Chapter 1
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Efficacy of Physiologic Insulin Resensitization as a Treatment for Insulin Resistance Pathophysiology

Frank Greenway [a], Brian Loveridge [b], Richard Marchase [b], Zach Villaverde [b], Carol Wilson [b], Michael Alexander [c], Scott A. Hepford [b] and Jonathan R. T. Lakey [c,d*]

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ABSTRACT

Diabetes was the eighth leading cause of death in the United States in 2021 based on the 103,294 death certificates in which diabetes was listed as the underlying cause of death. The prevalence of Type 2 diabetes mellitus (T2DM) has increased from 2.5% of the US population in 1990 and rose to 11.6% of the total US population, or 38.4 million people, in 2021. This chapter has three purposes such as exploring insulin resistance pathophysiology, addressing the role of the insulin receptor (InsR) in the regulation of glucose homeostasis; and reviewing literature for clinical outcomes and molecular mechanisms that support the use of Physiologic Insulin Resensitization (PIR) as an effective treatment to address IR, of which diabetes and its complications are the most common diagnoses. 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. Using physiologic insulin resensitization is a logical clinical solution to restore physiologic insulin function. The study also suggests that the

[a] Clinical Trials Unit, Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA.
[b] Wellcell Global, Houston Texas, USA.
[c] Department of Surgery, University of California Irvine, Irvine, California, USA.
[d] Department of Biomedical Engineering, University of California Irvine, Irvine, California, USA.
**Corresponding author: E-mail: jlakey@uci.edu;*

complications, hospitalizations, medication costs, and emergency room visits may be reduced using physiologic insulin resensitization.

Keywords: Diabetes; type 2; insulin therapy; diabetic complications.

1. INTRODUCTION

The prevalence of Type 2 diabetes mellitus (T2DM) has increased from 2.5% of the US population in 1990 and rose to 11.6% of the total US population, or 38.4 million people, in 2021. Of those 38.4 million, 29.7 million were diagnosed, 8.7 million were undiagnosed, and 97.6 million people aged 18 years or older had prediabetes [1]. This is an astounding 364% increase in 25 years.

Diabetes was the eighth leading cause of death in the United States in 2021 based on the 103,294 death certificates in which diabetes was listed as the underlying cause of death. In 2021, diabetes was mentioned as a cause of death in a total of 399,401 certificates. The cost of diabetes, which was updated on November 2, 2023, was:

- $412.9 billion: Total cost of diagnosed diabetes in the U.S. in 2022.
- $306.6 billion accounted for direct medical costs.
- $106.3 billion accounted for indirect costs.

After adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.6 times higher than what expenditures would be in the absence of diabetes [2].

The International Diabetes Federation's 10th edition of its IDF Diabetes Atlas (2021) is the current version of its work first published in 2000. It claims to be "the authoritative resource on the global impact of diabetes. It provides statistics on diabetes prevalence, diabetes-related mortality and health expenditure at the global, regional and national level." They conclude in their 10th edition that "diabetes is one of the fastest growing global health emergencies of the 21st century." In its "Diabetes Facets and Figures" section it states that by 2045, 1 in 8 adults, or about 783 million people, will be living with diabetes, which reflects an increase of 46%, and that more than 90 percent of people with diabetes have T2DM [3].

Indirect costs associated with diabetes include costs from workdays missed due to health conditions (absenteeism), reduced work productivity while working due to health conditions (presenteeism), reduced workforce participation due to disability, and lost productivity for those not in the workforce and due to premature mortality [4].

The current guidelines from the ADA 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 T2DM on Metformin AND diagnosed with EITHER heart failure (HF) OR chronic kidney disease (CKD), as

clearly discussed by Colling, et al., in Diabetes Care, Volume 44, Issue 6, June 2021 [4a]. They conclude that "[e]vidence from cardiovascular outcome trials of glucose-lowering medications demonstrates cardiac and renal benefits of GLP-1 RAs and SGLT2is, which are now recommended for patients with cardio-renal comorbidities independent of HbA1c." They add that "33% of primary care patients with T2DM would be recommended treatment with one of these classes based on strict comorbidity definitions," but that "further work is required to evaluate the uptake of new recommendations and to assess the need for additional support for providers caring for patients with diabetes to implement evidence-based therapy in a timely manner [5]." We urge a thorough review by practitioners.

