Diabetic Autonomic Neuropathies

Roy Freeman, MD

Center for Autonomic and Peripheral Nerve Disorders
Department of Neurology, Beth Israel Deaconess Medical Center
Harvard Medical School, Boston, Massachusetts, U.S.A.

Disclosures

No disclosures related to this presentation

Prevalence of diabetes
- the US perspective -

- 25.8 million people in USA (8.3% of the population)
  - Type 1 diabetes (5-10%)
  - Type 2 diabetes (90-95%)
- 79 million people prediabetes
- $245 billion of annual U.S. health-care costs
  - $176 billion for direct medical costs
  - $69 billion in reduced productivity

CDC National Diabetes Fact Sheet, 2011

- CDC estimate if current trends continue, 1 in 3 Americans could have diabetes in 2050

hhttp://www.cdc.gov/media/pressrel/2010/r101022

Prevalence of diabetes
- the US perspective -

- 25.8 million people in USA (8.3% of the population)
  - Type 1 diabetes (5-10%)
  - Type 2 diabetes (90-95%)
- 79 million people prediabetes
- $245 billion of annual U.S. health-care costs
  - $176 billion for direct medical costs
  - $69 billion in reduced productivity

CDC National Diabetes Fact Sheet 2011

- Predicted 29.6 million in 2030

http://www.idf.org/diabetesatlas/5e/the-global-burden

Background:

- Diabetes mellitus
  - World wide prevalence estimated to increase from 171 million in 2000 to 366 million in 2030

http://www.who.int/diabetes/facts/world_figures/en/index.html

- Diabetes peripheral neuropathy
  - Newly diagnosed diabetics - 7.5% after 25 years ~ 50%
  - Cross-sectional data 55% in T1DM and 54% in T2DM

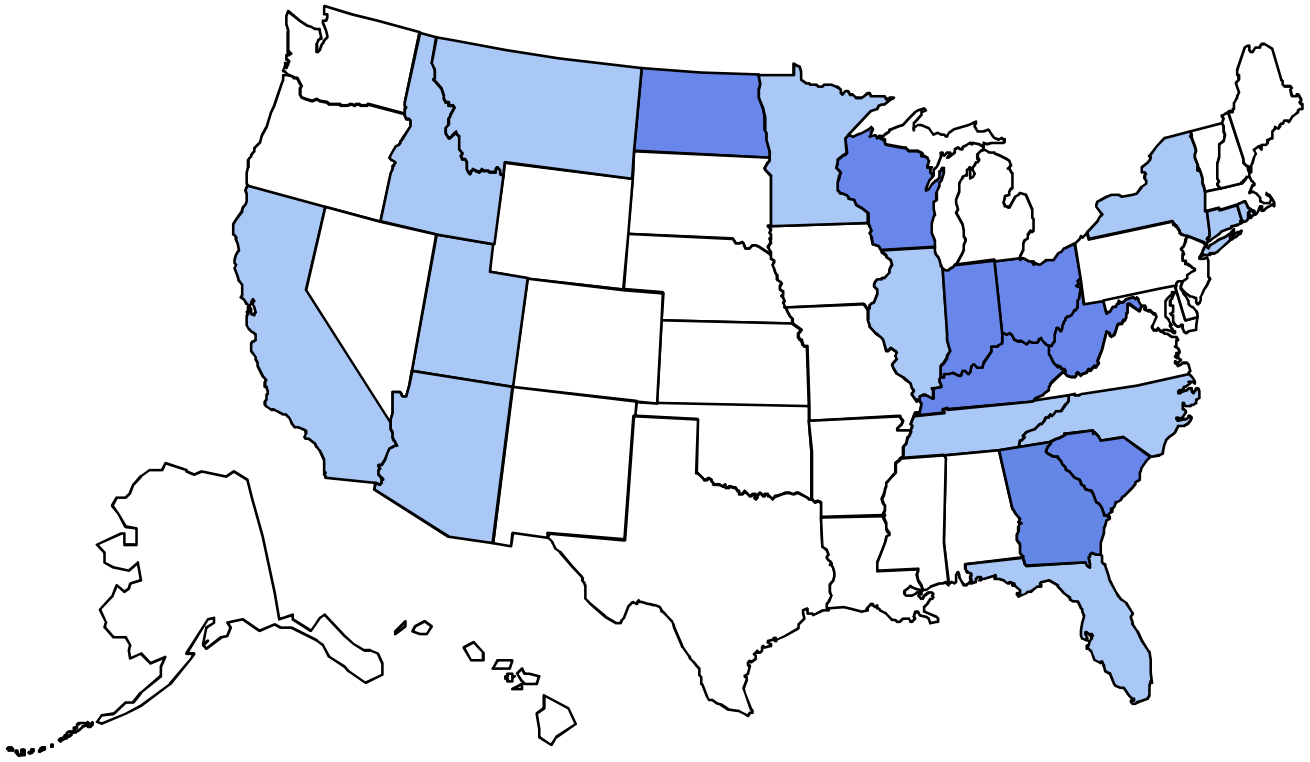
Pirart J, Diabetes Care 1978; 1: 168-188

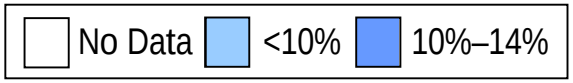
Dyck et al. Neurology. 1993;43:817-824

Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ?GE0, or ~ 30 lbs. overweight for 5' 4" person)

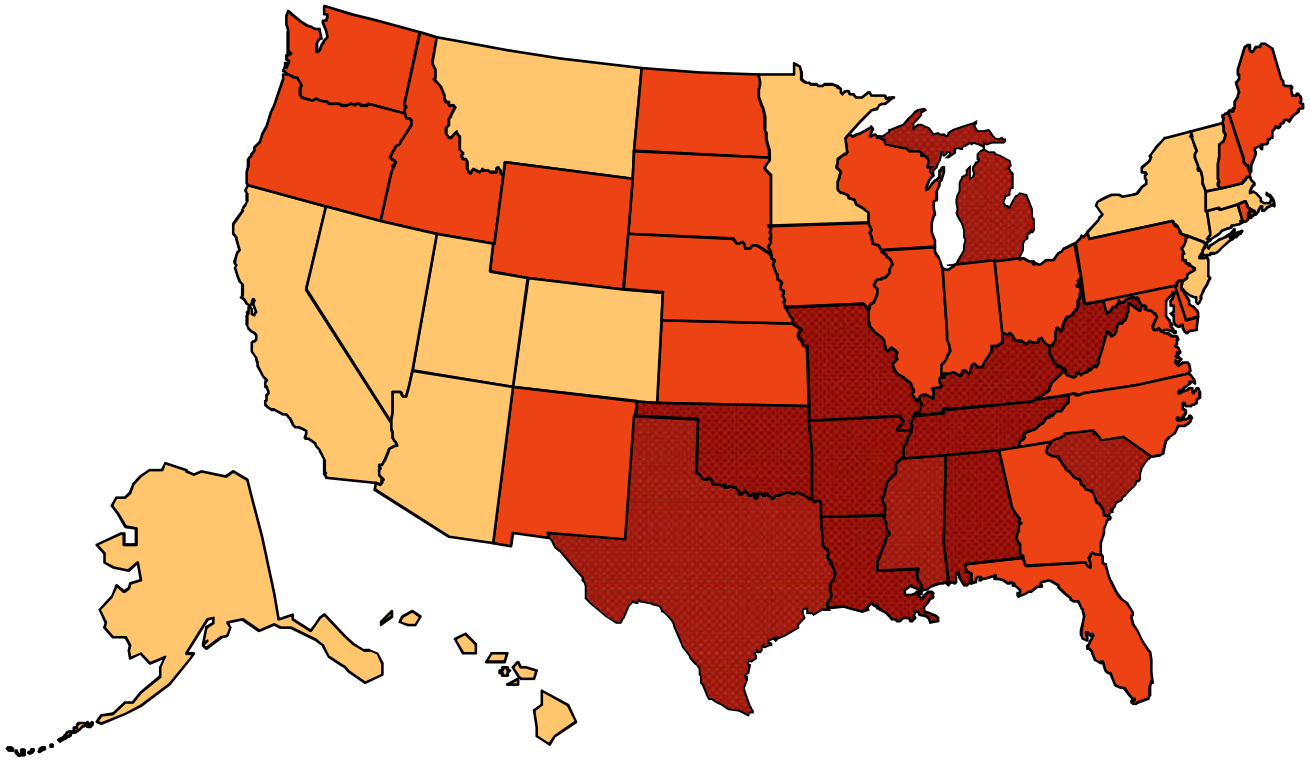


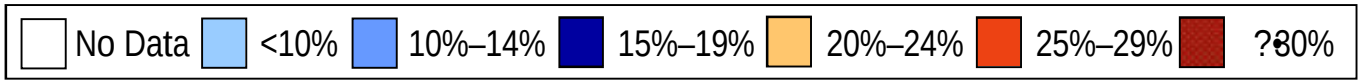


Obesity Trends* Among U.S. Adults

BRFSS, 2010

(*BMI ?30, or ~ 30 lbs. overweight for 5' 4" person)






© 2005 http://philip.greenspun.com/copyright/

Estimated diabetes cases (million) 2000 - 2030

	2000	2030
• World Wide	171	552
• India	31.7	101
• China	20.8	129
• Brazil	12.4	19.6
• Bangladesh	8.4	16.8
• Egypt	7.3	12.4

http://www.idf.org/diabetesatlas/5e/the-global-burden
http://www.who.int/diabetes/facts/world_figures/en/index.html

Diabetic Autonomic Neuropathy

- Autonomic neuropathy associated with generalized distal polyneuropathy
- Autonomic neuropathy associated with impaired glucose tolerance
- Treatment induced painful autonomic neuropathy
- Transient autonomic dysfunction

Diabetic Autonomic Neuropathy

- Autonomic neuropathy associated with generalized distal polyneuropathy
- Autonomic neuropathy associated with impaired glucose tolerance
- Treatment induced painful autonomic neuropathy
- Transient autonomic dysfunction

Epidemiology:

Background:

- Diabetes mellitus
  - World wide prevalence estimated to increase from 171 million in 2000 to 552 million in 2030

http://www.who.int/diabetes/facts/world_figures/en/index.html

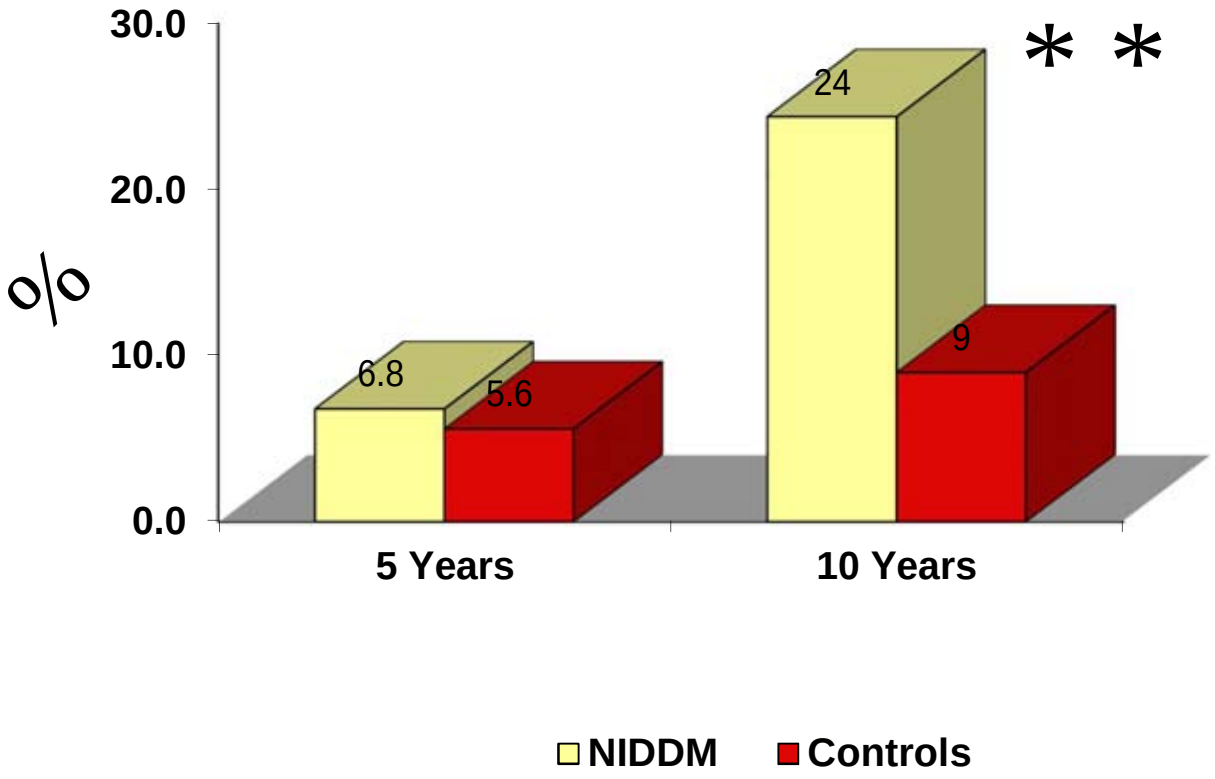
- Diabetes peripheral neuropathy
  - Newly diagnosed diabetics - 7.5% after 25 years ~ 50%
  - Cross-sectional data 55% in T1DM and 54% in T2DM

Pirart J, Diabetes Care 1978; 1: 168-188

Dyck et al. Neurology. 1993;43:817-824

Epidemiology of generalized autonomic neuropathy:

