



## REVIEW

# Physiologic hormone administration improves HbA1C in Native Americans with type 2 diabetes: A retrospective study and review of insulin secretion and action

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## Summary

Insulin is secreted in pulses from pancreatic beta-cells, and these oscillations maintain fasting plasma glucose levels within a narrow normal range. Within islets, beta-cells exhibit tight synchronization of regular oscillations. This control circuit is disrupted in type 2 diabetes, and irregularities in pulse frequency and amplitude occur. The prevalence of type 2 diabetes is three times higher in American Indian and Native Alaskans compared to Whites, and their genetic ancestry is associated with low beta-cell function. Obesity in this population compounds their vulnerability to adverse outcomes. The purpose of this article is to review insulin secretion and action and its interaction with race. We also present the results from a 6-month retrospective chart review of metabolic outcomes following intravenous physiologic hormone administration to 10 Native Americans. We found reductions in hemoglobin A1C (baseline: 9.03%  $\pm$  2.08%, 6 months: 7.03%  $\pm$  0.73%,  $p = 0.008$ ), fasting glucose (baseline: 176.0  $\pm$  42.85 mg/dL, 6 months: 137.11  $\pm$  17.05 mg/dL,  $p = 0.02$ ), homeostatic model assessment of insulin resistance (baseline: 10.39  $\pm$  4.66, 6 months: 7.74  $\pm$  4.22,  $p = 0.008$ ), and triglycerides (baseline: 212.20  $\pm$  101.44, 6 months: 165.50  $\pm$  76.48 mg/dL,  $p = 0.02$ ). Physiologic hormone administration may improve components of the metabolic syndrome. The therapy warrants investigation in randomized controlled trials.

## KEYWORDS

HbA1C, Native Americans, pulsatile insulin secretion, type 2 diabetes

## 1 | INTRODUCTION

American Indians and Native Alaskans represent a substantial and growing proportion of the US population. In 2020, 7.1 million people in the United States identified as American Indian and Native Alaskan alone or in combination with other race groups. The American Indian and Native Alaskan population is projected to be 10.1 million in 2060, which would constitute 2.5% of the total US population.<sup>1</sup> The health

disparities are more than apparent in their life expectancy that is the lowest at birth (71.8 years) compared with the non-Hispanic White (78.8 years), non-Hispanic Black (74.8 years), and Hispanic (81.9 years) populations.<sup>2</sup> Coronary heart disease is the leading cause of death among American Indians and Native Alaskans, and diabetes is the most important risk factor for coronary heart disease in this population.<sup>3</sup> Comorbid conditions such as obesity are present in 69.6% of patients 18 years and older with type 2 diabetes, in the American

Indian and Native Alaskan population.<sup>4</sup> Age-adjusted prevalence of diabetes is three times higher, and diabetes mortality rates are 2.3 times greater in American Indian and Native Alaskans compared to non-Hispanic Whites.<sup>5</sup>

Type 2 diabetes is a multifactorial disease often associated with obesity, insulin resistance, impaired control of hepatic glucose production, and pancreatic beta-cell dysfunction.<sup>6,7</sup> Genetics play an important role in type 2 diabetes, and the high rates of concordance of the disease in twins exemplify this association.<sup>8</sup> Although each genomic polymorphism contributes only a very small amount of disease risk, and causal variants have been difficult to identify, the majority of genetic variants associated with type 2 diabetes are linked to disturbances in pancreatic islet function.<sup>9</sup> An important outcome has been a paradigm shift in the field towards the recognition that reduced beta-cell function lies at the crux of the etiology of type 2 diabetes.<sup>7</sup> Islet beta-cells are equipped with glucose-sensing machinery that ensures a coordinated release of insulin, with exactly the right dynamics, to maintain blood glucose concentrations within the euglycemic range.<sup>10</sup> Accordingly, insulin is secreted from the pancreatic beta-cells in a pulsatile fashion in humans, and these oscillations help to maintain fasting plasma glucose concentrations within a narrow normal range.<sup>11</sup>

Insulin secreted from islet beta-cells flows directly into the portal vein and passes through the liver before entering systemic circulation. Access to the portal vein is anatomically challenging. However, analytic methods for quantifying pulse timing and mass and modeling of insulin kinetics have grown in sophistication over the past 20 years, which has enhanced our understanding of the physiology underlying insulin secretion and its biological advantages. Insulin secretion is disrupted in type 2 diabetes, and systemic pulsatile insulin infusion has been investigated as a therapeutic option, with promising results.<sup>12-14</sup> The purpose of this article is to review insulin secretion and action and its interaction with race. We also present the results from a six-month retrospective chart review of glycemic outcomes following physiologic hormone administration to Native Americans.

