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Improved HOMA-IR Insulin Sensitivity and Glycemic Control Utilizing Physiologic Insulin Resensitization

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Abstract

Type 2 diabetes (T2DM) is a chronic metabolic disorder resulting in the inability to regulate glucose metabolism due to either insulin resistance, the lack of insulin secretion or both. Unfortunately, new cases of diabetes continue to rise globally mainly due to the increase in obesity. Left untreated, chronic hyperglycemia can result in devastating micro and macrovascular complications such as heart disease, stroke, kidney failure, blindness, and diabetic neuropathy. A hallmark of T2DM is progressive insulin resistance and metabolic dysfunction that plays a central role in the myriad complications found in this condition. A simple measure of insulin resistance is calculated with the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). It is calculated according to the formula: fasting glucose (nmol/L) X fasting insulin (microU/L)/22.5. Greater than 1.9 indicates early insulin resistance, while greater than 2.9 indicates significant insulin resistance. Reversing insulin resistance, in the setting of T2DM, may play a critical role in improving the complications of this chronic disease. As such, physiologic insulin resensitization (PIR) has been used as a novel approach to treat patients suffering from progressive insulin resistance and later stage complications of T2DM. In this case study, we present a case series of T2DM patients that who improved HOMA-IR and A1C glycemic control utilizing PIR.

Keywords: Diabetes; Insulin resistance; Insulin sensitivity; Physiological Insulin Resensitization; PIR; HOMA-IR.

Introduction

Diabetes is a chronic disease affecting more than 30 million Americans resulting in the inability to regulate glucose metabolism [1]. The two most common forms are type one diabetes (T1DM) and type two diabetes (T2DM). T1DM is an autoimmune condition that targets and destroys insulin-producing beta cells of the pancreas leading to very little or no insulin being produced. T2DM is a condition where glucose is not able to enter cells from either resistance to secreted insulin on a background of decreased beta cell mass in the pancreas [2]. T2DM is frequently associated with obesity and which may be associated with reversal in hyperglycemia with aggressive and early use of metformin, thiazolidinediones or GLP-1 agonists; or if significant weight loss can be achieved pharmacologically or via gastrointestinal procedures like gastric sleeve or Roux n Y surgeries [3]. Currently, T2DM can be treated by diet and exercise, oral medications such as metformin, TZD, DPP4, sulfonylureas, SGLT2 inhibitors, bromocriptine agonists and one GLP1-RA as well as injectable incretins such as GLP-1 and GLP/GIP, and since 1921, insulin. Except for the TZDs and perhaps

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the incretins, none act to reduce the core problem of insulin resistance with T2DM [4, 5]. Additional modalities that improve insulin resistance may allow the return of insulin to its physiologic action and decrease widespread damage to multiple tissues. As the incidence of T2DM continues to rise, many are seeking ways to develop newer strategies to manage the progression of the disease. Finding additional ways to treat diabetes continues to be a growing challenge because many of the medications used by T2DM patients cause side effects or do not completely normalize glucose or are cost prohibitive [3-5]. These challenges have led to the development of a novel therapy using ultra small doses of insulin intravenously in attempts to mimic the body's normal release of insulin to treat diabetes [7, 8]. Physiologic Insulin Resensitization (PIR) uses precision dosing patterns of insulin consistent with normal hormone secretion and more closely resembles the body's natural signaling pathway. As part of the pathophysiology of T2DM, hyperinsulinemia worsens and self-perpetuates insulin resistance [7-13]. PIR avoids the overexposure to sustained elevated insulin and may allow downregulated insulin receptors to return to normal levels [14-15]. As the patient's insulin resistance improves, current medications including insulin may be reduced or eliminated.

In this case study we report on the improvement in diabetic neuropathy symptoms and changes in HOMA-IR in 12 patients at two separate clinical sites who received PIR treatment over a period of at least 3 months where baseline HOMA-IR and A1c were compared to post-treatment assessments of these diabetic markers.

