

IS HOMOCYSTEINE TO NERVES AS CHOLESTEROL IS TO VASCULATURE ?

ALLEN MARK JACOBS DPM, FACFAS, FAPWCA

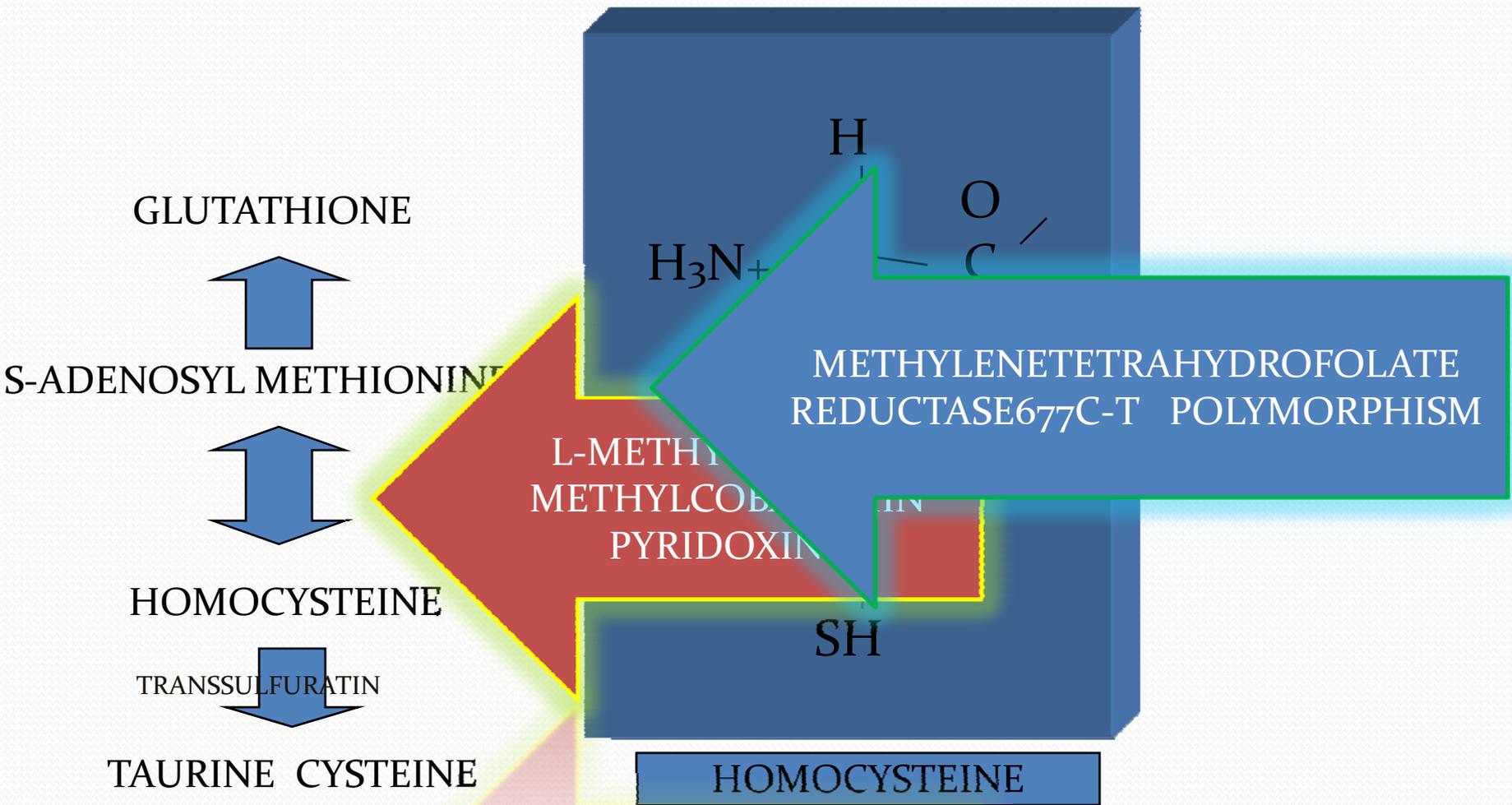


DISCUSSION

- ARE ELEVATED HOMOCYSTEINE LEVELS FOUND IN PATIENTS WITH DIABETES ?
- DOES A CORRELATION EXIST BETWEEN ELEVATED HOMOCYSTEINE LEVELS AND NEUROPATHY IN THE PATIENT WITH DIABETES ?
- WHAT ARE THE PATHOPHYSIOLOGIC MECHANISMS OF HOMOCYSTEINE ASSOCIATED DIABETIC NEUROPATHY ?
- ARE HOMOCYSTEINE LOWERING AGENTS EFFECTIVE IN REDUCING NEUROPATHY ASSOCIATED SIGNS AND SYMPTOMS ?

WHAT IS HOMOCYSTEINE ?

- HOMOLOGUE OF AA CYSTEINE



HOMOCYSTEINE AND COMPLICATIONS IN DM

- ELEVATED HOMOCYSTEINE LEVELS A RISK FACTOR FOR:
 - CARDIOVASCULAR Dx
 - RETINOPATHY
 - NEPHROPATHY



PREVELENC IN DIABETES

- 5⁰%-7⁰%*
- ELEVATED
 - SENSORY NEUROPATHY
 - AUTONOMIC NEUROPATHY
 - ULCERATION
 - PAD
 - FRACTURES



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ETIOLOGY OF ELEVATED HOMOCYSTEINE LEVELS IN DIABETES MELLITUS

- DIET (FOLIC ACID, B6,B12)
- DIABETES
- METFORMIN
- INSULIN
- RENAL DISEASE
- INACTIVITY
- ALCOHOL CONSUMPTION
- SEIZURE MEDICATIONS (LEVDOPA)
- LIPID LOWERING AGENTS (FIBRATES, STATINS, NITRATES)
- HYPOTHYROIDISM
- INFLAMMATORY BOWEL DISEASE
- HOMOCYSTINURIA
- METHYLENE-TETRAHYDROFOLATE-REDUCTASE DEFICIENCY

METFORMIN

- INCREASED HCy GREATER THAN 6 MONTHS
- EFFECT DUE TO MALABSORPTION OF B₁₂
- 26.7% LOWER COBALAMIN
- 21.6% LOWER HOLOTRANSCOBALAMIN

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ALCOHOL AND HOMOCYSTEINE

- ELEVATED HOMOCYSTEINE COMMON IN ALCOHOLISM
- MTHFR POLYMORPHISM
 - REDUCED MTHFR ACTIVITY IN ALCOHOLICS
 - MTHFR “PROTECTIVE” FROM ALCOHOLISM
 - ALCOHOLICS WITH NORMAL MTHFR ACTIVITY DO NOT DEMONSTRATE NEUROLOGIC MANIFESTATIONS

Relation between homocysteinaemia and diabetic neuropathy in patients with Type 2 diabetes mellitus

A. Ambrosch*†, J. Dierkes*, R. Lobmann‡, W. Kühne‡, W. König†, C. Luley* and H. Lehnert‡

*Institute of Clinical Chemistry, †Institute of Microbiology and Department of Medicine, ‡Division of Endocrinology and Diabetes, University Hospital Magdeburg, Germany

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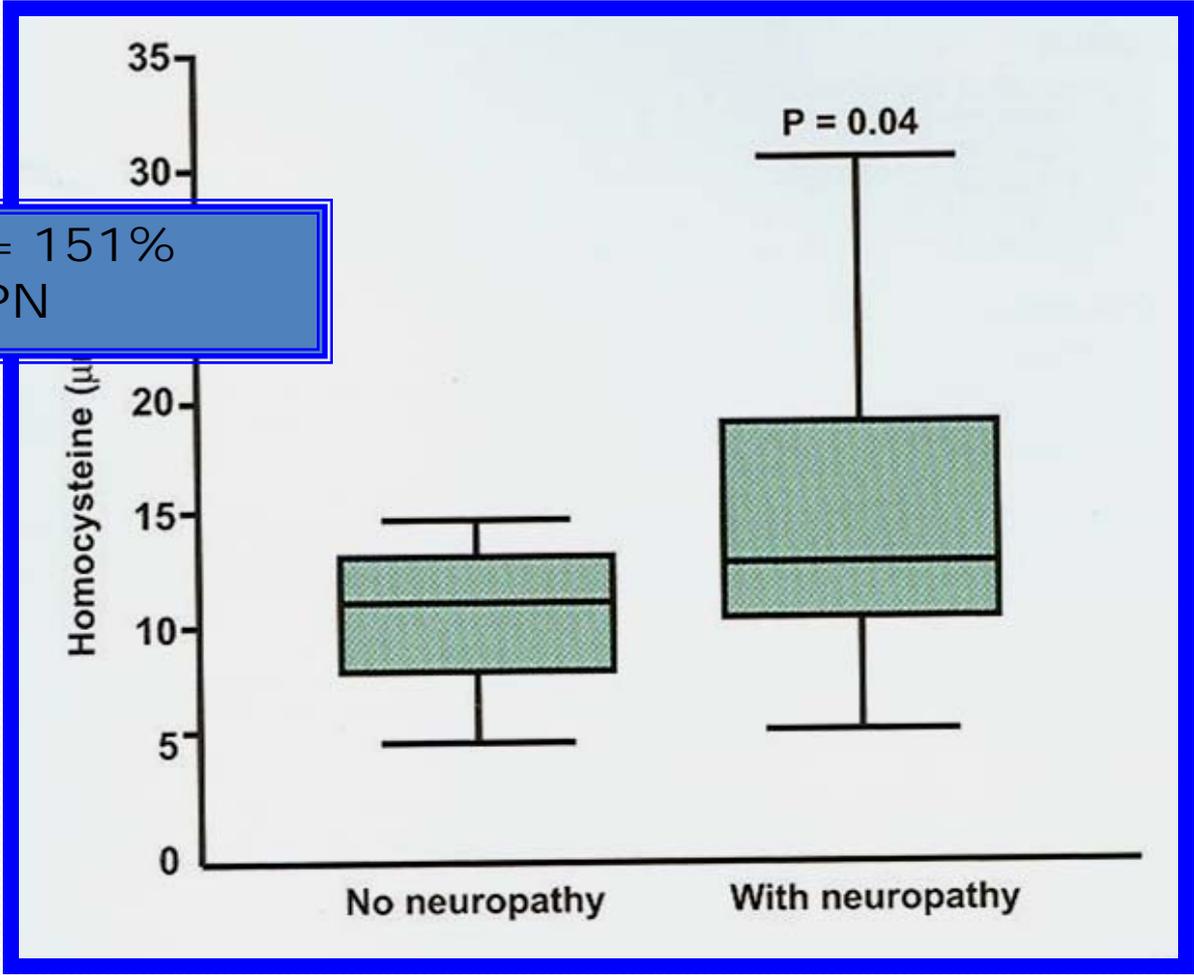
Abstract

Aims Limited data are available on determinants of diabetic neuropathy as its pathogenesis is multifactorial. Since homocysteine exhibits toxic effects on vascular endothelial cells, the association between homocysteine and the prevalence of neuropathy in Type 2 diabetes mellitus was investigated.

