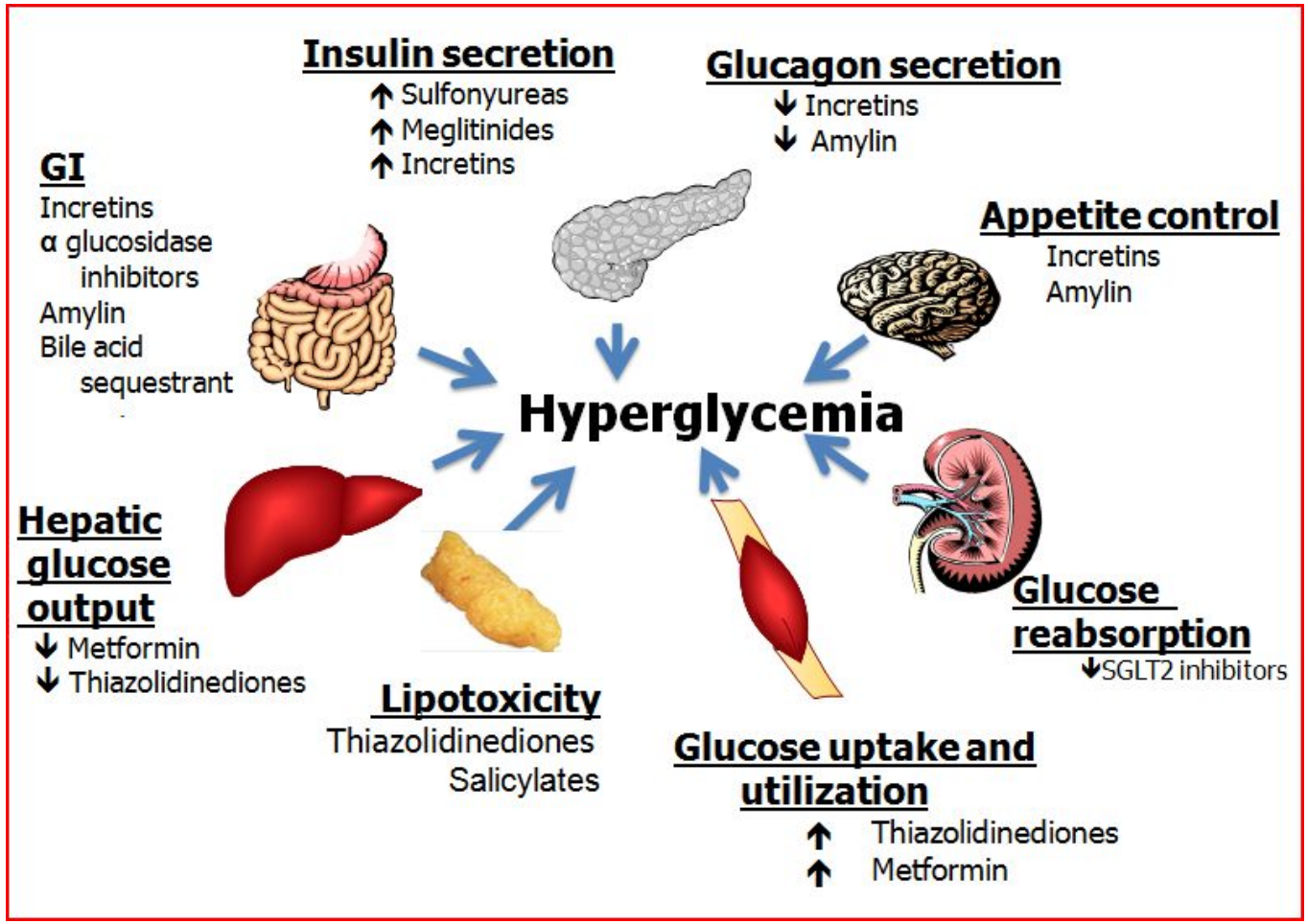
Artificial Pancreas Treatment®

Gordon K. Lam, MD, FACP, FACR

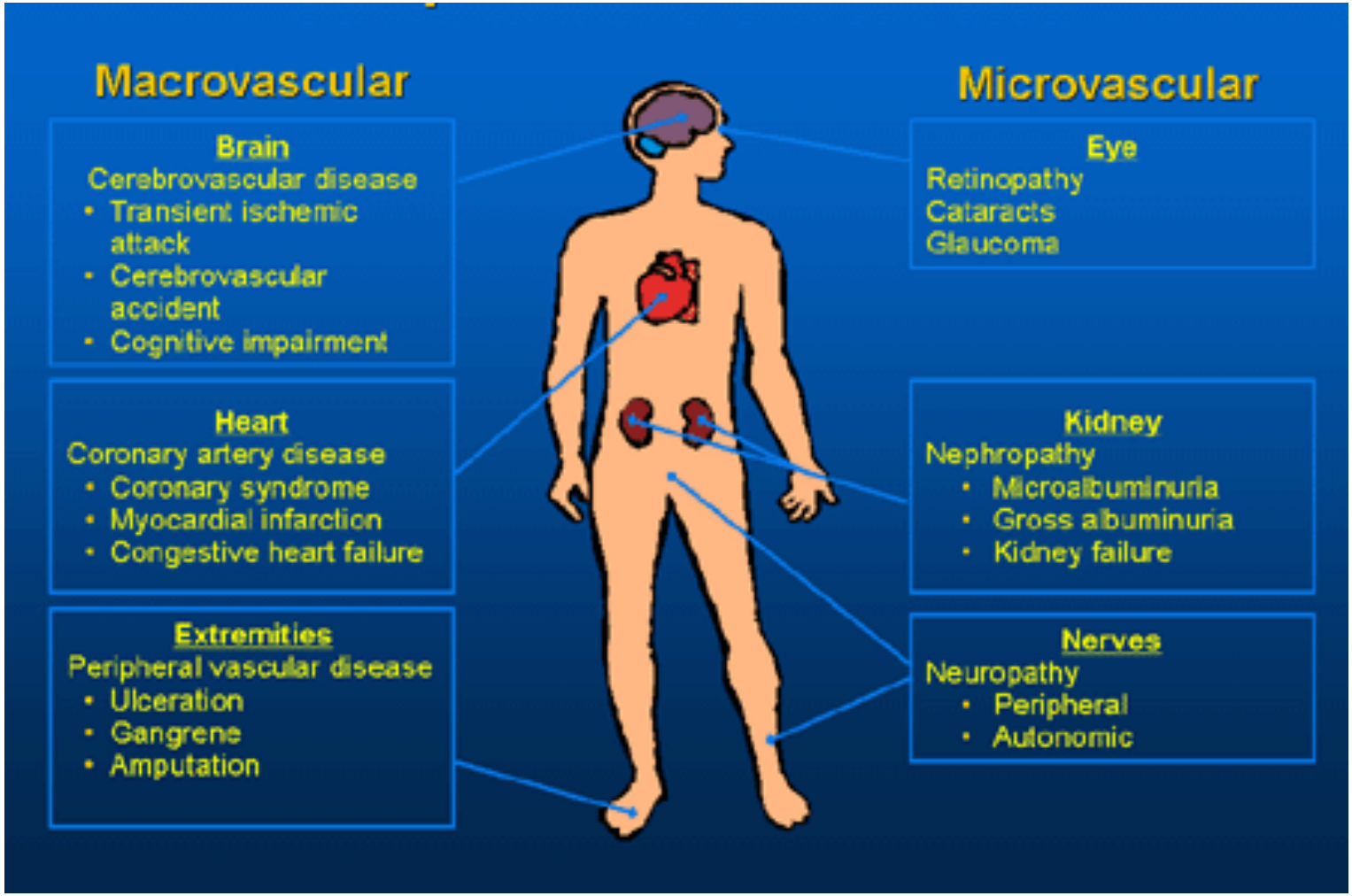
North Carolina, USA

January 31, 2014

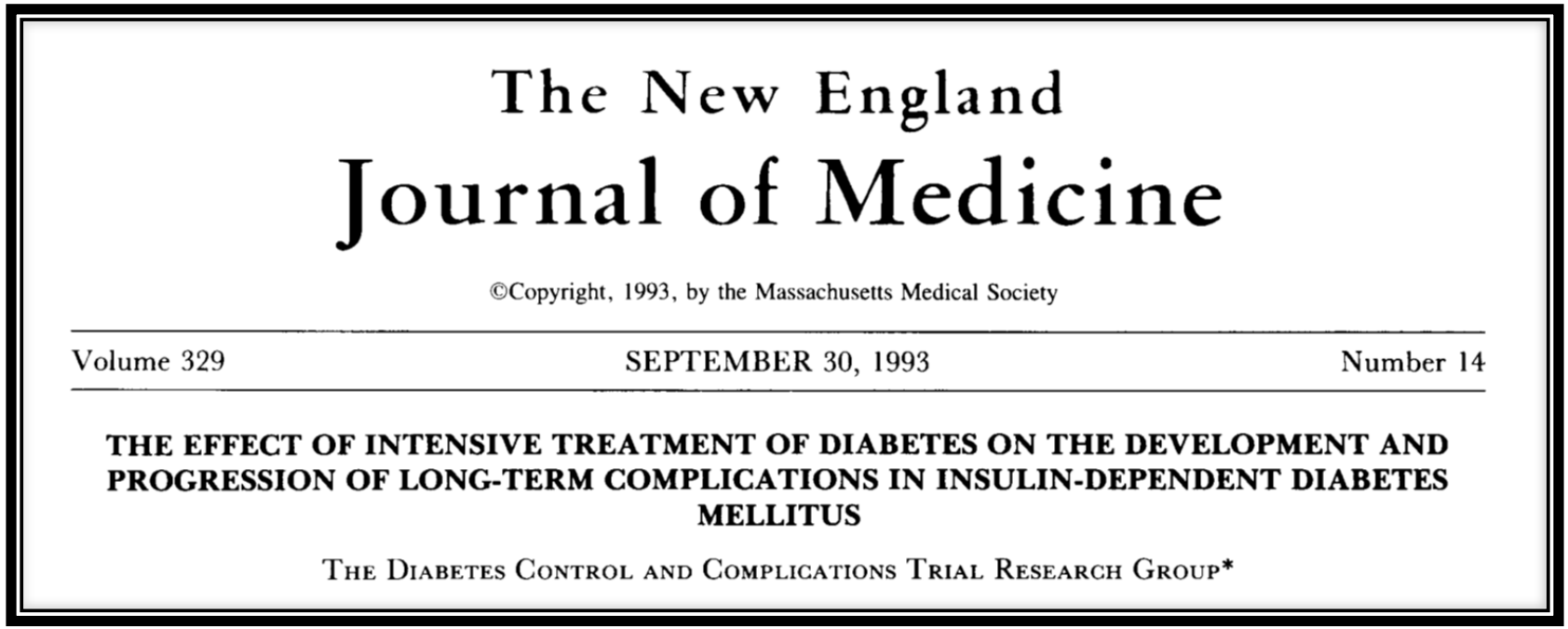
Traditional Treatment of diabetes



Complications of diabetes



DCCT – Diabetic Control and Complications Trial
Tight Blood Glucose Control Does Not Stop Complications



The New England
Journal of Medicine

Volume 329 SEPTEMBER 30, 1993 Number 14

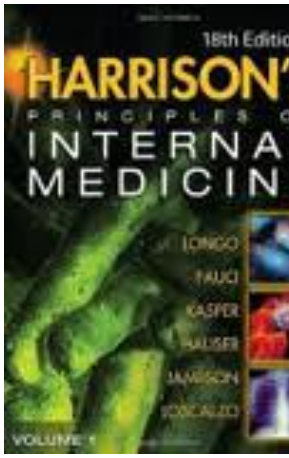
THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

