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Effects of Periodic Intensive Insulin Therapy: An Updated Review

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ABSTRACT

Background: Traditional insulin treatment for diabetes mellitus with insulin administered subcutaneously yields nonpulsatile plasma insulin concentrations that represent a fraction of normal portal vein levels. Oral hypoglycemic medications result in the same lack of pulsatile insulin response to blood glucose levels. Intensive treatments of significant complications of diabetes are not recommended due to complicated multidrug regimens, significant weight gain, and the high risk of hypoglycemic complications. Consequently, advanced complications of diabetes do not have an effective treatment option because conventional therapy is not sufficient. Intensive insulin therapy (IIT) simulates normal pancreatic function by closely matching the periodicity and amplitude of insulin secretion in healthy subjects; however, the mechanisms involved with the observed improvement are not clearly understood.

Objective: The current review aims to analyze the pathophysiology of insulin secretion, discuss current therapies for the management of diabetes, provides an updates on the recent advancements of IIT, and proposes its mechanism of action.

Methods: A literature search on PubMed, MEDLINE, Embase, and CrossRef databases was performed on multiple key words regarding the history and current variations of pulsatile and IIT for diabetes treatment. Articles reporting the physiology of insulin secretion, advantages of pulsatile insulin delivery in patients with diabetes patients, efficacy and adverse effects of current conventional insulin therapies for the management of diabetes, benefits and shortcomings of pancreas and islet transplantation, or clinical trials on patients with diabetes treated with pulsed insulin therapy or advanced IIT were included for a qualitative analysis and categorized into the following topics: mechanism of insulin secretion in normal subjects and patients with diabetes and current therapies for the management of diabetes, including oral hypoglycemic agents, insulin therapy, pancreas and islet transplantation, pulsed insulin therapy, and advances in IIT.

Results: Our review of the literature shows that IIT improves the resolution of diabetic ulcers, neuropathy, and nephropathy, and reduces emergency room visits. The likely mechanism responsible for this improvement is increased insulin sensitivity from adipocytes, as well as increased insulin receptor expression.

Conclusions: Recent advancements show that IIT is an effective option for both type 1 diabetes mellitus and type 2 diabetes mellitus patient populations. This treatment resembles normal pancreatic function so closely that it has significantly reduced the effects of relatively common complications of diabetes in

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comparison to standard treatments. Thus, this new treatment is a promising advancement in the management of diabetes. (Curr Ther Res Clin Exp. 2019; 80:XXX–XXX).

Introduction

Diabetes is a chronic disease with dire consequences for personal health and a staggering effect on society and the economy. Since the discovery of insulin extracted from bovine pancreas in 1922, subcutaneous insulin injection has remained a standard treatment for patients with diabetes. Despite the widespread use of subcuticular insulin, diabetes remains a progressive disease. In comparison to intensive insulin therapy (IIT), the current conventional insulin therapy fails to achieve the tight glycemic control that could prevent long-term complications.[1,2] Although multiple factors, such as medication adherence and lifestyle habits, can affect diabetes management and outcomes, improvements in insulin therapy are easier to explore and implement. The lack of efficacy from the current insulin therapy may be attributable to the method of administration rather than quality of exogenous insulin.[3] The subcutaneous delivery of insulin does not have the ability to activate the liver to start a physiologic metabolic cycle. Because the liver normally accounts for approximately 50% of the glucose absorbed in a meal, the loss of proper hepatic glucose metabolism is a key contributor to the inability of patients with diabetes to achieve blood glucose hemostasis.[4] Intensive studies and numerous published articles show evidence suggesting it is not possible to obtain the concentration of insulin required for normal liver functioning through subcutaneous injections of insulin due to its limited absorption rate and blunted strength.[5] Thus, it was theorized that those enzymatic processes in a normal liver that are required to initiate carbohydrate metabolism can be "reactivated" in patients with diabetes with proper signals; that is, concurrent high levels of oral glucose and intravenous insulin administration. This hypothesis is responsible for the development of hepatic activation process via pulsed intravenous insulin delivery under controlled pressure.