Methods A total of 65 Type 2 diabetic patients were consecutively enrolled into the study. Neuropathy was diagnosed according to clinical symptoms, clinical examination, electrophysiological sensory testing and autonomic function testing. With regard to homocysteine-related parameters, plasma homocysteine, folate, vitamin B12, vitamin B6 and renal function (creatinine, ceratinine clearance, cystatin C) were measured, and the C677T polymorphism of the methylenetetrahydrofolate reductase gene was determined.

Results Forty-three of the Type 2 diabetic patients were classified as suffering from neuropathy. Both patient groups were comparable with regard to demographic data, blood pressure, glucose metabolism, renal function and homocysteine-related vitamins. In contrast, homocysteine levels ($P = 0.04$) and the frequency of hyperhomocysteinemia ($\geq 15 \mu\text{mol/l}$) ($P = 0.01$) were significantly increased in neuropathic patients. In a logistic regression model with neuropathy as dependent variable, homocysteine (adjusted for creatinine, homocysteine-related vitamins, HbA_{1c} and duration of diabetes) was the only significant variable associated with the prevalence of neuropathy (odds ratio for homocysteine per 5 $\mu\text{mol/l}$ increase: 2.60 (95% confidence interval 1.07–

EACH 5 Umol/L = 151% INCREASE IN DPN



HOMOCYSTEINE AND NEUROPATHY

- NEUROPATHY PREVALENCE HIGH
- HOMOCYSTEINE IS A RISK FACTOR
- PREVALENCE OF NEUROPATHY INCREASED BY GLUCOSE LEVEL
 - 5%, 8%, 15%
- NEUROPATHY ASSOCIATED WITH DEFORMITY

HOMOCYSTEINE AND AUTONOMIC NEUROPATHY

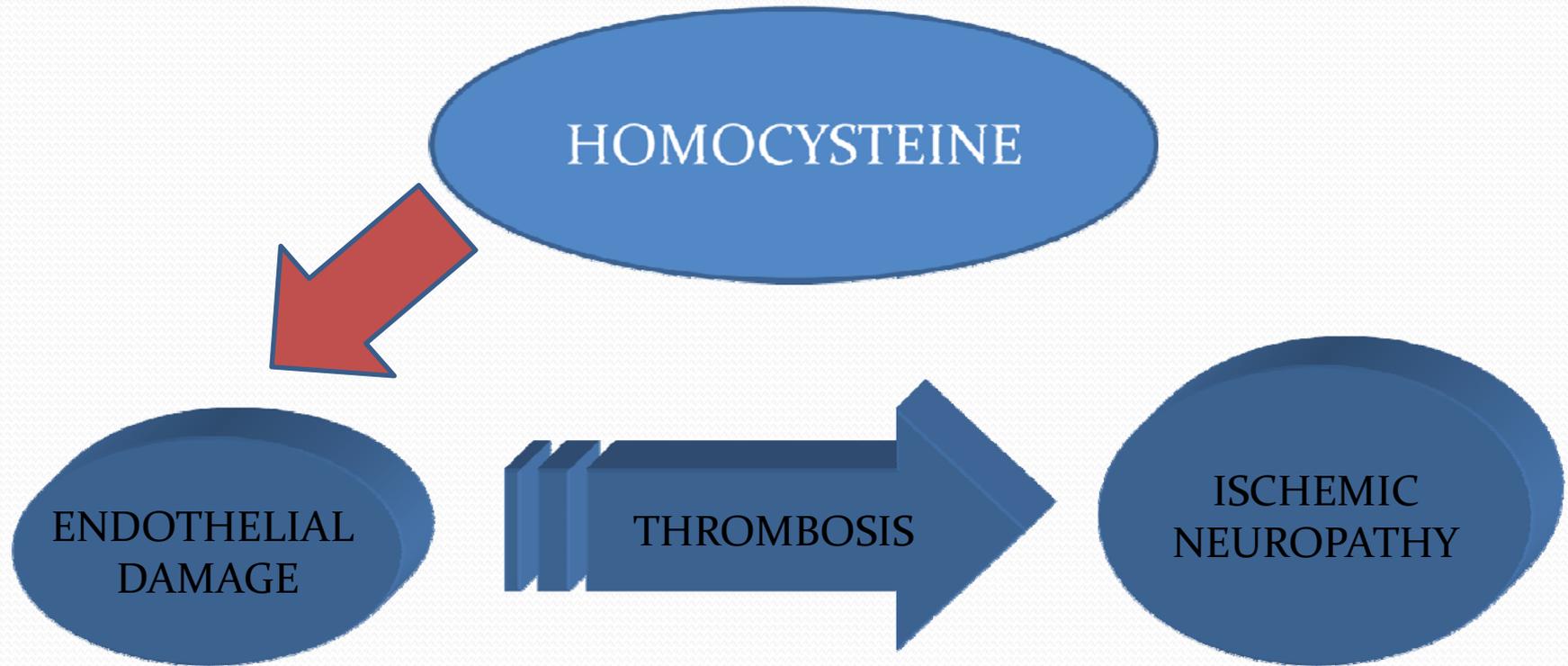
- ELEVATED HOMOCYSTEINE LEVELS ARE AN INDEPENDENT RISK FACTOR FOR DIABETIC AUTONOMIC NEUROPATHY



