V-THREE INJ.

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V-THREE INJ. (10 Amp)

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Feature

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Prescription drug

Approval date: May 11, 2023

Main ingredient: Niacin 50mg/mL

Dosage and administration: 10~100mg of niacin per day for adults, subcutaneously, intramuscularly, or intravenously. Increase or decrease appropriately depending on age and symptoms.

Indication

1. Prevention and treatment of vitamin B3 deficiency: pellagra, etc.

2. Supplementation when the demand for vitamin B3 increases and intake from food is insufficient

: wasting disease, pregnant women, lactating women, heavy physical labor, etc.

3. Among the following diseases, cases presumed to be related to vitamin B3 deficiency or metabolic disorder

(1) Angular stomatitis, stomatitis, glossitis

(2) Contact dermatitis, acute and chronic eczema, photosensitivity dermatitis

(3) Meniere's syndrome

(4) Peripheral circulatory disorder

(Raynaud's phenomenon, cold extremities, chilblains, frostbite)

(5) Tinnitus, hearing loss 6) Paralysis due to SMON

(Subacute myelo-optico neuropathy)

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Precautions for use

- **Dosage prohibited**

Patients with severe hypotension or arterial bleeding
(Blood pressure may be further lowered due to vasodilation.)

- **Administration with caution**

1) Patients with peptic ulcer or a history of peptic ulcer
(Peptic ulcer may be aggravated by large dose administration.)
2) Patients with liver or gallbladder disease or a history of peptic ulcer
(Large dose administration may cause liver failure accompanied by cholestasis, abnormal arrangement of hepatocytes, and formation of nodules in fibrous tissue.)
3) Patients with impaired glucose tolerance
(Glucose tolerance may be reduced by large dose administration.)

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Adverse reactions

Institutional system	Adverse reactions (frequency unknown)
Immune system disorders (stop administration if adverse reaction occurs)	Rash, lip swelling, shock-like symptoms
Respiratory, thoracic and mediastinal disorders	cough
Systemic disorders and administration site pathology	flushing of the face and skin, heat in the head and extremities, paresthesia of the whole body, pruritus, excessive sweating
Investigations	Increased serum aminotransferases, delayed BSP excretion
Hepatobiliary disorders	jaundice
Metabolic and nutritional disorders	Decreased glucose tolerance (long-term, large dose), hyperuricemia (long-term, large dose)
Gastrointestinal disorders	Nausea, vomiting, abdominal heaviness, abdominal pain, diarrhea, chest discomfort
nervous system disorders	Headache, heaviness in the head, dizziness
Heart failure	Heart palpitations

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Niacin,
The main ingredient of
V-Three

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What’s NIACIN?

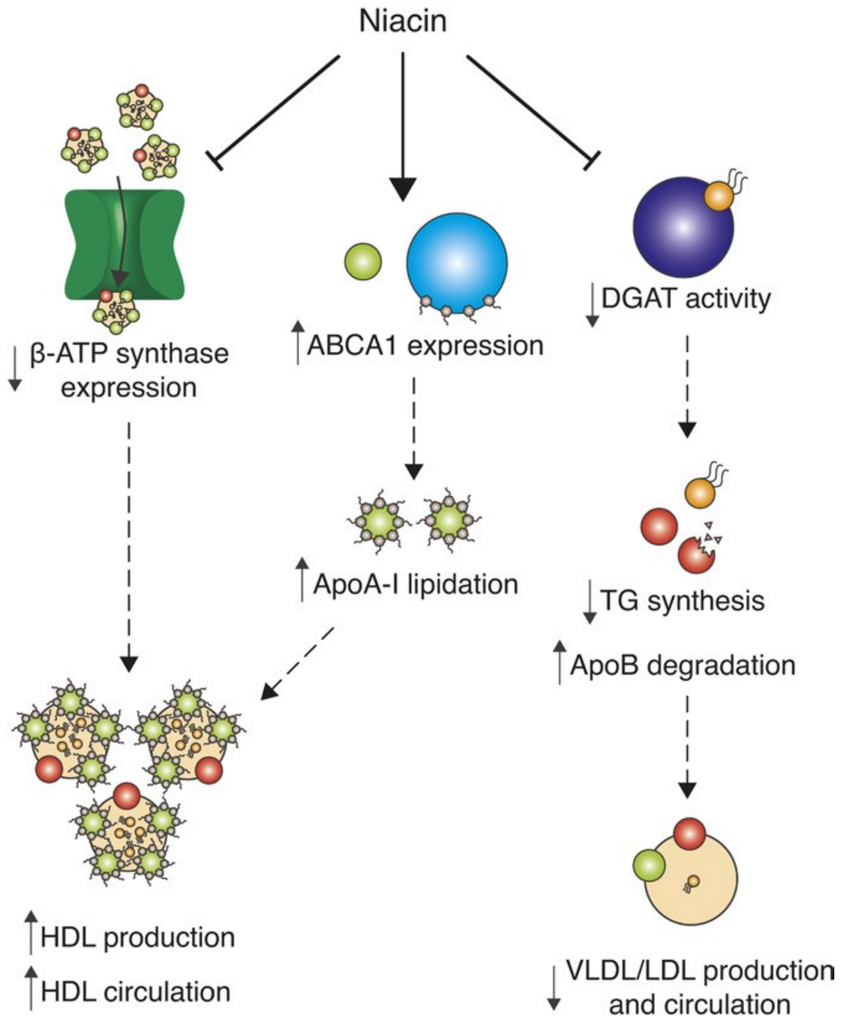
- **Niacin, the first hyperlipidemia drug**
  Used for a long time as a hyperlipidemia treatment for various ages
  Widely used as a first-line treatment drug before the development of statins

