

Pulsatile Insulin Infusion as a Treatment Option for Patients with Type 2 Diabetes and Stage III Kidney Failure - Results from a Pilot Study

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Abstract

Introduction: Mimicking the physiological pancreatic pulsatile insulin secretion has led to the concept of pulsatile insulin infusion therapy (PIT).

Methods: This pilot study investigated the effect of once weekly PIT for 3 months on kidney function in patients with type 2 diabetes and chronic renal failure (glomerular filtration rate (GFR) < 60 mL/min or GFR < 75 mL/min with macroproteinuria).

Results: Of 22 enrolled type 2 patients, 17 completed the trial per protocol (7 women, 10 men, age: 69 ± 7 yrs., HbA1c: 7.9 ± 1.0%). After 3 months, mean GFR improved by 12% (from 47.6 ± 10.0 mL/min to 53.3 ± 11.9 mL/min, p < 0.01) and mean serum creatinine decreased by 7% (1.4 ± 0.3 mg/dL/1.3 ± 0.3 mg/dL, p < 0.05). Systolic blood pressure improved by 6% (p < 0.05), while HbA1c and body weight remained stable. The treatment satisfaction score improved from 3.7 ± 2.7 to 2.7 ± 2.1 (p < 0.005). The PIT procedures were well tolerated and only few cases of muscle cramps were considered to be related to the treatments.

Conclusion: Improvements in kidney function, systolic blood pressure and treatment satisfaction were observed after 3 months of PIT in patients with type 2 diabetes and renal failure in this pilot trial. These results will now be used to plan for appropriately designed controlled confirmatory studies.

Keywords: *Pulsatile Insulin Infusion Therapy (PIT); Type 2 Diabetes; Stage III Kidney Failure*

Abbreviations

BG: Blood Glucose; COVID: Corona Virus Disease; GFR: Glomerular Filtration Rate; MDRD: Modification of Diet in Renal Disease; PIT: Pulsatile Insulin Treatment

Introduction

The insulin-secreting β -cells physiologically release insulin in regular pulses with a frequency of 10 - 12 pulses/h [1,2]. This pulsatility of insulin secretion is regarded as a central factor for the maintenance of the sensitivity of vascular insulin receptors, which induce vasodilation and vasoprotection in the periphery [2-4].

The early loss of pulsatile insulin secretion seen in patients with type 2 diabetes [5] and the development of diabetes-associated micro-circulation disorders in patients with type 1 and type 2 diabetes can be attributed to the missing pulsatile insulin signal [6,7]. This led to the hypothesis that a temporary mimicking of insulin pulsatility through applying insulin in small doses intravenously in patients with diabetes can improve metabolic control and reduce vascular insulin resistance [8], and may e.g. have a positive influence on kidney function.

It has been shown that short-term pulsatile intravenous insulin administration (pulsatile insulin therapy, PIT) leads to a significant increase in insulin sensitivity [9-11]. The effects of PIT on the progression of chronic renal failure in patients with type 1 diabetes were studied in randomized studies. It was shown that regular PIT over one year in combination with standard diabetes therapy, in comparison to patients that stayed on their standard diabetes therapy without PIT, leads to a significant reduction in nephropathy progression in such patients [12-14]. Besides the renal effects, positive effects of PIT on metabolic control, arterial hypertension and other diabetes complications and co-morbidities in such patients have been reported [15-18]. However, awareness of PIT's existence is low, and only very few clinical sites offer it as a treatment option.

No results from documented studies have been published to date about the impact of PIT on kidney function in patients with type 2 diabetes.

Purpose of the Study

The purpose of this pilot study was to start closing this gap, and to explore the potential efficacy of PIT in patients with type 2 diabetes and impaired kidney function.

Patients and Methods

This study was conducted at two sites (Endocrine Associates of Western Village, Long Island City, NY and Pfützner Science and Health Institute, Mainz, Germany). The study started in Q4 2019 in the US and in Q1 2020 in Europe. The COVID pandemic hampered study performance massively. It was therefore decided to focus on enrollment of patients with type 2 diabetes, and to stop enrollment in April 2020 (enrollment status: 24/32 planned patients) after a sufficient number of type 2 patients were included.

The study was approved by the respective Ethical Review Boards and was performed in accordance with all applicable human research standards. Participants had to be diagnosed with type 2 diabetes (> 2 years) and had to show indications of impaired kidney function (glomerular filtration rate (GFR) between 30 to 60 mL/min or GFR < 75 mL/min with proteinuria). Exclusion criteria were current (or history of) dialysis treatment or inability to participate in the weekly PIT procedures.