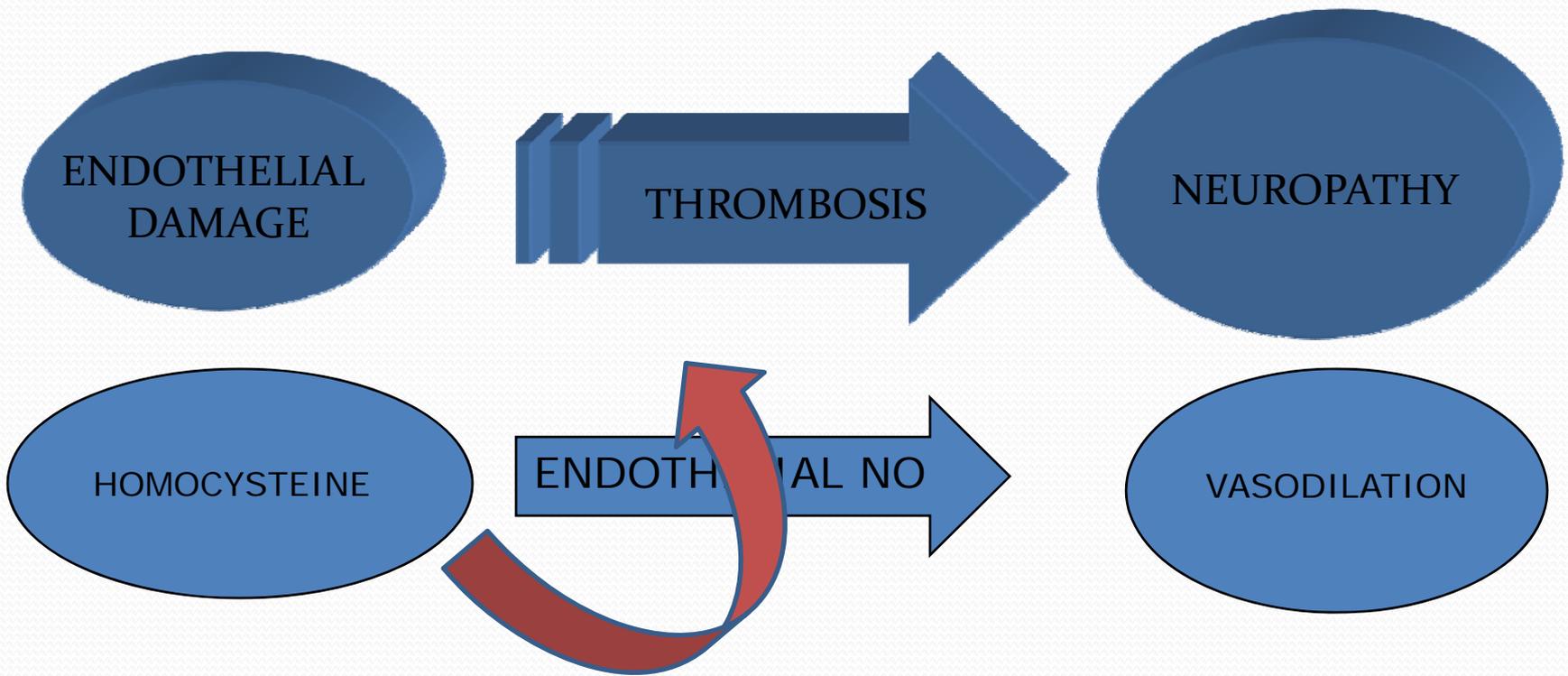
ERECTILE DYSFUNCTION

- RISK FACTORS FOR ED;
 - SMOKING
 - ELEVATED HgA_{1C}
 - HOMOCYSTEINE LEVELS

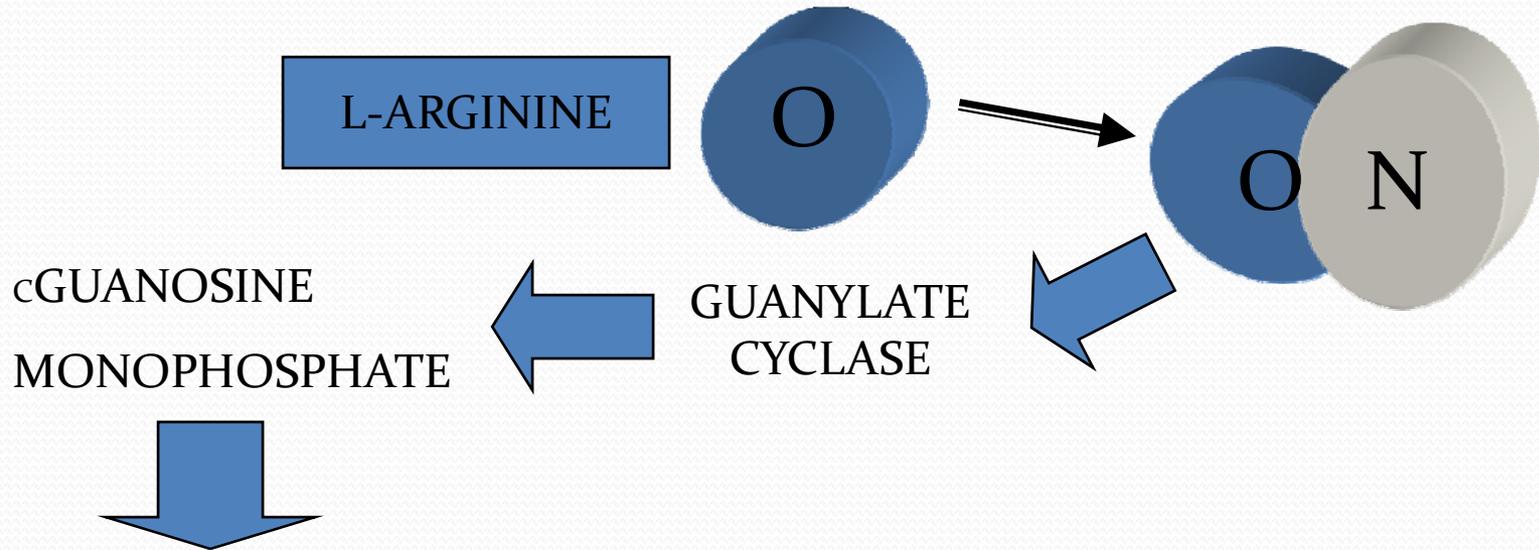
NEUROPATHY AND HOMOCYSTEINE IN DM



NEUROPATHY AND HOMOCYSTEINE IN DM



NITRIC OXIDE



SMOOTH MUSCLE RELAXATION

MODULATION OF RESPONSE

VASOCONSTRICTORS

CYTOKINES

ENDOTOXINS

NITRIC OXIDE

- CONSTITUTIVE NOS
 - nNOS
 - eNOS
- INDUCIBLE NOS
 - TISSUE SPECIFIC STIMULI
 - INFLAMMATORY CYTOKINES
 - BACTERIAL LIPOPOLYSACCHARIDS

STREPTOZOTICIN-INDUCED DM

- iNOS PROTECTIVE OF PEROXYNITRATE INJURY
- NITROSATIVE STRESS UNDERLIES PERIPHERAL NERVE DYSFUNCTION IN AXONS AND SCHWANN CELLS IN DIABETIC NEUROPATHY
- PEROXYNITRATE ASSOCIATED WITH:
 - DECREASED MOTOR NCV
 - DECREASED NEURAL BLOOD FLOW
 - DECREASED NOCICEPTION
 - INCREASED PAW WITHDRAWAL PRESSURES

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REDUCTION OF HOMOCYSTEINE

- FOLIC ACID REDUCES HOMOCYSTEINE
- VITAMIN B₁₂, B₆ ARE COFACTORS
- FOLIC ACID SUPPLEMENATTION REDUCES HOMOCYSTEINE

REDUCTION OF HOMOCYSTEINE

- VITAMIN B6 INVOLVED IN HOMOCYSTEINE METABOLISM
- SUBCLINICAL B6 DEFICIENCY MAY BE PRESENT
- MAY BE COMMON IN THE ELDERLY
- RESULTS IN ELEVATED HOMOCYSTEINE
- RESULTS;
 - IMPAIRED COGNITIVE FUNCTION
 - ALZHEIMER'S DISEASE
 - CARDIOVASCULAR DISEASE

HOMOCYSTEINE AND GENERAL NEURAL (COGNITIVE) FUNCTION

- INVERSE RELATIONSHIP BETWEEN HOMOCYSTEINE AND COGNITIVE FUNCTION OVER 60 YEARS OF AGE
- FOLIC ACID SUPPLEMENTATION IMPROVED COGNITIVE FUNCTION EVEN WITH NORMAL B₁₂

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VITAMIN B12, FOLIC ACID, AND GENERAL NEURAL (COGNITIVE) FUNCTION

- PLAYS A ROLE IN THE PREVENTION AND TREATMENT OF;
 - MOOD DISORDERS
 - DEMENTIA
 - ALZHEIMER'S DISEASE
 - VASCULAR DEMENTIAS

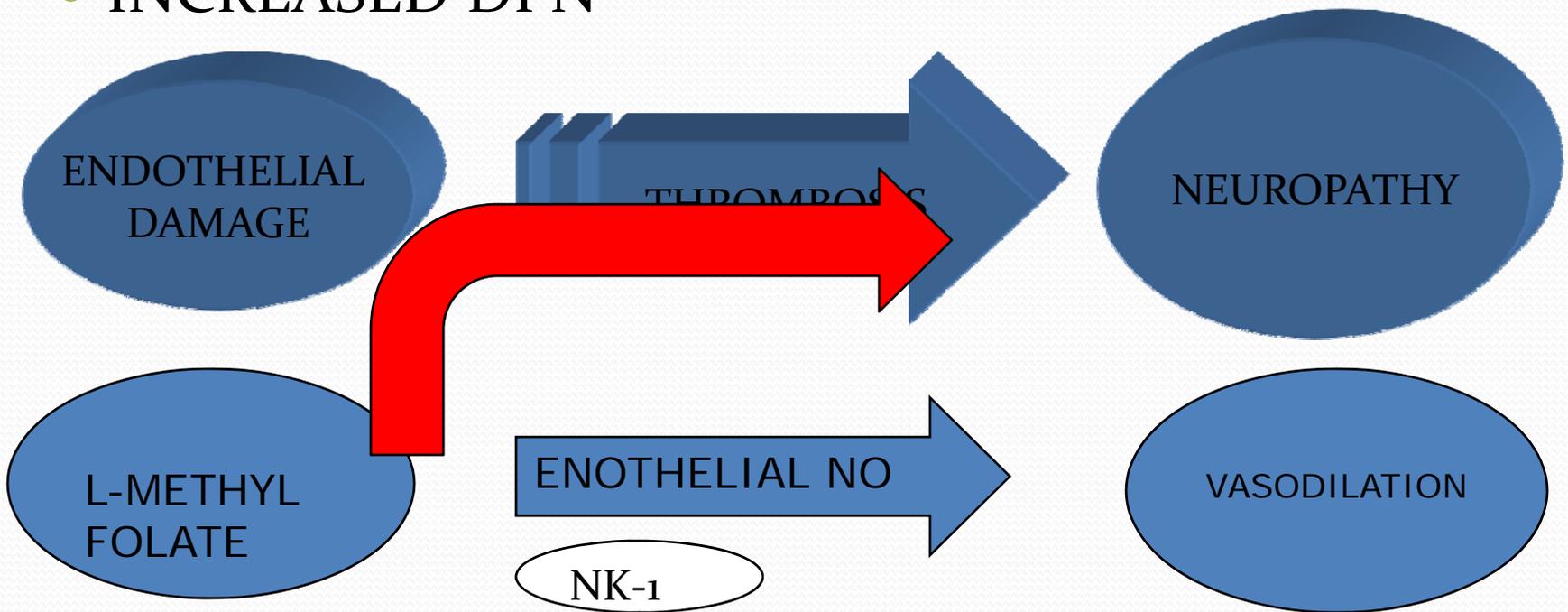
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NEUROPATHY AND HOMOCYSTEINE IN DM

- INCREASED DPN



Effects of methylcobalamin on diabetic neuropathy

Basim A. Yaqub^a, Abdulaziz Siddique^b and Riad Sulimani^c

Divisions of ^aNeurology and ^cEndocrinology, and ^bDepartments of Medicine and Pharmacy, King Khalid University Hospital, Riyadh, Saudi Arabia

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Key words: Diabetes mellitus; Peripheral neuropathy; Nerve conduction studies; Methylcobalamin

Summary

We studied the clinical and neurophysiological effects of methylcobalamin on patients with diabetic neuropathy. In a double-blind study, the active group showed statistical improvement in the somatic and autonomic symptoms with regression of signs of diabetic neuropathy. Motor and sensory nerve conduction studies showed no statistical improvement after 4 months. The drug was easily tolerated by the patients and no side effects were encountered.