Methods

Development of Physiologic Insulin Re sensitization (PIR)

In our study, we explore a novel therapeutic protocol that utilizes precision insulin dosing as an adjunct in treating the systemic complications of diabetes by following improvements in HOMA-IR utilizing PIR. This modality has the potential to produce a material improvement in current diabetic care by more closely patterning the body's own method of regulating insulin. This treatment employs precision dosing of fast acting IV insulin in an attempt to approximate the normal physiologic insulin signaling pathways [7,8,14]. The goal of PIR is to counter the negative feedback of aberrant insulin messaging which may minimize the negative effects of unopposed glucagon that leads to decreased insulin receptor expression [9,10]. This treatment is focused on transforming the way diabetes is managed via symptom suppression by adding a potent adjunctive companion method to overcome insulin resistance and may improve carbohydrate metabolism. Employing this patient specific precision IV insulin dosing, the objective is to improve insulin response at the 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. Additionally, oral glucose is administered at individualized intervals to stimulate the digestive system and trigger metabolic activity. With the potential improvement in carbohydrate metabolism, insulin resistance may diminish and consequently improve cellular energy stores to promote tissue growth, repair, and regeneration [14].

The PIR precision dosing pattern of insulin is consistent with normal hormone secretion and more closely approximates the body's natural signaling pathways. Modulating insulin receptor response is a multifaceted process to attempt to overcome the dysfunction of insulin response in T2DM. As the patient's insulin resistance improves, healthcare providers can titrate other medications to optimize treatment regimens. In general, PIR may permit lowering dosing of subcutaneous insulin and other diabetes medications which often promote the secretion of insulin or inhibit the production of glucose.

Weekly treatment plan

PIR treatment is administered in two-to-three hour infusion sessions, beginning twice weekly for one to four weeks, and then changing weekly for an additional 10-12 weeks, after which a set of follow-up labs are drawn to compare with a patient's baseline. From there, qualified medical professionals in the clinic determine whether a patient follows a more typical treatment path of one infusion every two weeks or if the patient requires another 12 weeks of weekly treatments before another evaluation. Biweekly treatments typically continue for additional three months with re-evaluations, and then further spacing of treatment frequency and length of treatment is determined based on the patients' level of response and health outcomes.

HOMA-IR

HOMA-IR stands for Homeostatic Model Assessment of Insulin Resistance. The HOMA calculation addresses the presence and extent of any insulin resistance experienced by diabetic patients [16,17] TheBloodCode.com is used to plug in values and obtain the HOMA calculation [18]. A Low HOMA-IR indicates greater insulin sensitivity; conversely, a higher HOMA-IR relates to a higher degree of insulin resistance. The higher the number, the more resistant an individual is to insulin. Patients with HOMA-IR value above 2 will need changes in medical approach and health habits to bring the number down into the lower insulin-sensitive range.

Results

Summary of Results

We collected HOMA and A1c data from 12 patients (ages 50-80 years old) before and after PIR treatment (Table 1). As can be seen in Table 1, baseline HOMA was much

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higher in patients before PIR treatment. HOMA decreased approximately 20-40% across patients post PIR treatment. Additionally, A1c was much higher in patients prior to PIR treatment whereas A1c decreased (5-40%) in patients post-PIR treatment.

Specific Case Reports

C.D. is a 73-year-old female with diabetes who presented with severe neuropathy and sleeplessness. Her initial labs reported a HOMA-IR score of approximately 4.4 and an HbA1c of 7.6. These numbers indicated that she showed insulin resistance prior to beginning treatment. The labs also reflected an eGFR of 34mL/min/1.73m3, indicating that she had been diagnosed with Diabetic CKD stage 3b. She began receiving PIR treatment biweekly for the first 3 months. At her first follow-up evaluation, she reported improved neuropathy and better sleep. In that time, her A1c decreased to 7.2 and her HOMA- IR score dropped to 2.8, a 36% decrease in 3 months. Her eGFR improved to 53 mL/min/1.73m3 in that same time period. She continued on treatment and has presently been on active treatment for over a year, maintaining weekly treatments with immediate plans to transition to biweekly treatments. In that year, her HOMA-IR score has continued to decrease, and her most recent labs in September 2023 has been reported at 0.5. This is an 89% decrease over the course of the last year, and places her now in the category of "insulin sensitive." She has continued to see improvements in her neuropathy and sleep and has expressed satisfaction and appreciation for being referred into the PIR treatment program.

