Diabetes Relief℠

Get your life back℠

Physiologic Insulin Delivery – A Common Sense Approach to a Complex Problem

The Food and Drug Administration approved 15 new diabetes drugs between 2013 and 2016[1]. Almost 300 companies are involved in developing drugs for type 2 diabetes alone, and additional companies are working on type 1 diabetes and diabetes complications. Still others are developing new drug delivery devices. The teams dedicated to discovering new molecules should be applauded - diabetes mellitus is a huge public health issue.

According to the American Diabetes Association, the total economic cost of diabetes in the U.S. increased from $205 billion in 2007, to $327 billion in 2017. Medicare spent $11 Billion in 2013 on dialysis alone. Amputations cost between $73,000 to $120,000 for hospital and follow-up care. As the occurrence of diabetes continues to rise along with the ballooning costs of treatments, pharmaceutical companies continue to seek proprietary compounds for development. In recent years, the US FDA has approved several drugs with novel mechanisms of action. These include GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors. Like their predecessors, these therapies are expected to have rather predictable outcomes of managing hyperglycemia without addressing the root and underlying pathophysiology that leads to the debilitating complications of diabetes and metabolic syndrome.

Ultimately, these treatments and others in development aspire to reduce hyperglycemia by increasing the availability of insulin. However, there is an approach to treating diabetes and other metabolic disorders that produces superior outcomes by mimicking the body's natural method of regulating insulin. The science behind rhythmic or physiologic insulin excretion by the pancreas is not new; the phenomenon has been documented by researchers for decades.

Rather than a continuous flow or stream, the pancreas releases insulin in the same way many other hormones are secreted−in short pulses. The beta-cells in the islets of Langerhans excrete insulin in a slow rhythm. This phenomenon was first observed in 1979 as healthy fasting subjects had their insulin levels monitored every minute for one to two hours[2] (figure 1).

[1] FDA.gov

[2] Normal pulses of insulin, C-peptide, and glucose measured in blood from a peripheral vein. 1979 Lang DA, et al.

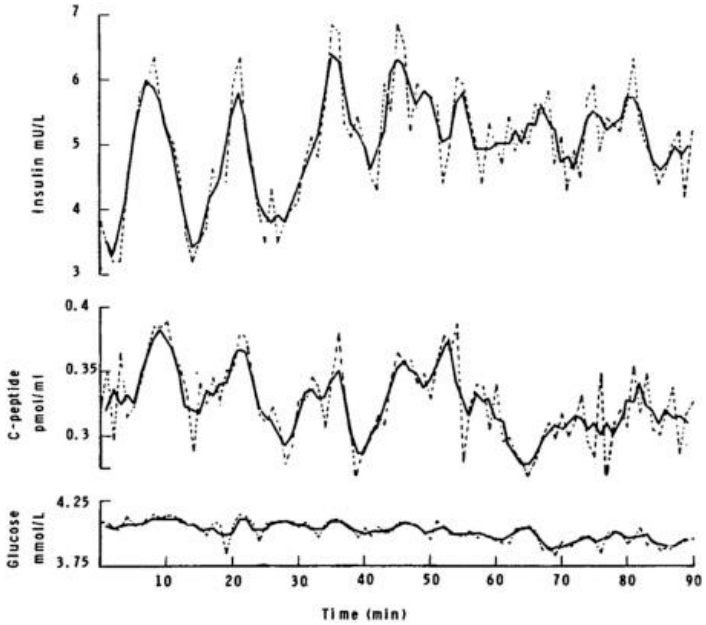

Figure 1

Insulin levels in the blood are not static, but pulse every few minutes. C-peptide, which is secreted along with insulin, follows the same pattern. Corresponding changes in glucose levels are present but less dramatic. After consuming a carbohydrate meal, the height of each peak increases as more insulin is released in each pulse while the pulses continue at the roughly the same frequency. These spikes of insulin are approximately every 5-6 minutes. As well as these fast cycles, an ultradian rhythm made up of slower oscillations of insulin every 80–180 minutes has also been measured. [3]

