CONNECTICUT
DIABETES CENTER

inSolutions
Diabetes Treatment Reimagined

Groundbreaking Diabetes Treatment
Physician Directed
Physiologic Insulin Resensitization (PIR).

Introducing a cutting-edge solution to metabolic failure that focuses on treating the root cause of diabetes instead of merely masking symptoms.

Connecticut Diabetes Center

17 Farmington Ave
Plainville, CT 06062

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Dear Colleague:

Do you have diabetic patients who despite their best efforts to follow a conventional therapy regimen, still develop secondary complications that continue to progress and worsen? Even those with improved A1C?

Are you frustrated because you have nothing to help patients who experience the relentless pain of diabetic neuropathy? Do you worry about patients who are at risk of amputations, or kidney failure and for whom you fear dialysis is just around the corner? If you answered YES to any of these questions, we would like to help. If you give us just 90 days, we believe we can help most of your metabolically impaired patients.

At ***Connecticut Diabetes Center*****,** patients are experiencing amazing clinical results with just a few sessions on our pioneering, patented ***Physiologic Insulin Resensitization*** (PIR) infusion treatments. These improvements go far beyond controlling hyperglycemia and reducing HgbA1c. Our therapy restores insulin sensitivity by closely biomimicking the body's natural physiology.

Unlike traditional programs, our patients report experiencing improvement in many of the secondary diabetic health complications such; neuropathy pain, energy, sleep, eyesight, blood pressure, foot wounds, memory etc…. In addition most can decrease medications and are able to lower their HgbA1c. Your patients could experience these and many other benefits as well. And with less pain and more energy, patients are much more likely to adhere to diet and exercise regimens.

We use a patented system called ***Physiologic Insulin Resensitization (PIR)*** which utilizes an **FDA Approved** device and time honored fast-acting insulin to deliver insulin as a hormone mediator in dynamic and physiologic manner. We believe our approach represents an enormous step forward in the treatment of diabetes and other metabolic disorders. We want to work in collaboration with you to help your patients.

We brought this revolutionary treatment into our clinic because we feel physicians can do more than just strive for better glycemic control yet worry while your patients deteriorate and their complications progress. We are confident that once you learn more about PIR, you will be as excited as we are to introduce this to our local diabetic patients. Feel free to call (860) 351-5528 or email me at DrHenry@CtDiabetesCenter.com to discuss if referring your metabolically impaired patients to a **PIR** provider, might be beneficial to their health and quality of life.

Warm Regards,

Maria Henry, MD
Connecticut Diabetes Center
Medical Supervisor

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OPEN LETTER TO PHYSICIANS

Esteemed Colleagues,

For the past 25 years, as an internal medicine physician, I have encountered many patients who suffer from diabetes and the resulting complications of this terrible disease. When I learned of this innovative approach in treating metabolic failure, I wanted to bring this modality to diabetic patients to improve their lives.

The key to what makes our ***Connecticut Diabetes Center*** so unique is that we use insulin as a hormone rather than a drug. By Precision delivering insulin in a manner that bio-mimics the normal physiologic insulin secretion, we up-regulate insulin receptor activity and reduce insulin resistance.

With improved insulin sensitivity, carbohydrates can more readily enter cells and be converted into ATP via oxidative phosphorylation. Increasing cellular energy, at the mitochondrial level, allows damaged tissues to grow, repair and regenerate. Thus, our modality not only stabilizes, but in many instances can help reverse complications of diabetes.

We use a patented system called ***Physiologic Insulin Resentization (PIR)*** which utilizes an **FDA Approved** device and time honored fast-acting insulin to deliver insulin as a hormone mediator in dynamic and physiologic manner. With this approach, we meld today's technology with established scientific principles, known for decades.

This diabetic treatment has been used in many countries for over a decade. Since inception in the United States in 2015, PIR is available at 200 clinics and we are the first to bring it to Connecticut. We believe our approach represents a significant step forward in the treatment of diabetes and other metabolic disorders. As insulin sensitivity improves, patient's medical profiles often improve as well. It is important to understand that we work together with the patient's medical provider to complement existing treatments. We hope to work with you to combat the myriad of complications of diabetes.

Respectfully,

Maria Henry M.D.
Connecticut Diabetes Center
Medical Supervisor

Open Letter to Endocrinologists

Re: Open Letter to Endocrinologists

Dear Colleagues,

For the past 20 years, I have been fortunate to care for diabetic patients. For me, it began in medical school, treating patients in our comprehensive care clinic. Most patients were underinsured or uninsured. To complicate matters, formulary and educational services were limited. For my first five post-graduate years, I continued to care for patients in the public hospital system in Louisiana. We had no fellows and no interventional services where I did residency. This resulted in my directing the care of numerous patients with end organ failure such as endstage renal disease, cardiovascular disease, proliferative retinopathy, peripheral neuropathy, and non-healing wounds. It was abundantly clear that we had a limited ability to prevent the devastating complications of diabetes in that setting.

I have been in private practice since 2008 and, fortunately, with the help of diabetes educators, nutritionists, and newer medication, my outcomes have greatly improved.

Medications like SGLT-2 inhibitors and GLP-1 receptor analogues have been a great help in reducing A1c and complications in my Type 2 diabetics. Whilst continuing to use these medications, insulin, and adjunctive insulin sensitizers like metformin and pioglitazone, I have been continually looking for ways to combat the tide of insulin resistance and metabolic failure.

In my type 1 diabetics, CGMs, smart pumps, and ultra-rapid acting insulins have improved glycemic awareness and control.

All of this being true, these medications and devices are costly and not available to many of our diabetic patients. When I learned of Diabetes Relief's innovative approach to treating insulin resistance, metabolic failure, and complications in both Type 1 and Type 2 diabetics, I was very intrigued. I proudly joined their team.

The key to what makes our multi-patented modality unique is that we use insulin as a hormone rather than as a drug. As an endocrinologist, this speaks to me. This protocol bio-mimics normal physiology. The result is a re-sensitization of insulin receptors and an improvement in insulin

resistance. As such, it follows the new designation by the FDA of insulin as a “biologic” rather than as a drug.

With improved insulin sensitivity, carbohydrates can more readily enter cells and be converted to ATP via oxidative phosphorylation. Increasing cellular energy, at the mitochondrial level, allows damaged tissues and organs to grow, repair, and regenerate. Furthermore, by improving carbohydrate metabolism, the treatment aims to reduce the chronic inflammatory state induced by excessive fat metabolism. Thus, our modality not only helps to stabilize the chronic inflammatory state of diabetes but in many instances can help overcome complications. There is no other treatment out there that can offer both of these outcomes in our diabetic patients.

We utilize an FDA-approved device and time-honored, fast-acting insulin to deliver insulin as a hormone mediator in a precision dosing protocol. With this approach, we meld today’s technology with established scientific principles, known for decades. We believe our approach represents a significant step forward in the treatment of diabetes and other metabolic disorders. As insulin sensitivity improves, patients’ medical profiles often improve as well. It is important to understand that we work in tandem with medical professionals to complement existing treatments with the goal to combat the myriad complications of diabetes.

Respectfully,

Justin W. Fontenot, M.D.
Endocrinology and Metabolism

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What is PIR?

Physician-Directed Physiologic Insulin Resensitization (PIR) is a multi-patented adjunct modality designed to addresses the root cause of metabolic disorders and diabetes. PIR provides a groundbreaking tool for physicians to precisely administer insulin *as a hormone* in a way that achieves the desired benefits but at the same time **avoids the Number One negative side effect: progressive insulin resistance.** Such insulin resistance results from a compromised carbohydrate metabolism, and a chronic inflammatory state ensues. This in turn damages macro and micro-vascular beds and leads to progressive tissue damage and organ dysfunction.

PIR is The Solution.

PIR is an intravenous infusion protocol designed to bio-mimic the insulin hormone secretion in a more physiologically identical manner. Rather than administering insulin conventionally as a drug to merely suppress symptoms--which typically cause significant side effects-- PIR is novel in its unique ability to administer insulin as a "hormone communicator" to better facilitate an optimized metabolism. By delivering insulin in a manner that bio-mimics normal physiology, PIR can up-regulate insulin receptor activity and reduce insulin resistance. This targets a broken carbohydrate metabolism and addresses the root cause of this disease process.

By achieving insulin sensitivity at the insulin *receptor* level, glucose can more readily enter cells and be converted into ATP. Through increased cellular energy and reduced inflammatory mediators, we repair and regenerate the body's cells, peripherally at first; and then through repeated treatment sessions cellular restoration progresses to the organs. Because of it's unique "bio-mimicking" abilities, PIR has been consistently shown to help the body stabilize AND reverse complications of diabetes.

The Physician-Directed PIR treatment includes an intravenous precise administration of FDA-approved fast-acting insulin using an FDA-approved portable external pump. Along with the insulin hormone, the patient is given small, specific amounts of oral glucose (ingested as a dextrose liquid) to stimulate the digestive system and its role in the metabolism process during treatment.

PIR patient satisfaction and compliance is very high, however, if a patient stops maintenance treatments, the improvements experienced from this modality can diminish over time.

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TREATMENT INFORMATION

What Is Physiologic Insulin Resensitization?

Physiologic Insulin Resensitization is a groundbreaking multi-patented approach providing physicians with the tools that allow insulin to be administered as a hormone rather than a drug. This method of treatment addresses the primary cause of diabetes, metabolic failure. Using insulin in a manner that bio-mimics normal physiology reduces insulin resistance, helping blood sugar enter each cell and be converted into energy.

Increasing cellular energy allows damaged tissues and organs to grow, repair, and regenerate. In many cases, this approach has shown the ability to stabilize and reverse complications of diabetes and other metabolic disorders.

Typical Care Plan

Every patient's degree of insulin resistance and ability to metabolize carbohydrates is unique, so we begin with a consultation to determine medical necessity and establish a physician-directed individualized care plan.

The patient's unique care plan typically includes an "Induction Phase" where we start off with weekly infusions. As the patient notices improvements over the first 90 days, the visits are reduced to every 2 weeks, every 3 weeks etc... Next, the "Maintenance Phase" finds the balance between developing an optimized metabolism and maximizing the time between treatments.

Visits typically start with 2 hours, and patients are free to move around during the process (read, work, watch TV, etc). As patients improve, the time between visits is extended while visit duration is reduced. A two-hour visit about every four to six weeks is common for long term maintenance.

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What's the First Step?

Come in for a consultation so we determine medical necessity and if you qualify.

What Should I Expect from the Consultation?

Typical consultations take 30 to 60 minutes. This appointment may require blood work. A specialty trained and qualified physician will review your medical records and physical condition and answer any questions you may have.

Will You Work with My Doctor?

We will not replace your doctor. We do not require a referral or approval from your doctor but prefer to work with your doctor to co-manage your individualized care plan, which may include treatment, testing, supplementation, and education to achieve a better patient outcome.

Do you take my insurance?

Most insurance plans are accepted. No insurance? Ask about our self-pay options.

DIABETES COMPLICATIONS IMPROVEMENTS REPORTED

95% Neuropathy Improved

63% HbA1c Reduction

76% Improvement in at least one complication

41% Medications Reduction

* Schull Institute – Insulin Infusion Therapy on Diabetic Complications (2015)

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Reported Patient Improvements

- Neuropathy Diminished
- Energy Restored
- Weight Controlled
- Erectile Function Restored
- Retinopathy Diminished
- Amputations Prevented
- Medications Reduced
- Blood Pressure Controlled
- Blood Sugar Controlled
- Mood & Sleep Improved
- Wounds Healed
- Fatty Liver Reduced

"I haven't felt this good in years. It's like my neuropathy just disappeared and my energy levels have increased."
Wayne K.
Type 2 Diabetic - 18 yrs | Neuropathy - 10 yrs

"It's almost a miracle that my foot healed so well. I started treatment and within three weeks it had healed. The wound had been there for three months prior to treatment."
Greg B.
Diabetic - 10 years | Hypertension - 5 years | Neuropathy 8 Years

"My blood sugar is now controlled and my eyesight has improved so much I went from legally blind without glasses to now being able to read the captions on the TV with no glasses, and I'm down from six vials of insulin per month to only three."
Bruce B.
Type 2 Diabetic - 27 years

DIABETIC OUTCOMES REPORTED

95% Neuropathy Improved

76% Improvement in at least one complication

63% HbA1c Reduction

41% Medication Reduction

* Schull Institute – Insulin Infusion Therapy on Diabetic Complications (2015)

To learn more about our treatments,
please visit our website by using this QR Code.
(or visit www.CTDiabetesCenter.com)

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Insulin Resistance: A Receptor Story

Diabetes and other metabolic disorders have reached epidemic proportions. “Insulin resistance” – a pathologic condition in which cells fail to respond normally to insulin – is at the core of metabolic dysfunction. At **Connecticut Diabetes Center,** to achieve cellular restoration, we use physiologic insulin resensitization to overcome insulin resistance at the receptor level--in essence, bio-mimicking normal physiology.

1. Insulin is released from the pancreas in a physiologic cyclical pattern, a fact known for decades. **Herein lies the key; mimicking the body’s natural physiologic cyclical or rhythmic pattern.**
2. Insulin oscillations are mediated, in part, by firing of a pancreatic neuronal network that connects beta cells (Islets of Langerhans).
3. An insult (auto-immune, obesity, toxin, trauma, stress etc.) causes inflammation in the pancreas that disrupts pancreatic insulin rhythmicity.
4. When this physiologic pattern is impaired, a relative hyperglycemia results; pancreatic insulin secretion is dysregulated, and the loss of troughs results in relative hyperinsulinemia.
5. Hyperinsulinemia triggers a negative feedback loop and essentially functions as a toxin to insulin receptors; insulin receptors downregulate, refract, and unopposed glucagon decreases transcription of receptors.
6. **Inadequate receptor function is the phenotype of insulin resistance** and ultimately leads to metabolic disorders; genetics and/or differential receptor dysfunction determine the presenting symptoms, which most often include development of diabetes and many other metabolic disorders.
7. Peripheral precision administration of physiologic insulin intravenously (*i.e.* DRL RMX) replaces these lost signals in an effort to re-sensitize receptors to insulin by bio-mimicking the normal pancreatic axis.
8. When exposed to a dynamic rhythm of bio-identically randomized physiologic insulin, receptors upregulate, and the ability to metabolize carbohydrates is temporarily restored.
9. Binding of insulin to receptors facilitates the uptake of glucose into cells which can relieve hyperglycemia (if present); once inside the cell, glucose is readily processed (metabolized) through oxidative phosphorylation (TCA cycle) and other pathways to produce adenosine triphosphate (ATP), also known as cellular energy.
10. As cellular energy from carbohydrate metabolism becomes more readily available, energy-starved tissues can undergo growth and repair (cellular restoration). Neuronal tissues in particular, are extremely sensitive to decreases in energy from carbohydrate metabolism.

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Physiologic Insulin Resensitization

A Commonsense 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 symptom suppressive 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 primarily focus on managing hyperglycemia without restoring the broken insulin signals, that are the root cause of metabolic failure, leading to all the debilitating complications of diabetes and metabolic syndrome.

Ultimately, these symptom suppressive 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 bio-mimicking the body's natural method of regulating insulin. The science behind bioidentically randomized 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 hormone in the same way many other hormones are secreted–in short pulses. The beta-cells in the islets of Langerhans excrete insulin in a dynamic rhythm of boluses and rest periods. 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.

