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Review Article

Dynamic Diabetes Solutions: Physiologic Insulin Resensitization

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ABSTRACT

Diabetes is a disease currently affecting over 30 million Americans and is a leading cause of amputation, blindness, and chronic kidney disease. Treatment of diabetes with medications and lifestyle modifications alone have not eliminated these complications, because in part they lack the ability to restore the periodic cycles and rest periods of insulin that exist in healthy physiology. Insulin is excreted in a cyclical pattern by the pancreas, in a hormonal oscillation that is critical to maintain adequate insulin sensitivity at the insulin receptor level. Precision administration of exogenous insulin bio identically matching this physiologic profile is more effective at controlling blood glucose level and reducing complications of diabetes than standard drug therapy and lifestyle modifications alone. This matching of physiological insulin helps reduce inflammatory cascades responsible for a number of diabetic complications. In this article, we will review how insulin is secreted and functions physiologically and highlight a dynamic insulin delivery modality that mimics normal secretion profiles. This biomimicry reduces insulin exposure, which reduces the progression to or worsening of insulin resistance. We will review how various protocols have been enhanced resulting in reduction of diabetic complications, utilizing physiologic insulin resensitization (PIR).

KEYWORDS

Diabetes, Biomimicry, Treatment, Insulin Resistance, Insulin, Physiologic Insulin Resensitization, PIR.

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Introduction

The Food and Drug Administration approved 15 new diabetes drugs between 2013 and 2016. 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 [1]. Still others are developing new drug delivery devices. The teams dedicated to discovering new molecules should be applauded; diabetes mellitus is an immense public health issue reaching pandemic proportion.

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 [2]. 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. It is encouraging to see reductions in major cardiovascular endpoints and positive data for those suffering with renal complications of diabetes. However, the magnitude of such benefits is limited in scope, and is further limited due to significant costs and material adverse GI side effects, which preclude many patients from tolerating these novel drugs [3, 4].

Recent guidelines published March 5, 2018, from the American College of Physicians on diabetic management outline that over-aggressive HbA1c control can be counterproductive and harm patients due to complications of hypoglycemia and other untoward effects. This evidence-based review includes data from the landmark ACCORD trial that was terminated prematurely, because intensive glycosylated hemoglobin management led to increased morbidity and mortality. As such, ACP guidelines now target a HbA1c between 7-8%, rather than previous targets of 6.5-7%. Thus, the standard of practice for diabetic management is in flux, highlighting the significant limitations in addressing complications of diabetes with current treatment modalities [5]. Furthermore, on March 23, 2020, insulin was officially moved to the biologic regulatory framework by the FDA, highlighting the physiologic nature of this hormone peptide in regulating carbohydrate metabolism [6].

Given this dynamic landscape, an augmented approach to treating diabetes and other metabolic disorders is needed. Ideally, an approach that closely mimics the body's natural method of regulating insulin might also allow for restoration of normal physiology to achieve optimal clinical results. The science behind rhythmic or physiologic insulin excretion by the pancreas is not new; the phenomenon has been documented by researchers for decades. Likewise, attempts to investigate the potential therapeutic benefits of this approach have been studied and as technology and understanding improves, efforts to further maximize clinical benefits and deploy such treatment modalities should be undertaken.

Physiology of Insulin Release

Rather than a continuous flow or stream, the pancreas releases insulin in the same way many other hormones are secreted–in short periodic waves that dynamically change, based on the body's