Introduction

improves conduction velocity without interfering with

METHYLCOBALAMIN

- MAY BE REDUCED IN ELDERLY PATIENTS
- SUPPLEMENATION REVERSES SYMPTOMATIC SENSORY AND AUTONOMIC NEUROPATHY
- MAY EXERT A NEUROPROTECTIVE EFFECT

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AUTONOMIC NEUROPATHY

- VASOMOTOR ABNORMALITIES
- SUDOMOTOR ABNORMALITIES
- NEUROPATHIC EDEMA
- CHARCOT'S JOINT DISEASE
- VASCULAR CALCIFICATION

MORTALITY WITH CHARCOT'S JOINT DISEASE

MORTALITY

- 44.7% 3.7+/- 2.8 YEARS
- 34.0% 3.1 +/-2.7 YEARS

MAJOR AMPUTATION

- 23.4%
- 10.6%
- ULCERATION NON-INFLUENTIAL



AUTONOMIC NEUROPATHY

- 30% PATIENTS WITH DIABETES 1 OR 2
- SILENT MYOCARDIAL INFARCTION
- POSTURAL HYPOTENSION
- RESTING TACHYCARDIA
- NEUROGENIC BLADDER
- INTERMITTENT DIARRHEA
- HYPOGYCEMIC UNAWARENESS
- SUDOMOTOR ABNORMALITIES
- VASOMOTOR ABNORMALITIES
- NEUROGENIC EDEMA
- **53 % vs 15% 5 YEAR MORTALITY**

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METHYLCOBALAMIN FOR AUTONOMIC NEUROPATHY

- REVERSAL OF AUTONOMIC SIGNS
- REVERSAL OF AUTONOMIC SYMPTOMS
- NORMALIZATION OF AUTONOMIC NERVE DYSFUNCTION

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MOTOR NEUROPATHY IN DIABETES MELLITUS

- LESS DRAMATIC PRESENTATION
- NOT SOUGHT IN EXAMINATION
- NOT RECOGNIZED
- EFFECTS NOT APPRECIATED
- SPARSE LITERATURE

METHYLCOBALAMIN MOTOR NEUROPATHY

- IMPROVED SENSORY AND MOTOR NCV
- RESOLVED SYMPTOMS 20%
- IMPROVED 40%
- RETURN OF REFLEXES 60%
- REDUCED CRAMPING

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CHEN R-J, ZHENG Y-J., XU L-S. CHIN J CLIN REHAB 6(9), 2002

IS MOTOR NEUROPATHY COMMON ?

- 167 PATIENTS WITH DPN
- ELECTROPHYSIOLOGIC STUDIES
- **59.8% SENSORY-MOTOR**
- 18.6% PURE SENSORY NEUROPATHY
- 21.6% AUTONOMIC NEUROPATHY
- COMPRESSION NEUROPATHY COMMON

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MOTOR NEUROPATHY: MANIFESTATIONS

- EARLY
 - LOSS OF ANKLE REFLEX
 - DEFORMITY OF TOES
- LATE
 - INABILITY TO STAND ON HEELS
 - ATROPHY OF FOOT MUSCLES
 - INSTABILITY, FALLS



MOTOR NEUROPATHY

MOTOR
NEUROPATHY

ATROPHY OF
FOOT INTRINSIC MUSCLES

INSTABILITY OF
METATARASAL-PHALANGEAL
JOINTS

HAMMERTOE
DEFORMITY



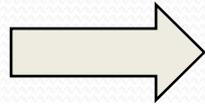
MOTOR NEUROPATHY AND FOOT ULCERS

- 318 PATIENTS WITH FOOT ULCER
- MOST COMMON FACTORS;
 - MALE GENDER
 - MOTOR NEUROPATHIES
 - MONONEUROPATHIES

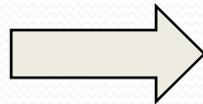


MOTOR NEUROPATHY

HAMMERTOES



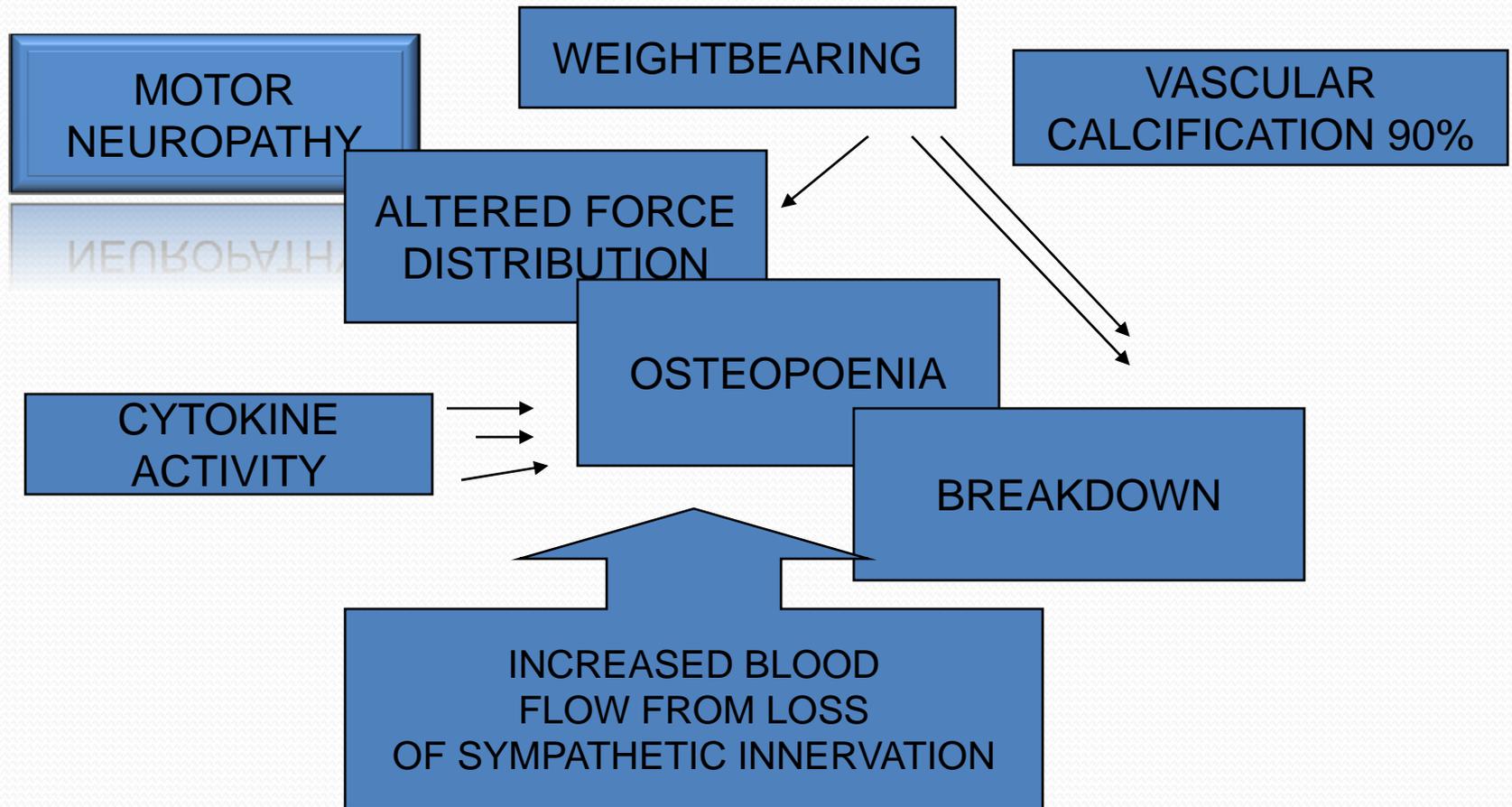
ANTERIOR FAT PAD DISPLACEMENT



INCREASED PLANTAR PRESSURE



THE CHARCOT FOOT



REVERSAL OF MOTOR NEUROPATHY

- METHYLCOBALAMIN ORAL X 1 YEAR
- NORMAL HEMOGLOBIN A₁C
- 1500 mcg DAILY
- IMPROVED MOTOR CONDUCTION VELOCITY

REVERSAL OF MOTOR NEUROPATHY

- METHYLCOBALAMIN 1500mcg DAILY
- 3 MONTH EVALUATION
 - RELIEVED CRAMPING
 - IMPROVED MOTOR CONDUCTION VELOCITY
 - REDUCED NEUROPATHIC PAIN
 - IMPROVED 2 POINT DISCRIMINATION

DEVATHASAN, G, TEO, WL., MYLVAGANAM, A. METHYLCOBALAMIN IN CHRONIC DIABETIC NEUROPATHY; A DOUBLE BLIND CLINICAL AND ELECTROPHYSIOLOGIC STUDY. CLINICAL TRIALS JOURNAL 22 (6), 534-536, 1985

MOTOR NEUROPATHY: ALPHA-LIPOIC ACID

- NATURAL ANTIOXIDANT
- 600 mg DAILY
- 3 MONTH STUDY
- MOTOR NERVE NCV IMPROVEMENT FROM 36.8 M/sec 41.3 M/sec

PYRIDOXINE

- REDUCED LEVELS IN DIABETES
- REDUCED LEVELS IN ELDERLY
- ASSOCIATED WITH NEUROPATHY
- SUPPLEMENTATION REDUCES SYMPTOMS

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METANX

- L – METHYFOLATE (FOLATE) 2.8 mg
- PYRIDOXAL 5'-PHOSPHATE (B 6) 25 mg
- METHYLCOBALAMIN (B 12) 2.0 mg

METANX

MECHANISM OF ACTION

- L-METHYLFOLATE
 - INCREASES NITRIC OXIDE
 - REDUCES HOMOCYSTEINE LEVELS
 - IMPROVED ENDOTHELIAL FUNCTION
 - METHYLCOBALAMIN (B₁₂)
 - FACILITATION OF NEURAL REGENERATION
 - COFACTOR FOR HOMOCYSTEINE REDUCTION
 - PIRIDOXAL 5'-PHOSPHATE (B₆)
 - NECESSARY FOR NEURAL FUNCTION
 - COFACTOR FOR HOMOCYSTEINE REDUCTION
- 

WHY METANX ??

- L-METHYFOLATE 7X MORE BIOAVAILABLE THAN FOLATE
- LOWERS HOMOCYSTEINE 3X COMPARED TO FOLATE

VITAMIN B FOR PERIPHERAL NEUROPATHY: COCHRANE DATABASE

- EFFICACY IS NOT CLEAR
- 13 STUDIES/741 PATIENTS
- 2 STUDIES NO SHORT TERM PAIN REDUCTION
- 1 STUDY VIBRATION DETECTION IMPROVED
- HIGHER DOSES IMPROVED PARASTHESIAS, PAIN, TEMPERATURE, VIBRATION, NUMBNESS
- STILL LIMITED DATA (INSUFFICIENT DATA)

Orally Administered L-methylfolate, Me-Cbl, and P-5-P Reduces Diabetic Peripheral Neuropathic Pain

Objective

- Examine the efficacy of L-methylfolate, Me-Cbl, and P-5-P compared to acetaminophen for the reduction of DPNP

Methodology

- 130 patients enrolled in RCT
- Patients received either L-methylfolate, Me-Cbl, and P-5-P twice daily (study group) or acetaminophen 500mg twice daily (active control group) for 20 weeks.
- A baseline visual analog scale (VAS) neuropathy pain scale was obtained and evaluated at 10 and 20 weeks.

