Alfalipoinska kiselina, Zn, L-karnozin i kompleks vitamina B - *Nuronorm* - uloga i značaj

Prof. dr Dragana Lavrnić
Klinika za neurologiju KCS

NURONORM ®

Aktivne komponente proizvoda:	1 tableta (1000 mg)	%PDU*
Alfa lipoinska kiselina	600 mg	-
L-karnozin	165 mg	-
Cink	7,5 mg	75
Nikotinamid (vit. PP)	9 mg	56
Pantotenska kiselina (vit. B5)	3 mg	50
Piridoksin (vit. B6)	1 mg	71
Riboflavin (vit. B2)	0,8 mg	57
Tiamin (vit. B1)	0,7 mg	64
Cijanokobalamin (vit. B12)	0,5 µg	20
Folna kiselina	100 µg	50

* **PDU:** preporučeni dnevni unos

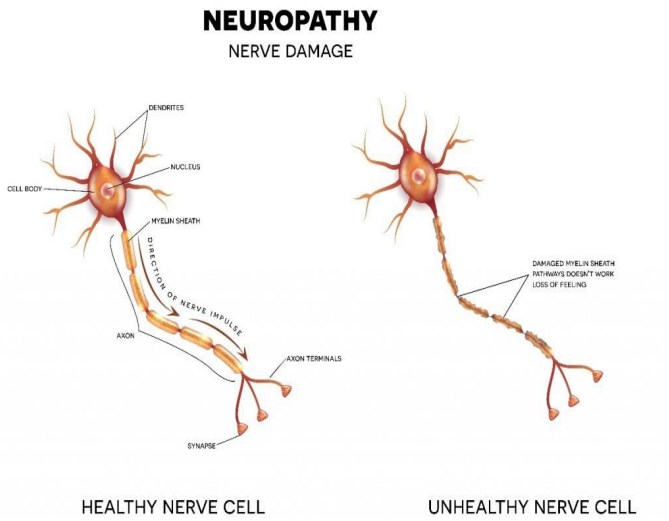
Periferna neuropatija

Definicija

- stanje koje nastaje kada su nervi koji nose poruke do i iz mozga i kičmene moždine od i do dela tela oštećeni ili oboleli.

Uzroci

- Generalizovane bolesti: dijabetes - jedan od najvažnijih uobičajenih oblika neuropatije, bubrežni poremećaji, hipotireoza, bolesti koje izazivaju hroničnu inflamaciju, deficijencija vitamina
- Povreda - fizička trauma poput saobraćajnih nesreća, padovi, prelomi, nervna kompresija , kao što je karpalni tunel sindrom
- Alkohol i toksini
- Infekcije i autoimuni poremećaji herpes simplex, virus varicella zoster, reumatoidni artritis i lupus, itd



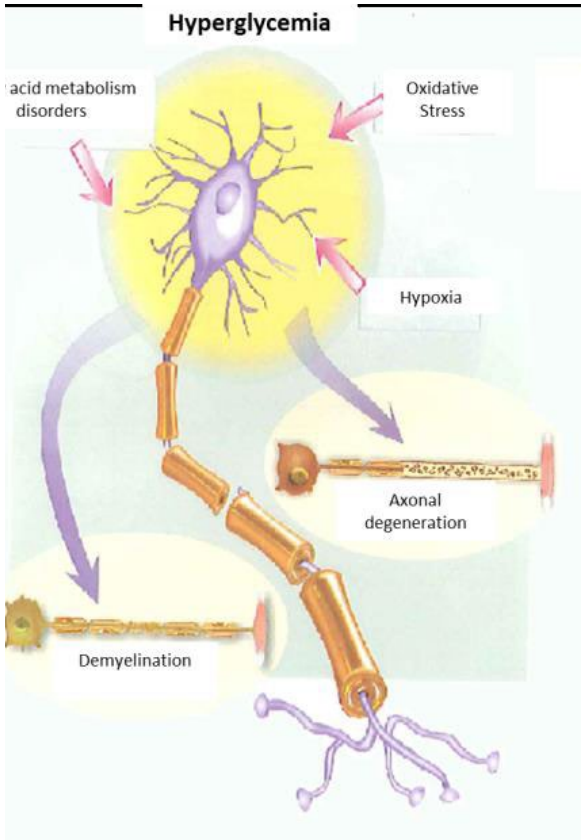
Dijabetesna neuropatija

Definicija

- Prisustvo simptoma i / ili perifernih znakova disfunkcije nerava kod osoba sa dijabetesom uz isključenje drugih uzroka kao što su nasledni faktori, inflamacija i druge metaboličke neuropatije
- Hronično progresivno oboljenje

Klasifikacija

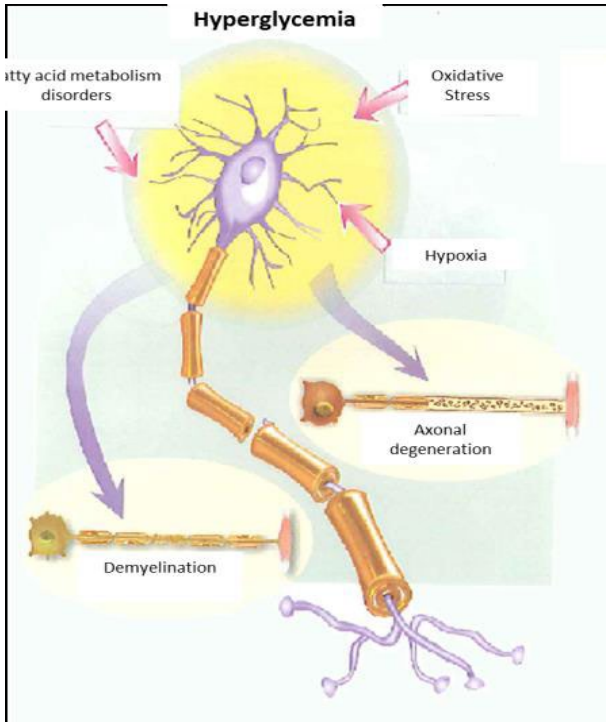
- PN se može manifestirati bolnim ili bezbolnim simptomi ili oboje
- Dve najčešće vrste DN povezane sa bolom su akutna senzorna neuropatija i hronična senzorimotorna neuropatija



Dijabetesna neuropatija

Kliničke manifestacije

- Promenjeno funkcionisanje perifernih nerava, bilo sa degeneracijom distalnih aksona ili demijelinizacijom nervnih vlakana. Patologija može uticati na senzorne ili motorne aksone ili na oboje.
- Ili sa bolnim ili bezbolnim simptomima ili sa oboje
- Hronična senzorna motorička neuropatija je najčešća oblik DPN-e, povezana sa simptomatskim bolom i kliničkim znacima neuropatije: osećaj trnjenja, ukočenosti, ubodni tip bola, parestezija i hiperestezija, dubok bol u nogama ili rukama....
- Gubitak senzacije u predelu ekstremiteta, fotosenzitivnost, osetljivost na pritisak i vibracije



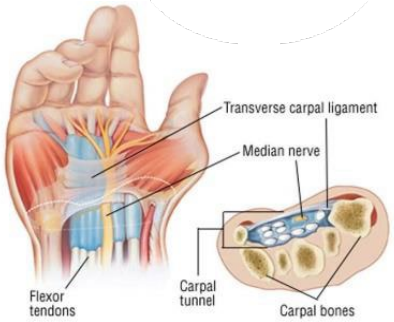
Epidemiologija

- 50 % pacijenata razvija perifernu neuropatiju 25 godina nakon inicijalne dijagnoze dijabetesa
- 1/3 dijabetičara ima dijagnozu PN
- Neuropatski bol pogađa 16% bolesnika sa dijabetesom i ima značajan uticaj na kvalitet života

Kompresivna neuropatija

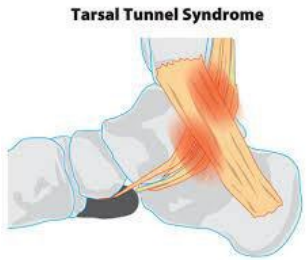
Definicija

- Stanje koje nastaje kada postoji disproporcija između zapremine perifernog nerva i prostora kroz koji nerv u ekstremitetu prolazi



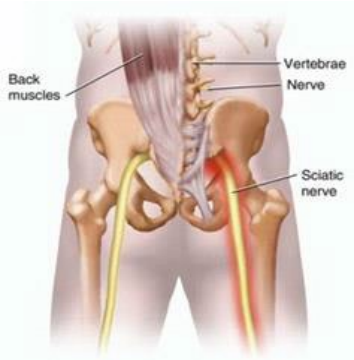
Kliničke manifestacije

- Trnjenje
- Ukočenost
- Osećaj žarenja
- Slabost mišića
- Bol



Tipovi

- Carpal tunnel sy
- Guyon's canal sy
- Tarsal tunnel sy
- Radikulopatije....