S.G. Is a 72-year-old male with diabetes who presented for PIR in January 2021. He had an A1c of 8.5 and a HOMA-IR score of 8.28 in his baseline labs, indicating he was insulin resistant. His chief complaint upon beginning the treatment was painful neuropathy. He was on several daily medications, including 500mg of Invokana, 300mg of gabapentin, 18u of Tresiba, and 5mg of Eliquis upon beginning PIR treatment. After 8 months of treatment, this patient's HOMA IR decreased to 4.3, a drop of 46%, as well as a decrease in HbA1c of approximately 7%. He has reported drastic improvements in energy and well-being, as well as an improvement of his neuropathy symptoms. This patient is today active on PIR for 33 months and in that time has completely eliminated Invokana and Eliquis from his medications and has reduced gabapentin utilization to 100mg per day and Tresiba to 15u per day. This patient is presently receiving one three-hour infusion every three weeks, with plans to transition to monthly infusions as his symptoms continue to improve.

S.N. is a 72-year-old male who was diagnosed with T2D in 2014. The diagnosis was made through a routine exam with his primary care provider. He presented to the clinic in October of 2019 with concerns regarding elevated blood sugars and worsening neuropathy in his feet. He had prediabetes for a number of years with metabolic disorder before his diagnosis of T2D. He states that his last Hb A1c at that time was around 6. He was not checking daily blood sugars and denied any hypoglycemic events biased on symptoms. He was prescribed Glimepiride and felt like it worked well to control his blood sugars; however he was not consistent

Table 1: Summary of HOMA-IR Case Series Results

Patient	Baseline HOMA	Post-PIR HOMA	Baseline A1C	Post-PIR A1C
52 y/o Female	21.8	12.6 (-42%)	6.7	5.9 (-11.9%)
57 y/o Male	16.8	11.4 (-32%)	11.4	10.9 (-4.4%)
60 y/o Female	14.8	11.3 (-24%)	6.9	6.4 (-7.2%)
63 y/o Female	6.9	4.0 (-42%)	8.7	7.5 (-13.8%)
64 y/o Male	19.8	4.4 (-78%)	8.1	6.5 (-19.8%)
71 y/o Female	16.2	13.2 (-19%)	6.8	6.1 (-10.3%)
72 y/o Male	8.3	3.4 (-59%)	8.5	8.2 (-3.5%)
73 y/o Male	4.4	2.8 (-36%)	7.6	7.2 (-5.3%)
74 y/o Female	8.3	3.2 (-61%)	8.5	6.5 (-23.5%)
76 y/o Female	10.9	7.7 (-29%)	11.8	7.6 (-35.6%)
77 y/o Male	27	16.6 (-39%)	7.5	6.4 (-14.7%)
88 y/o Female	8.3	3.4 (-59%)	8.5	8.2 (-3.5%)

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in taking this medication because he had GI side effects. His neuropathy was described as constant numbness all over his feet with intermittent tingling sensations. He reports having progressive neuropathy symptoms in his feet for the past 15 years. He feels like the last 6 months his neuropathy has progressed rapidly. Patient denied any amputations or history of lower leg ulcers or wound healing problems. Initial exam revealed an overweight (210 lbs., BMI 28 kg/m2) male with blood pressure of 157/84 mmHg and pulse of 59 bpm. Lower extremity exam revealed normal- looking feet with all skin intact. Pt had loss of sensation on the balls of feet to the toes and on the tops of his feet bilaterally with monofilament testing. Vibratory sensation was present. Laboratory testing revealed and HbA1c of 7.5% (normal < 6.5%); serum insulin 54 uIU/mL (normal 2.6-24.9 uIU/mL); c-peptide 7.1 ng/mL (normal 1.1-4.4ng/mL). CMP was within normal limits with the exception of a fasting blood sugar of 202 mg/dL (normal 65-99 mg/dL) and elevated liver AST 59 IU/L (normal 0-40 IU/L); ALT of 70 IU/L (normal 0-44 IU/L). Lipid panel was elevated with total cholesterol high at 222 mg/dL (normal 100-199mg/dL), and triglycerides high at 328 mg/dL (normal 0-149 mg/dL). Vitamin D level is low at 22.4 ng/mL (normal 30-100ng/mL). Patient had normal TSH, urinalysis, magnesium and vitamin B12. Prescribed medications included glimepiride, lisinopril, pravastatin, and zolpidem. After the patient had completed a few PIR treatments he noticed that he was feeling better and had more energy. Patient stated, "I haven't felt this good in a long, long time". He obtained a glucometer and has been checking and recording blood sugars regularly. He was reporting his FBS to be around 140-160. He had repeat laboratory testing at 6 months after initiating weekly PIR treatments. His HbA1c improved to 6.4% which was previously 7.5%, other labs that improved were fasting glucose 165 mg/dL, c-peptide 6.1 ng/ml and insulin 40.8 uIU/mL. His HOMA score improved from 27 to 16.6. A few months into his PIR treatments he noticed increased sensations in his feet where it was previously numb. He also reported that he could feel the inside of his shoes, which he hasn't been able to do in a long time. Patient stated, "I noticed I could feel my socks and I could feel the rocks when I stepped on them". He has noted a significant improvement in his neuropathy since beginning treatments. His most recent monofilament test revealed increased sensation on the balls of his feet and toes bilaterally. His left foot almost had full sensation.