This category of insulin treatment is also referred to as pulsatile intravenous insulin therapy, outpatient intravenous insulin therapy, chronic intermittent intravenous insulin infusion, hepatic activation therapy, metabolic activation therapy, or the Harvard Protocol. During each 6-hour session, insulin is infused intravenously in 7 to 10 pulses of approximately 2 units of insulin per pulse over 1 hour along with oral glucose administration, followed by a 1-hour rest period.[6] A patient's blood glucose is maintained between 8.33 mmol/L and 13.9 mmol/L throughout the session. A total of 3 treatments per session are given on the same day once per week.[7,8] Because hepatocytes and adipose tissues have been shown to have increased insulin receptors and enhanced insulin sensitivity when insulin is delivered in a pulsatile manner, this treatment attempts to provide insulin in a novel way that mimics the physiologic secretion of insulin in response to a carbohydrate load.[9,10] The initial trials provided encouraging but limited success.[6] The initial treatment as attempted did not effectively mimic normal human insulin bursts and it did not replicate the periodicity and amplitude of normal pancreatic function. In recent years, significant advancements have been made in pulse intravenous insulin treatment through the use of an insulin pump that infuses microdoses of insulin intravenously, causing oscillations of insulin consistent with the amplitude of normal insulin secretion without an ever-increasing baseline of insulin. Although previous treatment delivered a succession of increasing insulin concentrations to slowly increase the level of free insulin, the improved treatment delivers an insulin burst every 6 minutes to closely mimic the natural burst of insulin secretion from a normal pancreas.

The advanced IIT is an improvement over the original treatment. It mimics both the periodicity and amplitude of normal pancreatic insulin release and provides advantages in managing both type 1 and type 2 diabetes and associated secondary complications. The improved treatment involves 2 to 3 approximately 1-hour sessions during which pulses of microburst intravenous insulin and concurrent weight-based oral glucose doses are administered according to a standard protocol and under medical supervision, typically on an outpatient basis.[5,11] The treatment is individualized to each patient's ability to regulate resting carbohydrate metabolism measured through respiratory quotients and volume of carbon dioxide (VCO_2) using a metabolic cart. Although this treatment has shown remarkable advantages for patients with both type 1 and type 2 diabetes mellitus, the mechanisms involved with the improvement are not clearly understood.

This review highlights the pathophysiology of insulin secretion, discusses current therapies for managing diabetes, provides updates on the advancements of IIT, and proposes mechanisms that may explain the observed prevention or amelioration of diabetes complications by this treatment.

Methods

A comprehensive literature search was conducted on PubMed, MEDLINE, Embase, and CrossRef databased using the search terms *insulin secretion AND oscillations AND diabetic patients*, *pulsatile insulin secretion AND diabetic patients*, *diabetes management AND oral hyperglycemic agents*, *diabetes management AND insulin therapy*, *pancreas transplantation*, *islet transplantation*, *pulsed insulin therapy*, *pulsatile insulin therapy*, and *burst insulin infusion*. A screening of the title and abstract was conducted on original research, review articles, and case reports published in English from 1970 to 2019 using the following criteria: molecular mechanisms of insulin secretion; pulsatile insulin secretion in normal subjects and patients with diabetes; advantages of pulsatile insulin delivery in patients with diabetes; efficacy and adverse effects of current conventional insulin therapies for the management of patients with diabetes, including oral hypoglycemic agents, subcutaneous insulin therapy, and intrapulmonary insulin therapy; benefits and shortcomings of pancreas and islet transplantation; or clinical trials on patients with diabetes treated with pulsed insulin therapy or advanced IIT. Editorial letters were excluded from the analysis. A qualitative analysis was performed on each article after screening and articles were organized by topic: the mechanism of insulin secretion in normal subjects and patients with diabetes and current therapies for the management of diabetes, including oral hypoglycemic agents, insulin therapy, pancreas and islet transplantation, pulsed insulin therapy, and advances in IIT.