- Intensive insulin therapy (tight glucose control) delays the onset and slows the progression of diabetic complications in patients with IDDM, yet
- Development of retinopathy, neuropathy, and nephropathy still ranged 24-66%

Missing the forest for the trees

- Goal of most diabetic treatment is to reduce hyperglycemia and to re-establish euglycemia
- However, diabetes is a systemic metabolic disease
- Conventional therapy does not restore normal glucose metabolism or blood glucose control
- Conventional therapy does not recapitulate the endogenous insulin secretion and systemic metabolic effects



The Best Treatment Mimics Normal Insulin Secretion & Endogenous insulin is secreted in a pulsatile manner

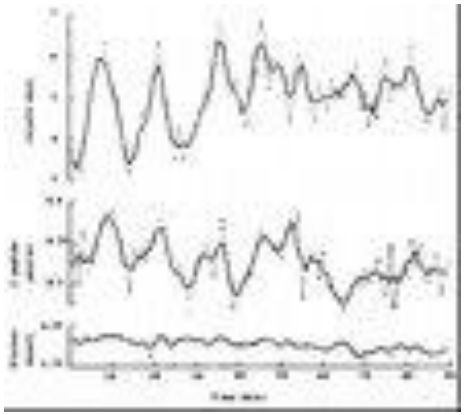
The NEW ENGLAND JOURNAL of MEDICINE

Cyclic oscillations of basal plasma glucose and insulin concentrations in human beings

Lang DA, Matthews DR, Peto, J, Turner RC

1979;301:1023-1027

Based from Goodner CJ, et al. Insulin, glucagon, and glucose exhibit synchronous, sustained oscillations in fasting monkeys. *Science*. 1977; 195:177-79.



Endogenous insulin is secreted in a pulsatile manner

Diabetologia
Journal of the European Association for the Study of Diabetes (EASD)

Pulsatility of insulin and glucagon release: physiological significance and pharmacological implications

Lefebvre PJ, Paolisso G, Scheen A, Henquin JC

1987;30:443-53

Endogenous insulin is secreted in a pulsatile manner

Pulsatile insulin delivery has greater metabolic effects than continuous hormone administration in man: importance of pulse frequency

Paolisso G, Scheen A, Giugliano D, et al.

1991;72:607-615

Endogenous insulin is secreted in a pulsatile manner

Glucose-induced amplitude regulation of pulsatile insulin secretion from individual pancreatic islets

Bergsten P and Hellman B.

1993; M42: 670-4.

Endogenous insulin is secreted in a pulsatile manner

American Physiological Society
AMERICAN JOURNAL of PHYSIOLOGY
Endocrinology and Metabolism

Pulsatile (burst) insulin secretion accounts for 70% of total insulin secretion during fasting

Porksen N, Munn S, Steers J, et al.

Am J Physiol. 1995; 269:E478-88

Endogenous insulin is secreted in a pulsatile manner

Direct measurement of pulsatile insulin secretion from the portal vein in human subjects

Song SH, McIntyre SS, Shah H, et al.

2000; 85: 4491-4499

Endogenous insulin is secreted in a pulsatile manner

Pulsatile insulin secretion by human pancreatic islets

Song, SH, Kjems L, Ritzel R, et al.

2002; 87: 213-221

Why does pulsatile insulin matter?

- **Pulsatile delivery of insulin has a greater hypoglycemic effect**

  - Matthews DR et al. *Diabetes*. 1983; 32: 617-21.

- **Pulsatile insulin enhances peripheral glucose uptake**

  - Schmitz O et al. *Acta Endocrinologica*. 1986; 113: 559-63.

- **Pulsatile insulin maintains peripheral insulin receptor sensitivity.**

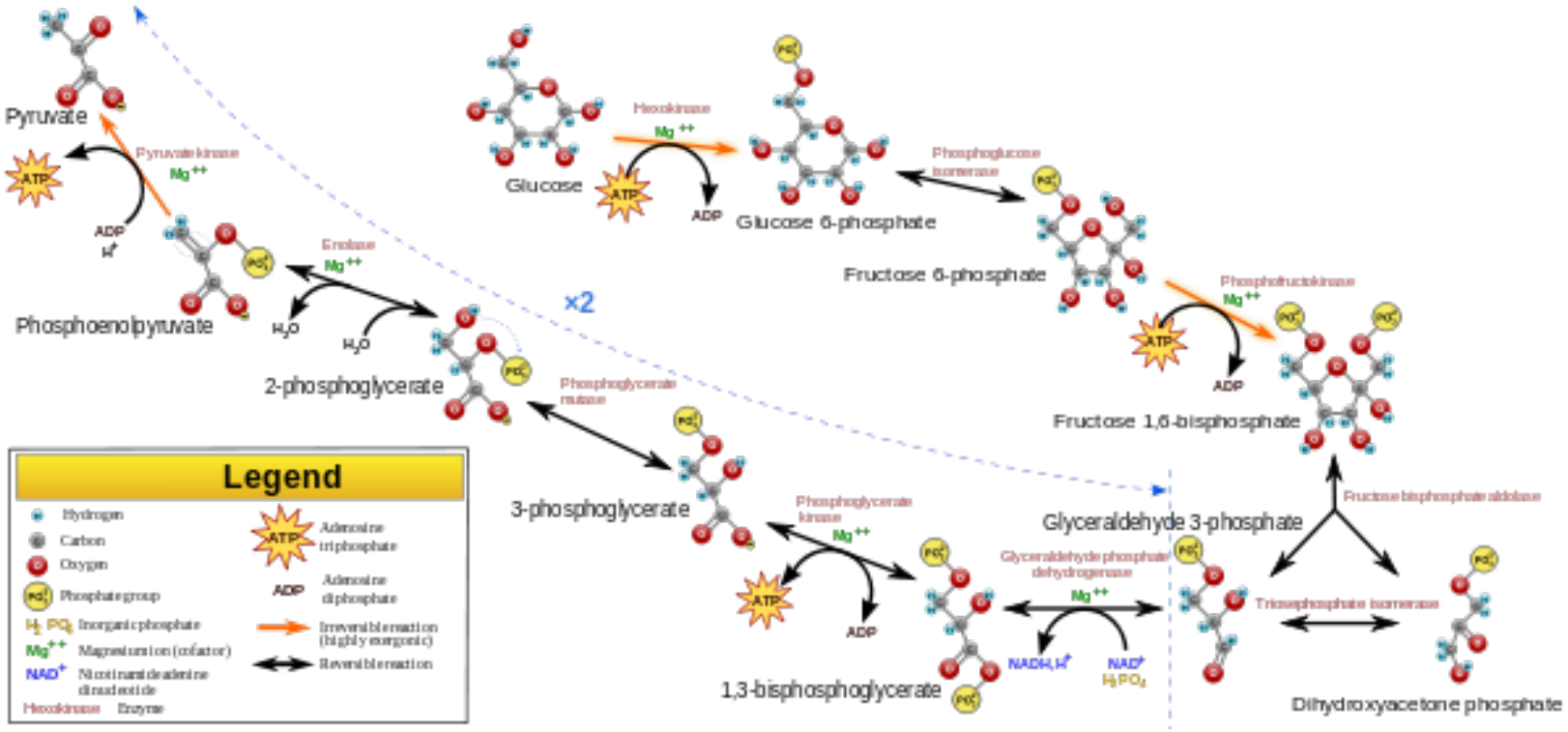
  - Ward GW et al. *Diabetes*. 1990; 39: 501-7.