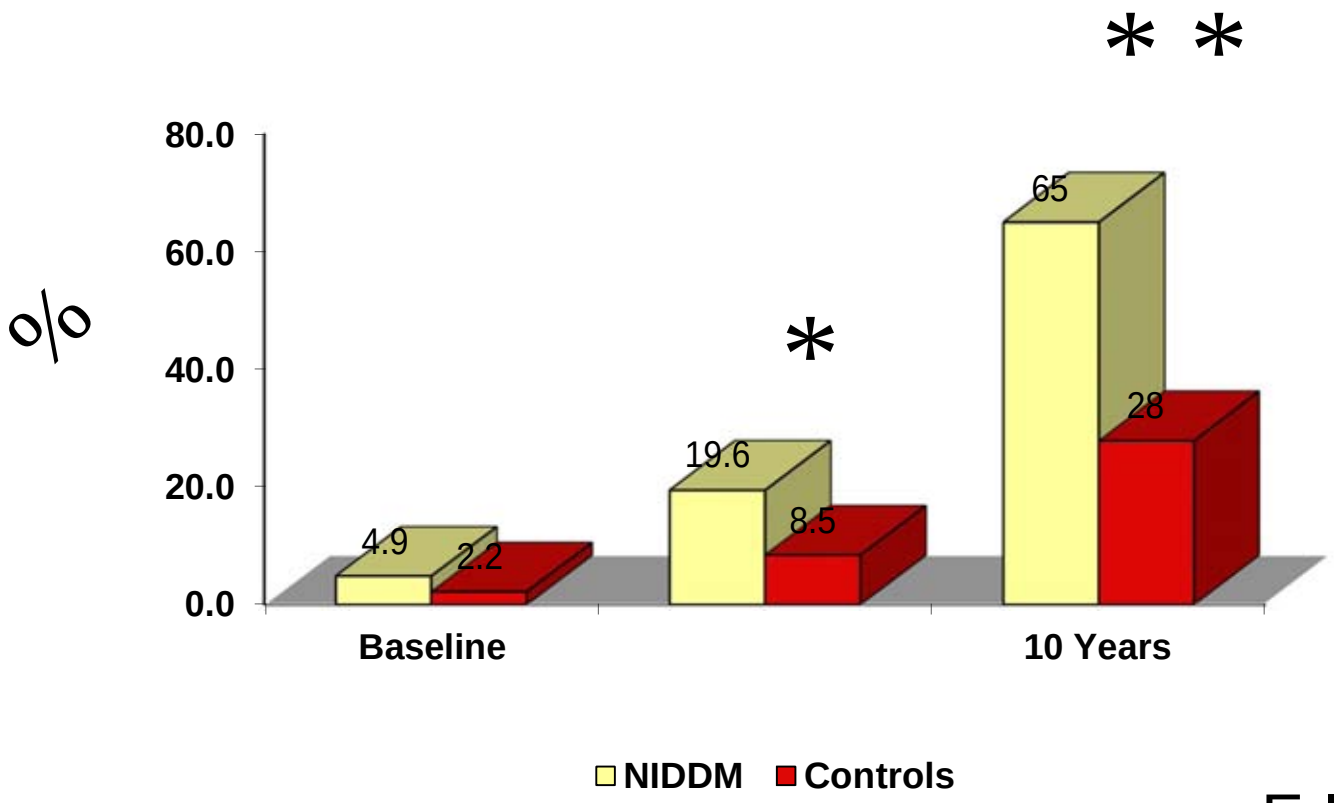
Prevalence of orthostatic hypotension - Kuopio study



SBP fall > 30 mmHg

Toyry et al. Diabetes 45: 308-315, 1996

Prevalence of abnormal R-R variation - Kuopio study



E:I ratio < 1.10

Toyry et al. Diabetes 45: 308-315, 1996

Diabetic autonomic neuropathy

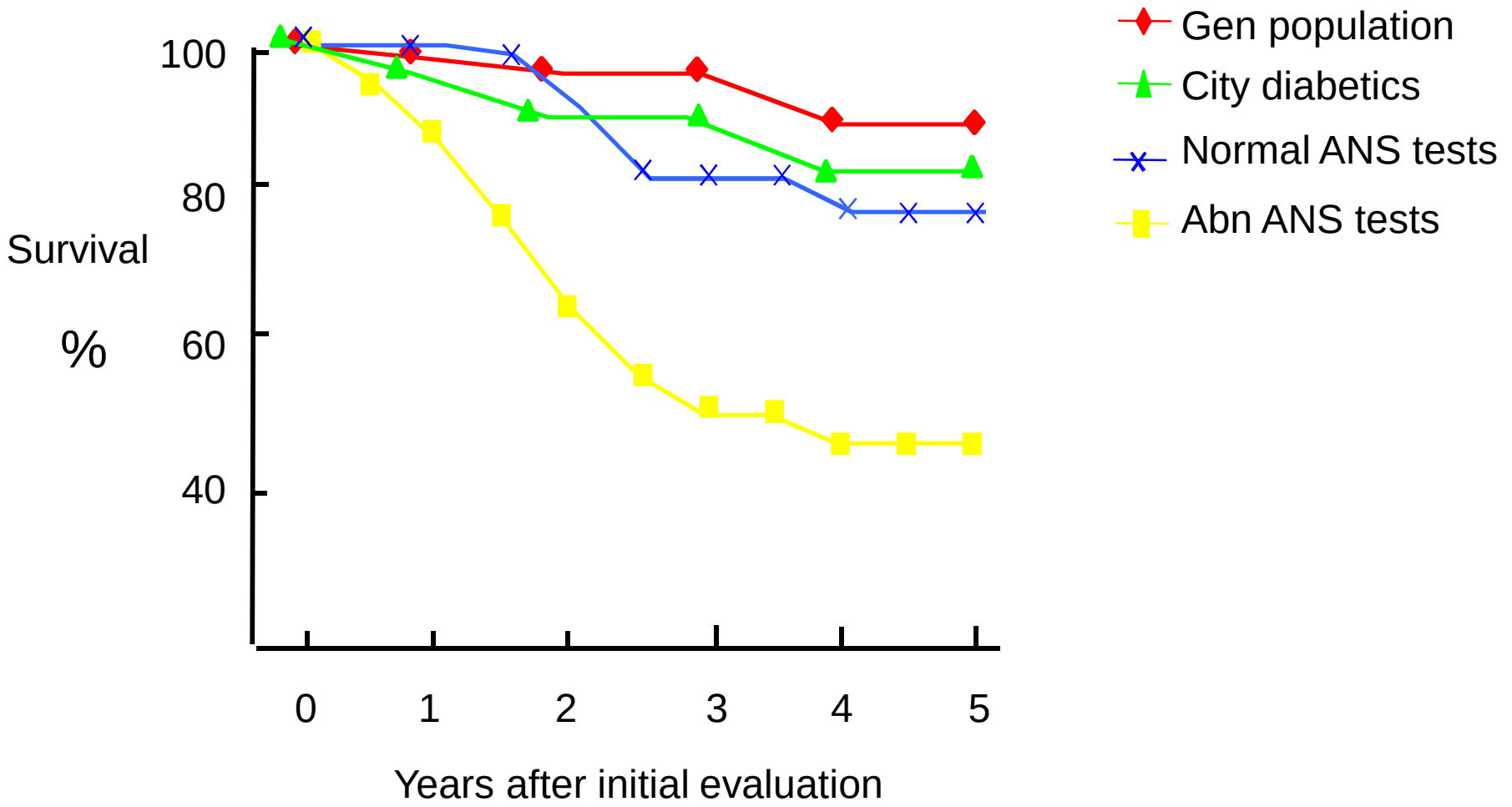
- Cardiovascular
- Gastrointestinal
- Urogenital
- Pupillomotor
- Sudomotor

Cardiovascular Autonomic Neuropathy

- Heart rate changes
  - Postural tachycardia
  - Resting tachycardia
  - Fixed heart rate
- Orthostatic hypotension
- Silent ischemia
- Loss of circadian patterns
- Exercise intolerance

Diabetic cardiovascular autonomic neuropathy

- Heart rate changes
  - Resting tachycardia
  - Fixed heart rate
- Orthostatic hypotension
- Reduced exercise tolerance
- Loss of circadian rhythm
- Silent cardiac ischaemia
- Vasomotor abnormalities
- Increased mortality

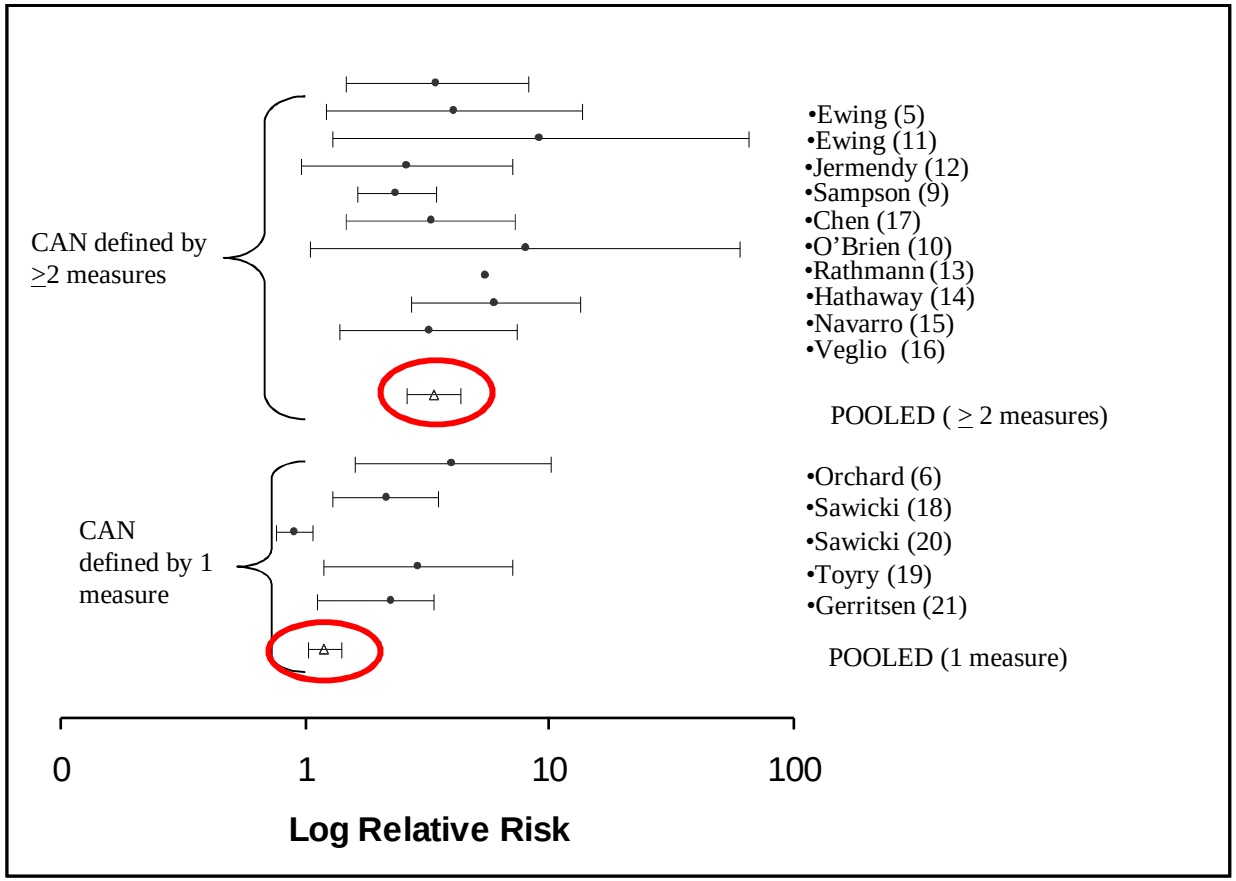


The natural history of diabetic autonomic neuropathy
Ewing et al. Q.J. Med 1980;45:95-108.

Relative risks for mortality with cardiovascular autonomic neuropathy

Pooled relative risk for 10 studies with CAN defined by two or more measures: 3.38 (95% confidence interval 2.61 – 4.38)

Pooled relative risk for 4 studies* with CAN defined by a single measure: 1.20 (95% confidence interval 1.02 – 1.41)



Maser et al. Diabetes Care 2003: 26:1895-1901

Autonomic neuropathy and mortality – recent studies

- Steno study 10 year prospective assessment
  - HRV an independent risk factor predicting cardiovascular mortality in type 1 diabetes.
  - Hazard ratios in a patients with and without nephropathy 3.3 (95% CI 1.0-10.7; P = 0.04)

- EuroDiab cohort
  - Autonomic neuropathy was an independent risk factor (2.40 [1.32–4.36]) for mortality
  - Exceeded value of the traditional risk factors (age, WHR, pulse pressure, and non-HDL cholesterol).

Astrup AS et al. Diabetes Care. 2006;29:334-9.