- **Pharmacological mechanism has been elucidated**

- **Used as an NAD^+ precursor for various diseases***
  Niacin is used for the purpose of increasing NAD^+ in the body, NAD^+ produced through niacin is applied to various diseases. such as Alzheimer's and Parkinson’s, mitochondrial metabolic. disorders, cancer, etc.

* Rudolf Altschul proved physiologically that niacin has various effects in addition to physiological effects related to the function of vitamins.

(Altschul R., Hoffer A., Stephen J.D. Influence of nicotinic acid on serum cholesterol in man. Arch. Biochem. Biophys. 1955;54:558–559)



Journal of Lipid Research, Volume 60, 2019 **741-746**

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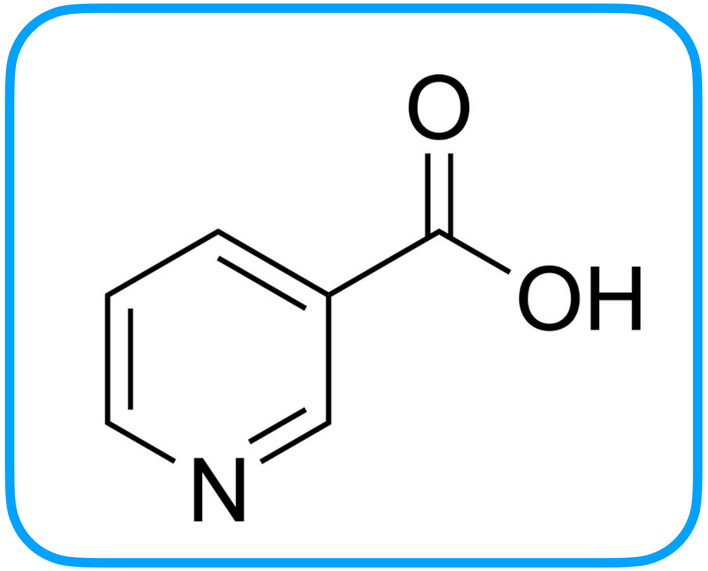
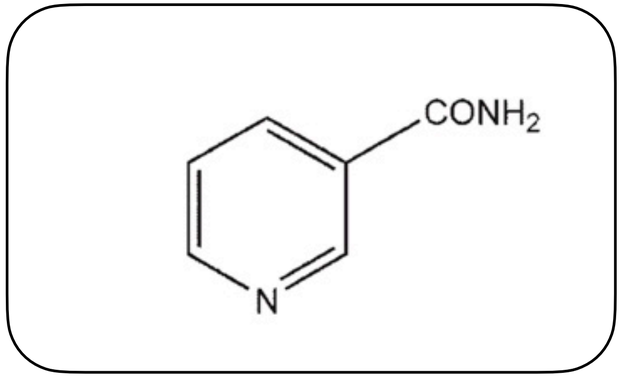
NIACIN or Nicotinamide



Niacin



Nicotinamide

- **Vitamin B3 is composed of two types: niacin and nicotinamide.**
  Immediate peripheral vasodilation is a unique characteristic of niacin.
  When administered as a main ingredient, V-Tree immediately expands the patient's peripheral blood vessels.