Physiologic insulin is more effective at activating insulin receptors than a constant exposure of insulin in the liver.[4] The pancreas releases insulin into the portal vein, which flows directly into the liver before spreading out through the rest of the body, so the liver experiences the greatest effect of these insulin waves. In contrast, a continuous exposure to insulin results in downregulation of insulin receptors and results in the phenomenon of insulin resistance.[5]

Diabetes is characterized by a disruption of this physiologic rhythm of insulin by the pancreas. This disruption is believed to be in part a result of inflammation in the pancreas that may result from a variety of causes including obesity, toxins, trauma, etc., and the resulting inflammation ultimately disrupts the neuronal network that coordinates this oscillating pattern. The slower, longer ultradian cycles of insulin secretion were found to be disrupted in diabetic patients.[6] In addition to the longer cycles, shorter rhythms are affected in diabetes mellitus as well. Individuals with type 2 diabetes have been found to have shorter and highly irregular wave-forms related to their insulin secretion profile.[7]

[3] Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. 1988 Polonsky KS, et al.
[4] Pulsatile insulin secretion dictates systemic insulin delivery by regulating hepatic insulin extraction in humans. 2005 Meier JJ, et al.
[5] Disordered insulin secretion in the development of insulin resistance and Type 2 diabetes. 2012 Schofield CJ, Sutherland C
[6] Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. 1988 Polonsky KS, et al.
[7] Association between insulin secretory pulse frequency and peripheral insulin action in NIDDM and normal subjects. 1996 Hunter, et al.

The question of causality was explored to determine whether the disruption in physiologic secretion of insulin was a sequela of or catalyst for diabetes. First-degree relatives of diabetic patients were studied in 1998 and were found to have abnormal insulin pulses compared to unrelated controls, suggesting that the abnormal oscillations in insulin secretion may be an early phenomenon in the development of type 2 diabetes.[8] Research performed more recently (2012) shed additional light on the role that abnormal insulin patterns play in the subsequent onset of diabetes. The physiologically normal pattern of insulin wave-forms is important for hepatic insulin signaling and glycemic control, and liver insulin resistance in diabetes is likely, in part, due to impaired physiologic insulin signaling.[9] Additionally, as disordered insulin secretion may cause intracellular insulin resistance, it may be an initiating factor in the progression to type 2 diabetes.[10]

To summarize the sampling from the research above, the physiologic secretion of insulin by the pancreas is well established, as is the evidence that impaired oscillations of insulin plays a significant role in the development of diabetes. Even though there are hundreds of teams developing molecules to manage the progression of the disease, the incidence and impact of diabetes continues to grow. It was this challenge that has led to the development of a novel therapeutic regimen that is producing superior outcomes by mimicking the body's own method of regulating insulin. Diabetes Relief's patented treatment improves hepatic glucose process and is an effective program that is poised to transform the way diabetes is managed.

Several clinical studies have shown this therapeutic approach to be safe and efficacious. *The Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy* was published in 2000. The purpose of this study was to assess the effects of pulsatile intravenous insulin therapy (PIVIT) on the progression of diabetic nephropathy in patients with type 1 diabetes mellitus (DM). This 18-month multicenter, prospective, controlled study involved 49 type 1 DM patients with nephropathy who were following the Diabetes Control and Complications Trial (DCCT) intensive therapy (IT) regimen. Of these, 26 patients formed the control group (C), which continued on IT, while 23 patients formed the treatment group (T) and underwent, in addition to IT, weekly PIVIT. Blood pressure in all patients was maintained below 140/90 mm Hg on antihypertensive medication, preferentially using angiotensin-converting enzyme (ACE) inhibitors. All study patients were seen in the clinic weekly for 18 months, had monthly HbA1c monitoring, as well as 24-hour urinary protein excretion and creatinine clearance (CrCl) determinations performed every 3 months. The HbA1c levels declined from 8.61% +/- 0.33% to 7.68% +/- 0.31% (P = .0028) in the T group and from 9.13% +/- 0.36% to 8.19% +/- 0.33% (P = .0015) in the C group during the study period. CrCl declined significantly in both groups, as expected, but the rate of CrCl decline in the T group (2.21 +/- 1.62 mL/min/yr) was significantly less than in the C group (7.69 +/- 1.88 mL/min/yr, P = .0343). The authors conclude that when PIVIT is added to IT in type 1 DM patients with overt nephropathy, it appears to markedly reduce the progression of diabetic nephropathy. The effect appears independent of ACE inhibitor therapy, blood pressure, or glycemic control.