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 2023. The ADA describes this work as "a set of comprehensive and evidence-based guidelines for managing type 1, type 2, gestational diabetes, and prediabetes based on the latest scientific research and clinical trials. It includes strategies for diagnosing and treating diabetes in both youth and adults, methods to prevent or delay type 2 diabetes and its associated comorbidities like cardiovascular disease (CVD) and obesity, and therapeutic approaches aimed at minimizing complications and enhancing health outcomes" [6]. Nowhere in the publication do we find a discussion of PIR to treat diabetes.

We also note that the Food & Drug Administration (FDA) has updated the content of its Drug Safety Communications as of January 19, 2024, and contains this item: "01-11-2024 Update on FDA's ongoing evaluation of reports of suicidal thoughts or actions in patients taking a certain type of medicines approved for type 2 diabetes and obesity." Another recent posting was: "FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections [7]."

Clearly, costs will rise, side effects and FDA warnings will always be prevalent, and disability will continue to occur with respect to diabetes and other forms of metabolic disorders. We submit, however, that a treatment named Physiologic Insulin Resensitization should be considered. This complimentary treatment seems to reverse the major underlying pathophysiologic mechanism that leads to T2DM with far fewer negatives, if any. This treatment is effective because it treats Insulin Resistance (IR), not just the individual manifestations of diabetes. Moreover, unlike other medications cited in the publications mentioned above, side effects are minimal [4a].

For nearly forty years researchers and clinicians have used treatment procedures that administer periodic infusions of insulin in ways that attempt to bio-mimic the non-diabetic's natural secretions and rest periods of insulin from the pancreas.

Published articles describe this treatment approach and have reported on various diabetic comorbidities. Although effective, the exact cellular and molecular mechanisms behind the use of infusions of insulin were previously not well understood. This chapter has three purposes: (1) To explore insulin resistance

pathophysiology; (2) to address the role of the insulin receptor (InsR) in the regulation of glucose homeostasis; and (3) review of literature for clinical outcomes and molecular mechanisms that support the use of Physiologic Insulin Resensitization (PIR) as an effective treatment to address IR, of which diabetes and its complications are the most common diagnoses.

2. THE RISE OF TYPE 2 DIABETES

In general, two main hypotheses were generated for the etiology and pathogenesis of type 2 diabetes (T2DM). The first hypothesis is that the development of IR is the underlying cause leading to manifestations of T2DM. IR causes hyperglycemia, which is the cause of most diabetic complications. IR also contributes to hyperinsulinemia, the over-production of insulin by beta cells. Over time, beta cells will be exhausted and die, which leads to further disease progression and more hyperglycemia. The second hypothesis is the defect in insulin secretion, which is well-reported in T2DM [4a,8].

As stated, T2DM is driven by IR. A common perception of T2DM 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 [9]. 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 T2DM [4a,10].

Therefore, an alternative explanation for the progression of T2DM 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 T2DM. In this chapter, we offer the hypothesis that it is an insulin secretion defect that drives the IT responsible for the pathophysiology of T2DM.

3. PHYSIOLOGIC HORMONE SECRETION

Insulin as a hormone is released from the pancreatic islet cells in an oscillatory pattern triggered by changes in circulating glucose and glucagon. Insulin's principal counter-regulatory hormone is glucagon, and together they regulate blood glucose concentrations [11]. Insulin mediates its actions through binding to insulin receptors [12]. A ligand is any atom or molecule attached to a central atom in a coordination or complex compound [13]. Insulin Receptors (InsR) 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 [4a]. When hormone receptors, designed to respond to the presence of its ligand, are exposed to constant stimulation with that hormone, the receptors down-regulate and become "tolerant" or "resistant" to stimulation. The InsR is a viable pharmacological target since glucose transport is inhibited in insulin resistance [14].

T2DM is driven by insulin resistance (IR) [15]. A common perception of T2DM progression is that the IR is countered by increasing insulin secretion until the islet beta cells in the pancreas can no longer keep up with the insulin demand and die progressively of exhaustion [16]. 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 T2DM [17,18].

Therefore, an alternative explanation for the progression of T2DM 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 T2DM. In this chapter, we offer the hypothesis that it is an insulin secretion defect that drives the IR responsible for the pathophysiology of T2DM.

Insulin is a naturally occurring hormone. Recent progress through cryoelectron microscopy has made it possible to describe the initial insulin ligand binding events in atomistic detail. Detailed interactions explain the insulin ligand binding pathway [19].