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Key Features

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1. Peripheral vasodilation

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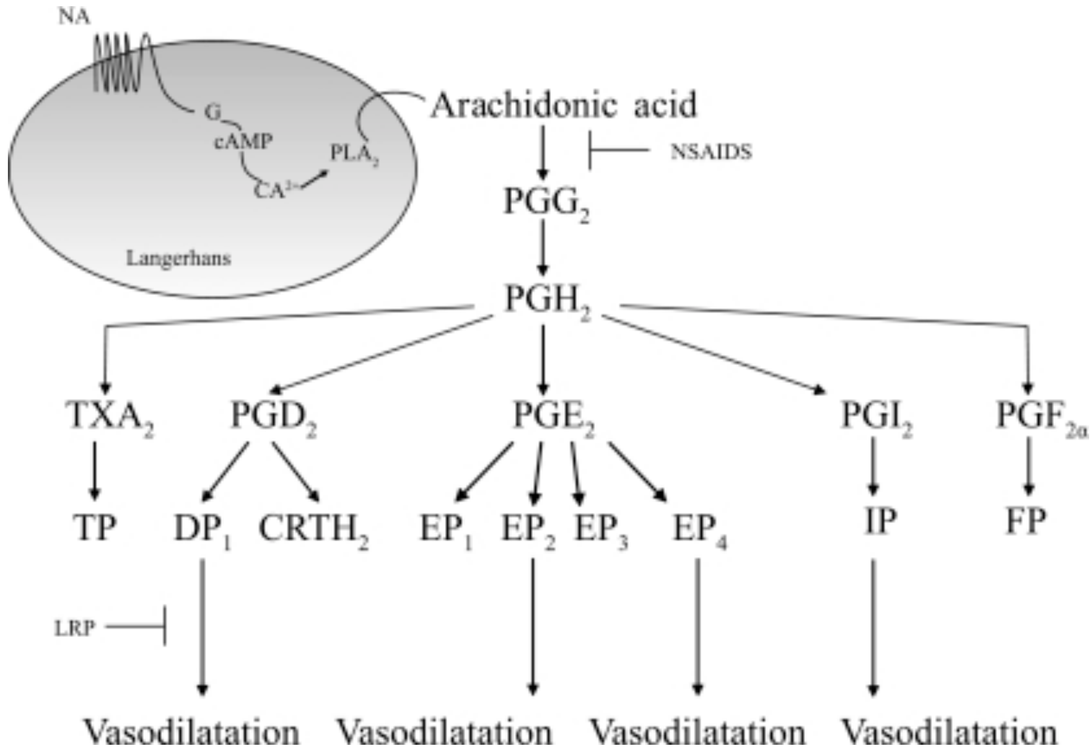
Peripheral vasodilation mechanism

- **Niacin activates arachidonic acid to dilate peripheral blood vessels.**

Activation of arachidonic acid increases PGD2 and PGE2

Activation of GPR109A increases cAMP, releasing arachidonic acid from cell membranes. Afterwards, prostaglandin, prostacyclin, and thromboxane are produced to dilate peripheral blood vessels.

- **Vasodilation is a non-allergic reaction**



Niacin activates GPR109A, inducing vasodilation by increasing prostaglandins induced by arachidonic acid.

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Int J Clin Pract, September 2009, 63, 9, 1369–1377

2. GPR109A

(antioxidant, anti-inflammatory, lipid improvement, etc.)

