Intensive initiation of insulin therapy in patients with newly diagnosed type 2 diabetes mellitus: a different take on current stepwise approaches

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Introduction

Type 2 diabetes mellitus (T2DM), previously regarded as being a disease borne exclusively from following a poor lifestyle,¹ affects at least 415 million individuals worldwide, a number which is believed will increase to 640 million by 2040.² As our understanding of T2DM improved over time, it became clear that the condition is underpinned by interactions between poor lifestyle choices and highly varying genetic constructs that involve more than 400 genes.^{3,4} Although a comprehensive review of the genetic architecture of T2DM falls beyond the scope of the current paper, it suffices to say that failure to regard the pathophysiology of T2DM and its subsequent treatment from a drastically different perspective, will result in an increasing burden of the condition on society. This is especially realistic, since despite the fact that oral hypoglycaemic drugs have been used since 1955,⁵ current approaches fail to arrest the continuous global rise in the number of T2DM cases.

Irrespective of the specific aetiological mechanisms of T2DM that may contribute to disease progression in different patients, one core trait is observed in all patients with the condition, i.e. the inadequate capacity of pancreatic beta-cells to adjust insulin secretion in response to decreased insulin sensitivity.^{6,7} In turn, this trait is bidirectionally associated with three overarching pathophysiological constructs that are observed in most T2DM patients, i.e. i) resistance to the action of insulin in target tissues, ii) abnormal patterns of insulin secretion, and iii) increased hepatic gluconeogenesis.⁸ In this paper, we will afford attention to the role that a progressively depleting beta-cell reserve, either with respect to insulin-secreting capacity or physical cell mass, plays in the pathogenesis and prognosis of the condition. We will further illustrate how current pharmacotherapeutic approaches may be counterproductive for our efforts to ensure lasting therapeutic outcomes and how intensive insulin therapy in the early stages following its diagnosis, may improve the long-term prognosis of the condition.

Mechanisms contributing to the depletion of beta-cell reserve and function

Before we delve deeper into how the beta-cell reserve is eroded over time, it is important to note that the pancreas, most notably so the beta-cells in the islets of Langerhans, present

with a noteworthy ability to adjust its rate and concentration of insulin secretion to compensate for an increased demand.⁹ Such an increase in insulin demand, which places beta-cells under significant physiological pressure, generally arises due to any one or more of the following reasons: an overly sedentary lifestyle, dietary overindulgence and obesity, puberty and pregnancy.¹⁰

That said, once beta-cells begin to fail in adjusting insulin output in response to an increased degree of insulin resistance and/or an increased insulin demand, T2DM follows. It is well-known that T2DM is associated with reductions in beta-cell mass to the extent of 24–65%, depending on the patient cohort investigated.^{3,7} Since beta-cell loss is not constant between T2DM patients and considering that not all patients share the same underlying disease-related architecture, a significant body of work has been done over the past few decades to shed more light onto when and how beta-cell loss is triggered. However, beta-cell loss is not the only contributor to depleting insulin levels, since reductions in insulin secretion are oftentimes far greater than what can be accounted for by beta-cell loss (T2DM patients have been shown to present with 50–97% less insulin, compared to healthy controls.)^{7,11} While reductions in beta-cell mass are largely contributable to increased rates of apoptosis, the processes underlying the loss of beta-cell function are more complex and involve among others, differentiation of beta-cells to non-insulin expressing cell types. Collectively, changes in the beta-cell mass and function are triggered and underpinned by several key aspects that are often characteristic of T2DM patients.

Obesity, immunity, and beta-cell loss

The importance of visceral obesity in the progression and prognosis of T2DM cannot be overstated. Being obese contributes to insulin resistance, impaired glucose tolerance and ultimately T2DM in several distinct, but interrelated ways. Visceral adipose tissue is characterised by high rates of lipolysis, despite insulin being an anti-lipolytic hormone. However, since visceral adipose tissue is more sensitive to the effects of cortisol, a potent lipolytic steroid, increased visceral adipose mass contributes to high concentrations of circulating free fatty acids.^{12,13} From a diabetic perspective, this situation is not ideal, since excessive circulating free fatty acid levels compete with glucose for the available storage space in especially skeletal muscle,¹⁴ contributing to