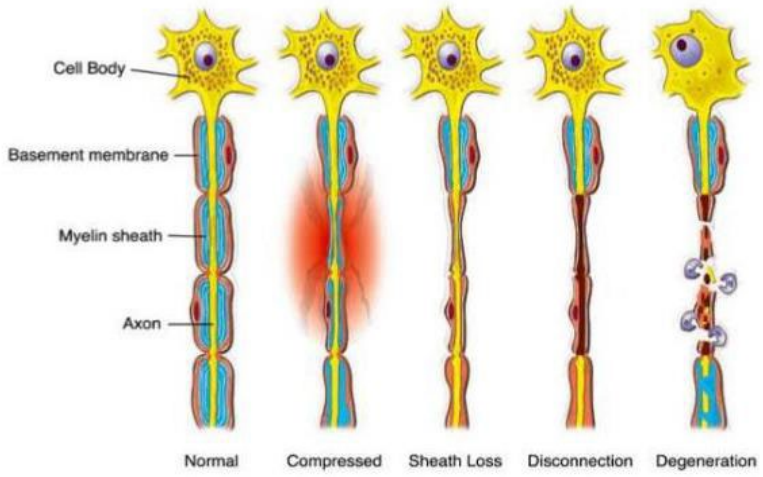


Kompresivna neuropatija

Patofiziologija

- U razvoj kompresivne neuropatije su uključeni i ishemijski i mehanički faktori

pritisak → ↓ protok → lok. ishemija → oštećena transmisija → demijelinizacija → ožiljno tkivo



Alfa-lipoinska kiselina-ALA

- Ljudsko telo sintetiše de novo samo male količine od masnih kiseline i cisteina u mitohondrijama jetre i drugih tkiva
- Izvori iz hrane: crveno meso, jetra, bubreg, spanać, brokoli, paradajz
- Esencijalni kofaktor u Krebsovom ciklusu

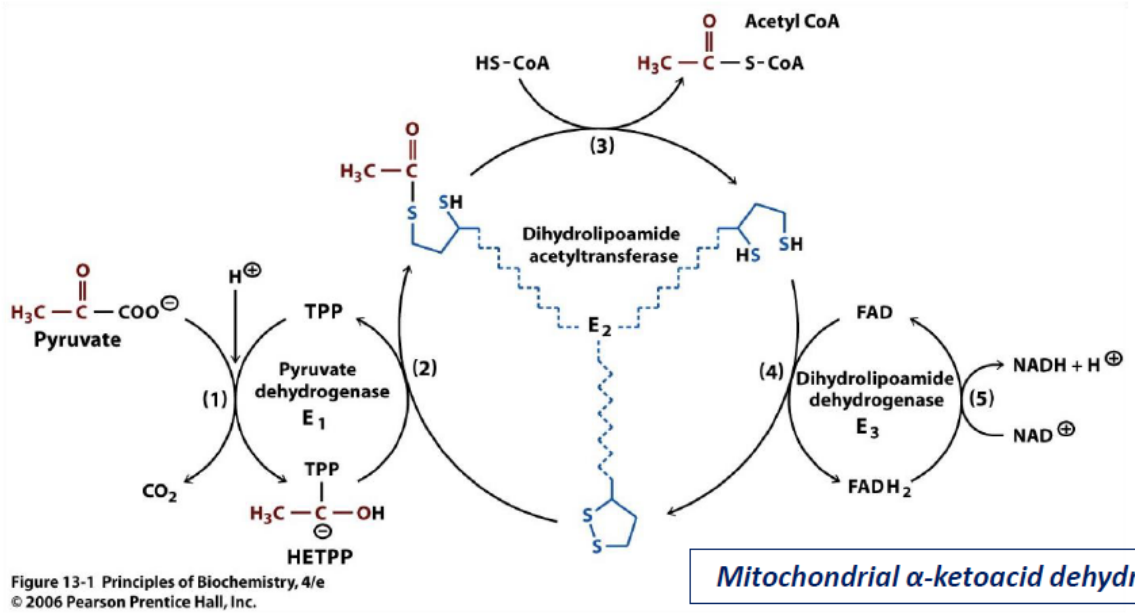


Figure 13-1 Principles of Biochemistry, 4/e
© 2006 Pearson Prentice Hall, Inc.

Mitochondrial α-ketoacid dehydrogenases

ALA-farmakokinetika

- Apsorbuje se iz tankog creva i distribuira do jetre putem portalne cirkulacije i do različitih tkiva u organizmu putem sistemske cirkulacije.
- Iako je liposolubilna, za njenu apsorpciju nije potrebni prisustvo dijeteskih masnih kiselina.
- Nakon distribucije u različita tkiva, nalazi se intracelularno, u mitohondrijama i ekstracelularno.
- Primarno se metaboliše u jetri.
- Lako prolazi hemato-encefalnu barijeru.
- Poluživot je 30 minuta.

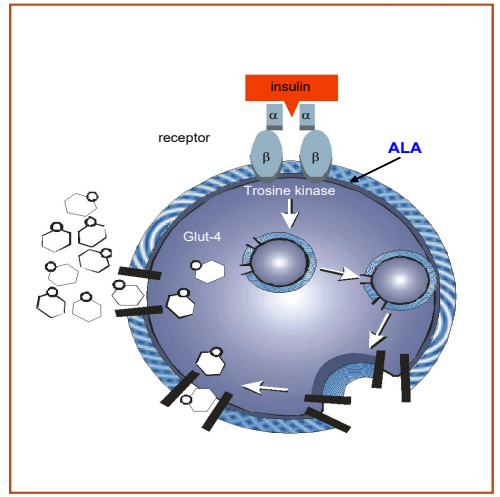
Teichert J, et al, 1998, Hermann R et al, 1996

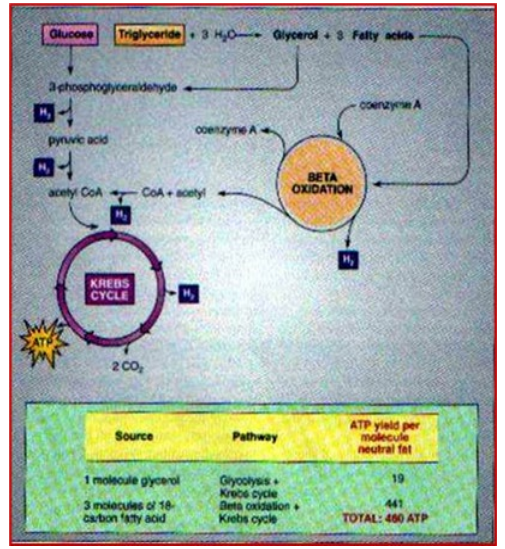

Antinociceptivno dejstvo
Antiinflamatorno dejstvo
Metaboličko dejstvo
Dejstvo na mikrocirkulaciju
Direktno dejstvo na periferne nerve
Antioksidativno dejstvo
ALA

NURONORM ®

ALA-Metabolički efekti

- **ALA je koenzim piruvat- i alfa-ketoglutarat dehidrogenaze**
- **Poboljšava insulin-regulisanu potrošnju glukoze kod animalnih modela insulinske rezistencije i kod bolesnika sa DM tip2**
- **Oponaša dejstvo insulina aktivacijom signalne kaskade na nivou ili pre dejstva fosfatidilinozitol 3-kinaze**
- **Stimuliše aerobnu oksidaciju glukoze**
- **Poboljšava insulinom indukovanu sintezu glikogena**

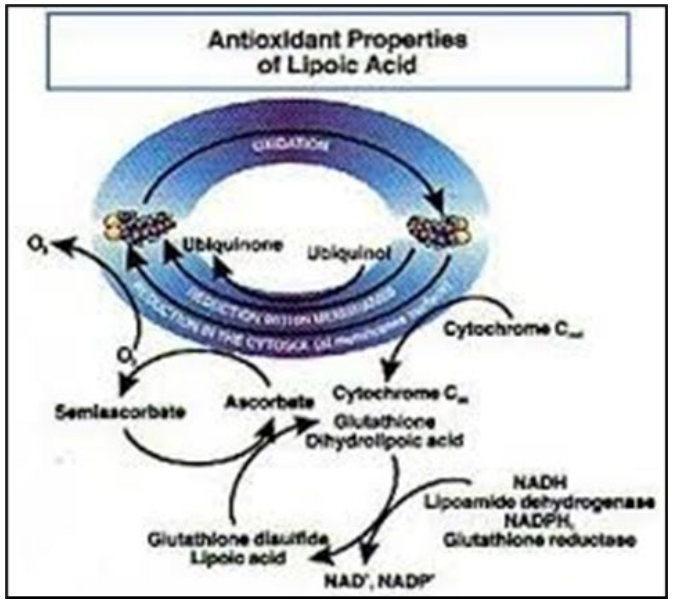




Konrat T et al. Diabetes Care 1999;22:280-7.