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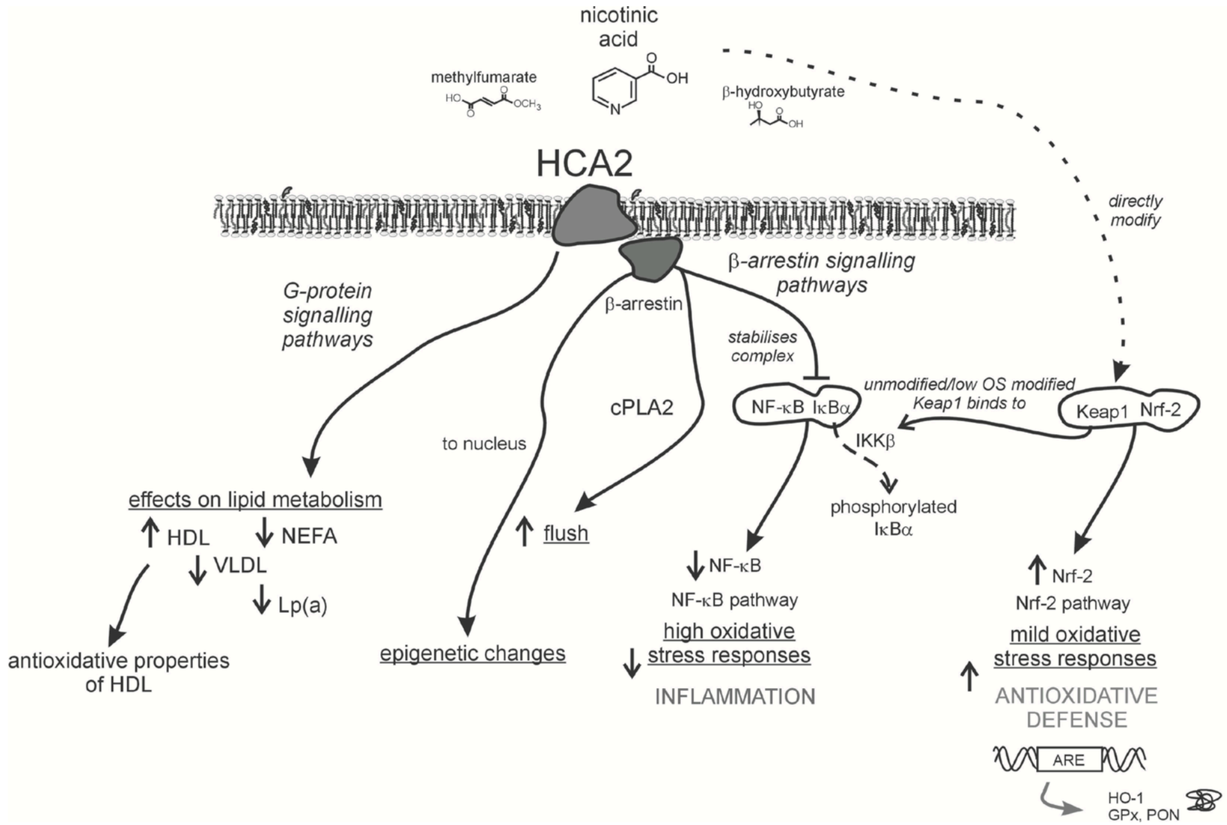
Effect of GPR109A derived from Niacin

- **Reduces OS (oxidative stress) and inflammation**

  Niacin activates Nrf2, reduces NF-kB Anti-inflammatory and antioxidant effects by increasing adiponectin secretion
  Improves ED (Endothelial dysfunction) by decreasing IL-6, TNF-a secretion and CD36, p65

- **Reduces platelet aggregation and blood viscosity due to lipid-lowering effect**

  Niacin reduces blood viscosity due to indirect antioxidant effect by increasing HDL



Effect of GPR109A

*S. H. Ganji, et al, Athero- sclerosis **202** (2009) 68–75*
*E. P. Plaisance et al, Am. J. Physiol. Endocrinol. Metab. **296** (2009)*
*R. S. Rosenson et al, Atherosclerosis **171** (2003) 87–96*

M. Zeman et al., Acta Pharm. 66 (2016) 449–469.

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3. Increase NAD^+

(Improvement of mitochondrial metabolism and Sirtuins)

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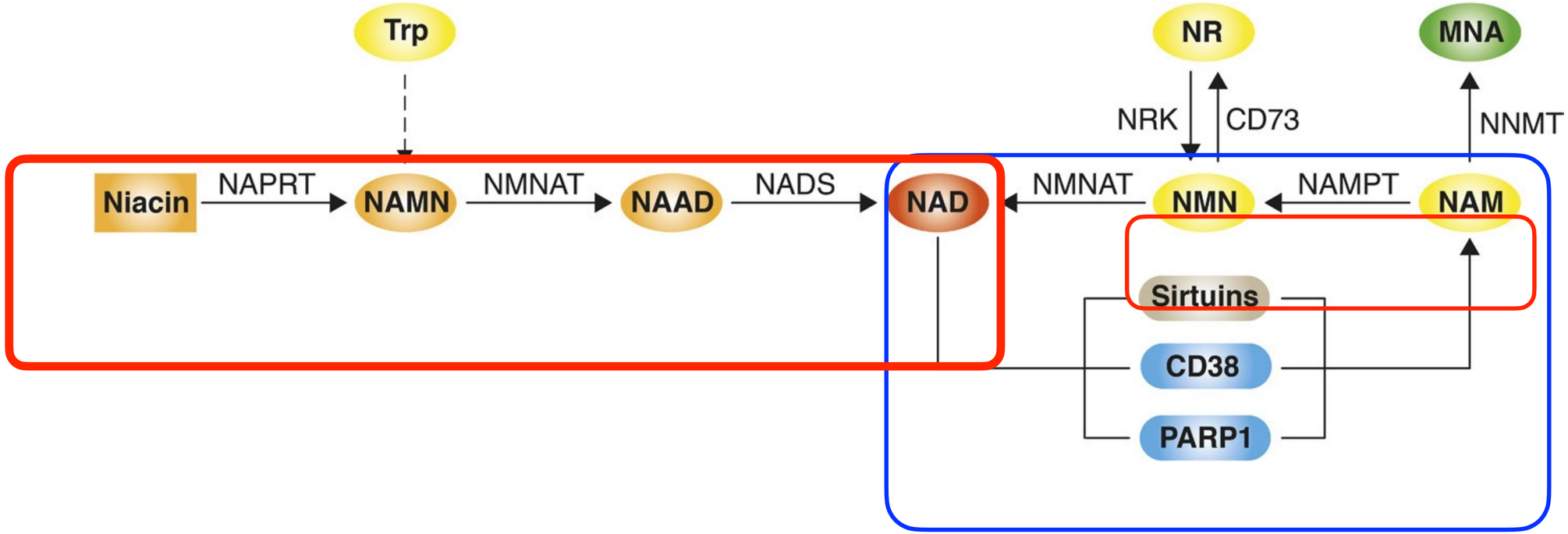
Pathway of NAD+ production from niacin



