Effect of Physiologic Insulin Resensitization Therapy in Patients with Diabetes

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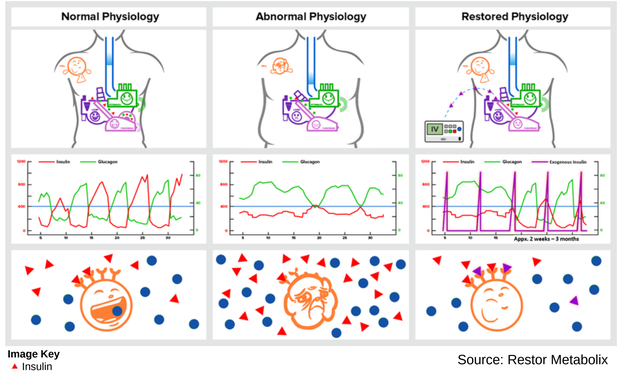
Background

Diabetes Mellitus (DM) is one of the fastest growing and most financially burdensome illnesses worldwide. According to the Centers for Disease Control and Prevention (CDC), around 14.7% of the adult U.S. population (37.1 million) have DM, and another 38% (96 million) of U.S. adults have prediabetes[1]. Additionally, DM can lead to various complications, including diabetic peripheral neuropathy (DPN) and lower-limb amputations, cardiovascular disease (CVD), and diabetic kidney disease (DKD)[2,3].

The pathophysiology behind Type 2 Diabetes Mellitus (T2DM) can be attributed to lack of insulin secretion over time and the development of insulin resistance (IR). Insulin is released by the pancreas in response to the body's need after ingestion of a carbohydrate meal[2]. This insulin is secreted in a period of intervals every four to eight minutes in the body and has characteristic "peaks" and "troughs"[4]. These "troughs" represent a rest period in which the insulin receptor is able to reset and prepare for its next activation in the insulin release cycle[5]. In T2DM, it is suspected that the insulin receptors are in a constant state of stimulation, leading to a down-regulation of the insulin receptors, which can lead to a decrease in glucose re-uptake in the body[3]. Chronic hyperglycemia has the greatest effect on pancreatic β cells and vascular endothelial cells[6]. β cell dysfunction can lead to a further increase in insulin down-regulation and a decrease in overall insulin synthesis. In addition, chronic hyperglycemia can lead to an increase in vascular related diabetic complications such as nephropathy, hypertension, neuropathy, and retinopathy[6]. In Type 1 Diabetes Mellitus (T1DM), pancreatic β cells are destroyed due to immune destruction, leading to an absolute deficiency in insulin[7].

Physiologic Insulin Resensitization (PIR) is a complementary therapy to traditional insulin medications that works by using intravenous insulin infusions that mimic normal insulin release in the body, ultimately administering insulin as a hormone rather than as a drug. The intravenous infusions work to simulate the body's normal physiological insulin cycle with infusions occurring every 4 to 8 minutes over a 2-to-4-hour session. These infusions work to upregulate insulin receptors in the body with the intention that glucose utilization will be more efficient and increase total ATP available in the body **(Image 1)**. Not only does this increase energy available to cells, but it will also help decrease oxidative stress as energy consumption would not be solely reliant on the breakdown of fats[4,5,8]. This study seeks to assess the effects of PIR on biomarkers that are associated with complications with DM such as hypertension, chronic kidney disease, and chronic hyperglycemia.

Image 1. Physiologic Insulin Resensitization



Source: Restor Metabolix

Methods

A four-site chart review was performed for all patients with DM who received PIR therapy from one of four Restor Metabolix clinics (Appling, Asheville, Athens, and Blackshear).There were 67 adult diabetic patients who were included in the analysis under the criteria of having at least 2 sets of lab work, the first taken prior to PIR therapy initiation and the last taken after subsequent treatment. Weight, Body Mass Index (BMI), Hemoglobin A1c (HbA1c), fasting glucose, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) were compared across the first and last visits. Time between first visit and last visit was measured. Continuous variables were measured as means and standard deviations, medians and interquartile ranges, and minimum and maximum values. Differences were calculated to represent the absolute change in patients' lab values between the first and last visits and were compared using the paired t-test or the Wilcoxon-signed rank test. The independent t-test and Wilcoxon rank-sum test were used to compare the difference in values by DM type, clinic location, and patient sex. Two-tailed tests were performed, and statistical significance was determined with a $p<0.05$. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Results

The average length of time in days between the first and last lab work collection in the clinic was found to be 129 days (±54.2). The distribution of DM type among patients was 10.4% T1DM, 83.6% T2DM, and 6% were diabetic due to another condition. Gender distribution of patients was 46.3% identifying as male and 53.7% identifying as female. Patient distribution among the four clinics were as follows: Appling (49.2%), Asheville (6.0%), Athens (20.9%), and Blackshear (23.9%). Three variables were found to have statistically significant changes between the first and last PIR visit **(Table 1)**. The median difference in HbA1c % was -0.4 (-0.9, 0.1) (p = 0.0006). The mean difference in systolic blood pressure in mmHg was -7.5 ±20.9 (p = 0.0257). The mean difference in weight in pounds was -2.9 ±7.3 (p = 0.0300). While the other metrics measured did not show statistically significant changes, a trend towards better health outcomes with respect to diastolic blood pressure, BMI, and eGFR was noted. There were no statistical differences between DM type, clinic location, or patient gender.