a progressive increase in both basal and postprandial plasma glucose concentrations. Without downplaying the importance of the intricate physiological changes that ensue, it is sufficient to note that plasma glucose that cannot be stored in skeletal muscle, finds its way to tissues that do not normally store glucose, i.e. vascular endothelium and even the beta-cells themselves.¹⁰ Translocation of glucose to these and other non-skeletal tissue, results in adaptive immune responses against these tissues, contributing to premature apoptotic processes.¹⁵ Another way in which obesity contributes to impairing beta-cell mass and function is through increased leptin and adipokine secretion. Whereas constant increases in leptin concentrations result in leptin resistance and disturbances in energy balance,¹⁶ increased adipokine release contributes to exacerbating anti-beta-cell immune responses. In fact, the relationship between beta-cell directed immunity and T2DM became clear following observations that anakinra, an interleukin-1 receptor antagonist, improved the insulin response and reduced the concentrations of glycated haemoglobin (HbA_{1c}) in patients suffering from T2DM; these effects lasted up to 40 weeks after the withdrawal of 13-week anakinra treatment.¹⁷

Glucotoxicity

In addition to the role that obesity plays to increase circulating glucose levels, T2DM patients concomitantly suffer from what is known as glucotoxicity. Glucotoxicity broadly refers to the chronic exposure of beta-cells to elevated levels of plasma glucose levels. This impacts pancreatic physiology in two major ways. First, chronic exposure to high concentrations of glucose contributes to a lower degree of first-phase insulin release, which, albeit being more of a metabolic impulse rather than being regulated in a glucose concentration-dependent manner, exacerbates the already high degree of hyperglycaemia.¹⁸ Second, glucotoxicity contributes to a gradual decrease in the overall ability of pancreatic beta-cells to synthesise and secrete insulin via several distinct mechanisms,¹⁹ which ultimately impacts on the basal glucose homeostasis²⁰ by feeding into the cycle of increasing circulating plasma glucose levels.

Changing lanes: A case for early insulin initiation

Current stepwise pharmacotherapeutic approaches to the treatment of T2DM, especially in the public healthcare sector of South Africa,²¹ have been designed to avoid the use of insulin until late in the disease progression. Usually consisting of metformin for two to three months (administered in combination with advocating lifestyle changes) to which a sulfonylurea is added if an adequate response is not obtained, these measures generally fail with respect to one crucial aspect: it likely is too little, too late. Patients mostly gain access to the first-line pharmacotherapeutic intervention, i.e. metformin, only once they have been diagnosed with T2DM. Since chronic and noteworthy pathophysiological processes have already been contributing for several years to an ultimate T2DM diagnosis, current treatment approaches fail to recognise the contribution of gradual changes in the normal glucose homeostasis to the ultimate development of T2DM. It has been shown that the pancreas loses its ability to rapidly

respond to fluctuating plasma glucose levels within the two years preceding an accurate T2DM diagnosis.²² Moreover, the use of sulfonylureas in addition to metformin in the second-line treatment of T2DM is aimed at increasing insulin release from an already burdened and rapidly deteriorating beta-cell reserve and is bound to fail, as is often observed in clinical studies.²³⁻²⁵ That said, the initial increase in insulin release following sulfonylurea initiation, is thought to succeed in reducing glucose to such an extent that insulin sensitivity improves throughout the initial phases of treatment. It is also true that over the long term, insulin release can adjust to levels lower than it was before the initiation of treatment, likely pointing to the gradual improvement of the insulin response.²⁶ Yet, despite this being possible, sulfonylurea treatment failure remains a clinical dilemma, most likely because it relies on further burdening the already deteriorating beta-cell capacity.

How insulin therapy can protect beta-cell function in the long term

The question thus arises whether any alternatives to the current approaches can be followed? In short, the answer is yes and while we will not afford attention to anti-diabetic drug classes added to the arsenal of available options over the past decade or two, we will frame this answer against the background of using insulin as a viable alternative in the initial stages of the condition.

An abundance of evidence disseminated over the past two decades points to intensive, short-term insulin treatment during the initial stages following a T2DM diagnosis and even during the pre-diabetes phases characterised by insulin resistance and impaired glucose tolerance, as a viable alternative or addition to current therapeutic approaches.²⁷⁻³¹ How exogenous insulin administered immediately once a T2DM diagnosis has been made may act to improve glucose homeostasis, has not yet been elucidated in full. It is likely that acute and meticulously maintained reductions in plasma glucose concentrations which are realised following intensive insulin therapy, may abrogate the influence of glucotoxicity on the pancreatic beta-cells to such an extent that beta-cell function and responsiveness are restored and maintained.^{27,32} Indeed, two- to three-week intensive insulin therapy in newly diagnosed T2DM patients has been shown to induce marked reductions in plasma glucose concentrations and improve the first-phase insulin release, which can be maintained for at least one year following such intervention. This result was also found to be significantly more robust than in patients using sulfonylureas for the same period. Moreover, as opposed to patients that used sulfonylureas or other oral hypoglycaemics, the said improvements resulting from insulin treatment, did not require the use of other oral hypoglycaemic agents during the year following the intensive treatment window to maintain the therapeutic benefit; metabolic improvements in the insulin-treated cohort could be maintained by diet only.^{27,28} Another mechanism by which intensive short-term insulin treatment may slow disease progression is by means of rapidly reducing the HbA_{1c} concentration. This is normally observed within 2–5 weeks after such interventions. Since HbA_{1c} is regarded as a longer-term indicator of the diabetic state, this is especially remarkable.³³