Soedamah-Muthu et al. Diabetes Care. 2008; 31:1360-1366

Possible factors:

- Silent ischaemia
- Sympathetic-parasympathetic nervous system imbalance
- Impaired baroreflex sensitivity
- QT interval prolongation
- Myocardial ischaemia - autonomic interactions
- Distal sympathetic denervation with islands of proximal hyperinnervation

Treatment of diabetic autonomic neuropathy

- Symptomatic
- Disease modification

Disease modification

- Type 1 diabetes –follow-up of the DCCT cohort
  - Persistent benefit of prior intensive therapy on prevalence and incidence of cardiac autonomic neuropathy in former intensive therapy subjects 13 to 14 years after the conclusion of the DCCT.
  - Reduced the risks of incident CAN by 31%
  - Reduced prevalence of abnormal R-R variation (30.2 vs 23.8%)
  - Despite no significant difference in HbA1c by year 5

- Type 2 diabetes – Steno study
  - 160 patients with type 2 DM and microalbuminuria randomized to conventional or intensive, multi- factorial care
  - BP control, HbA1c, Cholesterol and TGL, ACE inhibition, ASA

Gœde P et al. NEJM 348:383-393, 2003
Pop-Busui, R, Circulation. 2009; 119:2886-2893

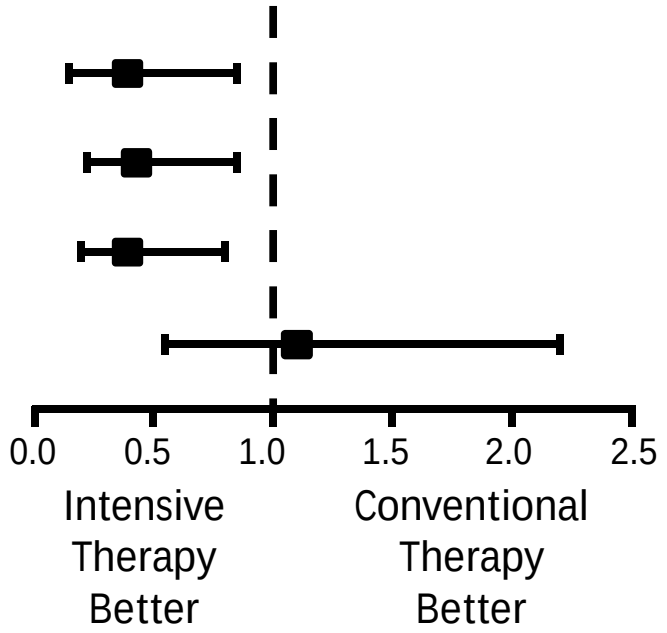
Disease modification

- Type 2 diabetes – Steno study
  - 160 patients with type 2 DM and microalbuminuria randomized to conventional or intensive, multi- factorial care
    - BP control,
    - HbA1c,
    - Cholesterol and TGL,
    - ACE inhibition,
    - ASA

Gœde P et al. NEJM 348:383-393, 2003

Intensive vs. conventional multimodal therapy and microvascular complications

Variable	Relative Risk (95% CI)	P Value
Nephropathy	0.39 (0.17 – 0.87)	0.003
Retinopathy	0.42 (0.21 – 0.86)	0.02
Autonomic neuropathy	0.37 (0.18 – 0.79)	0.002
Peripheral neuropathy	1.09 (0.54 – 2.22)	0.66



The greatest risk reduction conferred by intensive therapy occurred with autonomic neuropathy

Gœde P et al. NEJM 348:383-393, 2003

Disease modification

- Type 1 diabetes –follow-up of the DCCT cohort
- 13 to 14 years after the conclusion of the DCCT.
- Persistent benefit of prior intensive therapy on prevalence and incidence of cardiac autonomic neuropathy in former intensive therapy subjects
  - Reduced the risks of incident CAN by 31%
  - Reduced prevalence of abnormal R-R variation (30.2 vs 23.8%)
  - Despite no significant difference in HbA1c by year 5
  - “Metabolic memory” “Legacy effect”

Effects of Prior Intensive Insulin Therapy on Cardiac Autonomic Nervous System Function in Type 1 Diabetes Mellitus.

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC)

Pop-Busui, R, Circulation. 2009; 119:2886-2893

Gastrointestinal Autonomic Neuropathy

- Esophageal dysmotility
- Gastroparesis diabeticorum
- Constipation
- Diarrhea
- Fecal incontinence

Gastroparesis

- Bloating
- Anorexia
- Early or prolonged satiety
- Upper abdominal distension
- Epigastric discomfort
- Postprandial nausea and vomiting of undigested food

Symptoms of Bladder Dysfunction

- Suprapubic fullness
- Frequency
- Nocturia
- Urgency
- Incontinence

Diabetic autonomic neuropathy

- Cardiovascular
- Gastrointestinal
- Urogenital
- Pupillomotor
- Sudomotor

Diabetic Autonomic Neuropathy

- Autonomic neuropathy associated with generalized distal polyneuropathy
- Autonomic neuropathy associated with impaired glucose tolerance
- Treatment induced painful autonomic neuropathy
- Transient autonomic dysfunction

Criteria for the diagnosis of diabetes (ADA)

Normoglycemia	IFG or IGT	Diabetes*
FPG <110 mg/dl	FPG ?á110 and <126 mg/dl (IFG)	FPG ?á126 mg/dl
2-h PG <140 mg/dl	2-h PG ?á140 and <200 mg/dl (IGT)	2-h PG ?á200 mg/dl Symptoms of diabetes and casual plasma glucose concentration ?á200 mg/dl

Background: Idiopathic neuropathy and impaired glucose tolerance

- Intensive control of blood glucose delays the appearance and progression of peripheral neuropathy
- ~10% of patients with diabetes have a peripheral neuropathy at the time of diagnosis – frequently painful and with small fiber features
- 20-50% of patients with a peripheral neuropathy have no cause found

Autonomic dysfunction is present in recently diagnosed diabetic individuals

Pfeifer MA et al. Autonomic neural dysfunction in recently diagnosed diabetic subjects. Diabetes Care. 1984;7:447-453.

Lehtinen JM et al. Prevalence of neuropathy in newly diagnosed NIDDM and nondiabetic control subjects. Diabetes. 1989;38:1307-1313.

HRV is inversely associated with plasma glucose levels and is reduced in diabetes and subjects with impaired fasting glucose levels.

Singh JP et al. Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). Am J. Cardiol. 2000;86: 309-312

Idiopathic neuropathy and impaired glucose tolerance

- 121 patients with idiopathic polyneuropathy
- 29 of 89 tested had frank diabetes mellitus
- 15 of 61 (25%) had impaired glucose tolerance (140-200 mg/dl 2 h after a 75-g glucose load)
- 35% of patients with neuropathic pain had IGT
- Twice the prevalence found in unselected population studies

Singleton JR et al. Painful sensory polyneuropathy associated with impaired glucose tolerance. Muscle Nerve 24:1225-1228, 2001

- Among community based control subjects 23.2% had IGT, 35.9% had IFG

- Prevalence of polyneuropathy:
  - 28.0% in the diabetic subjects
  - 13.0% in those with IGT
  - 11.3% in those with IFG
  - 7.4% in those with NGT

- In the diabetic group:
  - Polyneuropathy was associated with age, waist circumference, and peripheral arterial disease (all $P < 0.05$).

Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy

Ziegler D. et al Diabetes Care 31:464-469, 2008

cardiovascular autonomic neuropathy

Autonomic dysfunction, impaired glucose tolerance and diabetes

- Autonomic impairment is present in some patients at the time of diabetes diagnosis
- Autonomic impairment is observed in patients with IGT

Suggests autonomic dysfunction may be present after a relatively brief exposure to hyperglycemia or develop in conjunction with obesity or insulin resistance

- Cross-sectional studies of non-diabetic adults reveal markers of autonomic functioning are inversely associated with obesity, insulin resistance, and fasting glucose
- Evidence that autonomic dysfunction may predict development of diabetes

Suggests autonomic dysfunction may be associated with the development of diabetes in healthy adults

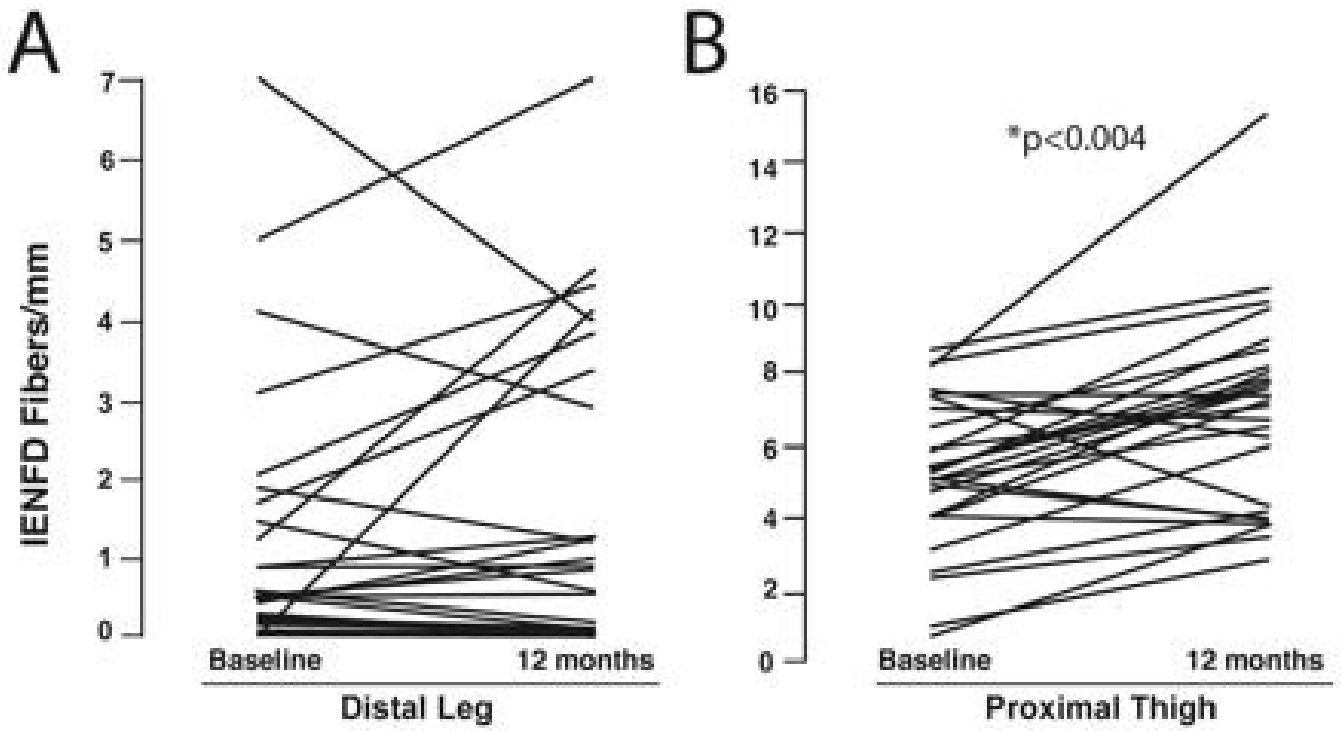
Impaired Glucose Tolerance Neuropathy Features

- Autonomic function testing abnormal in approximately 30%
- Signs: impairment of light touch and pain>vibration
- Ankle reflexes frequently intact
- Abnormalities of quantitative sensory testing and skin biopsy
- Exclusion of all other common causes

Impaired Glucose Tolerance Intervention

- Improvement in proximal IENFD of 1.3 ± 2.2 fibers/mm ($P < 0.004$). Distal IENFD improved 0.3 ± 1.1 fibers/mm ($P < 0.12$)
- Improvement in foot sweat volume of 0.3 ± 0.8 ($P < 0.05$) measured using QSART. No significant change in sweat volumes was observed at the distal leg or thigh.
- Pain generally improved, although the change did not reach significance. The 100-mm VAS improved from 36.4 ± 19.4 to 32.8 ± 26.3 mm ($P < 0.4$)

Smith et al. Diabetes Care 29:1294-1299, 2006



- Distal IENFD improved 0.3 ± 1.1 fibers/mm, and the proximal IENFD improved 1.3 ± 2.2 fibers/mm ($P < 0.004$).
- Improvement in proximal thigh IENFD was observed in 70% of subjects compared with 31% for the ankle.

Smith et al. Diabetes Care 29:1294-1299, 2006

Impaired Glucose Tolerance Intervention

- Interventions:
  - Reduce body weight 7%
  - Increase aerobic exercise to 150 min/week
  - Medical management
- Diet and exercise counseling resulted in significant improvement in weight, glucose, and cholesterol
- Improvement in metabolic parameters was associated with significant improvement in measures of small-fiber function.

Smith et al. Diabetes Care 29:1294-1299, 2006

Diabetic Autonomic Neuropathy

- Autonomic neuropathy associated with generalized distal polyneuropathy
- Autonomic neuropathy associated with impaired glucose tolerance
- Treatment induced painful autonomic neuropathy
- Transient autonomic dysfunction

Treatment induced neuropathy

A reversible painful autonomic neuropathy

- “Insulin neuritis” first reported in 1933
- Recent reports have described treatment induced neuropathy in individuals with type 1 and type 2 diabetes
- Treated with oral hypoglycemic agents or with insulin.
- Pre-treatment glycosylated hemoglobin (A1C) is characteristically high
- Glycemic control is usually rapid

Caravati, CM. Insulin neuritis: a case report. Va Med Monthly. 1933; 59:745-746.

Gibbons, C and Freeman, R. Treatment induced neuropathy. Annals of Neurology 2010

Treatment induced neuropathy

A reversible painful autonomic neuropathy

- 16 cases (9 T1 and 7 T2 DM)
- Neuropathy clinic of Joslin Diabetes Center
- Rapid sustained glycemic control
- Follow prospectively for 18 months
- Examinations and pain scores ~ 3 months
- Assessments
  - Structured examination
  - Questionnaires
  - Autonomic testing
  - Skin biopsy
  - Retinal examinations and spot urine for microalbumiuria

Caravati, CM. Insulin neuritis: a case report. Va Med Monthly. 1933; 59:745-746.

Gibbons, C and Freeman, R. Treatment induced neuropathy. Annals of Neurology 2010

Acute Painful Neuropathy

Treatment induced neuropathy

Summary

- Pain may occur distally in a length-dependent fashion or be more generalized and involve proximal sites including the trunk.
- Cardiovascular, gastrointestinal, genitourinary, and sudomotor symptoms accompany the painful neuropathy.
- Orthostatic symptoms are common
- Tests measuring sympathetic and parasympathetic function are abnormal

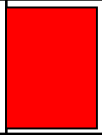
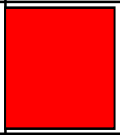
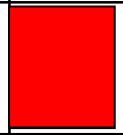
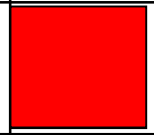
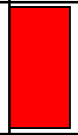
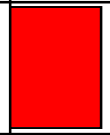
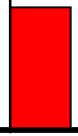
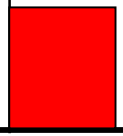
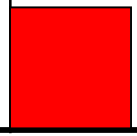
Caravati, CM. Insulin neuritis: a case report. Va Med Monthly. 1933; 59:745-746.