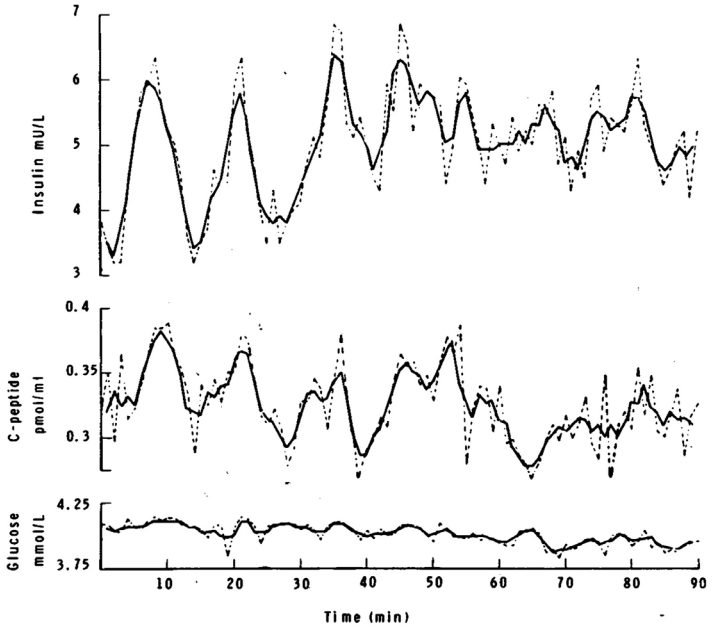

Figure 1: A three-minute moving average (continuous line) of the fasting plasma insulin, C-peptide and glucose concentrations taken at one-minute intervals. The dashed line shows the "unsmoothed" data. Smoothing reduces the rapid fluctuations, which are probably due to "noise," and also blunts the amplitude. The simultaneous insulin and C-peptide cycles disappear after 50 minutes. Reproduced from [6].

demands. The beta-cells in the islets of Langerhans excrete insulin in a dynamic rhythm. This phenomenon was first observed in 1979 as healthy fasting subjects had their insulin levels monitored every minute for one to two hours (Figure 1) [7].

Insulin levels in the blood are not static but oscillate 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 and rest period continue at the roughly the same frequency. These dynamic peaks and valleys of insulin are approximately every 4-8 minutes. Insulin levels drop to near zero at the center of the troughs while glucagon levels remain above zero in their respective troughs. Since the half-life of IV insulin being approximately 2 minutes, this physiology would suggest the insulin finished its effects in 2 minutes, thus leaving at least 2 more minutes for the insulin receptors to have adequate time to reset in an environment of near zero stimulant. In addition to these fast cycles, an ultradian rhythm made up of slower oscillations of

insulin every 80–180 minutes has also been observed [8].

Physiologic insulin secretion is characteristic of a normal hormone secretion and appears to be more effective at activating insulin receptors than a constant exposure of insulin. The phenomenon is most readily observed in the liver. 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 most direct impact of these insulin pulses. In contrast, a continuous exposure to insulin results in downregulation of insulin receptors and results in the phenomenon of insulin resistance [9].

Type 2 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 dynamic oscillating pattern. The slower, longer ultradian cycles of insulin secretion was found to be disrupted in diabetic patients. In addition to the longer cycles, shorter rhythms are affected in diabetes mellitus as well. Individuals with type 2 diabetes compared to normal individuals have been found to have shorter and highly irregular waveforms related to their insulin secretion profile [10].

The question of causality was explored to determine whether the disruption in physiologic secretion of insulin is a sequela of, or a 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 [11]. Research performed more recently shed additional light on the role that abnormal insulin patterns play in the subsequent onset of diabetes [12]. The physiologically normal pattern of insulin waveforms 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. Additionally, as disordered insulin secretion may cause intracellular insulin resistance, it may be an initiating factor in the progression to type 2 diabetes [12]. This phenomenon and the implications were explored in even greater detail in a recent review article published by the American Diabetes Association [13].

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 play a significant role in the development of insulin resistance and diabetes.

Development of Physiologic Insulin Resensitization (PIR)

Even though there are hundreds of teams developing molecules to manage the progression of the disease, the incidence and negative impact of diabetes continues to grow. This challenge has led to the development of a novel therapeutic modality that has potential to produce superior outcomes by biomimicking the body's own method of regulating insulin. This treatment employs dynamic biomimicry precision dosing to approximate the normal physiologic insulin signaling which serves to counter the negative feedback of aberrant insulin messaging and helps minimize the negative effects of unopposed glucagon that leads to decreased insulin receptor expression [14]. This modality is focused on transforming the way diabetes is traditionally managed via symptom suppression by providing clinicians a potent adjunctive companion method to overcome insulin resistance and improve carbohydrate metabolism. The goal of PIR is to enable cellular repair by attempting to restore physiologic hormonal secretory insulin patterns necessary to alleviate the systemic complications of diabetes. Simultaneously, by inducing the body to shift metabolic activity to consume carbohydrate rather than fat, the harmful effects of increased oxidative stress and free radical production adding to endothelial tissue damage are significantly reduced. In addition, this shift of metabolism maintained or increased available level of adenosine triphosphate for energy.