ALA-antioksidativni efekat

- **Slobodna ALA, a posebno njena redukovana forma DHLK, ima jako antioksidativno dejstvo.**
- **Sposobna da stvara komplekse sa ketonima i aldehidima, kao i sa metalima i metaloidima, da reaguje sa slobodnim radikalima, stabilizuje funkciju tiola i da redukuje manje elektronegativne SH- i non-SH-redox sisteme.**
- **DHLK ima sposobnost da regeneriše endogene antioksidanse, vitamin E, vitamin C i glutation.**



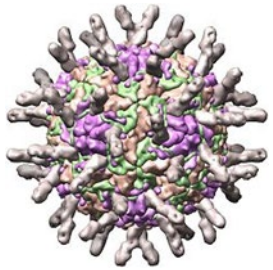
Alpha Lipoic Acid

- One of the strongest antioxidants known
- Enhances the benefits of vitamins C and E
- Aids in moisture retention
- Leaves skin more youthful and supple

Androne et al. In vivo 2000;14:327-30

ALA-anti-inflamatorni efekat

- Pokazan je supresivni efekat ALA na inflamatorne procese ćelije pankreasnih ostrvaca čime se objašnjava njen protektivni efekat na razvoj DM
- ALA inhibira akutnu fazu inflamacije i inflamatorni bol (oslobadjanje NO iz inflamatornih makrofaga)
- Inhibira ekspresiju ICAM-1(Intercelularni adhezioni molekul 1) 1 i VCAM-1 (vaskularni adhezioni ćelijski protein 1) u endotelijalnim ćelijama mozga
- Inhibira T ćelijsku migraciju u kičmenu moždinu u EAE
- Inhibira COX-2 aktivnost i produkciju PGE2
- Imunomodulatorni efekat ostvaruje smanjenjem populacije CD4 limfocita

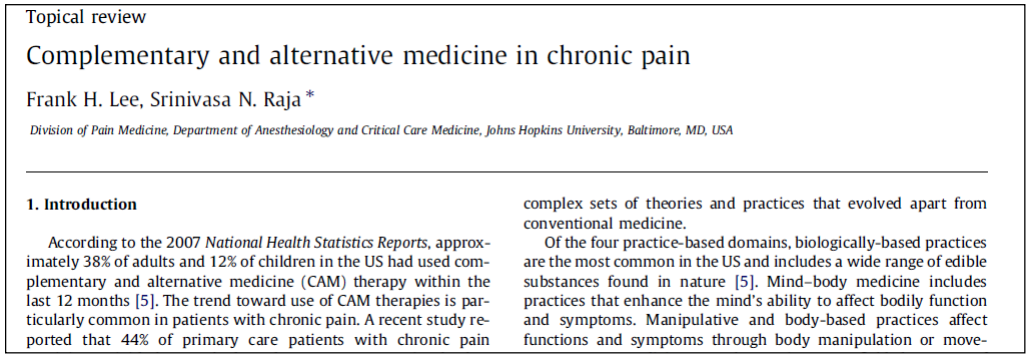


ALA-antinociceptivni efekat

- **ALA selektivno inhibira Cav3.2 T-tip kalcijumskih kanala na nociceptorima u dorzalnim ganglijama kičmene moždine: sprečava ulazak Ca u senzorne neurone dorzalnih ganglija, smanjuje ćelijsku ekscitabilnost nociceptora i smanjuje transmisiju bola ka somatosenzornom korteksu**

- **Lokalna aplikacija ALA blokira T-kanale, sprečava perifernu senzitizaciju i sprečava nastanak neuropatskog bola**

- **ALA inhibira i T kanala u CNS i ima ulogu u centralnoj modulaciji bola**



Topical review

Complementary and alternative medicine in chronic pain

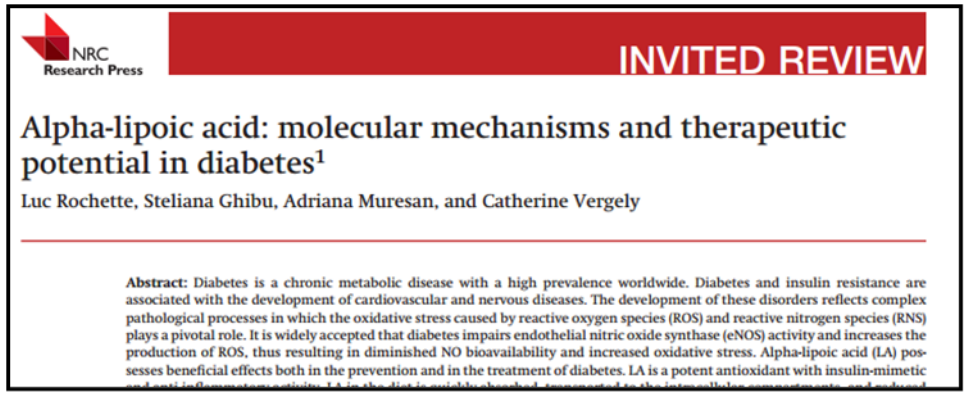
Frank H. Lee, Srinivasa N. Raja *

Division of Pain Medicine, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, MD, USA

1. Introduction

According to the 2007 *National Health Statistics Reports*, approximately 38% of adults and 12% of children in the US had used complementary and alternative medicine (CAM) therapy within the last 12 months [5]. The trend toward use of CAM therapies is particularly common in patients with chronic pain. A recent study reported that 44% of primary care patients with chronic pain complex sets of theories and practices that evolved apart from conventional medicine.

Of the four practice-based domains, biologically-based practices are the most common in the US and includes a wide range of edible substances found in nature [5]. Mind–body medicine includes practices that enhance the mind's ability to affect bodily function and symptoms. Manipulative and body-based practices affect functions and symptoms through body manipulation or move-



NRC Research Press

INVITED REVIEW

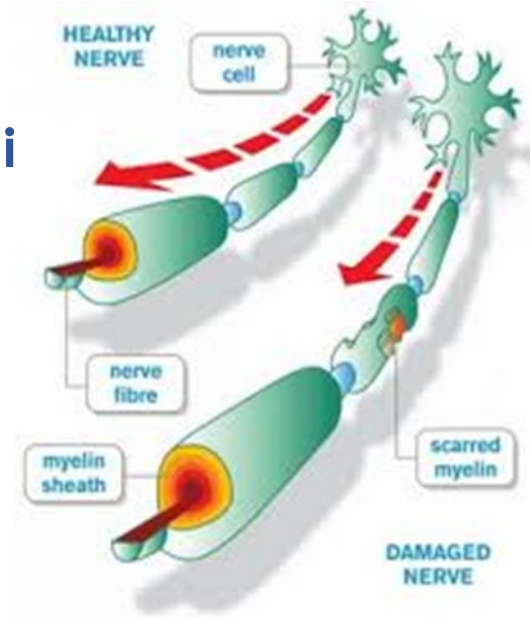
Alpha-lipoic acid: molecular mechanisms and therapeutic potential in diabetes[1]