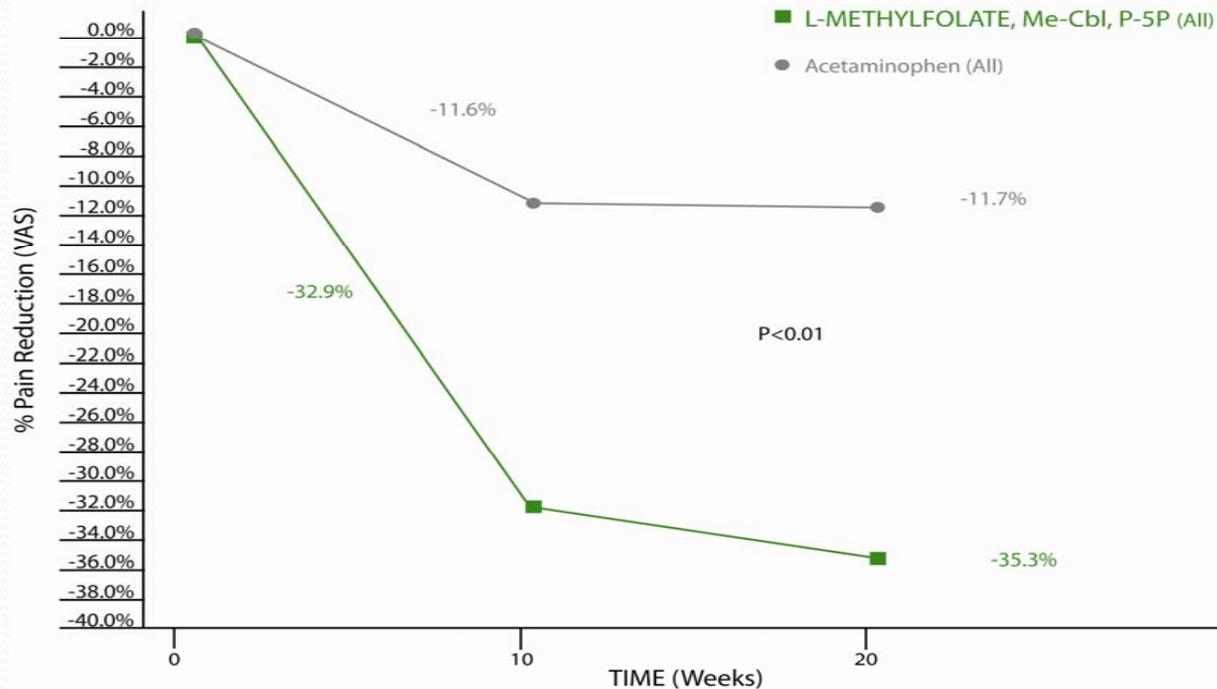
PATIENT CHARACTERISTICS

Table 1. Baseline comparison

	Treatment		p-value
	Study Group (n=45)	Active Control Group (n=52)	
Sex, %(n)			
Males	67%(30)	48%(25)	0.07
Females	33%(15)	52%(27)	
Duration of diabetes, mean(SD) – yrs	7.63(6.35)	8.17(6.26)	0.67
Duration of symptoms, mean(SD) – yrs	3.61(2.63)	3.60(2.63)	0.97
Baseline VAS score, mean(SD)	4.80(1.65)	3.19(1.56)	<0.001

Study Results: % Change

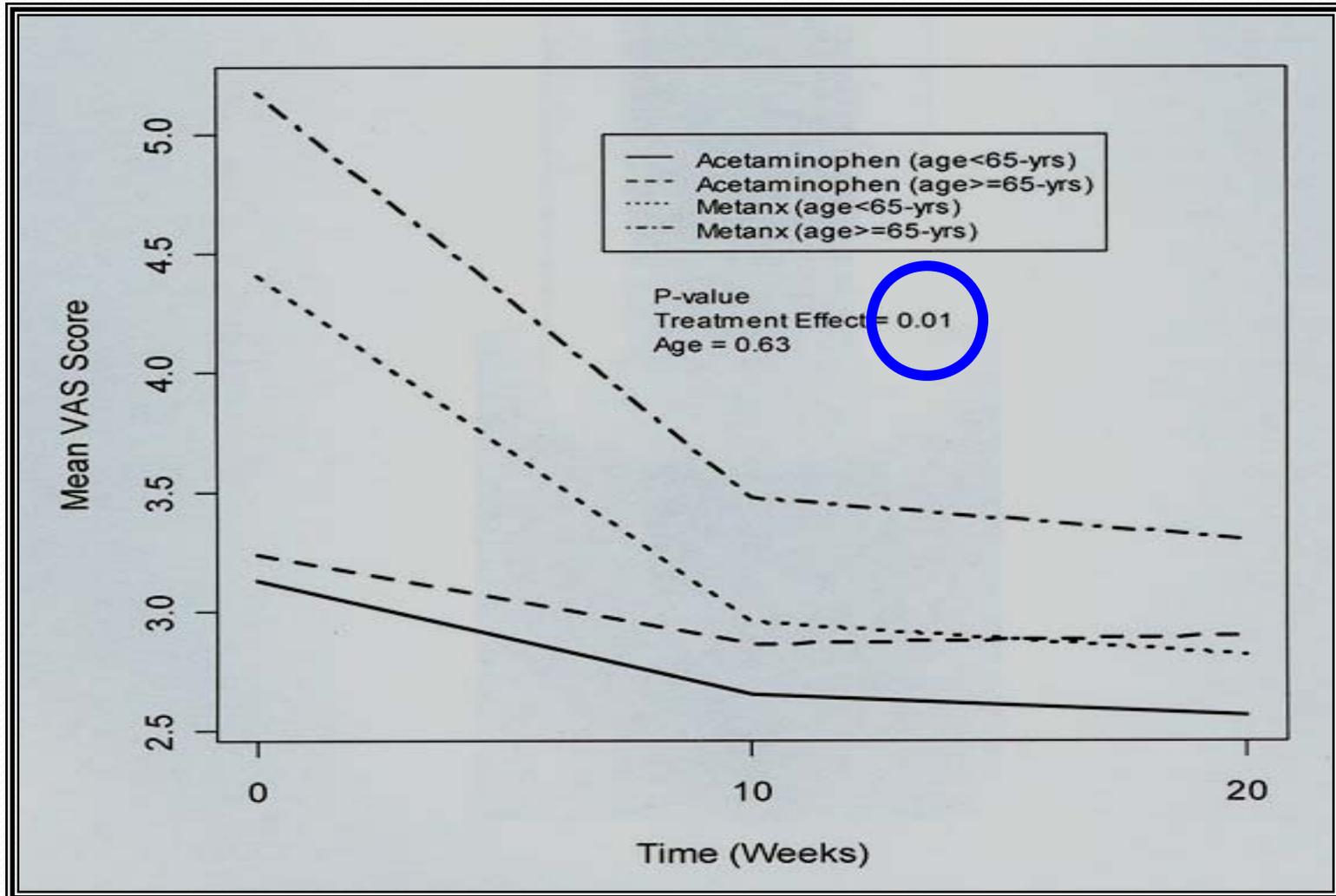
L-METHYLFOLATE, Me-Cbl, P-5P vs. ACETAMINOPHEN
PERCENT CHANGE FROM BASELINE VAS
ANALYSIS OF ALL SUBJECTS
(PERCENT)



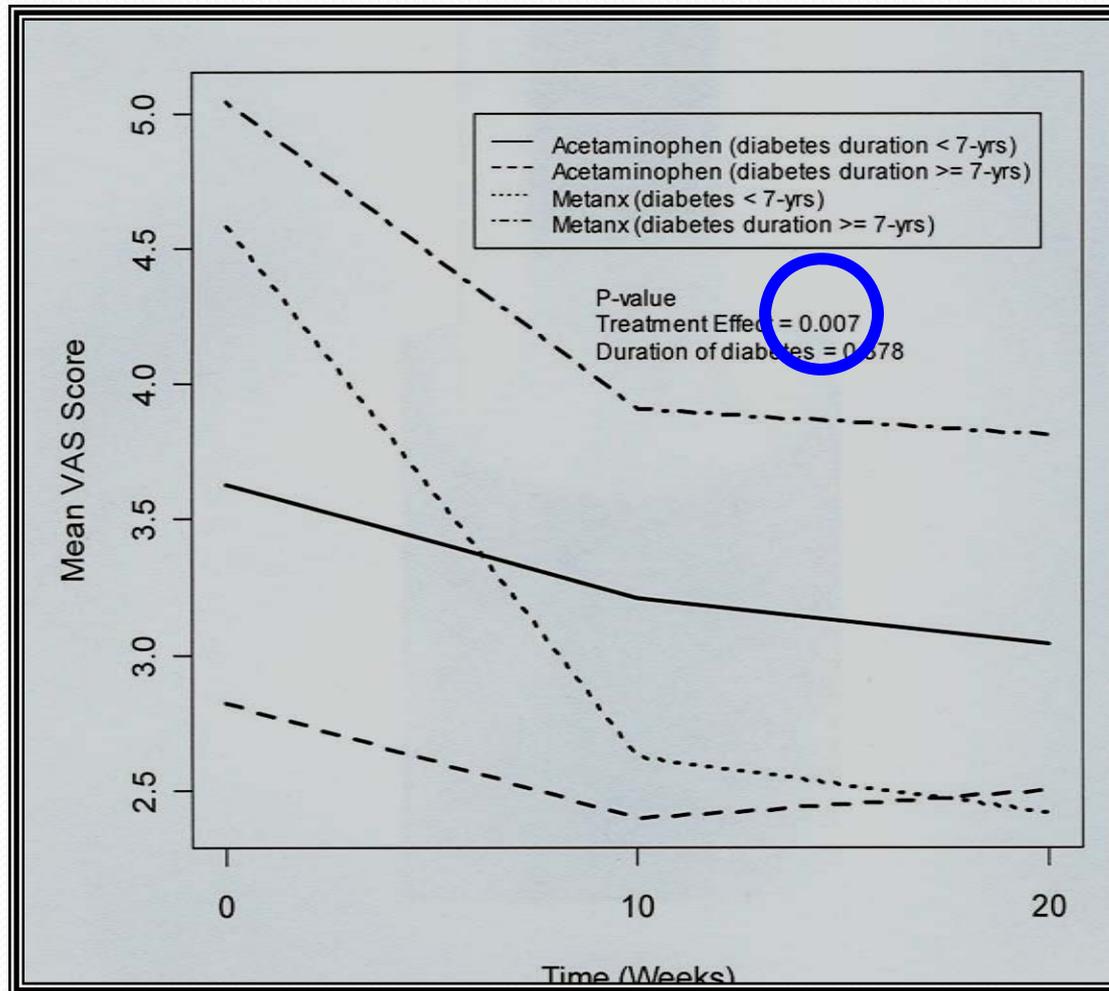
DPNP Analysis

- 35% vs. 11.7% pain reduction @ 20 weeks
- 32% vs 11.6% pain reduction @ 10 weeks