Insulin secretion in healthy subjects and patients with diabetes

Insulin secretion in pancreatic beta cells is mediated by the oscillations in the ratio of adenosine triphosphate to adenosine

diphosphate (ATP:ADP) and cytoplasmic calcium ion concentration in response to changes in glucose concentration.[12]

In brief, glucose transporter 2 allows the rapid diffusion of glucose into cells.[13] At high glucose levels (>2.5 mM), glucokinase phosphorylates glucose, leading to a dose-dependent increase in ATP:ADP.[14] ATP-sensitive potassium channels close in response to the rise in ATP:ADP, causing membrane depolarization.[15] Voltage-dependent calium ion channels open to allow the influx of calcium ions that signal the exocytosis of insulin granules.[16]

In both experimental animal and healthy humans, insulin is secreted in a pulsatile manner into portal circulation with a mean period of 5 minutes.[17] Two years after the discovery that plasma insulin levels oscillate in healthy subjects, patients with type 2 diabetes were demonstrated to have an altered pattern of pulsatile insulin release.[18] A similar impairment in the insulin pulsatility was observed in patients with type 1 diabetes compared with control patients with similar plasma glucose levels after fasting.[19] Type 2 diabetes is characterized by increased insulin resistance with decreased glucose clearance rate, and patients with type 2 diabetes were found to have irregular insulin pulses with higher frequency.[9] Another study revealed that a longer insulin pulse period was associated with decreased insulin sensitivity, indicating that increased pulse frequency could be linked to insulin resistance as noted in patients with type 2 diabetes.[20] More specifically, a study that measured insulin pulses over a 24-hour period found that insulin pulses of patients with type 2 diabetes have reduced amplitude when compared with matched controls.[21] Patients with obesity and diabetes were also shown to have insulin pulses with lower amplitude than control patients with obesity, and weight loss in these patients was accompanied by an increase in pulse amplitude.[22] Further studies found that ability of entrainment to small oscillations in plasma glucose concentrations was lost in patients with type 2 diabetes, which contributed to the diminished abilities to regulate insulin pulses.[23,24]

Pulsatile insulin delivery is superior to continuous delivery in patients with diabetes by enhancing hepatic insulin action and signaling.[25] In patients with type 1 diabetes mellitus, insulin delivered in a pulsatile manner markedly reduces hepatic glucose production in comparison to continuous insulin delivery, possibly due to the increased insulin sensitivity by limiting the downregulation of hepatic insulin receptors.[26] A higher level of hepatic insulin extraction was observed with insulin pulses of larger amplitude than smaller insulin pulses or continuous insulin infusion, leading to a lower fluctuation in the amplitude of peripheral insulin pulses.[27]

Current therapies for diabetes

Diabetes is a progressive disease that often requires multiple therapies to effectively maintain long-term glycemic control and prevent further complications. Biguanides are recommended as a first-line agent by reducing hepatic glucose production and improve insulin sensitivity.[28,29] Sulfonylureas are commonly used to increase endogenous insulin production by increasing beta-cell function.[30] Thiazolidinediones acts as insulin sensitizers to lower insulin resistance by activating the peroxisome proliferator-activated receptors.[31] Treatment of diabetes with incretin-based therapies can increase insulin secretion and inhibit glucagon secretion and is associated with lower rates of hypoglycemia compared with other diabetes treatment.[32] However, they have been linked to the suppression of gastrointestinal motility and pancreatitis.[33] Alpha-glucosidase inhibitors are used to lower postprandial blood glucose and insulin levels by delaying carbohydrate absorption.[34] Sodium-coupled glucose cotransporter 2 inhibitors have been used to inhibit glucose reabsorption in the proximal tubule to lower blood glucose independently of patient's insulin secretion or sensitivity, but their long-term side effects are still unclear.[35] Failure of monotherapy in patients with diabetes is common and requires additional therapies and insulin use to maintain long-term glycemic control, leading to significant weight gain, high risk of severe hypoglycemia, and low adherence to complicated multidrug regimens.

