

Recent Technological and Pharmacological Advances in Type 1 Diabetes

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A vast majority of patients with type1 diabetes (T1D) are not at the glycemic goal of an HbA1c of less than 7% [1-3]. It continues to remain a very tough disease and the patients often get very frustrated while managing the unpredictable fluctuations of blood glucose coupled with emotional volatility. This subsequently translates to wild control of diabetes with increased microvascular and macrovascular complications and diminished quality of life. Lind et al. [4] has demonstrated a markedly elevated risk of total and cardiovascular mortality in patients with T1D. This increased risk was related both to glycemic control and to renal dysfunction. The total and cardiovascular mortality was ten times that of the normal population in patients with HbA1c >9.5%. Patients with HbA1c >9.5% had a risk of total and cardiovascular mortality of 10 times that of the normal population. This risk was further amplified in those with impaired renal function. A higher mortality was also shown in the conventional DCCT group when compared with general population over a mean follow up of 27 years [5]. Mortality increased significantly with increasing mean HbA1c, more so among females than males, especially for HbA1c >9% [5]. Intensification of insulin treatment facilitates good glycemic control but is faced with risk of increased hypoglycemia and weight gain. In the DCCT trial, the intensively treated group gained 4.75 kg more weight compared to conventionally treated group over a period of 6 years [6]. In this context, it is imperative that novel pharmacological and technological approaches to treatment of type1 diabetes (T1D) are devised.

The landmark discovery of insulin by Banting & Best in 1921 [7] was awarded the Nobel Prize in medicine. Since then, advances in the treatment of T1D have focused on preparations of insulin with different rates of absorption from the subcutaneous tissue either through the addition of other proteins like protamine or the creation of analogs of human insulin [8]. These modifications allowed the availability of insulin preparations, which have either prolonged bioavailability or a more rapid absorption than human insulin [8]. More recently, the advent of a faster acting insulin aspart should facilitate blunting of post-prandial glucose excursions with potentially less risk of hypoglycemia as it not only kicks in promptly but also wears off more quickly thus mimicking the first phase insulin secretory response to some degree [9]. It is currently awaiting regulatory approval from FDA for its use in United States [10].

In addition, the continuous subcutaneous insulin infusion (CSII) with the use of pumps has contributed to a more predictable absorption and bioavailability of insulin and thus an improved glucose homeostasis. Frequent or continuous glucose monitoring (CGM) may also contribute to an improvement in glycemic control [11]. On July 21, an FDA advisory panel voted 8-2 to allow patients to use Dexcom's G5 CGM data for making treatment decisions without finger stick verification. The panel's recommendation will now be considered by the FDA which, if accepted, will carve a path forward for Medicare coverage of the device [12]. This is likely to benefit patients with both type1 and type 2 diabetes (T2DM) but T1D patients are likely to benefit the most.

Mini Med 630 G system (integrated insulin pump and CGMS) also has smart guard technology that can act for you if your glucose level goes below a preset limit [13]. If you don't respond to alerts, it can pause insulin delivery for up to two hours. This feature helps to reduce hypoglycemia at all times and thus improve quality of life. Animas Vibe was the first system to integrate insulin pump with Dexcom G4 CGM technology [14] followed by T: Slim G4 Insulin Pump which also has touch screen technology to navigate through its different pump and CGM functions [15]. Unlike traditional insulin pumps, Omnipod system has no tubes and uses a Pod for delivery of insulin and can be used in conjunction with any available CGM. Abbott has recently launched a Free style Libre CGM for use in Europe (not currently available in United States). It includes a very tiny glucose sensor (0.2 inches in length, about the thickness of a hair) worn under the skin and connected to a water resistant, plastic on-body patch the size of a one-dollar coin. The sensor remains inserted for 14 days and does not require finger stick calibrations (it's "factory calibrated"). After putting it on the upper arm and waiting one hour, it immediately begins reading glucose and trend information [16].