- **Niacin continuously generates NAD+ by NAPRT.**

  It continuously generates NAD+ in the body regardless of the concentration of NAD+ in the body, thereby increasing the total amount of NAD+ in the body.

  The generated NAD+ activates sirtuins to prevent and treat diseases such as energy production, DNA repair, and mitochondrial activation.

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Peripheral circulatory disorders, tinnitus, hearing loss, Meniere's disease

(Improvement due to vasodilation function)

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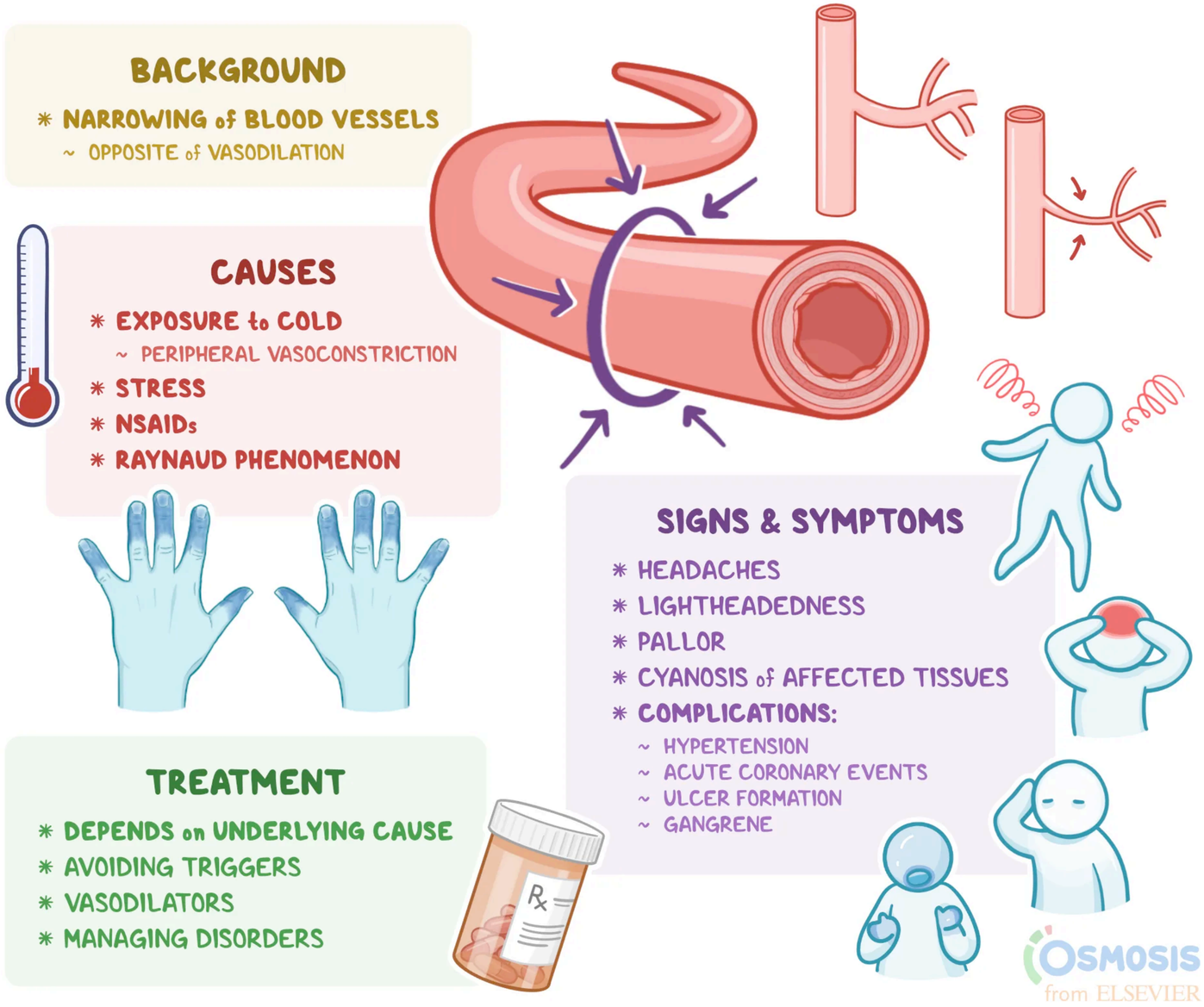
Peripheral vasodilation alone can improve a variety of symptoms.