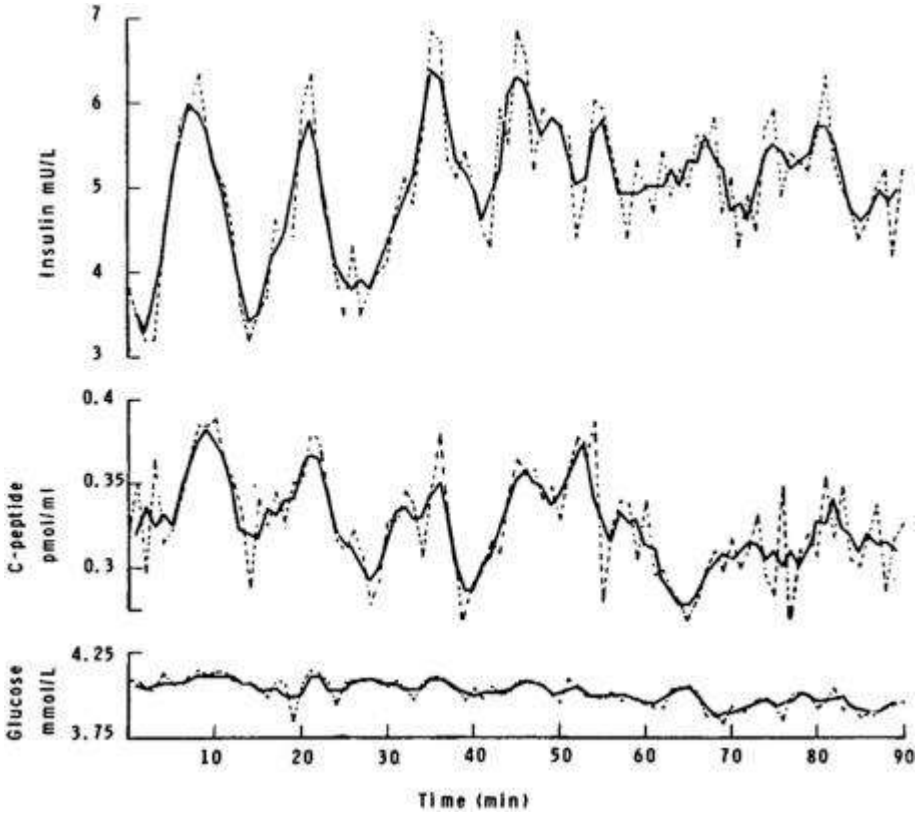

Figure 1

Insulin levels in the blood are not static but pulse and rest 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 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 Resensitization 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]

[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

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 waveforms related to their insulin secretion profile.[7]

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 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. [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 and many other metabolic disorders. 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 bio-mimicking the body's own method of regulating insulin. By achieving insulin sensitivity at the insulin receptor level, glucose can more readily enter cells and be converted into adenosine triphosphate. The Diabetes Relief and RestorMetabolix (DRL RMX) patented and patent pending treatment protocol is an effective program that is poised to transform the way diabetes and other metabolic disorders are addressed.

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

[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.
[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

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 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 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 DRL RMX has developed and refined a therapeutic process that further improves upon the pioneering work in this field. DRL RMX utilizes an intravenous precision administration of FDA-approved fast-acting insulin with an FDA-approved portable pump to achieve biomimicry of insulin as a hormone communicator to stimulate the metabolism through better oxidative phosphorylation.- 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, DRL RMX 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 pathophysiology, DRL RMX facilitates carbohydrate metabolism which enhances growth to repair and regenerate the body's cells, peripherally at first; and then through repeated treatment sessions, cellular restoration progresses to the organs, helping the body to naturally return to its more normal physiologic state 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, DRL RMX 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 desensitize and downregulate receptors, DRL RMX 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.

Diabetes Relief
Get your life back

Brandi M.

PRE TREATMENT

- ❑ Hgb A1c–7.8%
- ❑ Chronic fatigue
- ❑ Dry feet, severe fissures
- ❑ Neuropathy for 2 years

CURRENT STATUS

- ❑ Hgb A1c–6.9%
- ❑ Marked increase in energy
- ❑ Dryness gone, fissures healed
- ❑ Complete return of sensation

"Before treatment my feet and hands had severe pain and my blood sugar was like a roller coaster. After treatment the pain is gone in my hands and feet and my blood sugars have leveled out at a healthy number."

Brandi M.
Type 1 diabetic – 6 years
Hypothyroidism – 6 years

Diabetes Relief®
Get your life back

Katherine K.

PRE TREATMENT

- ❑ Neuropathy in feet
- ❑ Uncontrolled blood sugar
- ❑ Insulin resistant
- ❑ Hair loss

CURRENT STATUS

- ❑ Neuropathy pain is gone
- ❑ Vastly improved blood sugar
- ❑ Insulin dosages reduced 3x
- ❑ Hair thicker, stopped falling out

"The doctor said my eyes had improved since my last visit. The macular degeneration has not gotten any worse in the last year… weight going down, blood sugar going down."

Katherine K.

Type 2 diabetic – 8 years

Diabetes Relief
Get your life back

Dejaun D.

PRE TREATMENT

- ❑ Blurred Vision
- ❑ Open sores under feet
- ❑ Low Energy

CURRENT STATUS

- ❑ Vision almost 20/20
- ❑ Healing after 3 treatments
- ❑ Increase in energy

"When I first started my treatment I was dealing with low energy… a couple of open sores under my feet… my vision was clearly effected. After 3 treatments I began to feel the difference… now things have totally changes, more energy seeing almost 20/20 without glasses"

Dejaun D.
Type 2 diabetic – 1 year

Diabetes Relief
Get your life back

Gloria M.

PRE TREATMENT

- ❑ Burning and itchy feet
- ❑ High Blood pressure
- ❑ Low Energy
- ❑ Depression

CURRENT STATUS

- ❑ Burning and itchy feet gone
- ❑ Blood pressure stable
- ❑ Increased energy
- ❑ Happy

"Before the treatment my feet would tingle, burn and itch. Feel like pens were sticking in all parts."

Gloria M.
Type 2 diabetic – 23 years

International Journal of
Molecular Sciences

MDPI

Review

Physiologic Insulin Resensitization as a Treatment Modality for Insulin Resistance Pathophysiology

Frank Greenway [1], Brian Loveridge [2], Richard M. Grimes [3], Tori R. Tucker [4], Michael Alexander [5], Scott A. Hepford [6], Justin Fontenot [7], Candi Nobles-James [8], Carol Wilson [9], Adam M. Starr [10], Mohammed Abdelsaid [11], Stanley T. Lewis [12] and Jonathan R. T. Lakey [5,*]

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Abstract: Prevalence of type 2 diabetes increased from 2.5% of the US population in 1990 to 10.5% in 2018. This creates a major public health problem, due to increases in long-term complications of diabetes, including neuropathy, retinopathy, nephropathy, skin ulcers, amputations, and atherosclerotic cardiovascular disease. In this review, we evaluated the scientific basis that supports the use of physiologic insulin resensitization. Insulin resistance is the primary cause of type 2 diabetes. Insulin resistance leads to increasing insulin secretion, leading to beta-cell exhaustion or burnout. This triggers a cascade leading to islet cell destruction and the long-term complications of type 2 diabetes. Concurrent with insulin resistance, the regular bursts of insulin from the pancreas become irregular. This has been treated by the precise administration of insulin more physiologically. There is consistent evidence that this treatment modality can reverse the diabetes-associated complications of neuropathy, diabetic ulcers, nephropathy, and retinopathy, and that it lowers HbA1c. In conclusion, physiologic insulin resensitization has a persuasive scientific basis, significant treatment potential, and likely cost benefits.

Keywords: insulin resistance; diabetes; metabolic disorder; obesity; insulin infusion; physiologic insulin resensitization; PIR; treatment modality; neuropathy; nephropathy; retinopathy; cardiovascular disease; chronic kidney disease; CKD

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1. Introduction

The prevalence of type 2 diabetes has increased from 2.5% of the US population in 1990 and constituted 10.5% of the total US population or 13.0% of US adults in 2018 [1]. This is an astounding 320% increase in 28 years. In addition, a third of American adults, approximately 88 million people, have prediabetes [2]. Patients with pre-diabetes will

progress to diabetes at a rate of 5–10% per year [3]. While, currently, we have a major diabetes-associated health care problem, a surge of new diabetes patients looms. An already overburdened health care system can expect major increases in the long-term complications of type 2 diabetes, which include neuropathy, retinopathy, nephropathy, ulcers, amputations, and atherosclerotic cardiovascular disease. Diabetes is a very expensive disease that cost the US economy in 2017 an estimated $327 Billion in direct medical costs and another $90 Billion in lost productivity. Given that the annual direct medical cost for treating diabetes increased from $245 Billion to $327 Billion per year between 2012 and 2017 [4], it is not unreasonable to assume that the cost of treating diabetes in 2021 will approach $400 Billion. This expenditure is high and increasing because it is directed toward a progressive disease for which therapy is designed to slow the progression of diabetes-associated conditions until death occurs.

We first turned our attention to the most current guidelines from the American Diabetes Association (ADA), which has recommend the use of medications classified as sodium-glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) for individuals with T2D on Metformin AND diagnosed with EITHER heart failure (HF) OR chronic kidney disease (CKD) [5], as clearly discussed by Colling, et al. [6]. They conclude that "the introduction of SGLT2is and GLP-1RAs has led to rapid changes in recommendations for the medical management of T2D" [6]. Moreover, Colling, et al. detail classes of patients for whom preferential use of GLP-1RAs and SGLT2is is and is notrecommended, and we urge a thorough review by practitioners [6]. The ADA's "Standards of Medical Care in Diabetes" was originally approved in 1988 and the work is updated annually, most recently in December of 2020. Considerations and requirements are discussed in "Introduction: Standards of Medical Care in Diabetes—2021" [7].

We also note that the Food & Drug Administration (FDA) has published a March 2020 Update to its Drug Safety Communications from 2015 [8]. Further, The American College of Cardiology published on January 19, 2021, an expert analysis by Rishav Adhikari and Michael Blaha, who found that (1) uptake of these cardioprotective drugs in 2020 remained low; (2) cardiologists account for a minute percentage of prescribing for these drugs, even though their primary benefit is cardiovascular risk reduction; and (3) barriers to adoption by cardiologists include lack of knowledge about these medications and cardiologists' perception that diabetes care is not their responsibility [9].

Clearly, costs will rise, side effects and FDA warnings will always be prevalent, and disability will continue to occur. However, there is a complimentary treatment that reverses the major underlying pathophysiologic mechanism that leads to T2DM with far fewer negatives, if any. This treatment is effective because it directly reverses insulin resistance (IR), not just the individual manifestations of diabetes. Moreover, unlike other medications cited, side effects are minimal, if at all. For nearly forty years, researchers and clinicians have utilized a treatment modality that dynamically administers periodic infusions of insulin that bio-mimic the non-diabetic's natural secretions and rest periods of insulin from the pancreas [4]. There have been multiple articles describing this treatment approach that have reported efficacious clinical outcomes on various diabetic comorbidities. Although effective, the exact cellular and molecular mechanisms behind the use of periodic infusions of insulin was undetermined. This article has two purposes: (1) To explore insulin resistance pathophysiology and (2) to review literature for clinical outcomes and molecular mechanisms that support the use of physiologic insulin resensitization as an effective treatment modality to address insulin resistance, of which diabetes and its complications are the most common results.

2. The Rise of Type 2 Diabetes

In general, two main hypotheses were generated for the etiology and pathogenesis of type-2 DM. The first hypothesis is that the development of insulin resistance (IR) is behind type 2 diabetes. IR causes hyperglycemia, which is the cause of most diabetic complications. IR also causes hyperinsulinemia, i.e., the over-production of insulin by βbeta cells. Over

time, beta cells will be exhausted and die, which leads to further disease progression and more hyperglycemia. The second hypothesis concerns the defect in insulin secretion, which is well reported in type 2 diabetes.

As stated, type 2 diabetes is driven by IR. A common perception of type 2 diabetes progression is that the IR is countered by increasing insulin secretion until the beta cells in the pancreas can no longer keep up with the insulin demand and die progressively of exhaustion [3]. Another possible sequence of events is that the IR could begin with a defect in insulin secretion. A defect in the first phase of insulin secretion is well known to be an early characteristic of type 2 diabetes [10,11]

Therefore, an alternative explanation for the progression of type 2 diabetes is that impaired insulin secretion is a corollary to the progression of obesity, thus, triggering a cascade leading to islet cell destruction and the long-term complications of type 2 diabetes. In this manuscript, we offer the hypothesis that it is an insulin secretion defect that drives the IR responsible for the pathophysiology of type 2 diabetes.

3. Physiologic Hormone Secretion

Hormones that are released in an oscillatory pattern have receptors that are physiologically designed to bind the ligand, bring it into the cell, separate the receptor from its ligand and return the receptor to the cell surface. This rest period, or trough, of these oscillations gives sufficient time for this physiologic sequence to take place prior to the next peak in this cycle. When hormone receptors designed to respond to pulses of its ligand are exposed to constant stimulation with the hormone, the receptors down-regulate and become "tolerant" or "resistant" to stimulation. The amount of down regulation can be variable; for example, the gonadotropin-releasing hormone receptor is an example of a receptor that is particularly sensitive to down-regulation from a constant stimulation by its ligand. Leuprolide is a long-acting agonist of the gonadotropin-releasing hormone receptor that is given as an injection and stimulates the receptor continuously for 1–3 months. This receptor agonist down-regulates the receptor to the extent that the sex hormone secretion is blocked. In fact, leuprolide is used to block puberty or to achieve a chemical castration in the treatment of hormone-sensitive cancer [12].

3.1. Physiologic Insulin Secretion

Physiologic insulin consists of discrete oscillatory secretions and distinct rest periods to stimulate ligand/receptor activation. The beta cell secretes insulin with a dynamic periodicity of 4–8 min, and most commonly 5–6 min, based on the body's demands (Figure 1) [13].

Beta cells in the islets are in close contact to one another, which allows islets to secrete insulin in such a pattern, but it requires a network of autonomic nerves to allow the pancreatic beta cells to coordinate this dynamic profile [14]. The insulin pulses are responsible for timing of dynamic glucagon secretion that occur normally anti-synchronous from the cycling of insulin [15]. Measuring the cycling of insulin is made more difficult by the fact that the beta cells secrete the insulin into the portal circulation and the concentrations in the portal vein are five times higher than in the peripheral circulation due to hepatic extraction [16]. The insulin receptor in its upregulated state senses a basal level of insulin that is about 30% of the total, and 70% is due to pulses secreted over that baseline. The increase in insulin at meals is accounted for by an increase in the amplitude of the insulin spikes and not a change in the time between oscillations. Although there is a high rate of clearance of insulin by the liver, C-peptide is secreted in an equimolar ratio to insulin, but C-peptide reaches the peripheral circulation without hepatic clearance. The deconvolution method of measuring the spike frequency from the peripheral blood depends on the differential kinetics of insulin and C-peptide [16]. Insulin resistance (IR) is associated with a reduction in the amplitude of insulin cycling and an increase in the basal level of insulin, creating more of a constant rather than oscillatory pattern of insulin stimulation of its receptor. Although obesity is associated with an increase in beta cell mass, by the time type 2 diabetes develops, there has been a 65% reduction in beta cell mass due to apoptosis associated with increased

levels of amylin that is secreted in equimolar amounts to insulin [17]. This reduced beta cell mass loses the ability to maintain insulin oscillation, and a reduction in glucose-stimulated insulin secretion leads to hyperglycemia. The peripheral level of insulin is higher with an increased ratio of proinsulin to insulin, but the peaks in insulin secretion are not as high as in people with normal glucose tolerance. The lack of insulin pulses decreases hepatic clearance of insulin leading to peripheral hyperinsulinemia [18]. The insulin receptor can bind insulin in two ways, with high affinity and with low affinity. The affinity decreases as the insulin levels increase. Thus, the changing of receptor affinity for insulin is another property that contributes to hyperinsulinemia [19].

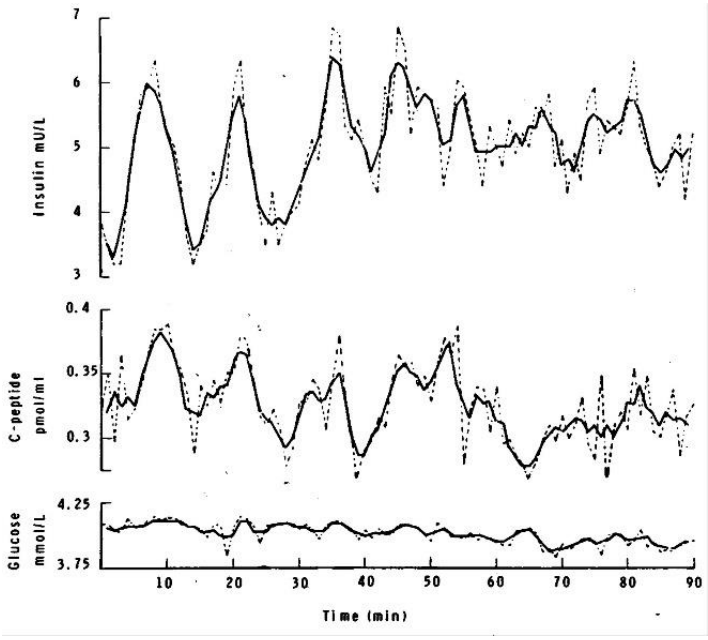

Figure 1. A three-minute moving average (continuous line) of the fasting plasma insulin, C-peptide and glucose concentrations taken at one-minute intervals. The dashed line shows the "unsmoothed" data. Smoothing reduces the rapid fluctuations, which are probably due to "noise," and also blunts the amplitude. The simultaneous insulin and C-peptide cycles disappear after 50 min. Reproduced from [13].