VAS REDUCTION BY AGE



VAS REDUCTION AND DURATION OF DIABETES



Orally Administered L-methylfolate, Me-Cbl, and P-5-P Reduces Diabetic Peripheral Neuropathic Pain

Conclusion

- Orally administered L-methyl folate, Me-Cbl, and P-5-P is effective in reducing burning pain associated with DPN.
- Most efficacious when administered early following the diagnosis of diabetes, and when symptomatology <5 years.

L-Methylfolate, Me-Cbl, and P-5-P Supplementation to Pregabalin Partial-Responders for Management of Painful Diabetic Neuropathy

Objective

- Determine the effects of L-methylfolate, Me-Cbl, and P-5-P on burning paresthesias in patients with DPNP who had obtained partial symptoms resolution with pregabalin.

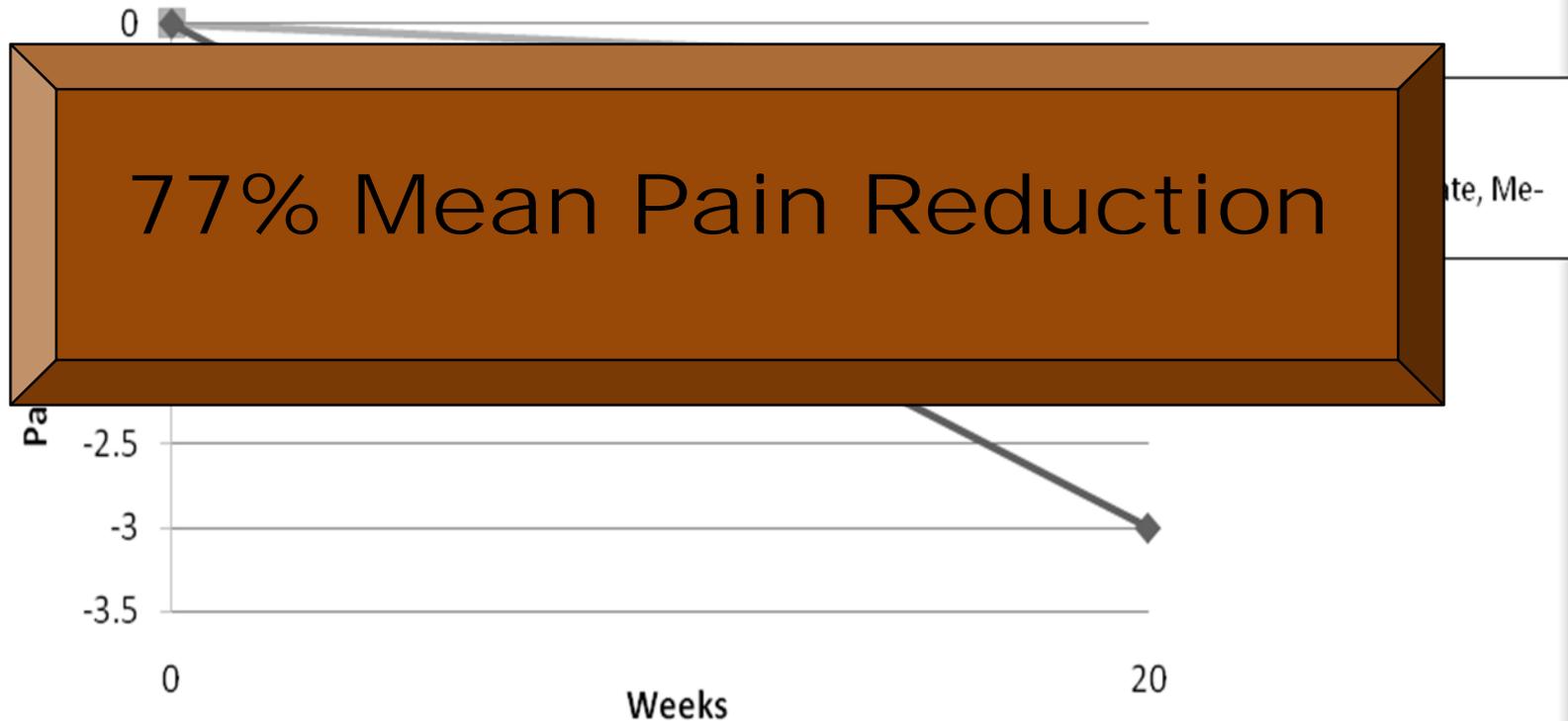
L-Methylfolate, Me-Cbl, and P-5-P Supplementation to Pregabalin Partial-Responders for Management of Painful Diabetic Neuropathy

Methodology

- ❑ 24 consecutive patients who received pregabalin > 4 months with partial (<50% NPS reduction) resolution of paresthesias were enrolled.
- ❑ Study group (n=16) continued the pretrial pregabalin dose to which oral L-methylfolate, Me-Cbl, and P-5-P was added twice daily.
- ❑ Control group (n=8) maintained pregabalin therapy.
- ❑ A numeric pain scale (0-10) was evaluated at baseline and 20 weeks.

STUDY RESULTS

Mean Pain Reduction from Baseline



**Pregabalin / L-methylfolate, Me-Cbl, P-5P compared to Pregabalin at 20 weeks

L-Methylfolate, Me-Cbl, and P-5-P Supplementation to Pregabalin Partial-Responders for Management of Painful Diabetic Neuropathy

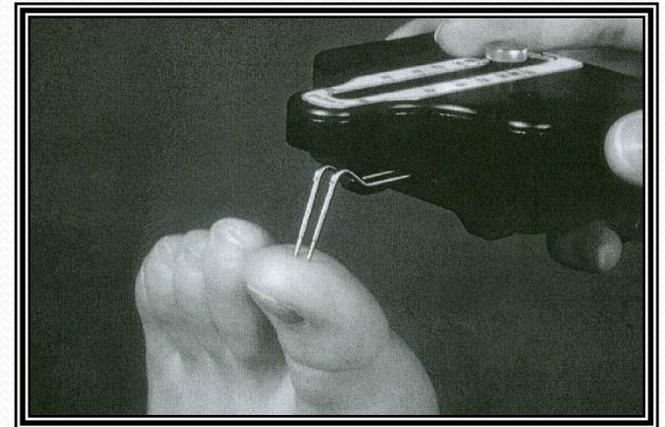
Conclusion

- ❑ The addition of L-methylfolate, Me-Cbl, and P-5-P, twice daily reduces diabetic neuropathic pain in partial responders to pregabalin
- ❑ No increased incidence of adverse drug sequella was noted