- **Pulsatile insulin upregulates metabolic enzymes of glycolysis and the Kreb's cycle**

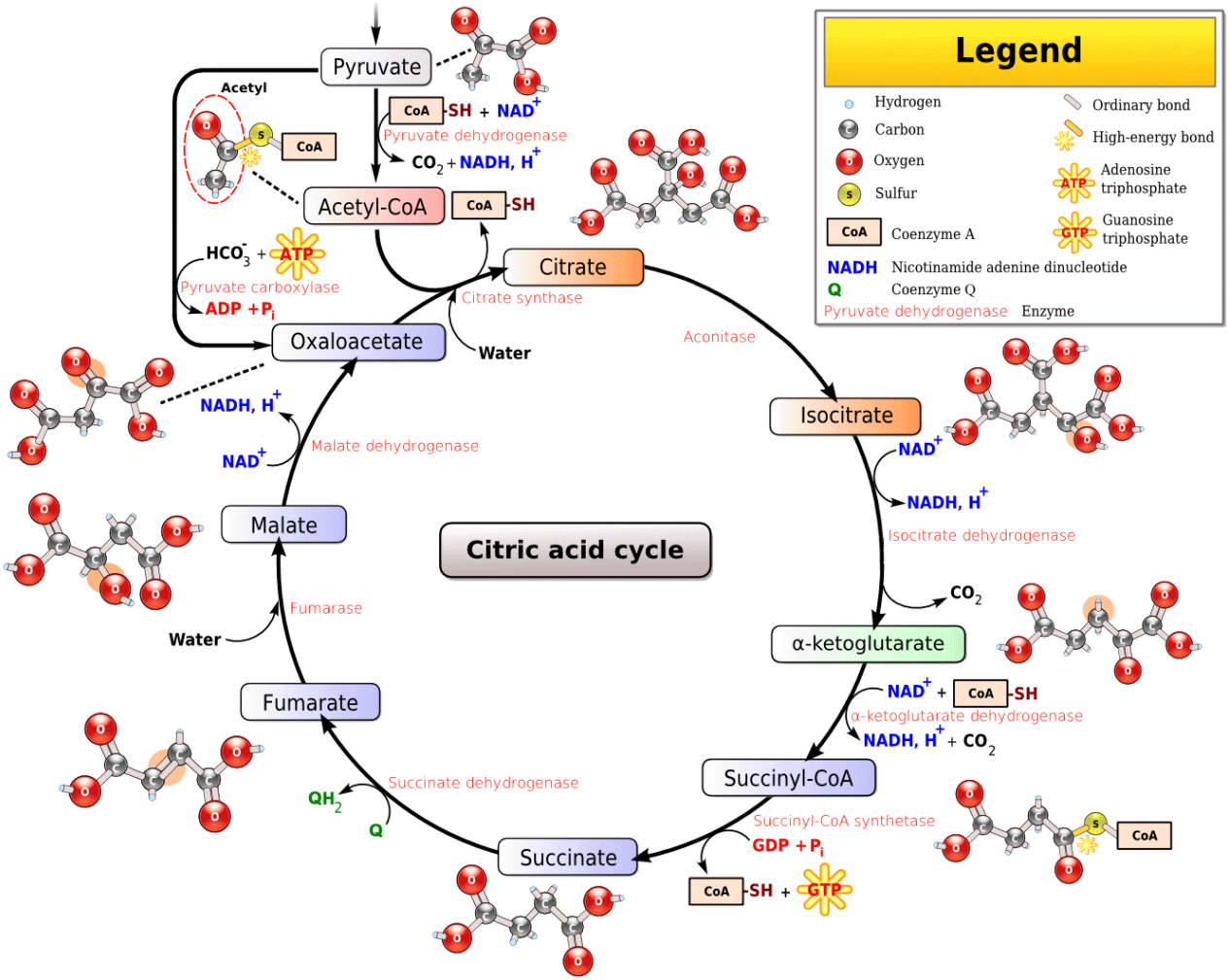
1. Glucokinase (hexokinase)
2. Phosphofructokinase
3. Pyruvate kinase
4. Pyruvate dehydrogenase
5. Acetyl-CoA carboxylase