## 2 | INSULIN SECRETION

Insulin secretion occurs primarily in response to an increase in circulating glucose concentration in the post-prandial state. The metabolism of glucose generates ATP, which closes ATP-sensitive potassium channels to cause membrane depolarization and the consequent activation of voltage-gated Ca<sup>2+</sup> channels. The rise in intracellular Ca<sup>2+</sup> levels precipitate the exocytosis of insulin secretory granules that are primed for release. This first phase of insulin secretion causes a sharp peak that declines within 10–20 min following the glucose stimulus. A secondary set of stimuli amplifies the first phase insulin secretion to sustain insulin concentrations during the entire post-absorptive phase that lasts for several hours and is a period referred to as the second phase. At this time, Ca<sup>2+</sup> is at a maximal level, and the release of insulin is independent of potassium channel mechanisms. During the second phase, the beta-cell's internal storage is tapped to complement the pool of readily releasable insulin granules.<sup>10</sup>

## 3 | OSCILLATIONS IN BIOLOGICAL SYSTEMS

Rhythmic activity in biological systems is ubiquitous. When the cell is challenged by an external signal that varies within a physiologic range, specialized structures within the cell, typically the cell membrane, activate a mechanism that generates a cellular oscillation. This mechanism facilitates a stable output that varies continuously within a range. Oscillation provides an efficient mechanism for grading the response to a signal. The frequency is likely to be stable, and the system is capable of fairly accurate regulation through variations in the amplitude. In highly evolved systems, it would be improbable that the oscillations occur without good reason, but rather that they confer a measure of functional advantage over steady-state systems resulting in enhanced precision of control.<sup>15</sup> Thus, the beta-cell secretes insulin in properly timed intermittent bursts of activity, and the loss of this capacity is associated with dysfunction and disease.<sup>16</sup>

Lang et al.<sup>17</sup> were the first to report oscillations in insulin secretion in humans and like another early study of *in vivo* insulin oscillations estimated that the period between pulses was 10–15 min.<sup>17,18</sup> These pioneering studies were conducted prior to the 1990s and measured basal insulin levels in fasted humans where the plasma insulin levels approached the limits of detection of the insulin assays available at the time. Moreover, the analytic techniques and computing systems available to quantify insulin pulses were not as advanced as they are today.<sup>19</sup> Subsequent studies have shown that the period of the pulse is generally invariant and in the range of 4–6 min.<sup>20-23</sup> Prolonged intervals in insulin oscillations known as ultradian and having a period of 80–180 min have also been observed in measurements conducted over a 24-h period.<sup>24</sup>

*In vivo*, pulsatile insulin secretion from numerous islets scattered throughout the pancreas is a coordinated response. Many hypotheses have been proposed to account for islet pulsatility, particularly using mathematical modeling.<sup>25-29</sup> Within islets, beta-cells exhibit tight synchronization of regular oscillations, and this coordinated activity of beta cells is primarily mediated by strong electrical coupling via gap junctions to ensure a normal pulsatile release of insulin.<sup>30</sup> Mathematical models also emphasize the dependency of these interactions on the extracellular concentrations of glucose.<sup>31</sup> In theory, plasma glucose could increase plasma insulin by altering various characteristics of the pulse such as amplitude, frequency, plateau fraction, or all three.<sup>19</sup> However, elevations in glucose concentrations increase the mass but not the frequency of plasma insulin bursts, which has been confirmed in several studies.<sup>20,32,33</sup>

## 4 | PULSATILE INSULIN SECRETION IN TYPE 2 DIABETES

Following exposure to insulin, its receptors are quickly internalized and only reappear at the cell surface after a period of recovery. During this recovery period, the autophosphorylated receptors release bound insulin and are dephosphorylated before returning to the cell surface.

The rest and recovery period is broadly compatible with the timing of insulin pulses. Furthermore, the rest period that follows each pulse is necessary for the negative feedback present in the insulin signaling pathway sufficient time to decay.<sup>19</sup> In patients with type 2 diabetes, the oscillations were found to be shorter and highly irregular.<sup>34,35</sup> In relatives of patients with type 2 diabetes without fasting hyperglycemia, the pulses were found to be irregular.<sup>11</sup> Entrainment or the process where small, subthreshold changes in plasma glucose regulate insulin pulses and contribute to islet synchronization of regular oscillations is disrupted in prediabetes and type 2 diabetes.<sup>36,37</sup>