R.E. is a 57-year-old male who was diagnosed with T2DM in 2015. The diagnosis was made during a routine exam with his primary care provider. He presented to our clinic in April of 2020 with health concerns regarding elevated blood sugars, lower leg neuropathy and obesity. Diabetic complications included uncontrolled blood sugars, neuropathy, hyperlipidemia, and hypertension. He also has associated symptoms of urinary frequency and polydipsia. His Hemoglobin A1c results typically ranged over 11%. He did not check his blood glucose regularly. He initially started on Metformin in 2015 but stopped it soon after due to side effects. When presented to the clinic he was not taking any diabetic medications. His neuropathy was described as numbness and tingling in feet and he had noticed some symptoms starting on his hands as well. He did not have any history of amputations or ulcers on his feet. Initial exam revealed an obese 250-lb. male with a blood pressure 149/95 mmHg and a pulse of 86 bpm. Lower extremity exam showed he had full sensation throughout both feet bilaterally with monofilament testing. Laboratory testing revealed HbA1c of 11.4 (normal < 6.5); serum glucose of 377 (normal 65-99); urinalysis showed 3+ glucose (normal negative). Patient had a normal complete blood count, c-peptide, insulin, and albumin/creatinine ratio. Pt was not taking any prescribed medications at that time. Within a few weeks of beginning PIR treatments, the patient began to notice improvement in energy, blood sugar control and neuropathy. Fasting blood sugars were improving, now in the 320s from the 400s prior to beginning treatment. Patient states, "I am already starting to feel an improvement." He noted that his energy has been better and also feeling "a little bit of change" in his feet. After 3 months of treatments labs were drawn to see progress. His CMP showed a fasting glucose of 310 which was down from 377. HbA1c was 10.9, down from 11.4. HOMA score was 12.5, down from 16.8 indicating improved insulin sensitivity. Kidney function had improved, with electrolytes and liver function within normal limits. Creatinine has improved to 1.0, down from 1.18. GFR is 83, up from 68 and Albumin/creatinine ratio is 12. Patient states that "it feels like treatments are helping." Unfortunately, this patient did not continue treatments and stopped treatments at about 5 months.

In addition to the four cases above, the clinics in St. Augustine and Utah also reported eight additional patients who have each been on PIR for a minimum of 6 months. Those patients reported over their active treatment period an average decrease in their HOMA IR of 42% over that 6-month period, as well as an average decrease in their HbA1c of 13% over the same period. All patients were on their individualized PIR treatment plan as determined by the presiding physicians in the clinics.

Discussion

As previously reported in Villaverde et al. [19] using PIR that three patients improved their kidney function after 5-6 months based on their laboratory metrics and chronic kidney disease (CKD) stage classification. Their blood-urea-nitrogen (BUN) showed a mean improvement from 27 to 13 mg/d and their creatinine from 1.7 to 1.2 mg/dL. Their estimated glomerular filtration rate (eGFR) increased from 33, 34, and 54 to 55, 42, and 74 cc/min, respectively. Dailey et al. [14] in a multicenter, prospective controlled trial followed 23

patients receiving pulsatile insulin for 18 months as well as 26 from 33, 34, and 54 to 55, 42, and 74 cc/min, respectively. HOMA-IR is a measure of insulin resistance that relies on insulin load and glucose testing [16, 17]. In these patients, we observed an effective decrease of HOMA-IR by 20-40% after PIR treatment. While none of the patients' HOMA-IR reached healthy threshold yet [17], it still indicates the efficacy of PIR in improving insulin sensitivity. It's not yet known what duration of PIR treatment would restore insulin sensitivity fully, which will be the subject of future studies, especially with patients of less severe diabetes stage.