3.1 Physiologic Insulin Secretion

Physiologic insulin consists of discrete oscillatory secretions and distinct rest periods to stimulate ligand/receptor activation. The pancreatic beta cell secretes insulin with a dynamic periodicity of 4-8 minutes, and most commonly 5-6 minutes, based on the body's demands (Fig. 1) [20]. Beta cells in the islets are in close contact with 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 cadence [4a,21]. The insulin flux is responsible for the timing of glucagon secretion that occurs in a normally anti-synchronous fashion from the cycling of insulin [4a,22].

Measuring the patterns of insulin secretion 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 [23]. 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 [4a]. 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 [4a]. The deconvolution method of measuring the spike frequency from the peripheral blood depends on the differential kinetics of insulin and C-peptide [24]. [*Id.*]. 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 [4a]. 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 [4a,25]. 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 release decreases hepatic clearance of insulin leading to peripheral hyperinsulinemia [4a,26]. 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 [4a,27].

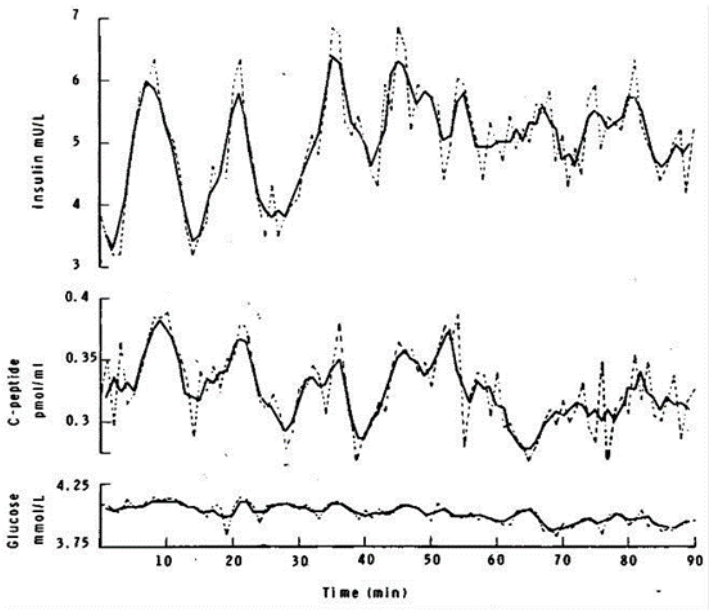

Fig. 1. A three-minute moving average (continuous line) of the fasting plasma insulin, C-peptide and glucose concentrations taken at one-minute intervals. The dashed line shows the "unsmoothed" data. Smoothing reduces the rapid fluctuations, which are probably due to "noise," and also blunts the amplitude. The simultaneous insulin and C-peptide cycles disappear after 50 min. Reproduced from Lang, D.A.; Matthews, D.R.; Peto, J.; Turner, R.C. Cyclic oscillations of basal plasma glucose and insulin concentrations in human beings. N. Engl. J. Med. 1979, 301, 1023–1027; PMID: 386121 DOI: 10.1056/NEJM197911083011903 [28]

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 T2DM, an overnight infusion of somatostatin gave the beta cells a rest from constant stimulation by insulin and

restored insulin pulse mass and normal insulin secretion [29]. Hepatic IR in dogs was achieved with a constant infusion of insulin that produced a 50% increase in the portal vein level of insulin [4a,30]. 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 (1mU/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 minutes followed by a 7-minute 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. 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. Norton and DeFronzo provide a thorough discussion of normal glucose homeostasis, normal glucose metabolism, insulin signaling, and insulin resistance [31].

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 [32,33]. 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, a lack of physiologic peaks and troughs leads to refractory delays in receptor activity [4a]. Finally, modulating the insulin signaling pathway and restoring insulin sensitivity may potentially be a novel target for disease modification [34].

4.1 Implications for Treatment

A genetic aspect of 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 [35]. Even people who are just close relatives of people with type 2 diabetes often have impaired insulin oscillatory patterns [4a,36].

4.2 Diet

From a dietary perspective, the Framingham study suggests that diets with a lower glycemic index are associated with greater insulin sensitivity [37]. A low carbohydrate diet is associated with a reduction in IR compared to a high carbohydrate diet [38]. The improvement in insulin oscillation was proportional to residual insulin sensitivity after weight loss [4a,39]. 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 proven very difficult to obtain patient

cooperation in adopting and maintaining an appropriate diet that minimizes carbohydrates and results in achieving and maintaining weight loss [40].