The above being said, the dose of insulin needed to attain euglycaemic control during the intervention phase seems to be inversely correlated with the long-term therapeutic outcomes. In other words, the lower the dose needed to reach proper euglycaemic values during the intensive treatment period, the better the long-term outcome. This can putatively be ascribed to the possibility that patients who respond better to insulin during treatment may present with a lesser degree of insulin resistance at baseline²⁷ and that individuals in this group are likely diagnosed with T2DM at an earlier stage. This finding highlights the utter and vital importance of reaching patients quicker. It must be stressed that while obesity plays a major role in the pathogenesis of T2DM, differences in body weight measured one year after insulin therapy were in no means correlated with the success of short-term, intensive insulin therapy.²⁷ Further, the benefit of using intensive short-term insulin therapy in patients with newly diagnosed T2DM, transgresses disease boundaries. Not only does such intervention restore glycaemic control, but it also improves or ameliorates other markers of pathology, commonly associated with T2DM, e.g. abnormal lipid profiles.²⁸ Taken together, it is likely that short-term and intensive insulin therapy facilitates a period of beta-cell rest during which the metabolic demands on pancreatic insulin secretion are reduced because of the administration of exogenous insulin. This in turn purportedly protects the beta-cell reserve sufficiently enough, that it is able to maintain truly long-lasting euglycaemic homeostasis.

How should insulin be initiated, maintained and can it be withdrawn?

The question can be asked why such interventions are not used more often? Interestingly, the answer to this question lies more in psychology, than in metabolic science. Both patients and clinicians are hesitant to initiate insulin therapy, a trend commonly referred to as *psychological insulin resistance*.^{34,35} While multiple reasons for psychological insulin resistance exist, some of the major obstacles that prevent stakeholders from engaging in insulin-based therapies include disbelief and mistrust.³⁶ Considering the immense therapeutic benefit of adequate, well-planned and intensive short-term insulin therapy alluded to above, psychological resistance to insulin-based treatment interventions remains an obstacle that should be overcome. There is indeed no scientific evidence to support the 'one algorithm fits all' approach, proposed by current treatment guidelines.

When the decision is made to initiate insulin treatment, some considerations need to be kept in mind. First, patients presenting with acute or chronic diabetic complications at the time of diagnosis should be afforded special care and must not be considered as ideal candidates for short-term intensive insulin therapy.²⁸ Second, patients should preferably already be stabilised on a diabetic diet before the onset of insulin therapy. This will ease the process of lifestyle and dose-ranging adjustments. Third, multiple daily injections or continuous insulin infusion are both suitable methods for such intervention. Insulin should be introduced at a dose of 0.4–0.5 IU/kg/day, or as adjusted according to the discretion of the clinician, while the

total daily dose should be divided more or less equally between intermediate-acting basal and short-acting post-prandial (bolus) needs.²⁸ Long-acting insulin formulations, e.g. detemir or glargine, should not be considered for this protocol. Once initiated, treatment should be adjusted to reach target glucose values of < 6 mmol/l before breakfast, and < 7 mmol/l two hours after meals. To reach this outcome, insulin doses could gradually be adjusted daily.²⁷⁻²⁹ Following the two- to three-week treatment protocol, patients should be followed up on a monthly basis to establish whether the treatment response is maintained and to decide on and introduce adequate therapeutic maintenance strategies.

Conclusion

In conclusion, the evidence presented over the past two decades points to the likelihood that beta-cell mass and function in patients with T2DM can be rescued, restored, and maintained through the rapid and intensive introduction of short-term, intensive insulin therapy.²⁹ Although this approach will likely not be of benefit to all patients in terms of attaining long-term therapeutic benefit, current pharmacotherapeutic strategies, which fail to assist in preserving beta-cell integrity and rather place it under more severe physiological stress, are counterproductive in the long term. We therefore propose that in patients newly diagnosed with T2DM, consideration should be afforded to short-term, intensive insulin treatment as a viable alternative or addition to current first-line interventions.

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