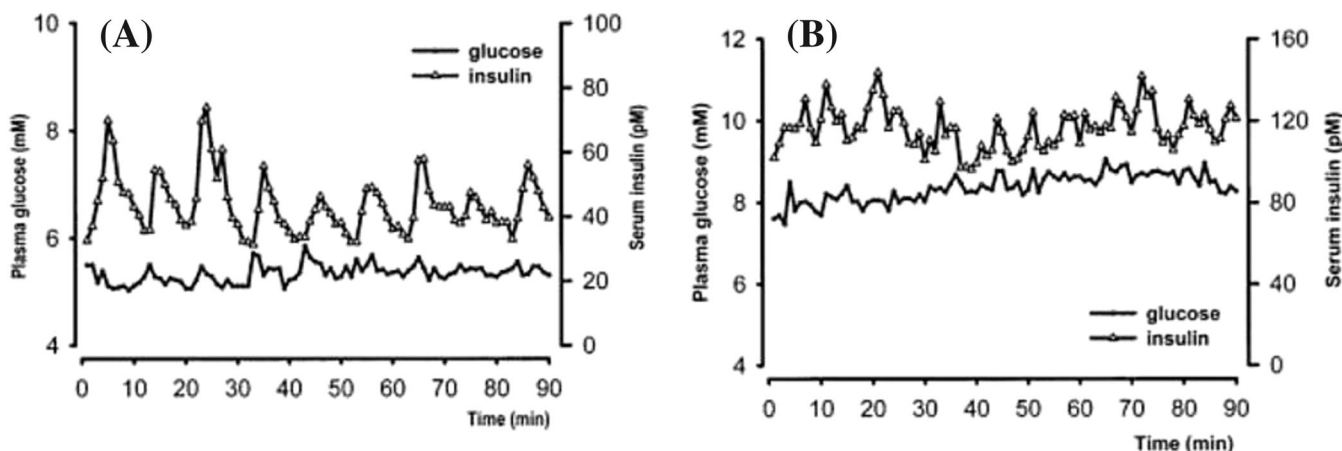
Hollingdal et al.<sup>38</sup> showed that following glucose pulsed infusions (every 10 min), small excursions in plasma glucose concentrations occur in healthy subjects and in those with type 2 diabetes. However, glucose pulsed infusions induced synchronized insulin oscillations in the healthy subjects but failed to entrain oscillatory insulin release in subjects with type 2 diabetes. (Figure 1). Persistent exposure of insulin-sensitive tissues to large amounts of insulin precludes receptor rest and recovery, which can downregulate insulin receptor binding affinity and insulin receptor numbers.<sup>39–42</sup> Whether impaired pulsatile secretory pattern in type 2 diabetes develops as a consequence of increased beta-cell workload or whether they reflect a genetically inherited defect of beta-cell function remains to be established.<sup>43</sup>

## 5 | INSULIN EXTRACTION

A proportion of insulin secreted by beta-cells directly into the portal vein and delivered to the liver is cleared through a receptor-mediated process.<sup>44–46</sup> In humans, ~50% of insulin delivered to the liver is cleared during first pass transit, and subsequent passes account for an additional ~20%. The insulin concentration presented to the liver exhibits oscillations with an amplitude of ~200–500 pmol/L in the fasted state, which increases to ~1000–5000 pmol/L in response to glucose infusion or ingestion.<sup>47,48</sup> In striking contrast, the insulin pulse

amplitude reaching systemic circulation is reduced by ~10-fold compared to the portal vein.<sup>47</sup> Using the hepatic vein catheterization technique, the importance of pulsatile insulin delivery to the liver was demonstrated. Pulse amplitude was shown to be the predominant determinant of hepatic insulin clearance and delivery to extrahepatic insulin sensitive tissues. Basal non-pulsatile insulin secretion had no association with hepatic insulin clearance.<sup>49</sup> Using a modeling approach in conjunction with c-peptide deconvolution to assess insulin kinetics, Smith et al.<sup>50</sup> showed that the insulin secretion rate is higher in individuals with obesity and impaired glucose tolerance compared to lean controls without impairments in glucose homeostasis. While extraction by extrahepatic tissues in response to glucose ingestion increases linearly as insulin delivery into systemic circulation rises, the capacity of the liver to extract insulin is a saturable process that can reach a maximum capacity. Small differences between the rate of insulin secretion and removal between the groups with normal and impaired glucose metabolism resulted in striking differences in plasma insulin concentrations.<sup>50</sup> Thus, the limited capacity of the liver to extract insulin enhances the amount of insulin delivered into systemic circulation and could predicate hyperinsulinemia. The authors concluded that there was no intrinsic defect in hepatic or extrahepatic insulin extraction and that hyperinsulinemia in people with obesity stems primarily from beta-cell hypersecretion in conjunction with a saturable insulin extraction process.<sup>50</sup>

The evidence for saturable hepatic insulin extraction is consistent with increasing arterial concentrations of insulin, following continuous insulin infusion in fasted dogs.<sup>45</sup> The modeling approach in the study by Smith et al.<sup>50</sup> was developed using a modified frequently sampled intravenous glucose test that included a continuous infusion of insulin.<sup>51</sup> Whether different conclusions relating to hepatic insulin extraction would have been drawn if physiologic pulsatile insulin secretion were considered in these studies<sup>45,50</sup> remains to be determined. Nevertheless, the hepatic capacity for extraction of insulin may render it an important site for control of the proportion of secreted insulin