Insulin therapy

Bovine insulin was first extracted and used as a subcutaneous treatment for patients with type 1 diabetes by Banting and Best in 1922.[36] Since its discovery, subcutaneous insulin administration still remains an essential therapy to achieve tight glycemic control. As indicated in the Diabetes Control and Complications Trial, intensive insulin injection regimens are associated with significant weight gain and an increase in severe hypoglycemic events.[1] Rapid- and long-acting insulin analogues as well as insulin-infusion pumps have been developed in an attempt to attain and maintain near-euglycemia.[37] Studies have suggested that continuous insulin delivery using insulin pumps could be beneficial in patients with diabetes with frequent, unpredictable hypoglycemia or dawn phenomenon.[38] Intrapulmonary insulin administration through inhalation offer a more convenient method for insulin delivery and has been demonstrated have a longer duration with a comparable absorption rate to rapid-acting insulin.[39] Its short-term efficacy and safety have been studied in both patients with type 1 and type 2 diabetes, showing either similar or improvement in glycemic control in comparison to conventional insulin injections after 3 months with no marked change in pulmonary function.[40,41] The benefits of inhaled insulin are mainly due to a reduction in the need of multiple insulin injections, leading to a reduction in the significant weight gain phenomenon and improved adherence, especially in patients who are unwilling to comply with insulin injections.[42] Although inhaled insulin therapy is an appealing option, its cost is significantly higher than subcutaneous insulin.[43] Studies to establish clear dosage guidelines, particularly in patients with compromised lung function, and the clinical consequence of increased production of anti-insulin antibody are still lacking.[44,45] In addition, limited large-scale studies on the long-term potency and safety of inhaled insulin prevent its widespread clinical use. Despite significant developments, current insulin therapy has limited success in replicating the pulsatile pattern of natural insulin secretion or effectively maintains long-term glycemic control, leading to the development of microvascular and macrovascular complications.

Pancreas and islet transplantation

Beta-cell replacement is an appealing therapy by allowing patients with type 1 diabetes to be insulin independent with higher quality of life and reduced vascular complications. Pancreas transplantation is recommended for patients who undergo kidney transplant because they are required to take immunosuppressants.[46] Donor pancreas supplies are limited and the procedure carriers a significant risk of surgical complications.[47] Islet transplantation is a less invasive procedure in which islets are infused into the liver via the portal vein. In comparison to pancreas transplantation, islet transplantation has lower rates of long-term complications with a comparable rate of insulin independence after 3 years.[48,49] Similar to normal insulin secretion, insulin secreted by transplanted islets directly enters the liver via the hepatic sinusoid for extraction.[50] In addition, studies have reported that intraportally transplanted islets secrete insulin in a pulsatile manner and response to glucose stimulation through the amplification of pulse size.[50,51] Barriers to the widespread application of islet transplantation are the lack of donors and difficulty achieving sufficient adequate quality islets after isolation. However, islet transplantation is a rapidly evolving therapy and undergoing extensive research to improve

islet isolation, enhance posttransplant islet function and survival, develop alternative islet sources, and reduce immune response activity.

Pulsed intravenous insulin treatment

Early trials conducted at the University of California, Davis, and Scripps Clinic using pusled insulin therapy attempted to replicate the normal insulin secretion of the pancreas by delivering a series of successively increased insulin bursts into an intravenous catheter, leading to an increasing free insulin level during the treatment. Studies have suggested that insulin delivered through intravenous pulses could reach the hepatic sinusoids of patients with diabetes to restore normal liver metabolic processes similar to those seen in individuals without diabetes.[5] In comparison to healthy subjects, pulsed insulin therapy exposes other organs, such as the heart, lungs, kidneys, and central nervous system, to concentrated pulses of insulin, which perhaps could be a contributing factor to its clinical benefits. In a study of 20 patients with type 1 diabetes with brittle diabetes, treatment with pulsed intravenous insulin for an average of 41 months reduced the average glycated hemoglobin (HbA1c) level to 7.0% compared with the baseline level of 8.5%.[7] Both major and minor hypoglycemic events also decreased from 3.0 to 0.1 per month and 13.0 to 2.4 per month, respectively. Patients with type 1 diabetes with hypertension and nephropathy had a significant improvement in blood pressure control after 3 months of pulsed insulin therapy, as evidenced by a lower dose of antihypertensive medication required to maintain a blood pressure $\leq$140/90 mm Hg.[52] Similarly, the addition of pulsed insulin therapy to conventional insulin therapy in a multicenter, prospective, controlled clinical trial significantly lowered HbA1c level and rate of decline in creatinine clearance compared with pulsed insulin therapy alone after 18 months.[53] In a clinical trial involving 74 patients with type 1 diabetes, pulsed insulin therapy in addition to intensive subcutaneous insulin therapy significantly decreased the HbA1c level and prevented worsening of abnormal circadian blood pressure pattern in the group receiving pulse intravenous insulin treatment but not the control group that received only intensive subcutaneous insulin therapy after 3 months.[54] In a small clinical trial, pulsed insulin therapy was found to alleviate symptoms of severe orthostatic hypotension in patients with type 1 diabetes.[8]