Several clinical studies have shown the safety and efficacy of early iterations of such a treatment strategy. Dailey GE et al. performed a study to assess the effects of a dynamic insulin approach on the progression of diabetic nephropathy in patients with type 1 diabetes mellitus (DM) [15]. 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 treatment. 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 this treatment 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 [15].

Subsequent to these findings, a follow up study was done by Aoki et al. [16]. In this clinical trial, the investigators set out to assess the effects of dynamic insulin delivery 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 dynamic insulin. Study patients had follow-up consultations weekly for at least 12 months, monthly hemoglobin A1c (by high-performance liquid chromatography), and semiannual creatinine clearance determinations. The results showed hemoglobin A1c 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 such an approach 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 [16].

In 2015, the Schull Institute of Houston, Texas, performed a retrospective analysis on 49 patients receiving the intravenous insulin treatment, compared to 11 patients who did not receive this treatment but otherwise received standard care for their diabetes. Of these patients, after 6 months on the intravenous insulin treatment, 95% reported improved neuropathy symptoms, 76% reported improvement in at least one diabetic complication compared to 27% in control group, 24% reported no worsening of complications. HbA1c was reduced in 63% of the patients receiving the intravenous insulin treatment. In addition, 41% of treated patients reduced their daily dose of diabetic medications compared to 9% in the control group [17].

In 2020, a study performed by Humana Medicare Advantage Global Risk Provider Island Doctors group analyzed 21 patients that underwent the intravenous insulin treatment. The patients have both type 2 diabetes and a diagnosis of distal peripheral neuropathy (DPN). These patients received intravenous insulin treatment for 6 months. At the end of the study, 52% of patients showed weight reduction, 67% reduced their HbA1c, 62% showed improved EGFR, and 57% showed LDL reduction.

Significant advances in pump technology, dosing protocols, and algorithms have resulted in marked refinements in the pioneering work in this field. As a result, precision dosing of physiologic insulin can be repeatable, individualized, and administered based on a patient's insulin resistance profile. By employing these latest advancements, the physiologic pattern of insulin secretion can be more precisely matched while better maintaining safety and, efficacy.

Employing PIR, clinicians are able to administer bio identical randomized precision doses of insulin to help reverse insulin resistance at the cellular insulin receptor level. This bio-mimicry dosing ranges from 4–8-minute intervals where adjustments to concentrations, volumes, pressures, and oscillations all occur on a patient-by-patient individualized basis. In addition to the patient receiving a physiologic pattern of insulin during a typical infusion, oral glucose is administered at individualized intervals to stimulate the digestive system and trigger the metabolism. As carbohydrate metabolism improves, ATP production is increased and inflammatory markers are reduced, cellular energy is then available for optimal tissue growth, repair, and regeneration.

The PIR precision dosing pattern is consistent with normal hormone secretion and more closely approximates the body's natural signaling pathways. As the patient's insulin resistance improves, healthcare providers can titrate other medications to optimize treatment regimens. In general, PIR permits lowering dosing of subcutaneous insulin and other diabetes medications that often promote the secretion of insulin or inhibit the production of glucose.

Furthermore, it is well established that progressive insulin use leads to worsening insulin resistance. This approach averts hyperinsulinemia and avoids "toxic" exposure to insulin receptors. Thus, a clinician can avoid the three major causes of progressive insulin resistance in diabetic patients: insulin receptor negative feedback downregulation from constant insulin exposure, refractory delay from aberrant signals, and unopposed glucagon (which decreases transcription of insulin receptors).

By overcoming insulin resistance, PIR may help amplify the benefits of other therapeutic modalities. Glucose can more readily enter the oxidative phosphorylation cycle and promote carbohydrate metabolism. This provides cells with more energy for tissue growth, repair, and regeneration. At the same time, this reduces the fat metabolism demands and begins to counter the inflammatory cascade of excessive lipid ketosis, lactic acid and free fatty acids. This modality can reduce the pharmaceutical needs of patients by mitigating the "toxicity" of excessive insulin exposure.