**FIGURE 1** Difference in insulin concentrations in adults (A) healthy controls and (B) with type 2 diabetes. Circulating insulin concentrations do not fall sufficiently in subjects with type 2 diabetes who have insulin secretory capacity, as in healthy controls. Reproduced with permission from Hollingdal et al.<sup>38</sup> Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

reaching the periphery. Moreover, hepatic insulin removal and hepatic insulin action are correlated.<sup>52,53</sup> Considering an evolutionary perspective, why would pancreatic insulin secretion be designed to flow directly into the hepatic portal vein rather than into systemic circulation, and in a pulsatile fashion, if there was not good reason for it? It is likely that the flow pattern evolved as a mechanism by which changes in hepatic insulin removal enabled the organism to compensate for insulin resistance by enhancing the amount of secreted insulin delivered into systemic circulation.<sup>54</sup>

Basal insulin degradation exhibits tremendous individual variability (22% to 77%).<sup>55</sup> Nutrient intake also alters insulin clearance. For instance, glucose-stimulated insulin secretion reduces hepatic extraction.<sup>56</sup> Similarly, fatty acids also alter hepatic insulin extraction.<sup>56–58</sup> The implications of these findings are that first pass hepatic insulin removal can be controlled by modifying the diet or by directly modulating endogenous insulin secretion.

## 6 | EFFECTS OF PULSATILE INSULIN SECRETION ON INSULIN ACTION

The hyperinsulinemic euglycemic clamp (hereinafter referred to as clamp) test involves a continuous infusion of insulin and a variable infusion of a dextrose solution to clamp blood glucose concentrations at ~5.5 mmol/L. The amount of glucose infused and the suppression of hepatic glucose production are measures of insulin action.<sup>59</sup> In subjects with type 1 diabetes, when the clamp was administered with pulsed insulin infusion, hepatic glucose output was suppressed at 40% of the insulin needed to achieve the same effect with a continuous insulin infusion.<sup>60</sup> In healthy subjects and in subjects with type 2 diabetes, glucose uptake by tissues increased during the clamp when the insulin infusion was pulsed compared to continuous.<sup>61,62</sup> In contrast, pulsatile delivery of insulin in humans during the clamp was shown to have greater effects in modulating hepatic glucose production than continuous infusion, without affecting glucose uptake by tissues.<sup>63</sup>

Mathematical and experimental modeling suggest that maximum connectivity between signaling nodes is achieved at physiologic concentrations of insulin, and hyperinsulinemic states lower the connectedness.<sup>64</sup> Moreover, in the context of gene transcription, noise in biology is considered beneficial for regulating functional flexibility, and hyperinsulinemic states diminish noise in signaling.<sup>64</sup> Releasing insulin in an intermittent fashion provides receptors with the necessary recovery time and may to some extent mitigate hyperinsulinemia during the clamp to improve connectedness in insulin signaling and action. In subjects with type 2 diabetes, Laedtke et al.<sup>65</sup> showed that somatostatin infusion overnight (to inhibit insulin secretion and provide rest to the receptors) restored mean insulin secretion to that of the control subjects without type 2 diabetes. The frequency of the pulses resumed after stopping somatostatin infusion in subjects with type 2 diabetes and was the same as the control group given saline treatment. Prior to somatostatin treatment, the amplitude of the pulses was lower in subjects with type 2 diabetes compared to the controls. However, somatostatin treatment improved insulin

pulse amplitude and insulin secretion in the subjects with type 2 diabetes.<sup>65</sup>

Laurenti et al.<sup>66</sup> used nonparametric stochastic deconvolution applied to peripheral c-peptide concentrations to characterize pulsatile insulin secretion. In subjects without a history of type 2 diabetes, they found no correlation between insulin pulse characteristics and hepatic insulin action or whole-body insulin action assessed during the clamp. The method for insulin pulse characterization was validated against sampling of blood from the hepatic vein and found to be concordant. By sampling from the hepatic vein that represents post-portal vein and post-liver pulsatility, this method excludes hepatic insulin extraction. In this study, hepatic insulin action was measured during the clamp where insulin (albeit a low dose [0.3 mU/kg/min]) was infused continuously. Additionally, the pulses were measured on a separate day from hepatic insulin action. Thus, the lack of correlation between insulin pulse characteristics and insulin action in subjects without type 2 diabetes found in this study<sup>66</sup> requires further evaluation. A critical limitation in investigations of the effect of pulsatile insulin secretion on hepatic insulin extraction in humans appears to be the anatomical difficulties in sampling blood from the portal vein.<sup>49,50,66</sup>

Using the computer program called Pulsar, Hunter et al.<sup>67</sup> determined the frequencies and amplitudes of short-term insulin oscillatory peaks in subjects with type 2 diabetes and a control group without diabetes. In both groups, the frequency but not the amplitude of insulin pulses correlated with glucose uptake by tissues measured during the clamp with continuously infused insulin. However, neither pulse frequency nor amplitude correlated with suppression of hepatic glucose production.<sup>67</sup> Other studies have investigated the effect of overnight pulsatile versus continuous basal insulin infusions on insulin action measured during a clamp test administered in the morning. In subjects with and without diabetes, they found no priming effect of basal pulsatile insulin on glucose uptake during the clamp.<sup>68,69</sup>

On the other hand, the importance of the pulsatile release pattern in regulating physiologic insulin action can be appreciated from experimental models demonstrating that the response of key phosphorylation events in the insulin signaling cascade in the fed state are robust when primed by fasted insulin pulses. It appears that pulses in the fasted state create a memory that sensitizes the signaling in the fed state.<sup>64</sup> Insulin infusion during the hyperinsulinemic euglycemic clamp to measure insulin action could be a confounding factor for two reasons: (1) the creation of non-physiologic insulin concentrations purported to be a cause of the dysregulation in glucose homeostasis and (2) use of a continuous insulin infusion to measure insulin action, and test its correlation with insulin pulses.