Gibbons, C and Freeman, R. Treatment induced neuropathy. Annals of Neurology 2010

Autonomic Symptoms

- Cardiovascular, gastrointestinal, genitourinary, and/or sudomotor symptoms in all subjects
- More prevalent than generalized DPN
- Orthostatic symptoms
  - lightheadedness seen in 69%, dizziness in 75%, presyncope in 52% and syncope in 31%
- Gastrointestinal
  - nausea in 69%, vomiting in 56%, diarrhea in 50%, loss of appetite in 43% and early satiety in 43%.
- Erectile dysfunction in 86% of males

Autonomic Symptoms

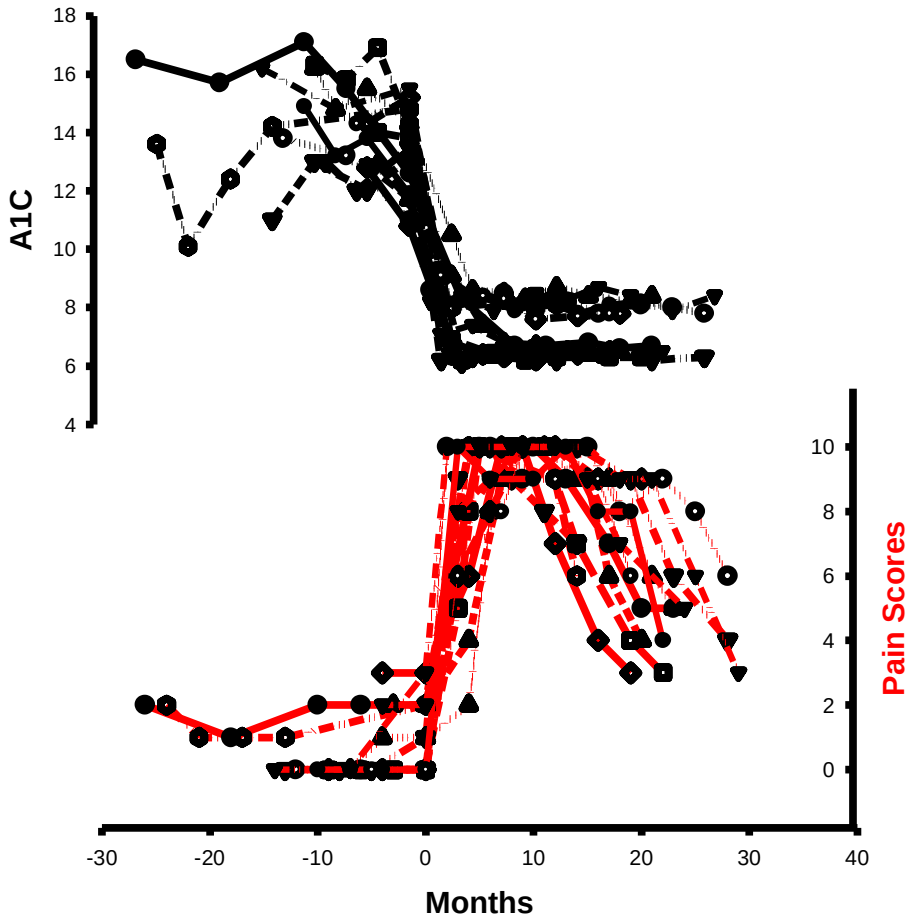
Drop in A1C over 3 months	2-2.9	3-3.9	4-4.9	5-5.9	?6
Syncope					
Orthostatic Intolerance					
Sexual Symptoms					
Sudomotor symptoms					
Nausea					
Gastroparesis					

Autonomic Test Abnormalities

- Parasympathetic nervous system abnormalities
  - Impaired HR Variability with deep breathing (62%) and Valsalva manoeuvre ratio (56%)
- Sympathetic nervous system abnormalities
  - Orthostatic hypotension in 69%
- Improved over 18 months
  - HR Variability with deep breathing abnormal in 48%;
  - Valsalva Ratio abnormal in 43%;
  - OH in 31%

Treatment induced neuropathy

- Reduced distal pain and thermal sensation (100%)
- All subjects reported severe 10/10 pain within 6-8 weeks of the onset of glucose control.
- Majority distal (81%) Generalized in 19%
- Hyperalgesia and/or allodynia in 57%

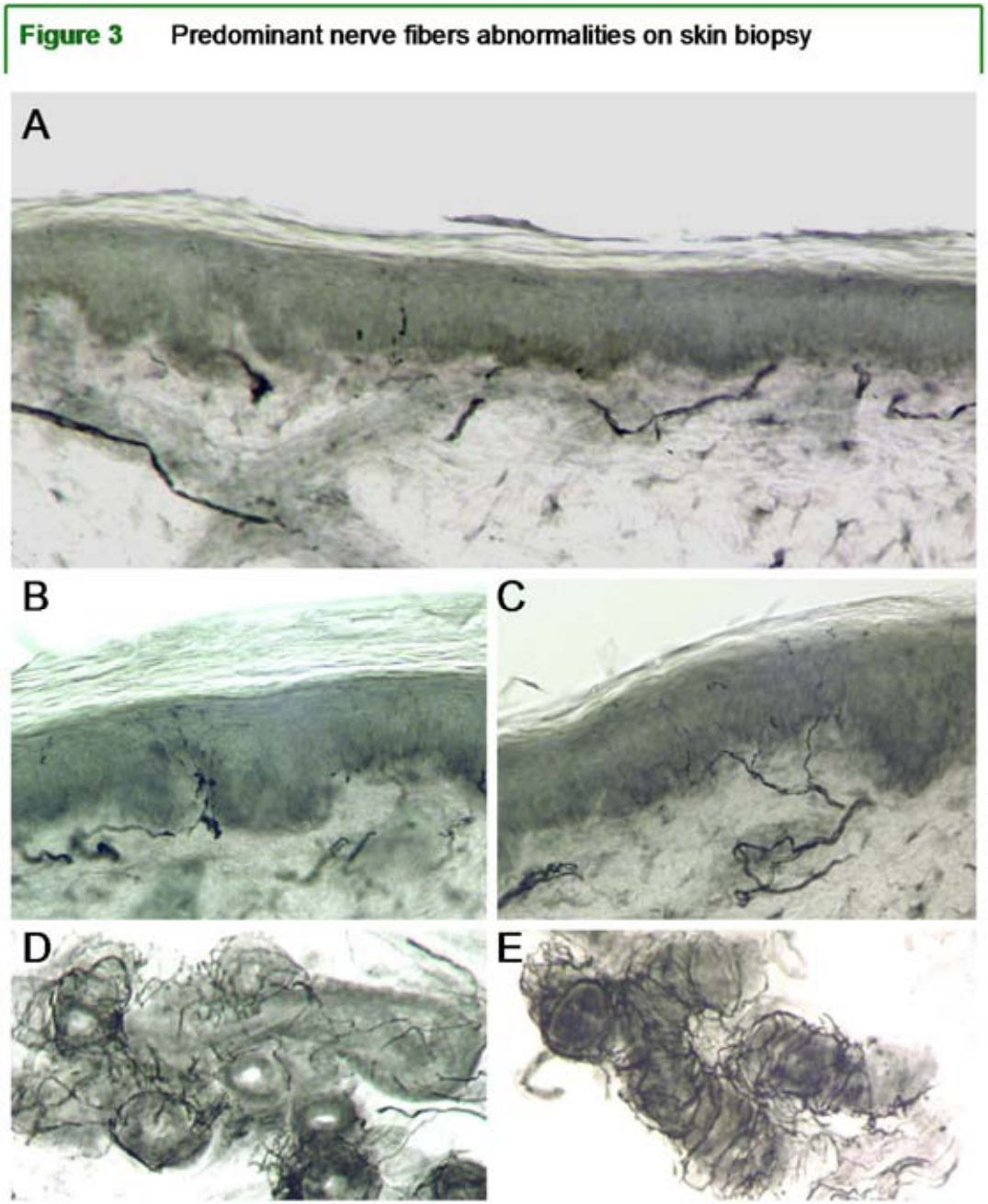


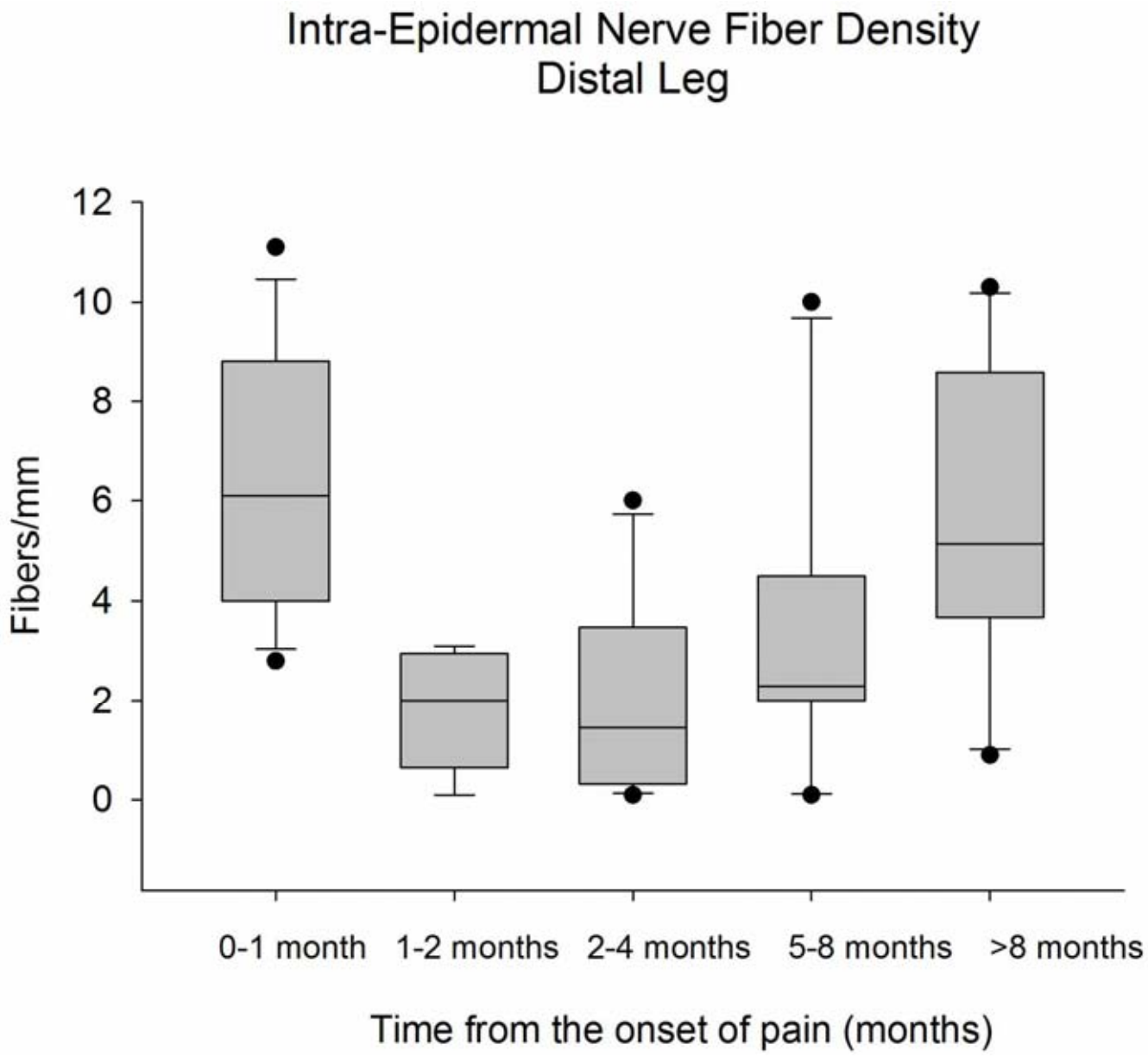
Caravati, CM. Insulin neuritis: a case report. Va Med Monthly. 1933; 59:745-746.