3.2. Insulin Sensitivity and Physiologic Secretion

The importance of oscillatory secretion signals in insulin sensitivity has been demonstrated in several ways. In patients with type 2 diabetes, an overnight infusion of somatostatin gave the beta cell a rest from constant stimulation by insulin and restored insulin pulse mass and normal insulin secretion [20]. Hepatic IR in dogs was achieved with a constant infusion of insulin that produced a 50% increase in the portal vein level of insulin [21]. Even more convincing was a study in which physiologic insulin delivery in patients with type 1 diabetes was compared to a constant infusion of insulin. A euglycemic insulin (1 mU/kg/min) clamp was performed on two occasions. On one occasion, it was infused continuously and, on the other occasion, it was infused for 3 min followed by a 7-min rest period. Despite a 40% reduction in the insulin dose, the suppression of hepatic glucose output was the same. When the total amount of insulin infused was held constant, the hepatic glucose output was 25–30% less in the cyclical condition [22]. It has also been shown in people with normal glucose metabolism that the dynamic pattern of insulin secretion enhances peripheral glucose uptake more than a continuous infusion [23].

4. Mechanisms of Insulin Resistance

Normally, insulin is secreted in a physiologic pattern, mediated by a pancreatic neuronal network connecting cells residing in the islets of Langerhans [24,25]. Dysfunctional

insulin rhythmicity can occur from a variety of insults (i.e., obesity, auto-immune disorders, toxins, trauma, stress etc.) that lead to inflammation of this network. When physiologic patterns of insulin secretion are disrupted, beta cells secrete insulin asynchronously. As a result of constant ligand/receptor exposure, a negative feedback loop downregulates insulin receptor responsiveness. In addition, lack of physiologic peaks and troughs leads to refractory delays in receptor activity. Finally, disrupted pulsation leads to unopposed glucagon levels, which decrease transcription of insulin receptors [26].

4.1. Implications for Treatment

A genetic aspect to insulin resistance (IR) involves abnormal insulin signaling and leads to type 2 diabetes. The children of parents with type 2 diabetes have IR that leads to type 2 diabetes later in their adulthood. These children exhibit higher levels of insulin and beta-cell dysfunction [27]. Even people who are just close relatives of people with type 2 diabetes often have impaired insulin oscillatory patterns [28].

4.2. Diet

From a dietary perspective, the Framingham study suggests that diets with a lower glycemic index are associated with greater insulin sensitivity [29]. A low carbohydrate diet is associated with a reduction in IR compared to a high carbohydrate diet [30]. The improvement in insulin oscillation was proportional to residual insulin sensitivity after weight loss [31]. This is, and has been, an approach that targets a reduction in a precursor of the disease manifestations and not just a single symptom. However, it has proved very difficult to obtain patient cooperation in adopting and maintaining an appropriate diet that minimizes carbohydrates and results in achieving and maintaining weight loss [32,33].

4.3. Medication

From the medication perspective, as one might predict for a disease driven by IR, insulin sensitizing medication such as metformin or the thiazolidinediones prevent or restore the abnormal insulin secretion associated with IR [34,35]. Repaglinide and glucagon-like peptide-1 agonists increase the insulin peak amplitude without affecting oscillatory frequency [36]. When people with diabetes require insulin, it is given as a subcutaneous injection in a manner that exposes the insulin receptor to a constant level of insulin. Interestingly, some of the common ways of measuring insulin sensitivity are based on fasting insulin and glucose values such as homeostatic model assessment for insulin resistance (HOMA-IR) [37], which may underestimate the role that physiologic insulin cycling plays in IR. All the medications described above deal with controlling the ***effects*** of existing diabetes, and not on treating its underlying ***causes***.

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, Dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose transport protein 2 (SGLT2) inhibitors. Thiazolidinediones' such as rosi- and pioglitazone are the only approved insulin sensitizing drugs that use insulin sensitization as the only mechanism. Physiologic insulin resensitization (PIR) is a true sensitizing strategy, as well. Rosiglitizone costs about $180–$190 a month but gives an increase of fat cells that fill with fat and increase obesity and therefore include cardiovascular safety concerns.

Although this review was written to focus on approaches that are true insulin sensitizers, such as insulin and the thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, through their independent mechanisms, have shown a positive effect on insulin resistance. The interested reader can refer to recent reviews on the molecular mechanisms of action of these medications [38,39], since the subject is beyond the scope of the present review.

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 from these novel drugs are limited in scope, while many patients are unable to tolerate due to material adverse side effects [40,41]. In addition, recent guidelines published 5 March 2018, from the American College of Physicians (ACP) 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 need to modify treatment modalities for optimal clinical outcomes [42]. Another important development was the reclassification by the FDA of insulin to the biologic regulatory framework in March of 2020, highlighting the physiologic importance of this hormone peptide in regulating carbohydrate metabolism [43].

4.4. Physiologic Insulin Resensitization

An alternative approach to counter IR in the euglycemic clamp of constant insulin infusion would be to reintroduce physiologic insulin delivery. This has been done by inserting an intravenous access connected to a precision infusion pump that can be programmed to dynamically deliver physiologic insulin typical of normal glucose metabolism. A more detailed description of physiologic insulin can be described as periodic cycling of up to 3 IU of regular insulin infused dynamically every 4–8 min (usually 5–6 min), based on the body's utilization for 2 to 4 h based on an individual patient weekly basis. Oral glucose is given to simulate a meal and to keep blood glucose in a therapeutic and safe range. Patients are observed until glucose is stable after the dynamic insulin infusion is administered [44]. The mechanism of PIR is directed at the pathophysiology of IR, found in type 2 diabetes. Through upregulation of the insulin receptor/ligand complex, it may be possible to bio-modulate physiologic response in a beneficial manner. Peripheral administration of IV insulin in a rhythmic pattern would then be able to replace lost physiological signals critical to cellular glucose metabolism. With improved ability to drive glucose into the mitochondrial oxidative phosphorylation cascade, improved energy production (in the form of ATP) could then occur. As such, energy depleted tissues would have the building blocks necessary to undergo healing, repair, and cellular restoration [45].

Physiologic insulin resensitization requires a pulsatile insulin delivery comparable to that of a healthy pancreas. Understanding this type of insulin delivery is necessary; over the years, scholars have studied and reported on this concept. Notably, in 2012, researchers Matveyenko et al. reported that pulsatile insulin delivery into the systemic circulation is more efficacious than constant insulin infusion [46]. The Matveyenko study also found that the timing of the insulin receptor is perfectly suited to entrain to the episodic delivery of insulin via the sinusoids directly to hepatocytes, and they concluded that hepatic insulin signaling is delayed and impaired when insulin is delivered in a nonpulsatile manner [46].

Ten years earlier, Porksen, et al., discussed pulsatile insulin secretion and reported that, in type 2 diabetes mellitus, both IR and impairment of insulin secretion characterizes the metabolic problem of the disease. High frequency of insulin oscillations in these patients corresponds to serial secretory insulin bursts [47].

This treatment approach has been reported to achieve physiological insulin concentrations in the portal vein based on animal work [48]. This treatment, with some variation on the amount of insulin and treatment frequency, has been evaluated in case series and clinical trials that are reviewed herein.

5. Studies of Physiologic Insulin Resensitization (PIR) Treatment

5.1. Foot Ulcer and Peripheral Neuropathy

Tucker et al. described two cases in which symptoms of diabetic neuropathy resolved with PIR. One was a 73-year-old male who displayed slow wound healing, erectile dysfunction, and numbness in his feet with a foot ulcer. Intermittent treatment with PIR achieved wound healing, numbness resolution, and a decrease in his insulin requirement from 120 to 28 units per day. The second was a 74-year-old female who experienced slow wound healing, a foot ulcer, weight gain, stage 4 chronic renal disease, numbness, pain, and tingling in her lower extremities. Over several months of receiving insulin administered in a physiologic manner, she experienced wound healing, improved sensation, and discontinuance of the gabapentin formerly taken for neuropathy pain. She also lost 15 kg, her daily insulin requirement dropped from 60 to 25 units per day, and her HbA1c dropped from 9.9 to 7.1% [49]. In another study Elliott et al. described a case series of 5 patients who were treated with physiologic insulin 1 h 3 times a day up to 5 days a week. The mean time to complete healing of foot ulcers was predicted from the literature to be 133 days, but the wounds in the 5 patients healed in a mean of 84 days [50]. The 37% reduction in the healing time was interpreted as providing a significant cost savings [51]. Dailey et al. randomly allocated 19 patients (12 men, 7 women) to either standard diabetic insulin-based care or to that care and additional day per week of 3 sessions of physiologic insulin over an 8-h period. When compared to baseline perceptions, patients receiving physiologic insulin reported significant improvement in diabetic nephropathy when compared to the control group ($p = 0.0144$) [52]. Eliott et al. reported on a study of 412 patients, 76% of whom experienced painful diabetic neuropathy and who were treated with 3 h of physiologic insulin per week for 3 months. Of those with painful diabetic neuropathy, 142 (47.5% experienced complete resolution of pain, 136 (45.5%) experienced partial resolution of pain and 21 (7%) experienced no improvement [51].

5.2. Diabetic Nephropathy

Villaverde et al. described three cases of chronic kidney disease, one in a patient with diabetes and two with pre-diabetes, that improved in response to physiologic insulin resensitization over 5–6 months. The estimated glomerular filtration rate (GFR) increased from 33, 34 and 54 cc/min to 55, 42 and 74 cc/minute, respectively. Blood urea nitrogen and creatinine improved from means of 27 and 1.7 mg/dL to 13 and 1.2 mg/dL, respectively. Not only is reversal of chronic kidney disease difficult to accomplish, but delaying renal replacement therapy is also associated with significant economic savings [53]. Manessis et al. reported an uncontrolled series of 17 patients with type 2 diabetes of greater than 2 years duration and stage 3 chronic kidney disease (GFR 30–60 cc/min) treated with weekly dynamic physiologic insulin for 3 months. The GFR increased by 12% from baseline (47.6 ± 10 cc/min to 53.3 ± 11.9, $p < 0.01$), creatinine decreased by 7% from baseline ($p < 0.05$), and systolic blood pressure decreased by 6% from baseline ($p < 0.05$) [54]. Quach and Manessis conducted a trial of 17 patients with chronic kidney failure. Patients received a total of 10 physiologic insulin infusion procedures over three months. GFR improved by an average of 10.8% and creatinine decreased by 6.8% [55]. Dailey et al. compared two randomly assigned groups of 49 patients who received either intensive diabetes treatment only (26) or intensive treatment plus physiologic insulin infusions (23). Creatinine clearance (CrCl) declined significantly in both groups, as expected, but the rate of CrCl decline in the group receiving physiologic insulin (2.21 ± 1.62 mL/min/yr) was significantly less than in the control group (7.69 ± 1.88 mL/min/yr, $p = 0.0343$) [52]. An overall summary of the physiologic insulin resensitization effect on diabetic nephropathy is provided in Table 1.

5.3. HbA1c

Tucker et al. reported a 74-year-old female who presented with numerous complications after 20 years of T2D that included slow wound healing, foot ulcers, kidney disease, neuropathy, and hypertension. Her comparisons before and after PIR treatment

included HbA1c reduction from 9.9 to 7.1, improved wound healing and discontinuance of Gabapentin for neuropathy, and discontinuance of her Humalog completely [49].

Table 1. Summary of benefits from physiologic insulin resensitization in treating diabetic nephropathy.

Improvements in the Progression of Diabetic Nephropathy	
Halting the Progression of CKD: CrCl (18 months) [52]	348%
Reversals of CKD: Improved EGFR (3.75 months) [53]	44%
Reversals of CKD: Improved EGFR (3 months) [54]	12%

Aoki et al. treated 20 patients with brittle type 1 diabetes for periods of 7–71 months with physiologic insulin and the mean HbA1c declined from 8.5% to 7.0% [56]. Aoki reported on another study of 31 patients with type 1 diabetes, many with diabetes complications, who were controlled on a physiologic insulin regimen with injections administered 4 times a day. These patients were treated with additional oscillatory intravenous insulin for 1 h during meals 3 times a day, 1 day a week, for 7 to 71 months. The HbA1c fell from 8.5% to 7.0%. Major hypoglycemic reactions fell from 3 to 0.1 per month, and minor hypoglycemic reactions fell from 13 to 2.4 per month [44].

5.4. Cost Reduction

All the studies above reflected reduced burden of disease. However, they did not study the actual or potential saving that may have accrued because of the intervention. Another study gave data for the likely savings that are possible. Elliott et al. reported an observational study that included 1524 patients with diabetes who had two or more complications and who were treated with 3-h (weekly or at longer intervals) physiologic insulin for 2 years [51]. The number of expected hospital admissions was 47 out of 100 patients per year, but only 5 were observed and the number of expected and observed emergency room visits per year was 58 and 7, respectively ($p < 0.0001$) [51].

6. Conclusions

Based on the evidence, loss of dynamic physiologic insulin signaling plays a major role in the pathophysiology of insulin resistance (IR). Given that IR is the accepted basis for type 2 diabetes. It, therefore, seems logical that the treatment of type 2 diabetes would be improved by switching from standard insulin treatment to a treatment that bio-mimics the normal physiologic insulin signaling process. Skjaervold et al. have been exploring the pharmacology of intravenous physiologic insulin administration as a prelude to a closed-loop intravenous insulin pump to replace the insulin pumps presently available that use a constant infusion of insulin administered by a subcutaneous route [57]. One can imagine that the next step in such a progression will be the inclusion of glucagon pulses in between the insulin pulses to further mimic the physiology of human insulin and glucagon secretion.

We firmly believe that the evidence supports the assertion that physiologic insulin secretion is crucial in the maintenance of normal cellular insulin sensitivity. Hence, using physiologic insulin resensitization is a logical approach to restoring normal insulin function. The case studies and clinical trials examining efficacy presented in this paper are insufficient to prove the hypothesis that biomimicry of the physiologic insulin administration in this manner is broadly efficacious. Randomized clinical trial are needed. However, these reports and studies have consistently shown improvement in the usually refractory conditions that are associated with diabetes. Moreover, they demonstrate that physiologic insulin resensitization can affect several of the untoward manifestations of diabetes and, thus, appears to address the root causes of IR. They also suggest that the complications, hospitalizations, medication costs, and emergency room visits may be reduced using physiologic insulin resensitization (Tables 2 and 3).

Table 2. Clinical Outcomes Utilizing Physiologic Insulin Resensitization.

Decreases in Hemoglobin A1c [49,58]
Reversals of Diabetic Neuropathy [49]
Improvements in Wound Healing [49]
Decreases in Insulin Requirements [49]
Improvements in Estimated Glomerular Filtration Rate (eGFR) [53,54]
Decreases in Systolic Blood Pressure (SBP) [54]
Reduce/Arrest Progression of Diabetic Nephropathy [49,52,54,58]

Table 3. Summary of study results discussed in this article.

Reference	Finding	Study Design	Results
Tucker et al.	Neuropathy	Case Series	Improved; discontinued Gabapentin
Tucker et al.	Foot Ulcer	Case Series	Healed quickly
Tucker et al.	HbA1c	Case Report	HbA1c decreased 2.8
Elliott et al.	Foot Ulcer	Case Series	Healed 1/3 more quickly
Dailey et al.	Nephropathy	Controlled Trial	Improved ($p = 0.0144$)
Elliott et al.	Neuropathy Pain	Case Series	93% improved, 47.5% resolved
Villaverde et al.	Nephropathy	Case Series	41% increase in GFR
Manessis et al.	Nephropathy	Case Series	12% increase in GFR
Quach et al.	Nephropathy	Case Series	11% increase in GFR
Dailey et al.	Nephropathy	Controlled Trial	Reduced decline in GFR
Aoki et al.	HbA1c	Case Series	HbA1c decreased by 1.5 T1D
Aoki et al.	HbA1c	Case Series	HbA1c decreased by 1; improved glycemic control
Elliott et al.	Hospitalizations	Case Series	Reduced hospitalizations

This needs further research that examines the treatment's effect on a broad array of diabetes complications. These studies should also include examining the cost of the treatment versus the costs avoided by it. If randomized controlled studies replicate the outcomes of case reports and studies examined in this review, administration of insulin in a physiologic manner represents a promising approach to reduce or avoid the looming increases in disease, disability, death and cost that will occur as the 88 million pre-diabetics progress to overt diabetes in the United States.

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Review article

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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 and oscillatory pattern by the pancreas, that is critical to maintain adequate insulin sensitivity at the insulin receptor level. 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 appears to reduce the progression to or worsening of insulin resistance. We will review how administration of insulin in this manner has been associated with reduction of diabetic complications.