## 7 | RACE DIFFERENCES IN INSULIN SECRETION AND EXTRACTION

Variations within the transcription factor 7 like 2 (*TCF7L2*) gene particularly the rs7903146 variant are highly associated with a

predisposition for type 2 diabetes in several different populations including those of European, Asian Indian, and Japanese origins.<sup>70–74</sup> This variant raises postprandial glucose concentrations and decreases peripheral concentrations of insulin in response to an oral glucose challenge.<sup>72</sup> In contrast, variation within *TCF7L2* does not confer major risk for type 2 diabetes in the Pima Indian population.<sup>75</sup> However, the Native American genetic ancestry is associated with low beta-cell function.<sup>76</sup> In Pima Indians followed for over 5 years, the cumulative incidence of type 2 diabetes (non-insulin dependent) was 39% in subjects with a low insulin secretory response assessed by an intravenous glucose tolerance test and low insulin action measured during a clamp.<sup>77</sup>

Results from a population of 448 Native Americans observed over a 7.9-year period showed that 32% of the cohort presented with type 2 diabetes. Low insulin clearance measured as metabolic clearance rate of insulin during the hyperinsulinemic euglycemic clamp was predictive of type 2 diabetes. Other risk factors, including age, sex, body fat, heritage, and insulin action during the hyperinsulinemic euglycemic clamp, did not influence the propensity for developing type 2 diabetes.<sup>78</sup> Among Native Americans, with declining insulin action, the reduction in insulin secretion manifests before blood glucose concentrations reach the diagnostic guidelines for impaired glucose tolerance.<sup>79</sup>

Similarly, in other races such as in Hispanics, low insulin clearance is associated with increased risk of incident diabetes after adjusting for demographics, lifestyle factors, indices of adiposity, and insulin secretion.<sup>80</sup> In Blacks, hepatic first-pass insulin extraction has been estimated to be two-thirds lower, whereas extrahepatic insulin clearance is similar, compared to Whites.<sup>81</sup> The low metabolic clearance rate may explain why Blacks have lower fasting c-peptide but higher fasting insulin concentrations than Whites, which is consistent with reduced insulin clearance.<sup>82</sup> In Black women without diabetes, insulin secretion is similar whereas the insulin response to glucose is higher and insulin clearance is lower than White women.<sup>83</sup> Together with data on reduced insulin clearance from the longitudinal study in Native Americans<sup>78</sup> and the genetic predispositions identified among Native Americans,<sup>75,76</sup> it appears that a metabolic phenotype predisposes them to type 2 diabetes independent of established risk factors.

## 8 | RETROSPECTIVE CHART REVIEW

Data on insulin secretion and action in Native Americans are sparse. We report the results of a retrospective chart review of 10 Native American patients receiving physiologic hormone administration over a 4 to 6-month period in a clinical practice setting.

### 8.1 | Subjects

Subjects in the study were Native Americans with a diagnosis of type 2 diabetes receiving physiologic hormone administration at First American Wellness, which is a clinic that delivers culturally respectful

health services to Native American tribal members and their families. Patients attend the clinic specifically to receive physiologic hormone administration. Therefore, there is no control group in this study.

### 8.2 | Methods

Physiologic pulsatile insulin was administered weekly for 4 to 6 months (depending upon response to the treatment assessed by blood glucose control), followed by once every 2 weeks and was individualized based on the response to the treatment. An intravenous (IV) access was obtained for administration of insulin by means of an external pump programmed to deliver insulin in pulses via peripheral IV so as to mimic the physiologic secretion of insulin from the pancreas. Insulin was infused intermittently every 4–8 min depending on the patient's response to the algorithm employed. The concentration of insulin infused (combined with 0.9% normal saline) was dynamic and is determined by a proprietary scale based on the hemoglobin A1C (HbA1C) initially and varies over time depending upon the response to treatment. Blood glucose was monitored throughout the pulsatile infusion period to maintain concentrations between 80 mg/dL to 180 mg/dL. Patients were given a dextrose drink to prevent decline of blood glucose to hypoglycemic levels. The procedure varied between 2 and 3 h depending upon stabilization of blood glucose concentrations. At the end of the procedure, patients ate a meal, and blood glucose concentrations were assessed before the patient was considered safe to return to the activities of daily living. Changes in metabolic outcomes from baseline up to 6 months for 10 patients were extracted from the medical records, and homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as follows: fasting glucose in mmol/L\*fasting insulin in  $\mu$ U/mL/22.5.<sup>84</sup>