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Reference

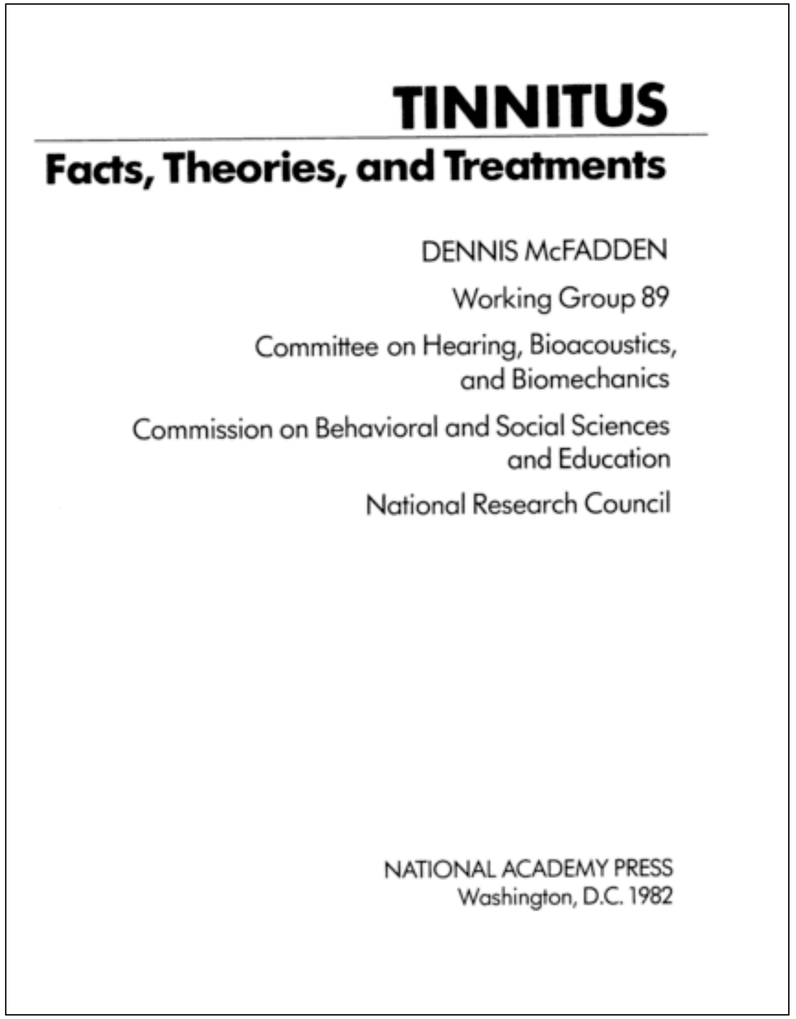
According to the National Academy of Sciences, niacin is used as a peripheral vasodilator to treat peripheral vascular disorders and migraines, and has long been used to treat some forms of Meniere's disease.

- Approximately 50% of patients experience relief of tinnitus while receiving long-term maintenance doses (initial injection followed by oral administration) of niacin (nicotinic acid).

(Miles Atkinson M.D. Annals of Otology, Rhinology & Laryngology 1946)

- Tinnitus severity was measured before and during niacin administration (initially by injection and then by mouth). As in the Atkinson study, most Meniere's patients reported improvement in tinnitus.