Gibbons, C and Freeman, R. Treatment induced neuropathy. Annals of Neurology 2010

Nerve fiber abnormalities on skin biopsy

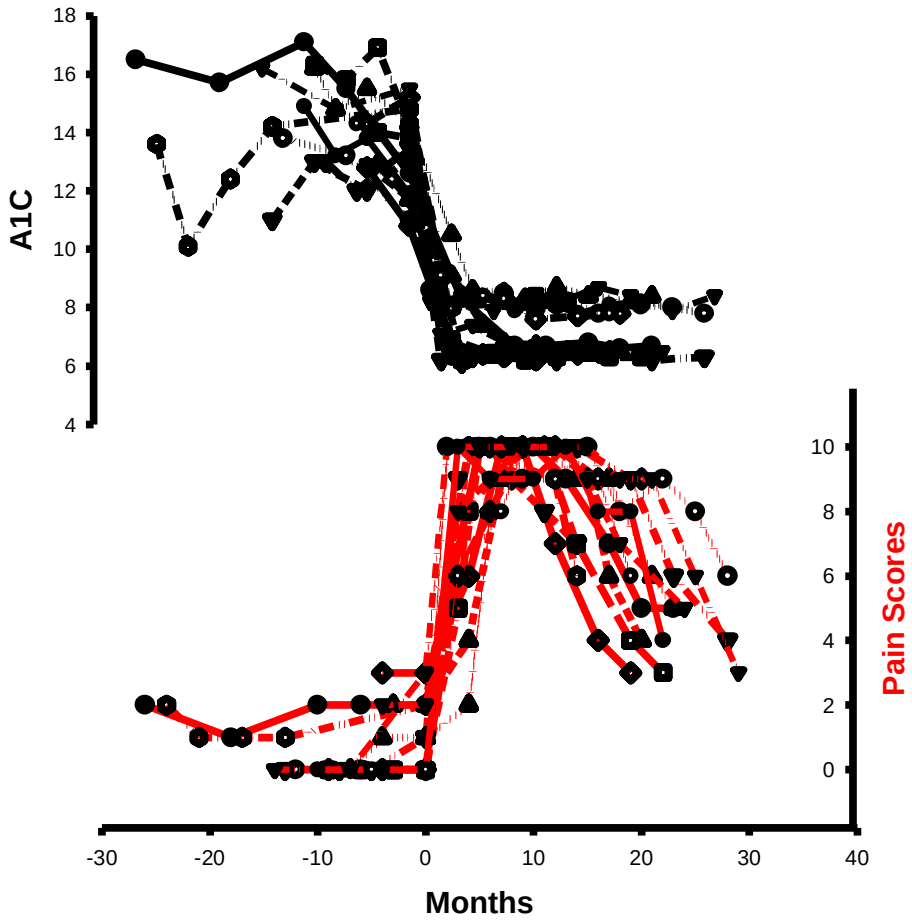
- Decreased IENFD (A)
- Nerve fiber swellings (B)
- Reduced sweat gland NFD (D)
- After 1 year improved IENFD and SGNFD (C and E)




Intra-Epidermal Nerve Fiber Density
Distal Leg
Fibers/mm
12
10
8
6
4
2
0
0-1 month
1-2 months
2-4 months
5-8 months
>8 months
Time from the onset of pain (months)

Treatment induced neuropathy

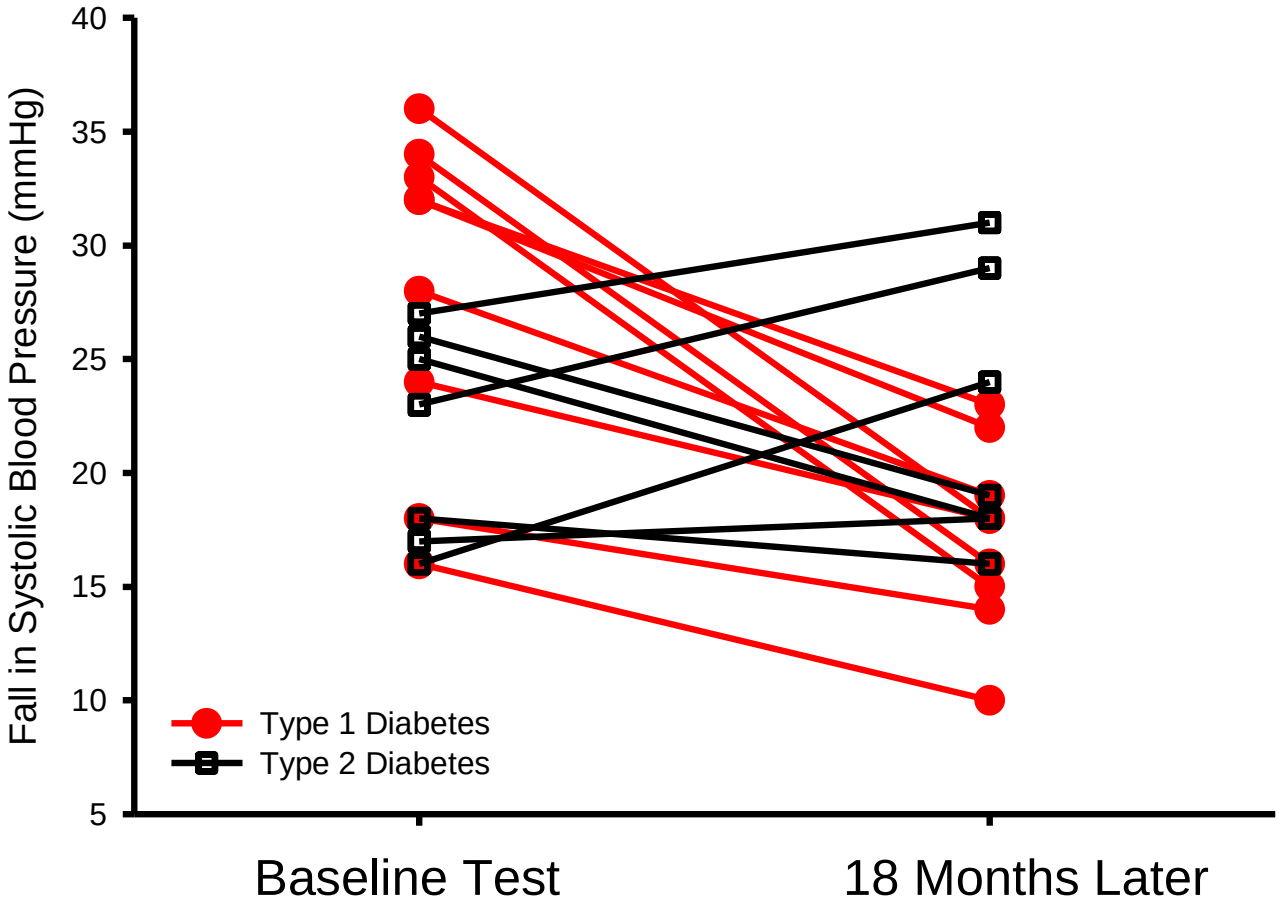
- Autonomic symptoms, tests, IENFD and pain tend to improve over time
- Time for a 50% reduction in pain (on maximal therapy) 15 months (12-28 months).
- Greater improvements were seen in type 1 vs. type 2 diabetic subjects



Caravati, CM. Insulin neuritis: a case report. Va Med Monthly. 1933; 59:745-746.

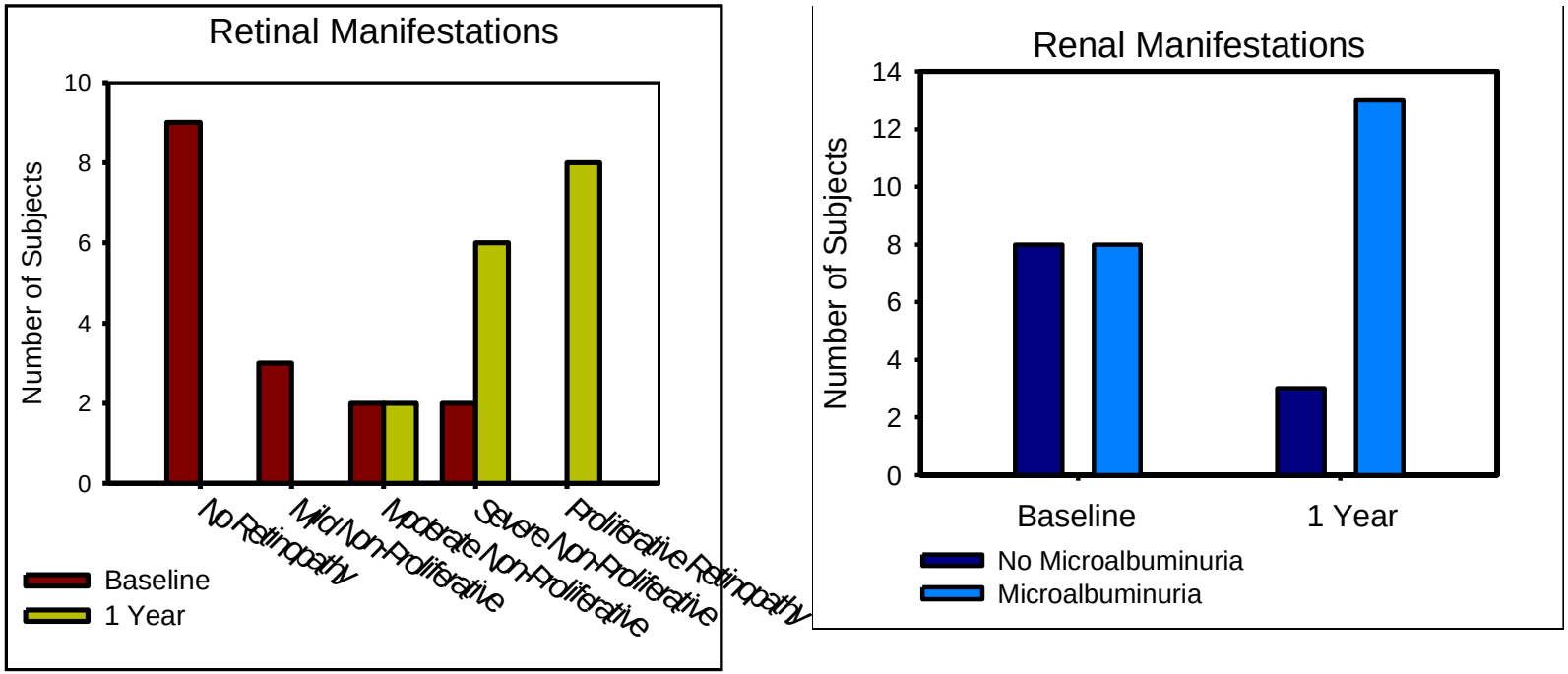
Gibbons, C and Freeman, R. Treatment induced neuropathy. Annals of Neurology 2010

Autonomic test abnormalities



Treatment induced neuropathy

A reversible painful autonomic neuropathy



Gibbons, C and Freeman, R. Treatment induced neuropathy. Annals of Neurology 2010

Treatment induced neuropathy

- The underlying pathophysiologic mechanism is unknown. Prior proposed mechanisms include:
  - Development of epineurial arterio-venous shunting causing endoneurial ischemia
  - Apoptosis due to sudden glucose deprivation
  - Recurrent hypoglycemia with microvascular damage
  - Ectopic pain from regenerating fibers/ axon sprouts
  - Insulin induced reduction in endoneurial oxygen tension due to AV shunting

- Novel mechanism - secondary to elevations in pro-inflammatory cytokine levels:
  - Progressive retinopathy is associated with elevated cytokines
  - Painful neuropathy is associated with higher circulating levels of cytokines
  - Acute hypoglycemia causes an increase in cytokines
  - Antecedent hypoglycemia leads to hyperalgesia

Treatment induced neuropathy

A reversible painful autonomic neuropathy

- “Insulin neuritis” first reported in 1933
- Recent reports have described treatment induced neuropathy in individuals with type 1 and type 2 diabetes
- Treated with oral hypoglycemic agents or with insulin.
- Pre-treatment glycosylated hemoglobin (A1C) is typically high
- Glycemic control is usually rapid

Caravati, CM. Insulin neuritis: a case report. Va Med Monthly. 1933; 59:745-746.

Gibbons, C and Freeman, R. Treatment induced neuropathy. Annals of Neurology 2010

Treatment induced neuropathy

A reversible painful autonomic neuropathy

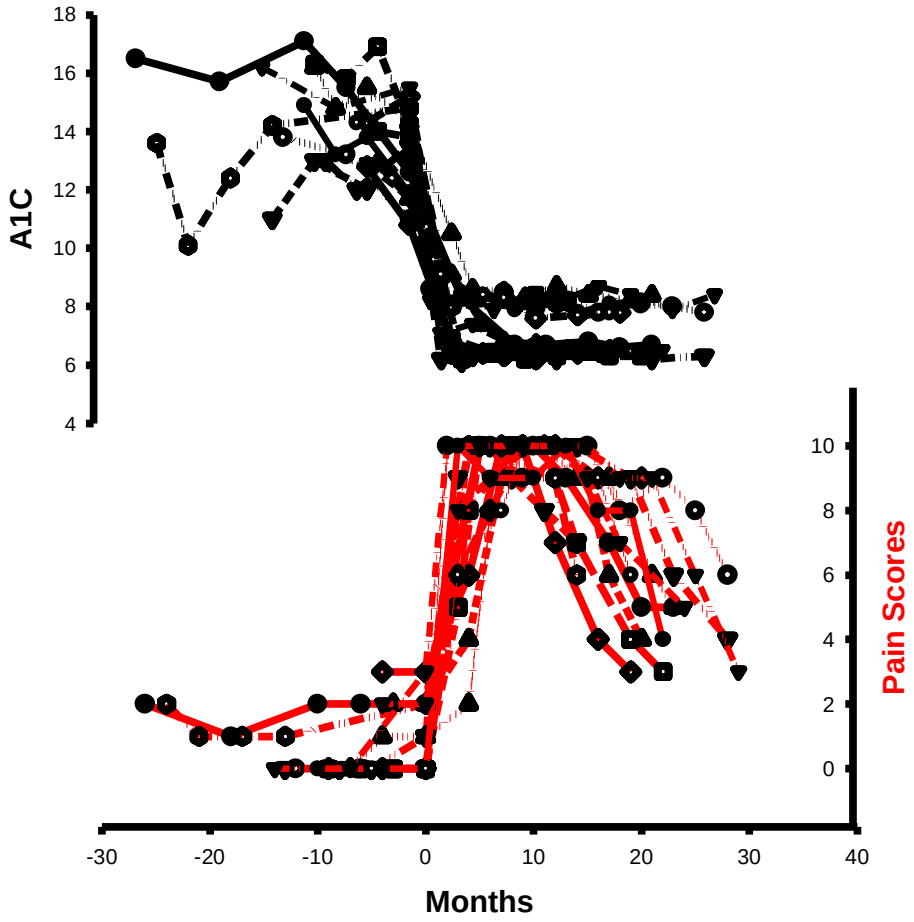
- Pain may occur distally in a length-dependent fashion or be more generalized and involve proximal sites including the trunk.
- Cardiovascular, gastrointestinal, genitourinary, and sudomotor symptoms accompany the painful neuropathy.
- Orthostatic symptoms are common
- Tests measuring sympathetic and parasympathetic function are abnormal

Caravati, CM. Insulin neuritis: a case report. Va Med Monthly. 1933; 59:745-746.