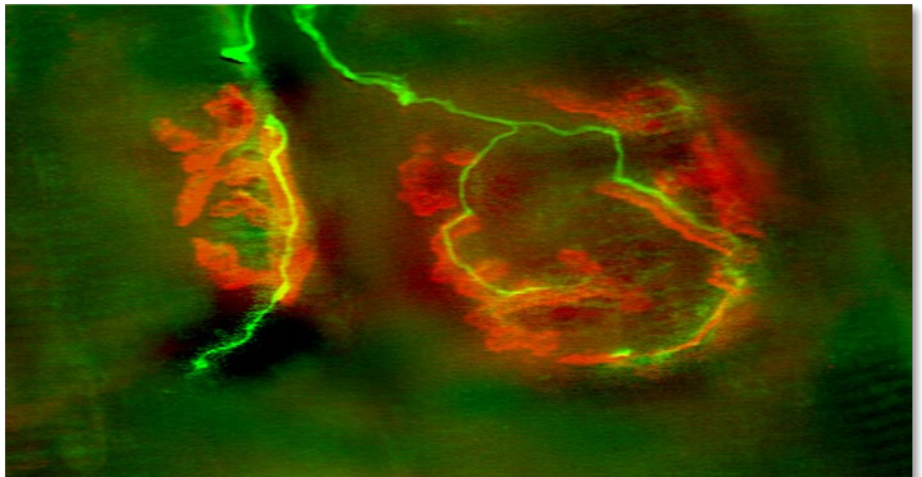
Luc Rochette, Steliana Ghibu, Adriana Muresan, and Catherine Vergely

Abstract: Diabetes is a chronic metabolic disease with a high prevalence worldwide. Diabetes and insulin resistance are associated with the development of cardiovascular and nervous diseases. The development of these disorders reflects complex pathological processes in which the oxidative stress caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS) plays a pivotal role. It is widely accepted that diabetes impairs endothelial nitric oxide synthase (eNOS) activity and increases the production of ROS, thus resulting in diminished NO bioavailability and increased oxidative stress. Alpha-lipoic acid (LA) possesses beneficial effects both in the prevention and in the treatment of diabetes. LA is a potent antioxidant with insulin-mimetic

ALA-direktno dejstvo (na periferne nerve)

- **Povećava fleksibilnost membrane slobodnih nervnih završetaka i vitro i in vivo**
- **Povećava broj nervnih završetaka koji ispoljavaju spontano terminalno grananje**
- **POBOLJŠAVA BRZINE PROVOĐENJA**





Kemplay et al. Neuropathol Appl Neurobiol 1988;14(4):275-88

ALA-efekat na mikrocirkulaciju

Effect of Antioxidant Treatment of Streptozotocin-Induced Diabetic Rats on Endoneurial Blood Flow, Motor Nerve Conduction Velocity, and Vascular Reactivity of Epineurial Arterioles of the Sciatic Nerve

Lawrence J. Coppey, Jill S. Gellett, Eric P. Davidson, Joyce A. Dunlap, Donald D. Lund, and Mark A. Yorek

We have shown that diabetes-induced reduction in endoneurial blood flow (EBF) and impaired endothelium-dependent vascular relaxation precede slowing of motor nerve conduction velocity (MNCV) and decreased sciatic nerve Na^+/K^+ ATPase activity. Furthermore, vascular dysfunction was accompanied by an accumulation of superoxide in arterioles that provide circulation to the sciatic nerve. In the present study, we examined the effect that treatment of streptozotocin-induced diabetic rats with antioxidants has on vascular and neural func-

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Effects of alpha-lipoic acid on microcirculation in patients with peripheral diabetic neuropathy.

Haak E[1], Usadel KH, Kusterer K, Amini P, Frommeyer R, Tritschler HJ, Haak T.
Author information

Abstract

Diabetic polyneuropathy is a serious complication in patients with diabetes mellitus. In addition to the maintenance of a sufficient metabolic control,alpha-lipoic acid (ALA) (Thioctacid, Asta Medica) is known to have beneficial effects on diabetic polyneuropathy although the exact mechanism by which ALA exerts its effect is unknown. In order to study the effect of ALA on microcirculation in patients with diabetes mellitus and peripheralneuropathy one group of patients (4 female, 4 male, age 60+/-3 years, diabetes duration 19+/-4 years, BMI 24.8+/-1.3 kg/m2) received 1200 mg ALA orally per day over 6 weeks (trial 1). A second group of patients (5 female, 4 male, age 65+/-3 years, diabetes duration 14+/-4 years, BMI 23.6+/-0.7

- Ostvaruje akutni i produženi povoljan efekat na mikrocirkulaciju vasa nervorum
- Povećava endoneuralni protok krvi
- Sprečava endotelijalnu disfunkciju
- Utiče na angiogenezu

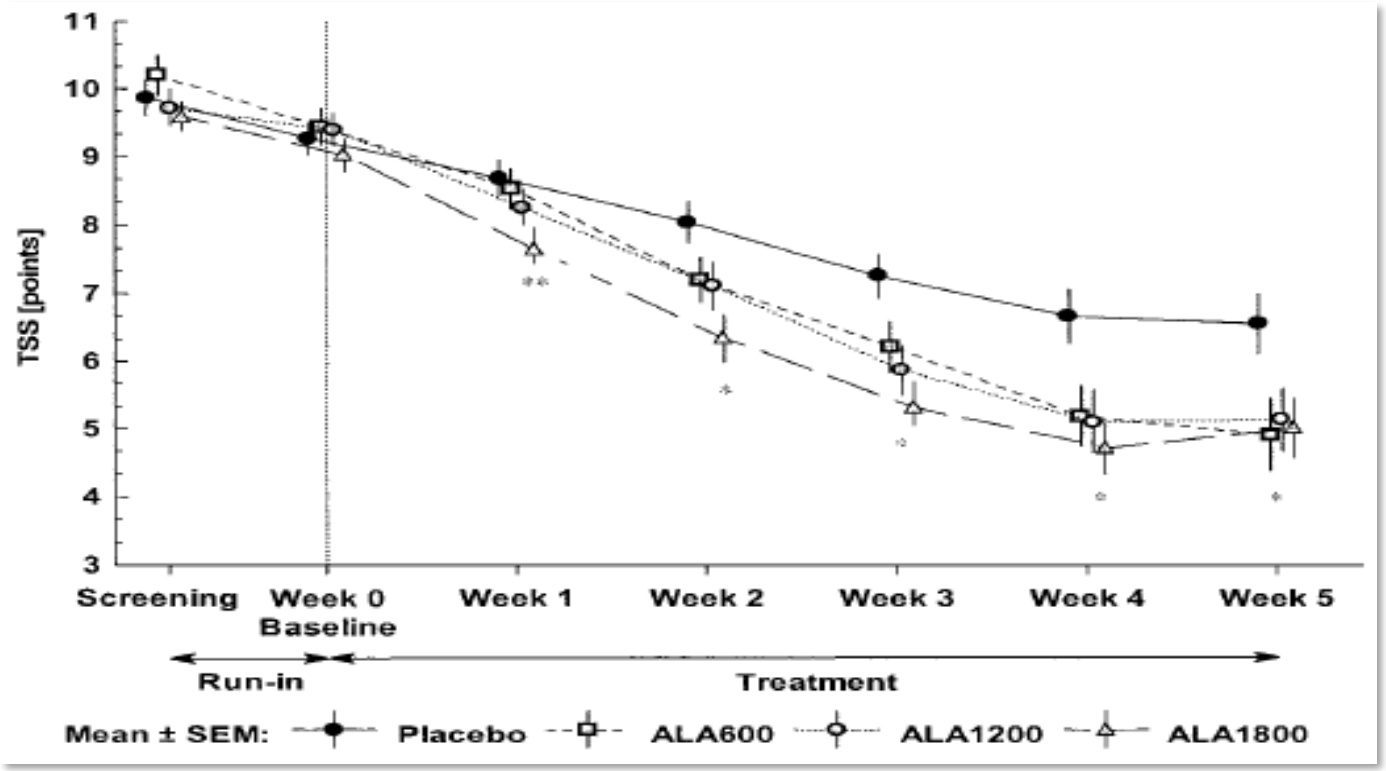
ALA-kliničke studije

studija	N	trajanje studije	doza p.o / i.v.	rezultat
DEKAN 1997	73	4 meseca	800 mg/p.o.	kardijalna funkcija poboljšanje
OPRIL 1999	24	3 nedelje	1800mg p.o/ 600mg i.v.	povoljan efekat na simptome i znake sa obe doze
ALADIN 1995	328	3 nedelje	100/600/1200 mg i.v.	značajno poboljšanje simptoma, optimalno: 600 mg
ALADIN II 1999	65	1 nedelja i.v. 2 godine p.o.	placebo/600/ 1200mg	značajno poboljšanje NCS: 600 i 1200mg
ALADIN III 1999	509	3 nedelje i.v. 6 meseci p.o.	placebo/600mg	tendencija poboljšanja simptoma
SYDNEY 2003	120	3 nedelje	600 mg i.v.	značajno poboljšanje simptoma i znaka
SYDNEY II 2006	181	5 nedelja	600/1200/1800 mg	značajno poboljšanje simptoma i znaka, optimalno: 600 mg
NATHAN I 2011	460	4 godine	600 mg p.o.	značajno poboljšanje simptoma i znaka

