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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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