Gibbons, C and Freeman, R. Treatment induced neuropathy. Annals of Neurology 2010

Treatment induced neuropathy

- Autonomic symptoms, tests, IENFD and pain tend to improve over time
- Greater improvements were seen after 18 months in type 1 vs. type 2 diabetic subjects

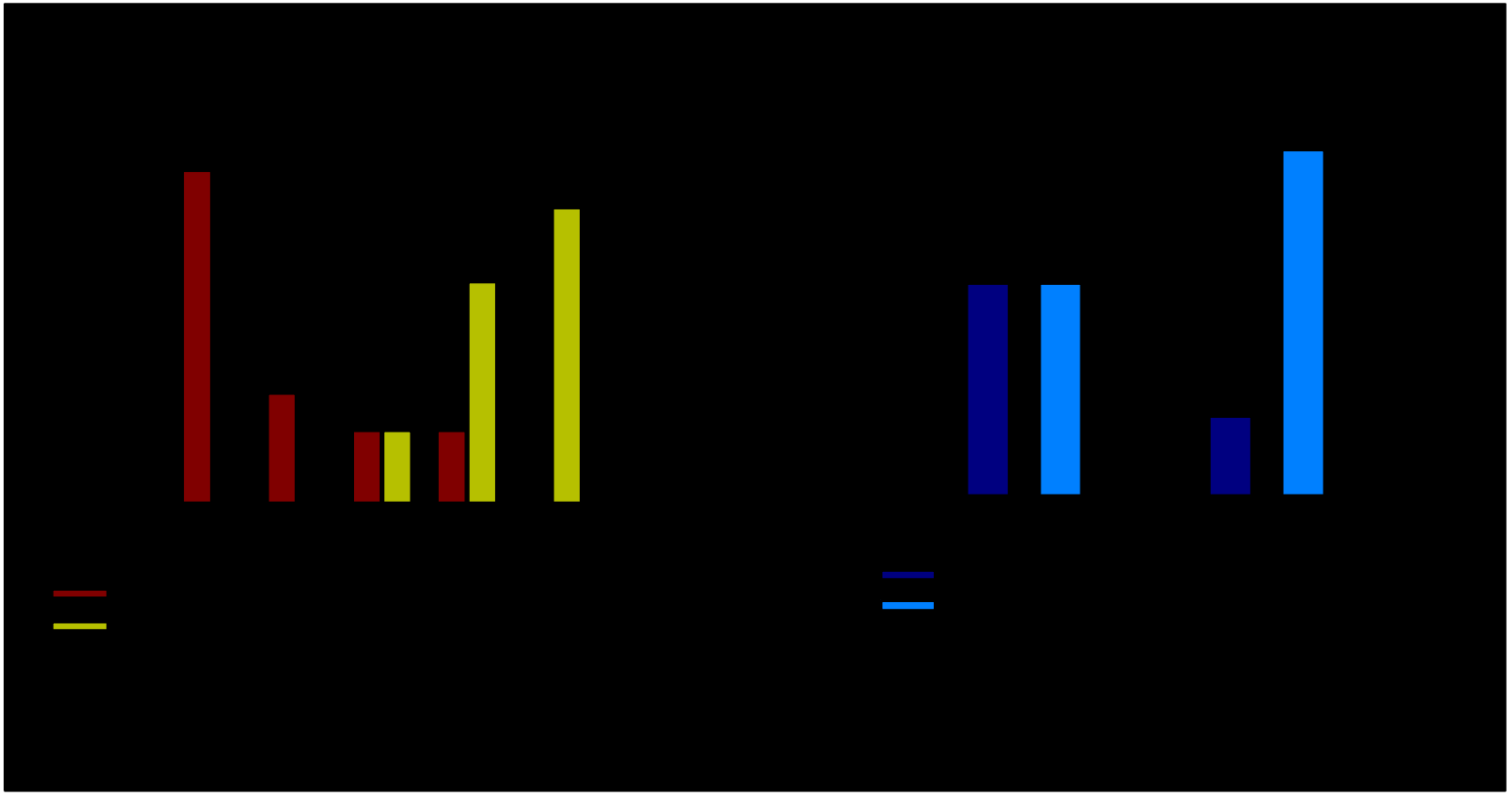


Caravati, CM. Insulin neuritis: a case report. Va Med Monthly. 1933; 59:745-746.

Gibbons, C and Freeman, R. Treatment induced neuropathy. Annals of Neurology 2010

Treatment induced neuropathy

A reversible painful autonomic neuropathy



Gibbons, C and Freeman, R. Treatment induced neuropathy. Annals of Neurology 2010

Treatment induced neuropathy

- The underlying pathophysiologic mechanism is unknown. Prior proposed mechanisms include:
  - Development of epineurial arterio-venous shunting causing endoneurial ischemia
  - Apoptosis due to sudden glucose deprivation
  - Recurrent hypoglycemia with microvascular damage
  - Ectopic pain from regenerating fibers/ axon sprouts
  - Insulin induced reduction in endoneurial oxygen tension due to AV shunting
- Novel mechanism - secondary to elevations in cytokine levels:
  - Progressive retinopathy is associated with elevated cytokines
  - Painful neuropathy is associated with higher circulating levels of cytokines
  - Acute hypoglycemia causes an increase in cytokines

Diabetic Autonomic Neuropathy

- Autonomic neuropathy associated with generalized distal polyneuropathy
- Autonomic neuropathy associated with impaired glucose tolerance
- Treatment induced painful autonomic neuropathy
- Transient autonomic dysfunction

U.S. Department of Health and Human Services

NIH News

National Institutes of Health

National Heart, Lung, and Blood Institute

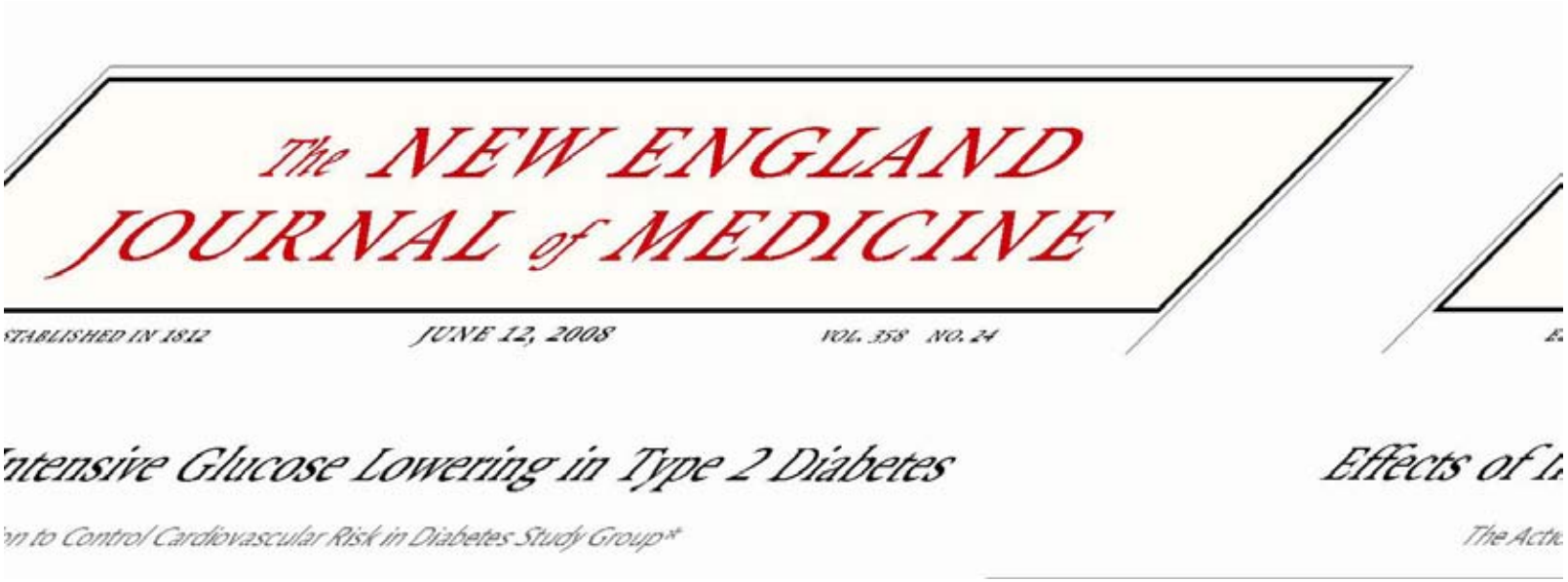
CONTACT:

Name: NHLBI Communications Office
Phone: (301) 496-4236
Email: nhlbi_news@nhlbi.nih.gov

EMBARGOED FOR RELEASE
February 6, 2008
10:30 AM

For Safety, NHLBI Changes Intensive Blood Sugar Treatment Strategy in Clinical Trial of Diabetes and Cardiovascular Disease

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health has stopped one treatment within a large, ongoing North American clinical trial of diabetes and cardiovascular disease 18 months early due to safety concerns after review of available data, although the study will continue.



The NEW ENGLAND JOURNAL of MEDICINE

STABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

ntensive Glucose Lowering in Type 2 Diabetes

n to Control Cardiovascular Risk in Diabetes Study Group*

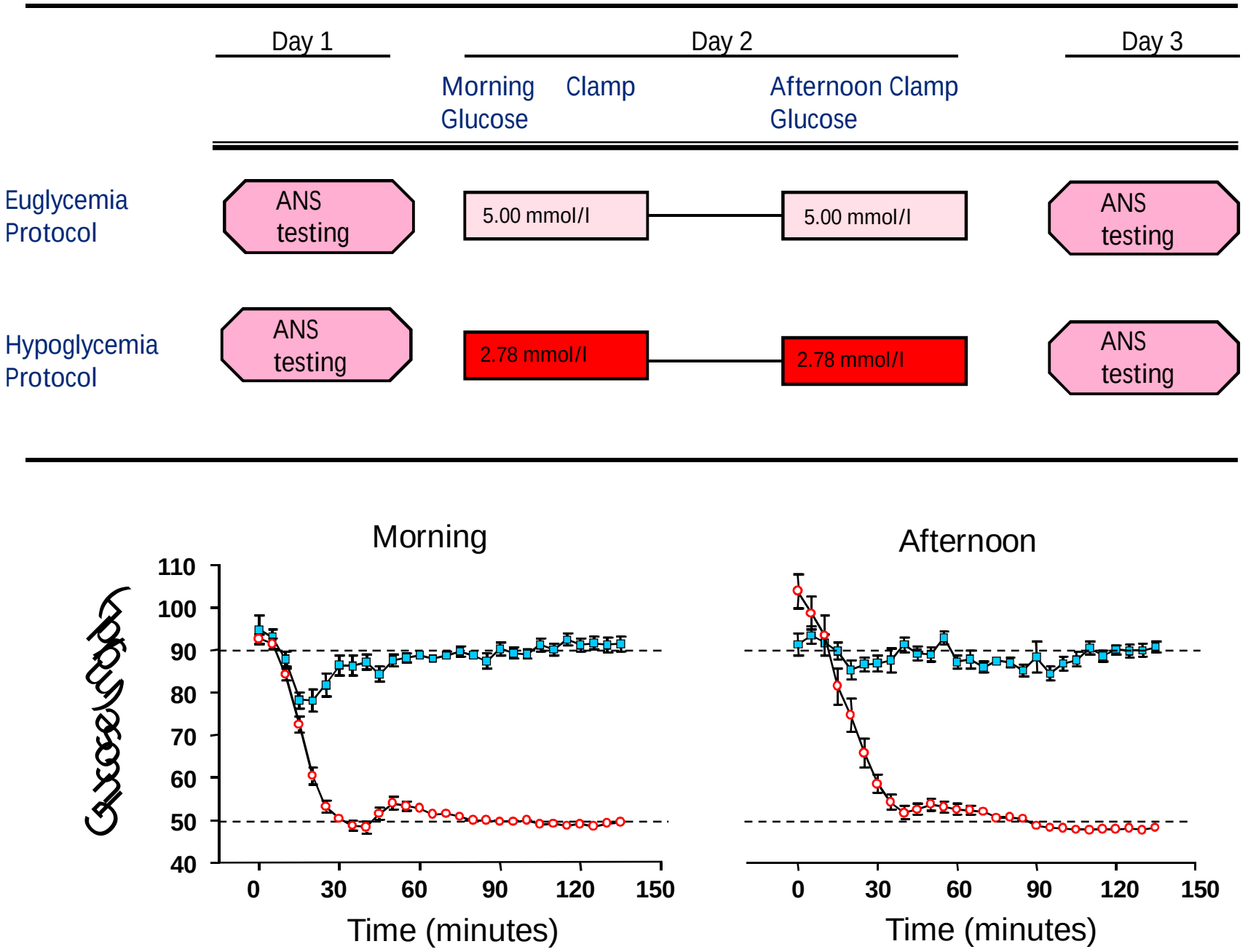
Effects of L

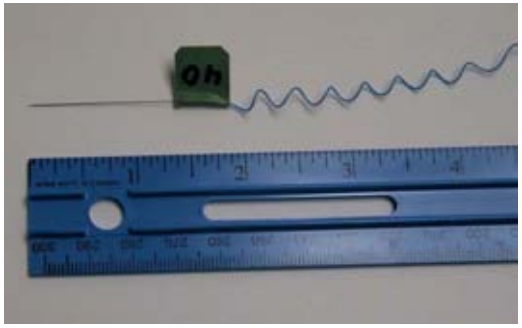
The Acth

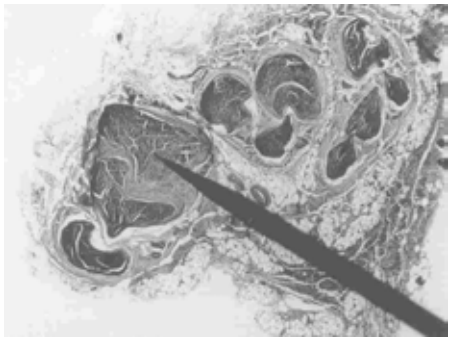
CONCLUSIONS

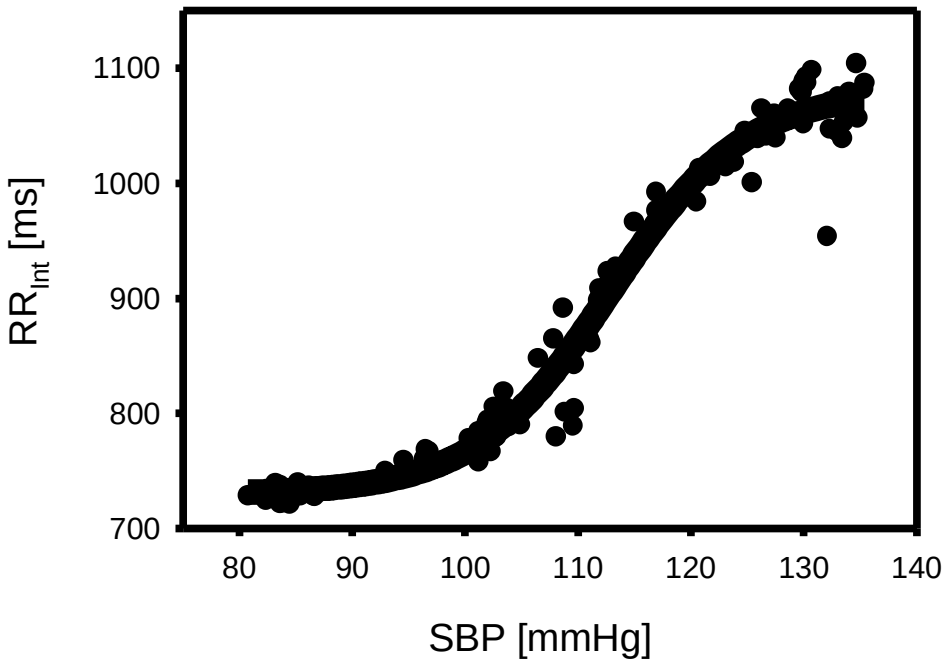
As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes.