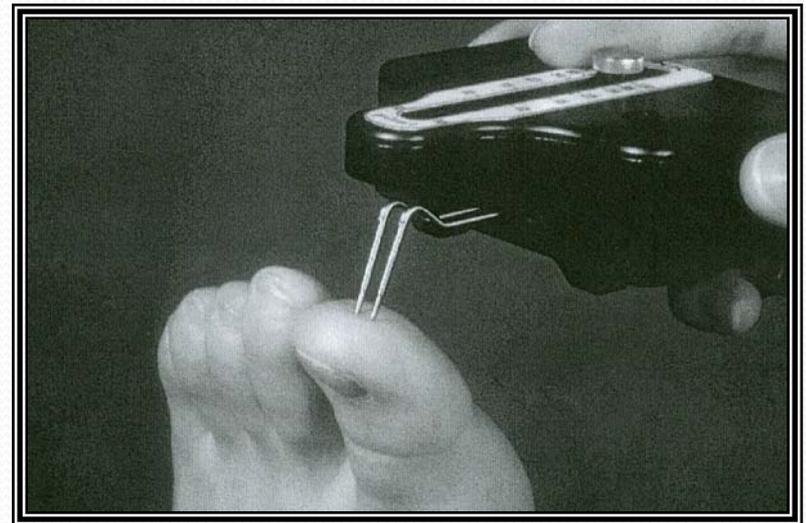
MACKIE WALKER DPM

DFCON 2008

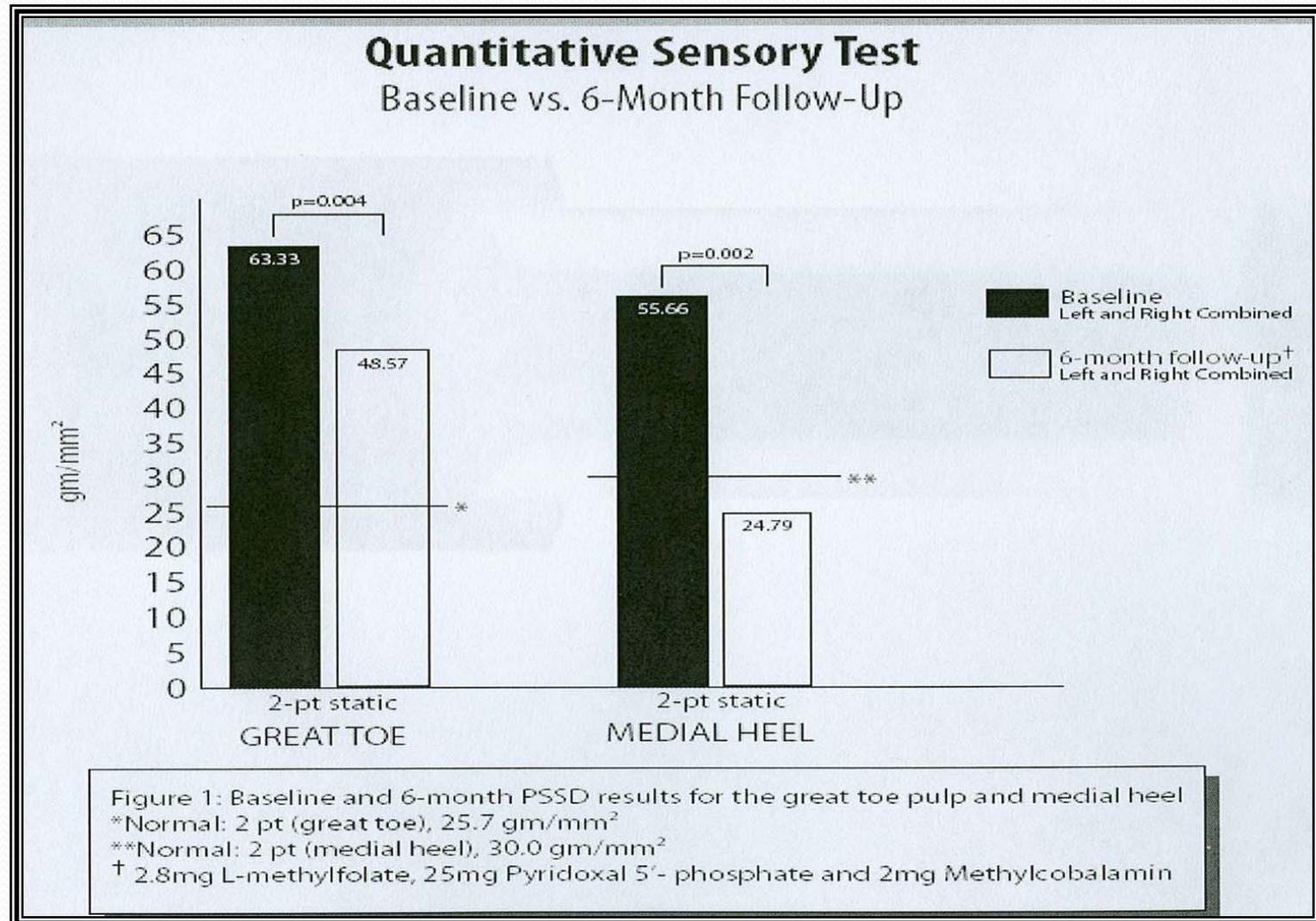
- 31 PATIENTS
 - SUBJECTIVE SYMPTOMS
 - ESTABLISHED SENSORY LOSS
- PRESSURE SPECIFIED SENSORY DEVICE
 - FOOT, MEDIAL HEEL, GREAT TOE PULP
- BASELINE, 6 AND 12 MONTHS



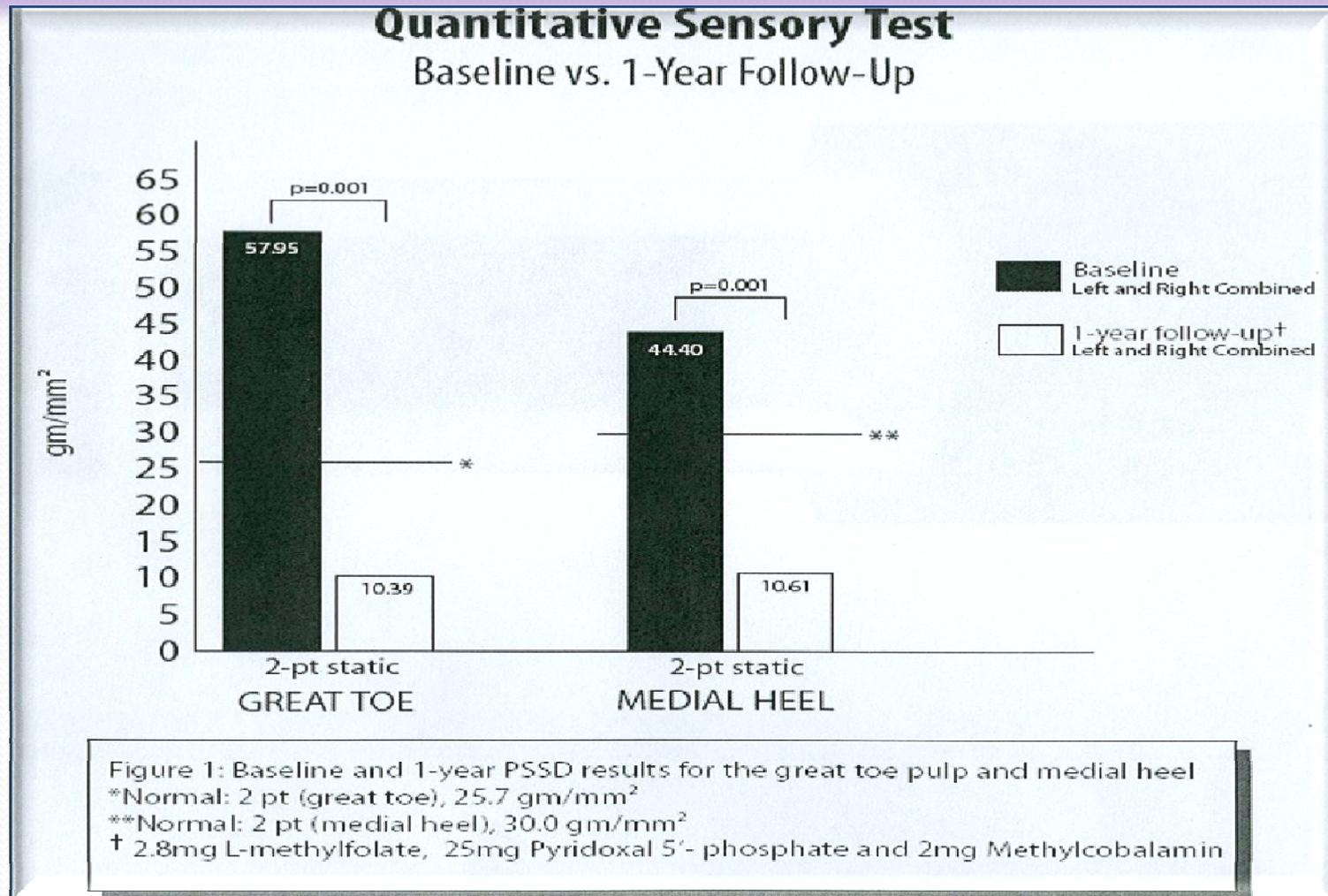
- ONE POINT STATIC TOUCH
 - PRESSURE THRESHOLD
 - MEASURE OF OVERALL SENSORY LOSS
- TWO POINT STATIC TOUCH
 - SURVIVING NERVE DENSITY
 - NORMATIVE 7.8mm



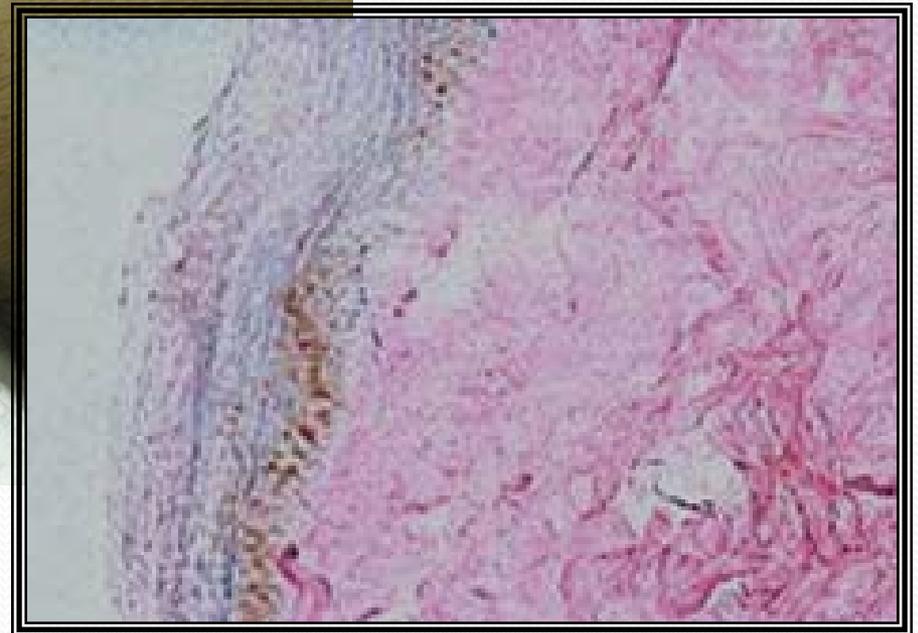
2 PT AT 6 MONTHS



RESTORATION OF CUTANEOUS SENSORIUM AT 1 YEAR



IENFD STUDIES



DIABETES

- REDUCED NERVE FIBER BRANCH DENSITY
- REDUCED PERIPHERAL NERVE BRANCH LENGTH
- EPIDERMAL AXON SWELLING
- DERMAL AXON SWELLING
- THINNING OF SUBEPIDERMAL NERVE PLEXUS
- SPROUTING OF NERVE TERMINALS
- ENCAPSULATION OF NERVE ENDINGS
- IMMUNOREACTIVE BASAL CELLS