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

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

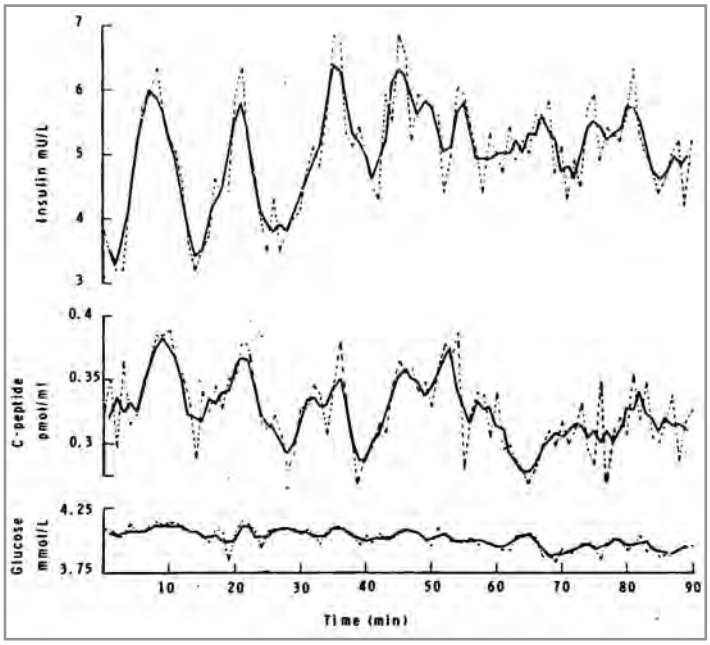

Figure 1: A three-minute moving average (continuous line) of the fasting plasma insulin, C-peptide and glucose concentrations taken at one-minute intervals. The dashed line shows the "unsmoothed" data. Smoothing reduces the rapid fluctuations, which are probably due to "noise," and also blunts the amplitude. The simultaneous insulin and C-peptide cycles disappear after 50 minutes. Reproduced from [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 troughs 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 many academic and commercial teams of scientists 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 a precise dosing to approximate the normal physiologic insulin signaling which serves to counter the negative feedback of aberrant insulin messaging and to 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 method to overcome insulin resistance and improve carbohydrate metabolism. The goal of PIR is to enable cellular repair by attempting to restore physiologic 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 can be reduced. In addition, this shift of metabolism potential to increase the level of adenosine triphosphate available for performance of vital cellular functions.

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 2021, a case series reported that longstanding diabetic neuropathy was reversed using PIR. In addition, these patients also noted improved wound healing, decreased A1c, and decreased insulin requirements [17]. Furthermore, another case series published in 2021 reported improved kidney function in patients with CKD utilizing PIR treatment modality [18]. These case reports suggest that longstanding complications of diabetes may be reversable. Prospective data sets are needed to validate these findings.

A recent prospective study, published in 2021, evaluated the potential to improve kidney function in type 2 diabetics with stage 3 kidney disease in an attempt to deliver physiologic signals. The results reported are as follows: Of 22 enrolled type 2 patients, 17 completed the trial per protocol (7 women, 10 men, age: 69 ± 7 yrs., HbA1c: 7.9 ± 1.0%). After 3 months, mean GFR improved by 12% (from 47.6 ± 10.0 mL/min to 53.3 ± 11.9 mL/min, $p<0.01$) and mean serum creatinine decreased by 7% (1.4 ± 0.3 mg/dL/1.3 ± 0.3 mg/dL, $p<0.05$). Systolic blood pressure improved by 6% ($p<0.05$), while HbA1c and body weight remained stable. The treatment satisfaction score improved from 3.7 ± 2.7 to 2.7 ± 2.1 ($p<0.005$). The treatments were well tolerated and only few cases of muscle cramps were reported in the study group [19]. In totality, the numerous potential clinical benefits of this modality are summarized in Table 1. The documented improvements in diabetic nephropathy and CKD are highlighted in Table 2.

Clinical Outcomes Utilizing Physiologic Insulin Resensitization

Table 1: Summary of documented benefits utilizing PIR modality.

Decrease in Hemoglobin A1c [16,17]
Reversal of Diabetic Neuropathy [17]
Improvement in Wound Healing [17]
Decrease in Insulin Requirements [17]
Improvement in Estimated Glomerular Filtration Rate (EGFR) [18,19]
Decrease in Systolic Blood Pressure (SBP) [19]
Reduce/Arrest Progression of Diabetic Nephropathy [15,16,18,19]

Improvements in Diabetic Nephropathy/CKD

Table 2: Summary of benefits utilizing physiologic insulin resensitization in the treatment of diabetic nephropathy/CKD.

Reduced Progression of CKD: CrCl (18months) [15]	-348%
Halted Progression of CKD: CrCl (12 months) [16]	Ø
Reversed CKD with Improved EGFR (3.75months) [18]	+44%
Reversed CKD with Improved EGFR (3months) [19]	+12%

Employing PIR, clinicians are able to administer bio identical randomized 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 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 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.

Conclusion

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. 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, inflammation, and inability to repair and replace aging cells. By addressing impaired pancreatic signaling and restoring metabolic dysfunction, it may be 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 desensitize and downregulate receptors. PIR offers a dynamic, dosing approach designed to improve the efficiency of insulin by providing a more precise physiologic delivery. With minimal abatement from current treatments, it is clear that, treatment must go beyond control of hyperglycemia and address the core defects that have propelled this condition into a global health crisis.

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Research Article

Improved Kidney Function Following Physiologic Insulin Resensitization Treatment Modality

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Abstract

Diabetes affects millions of people worldwide and is a leading cause of amputation, blindness, neuropathy, and chronic kidney disease. Chronic kidney disease results in the prolonged impairment of kidney function. Common medications and lifestyle modifications do not eliminate the long-term complications of diabetes, because they lack the ability to restore the periodic cycle of insulin that exists in healthy physiology. Our study used a precise administration of exogenous insulin, mimicking the physiologic profile of insulin secretion, which is more effective at stabilizing cellular blood glucose uptake and reducing diabetic complications than current drug and lifestyle modifications alone.

In this case study report, we evaluated three diabetic or pre-diabetic patients who showed improvements in kidney function after beginning this treatment modality. We monitored their chronic kidney disease symptoms before and after the physiological insulin resensitization (PIR) process.

We showed that the patients improved in kidney function after several months based on their laboratory metrics and CKD stage classification.

Key Words: diabetes; chronic kidney disease; treatment modality; physiological insulin resensitization

Introduction

Diabetes mellitus affects millions of people worldwide, and its complications cost hundreds of billions of dollars to treat. Diabetes is a metabolic disorder that affects the way humans metabolize glucose [1]. Glucose is of vital importance to human health, as it is the main energy molecule for muscles and organs such as the brain. Diabetes is typically identified via sustained hyperglycemia [1]. This hyperglycemia is caused by at least one defect along the insulin secretion and reception pathway in the body [1].

The two most common types of diabetes are Type 1 and Type 2 diabetes [1]. Type 1 diabetes (T1D) is an autoimmune disease that results in the immune system destroying insulin-producing beta cells in the pancreas. T1D typically manifests itself in early adolescence, and T1D patients are dependent on exogenous insulin for survival [1]. Type 2 diabetes (T2D) is the more common of the two and is typically believed to be caused by inadequate insulin secretion from the pancreas or decreased cellular response to insulin [1]. Onset of T2D is typically believed to be associated with obesity or poor diet [1]. In people developing T2D, hyperglycemia is caused by either a decrease in insulin sensitivity, a failure to produce enough insulin or both. In the case of decreased insulin sensitivity, abnormal insulin secretion from the pancreas results in consistent exposure of cells to insulin. Cells consequently downregulate the associated insulin receptors, and the patient takes up less glucose into his or her cells, prompting the pancreas to produce more insulin in a positive feedback loop [1]. Eventually, the patient has so few responsive receptors that glucose cannot be taken up into cells, and the patient suffers from chronic hyperglycemia [1]. In the case of insulin deficiency, genetic defects or chronic overproduction of insulin can result in not enough insulin being secreted from the pancreas. In this case, hyperglycemia is sustained because a patient does not produce enough insulin for the cells to uptake the glucose in the bloodstream [1]. Both of the above scenarios result in T2D characterized by hyperglycemia, which can lead to other detrimental effects on the body.

One potential effect of diabetes is increased inflammatory response. Inflammation has been hypothesized to originate from decreased insulin

sensitivity, as well as obesity and increased lipolysis [2]. Insulin has been shown to suppress certain inflammation-promoting transcription factors such as IL-6, CRP, and TNF-α. Diabetes can decrease production or uptake of insulin, which removes the suppression of these transcription factors and results in inflammation [2]. Type 2 diabetics can develop obesity because their blood sugar is not being effectively metabolized; thus, the body stores the blood sugar as fat before it can be utilized through the fat metabolism pathway [2]. Obesity results in increased numbers of adipocytes, which constitutively express inflammatory markers, like IL-6 and CRP as mentioned above [2]. Finally, increased lipolysis because of T2D results in higher free fatty acid concentrations in the blood, which contributes to increased cellular oxidative stress through the buildup of oxygen radicals, and tissue inflammation [2]. The combination of sustained hyperglycemia and inflammation in the body as a result of diabetes contributes to many of the complications that arise in diabetic patients [2].

Many complications can arise from chronic hyperglycemia and inflammation associated with diabetes and other metabolic disorders. Some of the more common complications include cardiovascular disease, wound ulceration, peripheral neuropathy in limbs, and nephropathy leading to chronic kidney disease (CKD) and kidney failure [3]. Chronic kidney disease is of growing concern, as the number of people per year initiating treatment for diabetic CKD leading to end-stage kidney disease (ESKD) and dialysis increased more than 18-fold between 1980 and 2011, with numbers continuing to climb [3]. Diabetic CKD, also known as diabetic kidney disease (DKD), is also the single strongest predictor of mortality in diabetic patients, warranting it special attention in medicine [3].

Chronic kidney disease is the result of prolonged impairment of kidney function. Kidney function is best measured through a patient's estimated Glomerular Filtration Rate, or (e) GFR [4]. Clinically, a patient is diagnosed with CKD if he or she exhibits one or both of the following for at least three months: an eGFR of below 60mL/min or at least one other marker of kidney damage [4]. These markers include albuminuria or proteinuria, abnormal urine electrolyte levels, structural abnormalities in the kidney, and others [4]. Diabetic patients are at unique risk for developing CKD because two of the side effects of diabetes, hyperglycemia and inflammation, affect pathways that lead to impaired kidney function [3]. Hyperglycemia changes the typical progression of glycolysis in cells, resulting in upregulation of transcription factors and substrates that lead to glomerular hyperfiltration or capillary obstruction. Over time, hyperfiltration and blood vessel obstruction damage the kidneys and can result in DKD [3]. Inflammation results in increased levels of inflammatory cytokines in the blood, which are hypothesized to increase endothelial cell permeability as well as induce apoptosis in endothelial cells. Degradation of endothelial linings can contribute to abnormal amounts of protein or electrolytes in urine, as well as decreased eGFR in damaged nephrons [3].

Chronic kidney disease is generally separated into six stages based on a patient's eGFR. Stage 1 CKD is "normal" and is characterized as an eGFR of 90 mL/min or higher. Stage 2 CKD is within the range of 60 mL/min to 89 mL/min, and kidneys are considered mildly impaired. Patients with an eGFR below 60 mL/min are then diagnosed with CKD and placed into CKD stage 3. Stage 3 is further divided into 3a and 3b and signals moderate impairment in kidney function. Stage 3a falls within eGFR ranges of 45 mL/min to 59 mL/min and stage 3b within 30 mL/min and 44 mL/min. CKD Stage 4 denotes significant impairment and risk for renal failure. Stage 4 eGFRs range from 15 mL/min to 29 mL/min. Below 15 mL/min is CKD Stage 5, which is essentially renal failure [4]. Patients at CKD Stage 5 are highly likely to require dialysis or a kidney transplant [4]. Dialysis and surgery can be costly and significantly impact a patient's quality of life. Current widely accepted treatments focus on slowing the progression of CKD and attempt to restore "reversible" factors of CKD to normal to reduce its severity [5]. Once a diabetic patient begins to lose kidney function, however, it is extremely difficult to arrest this progression, because the underlying contributors, high blood sugar and inflammatory tissue damage, are still present in the patient. This study seeks to explore the effect of Physiologic Insulin Resensitization on diabetic and pre-diabetic patients in varying stages of CKD. More specifically, we want to determine whether physiologic insulin resensitization displayed any noticeable effects on the kidney function of patients currently receiving the treatment modality in a real-world clinical setting.

Description of Physiologic Insulin Resensitization (PIR)

In our study, we utilize a novel therapeutic protocol that uses insulin as a biologic adjunct in treating the systemic complications of diabetes regarding kidney function. The advantage of this protocol is mimicking the body's own method of insulin regulation, especially mimicking the normal physiologic and periodic insulin signaling. This protocol was designed to counter the negative effect of insulin messaging, as well as unopposed glucagon effect on reducing insulin receptor expression [2]. Effectively, this protocol serves as a potent adjunctive companion method to overcome insulin resistance, or insulin toxicity and improve carbohydrate metabolism.

This bio-mimicry precision dosing ranges dynamically between 4- to 8-minutes intervals where adjustments to concentrations, volumes, pressures, and oscillations of insulin are varied on an individualized basis. Oral glucose is used at individualized intervals to trigger carbohydrate metabolism, which as carbohydrate metabolism improves, ATP production is increased, and inflammatory markers are reduced, leading to higher available cellular energy [7].

The PIR precision dosing pattern of insulin 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, which often promote the secretion of insulin or inhibit the production of glucose and are costly [7]. This study was performed as an observational evaluation of patients who are already undergoing PIR treatment at Island Doctors and have their kidney function monitored as a part of the treatment.

Consent for study

Before any patient begins the PIR treatment modality at the Island Doctors clinic in Palm Coast, Florida, the patient signs a consent document to their information being used anonymously for the purpose of scientific studies. Patient data shown in this manuscript complies with the terms of this agreement.

Clinical Presentation

Tables 1-3 are results from three male patients who have been on PIR infusion treatment for at least five weeks. These three patients were selected from more than 80 current patients for exceptional changes in metrics related to kidney function. Table 1 identifies patients based on their ID number at the clinic where they receive their PIR infusion treatments. Their ages are also noted. These patients range from 75 at the youngest to 85 at the oldest. It is worth noting that only one of the patients, patient 8, was referred to the PIR clinic for CKD stage 3. The other two patients were referred for other reasons relating to PIR. Only patient 32 is clinically diabetic. The other two patients are pre-diabetic, but all three of them have low eGFR scores that would classify them as CKD stage 3 or higher.

Table 1: PIR Patient Demographic Information		
Patient ID	**Age**	**Reason for Starting the PIR Treatment Modality**
8	77	CKD Stage 3/Peripheral Neuropathy
30	75	Ulcerated Wound
32	85	Diabetic Neuropathy

Table 1: Patient characteristics enrolled in this study. Basic demographic information as well as the reason for referral to the PIR treatment modality is also shown.

Table 2 outlines the relevant metrics for assessment of patient kidney function. Each of the three patients observed in this case study was on the treatment modality for at least 5 weeks prior to re-evaluation of these metrics. This translates to a minimum of 8-10 infusions for patient 32, and approximately 20 for patients 8 and 30 after 15 weeks of the treatment modality. The primary indicator for CKD, eGFR, showed a positive percent change between the base and the first test for each of the three patients. Patient 8 showed the highest percentage increase of 67%, but all three of these patients increased at least 25% in this short window of treatments. Furthermore, patient 8 regressed classification from CKD stage 3b to 3a, and patient 30 regressed from 3a to 2. These patients additionally showed decreases in both BUN and Creatinine in their urinalysis tests. The patients' BUN scores decreased anywhere from 21% to 46% over this timeframe, and Creatinine decreased between 18% and 34%. These changes are all positive developments in kidney health of these patients.