Advances in IIT

In comparison to conventional IIT, which does not closely mimic the periodicity and amplitude of normal pancreatic function, a new alternative is improved treatment for patients with diabetes wherein insulin is administered intravenously in a microburst pulsatile manner with an amplitude of normal insulin release without increasing the baseline level of insulin. A treatment session consists of 2 to 3 1-hour intravenous insulin infusions with a 30-minute rest between each treatment using an insulin pump, which involves the pulsatile delivery of microburst insulin under controlled pressure based on programmed information that includes oral glucose intake and the average caloric need of the individual in accordance with body weight. This insulin pump delivers fast-acting insulin every 6 minutes through a peripheral vein in the hand or forearm. Capillary blood glucose levels are monitored every 24 minutes. One method used to determine the effectiveness of this treatment involves measurement of carbohydrate metabolism. To measure carbohydrate metabolism, indirect calorimetry is used. This process involves measurement of oxygen consumption and VCO_2. The respiratory exchange ratio (RER) indicates the metabolic rate by measuring the carbon dioxide produced per unit of oxygen indicated in the following equation:

Table 1
The effects of intensive insulin therapy on metabolic rate measurements.

	Baseline mean (n = 311)	End-of-treatment mean (n = 311)
VO_2 (L/min)	271.7	283.8
VCO_2 (L/min)	246.9	270.5
CHO oxidized (%)	66.1	78.0
Respiratory exchange ratio*	0.91	0.96
Resting metabolic rate (kcal)	1916	2021

CHO = carbohydrate; VCO_2 = carbon dioxide output; VO_2 = oxygen consumption.
* VO_2/VCO_2.

VCO_2/oxygen consumption. This ratio varies depending upon the metabolic component utilized. In lipid metabolism, which is typically present in diabetic patients, the RER is 0.7. In efficient carbohydrate metabolism, this ratio equates to 1.0, which is the greatest value of all macronutrients. Thus, a greater RER value is indicative of greater carbohydrate metabolism and less lipid metabolism. In a recent study, including 311 patients, this advanced IIT was used in addition to their typical insulin regimen and oral hypoglycemic agents. The results demonstrated a significant change in the post-treatment RER relative to both baseline and midtreatment RER (Table 1). Therefore, carbohydrate oxidation significantly increased with the addition of this treatment, which indicated that insulin favors carbohydrate oxidation rather than lipids for energy production.[11] The results demonstrated that this type of pulsed insulin infusion has a dramatic effect on carbohydrate metabolism, overcoming the reduction of resting metabolic rate seen with conventional subcuticular insulin treatment. This improvement is especially important because the inability to properly metabolize carbohydrates represents a core dysfunction in diabetes. By preferentially converting energy production to carbohydrate metabolism, relative to lipids, patients with diabetes avoid the consequences of elevated free fatty acids, which trigger a cascade of inflammatory processes. Several other studies assessing various complications of diabetes have demonstrated the effectiveness of this new therapy.