ALA-moguća indikaciona područja

- **Dijabetesna neuropatija, posebno bolna dijabetesna neuropatija**
- **Insulinska rezistencija, gojaznost, hiperlipidemija**
- **Cervikalna i lumbosakralna radikulopatija**
- **Carpal tunel sy**
- **CIDP**
- **Toksične neuropatije (alkoholna i citostaticima indukovana)**
- **Multipla skleroza**
- **Alzheimerova bolest**
- **Stanja posle traume mozga i posle moždanog udara**
- **Mitohondrijske bolesti.....**

SYDNEY II STUDIJA



ALA per os tokom 5 nedelja:

↓ simptomi neuropatije (Total Symptom Score - TSS i Neuropathy Symptoms Change - NSC)

↓ znaci neuropatije (Neuropathy Impairment Score - NIS)

↑ doze - slična efikasnost, ↑ ND (mučnina, povraćanje, vrtoglavica)

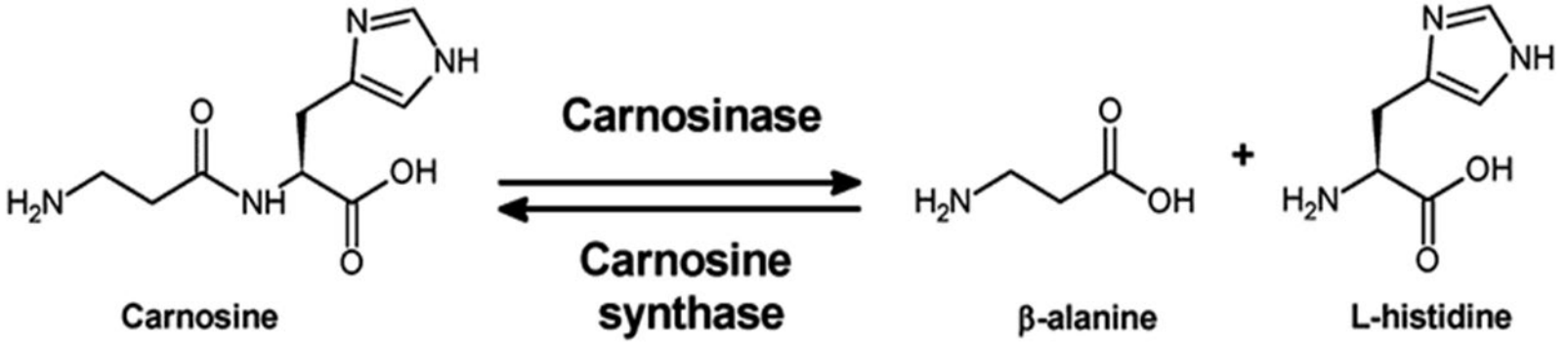
Ziegler D et al. Diabetes Care 2006;29:2365–70.

ALFA LIPOINSKA KISELINA

DRUGE POTENCIJALNE INDIKACIJE

- **metabolički sindrom** (gojaznost, glukozna intolerancija)
- **burning mouth sy**
- **kompresivne neuropatije** poput CTS i radikulopatija
- eksperimentalno indukovana hemoterapijske neuropatije → aLA povećava ekpresiju frataxina → sprečava oštećenje mitohondrija → ↓ neurotoksičnost (**toksične neuropatije**)
- **CIDP**
- ALA modulira funkciju glijalnih ćelija – smanjuje oksidativni stres i povećava preuzimanje glutamata (potencijalni neuroprotektivni efekat kod **neurodegenerativnih** i **mitohondrijalnih**)
- u nervnom tkivu **posle povreda** (i moždanog udara) ALA indukuje angiogenezu i smanjuje stvaranje glijalnih ožiljaka → neuroprotektivno dejstvo

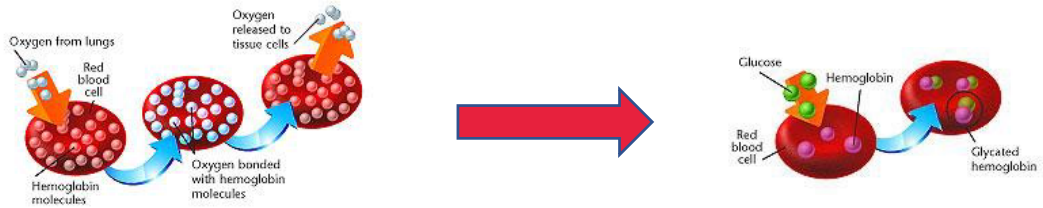
KARNOZIN



Prisutan u CNS, mišiću i očnom sočivu

KARNOZIN-dijabetes

- **Poboljšava metabolizam glukoze** preko IGFBP1 kod miševa sa dijabetesom, a nakon stresa preko uticaja histaminergičkog NS
- kulturi ćelija smanjuje modifikaciju LDL glikolaldehidom što **smanjuje deponovanje holesterola u makrofagima**
- **Prevenira ranu fazu oksidacije i glikacije lipida i inflamaciju** kod gojaznih pacova i miševa
- Smanjuje Tg i AGE i **stabilizuje ateroskleroske plakove** kod miševa sa dijabetesom
- Smanjuje apoptozu i AGE time ostvaruje protektivni efekat na **dijabetesnu nefropatiju**
- Protektivno deluje i na **dijabetesnu retinopatiju** preko ↑Hsp27 i ↓Ang-2
- Smanjenjem AGE smanjuje rizik od **dijabetesne katarakte**
- Poboljšava **zarastanje rana** kod dijabetesa



KARNOZIN-druge indikacije

ANIMALNI MODELI I KULTURE ĆELIJA

- **Moždani udar, trauma CNS: ↓ inflamacija, oksida[illegible], apoptoza, autofagija**
- **Febrilni status epilepticus: protektivno**
- **Parkinsonizam: ↓ inflamacija, oksidati[illegible]apoptoza**
- **Alzheimer: ↓ amiloidne plakove [illegible]drijalna fja**
- **VaD: ↓ oksidativni stres, akti[illegible]je i degradacija mijelina**
- **Toksična lezija bubre[illegible]sidativno**
- **Toksična, septič[illegible]na lezija jetre: antioksidativno, antiinflamatorno i antifibrotičko**
- **Infarkt mioka[illegible] CMP: antioksidativno**
- **Artritis: antiinflamatorno, hondroprotektivno**
- **Tumori: indukcija apoptoze, efekat na a(na)erobni metabolizam**

Usporava starenje!!

CINK

KOFAKTOR >200 ENZIMA

metabolizam nukleinskih kiselina, metabolizam proteina, Zn finger proteini, integritet bioloških membrana...

Antioksidans

↑SOD

Insulinski mimetik

↓GSK-3β ↓PTP 1B

Analgetik

NR2A NMDA r.

CINK-komplikacije dijabetesa

Table 6: Logistic regression analysis of risk factors related to low serum zinc level

Factors	*OR* (95% *CI*)	*P*
Sex	1.200 (0.674–2.136)	0.535
Age	0.955 (0.928–0.983)	0.002*
Diabetes duration	0.950 (0.905–0.996)	0.034*
HbA1c	0.744 (0.632–0.877)	0.000*
C-P	0.959 (0.707–1.300)	0.787
2-h C-P	1.069 (0.930–1.228)	0.349
TC	0.916 (0.695–1.207)	0.534
TG	1.503 (1.196–1.888)	0.000*
eGFR	1.200 (0.674–2.136)	0.535
DR	0.855 (0.367–1.995)	0.718
DN	0.326 (0.150–0.711)	0.005*
DPN	0.848 (0.479–1.501)	0.571

*Statistical significance. *OR*: Odds ratio; *CI*: Confidence interval; HbA1c: Hemoglobin A1c; C-P: C-peptide; TC: Total cholesterol; TG: Triglyceride; eGFR: Estimated glomerular filtration rate; DR: Diabetic retinopathy; DN: Diabetic nephropathy; DPN: Diabetic peripheral neuropathy.