(G Flottorp, C Wille. Acta Oto-Laryngologica, 1954)


TINNITUS

Facts, Theories, and Treatments

DENNIS McFADDEN

Working Group 89

Committee on Hearing, Bioacoustics, and Biomechanics

Commission on Behavioral and Social Sciences and Education

National Research Council

NATIONAL ACADEMY PRESS
Washington, D.C. 1982

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Tinnitus: Facts, Theories, and Treatments. National Academy of Sciences.2018

Reference

NICOTINIC ACID TREATMENT OF TINNITUS

A CLINICAL—AUDIOLOGICAL EXAMINATION

BY GORDON FLOTTORP AND CAMILLO WILLE
OSLO, NORWAY

Tinnitus or ringing in the ears has always been a troublesome symptom in many morbid conditions, both generally and in diseases of the ear and adjoining regions. It is well-known that tinnitus in some cases may be of such an intense character that the patient after a shorter or longer period develops insomnia, becomes mentally depressed, irritable and nervous. In some of these patients tinnitus has been a partsystem in an otherwise tractable general condition. In the great majority of these patients however, the symptom is a crux medicorum. Several different methods of treatment and a variety of medicaments have been tried without great success. The result is that the patient continually consults various physicians and usually receives scarce encouraging advice regarding this discomfort. It is with this as background that we desired to try to contribute with a closer study of the prognosis and treatment of tinnitus.

By the term tinnitus is understood any experience of sound that is not due to external causes such as acoustic or electric stimuli [Fowler (1), Atkinson (2), Jones and Knudsen (3)]. According to Fowler there are two types of tinnitus:

A) Vibratory tinnitus.
B) True tinnitus (or non-vibratory tinnitus).

Vibratory tinnitus is often called objective tinnitus (see Engström and Graf (4), a.o.), because it is possible to register it by auscultation. It is of mechanical origin e.g. caused by muscular contractions (spasms) or by turbulent streaming in blood vessels located close to the ear (»Nonnensausen»).

The literal tinnitus is the non-vibratory or true tinnitus, which is also the most common type of ringing in the ears.

The mechanism of the true tinnitus is not fully understood. However, the causes must be numerous.

The biochemical-toxic etiology is well-known: tinnitus is evoked by several drugs, of which salicylate, quinine and quinine derivates are best known. Quinine is assumed to be a protoplasmic poison with a specific affinity to the eighth nerve. [Forbes (5)]. — Covell (6, 7) has shown that quinine and sodium salicylate produces degenerative changes in the cytologic constituents of the cells of stria vascularis and the hair cells (Corti's organ).

Insufficient blood supply to the inner ear, as a result of changed osmotic condi-

From the Audiological Institute and Out-patient Department, Department of Otolaryngology. (Head: Professor Odd Opheim, M.D.), University Hospital, Rikshospitalet, Oslo, Norway.

VM
Vascular Medicine
15(3) 171–179

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http://vmj.sagepub.com
SAGE

Effect of niacin ER/lovastatin on claudication symptoms in patients with peripheral artery disease

William R Hiatt[1], Alan T Hirsch[2], Mark A Creager[3], Sanjay Rajagopalan[4], Emile R Mohler[5], Christie M Ballantyne[6], Judith G Regensteiner[7], Diane Treat-Jacobson[8] and Rita A Dale[9]

Guest Editor: Thom Rooke

Abstract

In patients with peripheral artery disease (PAD), statins may improve the symptoms of claudication. The Intermittent Claudication Proof of Principle (ICPOP) study tested the hypothesis that the combination of extended release niacin plus lovastatin would improve exercise performance in patients with PAD and claudication compared with a diet intervention. A phase 3 double-blind, parallel-group, multi-center, 28-week multi-national study evaluated subjects with a history of claudication who had an ankle–brachial index (ABI) ≤ 0.90, a reproducible peak treadmill walking time (PWT) of 1–20 minutes, and a low-density lipoprotein (LDL)-cholesterol level < 160 mg/dl (< 4.1 mmol/l). Subjects were randomly assigned to low-dose niacin 1000 mg plus lovastatin 40 mg (low niacin–statin), high-dose niacin 2000 mg plus lovastatin 40 mg (high niacin–statin), or diet intervention (diet). The co-primary efficacy endpoint of percent change in PWT and claudication onset time (COT) at 28 weeks was assessed using a graded treadmill protocol. At completion, 385 subjects were analyzed for safety and 370 subjects were analyzed for efficacy. The primary efficacy analysis showed no statistical significance for overall treatment effect at week 28 for the co-primary endpoint of PWT and COT. The PWT component of the primary endpoint increased 26.5% on diet, 37.8% on high niacin–statin ($p = 0.137$) and 38.6% on low niacin–statin ($p = 0.096$). Flushing as the most common event leading to discontinuation and treatment was associated with increases in liver enzymes, fasting blood glucose concentration and a decrease in platelet count.