More recently, a lot of work has been done on closed loop system wherein information provided by CGM devices is used to adjust insulin doses on a real-time basis, every 5-10 minutes. This will facilitate good glycemic control with less risk of hypoglycemia. There are several groups working on different closed loop systems. Medtronic has recently submitted to the FDA for regulatory approval in 2017 for 670 G pump which will adjust the basal insulin rates throughout a 24 hour period but will still require input of bolus dose before meals and correctional doses as and when needed. Group of researchers in Boston is advancing the work on a pump called the iLet Bionic pancreas that combines both the insulin and glucagon into small cartridges that go into the pump [17]. This system requires weight to initiate the system but does not require carbohydrate counting for the meal bolus. The user enters the carb amount as more or less than usual. The algorithm being adaptive learns the user's basal insulin requirements and the requirement for meals. They will be submitting for regulatory approval once they complete the necessary pivotal trials. A group from the University of Virginia also uses a closed-loop system and are working with a commercial group called Type 0 and are beginning a large pivotal study within the next year. Bigfoot Biomedical is using the Asante pump and their own algorithm with focus on the total management of diabetes and providing the services and background you need for supplies and support. A team in

Cambridge, England, is working on a closed loop system called "controlled range" system [18].

In United States; 40-50 % of patients with T1D have metabolic syndrome [3,19] necessitating pharmacological advances with special focus on non-insulin adjunct therapies that have complementary benefits of weight loss, insulin dose reduction and blood pressure lowering in addition to glycemic control. Pharmacologic agents approved for treating T2DM have dominated the scene here. Pramlintide which suppresses glucagon from the α -cell in addition to appetite suppression and reduction in gastric emptying rate was evaluated in T1D patients in randomized clinical trials. This trials yielded inconsistent results in terms of HbA1c lowering [20-22]. Furthermore, a very high incidence of nausea and its dosing with each meal (i.e at least 3-4 times a day) did not bode well for T1D patients. Metformin that could potentially be useful through inhibition of hepatic gluconeogenesis and by counteracting insulin resistance also has demonstrated lackluster and inconsistent results [23].

Glucagon-like peptide-1 receptor agonist (GLP-1RA), stimulates insulin secretion, improves β -cell function, and inhibits glucagon release from α -cell in a glucose-dependent manner in T2DM. Furthermore, it decreases food intake through appetite suppression and reduced gastric emptying which contributes to weight loss in T2DM. Non-randomized studies with GLP-1RA in T1D were conducted anticipating similar benefits in T1D except the insulin secretory function due to the absence of β -cell function in this population. These studies showed promising results in terms of reduction in HbA1c, fasting and postprandial hyperglycemia, post-prandial glycemic excursions, post-prandial glucagon levels, insulin requirements and body weight without additional hypoglycemia [1,2,24-30]. These benefits were demonstrated in both thin and well-controlled patients with T1D (reduction of mean HbA1c by 0.4% from a baseline HbA1c of 6.5%) and in obese and overweight patients with T1D [24,26,27,29,30]. In one retrospective study in overweight and obese patients (mean BMI of 33 kg/m² with poorly controlled type 1 diabetes (mean HbA1c: 7.9) liraglutide was also associated with a reduction in HbA1c of 0.5% over a period of 6 months along with an impressive fall in systolic blood pressure by 10mmHg (baseline: 130 mm Hg) [2]. Impressive results from non-randomized studies propelled the conduct of randomized clinical studies to confirm the benefits and explore potential underlying mechanisms.

The first exploratory study assessing the dose response relationship demonstrated that the addition of 1.2 and 1.8