Kod bolesnika sa DM postoji deficit Zn u serumu usled prekomernog izlučivanja putem bubrega!

Luo YY et al. Chin Med J (Engl) 2015;128(24):3276–82.

CINK u terapiji dijabetesa

ANIMALNI MODELI I KULTURE ĆELIJA

- **Poboljšava kontrolu glikemije**
- **Poboljšava PH nalaz u pankreasu**
- **Smanjuje glikaciju albumina**
- **Poboljšava perifernu neuropatiju inhibišući oksidativni stres**
- **Karnozin sa cinkom je potentniji nego sam karnozin u poboljšanju senzornih simptoma kod miševa sa DM**
- **Prevenira razvoj dijabetesne CMP kod miševa i pacova**
- **Poboljšava hipokampalnu neurogenezu kod pacova**
- **Moduliše renalne promene kod dijabetesa**

B VITAMINI

Tiamin ***B1***	**Piridoksin** ***B6***	**Cijanokobalamin** ***B12***
Suprimira nociceptivni i neuropatski **bol** [1]	Pojačava aktivnost **antinociceptivnih** neuromedijatora (Nor i Ser) [4]	Ima **analgetski** efekat (uglavnom antinociceptivni) [5]
Poboljšava **energetske** procese u nervnom tkivu (sinteza ATP), smanjuje oksidativni stres [2]	Poboljšava **sintezu** proteina koji su strukturni elementi nervnih vlakana, sintezu masti i **energetski** metabolizam	Učestvuje u **sintezi** mijelinskog omotača aksona (kofaktor sukcinil-koenzim A transferase)
Učestvuje u aksonalnom transportu i sinaptičkoj **transmisiji** [3]	Učestvuje u sintezi ključnih **neurotransmitera**	Učestvuje u sintezi **neurotransmitera**

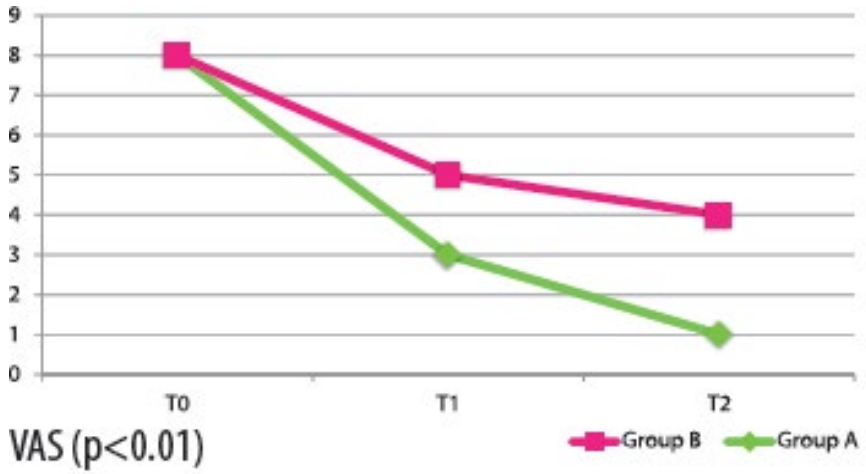
NURONORM ®

1 Sanches-Ramirez et al. 2006; 2 Schmid et al. 2008; 3 Iwata et al.1982; 4 Fu et al. 1988; 5 Mauro et al. 2000.

NURONORM-Bolna sakralna neuropatija

A: 60 pts. 90 dana Nuronorm+PGB 75mg → 90 dana Nuronorm

B: 60 pts. 180 dana PGB 75mg

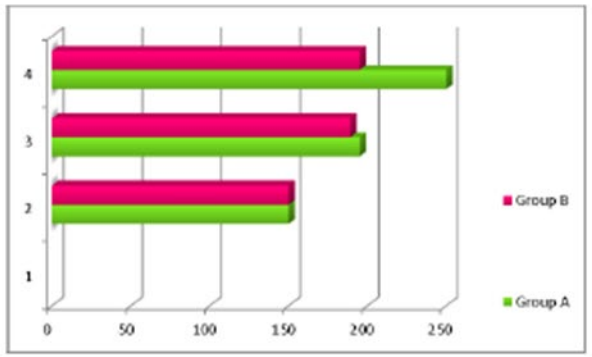


Malaguti S et al. Clin Neurophys 2011;122(suppl 1).

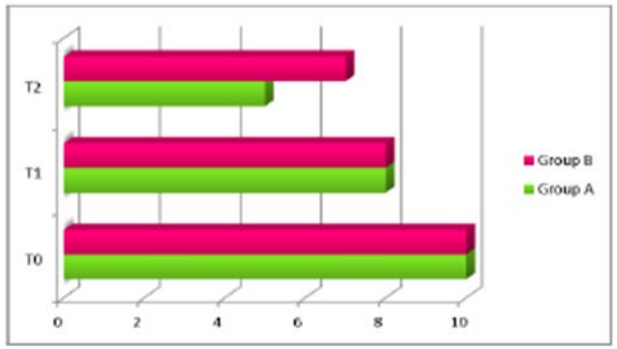
NURONORM-Bolna sakralna neuropatija

At T2 the EDX were improved in both groups (SEP, PNTML $p<0.01$).

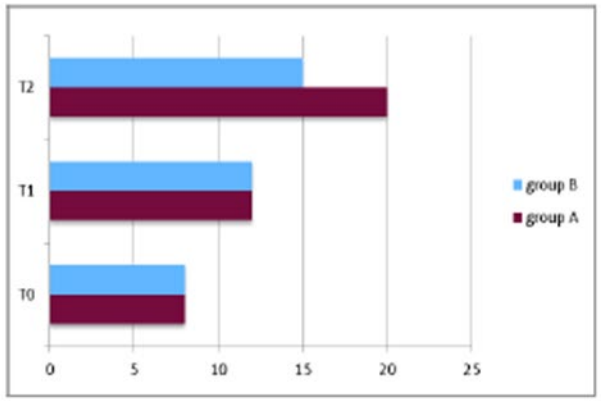
In T2 the clinical and EDX improvement in group A is higher than in group B ($p<0.05$).



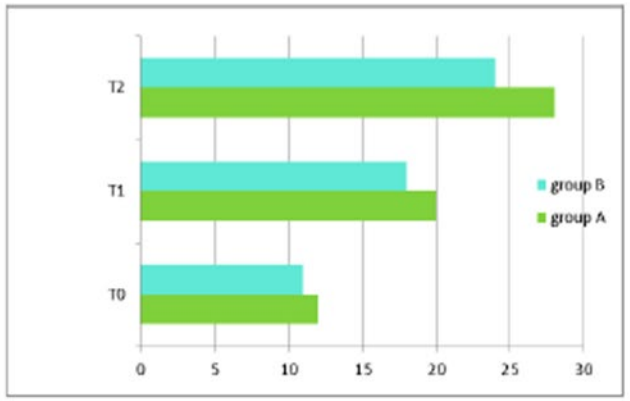
Bladder capacity (ml)



Urinary frequency/24 h



IIFF-5



FSFI full score

Zaključak:
Kombinacija PGB+Nuronorm je pokazala bolju efikasnost u odnosu na sam PGB u smanjenju bola i uspostavljanju neuralne reinervacije.
Ova kombinacija nije pokazala nuspojave prilikom dugotrajne terapije.