#### 8.2.1 | Statistical analysis

The means and standard deviations for the metabolic outcomes were determined and compared to baseline. Generally, insulin is not measured in a clinical setting. The medical records contained baseline and follow-up insulin measures for three patients, baseline measure for one patient, and follow-up measure for one patient. Values were imputed for the patient missing the baseline measure and the patient missing the follow-up measure. The missing values were imputed by using the overall mean of the available values and adding in random error based on the standard deviation of the available values. Therefore, the HOMA-IR was calculated and compared to baseline for five patients. We used paired t tests, and statistical significance was set at  $\alpha = 0.05$ .

### 8.3 | Results and discussion

Baseline characteristics of the subjects are presented in Table 1. HbA1C reduced from baseline by two percentage points (baseline:

**TABLE 1** Baseline characteristics of patients included in the analysis and their change in medications over the duration of the study.

Patient	1	2	3	4	5
Age (years)	71	74	78	61	47
Gender	Female	Female	Male	Male	Female
SBP	Not available	144	133	139	115
DBP	Not available	81	78	89	73
Body Weight (kg)	59.1	65.9	102.7	99.6	100.0
BMI	25.4	28.0	36.6	30.6	36.7
Glucose (mg/dl)	138	139	175	173	141
HbA1c (%)	7.1	7.2	9.9	7.8	0.07
GFR	99	89	56	146	103
AST (IU/L)	36	18	23	37	13
ALT (IU/L)	28	15	20	76	22
Total Cholesterol (mg/dL)	125	179	195	210	191
LDL (mg/dL)	60	101	98	148	124
Triglycerides (mg/dL)	104	167	324	280	109
HDL (mg/dL)	44	51	32	44	45
Medications	Metformin 1000 mg BID	Metformin 500 mg BID	Metformin 500 mg QD, Levemir 90 units BID	Metformin 1000 mg BID, Tradjenta 5 mg QD	Metformin 500 mg QD
Medication change	No change	No change	Levemir 70 units QD	No change	No change
Other conditions	Cataracts	Neuropathy, glaucoma, hypertension	Neuropathy, cataracts, CAD, hypertension	Neuropathy, glaucoma, hypertension	Hypertension, hyperlipidemia

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transferase; BID, twice daily; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; PRN, as needed; QD, every day; SBP, systolic blood pressure.

TABLE 1 (Continued)

Patient	6	7	8	9	10
Age (years)	58	48	60	55	41
Gender	Female	Male	Female	Male	Male
SBP	129	129	119	114	111
DBP	74	81	90	71	68
Body Weight (kg)	138.7	153.6	68.2	86.4	155.9
BMI	54.2	51.5	27.5	28.9	46.6
Glucose (mg/dl)	176	173	278	250	191
HbA1c (%)	11.3	7.5	11.8	8.5	12.2
GFR	79	102	96	57	132
AST (IU/L)	13	16	32	22	25
ALT (IU/L)	16	21	53	36	41
Total Cholesterol (mg/dL)	154	128	202	82	210
LDL (mg/dL)	37	58	122	23	148
Triglycerides (mg/dL)	369	201	306	84	178
HDL (mg/dL)	43	30	36	42	56
Medications	Metformin 1000 mg QD, glipizide 10 mg QD, Bydureon 2 mg weekly	Metformin 1000 mg BID, Pioglitazone 30 mg QD	Metformin 1000 mg BID, 1000 mg BID	Metformin, 1000 mg BID	Levemir 50 U QD, Humalog 5 U PRN
Medication change	Metformin 1000 mg BID, Victoza 0.6 mg QD	No change	No change	Metformin 1000 mg BID, Januvia 100 mg QD	Levemir and Humalog discontinued
Other conditions	Neuropathy, hypertension, hyperlipidemia	Hypertension	Neuropathy, hypertension	Neuropathy, CAD hypertension	Hypertension, hyperlipidemia

Abbreviations: ALT, alanine amino transferase; AST, aspartate transferase; BID, twice daily; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; HbA1C, hemoglobin A1C; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; PRN, as needed; QD, every day; SBP, systolic blood pressure.