  - In: Greenspan FS, ed. *Basic and Clinical Endocrinology*, 3d ed. Norwalk CT: Appleton and Lange, 1991

Glycolysis


Pyruvate
ATP
ADP
Pyruvate kinase
Mg ++
Phosphoenolpyruvate
Enolase
Mg ++
H2O
H2O
2-phosphoglycerate
×2
Phosphoglycerate mutase
3-phosphoglycerate
Phosphoglycerate kinase
Mg ++
ATP
ADP
1,3-bisphosphoglycerate
Glyceraldehyde phosphate dehydrogenase
Mg ++
NADH,H+
NAD+
H3PO4
Glyceraldehyde 3-phosphate
Fructose bisphosphate aldolase
Triosephosphate isomerase
Dihydroxyacetone phosphate
Glucose
Hexokinase
Mg ++
ATP
ADP
Glucose 6-phosphate
Phosphoglucose isomerase
Fructose 6-phosphate
Phosphofructokinase
Mg ++
ATP
ADP
Fructose 1,6-bisphosphate
Legend
Hydrogen
Carbon
Oxygen
Phosphate group
Inorganic phosphate
Magnesium ion (cofactor)
Nicotinamide adenine dinucleotide
Hexokinase Enzyme
ATP Adenosine triphosphate
ADP Adenosine diphosphate
Irreversible reaction (highly exergonic)
Reversible reaction

Krebs cycle


Legend
Hydrogen
Carbon
Oxygen
Sulfur
Coenzyme A
Nicotinamide adenine dinucleotide
Coenzyme Q
Pyruvate dehydrogenase Enzyme
Ordinary bond
High-energy bond
Adenosine triphosphate
Guanosine triphosphate
Pyruvate
Acetyl
CoA
Pyruvate dehydrogenase
Acetyl-CoA
Citrate
Citrate synthase
Water
Oxaloacetate
Pyruvate carboxylase
ADP +Pi
Aconitase
Isocitrate
Isocitrate dehydrogenase
α-ketoglutarate
α-ketoglutarate dehydrogenase
Succinyl-CoA
Succinyl-CoA synthetase
Succinate
Succinate dehydrogenase
Fumarate
Fumarase
Malate
Malate dehydrogenase
Citric acid cycle

Pulsatile portal vein insulin delivery

Enhances hepatic insulin action and signaling

- Large percentage (~55-60%) of insulin secreted from the pancreas to the liver via the portal via is extracted

- Loss of pulsatile insulin secretion leads to intrahepatic molecular changes and altered gene expression consistent with development of hepatic insulin resistance

- Mechanism was delayed or impaired phosphorylation of intracellular insulin signaling proteins IRS-1, IRS-2, Akt, and Foxo1

Matvenyneko AV, et al. *Diabetes*. 2012; 61: 2269-79.

Flaws of subcutaneous insulin delivery

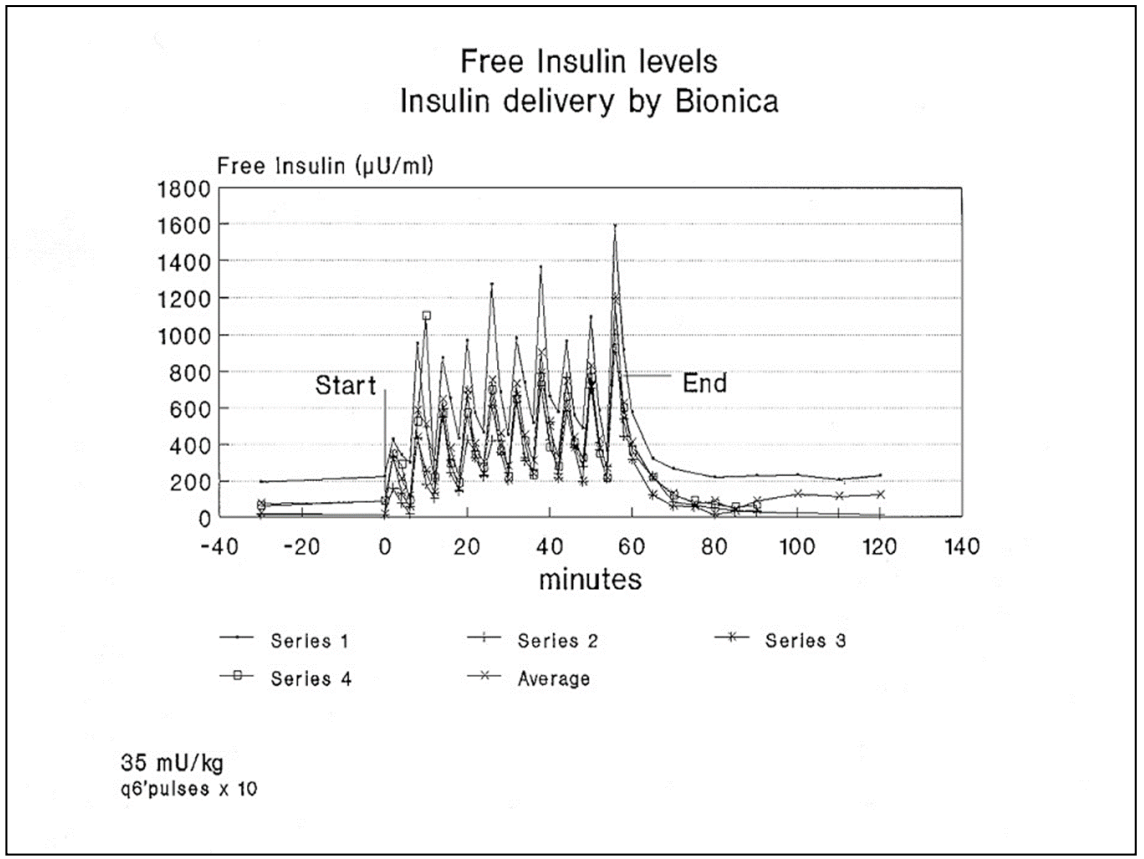
Pharmacokinetics

- Delayed absorption
- Intrapatient absorption variability (up to 35% → metabolic lability)
- Increases systemic insulin concentrations before reaching the liver
- Dosage attrition