mg of liraglutide to insulin led to significant reductions from the baseline HbA1c of 7.8% and 7.4% by 0.7% and 0.4% respectively [3]. Glycemic variability was reduced by 5% in 1.2 mg group. There was a 5 kg weight loss in both higher dose groups along with 17-20% reductions in insulin doses and a 3 mm fall in systolic blood pressure with 1.8 mg group only [3]. In addition, there was a dose dependent reduction in post prandial glucagon increases [3]. This study also showed for the first time that two higher doses of liraglutide lead to reduction in daily carbohydrate intake by approximately 50 grams over a period of 12 weeks [3]. Another prospectively randomized study, carried out in Denmark did not demonstrate significant improvements with 1.2 mg of liraglutide compared to placebo in HbA1c over 12 weeks. There was, however, weight loss and a reduction in insulin dose [31]. This study was conducted in normal weight patients. A 24 weeks randomized study from the same group in overweight and obese patients with poorly controlled T1D with 1.8mg of liraglutide demonstrated significant reduction in body weight and insulin requirements without any additional effect on HbA1c when compared with placebo [28,32]. This study also demonstrated reduction in hypoglycemic events [28,32]. A 4 weeks study also showed that addition of liraglutide to insulin treatment does not impair the counter-regulatory hormone responses during hypoglycemia or glycemic recovery from hypoglycemia in subjects with T1D [33].

More recently, two large multi-centered randomized double blind, placebo-controlled trials namely ADJUNCT ONE [34] and ADJUNCT TWO [35] were conducted to investigate the safety and efficacy of three doses of liraglutide (0.6 mg, 1.2 mg & 1.8 mg) versus placebo in a broad population of patients with T1D. In ADJUNCT 1; 1,398 people with T1D were treated for 52 weeks in a treat-to-target study design [34]. HbA1c level was reduced 0.34-0.54% from a mean baseline of 8.2% and significantly more for liraglutide 1.8 and 1.2 mg compared with placebo. There was a weight loss of 3.6 kg and 4.9 kg in 1.2 mg and 1.8 mg respectively with 15-20% reduction in the dose of insulin whereas people treated with placebo experienced a weight gain of around 1 kg (mean baseline of 86 kg in all groups). Clearly, these benefits are of value to obese and overweight patients with T1D. In ADJUNCT 2 trial; efficacy and safety of liraglutide added to capped insulin treatment (the average of the previous 7 consecutive days' total daily insulin dose) in 835 subjects with T1D over a period of 26 weeks was investigated [35]. The results here were very much in line with ADJUNCT 1 trial. In both trials, with higher dose liraglutide group/s c-peptide positive patients had a very impressive HbA1c

reduction in the magnitude of 0.7-0.8% vs 0.3-0.47% in the c-peptide negative T1D patients with markedly less incidence of symptomatic hypoglycemia and almost no episodes of hyperglycemia with ketosis [34,35]. The quality of life (treatment-related impact measures-diabetes [TRIM-D]) was much improved in liraglutide treated groups in both the trials [34,35].

There were higher rates of symptomatic hypoglycemia in all liraglutide groups in ADJUNCT 1 and in 1.2 mg group in ADJUNCT 2 in C-peptide negative T1D patients [34,35] and this can be mitigated by careful insulin titration. In both trials, there was a higher incidence of hyperglycemia (>300mg/dl) with ketosis (plasma ketone level>1.5mmol/L) in 1.8 mg group and this was attributed to nausea and concomitant reduction in insulin doses during initiation/escalation of the liraglutide dose. These did not translate into higher incidence of DKA. In fact the incidence of DKA in both trials [34,35] was \leq 1% compared to 5% in the T1D Exchange Clinical Registry reporting a DKA event in the 12 months before their enrollment, for the same period as ADJUNCT 1 [36]. The most common side effects of GLP-1 use in T1D is nausea and vomiting with frequency being similar to that seen in patient with T2DM.

Considering the results seen in above stated studies, further research should be directed towards overweight and obese patients with T1D with a composite primary endpoint of change in HbA1c, body weight and insulin dose [28]. The expense of the additional therapeutic intervention should also be weighed against the benefits of weight loss, improved glycemia with reduced insulin dose and possibly reduction in hypoglycemia as per the recent study [32]. Further studies should also focus on C-peptide positive T1D patients as they benefit the most with the least incidence of hypoglycemia and hyperglycemia with ketosis. It would also be of interest to see if addition of GLP-1 agents in this setting would preserve the residual c-peptide concentrations. This is extremely relevant as only 5% (20/407 patients) in 5 Trial Net intervention studies maintained their baseline c-peptide concentrations at 4 years post the diagnosis of T1D [37]. GLP-1 analogues (liraglutide and exenatide) have also shown beneficial effects in reducing post-prandial hyperglycemia when used as adjuvant therapy in the closed loop system [38,39]. The decision of Novo Nordisk (manufacturer of liraglutide) to not submit an application to expand the label of liraglutide for use in type 1 diabetes is not clear as certain groups (obese, overweight and c-peptide positive) clearly benefit from it.