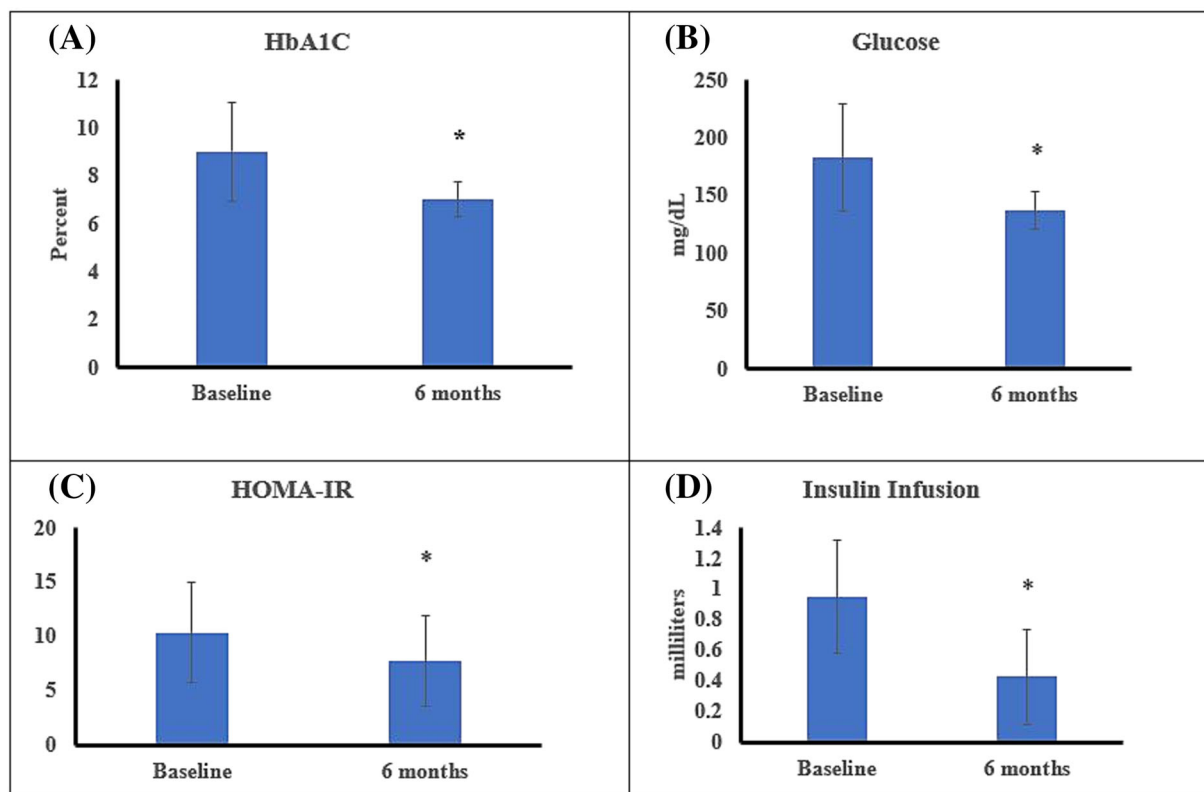
9.03%  $\pm$  2.08%, 6 months: 7.03%  $\pm$  0.73%,  $p = 0.008$ ), which represents a 22% reduction from baseline. Compared to baseline, there was a reduction in fasting blood glucose (baseline: 176.0  $\pm$  42.85 mg/dL, 6 months: 137.11  $\pm$  17.05 mg/dL,  $p = 0.02$ ), HOMA-IR (10.39  $\pm$  4.66, 6 months: 7.74  $\pm$  4.22,  $p = 0.008$ ), and the concentration of insulin infused in pulses (baseline: 0.95  $\pm$  0.34 mL, 6 months: 0.43  $\pm$  0.31 mL,  $p = 0.005$ , Figure 2A–D). Except for triglycerides (baseline: 212.20  $\pm$  101.44, 6 months: 165.50  $\pm$  76.48 mg/dL,  $p = 0.02$ ), none of the other outcomes measured (Table 1) were significantly different compared to baseline.

Our analysis of data from a retrospective chart review showed that in Native American patients, physiologic hormone administration for 4 to 6 months reduced fasting blood glucose and HOMA-IR, which was accompanied by a striking decline in HbA1C by two percentage points at approximately half the concentration of insulin infused. We also observed a reduction in triglyceride concentrations, which like insulin resistance is a component of the metabolic syndrome.

The rate of glucose metabolism within beta-cells primarily determines the magnitude of the insulin secretory response and is governed by several metabolic signaling pathways that ultimately converge to ensure a robust insulin secretion in response to nutrient consumption.<sup>10</sup> The finding that in type 2 diabetes insulin secretion is reduced more than the reduction in insulin content implicates beta-cell function rather than beta-cell number as being the more important factor in the etiology of the disease.<sup>7</sup> The increase in insulin

secretion by glucagon-like peptide-1 receptor agonists lends credence to the notion that even in established type 2 diabetes, sufficient and perhaps latent beta-cell capacity exists.<sup>7</sup>

Aoki et al.<sup>85</sup> treated patients who were insulin-dependent with systemic physiologic hormone administration (7–10 intravenous pulses [ $\sim$ 2 units of insulin per pulse]) over 1 hour, for three times per day. The treatment was initially twice weekly followed by one treatment per week. Data from patients receiving the treatment from 7 to 71 weeks showed a reduction in HbA1C from 8.5% (SE: 0.4%) at baseline to 7.0% (SE: 0.2%) at the time of the analysis. The study was conducted at the University of California, Davis, and the demographics of the population were not provided. Our analysis of HbA1C measured between 4 and 6 months following the start of physiologic hormone administration showed that in a small sample of 10 Native American patients, HbA1C reduced from baseline by two percentage points. The genetic predisposition among Native Americans for reduced beta-cell function and the finding that a low secretory response enhances the development of type 2 diabetes suggest that this population may be more responsive to treatments directed at the insulin secretory response. Moreover, the lack of an association of *TCF7L2* gene variant on type 2 diabetes risk in Native Americans,<sup>75</sup> although common in Whites, Asian Indians, and Japanese,<sup>70–74</sup> suggests that differences in metabolic phenotypes among races may influence the type of treatment to which they respond.