Bionica Pump

- Goal is to re-establish normal metabolism by recapitulating pulsatile insulin effects to the liver
- Uses a patented, FDA-cleared pump (Bonica) that re-approximates the periodicity and amplitude of pancreatic insulin secretion to the portal vein
- Achieves physiological insulin concentrations in the portal vein
- Adjunctive therapy (intended to be combined with daily intensive hypoglycemic therapy)

Bionica Pump
Mimics a Normal Pancreas Pulsed Insulin



- ISO 13485:2009 compliant
- US FDA cleared
- Australian (Therapeutic Good
- South Africa FDA
- Mexico COFEPRIS (FDA)
- Kingdom of Thailand FDA
- India exemption
- European CE

Bionica

- Developed in academic settings
  - Harvard (Joslin)
  - Scripps Clinic
  - Mayo Clinic
  - University of Arizona
  - Temple University
  - University of California-Davis
  - University of Maryland
- 16 clinical trials published in peer-reviewed journals
- Ongoing clinical trials in collaboration with Trina Health of the Carolinas

Bionica Pump


Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus

Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus

Aoki TT, Benbark MM, Okimura MC et al.

Lancet. 1993; 342: 515-7.

Results:

1.HgbA1c decreased from 8.5% to 7.0% at 41 months ($p < 0.0003$)

2.Frequency of major hypoglycemic events decreased from 3.0 events/ month to 0.1 events/month ($p < 0.0001$)

3.Frequency of minor hypoglycemic events decreased from 13.0 events/ month to 2.4 events/month ($p < 0.0001$)

Bionica Pump

Effect of chronic intermittent intravenous insulin therapy on antihypertensive medication requirements in IDDM subjects with hypertension and nephropathy

Aoki TT, Grecu EO, Prendergast JJ, et al.

Diabetes Care. 1995; 18(9): 1260-5.

Purpose: To assess the effects of CIIIT on hypertension control

Design: Prospective, randomized, crossover trial; 26 pts; 6 months

Outcome measures: Antihypertensive medication dosage requirements

Results: Dosage requirements decreased by 46% ($p < 0.0001$)

Conclusion: CIIIT improves BP control

Bionica Pump


Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus

Effect of intensive insulin therapy on progression of overt nephropathy in patients with type 1 diabetes mellitus

Aoki TT, Grecu EO, Gollapudi GM, et al.

Endocrine Practice. 1999; 5(4): 174-8.

Purpose: To assess the effects of CIIIT on progression of nephropathy

Design: Multi-center, retrospective, longitudinal study; 31 pts

Results: HgbA1c decreased from 8.6±0.6% to 7.6±0.3% (p=0.0062); CrCl remained unchanged (46.1±3.0 mL/min/1.73m^2 to 46.0±3.9 *mL/min/1.73m^2*)

Conclusion: Addition of CIIIT to intensive insulin therapy reduces progression of overt diabetic nephropathy in pts with type 1 DM

Bionica Pump

Effect of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy

Dailey GE, Boden GH, Creech RH, et al.

Metabolism. 2000; 49(11): 1491-5.

Purpose: To assess the effects of PIVIT on progression of nephropathy

Design: Multi-center, prospective, controlled study; 49 pts; type 1 DM; 18 mo

Results: Rate of CrCl decline was significantly less in PIVIT arm vs control (2.21±1.62 mL/min/yr vs. 7.69±1.88 mL/min/yr; p=0.0343)

Conclusion: PIVIT added to intensive insulin therapy reduces progression of diabetic nephropathy

Bionica Pump

Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 1429 – 1434
Metabolism Clinical and Experimental
www.metabolismjournal.com

Pulsatile intermittent intravenous insulin therapy for attenuation of retinopathy and nephropathy in type 1 diabetes mellitus

Larry A. Weinrauch[a,*], Jennifer Sun[a], Ray E. Gleason[a], Guenther H. Boden[f], R.H. Creech[e], George Dailey[d], Frank P. Kennedy[c], Matthew R. Weir[b], John A. D'Elia[a]
[a]William P. Beetham Eye and John Cook Renal Units, Joslin Diabetes Center, Boston, MA, USA
[b]University of Maryland, Baltimore, MD, USA
[c]Mayo Medical Center, Rochester, MN, USA
[d]Scripps Medical Center, San Diego, CA, USA
[e]Summit Medical Center, Nashville, TN, USA
[f]Temple University Health Center, Philadelphia PA, USA
Received 15 October 2009; accepted 6 January 2010

Abstract

Many hormones are secreted in a pulsatile fashion that is more efficient than continuous secretion when tested in vivo. A trial of multiple daily insulin doses with or without the addition of weekly pulsatile insulin infusion therapy was designed to determine if deterioration of renal and retinal function could be blunted. Sixty-five study subjects were evaluated prospectively in 7 centers. Thirty-six patients were randomly allocated to the infusion group and 29 to the standard therapy group. Mean serum creatinine was 1.6 mg/dL in both groups. Subjects were excluded if clearance was less than 30 mL/min. There were no significant differences between the groups with respect to age, duration of diabetes, sex distribution, glycohemoglobin, blood pressure, angiotensin-converting enzyme inhibitor use, proteinuria, or baseline diabetic retinopathy (DR) severity level (all eyes exhibited DR; 8 were deemed technically not amenable to evaluation). Progression of DR was noted in 31.6% of 57 patients (32.3% treated, 30.8% control; $P = 1.0$) with both eyes evaluable. For patients with 12 or more months of follow-up, 27.9% of 43 patients demonstrated progression of DR (32.0% treated, 22.2% control; $P = .57$). There were no significant differences between study groups with respect to progression or marked progression, nor was there any influence of duration of follow-up. Progression of DR was noted in 18.8% of 122 eyes that could be adequately evaluated (17.9% of 67 treated, 20% of 55 controls; $P = .39$). Serum creatinine increased to 1.7 mg/dL in the treatment group and to 1.9 mg/dL in the control group ($P = .03$). Statistically significant preservation of renal function by pulsatile insulin infusion was not matched by a statistically significant prevention of DR progression compared with standard diabetes care. Inadequate statistical power or duration of the study, or lack of further benefit of pulsatile insulin infusion on the retina in the presence of angiotensin-converting enzyme inhibition may be responsible.