4.3 Medication

From the medication perspective, as one might predict for a disease driven by IR, insulin-sensitizing medication such as metformin or thiazolidinediones prevent or restore the abnormal insulin secretion associated with IR [41,42]. Glucagon-like peptide-1 agonists also amplify insulin secretion via stimulation of cyclic AMP (cAMP)-stimulated protein kinase A (PKA) pathways [4a,43]. 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) [44], 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 treating its underlying causes [4a].

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 [4a]. These include GLP-1 agonists, Dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose transport protein 2 (SGLT2) inhibitors, each with a high-risk profile for adverse reactions. Thiazolidinediones such as rosi- and pioglitazone are the only approved insulin-sensitizing drugs that use insulin sensitization as the only mechanism [4a].

Physiologic Insulin Resensitization (PIR) is a true sensitizing strategy, as well. Rosiglitazone costs about $180–$190 a month but an increase in fat cells that fill with fat and increases obesity; therefore, cardiovascular safety becomes an additional concern [4a].

Although this chapter 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 [45,46] since the subject is beyond the scope of this chapter [4a].

It is encouraging to see reductions in major cardiovascular endpoints and positive data for those suffering from renal complications of diabetes. However, the magnitude of such benefits from these novel drugs is limited in scope, and many patients are unable to tolerate them due to material adverse side effects [4a.,47,48]. In addition, recent guidelines published on 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 [49] trial that was terminated prematurely because intensive glycosylated hemoglobin management led to increased morbidity and mortality [4a].

As such, ACP guidelines now target an 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 [50] Patient-focused treatment regimens require the treating physician to understand each patient's unique metabolism before prescribing treatment. Another important development was the reclassification by the FDA of insulin to the biological regulatory framework in March 2020, highlighting the physiologic importance of this hormone peptide in regulating carbohydrate metabolism [4a,51].

4.4 Physician-directed Physiologic Insulin Resensitization

An alternative approach to counter IR in the presence of constant insulin infusion would be to reintroduce physician-directed physiologic insulin delivery via precision dosing. This has been done by inserting intravenous access connected to a precision infusion pump that can be programmed to deliver insulin as directed by the physician for each patient, typical of normal glucose metabolism.

The mechanism of PIR is directed at the pathophysiology of IR found in T2DM. PIR can be described as a treatment providing insulin as needed based on the body's response to insulin delivered. 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 would then be able to replace lost physiological signals critical to cellular glucose metabolism. The classic role of mitochondria is oxidative phosphorylation, which generates ATP by utilizing the energy released during the oxidation of the food we eat. ATP is used in turn as the primary energy source for most biochemical and physiological processes, such as growth, movement and homeostasis [52]. With improved uptake of 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 increased ATP necessary to support tissue healing, repair, and cellular restoration [53].

Physiologic insulin resensitization requires an insulin delivery profile comparable to what we know to be the activity of healthy pancreatic islet cells. Understanding the physiology 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 [54]. 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 precision-dosed manner [4a,55]. The study also reported that insulin secretion occurs in cycles approximating a period of 5 minutes. Specifically, 6-minute

intervals containing a peak of insulin delivered followed by a resting period appeared to have a substantial increase in cellular glucose uptake as well as increased downstream activation of insulin signaling effectors. In 2022, Lewis, et al., discussed the physiologic secretion profile of insulin and its effect on insulin receptors, as well as the effects of non-physiologic insulin secretion (i.e. constant insulin exposure) on the downregulation of insulin receptors and subsequent reduction in cellular sensitivity to insulin [56].

This treatment approach has been reported to achieve physiological insulin concentrations in the portal vein based on animal work [57]. This treatment, with some variation in the amount of insulin and treatment frequency, has been evaluated in case series and clinical trials that are reviewed herein [4a].

5. STUDIES OF PHYSIOLOGIC INSULIN RESENSITIZATION (PIR) TREATMENT

5.1 Foot Ulcer and Peripheral Neuropathy

Tucker et al. anecdotally 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 [4a]. 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 [4a]. 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% [58].

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, which improved in response to PIR treatment 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 [4a,59].

5.3 HbA1c and Insulin Resistance

Tucker et al. reported a 74-year-old female who presented with numerous complications after 20 years of T2DM 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 [4a,60].
Rebello et al. performed a 10-person retrospective case study administering physiologic insulin for 2-3 hours one time per week to Native American patients and reported after six months of treatment a decrease in HbA1c of 2.00% (From 9.03% +- 2.08% to 7.03% +- 0.73%, p=0.008). In the same time window, the patient's fasting blood glucose decreased from an average of 176.0 mg/dL to 137.11 mg/dL (p = 0.02) [52]. In this same retrospective analysis, these 10 patients showed a change in their insulin resistance measured with the HOMA-IR model from 10.39 prior to beginning treatment to 7.74 after six months of treatment (p=0.008) [61].