Table 2: CKD Specific Metrics by Patient – Before and During PIR Treatment Modality										
Patient ID	Lab Date	Weeks on Infusion Treatment	BUN (mg/dL)	% Chg	Creatinine (mg/dL)	%Chg	eGFR (mL/min)	%Chg	Potassium (mmol/L)	%Chg
8	9/19/2020	0	28		1.9		33		5.1	
8	1/12/2021	15	15	-46%	1.25	-34%	55	67%	4.7	-8%
30	8/27/2020	0	19		1.3		53.8		3.8	
30	1/13/2021	15	15	-21%	0.99	-24%	74	38%	4	5%
32	9/17/2020	0	35		1.81		33		5.9	
32	1/18/2021	5	19	-46%	1.49	-18%	42	27%	4.3	-27%

Table 2: Kidney lab markers before and after beginning physiologic insulin resensitization for kidney function. Relevant metrics for kidney function as well as percent changes from baseline are outlined for each patient. Green labels indicate strictly positive developments in percent change. The date of the baseline labs – 0 weeks on the treatment modality – does not correspond with the first day of patient treatment. These dates correspond to the patients' most recent labs prior to beginning the treatment modality. The number of weeks on infusion treatments is tabulated separately.

Another development to note is the potassium level in patient 32. At the beginning of this treatment modality, this patient showed a potassium level of 5.9 mmol/L, which is higher than the normal upper boundary of 5.2. After 5 weeks of treatments, this patient showed a potassium of 4.3 mmol/L, decreasing 27%, and falling back within normal levels. Likewise, patient 8 showed potassium of 5.1mmol/L, which is almost at the upper limit of normal levels. After 15 weeks of treatments, that number decreased 8% to 4.7 mmol/L.

In terms of diabetes-specific results, Table 3 shows the change in each patient from their baseline labs. For the three patients, fasting blood glucose gave ambiguous results, with one patient decreasing, one patient increasing, and one staying roughly the same. However, Hemoglobin A1c did decrease in all three patients, even those who are not clinically diabetic. Hemoglobin A1C decreased most drastically in patient 32, the one patient of these three who is clinically diabetic, decreasing a full percentage point from 7.3% to 6.3%.

Table 3: Diabetes Specific Metrics by Patient – Before and During the PIR Treatment Modality						
Patient ID	Lab Date	Weeks on Infusion Treatment	Fasting BG (mg/dL)	%Chg	A1C (%)	%Chg
8	9/19/2020	0	116		6.3	
8	1/12/2021	15	100	-14%	6	-5%
30	8/27/2020	0	94		5.7	
30	1/13/2021	15	96	2%	5.6	-2%
32	9/17/2020	0	100		7.3	
32	1/18/2021	5	142	42%	6.3	-14%

Table 3: Diabetic lab markers before and after beginning physiologic insulin resensitization. Relevant metrics for diabetes as well as percent changes from baseline are outlined for each patient. Green labels indicate strictly positive developments in percent change. This information corresponds to the same rows/columns as Table 2

Discussion

The link between insulin resistance and progressive CKD is becoming apparent as more research shows physiologic effects on the kidneys of insulin resistance. A 2012 study by the American Society of Nephrology noted insulin resistance as a known complication of ESRD. [8] The study went on to show an inverse relation between insulin resistance and measured eGFR, which is one of the key metrics in determining severity of CKD. [8, 9]. Diabetic patients suffer from insulin resistance with or without CKD and ESRD, but this study also notes that insulin resistance is prevalent in non-diabetic ESRD patients as well. [8]

The goal of the PIR treatment is to return insulin secretion to normal physiological conditions, thereby reducing the level of insulin resistance in affected patients. The patients sampled in the results above display increased eGFR, which is correlated with reduced insulin resistance in both the diabetic and nondiabetic patients. This is potentially attributable to the PIR treatment.

Insulin resistance has also been shown to create structural changes in the kidney, including excess proliferation of cells, apoptosis inhibition, and reduction in endothelial functionality [6]. All these effects carry a risk of kidney injury and progressive CKD [6]. The PIR modality recalibrates the endogenous production of insulin to its physiologic "pulse-rest" intervals, which may allow these alternative insulin-signaling pathways to regain ordinary functionality. This may result in a restructuring of kidney tissues back to normal, and furthermore an improvement in kidney function after beginning the PIR treatment modality.

Conclusion

The principal objective of this study was to determine if the PIR treatment modality has any noticeable effect on kidney function in patients with diabetic CKD. Given the above results, it is possible that this modality has positive effects on kidney function in diabetic patients. Because the study was a real-world analysis and not a controlled study with explicit variables, further data and studies are required to support this notion. The next steps after this preliminary case study would be design and execution of a full controlled study among diabetic patients with CKD, in which the independent variable is the PIR treatment modality itself.

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Declaration of Interests

Dr. Roy Hinman, and Zach Villaverde are employees of Island Doctors, which administers the PIR treatment modality. Scott Hepford is employed by Well Cell Global LLC, which researches, advances and licenses the PIR treatment modality. Tori Tucker, Michael Alexander, and Dr. Jonathan Lakey are employees of the University of California Irvine and have no conflicts of interest in this study.

Consent for Publication

Patients provided their consent for anonymous inclusion of their data in publications.

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Case Report

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Case Series: Reversal of Diabetic Neuropathy Utilizing Physiologic Insulin Resensitization

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Abstract

Diabetes is a growing global problem that is currently on the rise. Type 2 diabetes (T2D) is a chronic condition that results from aberrant B-cell function coupled with progressive insulin resistance. The majority of Type 2 diabetic patients develop diabetic neuropathy, which can lead to devastating complications (i.e., infection, ulceration, osteomyelitis, & amputation). The proinflammatory state of diabetes, along with prolonged hyperglycemia damages peripheral nerves (most common in the lower extremities). Additionally, compromised wound healing exacerbates the risk when skin breakdown occurs in this patient population. To overcome these risks for T2D, physiologic insulin resensitization (PIR) has been used as a novel protocol to treat patients with severe neuropathy symptoms. In our case study, we present two patients who initially experienced a loss of sensation in their extremities and decreased wound healing. Using PIR treatment, we demonstrate that both patients experienced neuropathy reversal and improved wound healing.

Keywords: Diabetes, Insulin Sensitivity, Wound Healing, Neuropathy

Introduction

Diabetes is a chronic disease that results in the inability to regulate glucose metabolism and affects more than 30 million Americans. Type 2 diabetes (T2D) is a condition that affects the way in which insulin is secreted, and carbohydrates are processed. In T2D, the β-cells of the pancreas no longer secrete insulin in a coordinated cyclical pattern, leading to progressive insulin resistance [1, 2]. This resulted from a multifactorial pathway, including increasing tolerance at the receptor level (due to a negative feedback loop); receptor lag (from asynchronous signals); and decreased insulin receptor expression (secondary to unopposed glucagon) [2, 3]. Neuropathy is a common side effect of T2D, often resulting in numbness, pain, increased risk of falls, infection and amputation [4, 5, 6].

Traditionally in T2D, severity of the insulin resistance and beta-cell function is calculated based on the homeostatic model assessment (HOMA) [7]. Currently, T2D can be treated by diet and exercise, and oral medications such as metformin that are used to lower blood glucose and improve the body's response to insulin. As the incidence of T2D continues to rise, finding molecules to treat diabetes has become a growing challenge because many of the medications used by T2D patients can cause side effects. In severe cases with HOMA1-IR >2.5 or HOMA2-IR >1.8, exogenous insulin is needed to compensate for insufficient endogenous insulin to overcome the insulin resistance [7]. However, these treatments do not affect the underlying resistance to insulin.

These challenges have led to the development of a novel therapeutic protocol that bio mimics the body's own regulation of insulin to treat diabetes [8]. The development of physiologic insulin resensitization (PIR) uses precision dosing patterns of insulin that is consistent with normal hormone secretion and closely resembles the body's natural signaling pathway [9, 10, 11]. As the patient's insulin resistance improves, healthcare providers can titrate other medications to optimize treatment regimens further. PIR permits the ability to lower the dosing of subcutaneous insulin and other diabetic medications which most often promote the secretion of

insulin or inhibit glucose production [9, 10]. It is well established that progressive exposure to insulin can lead to worsening of insulin resistance [12, 13]. Using PIR treatment prevents the over-exposure of insulin receptors to toxic insulin levels.

In our case study we report on the improvement in diabetic neuropathy symptoms in two patients who received PIR treatment. Both patients have experienced a return of sensation in previous insensate extremities and improved wound healing. Additionally, both patients experienced a substantial decrease in the amount of insulin requirements to manage their blood glucose level.

Consent Approval

All patients who underwent the PIR treatment have consented for anonymous inclusion of their health records in scientific publications.

Case Report

Patient 1

Patient 1 is a 73-year-old male who was diagnosed with T2D in 2002 (Table 1). The diagnosis was made after presenting to primary care physician (PCP) with polydipsia, polyuria, and extreme fatigue/muscle weakness at work. He presented to our clinic in November of 2018 with concerns regarding slow wound healing and neuropathy, referred by podiatrist. Diabetic complications included neuropathy, erectile dysfunction, hyperlipidemia, and hypertension. HbA1c results typically ranged 7-7.4% on 60 units Lantus daily, 60-65 units Novolog daily, and Glucophage 1000 mg daily. Neuropathy was described as numbness in the feet that had slowly progressed over the years. He developed his first foot ulcer in September of 2018 after unknowingly injuring his right great toe. He was seen by a podiatrist shortly thereafter and was officially diagnosed with diabetic neuropathy. Patient states, "I had no sensation whatsoever in my feet." He received wound care to the right great toe for 2-3 months. Decreased sensation in feet resulted in poor balance and multiple falls.

Table 1: Improved Neuropathy with Physiologic Insulin Resensitization (PIR) Treatment

Patient Exam	Patient Cases			
	Patient 1		Patient 2	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Weight/BMI:	253lbs/33.4kg/m^2	242lbs	239lbs/37.44kg/m^2	206lbs/32.3kg/m^2
A1c:	6.6%	6.5%	9.9%	7.1%
Lantus Dose:	60 units	28 units	60 units	20-30 units
Insulin Dose:	60-65 units	0 units (weaned off)	Sliding scale	Off completely
Neuropathy Symptoms:	Numbness, poor balance, foot ulcer, lack of sensation	Resensitization, wound healing, improved balance	Numbness, tingling, pain in feet, ulcer, slow wound healing, amputation to toes	Increased sensation, improved wound healing, discontinue Gabapentin

Initial physical exam revealed an obese (253 lbs., BMI 33.4 kg/m2) male with a blood pressure of 158/86 mmHg and pulse of 57 bpm. Lower extremity exam showed 1+ pitting edema to the bilateral lower extremities and 2mm scabs to the tips of the 3rd-5th toes bilaterally. He had no sensation from the toes up to the level of the ankles bilaterally with monofilament testing. Laboratory testing revealed an HbA1c of 6.6% (normal < 6.5%); a vitamin D, 25-Hydroxy of 14.9 ng/mL (normal 30.0-100.00 ng/mL); and normal complete blood count, complete metabolic panel, urinalysis, lipid panel, TSH, c-peptide, magnesium, and vitamin B12. Prescribed medications included Lantus, Novolog, Glucophage, Aldactone, Cozaar, Lipitor, Plavix, Protonix, and Synthroid.

Within a few months of starting PIR treatments, patient began to experience improved sensation which started in the back of the heels and slowly worked its way up to the toes. Most recent monofilament testing showed reduced sensation rather than absent sensation. Patient states, "I can feel the bottom of my feet again." Balance has improved along with improved sensation in the feet and patient is no longer experiencing as many falls. Wounds that have developed since starting treatments have healed faster per patient report. He currently sees a podiatrist every 10 weeks for evaluation. He was completely weaned off Novolog within 7 months of starting treatment. Lantus dose has decreased from 60 units daily to 28 units daily. Weight is down from 253 lbs. to 242 lbs, and his current HbA1c is 6.5%.

Patient 2

Patient 2 is a 74-year-old female who was diagnosed with T2D in 1998 (Table 1). The diagnosis was made by routine exam with PCP. She presented to our clinic in March of 2018 with concerns regarding elevated blood sugars, weight gain, and slow wound healing. Diabetic complications included uncontrolled blood sugars, neuropathy (diagnosed in 2000), hypertension, stage 4 chronic kidney disease, impaired skin integrity, and foot ulcers. Her glycemic control had never been optimal despite a multiple-dose insulin regimen. Hemoglobin A1c results typically ranged 8-9%. Neuropathy was described as numbness, tingling, and pain that started in the feet and progressed upwards and into her ankles. Eventually, tingling and pain sensations subsided, and numbness predominated. She developed her first ulcer in 2018 after unknowingly injuring her left foot. Delayed treatment, due to delayed identification of the injury, and poor wound healing led to infection. She was treated with antibiotics, frequent wound care visits, a skin graft, and ultimately required an amputation of the tip of her left 2nd toe. She later developed additional ulcers, which led to the amputation of tip of the left 3rd and 4th toes. She was seen in the emergency room two times for complications related to diabetic ulcers and

was seeing her podiatrist one to two times per week for wound care.

Initial physical exam revealed an obese (239 lbs., BMI 37.44 kg/m2) woman with a blood pressure of 160/73 mmHg and pulse of 60 bpm. Lower extremity exam showed decreased sensation from the toes up to the level of the ankles bilaterally with monofilament testing. Laboratory testing revealed an HbA1c of 9.9% (normal < 6.5%); a serum creatinine of 2.07 mg/dL (normal 0.57-1.00 mg/dL); a GFR of 24 mL/min/1.73 (normal >59 mL/min/1.73); a vitamin D, 25-Hydroxy of 22.3 ng/mL (normal 30.0-100.00 ng/mL); and normal complete blood count, TSH, c-peptide, magnesium, and vitamin B12. Over-the-counter and prescribed medications included Lantus, Humalog, Tanzeum, Lasix, Coreg, Amlodipine, Benicar, Vitamin D3, Vitamin B Complex, Simvastatin, Prevalite, and Gabapentin.

Within a few weeks of beginning PIR, the patient began to develop increased sensation in her feet. With continued treatments, patient states, "I was able to feel the gas pedal while driving" and "I could feel it when I bumped my feet." Due to improved sensation, she was able to identify injuries to her feet when they occurred and was able to seek treatment earlier for any wounds that developed. Wound healing time also improved. Patient states, "My wounds were healing within weeks rather than months." Her most recent foot ulcer healed within one week without intervention. She currently sees a podiatrist every 60 days for evaluation and toenail clippings. She has required no further amputations for difficult wound infections. She was able to completely discontinue use of Gabapentin for neuropathy pain. Additionally, she has been able to reduce her daily lantus from 60 U/day to 25 U/day. She was able to discontinue her sliding scale Humalog completely. Most recent follow-up labs indicated stable kidney function and an improved HbA1c of 7.10%. Improvements in energy over the course of her treatments resulted in more motivation to increase physical activity. Current weight is down 33 lbs. from baseline (206 lbs., BMI 32.3 kg/m2).

Discussion

The total economic cost of diabetes in the U.S. increased from $205 billion in 2007, to $327 billion in 2017, with Medicare spending $11 Billion in 2013 on dialysis alone. Amputations cost between $73,000 to $120,000 for hospital and follow up care [14]. In recent years, the US FDA has approved several diabetes drugs with novel mechanisms of action. However, the magnitude of such benefits to these drugs 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 [15, 16].

Over-aggressive HbA1c control have been shown to be counterproductive and harmful, because of the ensuing hypoglycemia. This included data from the landmark ACCORD trial that was terminated prematurely, because intensive HbA1C control led to increased morbidity and mortality. This led to American College of Physicians (ACP) new guideline targeting patients' HbA1c between 7-8%. This highlights the evolving challenges to current treatment of diabetes [17].

Given this dynamic landscape, an augmented approach to treating diabetes and other metabolic disorders is needed. As such, an ideal approach that utilizes insulin as a biologic agent to closely mimic normal physiology is warranted. This case study demonstrates the clinical benefits of PIR [8-10]. The cases presented show marked improvements in longstanding diabetic neuropathy, with meaningful objective measures noted by both the patients and clinical team. These improvements have resulted in greater mobility, functionality, and protective proprioception. To our knowledge, reversing longstanding diabetic neuropathy in this manner is a novel treatment success. Furthermore, these patients also experienced improvements in HbA1c, wound healing, obesity, and blood pressure control. These benefits were accomplished while being able to reduce reliance on pharmacologic agents as insulin sensitivity improved with the addition of PIR.

Conclusion

We report in this case study that utilizing PIR as an adjunctive modality can reverse longstanding diabetic neuropathy, improve wound healing and several other important endpoints in diabetic management. As insulin sensitivity improves, many other positive clinical outcomes are demonstrated. When treating the underlying insulin resistance that progresses in the setting of type 2 diabetes, dramatic clinical improvements are possible with PIR. Our research team is aggressively pursuing larger case-controlled studies to demonstrate the clinical benefits possible by utilizing PIR as an adjunctive modality for this patient population.

Declaration

Funding

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Conflicting Interests

Brian Loveridge and Jennifer Hadley are employees of Well Cell Global, which performs PIR treatment.