During the initial visit blood samples were collected for determination of HbA1c and renal function parameters. Glomerular filtration rate (GFR; MDRD formula) was calculated from serum creatinine. Patients were subjected to diagnostic procedures for assessment of sensory neuropathy (tuning fork, determination of nerve perception thresholds: cold, warm, pain, vibration; QSense and Medoc, both Medoc, Israel). In addition, they completed a 7-item standard diabetes treatment satisfaction questionnaire at baseline and study end. Participants were required to rank their response on a scale from 1 (= very good/very rare) to 10 (= very bad/very often).

Pulsatile insulin treatment

Patients were initially randomised to receive PIT for 2h or 3h. There was no difference in the outcome and therefore the combined study results are presented. PIT was performed once weekly: Patients received a venous line for i.v. administration of insulin and glucose by means of programmable infusion pumps (e.g. Instalar 2020, Neuss, Germany). The pulsatile insulin infusion (10 pulses/h; up to 3 U/pulse) was run for 2h or 3h, respectively. Infusion rates of glucose (20% glucose solution) were adjusted throughout the PIT to maintain blood glucose (BG) levels between 80 mg/dL to 180 mg/dL. Patients were encouraged to consume food and glucose-containing drinks to prevent decline of BG to hypoglycemic levels. After completing the PIT, medical supervision was continued until stabilization of blood glucose (up to 3h) was observed. After 3 months, the baseline assessments were repeated.

Statistical methods

This pilot study was performed to enable sample size calculation for a planned confirmatory study. The statistical analysis was conducted with methods of descriptive statistics. Normally distributed parameters were compared between baseline and endpoint by means of the bilateral student’s t-test. All results were interpreted in an exploratory sense only and a p-value < 0.05 was considered statistically significant.

Results

Of the 22 enrolled patients with type 2 diabetes, one died from COVID-19 pneumonia after receiving a first PIT procedure, and one subject withdraw consent because of fear of SARS-CoV-2 infection. Of the remaining 20 patients, 17 participated in the study per protocol (7 women, 10 men, age: 69 ± 7 yrs., HbA1c: 7.9 ± 1.0%).

The changes in the outcome parameters between baseline and at study end are given in table 1 and figure 1. Glycemic control remained stable. Sensory nerve threshold assessments showed stable results for warm, cold, pain, and vibration perception. No increase in the frequency of hypoglycemic events was seen at any time during the study. A significant increase in GFR, a decrease in creatinine and systolic blood pressure, and an improvement in quality of life was observed.

Parameter	Baseline	Endpoint	Absolute/relative change
HbA1c [%]	7.9 ± 1.0	7.8 ± 0.9	-0.10/-1.3%
GFR [mL/min]	47.6 ± 10.0	53.3 ± 12.0**	5.7 ± 7.8/+11.9%
Creatinine [mg/dL]	1.43 ± 0.29	1.33 ± 0.34*	-0.10 ± 0.14/-7.0%
Systolic BP [mmHg]	139 ± 15	131 ± 14*	8 ± 15/-5.7%
diastolic BP [mmHg]	72 ± 6	72 ± 10	0 ± 11/0.0%
Body weight [kg]	100.1 ± 20.3	99.6 ± 19.8	-0.49 ± 2.22/-0.5%
Treatment satisfaction score	3.71 ± 2.33	2.86 ± 2.70***	-0.98 ± 0.85/-22.9%
Vibration perception [AU]	4.6 ± 3.3	4.5 ± 6.3	-0.1 ± 4.3/ -1.9%
Cold perception [°C]	26.6 ± 3.9	27.8 ± 4.5	1.2 ± 5.4/ +4.3%
Heat perception [°C]	39.4 ± 4.8	38.5 ± 3.4	-0.9 ± 4.4/ -2.3%
Pain perception [°C]	44.4 ± 4.3	43.0 ± 4.1	-1.4 ± 4.4/ -3.1%

Table 1: Changes in parameters evaluated in 17 patients with type 2 diabetes and impaired kidney function treated with PIT.

*, p < 0.05, **, p < 0.01, ***, p < 0.005.