Diabetic neuropathy

Peripheral diabetic neuropathy is a common complication of diabets occurring in 16% to 34% of the population with diabetes. The pathophysiology of this condition is not completely understood; however, it has been theorized to be a result of mechanisms such as the polyol pathway, microvascular changes, and oxidative stress.[55] Currently, this condition is treated by a variety of pharmacological interventions, including selective-serotonin reuptake inhibitors, tricyclic antidepressants, and anticonvulsants. These medications are typically used as adjunctive therapies to analgesic medications such as opiates because they have limited effectiveness when used alone. In a study of 412 patients with diabetes, this advanced IIT was implemented using the same methodology mentioned above to assess for a reduction in painful neuropathy. The patients were treated with this therapy on a weekly basis over a period of 3 months. No neurologic or analgesic treatments were used over the course of the study. The participants were assessed into 3 categories: no symptom improvement, significant symptom improvement, or complete resolution of symptoms. After 3 months of treatment, 47.5% of patients reported a complete resolution of symptoms, 45.5% reported a significant improvement in symptoms, and 7% reported no difference in symptoms.[11] Thus, this advancement is a viable treatment option for peripheral neuropathy.

Table 2
The effects of intensive insulin therapy on wound healing of peripheral diabetic ulcerations.

Case study	Ulcer size (cm^2)	Total pulsed intravenous insulin treatment	Days to heal
1	1	19	180
2	6.4	38	32
3	12	30	36
4	18	19	71
5	228.6	20	102
Literature cases[1,*]	6.12	None	133[†]

[1] Zimny S, Schatz H. Determinants and Estimation of Healing Times in Diabetic Foot Ulcers. J Diabetes Complications 2002;16(5): 327-32.
[*] Eight cases.
[†] Only 5 healed.

Table 3
A comparison of hospital utilization rates (adjusted for 2 years) in patients with diabetes treated with pulsed intravenous insulin and matched National Hospital Discharge Survey (NHDS) data.

	Study group	NHDS data
Total number of events counted	5	94
Total person-years	1524	1000
Incidence rate	0.003281	0.047
Incidence rate difference	−0.04372	

Table 4
A comparison of emergency room utilization rates (adjusted for 2 years) in patients with diabetes treated with pulsed intravenous insulin and matched US Agency for Healthcare Statistics (USAHS) data.

	Study group	USAHS data
Total number of events counted	7	116
Total person-years	1524	1000
Incidence rate	0.004593	0.058
Incidence rate difference	−0.005341	

Diabetic ulcerations

Diabetic foot ulcerations are a complication present in 4% to 10% of the population with diabetes with 5% to 24% resulting in amputation. Peripheral diabetic ulcerations occur in part from neuropathy, which can result in trauma to an extremity due to loss of sensation. These ulcerations commonly occur on the foot due to a combination of neuropathy, tissue deformities, poor wound healing, and possibly repetitive trauma. Traditional treatment includes wound debridement accomplished by implementing enzymatic, mechanical, and/or autolytic methods.[56]

A recent study entailed the aforementioned IIT for the diabetic ulcerations of 5 patients (Table 2). In that study, treatment was administered in the same fashion mentioned above up to 5 times a week. It was utilized as an adjunctive therapy to traditional diabetic wound care. The mean healing time of these wounds was 84.2 days compared with the average of 133 days. Therefore, the addition of this treatment yielded quicker healing time by 49 days, which equates to a 37% reduction relative to the average wound healing time.[57] There were also no amputations in the treatment group, which was an unexpected, but encouraging outcome.

Emergency room use

A retrospective analysis was conducted to determine whether or not advanced IIT has a beneficial effect on patients with diabetes as determined by hospital and emergency room use when compared with matched National Hospital Discharge Survey and US Agency for Healthcare Statistics for homologous patients.[11] Tables 3 and 4 show a 2-year retrospective study conducted at 14 treatment centers involving 1524 patients with type 1 and type 2 diabetes with 2 or more secondary complications of diabetes, that included patients with histories of multiple hospitalizations and emergency department visits before initiation of treatment. All study patients were treated with the protocol as described previously in addition to their regular hypoglycemic therapy. The clinical advantages of this advanced treatment on emergency room admissions and hospitalizations was clear: This retrospective study observed reduced hospitalization in a large group of patients with diabetes with 2 or more serious comorbidities to 1.65/1000/ year (vs National Hospital Discharge Survey estimated rate of 46.7/1000/year) and emergency department visits to 2.3/1000/year (vs US Agency for Healthcare Statistics estimated rate of 58.4/1000/year). This represents a significant reduction in hospital admissions and emergency department use.