Subsequent to these findings, other studies were conducted and published including *Effect of Intensive Insulin Therapy on Progression of Overt nephropathy in Patients with Type 1 Diabetes Mellitus* by researchers at the University of California, Davis. In this clinical trial investigators set out to assess the effects of chronic (long-term) intermittent intravenous insulin therapy (CIIIT) on the progression of overt nephropathy in patients with type 1 diabetes mellitus.

This retrospective longitudinal three-center study of 31 patients with type 1 diabetes mellitus and overt nephropathy who were receiving intensive subcutaneous insulin therapy (four insulin injections daily) and weekly CIIIT. Study patients had follow-up consultations weekly for at least 12 months, monthly hemoglobin

[8] Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. 1998 O'Rahilly S, et al.
[9] Pulsatile portal vein insulin delivery enhances hepatic insulin action and signaling. 2012 Matveyenko AV
[10] Disordered insulin secretion in the development of insulin resistance and Type 2 diabetes. 2012 Schofield CJ, Sutherland C

A_{1c} (by high-performance liquid chromatography), and semiannual creatinine clearance determinations. The results showed hemoglobin A_{1c} levels declined significantly from 8.6% +/- 0.6% to 7.6 % +/- 0.3% (P = 0.0062) during the study period, while the creatinine clearance remained essentially unchanged. The authors concluded that the addition of CIIIT to intensive subcutaneous insulin therapy in patients with type 1 diabetes mellitus seems to arrest or appreciably reduce the progression of overt diabetic nephropathy, as well as substantially improve their glycemic control.

By leveraging state-of-the-art technology and proprietary algorithms Diabetes Relief has developed and refined a therapeutic process that further improves upon the pioneering work in this field. Diabetes Relief utilizes the physiologic pattern of administration of insulin via intravenous infusions with FDA-approved devices and medications. These infusions are included as the centerpiece of a customized treatment plan that includes traditional recommendations for diet and exercise along with proprietary nutritional support. While other treatments seek to control the symptom of hyperglycemia, Diabetes Relief reduces insulin resistance by re-sensitizing insulin receptors. The complications of diabetes are not due to a direct toxic effect of hyperglycemia but rather a failure of cells to replicate and replace aging cells. By addressing the impaired pancreatic insulin pulse, Diabetes Relief facilitates carbohydrate metabolism which enhances growth and repair of tissue beds throughout the body and thus dramatically reduces both hyperglycemia and diabetic complications.

Current treatment modalities focus on controlling the symptom of hyperglycemia. The treatments have significant limitations in reversing the devastating complications that occur in progression of this disease. The literature is replete with detailed descriptions of cellular signals between the pancreases and liver which affect carbohydrate metabolism. Armed with this information, Diabetes Relief has developed a program to approximate normal physiologic signaling to restore insulin sensitivity. While others search for more ways to increase the availability of insulin that increases hyperinsulinemia and may ultimately desensitization and downregulate receptors, Diabetes Relief employs an alternate approach to improve the efficiency of insulin by providing a physiologic delivery. With the ever-growing epidemic of this disease, treatments need to go beyond control of hyperglycemia and address the core defects that have propelled this condition into a global health crisis.