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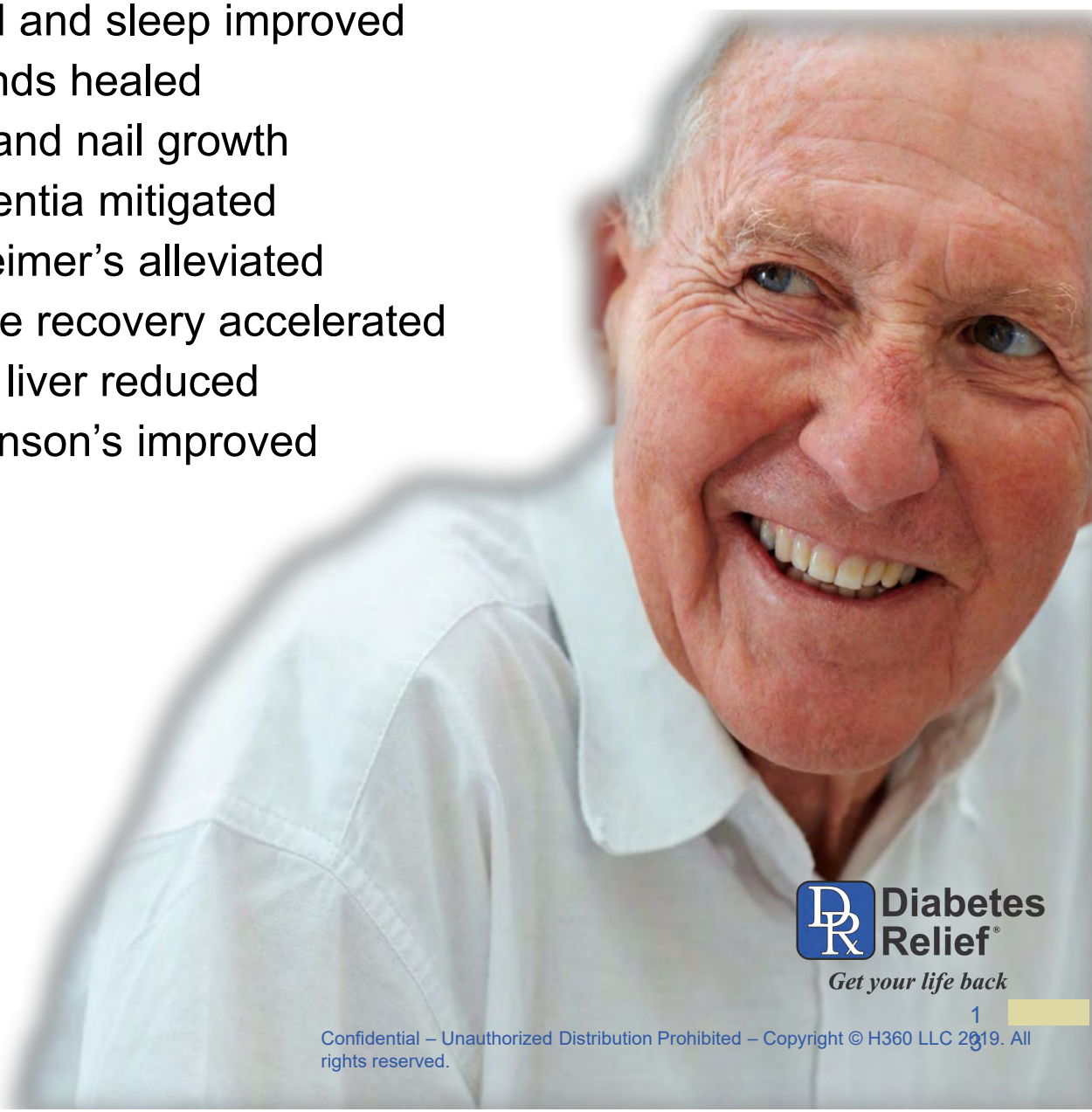
Our Patients Report:

- Neuropathy diminished
- Energy restored
- Weight controlled
- Erectile function restored
- Retinopathy diminished
- Amputations prevented
- Medications reduced
- Blood sugar controlled
- Blood pressure controlled
- Mood and sleep improved
- Wounds healed
- Hair and nail growth
- Dementia mitigated
- Alzheimer's alleviated
- Stroke recovery accelerated
- Fatty liver reduced
- Parkinson's improved



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FEATURE

Can Physiologic Insulin Resensitization Therapy Give Patients With Diabetes a Second Chance?

Yesenia Justiniano-Rosario, MD, ACHM, FAPWCA, FACCWS, WCC, DMO

August 2023

There are very few times in the life of a patient with a diabetic foot ulcer (DFU), neuropathic ulcer, or even arterial ulcer, when he or she gets a chance to reverse all the damage the disease has done to their body.

In my more than 14 years of wound care practice at a hospital base wound care center the only tool I had was hyperbaric oxygen therapy (HBOT). We were able to use this only with a lot of struggles, because the Centers for Medicare and Medicaid Services (CMS) and their policies only allowed us to use it under certain circumstances, and basically when we were at the point of no return despite the well-known benefits of the therapy overall.

What would you think if I told you there is something else in the market that can give us and our patients the opportunity of getting all the HBOT benefits plus a whole lot more without exposing them to that thin thread of limb-threatening condition to get "something" done?

Physiologic insulin resensitization (PIR) therapy is the not-so-secret weapon. With PIR I've achieved same neovascularization and new nerve ending formation that is achieved with HBOT in as low as 8–10 treatments, compared to 16–20 HBOT treatments. Over the last 3 years I haven't sent any patient for HBOT, and I haven't had a single amputation with a healing rate of 99.9% within my practice. Keep in mind that like with HBOT, revascularization and adequate local care must be our first and foremost to do in order for any kind of adjuvant therapy to succeed.

What Is Physiologic Insulin Resensitization Therapy?

PIR is a multi-patented treatment modality that provides clinicians with a unique and groundbreaking approach in which insulin is administered dynamically as a hormone rather than a drug. Intravenous access is connected to a precision infusion pump programmed to precisely deliver insulin in a way that simulates normal glucose metabolism. Blood sugar can now more readily enter each cell and be converted into energy. This addresses insulin resistance, which is the primary cause of diabetes, obesity, and other metabolic disorders. Increased cellular energy allows damaged tissues and organs to grow, repair, and regenerate.

Mechanism of Action

- This treatment modality is designed to reduce insulin resistance, which is the primary cause of type 2 diabetes and many other metabolic disorders.
- With improved insulin sensitivity at the insulin receptor level, glucose can more readily enter cells and be converted into adenosine triphosphate, also known as ATP—a molecule that carries energy within cells.
- Through increasing cellular energy, PIR is designed to repair and regenerate the body's cells, peripherally at first. Then, through repeated treatment sessions the cellular restoration progresses to the organ level, which helps the body naturally return to more normal physiologic behavior.
- Thus, the treatment has not only stabilized, but in many instances has reversed complications of diabetes and other metabolic disorders.

Infusion Treatment Modality

- The treatment includes an intravenous precision administration of Food and Drug Administration (FDA)-approved fast-acting insulin using an FDA-approved portable pump.
- The objective of the precise dosing is to achieve biomimicry of insulin as a hormone communicator to stimulate the metabolism—not simply to use insulin as a drug to suppress a high blood sugar, which typically causes insulin resistance at the insulin receptor level.
- The pump's patented biomimicry engineering combined with the treatment modality are designed to administer insulin bio-identically to the body's way of maintaining an optimized metabolism.
- Along with the insulin hormone, the patient is given small, specific amounts of glucose (ingested as a dextrose liquid) to stimulate the digestive system and its role in the metabolism process during treatment.

What Conditions Might Benefit From PIR?

Type 1 and type 2 diabetes patients have reported, and their medical professionals have reported to us: reduction in medication usage/dosage, HbA1c reduction, improvements in cases of diabetic peripheral neuropathy and chronic kidney disease, improved wound healing time, and retinopathy improvements.

A Closer Look at the Evidence for and Risks of PIR

There are several peer-reviewed articles and studies publications in the literature and others are underway to assess patient outcomes in various conditions as noted above.[1–3] Additionally, controlled clinical trials are being designed now with enrollment pending in the United States and abroad.

Possible risks: hypoglycemic symptoms, muscle cramps, nausea. Pickle juice, K+ tabs, dextrose 50, and Zofran are stocked in clinic in the event adverse reactions occur.

How Might PIR Be Used for Wound Healing?

Carbohydrate metabolism plays a crucial role in cell growth and proliferation. Glucose, a key component of carbohydrate metabolism, not only provides energy for cells but also supplies the necessary building blocks for synthesizing nucleic acids, proteins, and lipids. In the context of diabetes, proper control of blood glucose levels and metabolism is essential for wound healing. Prolonged hyperglycemia in diabetes can lead to energy deficiency in tissues, resulting in impaired wound healing over time. Hyperglycemia also hampers angiogenesis, the formation of new blood vessels required for tissue repair, by affecting key factors like hypoxia-inducible factor 1-alpha (HIF-1α) and vascular endothelial growth factor (VEGF).

Patients with diabetes with poorly controlled glucose levels often experience foot ulcers that heal slowly, get infected, or fail to heal completely. Underlying neuropathy and compromised microcirculation contribute to the development and poor healing of foot ulcers. Optimized glucose ATP production and reduced inflammation, achieved by utilizing glucose as the primary fuel source instead of fat metabolism, can benefit nerve and microvascular tissues in wound healing.

How Can Patients Access This Treatment?

Access is currently limited to physician locations across the country who have exceptional knowledge of insulin resistance and precision dosing of insulin and have licensed access to the FDA cleared infusion devises that give them a better control to precision dose to meet the individual needs of their patients.

What Should the Doctor or Patients Watch out For?

If doctors or patients are interested in pursuing this approach, they should seek out a licensed provider, in good standing with the medical board, that responsibly utilizes this modality to address insulin resistance and metabolic disorders in an adjunct way after other standards of care have failed to adequately address the patient’s health needs.

The doctor should be objectively measuring their patients’ improvements and adjusting the plan of care dynamically as the patient responds to treatment; typically decreasing in length and frequency over time.

What Questions Should I Ask if I Want to Refer a Patient?

- Does the patient have a medical necessity and have they failed other standards of care?

- Is the practice offering PIR or capable of precision dosing insulin to address hyperinsulinemia and other metabolic disorders while minimizing the known side effects of insulin, i.e., insulin resistance and obesity?

This is how small the insulin pump device looks.

Case Studies in Physiologic Insulin Resensitization Therapy

Case 1. A 69-year-old man presented with a right lateral foot ulcer due traumatic shoe injury more than six weeks previous. He had no previous local treatment. His past medical history indicates insulin-dependent diabetes, severe peripheral neuropathy with microvascular disease. He had a femoral-popliteal bypass in 2015. His LDL was 76 and his A1c was 11.2.

The patient started local care with enzymatic debridement and hydrofiber with silver. His first PIR treatment was 4/8/2023, discontinued on 5/30/2023—totaling 8 treatments in 4 weeks. The ulcer healed within four weeks.

Case 2. A 63-year-old man presented with a left plantar neuropathic ulcer of 8 weeks' duration. His past medical history indicates insulin-dependent diabetes, and a previous below-knee amputation due to gangrene. He had a history of bilateral lower extremity angioplasty 1 year previous, which was patent, with severe microvascular disease and peripheral neuropathy. His A1c was 8.9 and his LDL was 82.

The patient started local care with enzymatic debridement and Hydrofera (Hydrofera), then was lost to follow-up for more than 5 weeks. He returned and immediately started PIR, having his first PIR treatment on 8/11/2022, discontinuing on 9/13/2022 for 11 treatments in 6 weeks. The ulcer healed within six weeks.

Yesenia Justiniano-Rosario, MD, ACHM, FAPWCA, FACCWS, WCC, DMO, is a wound care and hyperbaric specialist at Well Cell Global.

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Do you have any Parkinson's Disease Patients?

Physiologic Insulin Resensitization (PIR) has been known to provide dramatic improvements in the symptoms of Parkinson's Disease.

There is growing evidence that patients with Type 2 diabetes have an increased risk of developing Parkinson's Disease and both these conditions share similar dysregulated pathways.

Insulin receptors are found in the basal ganglia and substantia nigra and insulin plays an essential role in regulating neuronal survival and growth, dopaminergic transmission, and maintenance of synapses. Several genetic and environmental risk factors for the incidence of Parkinson's Disease have been noted in recent studies, which have also suggested that metabolic syndrome, chronic kidney diseases (CKD), or cardiovascular diseases (CVD) are important risk factors for PD.

PIR treatments give "all" the cells in the body the "energy" they need to heal, even the cells that are not working in Parkinson's.

Melton D. - A Parkinson's patient going through a study with PIR:

Before treatment:	**After treatment:**
He could not drive himself	Now he can drive independently
Needed assistance of a walker to walk	Now walks freely with no walker
Speech was significantly impaired	Marked improvement in speech
Penmanship was illegible	Marked improvement in handwriting

Melton reports a significant reversal of symptoms and a substantial improvement in his quality of life and independence.

NOTE: Health Insurance does not currently pay for PIR as a treatment for Parkinson's Disease, except in the cases where the patient is also diabetic, or pre-diabetic.

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ARTICLE OPEN

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A nationwide cohort study on diabetes severity and risk of Parkinson disease

Kyungdo Han[1,4], Bongsung Kim[1,4], Seung Hwan Lee[2] and Mee Kyoung Kim[3]✉

There is growing evidence that patients with type 2 diabetes mellitus (DM) have an increased risk of developing Parkinson's disease (PD) and share similar dysregulated pathways. We aimed to determine whether the risk of PD increases as diabetes progresses among patients with type 2 DM. Using a nationally representative database from the Korean National Health Insurance System, 2,362,072 individuals (≥40 years of age) with type 2 DM who underwent regular health checkups during 2009–2012 were followed up until the end of 2018. The diabetes severity score parameters included the number of oral hypoglycemic agents, diabetes duration, insulin use, or presence of chronic kidney disease, diabetic retinopathy, or cardiovascular disease. Each of these characteristics was scored as one unit of diabetes severity and their sum was defined as a diabetes severity score from 0–6. We identified 17,046 incident PD cases during the follow-up. Each component of the diabetes severity score showed a similar intensity for the risk of PD. Compared with subjects with no parameters, HR values (95% confidence intervals) of PD were 1.09 (1.04–1.15) in subjects with one diabetes severity score parameter, 1.28 (1.22–1.35) in subjects with two parameters, 1.55 (1.46–1.65) in subjects with three parameters, 1.96 (1.82–2.11) in subjects with four parameters, 2.08 (1.83–2.36) in subjects with five parameters, and 2.78 (2.05–3.79) in subjects with six parameters. Diabetes severity was associated with an increased risk of developing PD. Severe diabetes may be a risk factor for the development of PD.

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INTRODUCTION

There is growing evidence that patients with type 2 diabetes mellitus (DM) have an increased risk of developing Parkinson's disease (PD) and share similar dysregulated pathways, which suggests the presence of common underlying pathological mechanisms[1–3]. Type 2 DM develops from insulin resistance, leading to a variety of detrimental effects on metabolism and inflammation. Similar dysregulation of glucose and energy metabolism are early events in the pathogenesis of sporadic PD. Insulin receptors are found in the basal ganglia and substantia nigra and insulin plays an essential role in regulating neuronal survival and growth, dopaminergic transmission, and maintenance of synapses[1]. Several genetic and environmental risk factors for the incidence of PD have been noted in recent studies, which have also suggested that metabolic syndrome, chronic kidney diseases (CKD), or cardiovascular diseases (CVD) are important risk factors for PD[2–7]. Because CKD or CVD could be a diabetes-related complication, we hypothesized that the risk of PD increases as diabetes progresses.

Assessing diabetes severity is important and could help identify people in need of targeted therapies and healthcare services[8–10]. Here, the severity of diabetes refers to diabetes duration, treatment status, and diabetes complications. The severity of diabetes may be evaluated by blood glucose status according to laboratory values, such as fasting blood glucose (FBG) and glycosylated hemoglobin A1c (HbA1c). However, it is difficult to assess diabetes severity using single values because these values can change and tend to wax and wane over time. As a general treatment flow in non-insulin-dependent states, such as type 2 DM, if exercise or diet does not improve glycemic control, monotherapy or dual therapy is started[8,9]. Moreover, if treatment control is not possible with monotherapy, patients must be treated with two or more drugs. Therefore, severity is also evaluated in terms of the number of oral hypoglycemic agents (OHAs)[8,9]. Insulin treatment is mostly prescribed for patients with type 2 DM who become insulin-deficient and/or have failed other OHAs, which is referred to as advanced diabetes[10]. Patients with type 2 DM who need insulin therapy are considered to display one of the indicators of diabetes severity. The current study investigated the association of diabetes severity with PD development using large-scale cohort data from the Korean general population.