1. Background

Pulsatile secretion of insulin from β-cells follows a pattern of oscillations of intracellular calcium. Increased efficiency of equimolar amounts of hormones administered in pulsatile fashion when compared with continuous infusion has been demonstrated for insulin [1,2], glucagon [3], and growth hormone [4]. Disruption of organized pulsatile secretion of insulin in type 2 diabetes mellitus and in aldosterone secreted from adrenocortical adenomata [5] has been noted. Pulsatile secretion of hormone is retained by the isolated β-cell [6] and the remnant parathyroid gland [7] despite separation from changes in plasma glucose or calcium.

The addition of pulsatile infusion to multiple daily subcutaneous injections has been reported to decrease elevated glycohemoglobin while diminishing hypoglycemic

Presented in part at the American Diabetes Association, 69th Scientific Sessions, June 5-9, 2009, and the American Society of Nephrology, 42nd Scientific Sessions, October 27-November 1, 2009.
ClinicalTrials.gov trial no. NCT00594152.
* Corresponding author.

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doi:10.1016/j.metabol.2010.01.004

Pulsatile intermittent intravenous insulin therapy for attenuation of retinopathy and nephropathy in type 1 DM

Weinrauch LA, Sun J, Gleason RE, et al.

Metabolism Clinical and Experimental. 2010; 59: 1429-34.

Purpose: To determine if pulsatile insulin therapy could blunt renal and retinal deterioration

Design: Multi-center, prospective, controlled study; 65 pts; type 1 DM; 22 mo

Results: No change in rate of DR (32.3% vs. 30.8%; p = 1.0); decreased rate of serum creatinine increase (1.7 mg/dL vs 1.9 mg/dL; p = 0.03)

Conclusion: Pulsatile insulin preserved renal function; DR progression unchanged

Bionica Pump

COMMENTARY

Loss of Pulsatile Insulin Secretion: A Factor in the Pathogenesis of Type 2 Diabetes?

John Wahren[1,2] and Åsa Kallas[2]

For many years, the prevailing view has been that the initiating event in type 2 diabetes is development of insulin resistance in peripheral tissues that triggers overproduction of insulin by pancreatic β-cells. Eventually, β-cells reach a stage at which they are unable to compensate for the insulin resistance, resulting in hyperglycemia and overt diabetes. The underlying cause of tissue insulin resistance is not well understood, but several putative mechanisms including ectopic lipid accumulation and low-grade activation of inflammatory pathways have been proposed (1). Recent evidence suggests that β-cell failure may occur in parallel with the development of insulin resistance (2), and β-cell failure may in itself be a cause of insulin resistance (3).

Insulin is secreted into the portal vein in a pulsatile fashion with approximately 5-min cycles (Fig. 1) (4–6). Insulin pulses may account for as much as 70% of the total insulin secretion in the basal state (4). This pulsatile β-cell secretion pattern is controlled by an intrinsic rhythm of intracellular Ca^{2+} oscillations (7). Adjacent β-cells in the islets adapt to each other via autocrine interaction, resulting in a coordinated secretion pattern. In addition, synchronization of all islets so that insulin release by the entire pancreas occurs in distinct peaks results from autonomic nervous system involvement (8). Interestingly, a pulsatile secretion of somatostatin takes place in phase with the insulin release, whereas pulsatile glucagon secretion is antisynchronous to that of both insulin and somatostatin (Fig. 1) (5). The resulting >20-fold variations in portal vein insulin-to-glucagon ratio may be of importance for short-term regulation of hepatic glucose metabolism.

A substantial decline in β-cell function is now believed to occur in the early stages of type 2 diabetes development. β-Cell mass is reduced by approximately 40–65% when patients present with type 2 diabetes (9). To compensate for decreased β-cell mass, the remaining β-cells produce high levels of insulin, but the pulsatile secretion pattern is modified in that the insulin pulses are markedly attenuated (4). This altered insulin secretion has several consequences, including effects on the autocrine regulation of insulin secretion (10), higher plasma levels of uncleaved proinsulin (11), and development of hepatic insulin resistance in both animals and humans. In addition, more insulin seems to escape hepatic retention, leading to elevated peripheral insulin levels. Insulin resistance has partly been ascribed to decreased number and downregulation of insulin receptors with subsequent effects on the intracellular signaling system, including insulin receptor substrate 1 (IRS-1). Normally, IRS-1 binds to the cytoplasmatic portion of the activated, autophosphorylated insulin receptor and becomes phosphorylated at several tyrosine residues, thereby initiating the intracellular signaling cascade of insulin (12).