Table 1. Absolute change in values between first visit and last visit

Characteristic	First Visit	Last Visit	Difference	p-value[a]
HbA1c, % (n=53)				0.0006
Mean (SD)	8.1 (± 1.5)	7.6 (± 1.3)	-0.5 (± 1.1)	
Median (IQR)	7.9 (7.1, 8.8)	7.2 (6.6, 8.2)	-0.4 (-0.9, 0.1)	
Min, Max	5.7, 12.1	5.6, 11.8	-4.5, 1.4	
Fasting Glucose, mg/dL (n=41)				0.2152
Mean (SD)	171.3 (± 57.4)	155.9 (± 54.1)	-15.4 (± 71.9)	
Median (IQR)	156.0 (138.0, 182.0)	145.0 (116.0, 183.0)	-10.0 (-49.0, 22.0)	
Min, Max	93.0, 407.0	60.0, 299.0	-275.0, 123.0	
Systolic, mmHg (n=42)				0.0257
Mean (SD)	142.2 (± 23.2)	134.8 (± 19.6)	-7.5 (± 20.9)	
Median (IQR)	140.0 (123.0, 159.0)	131.0 (122.0, 150.0)	-8.0 (-24.0, 8.0)	
Min, Max	96.0, 200.0	100.0, 176.0	-45.0, 40.0	
Diastolic, mmHg (n=42)				0.0545
Mean (SD)	79.2 (± 10.0)	75.0 (± 10.9)	-4.2 (± 13.7)	
Median (IQR)	80.5 (70.0, 84.0)	73.0 (67.0, 82.0)	-2.0 (-15.0, 4.0)	
Min, Max	60.0, 99.0	57.0, 108.0	-33.0, 29.0	
BMI, kg/m^2 (n=36)				0.0601
Mean (SD)	35.7 (± 10.1)	35.3 (± 9.9)	-0.5 (± 1.5)	
Median (IQR)	34.5 (30.7, 38.4)	34.2 (30.2, 37.6)	-0.4 (-1.1, 0.1)	
Min, Max	17.5, 83.2	17.7, 79.6	-3.8, 3.9	
Weight, pounds (n=38)				0.0300
Mean (SD)	224.0 (± 46.8)	221.1 (± 47.3)	-2.9 (± 8.0)	
Median (IQR)	225.0 (200.0, 253.6)	221.7 (193.0, 262.2)	-2.9 (-6.0, 1.6)	
Min, Max	99.0, 358.0	100.0, 342.5	-24.0, 13.0	
BUN, mg/dL (n=25)				0.5898
Mean (SD)	18.4 (± 8.3)	19.2 (± 7.9)	0.8 (± 7.3)	
Median (IQR)	17.0 (13.0, 19.0)	16.0 (14.0, 22.0)	1.0 (-1.0, 5.0)	
Min, Max	10.0, 47.0	5.0, 38.0	-14.0, 17.0	
eGFR, mL/minute (n=19)				0.2243
Mean (SD)	74.5 (± 23.3)	76.9 (± 22.8)	2.4 (± 8.5)	
Median (IQR)	74.0 (58.0, 92.0)	82.0 (60.0, 96.0)	2.0 (-4.0, 9.0)	
Min, Max	26.6, 120.0	28.0, 113.0	-14.0, 18.0	

HbA1c = Glycated hemoglobin; BMI = Body Mass Index; BUN = Blood urea nitrogen; eGFR = Estimated Glomerular filtration rate; SD = Standard Deviation; IQR = Interquartile Range; [a] derived from Paired t-test or Wilcoxon-signed rank test

Conclusion

PIR therapy has the potential to provide better health outcomes for patients who suffer from DM due to insulin resistance[2,3]. Our data indicated statistically significant decreases in HbA1C, weight, and systolic blood pressure between patients' first and last visit at the clinic.

The limitations of this study include a small sample size due to all four clinics being open for less than a year, and inconsistent patient data for the different variables. In addition, there were inconsistent times between each patient's first and last visit.

Future studies should be conducted that look for trends in HbA1c, weight, BMI, blood pressure, eGFR, and BUN over a longer span of time than what we were able to conduct. Ideally any future studies would be prospective in nature and capture lab values at consistent, regular intervals. In addition, future research is needed to determine how PIR treatments affect neuropathy, energy levels, LDL, and c-peptide values.

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