GI adverse effects like nausea and vomiting may limit the use of GLP-1 in T1D. This group of patients may benefit from SGLT-2 inhibitor therapy. SGLT2 inhibitors lower blood glucose concentrations by inhibiting renal tubular reabsorption of glucose and thus inducing glycosuria. The proof of concept studies have already shown the efficacy and safety of these agents in T1D (40-43). Recently, a randomized phase 2 clinical trial has shown significant improvements in the glycemic levels in T1D patients with canagliflozin 100 mg and 300 mg ((HbA1c reduction of 0.2-0.4% vs placebo) (44). Sotagliflozin which is a combined SGLT-1 and SGLT-2 inhibitor, has shown around 0.55% reduction in HbA1c over a period of 4 weeks with an increase of 14% in time spent in the target range of 70-180mg/dL glucose with concomitant reduction in bolus insulin dose and weight without additional hypoglycemia (45).

A recent case series reported seven cases of Euglycemic diabetic ketoacidosis (DKA) in patients with T1D on SGLT-2 inhibitor canagliflozin [46]. A phase 2 trial also showed increased incidence of DKA (4.3%, 6.0%, 0%) with canagliflozin 100 and 300 mg vs placebo [44]. DKA in this setting is believed to be due to a potential SGLT2 inhibitor-associated increase in glucagon, elevated free fatty acids (FFAs) inducing insulin resistance, and inadequate insulin to suppress hepatic ketogenesis in the setting of an acute illness and inadequate carbohydrate intake [47]. However, this complication is absent in patients with T1D treated with liraglutide despite reductions in insulin doses. Preliminary data also show that liraglutide suppresses ketogenesis acutely [48]. With this background; a recent study [47] hypothesized that the addition of dapagliflozin, another SGLT-2 inhibitor to insulin and liraglutide (i.e., triple therapy in T1D), would result in further improvement in glycemia without an increase in glucagon concentrations and mediators of ketosis.

There was an impressive HbA1c reduction of 0.66% from a mean baseline A1c of 7.8% with 2kg weight loss [47]. These effects were beyond those observed with the combination of insulin and liraglutide and despite increase in the mediators of ketosis. In the triple therapy group, there were significant increases in the plasma concentrations of glucagon by 35%; hormone-sensitive lipase by 29%; free fatty acids by 74%; acetoacetate by 67% and β -hydroxybutyrate by 254%. Urinary ketone levels also increased significantly. Two patients in the dapagliflozin group developed diabetic ketoacidosis. While the increase in glucagon probably accounts for the uniform increases in lipolysis and increases in plasma FFA, acetoacetate and β -hydroxybutyrate concentrations,

the occurrence of DKA is also triggered by reductions in insulin dosing which becomes necessary as the glycemic control improves with induction of glycosuria with SGLT-2 inhibitors [47,49,50]. GLP-1 agents and or SGLT-2 inhibitors in T1D although beneficial is an off-label treatment and it must be used only by a knowledgeable patient along with an endocrinologist who is well versed with it as it requires meticulous insulin dose titrations and monitoring [47].

Recent technological and pharmacological advances in area of T1D has generated tremendous excitement and is likely to revolutionize treatment of T1D. This in turn will facilitate a higher percentage of T1D patients achieving their goal HbA1c, reduce complications of T1D, improve quality of life, increase overall survival and on a much larger scale will cut down the healthcare expenditure and also contribute to enhanced national productivity due to less sick days.

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