Diabetic nephropathy

Diabetic nephropathy occurs in one third of all patients with type 1 diabetes and is the number-1 cause of chronic renal failure in developed nations. Several factors contribute to the development of nephropathy, which include activation of the polyol pathway, genetic expression, atypical protein kinase activation, oxidative stress, and generation of advanced glycation end products.[58] Typical treatment focuses on pharmacologic blood pressure management, diet and lifestyle changes, lipid level control, and glycemic control. Glycemic control is traditionally maintained using subcutaneous insulin injections and diet and activity regulation.[59]

The advanced IIT previously mentioned is a possible treatment option; however, it is still a relatively new technology. Consequently, no retrospective studies have been performed. Albeit less similar to normal insulin secretion than the newer treatment, IIT has been effective for diabetic nephropathy in recent research. A clinical study conducted in 2010 including 65 patients was conducted over a 6- to 22-month period. That study demonstrated a significant increase in serum creatinine in the control group, but not in the group receiving weekly IIT. Creatinine clearance decreased in both groups, although the decrease was less significant in the group receiving weekly IIT compared with standard care.[60]

Potential mechanisms

Considering that insulin is secreted into the portal vein, hepatocytes are the first cells to respond to changes in insulin release. A pulsatile secretion of insulin has been shown to decrease hepatic glucose production by 25% to 30% relative to typical treatment with the same insulin dosage regimen.[61] In addition, adipocytes displayed increased insulin sensitivity with pulsatile insulin release.[9] It is likely that the increased hypoglycemic action produced by this treatment is associated with greater expression of insulin receptors present in the target tissues. Insulin receptor expression was demonstrated to increase significantly in conjunction with oscillatory insulin release.[10] These oscillatory patterns could possibly lead to down-regulation of insulin receptors, which is significant due to the presence of insulin receptors on the beta cell itself.[62]

Cost-effectiveness, pitfalls, and practical applications of IIT

Unfortunately, the cost of pulsed insulin therapy or IIT has not been documented in the literature. However, the significant reduction in the number of hospital admissions and emergency room visits in patients treated with this therapy could considerably lower health care expenditures. In addition, the substantially faster recovery of diabetic foot ulcers and reduction in diabetic neuropathy pain after undergoing this therapy could not only improve the quality of life in patients with diabetes, but also represent a marked savings opportunity compared with

prolonged traditional therapies. Although pulsed insulin therapy is an appealing treatment for patients with diabetes with promising results, the inconvenience of having to visit a clinic that offers the therapy could be a concern that leads to decreased adherence. Each weekly therapy session, which lasts approximately 5 hours, requires time commitments from both patients and medical professionals. Although the side effects from this therapy have not been well studied, a trial has shown that no adverse complications were observed in more than 60 treated patients.[7] Patients undergo advanced IIT in addition to their standard diabetes regimen, which can include insulin injections, oral hypoglycemic agents, exercise, and diet.[11] The recent encouraging outcomes of advanced IIT in patients with diabetic foot ulcers, diabetic neuropathy, and diabetic nephropathy suggest that this promising treatment is a referral option that general practitioners can use to supplement conventional therapies and prevent long-term complications as part of preventative care for patients with diabetes.

Conclusions

Traditional insulin regimens are less efficacious than IIT due to its delivery, which is inferior in juxtaposition to a pulsatile administration. Recent advancements have shown that IIT is an effective option for patient populations with both type 1 and type 2 diabetes. This treatment resembles normal pancreatic function so closely that it has significantly reduced the effects of relatively common complications from diabetes such as neuropathy, nephropathy, and ulcerations in comparison to standard treatments. In addition, the improved IIT improves carbohydrate metabolism as well as decreases emergency room and hospital visits associated with diabetes. Thus, this new treatment is a promising advancement in the management of diabetes.

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Conflicts of Interest

A. Cimler, J. Elliott, S. Escovar, and J. Novak have previously treated patients using the pulsed insulin treatment described in this work and are employed by companies using the treatment. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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