of patients taking oral agents.<sup>3,16,23,24</sup> All these barriers to insulin therapy should be addressed on diagnosis of T2DM.

### Practical strategies for early insulin initiation

#### Insulin strategies

Patients with T2DM experience decline in beta cell function and, with time, need exogenous insulin therapy.<sup>11</sup> Before insulin therapy is initiated there are questions that the clinician should address.<sup>25</sup> First, how far from the individualised goal is the patient? According to several guidelines in the management of T2DM, target fasting glucose, postprandial glucose and HbA1c must be individualised.<sup>18,21</sup> In patients who are young, low risk, newly diagnosed with T2DM and who have no cardiovascular disease, target HbA1c should be less than 6.5%, fasting glucose should be between 4 mmol/l and 7 mmol/l, and postprandial glucose should be between 4.4 mmol/l and 7.8 mmol/l. In the majority of patients with T2DM, target HbA1c should be less than 7%, fasting sugar between 4 mmol/l and 7 mmol/l and postprandial glucose between 5 mmol/l and 10 mmol/l. In patients who are elderly, high risk with poor short-term prognosis and who have hypoglycaemic unawareness, target HbA1c should be less than or equal to 8%, fasting glucose should be between 4 mmol/l and 7 mmol/l, and postprandial glucose should be less than 12 mmol/l.<sup>10,21,22</sup>

Second, if insulin is initiated, which oral agent should be stopped? Patients with T2DM are usually managed with metformin and sulfonylurea. Pathophysiologically, when giving insulin to patients on metformin and sulfonylureas, sulfonylureas may be discontinued or may be continued, depending on the glycaemic control of the patient or insulin strategy used.

Lastly, what type of insulin programme should be started? Insulin strategies available are biphasic premixed insulin, basal insulin and basal-bolus insulin therapy. Biphasic premixed insulin added to metformin was compared with basal insulin added to metformin in terms of HbA1c. HbA1c was significantly reduced in patients on biphasic premixed insulin added to metformin.<sup>26</sup> Basal-bolus insulin therapy was compared with biphasic premixed insulin therapy in patients who failed on oral hypoglycaemic agents or who failed on oral hypoglycaemic agents combined with basal insulin therapy.<sup>27</sup> There was no difference between the two regimens in terms of HbA1c reduction, fasting and postprandial glucose reduction, weight gain and hypoglycaemic events.<sup>27</sup> The problem is that biphasic premixed insulin therapy is not physiological and the doses of intermediate-acting insulin and short-acting insulin are not flexible.<sup>28</sup> The one dose of

biphasic premixed insulin cannot be adjusted without affecting the other dose.<sup>28</sup> Basal-bolus insulin therapy, though physiological, has the disadvantage of multiple injections.<sup>29</sup> Which of these insulin strategies is chosen depends on HbA1c level. In a newly diagnosed T2DM patient, if HbA1c is between 7% and 10% or it is 1% to 2% above the individualised target, and insulin therapy is indicated, bedtime basal insulin should be initiated together with metformin and sulfonylurea.<sup>17,30</sup> In a newly diagnosed T2DM patient, if HbA1c is greater than 10% or it is 2% above the individualised target, and insulin therapy is indicated, basal-bolus insulin therapy or biphasic premixed insulin therapy should be initiated together with metformin.<sup>7,18,26,29,30</sup> In a patient already on metformin and sulfonylurea, if HbA1c is between 7% and 10% or it is 1% to 2% above the individualised target, basal insulin may be added. If a patient is already on bedtime basal insulin plus oral agents and HbA1c is greater than 10% or it is 2% above the individualised target, it is best to discontinue sulfonylurea, continue metformin, and to introduce basal-bolus insulin therapy or biphasic premixed insulin therapy.<sup>7,18,26,29,30</sup> Whichever insulin strategy is considered, fasting glucose, postprandial glucose and HbA1c should be assessed, and insulin therapy adjusted according to the individualised glycaemic target. The choice of insulin strategy must be discussed with the patient and agreed on to encourage adherence.

#### Insulin initiation

When insulin therapy is indicated, the question is always: How is insulin therapy initiated? If bedtime insulin therapy is indicated and the patient is lean, initiate with 5 to 10u of bedtime insulin, and if the patient is obese, initiate with 10 to 15u or initiate with 0.1–0.2u/kg of bedtime insulin depending on the degree of hyperglycaemia.<sup>11,21,31</sup> Bedtime insulin therapy is used together with oral agents. Monitor fasting blood glucose every morning and calculate average fasting glucose every three to seven days and increase the bedtime insulin by 2 to 5 units until the fasting sugar has reached the individualised target.<sup>11,21</sup> If pre-lunch or pre-dinner glucose, or both pre-lunch and pre-dinner glucose have not reached the individualised target, bolus insulin during one or more of the meals can be introduced. If biphasic premixed insulin is preferred as the initial therapy or patients have failed to reach their target after adding basal insulin therapy to oral agents, calculate the total daily insulin requirement by multiplying the weight of the patient by 0.3, then divide the total daily insulin into two doses, namely, 2/3 given before breakfast and 1/3 before supper. Alternatively, the patient can start with 10u biphasic premixed insulin twice a day,<sup>21</sup> or take the total insulin calculated and give 50% before breakfast and 50% before supper.<sup>7</sup> When fasting and pre-dinner glucose are controlled, in biphasic premixed insulin therapy, monitor postprandial glucose and introduce bolus insulin at lunchtime if indicated. If basal-bolus insulin therapy is preferred as initial insulin therapy, give half of the 24-hour insulin required as basal insulin and then the remaining half divided into three as bolus insulin at mealtimes.<sup>30,31</sup> When fasting glucose and postprandial glucose have reached individualised targets, monitor HbA1c every three months until target is reached. When HbA1c has reached individualised target level, monitor it every six months.

#### Conclusion

T2DM is a common public health problem associated with long-term complications if not well controlled.<sup>1–4,32</sup> Insulin is usually used as the last option in the management of T2DM.<sup>32</sup> Delay in insulin initiation is the common cause of prolonged exposure to hyperglycaemia, which results in diabetes-related complications.<sup>32</sup> Initiating insulin early in the management of T2DM will prevent

development of these complications. It is, therefore, important for clinicians to initiate insulin therapy early so as to reach individualised glycaemic targets early, thereby preventing T2DM-related complications.

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