In this issue of *Diabetes*, Matveyenko et al. (13) present new evidence regarding the effect of different modes of intraportal insulin delivery on hepatic intracellular insulin signaling and whole-body glucose utilization in animals. Insulin administration was either pulsatile (representing the healthy state), constant rate, or with reduced magnitude of the pulses (mimicking the defective insulin secretion of type 2 diabetes). Activation of intracellular insulin signaling via IRS-1 and IRS-2, Akt, and Foxo1 was evaluated. The investigators provide evidence that phosphorylation of these signaling proteins, as well as the mRNA expression of glucokinase, was delayed and impaired following constant rate and type 2 diabetes–like insulin infusions as compared with the pulsatile infusion. These findings provide the first direct evidence that the loss of pulsatile insulin secretion leads to intrahepatic molecular changes and altered gene expression consistent with the development of hepatic insulin resistance. Moreover, pulsatile insulin administration was accompanied by a modest decrease in plasma glucose levels, whereas both the constant infusion and the type 2 diabetes–mimicking infusion resulted in increased plasma glucose levels in the fasting state. The insulin secretion pattern appears to influence both blood glucose regulation and tissue insulin resistance. Finally, to extend these short-term results, the investigators used the human islet amyloid polypeptide (HIP) transgenic rat model of type 2 diabetes in studies covering up to 12 months. Compared with age-matched Sprague-Dawley control rats, the HIP rats exhibited a progressive loss of β-cell mass, decreased mass of insulin pulses, elevated fasting levels of glucose, and decreased levels of glucokinase mRNA.

The pulsatile secretion of insulin by the β-cells is not a piece of evolutionary whimsy, yet its possible functional importance and the consequences of the loss of this function in type 2 diabetes have received only limited attention to date. Therefore, the present results by Matveyenko et al. (13) represent a welcome tour de force of new information in this area and bring to the foreground the distinct possibility that loss of insulin pulsatility and β-cell dysfunction may not only be initiating events, but also drivers in the development of hepatic insulin resistance and progression of type 2 diabetes. The extent to which the present findings for rats and dogs translate to people with type 2 diabetes needs to be evaluated. A primary role for β-cell dysfunction

From the [1]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden, and [2]Cybis AB, Karolinska Institutet Science Park, Solna, Sweden.
Corresponding author: John Wahren, john.wahren@ki.se.
DOI: 10.2337/db12-0644

See accompanying original article, p. 2269.

Loss of pulsatile insulin secretion: A factor in the pathogenesis of type 2 diabetes?

Wahren J and Kallas A

Diabetes. 2012; 61: 2228-9.

- Based on Matveyenko AV et al paper *Diabetes*; 2012; 61:2269-79
- Peripheral insulin resistance leads to overproduction of insulin by pancreatic ß-cells
- Pulsatile secretion patterns are markedly attenuated
- Results in hepatic insulin resistance and downregulation of insulin receptors, further propagating type 2 DM

Artificial Pancreas Treatment

Protocol:

- Infusion of intravenous insulin (weight-based) precisely pulsed via Bionica pump to mimic pancreatic secretion
- Oral consumption of glucose solution during infusions
- Three hourly treatments with ambulation in-between each
- Insulin/glucose titration based on metabolism monitoring by carbon dioxide production (VCO_2) and blood glucose levels
- Induction: 2 consecutive days
- Maintenance: Weekly → biweekly

Bionica Pump

Safety

- Potential Adverse events:
  - Insulin: Hypoglycemia, hypokalemia, hypersensitivity syndromes, anaphylaxis, weight gain, HA
  - Glucose: Hyperglycemia, gastrointestinal upset
  - IV: Infusion reactions, injection site reactions

- Experience
  - Nearly 200,000 treatments
  - Clinics in US: California, Texas, Louisiana, Tennessee, North Carolina, Florida, Arizona
  - Clinics internationally: China, Thailand, Singapore, Australia, India
  - Pending: New York, New Jersey, Pennsylvania, South Carolina, Florida, UAE

Conclusions

- Diabetes is a systemic metabolic disease
- Diabetes continues to be an epidemic despite intensive hypoglycemic efforts to date
- Complications of diabetes account for its high burden of disease
- Conventional hypoglycemic therapy does not fully restore normal glucose metabolism or blood glucose control

Conclusions

- Endogenous insulin is normally released in a pulsatile manner from the pancreas in non-diabetic patients
- Pulsatile “burst” insulin delivery has significant physiologic effects and pharmacologic implications
- Trina Artificial Pancreas Treatment® uses a patented, FDA-cleared pump (Bonica) that re-approximates the periodicity and amplitude of pancreatic insulin secretion to the portal vein, before it was even discovered that these bursts were “normal”.
- Developed and studied in academic settings: Harvard, Mayo, Scripps, Temple, Univ. of Maryland, Univ. of Arizona, Univ. of California-Davis

Conclusions

- Clinical trial results:

  - Decreased HgbA1c, decreased hypoglycemic events, improved BP control, decreased progression of diabetic nephropathy, improved nerve conduction velocity.

- Safe adverse event profile

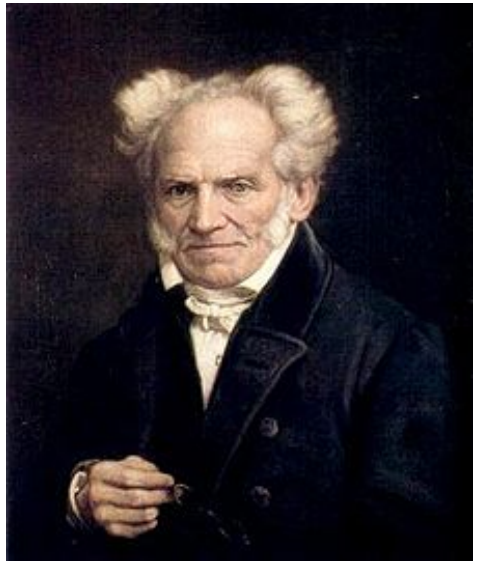
- Close to 200,000 treatments to date

- Indicated for both type 1 and type 2 diabetes

- No other treatment achieves normalized metabolism of carbohydrates

- No other treatment mimics a normal pancreas !

Parting thoughts



"All truth passes through three stages:

First, it is ridiculed.

Second, it is violently opposed.

Third, it is recognized as self-evident."

Father of Modern Philosophy Arthur Schopenhauer (1788-1860), German philosopher

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