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RESPONSE TO TREATMENT

- REGENERATION OF NERVES CAN BE DEMONSTRATED
 - PHARMACOLOGIC TREATMENT
 - SURGICAL DECOMPRESSION

- EBENEZER, G.J., HAUER, P., ET AL J. NEUROPATH AND EXP NEUROLOGY 66 (12) 2007
- POLYDEFKIS, M., HAUER, P., ET AL BRAIN 127 (7), 2004
- HSIEH, C-H., JENG, S-F ET AL J. NEUROTRAUMA 24 (10), 2007
- HEISH Y.L., CHIANG, H. ET AL. J. NEUROPATH AND EXP. NEUROLOGY 67 (2), 2008

DIABETIC NEUROPATHY

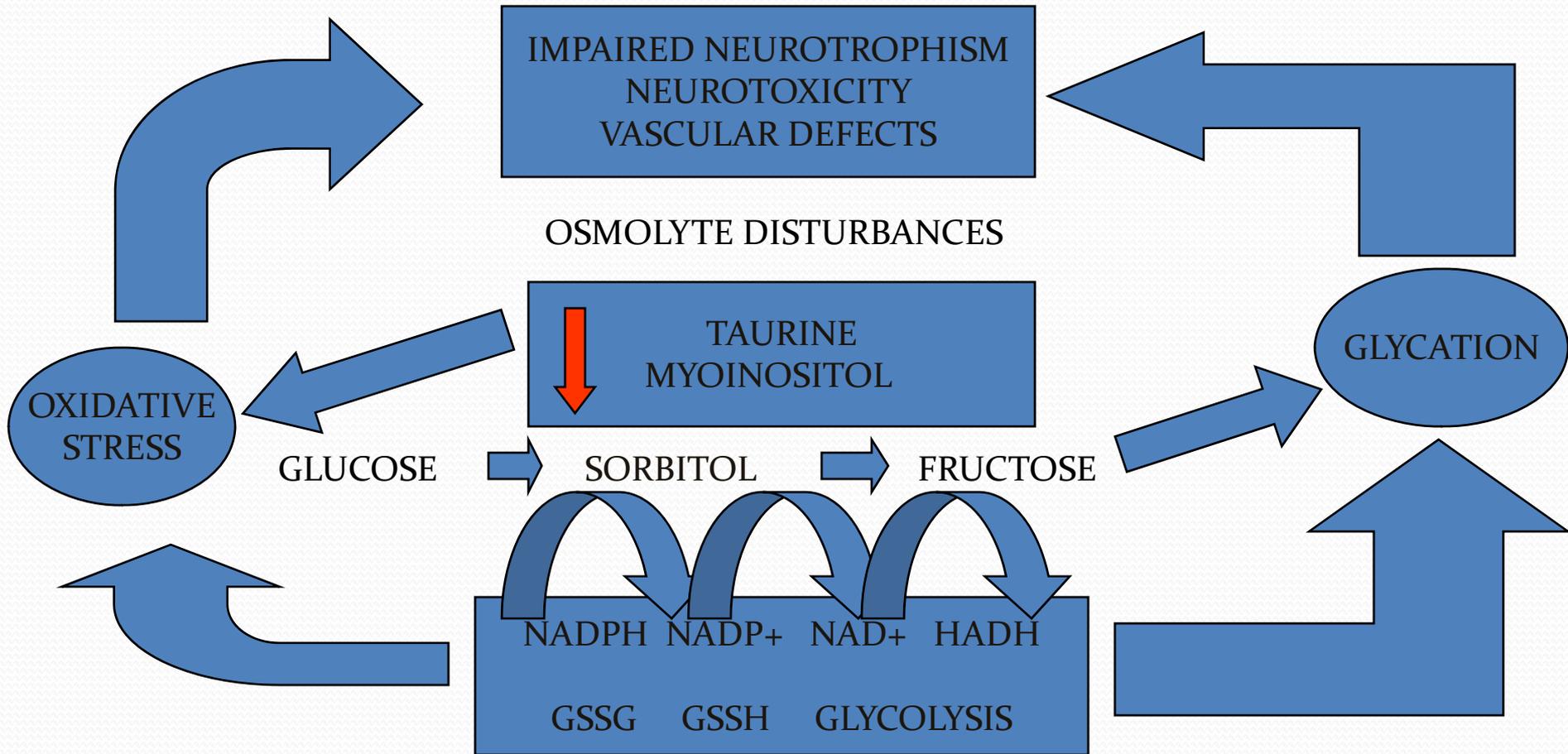
- 66% PATIENTS WITH DM
- 80% DPN
- 50% SYMPTOMATIC
- 10-20% ANTINOCICEPTIVE TX

CHEN H, LAMER TH, RHO RH ET AL. MAYO CLIN PROCEED. 79; 2004

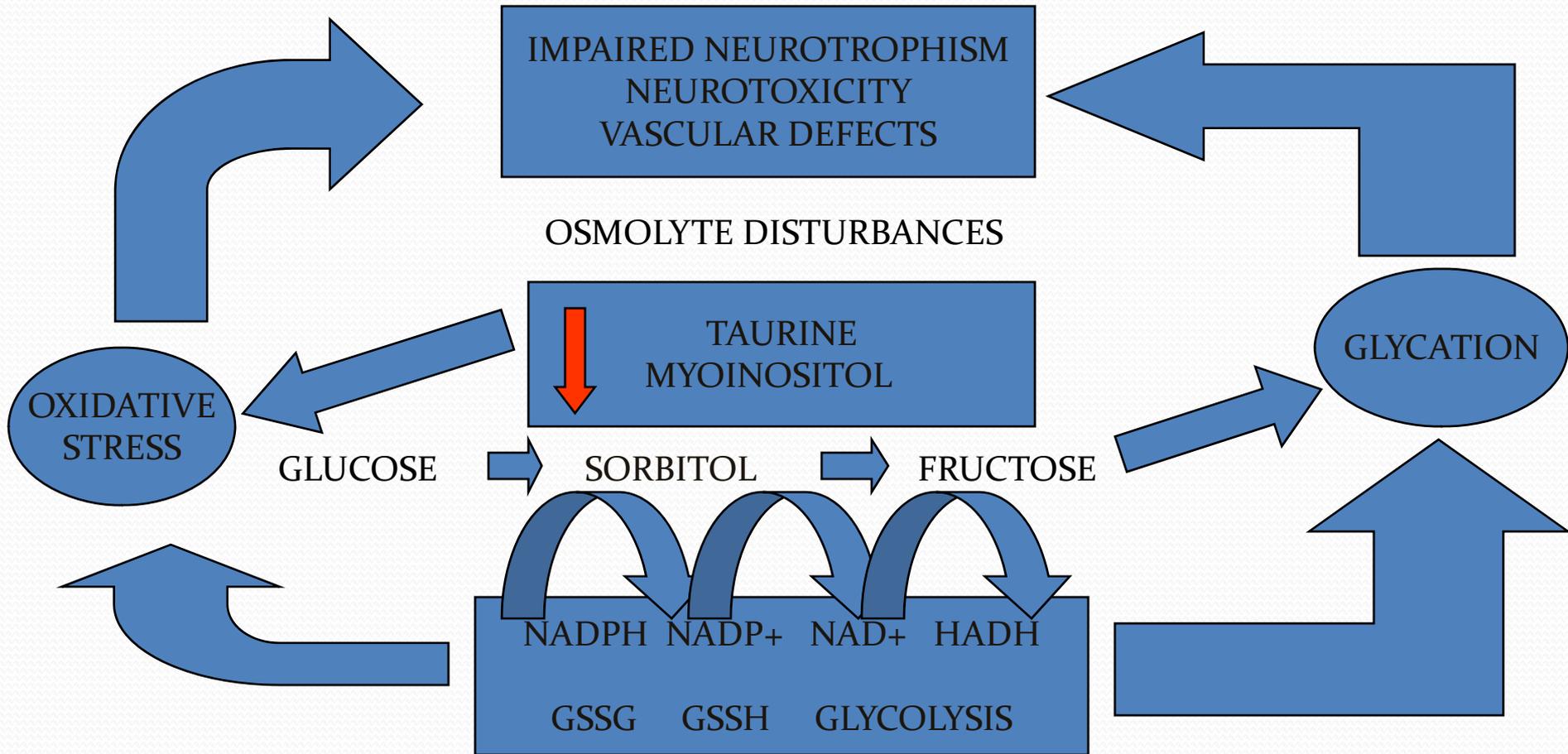
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DIABETIC NEUROPATHY: PATHOGENESIS



DIABETIC NEUROPATHY: PATHOGENESIS



RISK OF AMPUTATION: EVALUATION

- NEUROPATHY
 - NON-PAINFUL SENSORY
 - MOTOR NEUROPATHY
 - AUTONOMIC NEUROPATHY
- ALTERED BIOMECHANICS
- INCREASED PLANTAR PRESSURE
- OSSEOUS DEFORMITY
- PAD
- PRIOR HISTORY OF ULCER OR AMPUTATION
- SEVERE TOENAIL PATHOLOGY

SPECTRUM OF DISEASE

- SYMPTOMS, FEW FINDINGS
- FINDINGS, FEW SYMPTOMS



NEUROPATHY SCREENING

- 128-Hz TUNING FORK*
- PIN PRICK
- 10 GRAM FILAMENT*
- ANKLE REFLEXES
- > 87% SENSITIVITY

•PREDICTIVE OF FOOT ULCERATION

•BOULTON AJ, VINIK AL, ARREZO JC, BRIL V, FELDMAN EL, FREEMAN R, MALIK RA, MASER RE, SOSENKO JM, ZIEGLER D. DIABETIC NEUROPATHIES: A STATEMENT BY THE AMERICAN DIABETES ASSOCIATION. DIABETES CARE, 28; 2005

SUMMARY

- ELEVATED HOMOCYSTEINE LEVELS ARE FREQUENTLY ASSOCIATED WITH DIABETIC NEUROPATHY
- THE ADMINISTRATION OF L-METHYL FOLATE, METHYLCOBALAMIN, AND PYRIDOXYL-5-PHOSPHATE;
 - REDUCES HOMOCYSTEINE LEVELS
 - INCREASES NO LEVELS
 - REDUCES S/S OF SENSORY, MOTOR, AND AUTONOMIN NEUROPATHY