Conclusions

PIR is a dynamic modality for clinicians that can be used as the centerpiece of an individualized 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, the goal of PIR is to reduce insulin resistance by re-sensitizing insulin receptors by biomimicry. PIR provides clinicians with a toolset that can overcome the negative feedback loop of constant insulin exposure, recalibrate the refractory dysregulation of signaling, and overcome excessive glucagon exposure that leads to decreasing insulin receptor expression. The complications of diabetes are not only due to the direct toxic effect of hyperglycemia but also the metabolic compromise that leads to energy deficits, excessive inflammation, and inability to repair and replace aging cells. By addressing impaired pancreatic signaling and restoring metabolic dysfunction, it is possible to repair damaged tissues while also improving glycemic control.

The medical literature is replete with detailed descriptions of cellular signals between the pancreases and liver which affect carbohydrate metabolism. PIR however, approximates the normal physiologic signaling to restore insulin sensitivity at the cellular receptor level. Other treatments continue to create and exploit ways to increase the availability of insulin that increases hyperinsulinemia and may ultimately desensitization and downregulate receptors. PIR offers a dynamic, augmented approach to improve the efficiency of insulin

by providing a more precise physiologic delivery vehicle. With the ever-growing pandemic 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.

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References

1. Buse JB, Harmel M. New Diabetes Drugs in Development. 2017. https://www.medscape.com/viewarticle/876853. Accessed January 4, 2021.
2. Diabetes.co.uk. Cost of Diabetes. https://www.diabetes.co.uk/cost-of-diabetes.html. Accessed February 22, 2021.
3. Matthew P. Petersen (American Diabetes Association). Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 2018; 41(5): 917-928. DOI:10.2337/dci18-0007.
4. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019; 394(10193): 121-130. DOI:10.1016/S0140-6736(19)31149-3.
5. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019; 380(4): 347-357. DOI:10.1056/NEJMoa1812389.
6. Qaseem A, Wilt TJ, Kansagara D, et al. Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. Ann Intern Med. 2018; 168(8) : 569-576. DOI:10.7326/M17-0939.
7. Food and Drug Administration. FDA Works to Ensure Smooth Regulatory Transition of Insulin and Other Biological Products. https://www.fda.gov/news-events/press-announcements/fda-works-ensure-smooth-regulatory-transition-insulin-and-other-biological-products. Accessed February 22, 2021.
8. Lang DA, Matthews DR, Peto J, et al. Cyclic oscillations of basal plasma glucose and insulin concentrations in human beings. N Engl J Med. 1979; 301(19): 1023-1027. DOI:10.1056/NEJM197911083011903.
9. Hunter SJ, Atkinson AB, Ennis CN, et al. Association between insulin secretory pulse frequency and peripheral insulin action in NIDDM and normal subjects. Diabetes. 1996; 45(5): 683-686. DOI:10.2337/diab.45.5.683.
10. Meier JJ, Veldhuis JD, Butler PC et al. Pulsatile insulin secretion dictates systemic insulin delivery by regulating hepatic insulin extraction in humans. Diabetes. 2005; 54(6): 1649-1656. DOI:10.2337/diabetes.54.6.1649.
11. Polonsky KS, Given BD, Hirsch LJ, et al. Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. N Engl J Med. 1988; 318(19): 1231-1239. DOI:10.1056/NEJM198805123181903.
12. O'Rahilly S, Turner RC, Matthews DR. Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. N Engl J Med. 1988; 318(19): 1225-1230. DOI:10.1056/NEJM198805123181902.
13. Schofield CJ, Sutherland C. Disordered insulin secretion in the development of insulin resistance and Type 2 diabetes. Diabet Med. 2012; 29(8): 972-979. DOI:10.1111/j.1464-5491.2012.03655.x.
14. Bertram R, Satin LS, Sherman AS. Closing in on the Mechanisms of Pulsatile Insulin Secretion. Diabetes. 2018; 67(3): 351-359. DOI:10.2337/dbi17-0004.
15. Satin LS, Butler PC, Ha J, et al. Pulsatile insulin secretion, impaired glucose tolerance and type 2 diabetes. Mol Aspects Med. 2015; 42: 61-77. DOI:10.1016/j.mam.2015.01.003.
16. Dailey GE, Boden GH, Creech RH, et al. Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy. Metabolism. 2000; 49(11): 1491-1495. DOI:10.1053/meta.2000.17700.