**FIGURE 2** (A–D) Change from baseline in measures of glycemic control in Native Americans receiving physiologic hormone administration: (A) HbA1C ( $p = 0.008$ ,  $N = 10$ ); (B) fasting blood glucose ( $p = 0.02$ ,  $N = 9$ ); and (C) homeostatic model assessment of insulin resistance (HOMA-IR:  $p = 0.008$ ,  $N = 5$ ); (D) insulin infusion ( $p = 0.005$ ,  $N = 10$ ).



Pulse interval and insulin resistance exhibit a positive relationship whereby as insulin resistance increases the pulses become more frequent.<sup>86</sup> Our data show that systemic physiologic hormone administration improved fasting blood glucose and insulin resistance in the Native American population receiving physiologic hormone administration. The effect on fasting blood glucose and HOMA-IR translated into a sustained improvement reflected in HbA1C. Additionally, the physiologically administered insulin concentration needed to achieve glycemia reduced by approximately half compared to baseline, which is consistent with the study showing that hepatic glucose output was suppressed during the clamp at 40% of the insulin needed to achieve the same effect with a continuous insulin infusion.<sup>60</sup> The results suggest a cumulative effect whereby exogenous insulin pulses improved insulin resistance, which in turn had a beneficial effect on endogenous pulsatile insulin secretion.

The main limitation of our retrospective chart review is the lack of a control group, which makes it difficult to ascribe the results wholly to physiologic hormone administration. Patients visit the clinic to receive the treatment because they experience resolution of other diabetes complications that occur with improvements in blood glucose control. Furthermore, it is culturally inappropriate in the Native American population to withhold physiologic hormone administration (which they perceive as beneficial) and provide usual care. Therefore, respecting the culture precludes a control group. The treatment involves careful monitoring in a clinical setting to prevent hypoglycemia which may limit its widespread use. Patients also have considerable support and care perhaps in excess of routine diabetes clinical care, which may contribute to the outcomes. Nevertheless, physiologic hormone administration may improve outcomes in patients with type 2 diabetes and the therapy warrants investigation in randomized controlled trials.

## 9 | CONCLUSIONS

Blood glucose concentrations vary within a physiologic range, which is sensed by pancreatic beta-cells and to which they respond. Oscillations in insulin secretion confer reasonably accurate regulation through pronounced irregularity in amplitude, while the frequency does not significantly vary from an average value. Given the fluctuations in insulin concentrations, oscillatory control presents an enhanced precision of control. This control circuit is disrupted in type 2 diabetes and irregularities in frequency and amplitude occur.

Human studies examining the direct effect of systemic pulsatile insulin administration on insulin action largely demonstrate a measurable benefit. Studies examining the association between insulin pulses and insulin action provide mixed results. In novel methods used to model insulin kinetics, continuous insulin infusions were a component of the models or the stimulus to measure whole body or hepatic insulin action. Additionally, during the clamp, insulin is infused at non-physiologic doses, which contradicts the premise that exposure to high insulin concentrations precludes receptor rest and

recovery. Insulin is secreted directly into the portal vein, but access to the portal vein in humans presents an almost insurmountable challenge for studying pulsatile insulin secretion and its actions in the liver.

Despite the limitations of peripheral blood sampling, experimental and mathematical simulation-based approaches have contributed to our understanding of the physiology and kinetic parameters underlying insulin secretion and action. Systemic delivery of pulsatile insulin has therapeutic promise, which may have particular relevance to metabolic phenotype as determined by race. However, the real solution from the standpoint of a therapy as well as in elucidating the network properties of insulin secretion may lie in a method that simulates endogenous pulsatile secretion particularly in pathological states such as obesity and type 2 diabetes.

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## CONFLICT OF INTEREST STATEMENT

Tyler Morales, Katsya Chuon, and Shu Dong are consultants to First American Wellness (FAW), and Tyrone Lam is a consultant to and holds unregistered equity in FAW. Dan Purner is the Co-Founder and Chief Executive Officer of FAW and holds unregistered equity in FAW, Stanley Lewis is an equity holder and Scientific Advisory Board Member in Well Cell Global, which is a provider of a patented approach to physiologic insulin resensitization, and Jonathan Lakey is a past consultant to FAW. Candida Rebello, Robbie Beyl, and Frank Greenway have no conflicts of interest.

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