ALA-kod pacijenata sa DM II

International Journal of
Molecular Sciences

MDPI

Article

A Clinical Trial about a Food Supplement Containing α-Lipoic Acid on Oxidative Stress Markers in Type 2 Diabetic Patients

Giuseppe Derosa [1,2,3,4,*], Angela D'Angelo [1,2,4], Davide Romano [1] and Pamela Maffioli [1,3,5]

Abstract: The aim of this study was to evaluate the effect of a food supplement containing α-lipoic acid and of a placebo on glyco-metabolic control and on oxidative stress markers in type 2 diabetics. We randomized 105 diabetics to either a supplementation containing 600 mg of α-lipoic acid, 165 mg of *L*-carnosin, 7.5 mg of zinc, and vitamins of group B, or a placebo, for three months. We evaluated body mass index, fasting plasma glucose (FPG), post-prandial-glucose (PPG), glycated hemoglobin (HbA_{1c}), fasting plasma insulin (FPI), HOMA-index (HOMA-IR), lipid profile, high sensitivity C-reactive protein (Hs-CRP), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), malondialdehyde (MDA). There was a reduction of FPG, PPG, and HbA_{1c} with the food supplement containing α-lipoic acid compared with a baseline, and with the placebo. Concerning lipid profile, we observed a reduction of LDL-C, and Tg with the food supplement, compared with both the baseline, and the placebo. There was a reduction of Hs-CRP with the food supplement containing α-lipoic acid, both compared with the baseline and the placebo. An increase of SOD, and GSH-Px, and a decrease of MDA were reached by the food supplement containing α-lipoic acid, both compared with the baseline and the placebo. We can conclude that the food supplement containing α-lipoic acid, *L*-carnosin, zinc, and vitamins of group B improved glycemic control, lipid profile, and anti-oxidative stress markers.

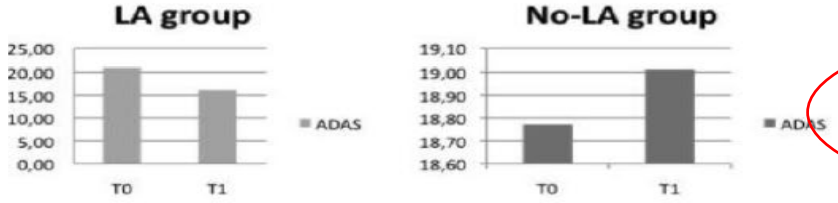
ALA- kod pacijenata sa Alzheimer-ovom b.

Effect of 90-day supplementation with alfa-lipoic acid and a multivitamins complex on cognitive functions of a group of elderly patients with Alzheimer disease

Servello A.[1], Vulcano A.[2], Pontecorvo ML.[2], Musacchio C.[3], Artini M.[1], Selan L.[1], Ettorre E.[2].

[1]Department of Public Health and Infectious Disease; [2]Department of Cardiovascular, Respiratory, Nephrological and Geriatric Science; Sapienza, Rome; [3]Italian Hospital Group - Guidonia

Background: Alzheimer's disease (AD) is the most common and most frequent form of dementia throughout the world. It affects 35 million of people and the cost of managing the disease is estimated at 604 billion US dollars annually. AD is characterized by two major neuropathological hallmarks. The deposition of neuritic, beta-amyloid peptide containing senile plaques in hippocampal and cerebral cortical regions of AD patients is accompanied by the presence of intracellular neurofibrillary tangles. Inflammation is another hallmark of AD. Inflammation, including superoxide production (oxidative burst) is an importante source of oxidative stress in AD patients. Lipoic acid (LA), a critical component of the antioxidant network, exhibits anti-amyloidogenicity for beta-amyloid fibrils in vitro. Many studies suggest that LA has the following anti-AD properties: to increase acetylcholine production by activation of choline-acetyltransferase; to increase glucose uptake, supplying more acetyl-CoA for the production for acetylcholine; to chelate redox-active transition metals, inhibiting the formation of hydrogen peroxide and hydroxyl radicals; to scavenge ROS increasing the level of reduced glutathione and down-regulating inflammatory processes. Recently, the use of antioxidant therapy has shown a slight ameliorating effect on the progression of AD. This study aims to analyse the therapeutic effect on cognitive functions of a compound with LA 600 mg and multivitamins complex, administered daily for 90-day, in a group of patients with mild AD.



Material and methods: 106 subjects, aged 70 or older, were selected in our Alzheimer Unit, to take part in the study, who met inclusion criteria: diagnosis of mild AD (DSM IV and NINCDS-ADRDA criteria) >6 months; MMSE >19/30; drug treatment by rivastigmine patch 9,5 mg/die and memantine 20 mg/die from at least 12 months; brain MRI that showed hyppocampal atrophy. Final determination for inclusion was based on a consensus diagnosis based on clinical, functional and neuropsychological informations, laboratory test results, and MRI clinical report. Laboratory test included: homocysteine, blood glucose and insulin (0' and 120' after breakfast), glycated haemoglobin, PCR and VES. The randomisation procedure was conducted by a computerized system. The subjects were randomised consecutively into two different group:

- LA Group (n=53): patients treated with LA 600 mg and multivitamins complex (carnosine, zinc, group B vitamins) daily for 90 days.
- No-LA Group (n=53): patients who had not been treated with LA

The subjects were assessed at baseline (T0) and after 90-day follow-up (T1). All the patients were evaluated through comprehensive geriatric assessment methods: *Mini Mental State Examination, Activities of Daily Living, Instrumental Activities of Daily Living, Hamilton Scale, Alzheimer Disease Assessment Scale-cognitive subscale*. Their cognitive impairment was then classified according to the *Clinical Dementia Rating Scale*.

Results: All 106 patients enrolled at the beginning of the study completed the observation period. In LA-group no side effects were recorded. Detailed data analysis revealed a significantly different result in the cognitive performance tests in the two groups under observation. The LA group obtained a better performance in ADAS-cog test (p=0,00), after 90 days, particularly in constructive (p=0,05) and ideational (p=0,01) praxis and in MMSE (p=0,04) and a significant reduction of the values of homocysteine (p<0,005). Progressive deterioration in cognitive test performance was instead observed in the nonLA group.

Conclusion: This study showed how daily use of a compound with lipoic acid 600 mg, carnosine, zinc and group B vitamins, associated to drug treatment of dementia, plays a protective role in delaying the evolution of cognitive impairment in patients with mild AD and in controlling the plasma levels of homocysteine, a risk factor for AD.

Journal of the Italian society of Internal Medicine, March 2014

ALA-kod pacijenata sa SPMS

Lipoic acid in secondary progressive MS

A randomized controlled pilot trial

OPEN

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ABSTRACT

Objective: To determine whether lipoic acid (LA), an endogenously produced antioxidant, slowed the whole-brain atrophy rate and was safe in secondary progressive MS (SPMS).

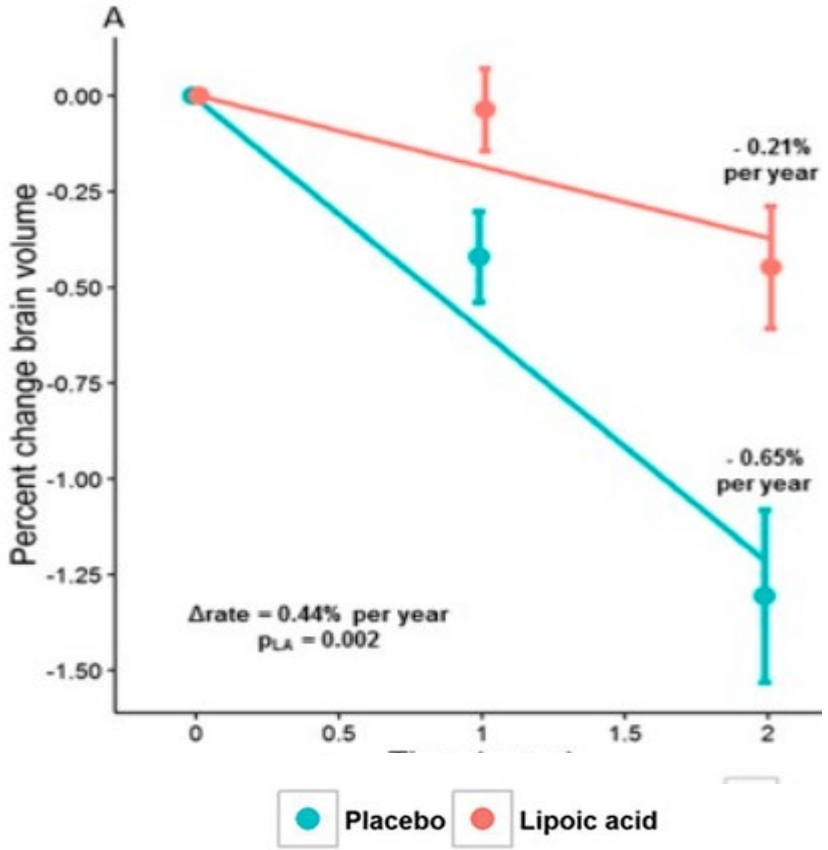
Methods: Patients with SPMS aged 40–70 years enrolled in a single center, 2-year, double-blind, randomized trial of daily oral 1,200 mg LA vs placebo. Primary outcome was change in annualized percent change brain volume (PCBV). Secondary outcomes were changes in rates of atrophy of segmented brain, spinal cord, and retinal substructures, disability, quality of life, and safety. Intention-to-treat analysis used linear mixed models.