Conclusion

PIR is an adjunct treatment approach that has been shown to improve outcomes and secondary complication of patients with progressive Type 2 diabetes. It was the focus of this case report to specifically describe the improvement in HOMA-IR and HbA1c following 6 months of PIR treatment. This case study reports positive outcomes and improvements in insulin sensitivity and other markers of diabetes over the evaluation period. Future studies include prospective randomized controlled trials in a larger cohort of type 2 diabetic patients. These outcomes further support use of the PIR approach and maybe considered evidence of its improvements in diabetic markers in patients with Type 2 diabetes.

Declaration

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Conflicting Interests: Brian Loveridge Natalie Parkin, and Shelly Messerly are employees of Diabetes Relief Utah, which performs PIR treatment. Zach Villaverde is a contracted consultant for Island Doctors, which performs PIR treatment and Well Cell Global, which holds patents for PIR technology.

Ethics Approval: Not applicable.

Consent to Participate: Not applicable

Consent for Publication: Not applicable

Code Availability: Not applicable

References

1. American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care 41 (2018): 917-928.
2. Satin LS, Butler PC, Ha J, Sherman AS. Pulsatile insulin secretion, impaired glucose tolerance and type 2 diabetes. Mol Aspects Med 42 (2015): 61-77.
3. Buse JB, Harmel M. New Diabetes Drugs in Development. (2017).
4. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomized placebo-controlled trial. Lancet 394 (2019): 121-130.
5. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 380 (2019): 347-357.
6. Qaseem A, Wilt TJ, Kansagara D, et al. Hemoglobin A1c Targets for Glycemic Control with Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update from the American College of Physicians. Ann Intern Med 168 (2018): 569-576.
7. Lang DA, Matthews DR, Peto J, et al. Cyclic oscillations of basal plasma glucose and insulin concentrations in human beings. N Engl J Med 301 (1979): 1023
8. Hunter SJ, Atkinson AB, Ennis CN, et al. Association between insulin secretory pulse frequency and peripheral insulin action in NIDDM and normal subjects. Diabetes 45 (1996): 683-686.
9. Meier JJ, Veldhuis JD, Butler PC. Pulsatile insulin secretion dictates systemic insulin delivery by regulating hepatic insulin extraction in humans. Diabetes 54 (2005): 1649- 1656.
10. Polonsky KS, Given BD, Hirsch LJ, et al. Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. N Engl J Med 318 (1988): 1231-1239.
11. O'Rahilly S, Turner RC, Matthews DR. Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. N Engl J Med 318 (1988): 1225-1230.
12. Schofield CJ, Sutherland C. Disordered insulin secretion in the development of insulin resistance and Type 2 diabetes. Diabet Med 29 (2012): 972-979.
13. Bertram R, Satin LS, Sherman AS. Closing in on the Mechanisms of Pulsatile Insulin Secretion. Diabetes 67 (2018): 351-359.
14. Greenway F, Loveridge B, Grimes RM, et al. Physiologic Insulin Resensitization as a Treatment Modality for Insulin Resistance Pathophysiology. Int J Mol Sci 23 (2022): 1884.
15. Dunn K, Hayes D, Petersen S, et al. Insulin Infusion Therapy on Diabetic Complications, Medications, Quality of Life, Hemoglobin A1C, and Metabolic Functioning: Retrospective Analysis. Houston, TX: Schull Institute (2015).

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DOI:10.26502/acmcr.96550644

16. Qu HQ, Li Q, Rentfro AR, et al. The Definition of Insulin Resistance Using HOMA-IR for Americans of Mexican Descent Using Machine Learning. PLoS One 6 (2011): 21041.

17. Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. BMC Endocr Disord 47 (2013).

18. The Blood Code. HOMA IR – Insulin Resistance Calculator (2023).

19. Villaverde Z, Tucker T, Alexander M, et al. Improved Kidney Function Following Physiologic Insulin Resensitization Treatment Modality. Endocrinology and Disorders 5 (2021): 1-4.

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