RESULTS

Baseline characteristics

During a median follow-up of 7.2 years (interquartile range, 6.0–8.1 years), there were 17,046 (0.72%) cases of incident PD. The baseline characteristics of subjects with incident PD were older age, more males, nonsmokers, higher prevalence of CKD, DR, or CVD, and more likely to receive insulin treatment or more oral antidiabetes medications (Table 1). Patients with type 2 DM who developed PD had lower levels of FBG and eGFR. The use of metformin, sulfonylurea, thiazolidinediones, or α-glucosidase inhibitors was higher in patients with PD. There was no difference in the use of dipeptidyl-peptidase 4 (DPP4) inhibitors depending on the presence of PD.

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Published in partnership with the Parkinson's Foundation

Table 1. Study subjects' baseline characteristics.

	Parkinson's disease		*P* value
	No	Yes	
N	2,345,026	17,046	
Age (years)	59.06 ± 10.69	68.2 ± 7.59	<0.001
Sex (male)	1,373,727 (58.6)	8099 (47.5)	<0.0001
Body mass index (kg/m^2)	25.02 ± 3.31	24.79 ± 3.13	<0.001
Smoking			<0.001
Non-smoker	1,335,654 (56.96)	12,344 (72.42)	
Ex-smoker	444,289 (18.95)	2818 (16.53)	
Current smoker	565,083 (24.1)	1884 (11.05)	
Alcohol drinking	226,713 (9.67)	774 (4.54)	<0.001
Regular exercise	495,348 (21.12)	3469 (20.35)	0.014
Income (lower 25%)	496,804 (21.19)	3275 (19.21)	<0.001
Systolic BP (mmHg)	129.25 ± 15.9	130 ± 16.2	<0.001
Diastolic BP (mmHg)	79.05 ± 10.27	77.77 ± 10.28	<0.001
Fasting glucose (mg/dL)	144.04 ± 46.51	137.53 ± 46.26	<0.001
eGFR (ml/min/1.73 m^2)	84.3 ± 35.59	76.69 ± 28.22	<0.001
Baseline TC (mg/dL)	196.17 ± 42.51	190.58 ± 42.58	<0.001
Dyslipidemia	1,011,422 (43.1)	8195 (48.1)	<0.001
Hypertension	1,383,458 (59.0)	12066 (70.8)	<0.001
Chronic kidney disease	280,481 (12.0)	3788 (22.2)	<0.001
Diabetic retinopathy	200,063 (8.5)	2740 (16.1)	<.0001
Myocardial infarction	53,746 (2.3)	619 (3.6)	<0.001
Stroke	173,656 (7.4)	3010 (17.7)	<0.001
Depression	243,096 (10.4)	3803 (22.3)	<0.001
Duration of diabetes ≥5 years	763,547 (32.6)	8171 (47.9)	<0.001
Pharmacologic therapy for DM			
Insulin	194,658 (8.3)	2402 (14.1)	<0.001
Number of OHAs ≥3	331,346 (14.1)	3392 (19.9)	<0.001
Medication			
Metformin	1,026,078 (43.8)	9394 (55.1)	<0.001
Sulfonylurea	968,067 (41.3)	9421 (55.3)	<0.001
DPPIV-inhibitors	154,635 (6.6)	1115 (6.5)	0.781
TZD	152,638 (6.5)	1370 (8.0)	<0.001
AGI	276,524 (11.8)	3109 (18.2)	<0.001

Values are expressed as mean ± standard deviation, or number (%).
BP blood pressure, *eGFR* estimated glomerular filtration rate, *TC* total cholesterol, *OHAs* oral hypoglycemic agents, *DPPIV-inhibitors* dipeptidyl-peptidase IV inhibitors, *TZD* thiazolidinedione, *AGI* alpha-glucosidase inhibitors.

Incidence and risk of PD according to diabetes severity score parameters

Each of the diabetes severity score parameters showed an association with a similar intensity to the risk of PD, even after adjustment for confounding factors (Table 2). Subjects with insulin use had an HR of 1.36 (95% CI: 1.30–1.42) for PD compared with those treated without insulin. The use of three or more OHAs and a diabetes duration of ≥5 years were also significantly associated with an increased risk of PD (Model 2, HR, 1.15; 95% CI: 1.11–1.20 and HR, 1.23, 95% CI: 1.19–1.28, respectively). The risk of PD increased significantly in subjects with CKD compared with subjects without CKD (adjusted HR, 1.20; 95% CI: 1.15–1.25). Patients with DR were associated with a significantly higher risk of PD than diabetics without DR (adjusted HR, 1.35; 95% CI: 1.30–1.41), even after adjusting for age, sex, BMI, alcohol intake, smoking, regular exercise, hypertension, dyslipidemia, and depression. There was also a significantly increased risk of PD in subjects with CVD (adjusted HR, 1.38; 95% CI: 1.33–1.45). The results of the sex-specific analysis are presented in Supplementary Tables 1, 2.

Incidence and risk of PD according to the diabetes severity score

The Kaplan–Meier curve (Fig. 1) shows the incidence probability of PD according to the diabetes severity score compared with the group without any diabetes severity score (score, 0). PD incidence was positively correlated with the score of diabetes severity (log-rank test, $P < 0.001$). The HR for patients with incident PD compared to patients without any diabetes severity score parameters gradually increased with the number of parameters (Table 3). After adjusting for possible confounding factors, the HR values (95% CI) of PD were 1.09 (1.04–1.15) in subjects with one diabetes severity score parameter, 1.28 (1.22–1.35) in subjects with two parameters, 1.55 (1.46–1.65) in subjects with three parameters, 1.96 (1.82–2.11) in subjects with four parameters, 2.08 (1.83–2.36) in subjects with five parameters, and 2.78 (2.05–3.79) in subjects with six parameters compared with subjects with no parameters. Subjects with three diabetes severity score parameters were at 55% higher risk of PD and those with five diabetes severity score parameters were at 108% higher risk, compared to those without any parameters.

Effect of fasting blood glucose levels in type 2 diabetes

The FBG levels associated with the lowest risk of PD were 120–130 mg/dL (Supplementary Table 3). There was a J-shaped association between the risk of PD and glycemic control, with both the too-low and high FBG showing a higher risk of PD. Multivariable-adjusted HRs (95% CI) of PD associated with FBG 140–149, 150–159, 160–169, 170–179, 180–189, 190–199, and ≥ 200 mg/dL were 1.10 (1.01–1.19), 1.10 (1.01–1.20), 1.10 (0.99–1.34), 1.21 (1.08–1.34), 1.20 (1.07–1.36), 1.17 (1.02–1.34), and 1.23 (1.14–1.34), respectively, compared with the FBG 120–129 mg/dL. The risk of PD was also increased when FBG was <100 mg/dL (HR, 1.09; 95% CI: 1.02–1.16). We found that FBG <100 mg/dL and ≥140 mg/dL were associated with an increased risk of PD. So, we assigned 0 points to FBG 100–139 mg/dl and 1 point to FBG <100 mg/dl or ≥ 140 mg/dl. We then summed these to give a diabetes severity score ranging from 0 to 7 points. When assessing the severity score ranging from 0–7, including the category of FBG levels, multivariable-adjusted HRs for PD risk increased continuously and linearly with increasing severity scores (Supplementary Table 4).

Association of PD risk and diabetes severity in subgroup analysis

We conducted a stratified analysis using age, smoking status, BMI category, and the presence of depression. A significant association between the diabetes severity score and the risk of PD was observed in all subgroups. There was a significant interaction between age and diabetes severity on the risk of PD (*P* for interaction <0.001). Compared with subjects >65 years of age, we observed a greater increase in the HR of PD with increasing diabetic severity scores in subjects aged 40–65 years old. The risk of PD according to the diabetes severity score was similar regardless of smoking, obesity, or depression (Fig. 2; *P* for interaction >0.05).

DISCUSSION

Diabetes severity, as measured by diabetic complication status, treatment complexity, and duration of diabetes, was strongly associated with an increased risk for PD. All characteristics

Table 2. The risk of Parkinson's disease stratified according to the diabetes severity parameters.

		Events (*n*)	Incidence rate (per 1000 person-years)	Model 1	Model 2
Duration of diabetes	<5 years	8875	0.813	1 (ref.)	1 (ref.)
	≥5 years	8171	1.543	1.37 (1.33, 1.41)	1.23 (1.19, 1.28)
Number of oral hypoglycemic agents	<3	13,654	0.983	1 (ref.)	1 (ref.)
	≥3	3392	1.460	1.31 (1.26, 1.32)	1.15 (1.11, 1.20)
Use of insulin	No	14,644	0.982	1 (ref.)	1 (ref.)
	Yes	2402	1.853	1.62 (1.55, 1.69)	1.36 (1.30, 1.42)
Chronic kidney disease	No	13,258	0.925	1 (ref.)	1 (ref.)
	Yes	3788	2.016	1.21 (1.17, 1.26)	1.20 (1.15, 1.25)
Diabetic retinopathy	No	14,306	0.965	1 (ref.)	1 (ref.)
	Yes	2740	1.984	1.56 (1.50, 1.63)	1.35 (1.30, 1.41)
Cardiovascular disease	No	13,615	0.921	1 (ref.)	1 (ref.)
	Yes	3431	2.392	1.60 (1.54, 1.66)	1.38 (1.33, 1.45)

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, BMI, alcohol drinking, smoking, regular exercise, hypertension, dyslipidemia, and depression.

indicative of diabetes severity had an additive association with the risk of PD in patients with type 2 DM. The coexistence of conditions such as retinopathy, nephropathy, CVD, the complexity of diabetes treatments, or the long duration of diabetes was more strongly associated with PD risk than the presence of a single condition alone. People with a diabetes severity score of 4 or higher had a more than doubled risk of PD compared with those with a score of 0, and those with a score of 6 had a 2.78-fold increased risk of PD. These associations became stronger for younger diabetic patients. Our population-based, large-scale cohort study suggests that advanced diabetes may be a risk factor for the development of PD.

The incidence of PD is proportional to the degree of exposure to hyperglycemia and the duration of diabetes[2]. Compared with the nondiabetes group, the adjusted HR was 1.038 in the impaired fasting glucose group, 1.185 in the diabetes duration <5 years group, and 1.618 in the diabetes duration ≥5 years group[2]. Other studies have also identified a long diabetes duration as a crucial factor that significantly increases the risk of PD in patients with DM[11]. Recent epidemiological studies have individually evaluated the association of the risk of PD with various diabetes medications. A recent UK study demonstrated that the use of DPP4 inhibitors and/or glucagon-like peptide-1 (GLP-1) mimetics is associated with a lower rate of PD compared to the use of other oral antidiabetic drugs[12]. GLP-1 receptor stimulation in the central nervous system (CNS) may impact insulin receptor signaling pathways and may also enhance neuronal survival pathways. GLP-1 receptor agonizts were introduced into Korea in 2011; therefore, there were few GLP-1 receptor agonizts users during this study period. The addition of thiazolidinediones, DPP4 inhibitors, or GLP-1 mimetics suggested as drugs to prevent PD may achieve more effective glycemic control, thus limiting the damaging effects of excess glycation on overall brain function. The status of patients requiring multiple antidiabetic medications should be interpreted as reflecting their insulin resistance and high glycemic burden. The Danish study found that any antidiabetic drug or insulin therapy was associated with an increased risk of PD[13].

There is growing evidence that a process analogous to peripheral insulin resistance occurs in the brains of PD patients, which suggests that loss of insulin signaling may contribute to the development of the pathological features of PD[1]. Although no data yet exists from human studies testing exogenous insulin in patients with PD, clinical trials in Alzheimer's disease (AD) have shown the potential utility of using insulin to restore insulin signaling defects[1]. Trials of intranasal insulin administered to patients with mild cognitive dysfunction and early AD led to improvements in verbal memory and cognition[14]. In our study, insulin use was associated with an increased risk of PD. Progression to treatment intensification is a sign of disease progression; therefore, progression to insulin therapy may represent the severity of disease progression in type 2 DM.

We found that each of the DM complications, including retinopathy, nephropathy, or CVD was associated with an increased risk of PD. Patients with diabetes without DR were reported to have a 1.54-fold increased risk of PD compared with patients without diabetes, whereas patients with DR had a 2.39-fold increased risk of PD compared with patients without diabetes[3]. It has been reported that patients with DR were associated with a significantly higher risk of PD than non-diabetic patients or in diabetes without DR. The retina is part of the CNS and uses dopamine as a key neurotransmitter[3]. Loss of dopaminergic amacrine cells in the retina was also found in diabetic mice. A 3-year follow-up study based on the Longitudinal Health Insurance Database in Taiwan reported that uremia in patients is associated with a 1.81-fold higher risk of developing parkinsonism than in patients without uremia[15]. The coexistence of chronic renal dysfunction and proteinuria is positively associated with the risk of PD[6]. Proteinuria has been recognized as a primary marker for renal damage because it can be detected earlier than the apparent decline in eGFR. Scholars examining the association of CKD and PD have suggested potential pathways explaining a future increased risk for PD, where the renin–angiotensin system (RAS), oxidative stress, and inflammation have a significant role. CKD conditions involve an altered RAS due to increased renin, which leads to increased circulating angiotensin II levels[16]. In conditions of an altered blood–brain barrier, angiotensin II reaches brain regions, binds to angiotensin receptors, and induces oxidative stress and microglia activation, followed by neuronal damage. It has been reported that a previous stroke is associated with an approximately twofold higher risk for PD in the Chinese population (HR, 1.94; 95% CI: 1.39–2.69)[17]. Cerebral ischemia potentially activates the dopaminergic pathway due to decreased expression of nicotinic acetylcholine receptors and plays a role in the clinical expression and deterioration of idiopathic PD symptoms. Small vessel disease is more common in patients with diabetes and may contribute to the appearance of "vascular parkinsonism," which may have been mistakenly diagnosed as PD[12,18]. The South Korean government has operated a rare intractable diseases (RID) registration program (V-code), which includes 167 conditions including PD. The V124

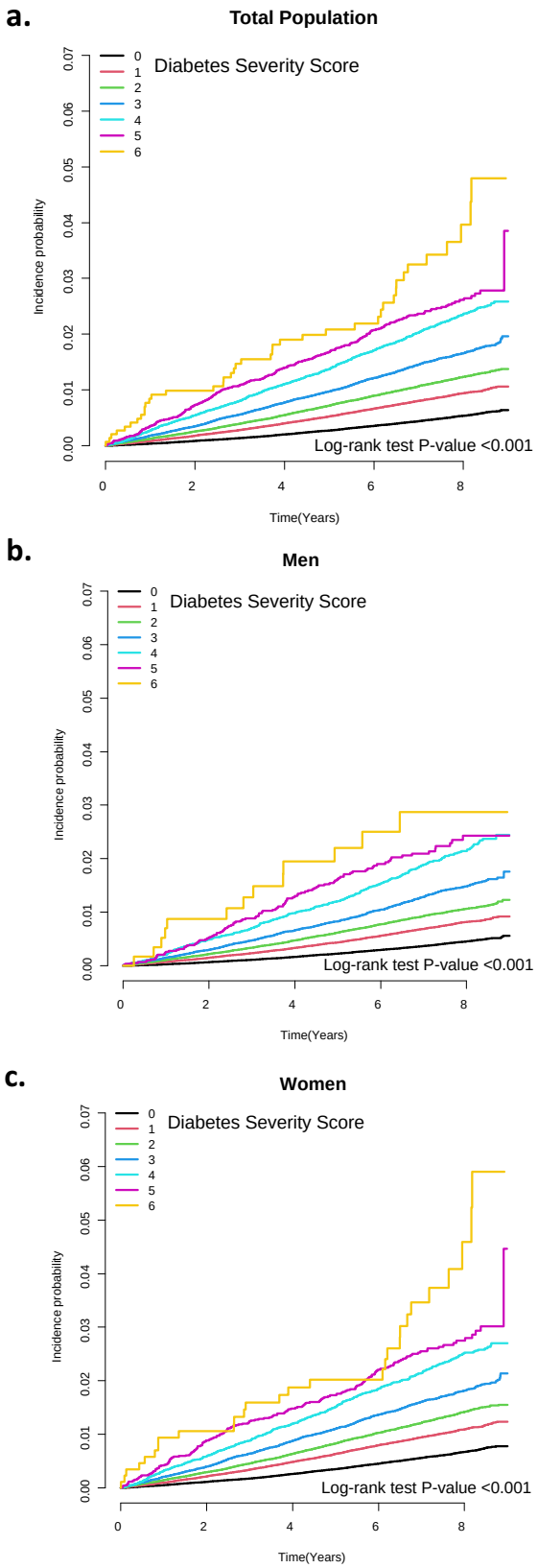

Fig. 1 Kaplan–Meier estimates for the cumulative incidence of Parkinson's disease according to the diabetes severity score (0–6). The probability of incident Parkinson's disease according to the diabetes severity score was analyzed for the total population (**a**), men (**b**), and women (**c**).

code yields a major benefit to PD patients who only must pay 10% of all medical expenditures; therefore, assigning this code to a patient requires careful and complicated documentation. To assign the V124 code to patients, diagnostic MRI findings and major parkinsonism syndromes, including tremor, bradykinesia, rigidity, and postural instability should be examined and confirmed by a neurologist. In Korea, this enables an accurate diagnosis of PD to be made[19].