Results: Participation occurred between May 2, 2011, and August 14, 2015. Study arms of LA (n = 27) and placebo (n = 24) were matched with mean age of 58.5 (SD 5.9) years, 61% women, mean disease duration of 29.6 (SD 9.5) years, and median Expanded Disability Status Score of 6.0 (interquartile range 1.75). After 2 years, the annualized PCBV was significantly less in the LA arm compared with placebo (−0.21 [standard error of the coefficient estimate (SEE) 0.14] vs −0.65 [SEE 0.10], 95% confidence interval [CI] 0.157–0.727, $p = 0.002$). Improved Timed 25-Foot Walk was almost but not significantly better in the LA than in the control group (−0.535 [SEE 0.358] vs 0.137 [SEE 0.247], 95% CI −1.37 to 0.03, $p = 0.06$). Significantly more gastrointestinal upset and fewer falls occurred in LA patients. Unexpected renal failure (n = 1) and glomerulonephritis (n = 1) occurred in the LA cohort. Compliance, measured by pill counts, was 87%.

Conclusions: LA demonstrated a 68% reduction in annualized PCBV and suggested a clinical benefit in SPMS while maintaining favorable safety, tolerability, and compliance over 2 years.

ClinicalTrials.gov identifier: NCT01188811.

Classification of evidence: This study provides Class I evidence that for patients with SPMS, LA reduces the rate of brain atrophy. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e374; doi: 10.1212/NXI.0000000000000374



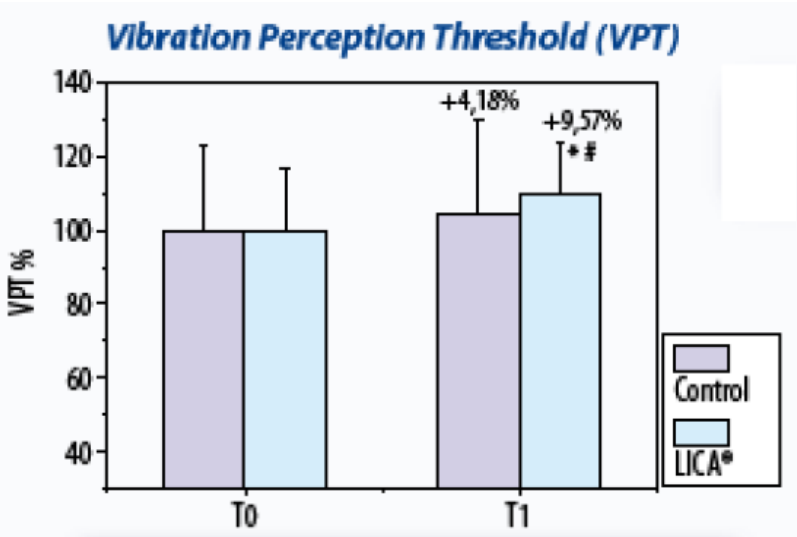
FARMAKOKINETIKA

DVOSLOJNA TABLETA SA PRODUŽENIM OSLOBAĐANJEM

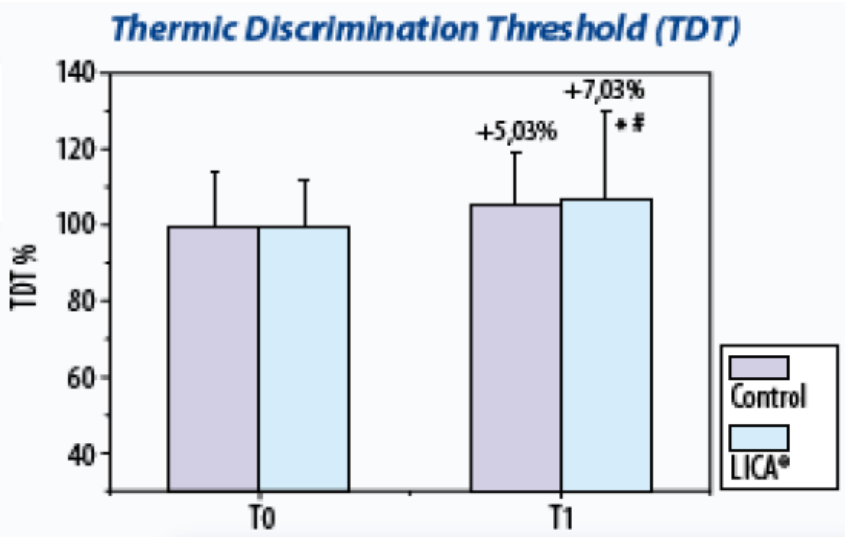
- omogućeno ravnomerno oslobađanje svih komponenata
- odlična bioraspoloživost svih aktivnih komponenata
- omogućeno duže održavanje terapijske koncentracije aLA
- poboljšan efekat, a smanjena ND aLA

NURONORM ®

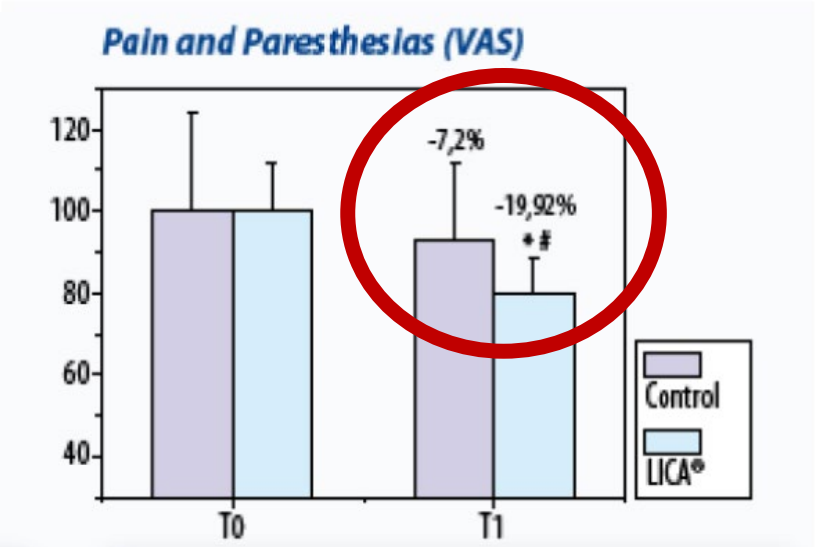
ALA vs. ALA-CARNOSINE-ZINK



VPT%, control vs. LICA® at T0 and T1
*p<0,05(T0vs.T1); #p<0,05 (control vs. LICA®)



TDT Score in percentage, T0 and T1, control LICA®
*p<0,05(T0vs.T1); #p<0,05 (control vs. LICA®)



Visual Analog Scale (VAS) in the control vs. LICA®, at the beginning (T0) and after 90 day-treatment (T1)
*p<0,05 (T0vs.T1); #p<0,05 (control vs. LICA®)

EFFECTS OF THE LICA®ASSOCIATION ON THE METABOLIC FACTORS OF THE DIABETIC PATIENT.
Mauro Febbrari, Specialist in Endocrinology and Metabolic Diseases, Bergamo

NURONORM-Mehanizmi dejstva (sumarno)

EFEKAT	aLA	karnozin	Zn	B vitamini
metabolički	+	+	+	+
antioksidativni antiinflamatorni	+	+	+	+
direktno dejstvo na nerv	+			+
mikrocirkulacija	+	+	+	+
analgetski	+	+	+	+

JEDINSTVENI SASTAV

NAJKOMPLETNIJI SASTAV:

- Alfalipoinska kiselina 600MG
- Karnozin
- Cink
- Kompleks vitamina B

UNAPREĐENA FARMAKOKINETIKA

- Dvoslojna tableta sa produženim oslobađanjem

PROŠIRENE INDIKACIJE

- Dijabetesna neuropatija
- Kompresivne neuropatije
- Neuropatije izazvane alkoholom
- Metabolički sindrom (gojaznost, glukozna intolerancija)
- Lumbalni bolni sindrom
- Posle povreda nervnog tkiva i moždanog udara