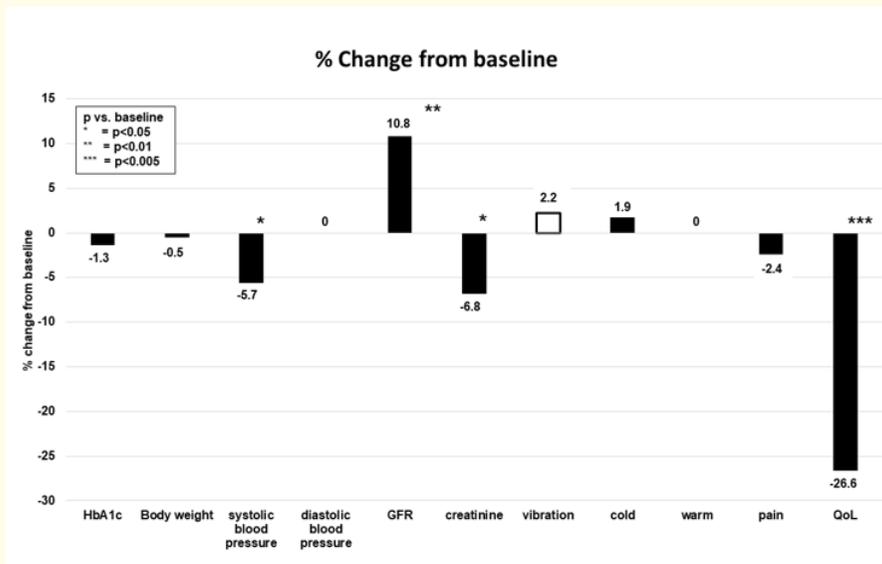


Figure 1: Changes in the key observation parameters evaluated in 17 patients with type 2 diabetes and impaired kidney function treated with pulsatile insulin treatment (a white bar represents an impairment and a black bar represents an improvement of the parameter).

The treatments were well tolerated. In particular, no hypoglycemic events were observed. Five serious adverse events were reported during the study (toe amputation, coronary revascularization, pacemaker insertion, urinary tract infection, COVID-19 pneumonia). None of them was classified to be associated with the PIT procedures. From 22 adverse events reported during the treatment procedures, the most frequent event (muscle cramping, 68% of all events) was classified as most likely related to the study procedure. Two patients reported dizziness and lethargy which was classified to be possibly related to the treatment procedures. From the time periods at home, between procedures, there were 53 adverse events reported. Amongst those, muscle cramps (8 reports/15%), dizziness (3/6%), and lethargy (3/6%) were classified as possibly related to the study procedures.

Discussion

This pilot study is the first report on a potential positive effect of PIT on patients with type 2 diabetes and impaired kidney function. The additional improvement in blood pressure (requiring a lower dose of antihypertensive drugs) is also of note. As early as the 1980's investigators have attempted to replicate normal insulin secretion of the pancreas by applying a series of successively elevated insulin pulses through a catheter. In these studies, it was shown that insulin delivered by intravenous pulses could reach the liver sinusoids of patients with diabetes to restore normal liver metabolic processes [8,15]. However, PIT also exposes many other organs, such as the heart, lungs, kidneys and central nervous system, to concentrated insulin pulses, which could potentially lead to clinically useful signaling effects of insulin including reduction of vascular insulin resistance.

Recent literature reports suggest that vascular insulin resistance, in particular the resistance of insulin receptors of peripheral and glomerular endothelial cells, plays an important role in the development and progression of diabetic nephropathy [19,20]. The insulin receptor is expressed on renal tubular cells and podocytes, and insulin signaling plays an important role in the viability and tubular function of podocytes. Renal sodium transport is maintained during insulin resistance and contributes to salt sensitivity of blood pressure in

hyperinsulinemia. Therapeutically, renal and vascular insulin resistance can be improved through an integrated holistic approach that aims to restore overall insulin sensitivity and improve insulin signaling [21]. Based on our results and the existing literature, we consider PIT to be an old but potentially effective way for the treatment of vascular insulin resistance in patients with type 1 and type 2 diabetes. The pulsatile insulin therapy protocol that we use in our sites mimics both the periodicity and amplitude of normal pancreatic insulin secretion and, according to our initial results, has the potential to result in improvements of diabetes-associated secondary complications.

In this pilot study, we did not observe improvements in glycemic control (HbA1c) over three months, which was occasionally reported in the literature as another effect of pulsatile insulin infusion treatment [8,11]. However, we tried to not focus on improvement of glycemic control in this study. When lacking a true and direct control group, it may be considered an advantage that there was no interference on the observation parameters by an improving glycemic control. Also, this observation is an indicator for the absence of a significant study effect, because this usually leads to improvement of glycemic control in diabetes trials, e.g. because of a more intense physician and patient interaction during the study period.

A well-known side effect of intravenous insulin application is that it can cause a relative hypokalemia, which can induce muscle cramps. If this adverse event occurred in a patient during PIT in our study, they were treated with oral substitution with potassium-containing mineral drinks. This measure resolved the event in a timely fashion, and no patient terminated an ongoing procedure because of this condition. In the following visits, preventive administration of oral potassium reduced the risk for muscle cramps with respect to both incidence and severity.

Conclusion

Based on the results of this pilot study, PIT appears to be a potentially effective way to induce an improvement of kidney function, systolic blood pressure, and treatment satisfaction in patients with type 2 diabetes. The results of this pilot trial will be used to design an appropriate prospective confirmatory study to investigate the effect of PIT when given on top of standard of care treatment.

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