(ClinicalTrials.gov number, NCT00000620.)

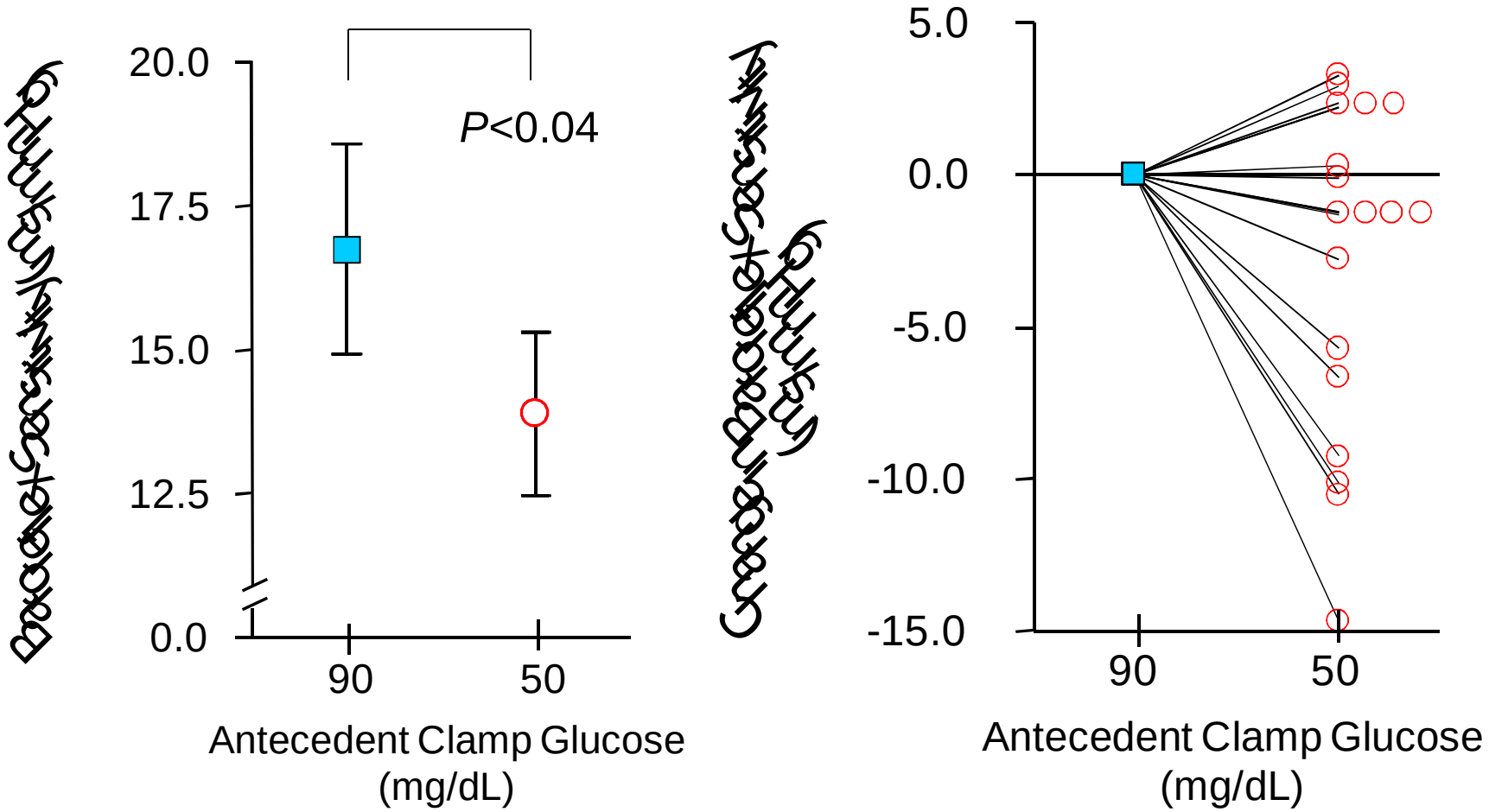

Day 1
Day 2
Day 3
Morning Clamp Glucose
Afternoon Clamp Glucose
Euglycemia Protocol
ANS testing
5.00 mmol/l
5.00 mmol/l
ANS testing
Hypoglycemia Protocol
ANS testing
2.78 mmol/l
2.78 mmol/l
ANS testing
Morning
Afternoon
Glucose (mg/dl)
110
100
90
80
70
60
50
40
0
30
60
90
120
150
Time (minutes)
Time (minutes)





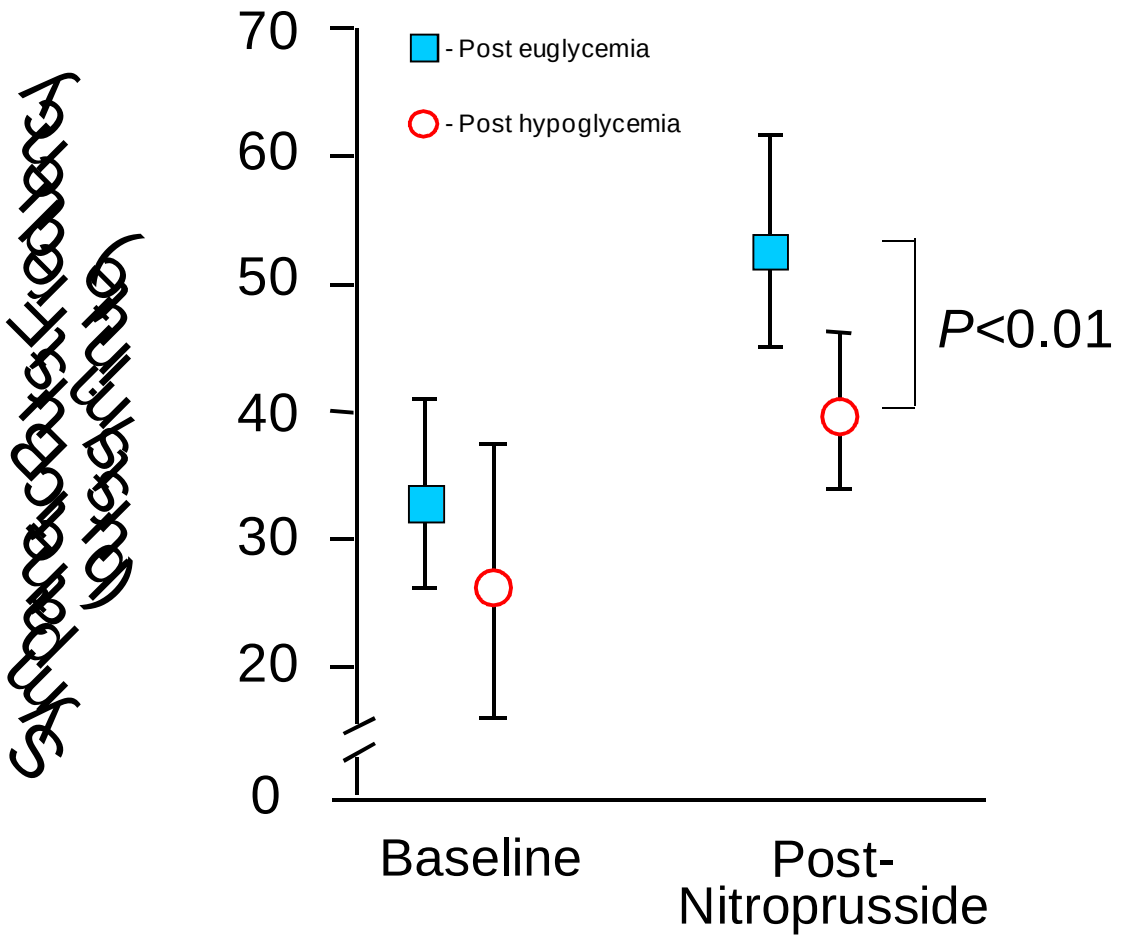


The cardiac vagal baroreflex assessed by the relation between RR_{int} and SBP during the rising portion of the BP trace. The slope of the linear portion of the sigmoid curve is the measure of the baroreflex sensitivity.



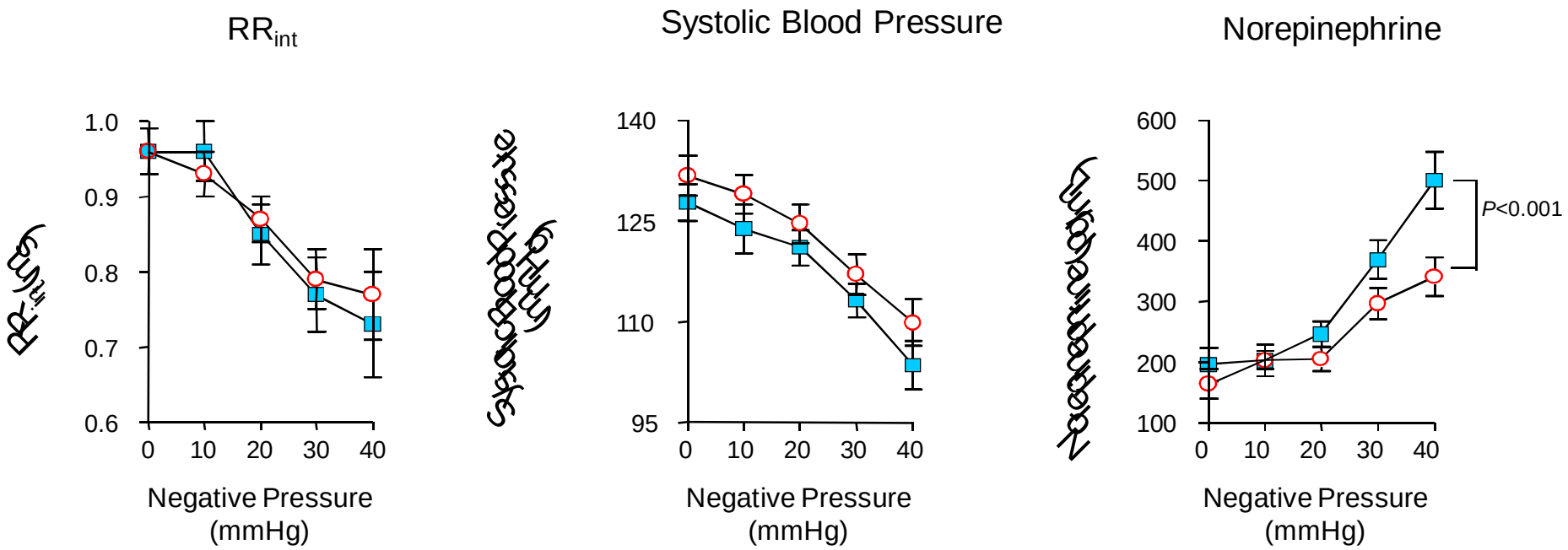
Antecedent hypoglycemia impairs autonomic cardiovascular function - implications for rigorous glycemic control.

Adler GK et al. Diabetes 2009; 58:1-8.