Notably, FBG <100 mg/dL and ≥140 mg/dL were associated with an increased risk of PD. The association was significant even after adjustment for confounders. Hypoglycemia, along with hyperglycemia, is also known to be an indicator of the severity of diabetes[10]. There was a J-shaped association between the risk of PD and glycemic control, with both the too-low and high FBG showing a higher risk of PD. Both high and low HbA1c levels outside the window of euglycemia have been associated with faster motor symptom progression in PD[20]. The magnitude of risk in our study was greater in younger subjects whereby genetic factors may exert relatively more of an effect. The association in elderly patients may be the consequence of disrupted insulin signaling secondary to lifestyle and environmental factors causing cumulative pathogenic brain changes[21]. Whether attributable to genetic predisposition, environmental factors, or both, disrupted brain insulin signaling could lead to shared dysregulated cellular pathways, including neuroinflammation, microglia activation, mitochondrial dysfunction, and increased oxidative stress, which ultimately promote synuclein aggregation and contribute to the development of PD[21]. This concept is supported by a higher risk among those with diabetes complications and those with long duration of type 2 DM. Our study is characterized by a focus only on patients with type 2 DM. Within patients with type 2 DM, we found the risk of PD increased in severe or complicated type 2 DM.

There is still no universal agreement on the optimal data needed to create a reliable diabetes severity measure, despite the presence of some diabetes-specific severity indices[10]. The clinical manifestations of more severe diabetes are a consequence of diverse and complex pathophysiological processes affecting different organ systems over time, making it difficult for a single severity measure to capture this complexity adequately[10]. Prior studies on diabetes severity used a grading system based on diabetes-related complications and glycemic control measures[10]. Some studies considered the type or patterns of prescribed therapies as a proxy for higher diabetes severity[8,22,23]. The complexity of treatment and the use of multiple antidiabetic drugs are also used as indicators of severity[8,22,23]. It was also reported that the use of more than three OHAs was associated with a 13% increased risk of new DM complications compared to the monotherapy (Relative risk 1.13, 95% CI 1.10–1.17)[24]. A short duration of diabetes was usually defined as 0–6 years and a long duration of diabetes was generally defined as ≥8–10 years. There is always some uncertainty about the duration of a diabetic state prior to diagnosis, and with a known duration over 5–6 years, reversal of type 2 DM after bariatric surgery or intensive weight management intervention was less likely to occur[22,25]. It was reported that for each 5-year increase in the duration of diabetes, the multiple adjusted risks of macrovascular events and all-cause death were increased by 13 and 15%, respectively[26]. Moreover, we previously reported a 62% increased risk of PD in the diabetic duration ≥5 years group compared to the non-diabetic group[2]. Patients with type 2 DM requiring insulin therapy are considered to display one of the indicators of severe diabetes[10,27]. In one study, the severity of type 2 DM was categorized into four levels using an automated algorithm based on two domains: insulin use and the presence of DM complications[27]. Therefore, the severity of DM was evaluated in terms of the number of OHAs ≥3, duration of diabetes ≥5 years, or insulin use.

This study had some limitations. First, this was an observational study. Therefore, the association found between the stratification

Table 3. The risk of Parkinson's disease according to the diabetes severity score.

	Total	Events (*n*)	Incidence rate (per 1000 person-years)	Model 1	Model 2
Total population					
0	1,221,120	5378	0.640	1 (ref.)	1 (ref.)
1	583,678	4667	1.153	1.22 (1.17, 1.27)	1.09 (1.04, 1.15)
2	332,552	3485	1.527	1.48 (1.41, 1.54)	1.28 (1.22, 1.35)
3	153,646	2141	2.076	1.84 (1.75, 1.93)	1.55 (1.46, 1.65)
4	55,942	1052	2.927	2.43 (2.28, 2.60)	1.96 (1.82, 2.11)
5	13,663	282	3.385	2.69 (2.39, 3.04)	2.08 (1.83, 2.36)
6	1471	41	4.846	3.67 (2.70, 4.99)	2.78 (2.05, 3.79)
Men					
0	769,185	2833	0.538	1 (ref.)	1 (ref.)
1	328,400	2236	0.990	1.22 (1.15, 1.29)	1.09 (1.01, 1.17)
2	176,952	1581	1.320	1.44 (1.35, 1.53)	1.24 (1.15, 1.35)
3	75,135	905	1.837	1.77 (1.64, 1.91)	1.48 (1.36, 1.63)
4	25,592	426	2.682	2.35 (2.12, 2.61)	1.89 (1.69, 2.12)
5	5964	105	3.047	2.57 (2.11, 3.12)	1.98 (1.61, 2.42)
6	598	13	3.986	3.24 (1.88, 5.58)	2.44 (1.41, 4.22)
Women					
0	451,935	2545	0.81148	1 (ref.)	1 (ref.)
1	255,278	2431	1.35926	1.22 (1.15, 1.29)	1.10 (1.02, 1.19)
2	155,600	1904	1.75594	1.50 (1.41, 1.59)	1.32 (1.23, 1.42)
3	78,511	1236	2.29444	1.88 (1.75, 2.01)	1.62 (1.49, 1.75)
4	30,350	626	3.12195	2.47 (2.26, 2.70)	2.02 (1.83, 2.23)
5	7699	177	3.62248	2.76 (2.37, 3.22)	2.17 (1.85, 2.54)
6	873	28	5.3852	3.93 (2.71, 5.71)	3.02 (2.08, 4.40)

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, BMI, alcohol drinking, smoking, regular exercise, hypertension, dyslipidemia, and depression.

parameters and endpoints may not be causal. To minimize the possible effects of reverse causality, we excluded those individuals with incident PD during the first year of follow-up. Second, because the identification of PD was based on nationwide claims data, we could not obtain clinical information and imaging findings. Third, the influence of other diabetic complications (e.g., diabetic neuropathy) could not be evaluated properly. The insurance claim database does not provide accurate diagnostic information for diabetic neuropathy. We did not study data on HbA1c or postprandial glucose levels, since it is difficult to conduct these tests for all participants in a mass screening program. Fourth, patients with severe or complicated diabetes are more likely to have increased contact with healthcare and this could result in bias from increased medical surveillance. Lastly, diabetes severity score was calculated by assigning equal weighting to all components in the overall score. This could be a limitation in this study without providing the reliability and validity of the scoring scheme. Both the Diabetes Complications Severity Index (DCIS), capturing the type and severity of complications, and a simple count of diabetes complications were similarly strongly associated with mortality and hospitalization in patients with type 2 DM[28]. According to the study on diabetes severity in the UK, the predictive value of simple count scores using 29 diabetes-related domains was slightly higher than the severity-weighted score[29].

In conclusion, our study consolidates the evidence that diabetes severity constitutes risk factors for PD in a population with DM. The strength of this study is the accurate diagnosis of PD using the V124 special code along with the ICD-10 diagnostic code based on the characteristics of the Korean health insurance system. Moreover, we conducted this study with a large number of subjects using a well-established and validated longitudinal national database with a 7-year follow-up. However, longer follow-up duration may reduce the possibility of reverse causation and support a temporal relationship between diabetes severity and the risk of PD. A novel finding is that the risk of PD increases as the diabetes severity score, which is measured by the increased complexity of diabetes medications, the duration of diabetes, and the presence of complications. Careful monitoring of neurological symptoms related to PD seems to be helpful for patients with progressive diabetes. Further studies are warranted to examine whether control of diabetes and its complications can decrease the risk of PD.

METHODS

Data source and study population

The National Health Insurance Service (NHIS) computerized database includes data for most of the Korean population, such as all insurance claims and most medical information. The NHIS database contains information regarding healthcare use, demographic characteristics, diagnostic data, procedures, and drug prescription records. The database also contains data from the registration program for rare and intractable diseases (V-code). The NHIS covers employees and regional insurance subscribers. All examinees were requested to have biannual health checkups, except nonoffice workers who are employee subscribers (annual health checkups). The results from these health examinations are compiled into preventive health checkup datasets, which constitute the largest nationwide cohort database of laboratory information in Korea[30–33].

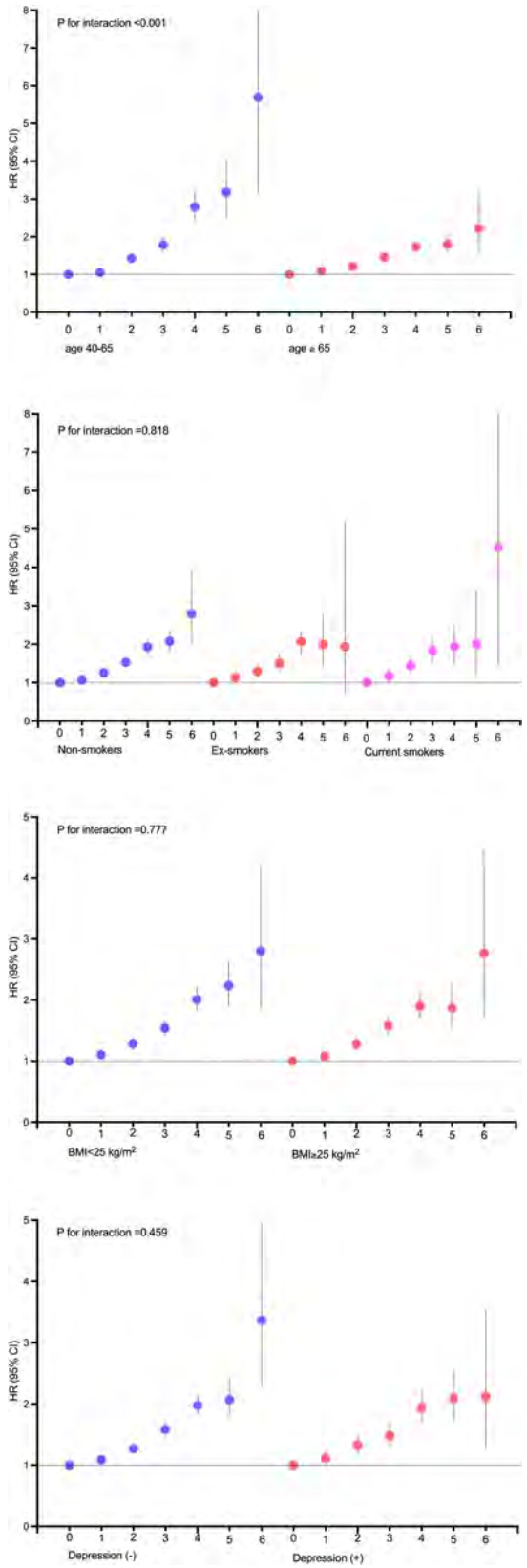

Fig. 2 Subgroup analyses of the association between the diabetes severity score and risk of Parkinson's disease stratified by age, smoking status, obesity, and the presence of depression. Hazard ratios and 95% confidence intervals of Parkinson's disease by the diabetes severity score. Adjusted for age, sex, body mass index, alcohol intake, smoking, regular exercise, hypertension, dyslipidemia, and depression.

From the NHIS database, we selected individuals with type 2 DM aged 40 years and older who had undergone health examinations provided by the NHIS at least once from January 1, 2009, to December 31, 2012. We excluded subjects with any missing data and those who were diagnosed with PD prior to enrollment. To avoid confounding by preexisting disease and to minimize the possible effects of reverse causality, those with a new diagnosis of PD during the first year of follow-up or those who died during the first year of follow-up were also excluded. A total of 2,362,072 subjects (1,381,826 men and 980,246 women) were included in the study population and were followed until their date of death or December 31, 2018, whichever occurred first (Supplementary Fig. 1). This study was approved by the Institutional Review Board of the Soongsil University (IRB approval number: SSU-202003-HR-201). Deidentified information was used for analysis; therefore, informed consent was not required.

Primary outcome

The primary outcome was the first recording of a diagnosis of PD after the index date, as identified by the International Classification of Disease (10th Revision [ICD-10]) code (G20) and the registration code (V124) for PD, which are assigned by neurologists or neurosurgeons. Since 2006, the South Korean government has operated a rare intractable diseases (RID) registration program (V-code). Patients who met the diagnostic criteria with physician certification were offered up to a 90% copayment reduction after RID program registration. Because the NHIS could refuse to pay hospital costs if a diagnosis did not meet specific criteria, cases are reviewed by medical institutions prior to submission to the NHIS and a reliable diagnosis can be presumed[30].

Data collection and definitions

The health examination provided by NHIS includes anthropometric and laboratory measurements. The general medical examination includes a survey of medical history, family history, lifestyle factors, blood pressure measurement, blood sampling, and urinalysis. Blood samples for the measurement of serum glucose and lipid levels were obtained after an overnight fast. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Information on smoking and alcohol consumption (heavy alcohol consumption defined as ≥30 g/day) was obtained using a questionnaire. Type 2 DM was defined according to the ICD-10 codes E11–14 for type 2 DM as either the principal diagnosis or the first to fourth additional diagnoses, and the prescription of one antidiabetic drug in each year or fasting glucose level ≥126 mg/dL. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. CVD was defined as prior myocardial infarction or prior stroke, diagnosed with one or more inpatient or outpatient records of ICD-10 codes within 3 years before the index date. Diabetic retinopathy (DR) was defined by the ICD-10 code H36.0 during hospitalization or this code having been recorded at least twice in an outpatient setting among patients with type 2 DM. DR was defined as an ICD-10 code within 3 years before the index date.

Definition of diabetes severity score

The diabetes severity score parameters used in this study were: the complexity of diabetes medications (i.e., insulin use or multiple OHAs), longer duration of diabetes, DR, diabetes-related renal complications (i.e., CKD), or presence of CVD. Each of these characteristics was treated as one unit of diabetes severity and their sum was defined as the diabetes severity score (0–6). If the number of OHAs in use was ≥3, a diabetes severity score of 1 was recorded, and if the diabetes duration was ≥5 years, a diabetes severity score of 1 was recorded. For example, a subject who uses insulin and has CKD has a diabetes severity score of 2. To identify

the effect of blood sugar itself on incident PD, we also analyzed the risk of PD according to the 10 mg/dL interval of FBG levels.

Statistical analysis

Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA), and a P value <0.05 was considered significant. The baseline characteristics of the subjects are presented as the mean ± standard deviation or n (%). Subjects were classified into seven groups according to their diabetes severity score. The incidence rate of PD was calculated by dividing the number of incident cases by 1000 person-years. The cumulative incidence of primary outcomes according to the diabetes severity score was presented using unadjusted Kaplan–Meier curves, and the log-rank test was performed to analyze differences between groups. Cox proportional hazards analyses were performed to evaluate the association of diabetes severity score or its stratification parameters with incident PD, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Model 1 was adjusted for age and sex. Model 2 was further adjusted for smoking status, alcohol intake, regular exercise, BMI, hypertension, dyslipidemia, and depression. Given the exploratory nature of this study, no adjustments were made for multiple comparisons. The potential effect modification by age, sex, obesity, and depression was evaluated using stratified analysis and interaction testing using a likelihood ratio test.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY

The datasets for this study are owned by the Korea NHIS (https://nhiss.nhis.or.kr/). There are no current sharing agreements, and data were held under a data use contract with the Korea NHIS.

CODE AVAILABILITY

No previously unreported custom computer code or algorithm was used to generate results in this study.

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AUTHOR CONTRIBUTIONS

K.H. and M.K.K. contributed to the concept and design of the study. B.K. and K.H. performed the statistical analysis. B.K., K.H., and M.K.K. wrote the manuscript and

S.H.L. edited the manuscript and contributed to the discussion. All authors critically revised and approved the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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