Loveridge et al. performed a 12-person retrospective case study on male and female diabetic patients ranging from 52 years of age to 88 years of age. In this case study, the patients' starting HbA1c averaged 8.4%. After three months of physiologic dosing of insulin approximately weekly, the patients' average A1c result had diminished to 7.3%, a reduction of 13.1% in a three-month period. This analysis also evaluated these patients' insulin resistance using the HOMA-IR model as in several previous studies mentioned in this review. This cohort of 12 patients began treatment with physiologic insulin at an average HOMA-IR score of 13.6. After three months of treatment, the same cohort showed a calculated average HOMA-IR score of 7.8, decreasing by an average of 42.4% in the first three months of treatment [62].

5.4 Cost Reduction

All the reports above reflected a reduced burden of disease. From the findings of reduced burden of disease, reduction of costs to both patients and the healthcare system can be extrapolated. A 2019 study evaluated the various costs of different amputations for patients in Qatar. The study found that combining direct costs of lower extremity amputation (LEA) along with total hospitalization costs yielded an average of $59,647 expended per patient [63]. The study also noted that approximately 3 in 4 patients who undergo LEAs are a result of DFUs. By improving the healing of DFUs, many amputations can be avoided, with each avoided amputation saving tens of thousands of dollars in medical expenditure.

Table 1. Clinical Outcomes Utilizing Physiologic Insulin Resensitization

Decreases in Hemoglobin A1c [60,61,62]
Reversals of Diabetic Neuropathy [58, 60]
Improvements in Wound Healing [60]
Decreases in Insulin Requirements [58]
Decreases in Insulin Resistance (via HOMA-IR) [61,62]
Improvements in Estimated Glomerular Filtration Rate (eGFR) [58]
Reduce/Arrest Progression of Diabetic Nephropathy [49,53]

Furthermore, diabetic nephropathy and the progression of diabetic kidney disease can result in dialysis or kidney transplants. Both of these result in high medical

costs. Annual medical costs for dialysis can range from USD $91,716 to $108,656 per patient per year, [64] and a renal transplant with associated post-transplant hospitalization costs can result in a total expenditure of $442,000 [65]. Physiologic Insulin Resensitization shows potential for improvement in diabetic nephropathy. Avoidance of nephropathy and Diabetic Kidney Disease progression has the potential to save hundreds of thousands of dollars for patients and global health organizations.

Table 2. 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
Villaverde et al.	Nephropathy	Case Series	41% increase in GFR
Rebello et al.	HbA1c	Case Series	Decrease in HbA1c of 22% and Fasting Glucose of 22%
Rebello et al.	HOMA IR	Case Series	Decrease in HOMA IR of 25.5%
Loveridge et al.	HbA1c	Case Series	Decrease in HbA1c of 13.1%
Loveridge et al.	HOMA IR	Case Series	Decrease in HOMA IR of 42.4%

6. CONCLUSIONS

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 [4a]. 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 [66]. 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 [4a].

We believe that the evidence supports the assertion that physiologic insulin secretion is medically necessary for the maintenance of normal cellular insulin sensitivity. Hence, using physiologic insulin resensitization is a logical clinical solution to restore physiologic insulin function. The utilization of PIR with a high safety profile monitored by the patient's physician has brought benefits to patients as observed by their treating physicians. These findings supported by laboratory results are consistent with expected improvement in diabetes based on key scientific principles of human insulin/glucose metabolism. Further randomized clinical trials can provide further clarity on which patients may benefit the most from PIR and to guide selecting PIR when underlying sequela of diabetes limit the patient's quality of life. Improved management of diabetes in a cost-effective manner is consistent with 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 1 and 2) [4a].

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 costs that will occur as the 88 million pre-diabetics progress to overt diabetes in the United States [4a].

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. Authors JRTL and BL conceptualized and designed the research work. Authors FG and JRTL analyzed the data, and prepared the draft of the manuscript, Authors BL, JRTL and SAH wrote, reviewed and edited the manuscript. Authors FG, JRTL and SH did the funding acquisition. All authors have read and agreed to the published version of the manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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