A decrease in the muscle sympathetic nerve response to a transient pharmacological hypotensive stress

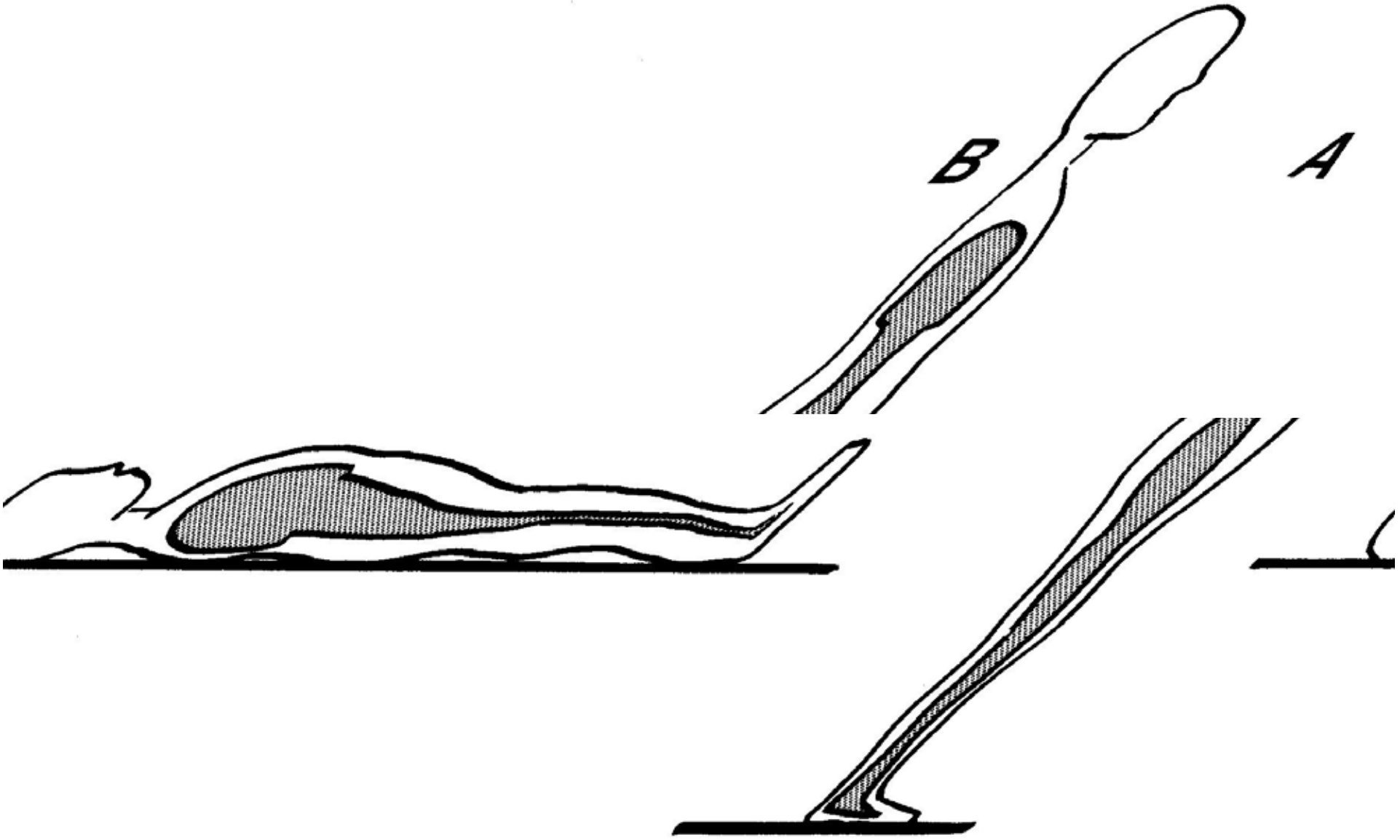
Simulated orthostasis induced by graded lower body negative pressure from 0 to 40 mmHg



Antecedent hypoglycemia decreases the norepinephrine response to LBNP

Treatment of Autonomic Dysfunction

Treatment of orthostatic hypotension



From Wieling in Clinical autonomic disorders: evaluation and management, 1997

Autonomic response to orthostatic change

- Blood pooling in dependent areas
- Baroreceptor mediated reflex response
  - Vasomotor
  - Cardiac
  - Endocrine
- SBP ê 5-10mmHg and DBP é 5-10mmHg
- HR é 10 - 20 bpm

Orthostatic Hypotension

- Impaired vasoconstriction
- Reduced central blood volume
  - Plasma volume
  - Red cell mass

TREATMENT OVERVIEW

- Non-pharmacological
  - Education
  - Prevention
- Pharmacological
  - Increase central blood volume
  - Enhance vasoconstriction

First Line Agents

- Mineralocorticoid
- Alpha-1 adrenoreceptor agonist

Second Line Agents

- NSAID
- Caffeine
- Erythropoietin
- Vasopressin Analogues
- Pyridostigmine
- L-DOPS

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Neurogenic Orthostatic Hypotension

Roy Freeman, M.B., Ch.B.

N Engl J Med 2008; 358:615-24.

Erectile dysfunction

Erectile Dysfunction

- Definition: ". . . the consistent or recurrent inability of a man to attain and/or maintain a penile erection sufficient for sexual performance"[1]
- Multifactorial—may impact total health and quality of life[2-4]

1. Recommendations of the 1st International Consultation on Erectile Dysfunction. In: Erectile Dysfunction; Jardin A, et al, eds. Plymouth, UK: Health Publication, Ltd; 2000:711-726. 2. Laumann EO, et al. JAMA. 1999;281:537-544. 3. Jonler M, et al. Br J Urol. 1995;75:651-655. 4. Fabbri A, et al. Hum Reprod Update. 1997;3:455-466.

PREVALENCE OF ERECTILE DYSFUNCTION

POPULATION	AGE (Yr)	ED (%)
Krimpen, Netherlands	50–78	11.0
Cologne, Germany	30–80	19.2
Iberian Peninsula, Spain	25–70	18.9
Perth, Australia	40-69	33.9
London, UK	16–78	19.0
Boston, Mass, USA	40–70	52.0

Shabsigh *Ann. Rev. Med.* 2003; 54:153-168

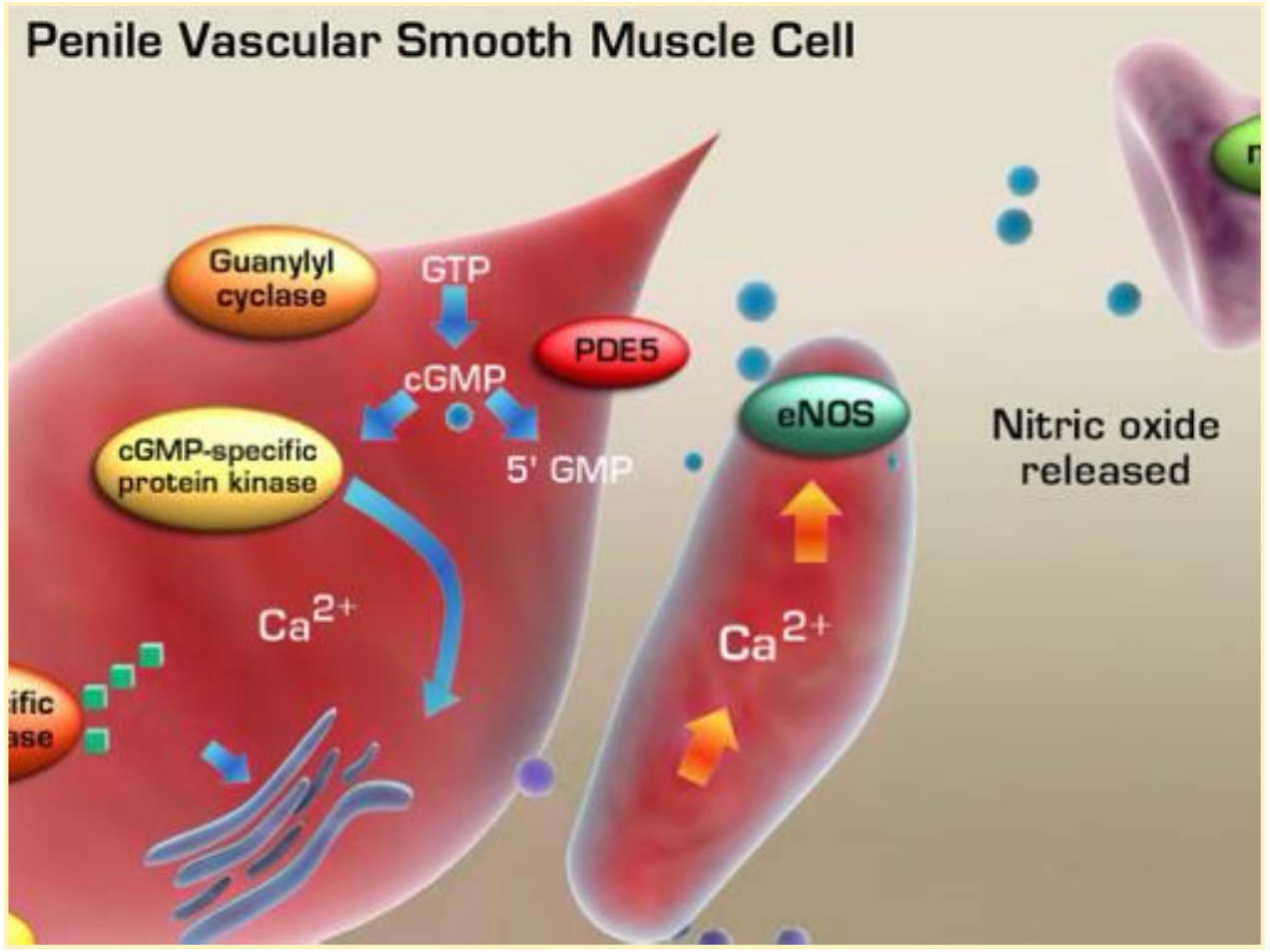
Treatment of erectile dysfunction

- Oral medications
- Intracavernosal injections
- Topical and intra-urethral agents
- Mechanical devices
- Surgical interventions
- Psychotherapy

Neurochemistry of erectile function

- Central and somatosensory stimulation
- NANC nerves and endothelial cells release NO
- Activates soluble guanylate cyclase
- Generates second messenger cyclic GMP
- Reduces cytosolic calcium
- Results in sinusoidal smooth muscle relaxation
- Cyclic GMP inactivated by phosphodiesterase 5

Biochemistry of Erection: Relaxation Mechanisms



eNOS = endothelial nitric oxide synthase; nNOS = neural nitric oxide synthase.

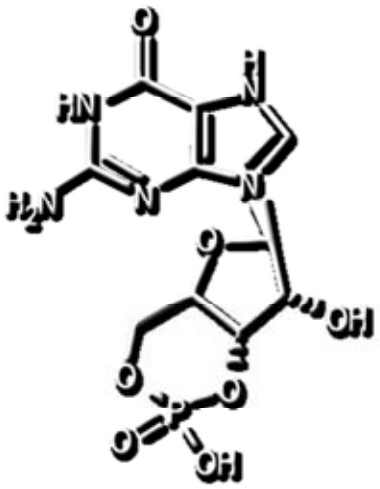
Lue TF. *N Engl J Med.* 2000;342:1802-1813.

PDE5 Inhibitors: Structural Chemistry

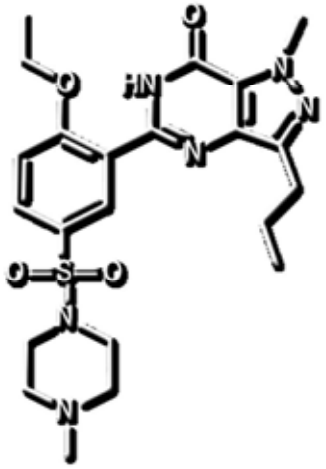
- Viagra (sildenafil citrate), Cialis (tadalafil), and Levitra (vardenafil HCl) are competitive inhibitors of PDE5
- They resemble cyclic guanosine monophosphate (cGMP) - the substrate
- Bind to the active site of PDE5
- Competitively displace cGMP from PDE5 site
- Subtle structural differences lead to an effect on potency, selectivity, and pharmacokinetic parameters including C_{max}, T_{max}, $t_{1/2}$, and bioavailability

Corbin JD, Francis H. *IJCP.*2002;56:453-459.

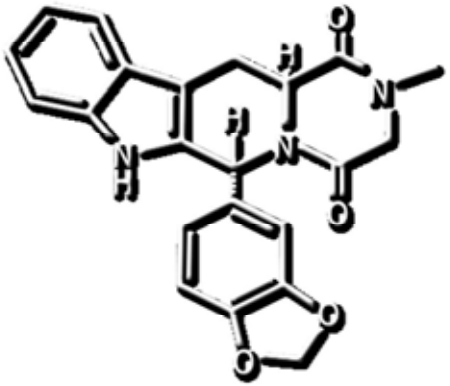
PDE5 Inhibitors: Structural Chemistry



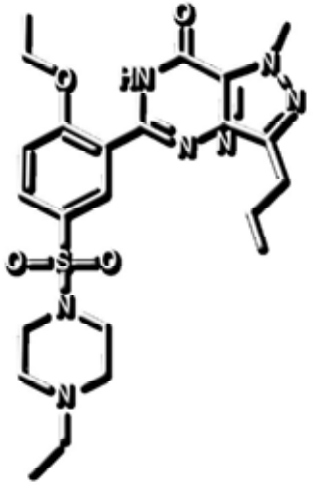
cGMP



Sildenafil



Tadalafil



Vardenafil

Pharmacokinetics of PDE5 Inhibitors

Parameter	Sildenafil citrate (fasted 100 mg)	Tadalafil (fasted 20 mg)	Vardenafil HCl (fasted 20 mg)
T_{max}, h	1.0	2.0 (0.5-6.0)	0.7-0.9
$t_{½}$, h	4.0	17.5	4.0–5.0
Bioavailability	40%	N/A	15%

Pharmacokinetics of PDE5 Inhibitors

Parameter	Sildenafil citrate (fasted 100 mg)	Tadalafil (fasted 20 mg)	Vardenafil HCl (fasted 20 mg)
T_{max}, h	1.0	2.0 (0.5-6.0)	0.7-0.9
$t_{½}$, h	4.0	17.5	4.0–5.0
Bioavailability	40%	N/A	15%

Prokinetic Agents

- Metoclopramide
- Domperidone
- Erythromycin
- H_2 receptor antagonists
- Proton pump inhibitors

Bowel Hypomotility

- Increase fiber
- Increase fluid
- Stool softener
- Osmotic laxative
- Minimal use of contact cathartics

Therapy of bladder hypomotility

- Behavioural therapy
- Compressive and reflex manoeuvres
- Catheterization and collecting devices
- Pharmacotherapy
- Electrical stimulation
- Surgery