Keywords

atherosclerosis; cholesterol, HDL; cholesterol, LDL; claudication; clinical trials; drug therapy; exercise test; hyperlipidemia; multicenter studies; peripheral arterial disease

Introduction

Peripheral artery disease (PAD) is a prevalent manifestation of systemic atherosclerosis that is associated with a high risk of cardiovascular events. Many individuals with PAD also suffer claudication that is associated with limb-related limitations in exercise capacity. Two major evidence-based guidelines recommend the dual PAD treatment goals of secondary prevention of cardiovascular events and symptomatic treatment for claudication in order to improve walking ability, exercise tolerance, and quality of life.[1,2] While cilostazol is approved to treat the symptoms of claudication, it does not prevent ischemic events.[3,4]

A pharmacological intervention that would improve exercise performance in PAD to reduce cardiovascular risk would be of significant benefit. Statins reduce the risk of cardiovascular events in PAD, and preliminary data have suggested that statins may reduce the need for leg revascularization.[5] In addition, statin therapy has been evaluated in three single-center studies where low-density lipoprotein (LDL)-cholesterol reduction was associated with significant improvement in the primary endpoint of an increase in treadmill exercise performance in two of the studies.[6–8] In patients with coronary artery disease, niacin in conjunction with statins has demonstrated favorable regression of coronary

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Article

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Nicotinamide riboside for peripheral artery disease: the NICE randomized clinical trial

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Check for updates

Mary M. McDermott[1,2], Christopher R. Martens[3], Kathryn J. Domanchuk[1], Dongxue Zhang[1], Clara B. Peek[1,4], Michael H. Criqui[5], Luigi Ferrucci[6], Philip Greenland[1,2], Jack M. Guralnik[7], Karen J. Ho[8], Melina R. Kibbe[9], Kate Kosmac[10], Donald Lloyd-Jones[1,2], Charlotte A. Peterson[11], Robert Sufit[12], Lu Tian[13], Stephanie Wohlgemuth[14], Lihui Zhao[2], Pei Zhu[1,4] & Christiaan Leeuwenburgh[14]

People with lower extremity peripheral artery disease (PAD) have increased oxidative stress, impaired mitochondrial activity, and poor walking performance. NAD+ reduces oxidative stress and is an essential cofactor for mitochondrial respiration. Oral nicotinamide riboside (NR) increases bioavailability of NAD+ in humans. Among 90 people with PAD, this randomized double-blind clinical trial assessed whether 6-months of NR, with and without resveratrol, improves 6-min walk distance, compared to placebo, at 6-month follow-up. At 6-month follow-up, compared to placebo, NR significantly improved 6-min walk (+7.0 vs. −10.6 meters, between group difference: +17.6 (90% CI: + 1.8,+∞). Among participants who took at least 75% of study pills, compared to placebo, NR improved 6-min walk by 31.0 meters and NR + resveratrol improved 6-min walk by 26.9 meters. In this work, NR meaningfully improved 6-min walk, and resveratrol did not add benefit to NR alone in PAD. A larger clinical trial to confirm these findings is needed. Clinical Trials.gov registration: NCT03743636.

People with lower extremity peripheral artery disease (PAD) have severe walking disability, but few effective treatments exist[1]. In PAD, lower extremity ischemia causes insufficient oxygen and nutrient delivery to lower extremity skeletal muscle, which increases oxidative stress, damages skeletal muscle fibers, and impairs mitochondria function.[2–7].

NAD+ is an essential coenzyme for mitochondrial respiration and a co-substrate for enzymes involved in metabolic regulation, cellular stress resistance, and DNA damage repair, such as poly (ADP-ribose) polymerase (PARP)[8,9]. In preclinical study, NAD+ activated endothelial nitric oxide synthase (eNOS) and reduced oxidative stress to increase nitric oxide abundance[10]. Greater NAD+ abundance increased sirtuin1 (SIRT1) expression and improved skeletal muscle health, mitochondrial activity, and nitric-oxide-mediated endothelial function[11–13]. Nicotinamide riboside (NR) is a precursor to NAD+ and is available as an over-the counter supplement. In 2022, sales of NR in the U.S.

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Use in diabetic patients

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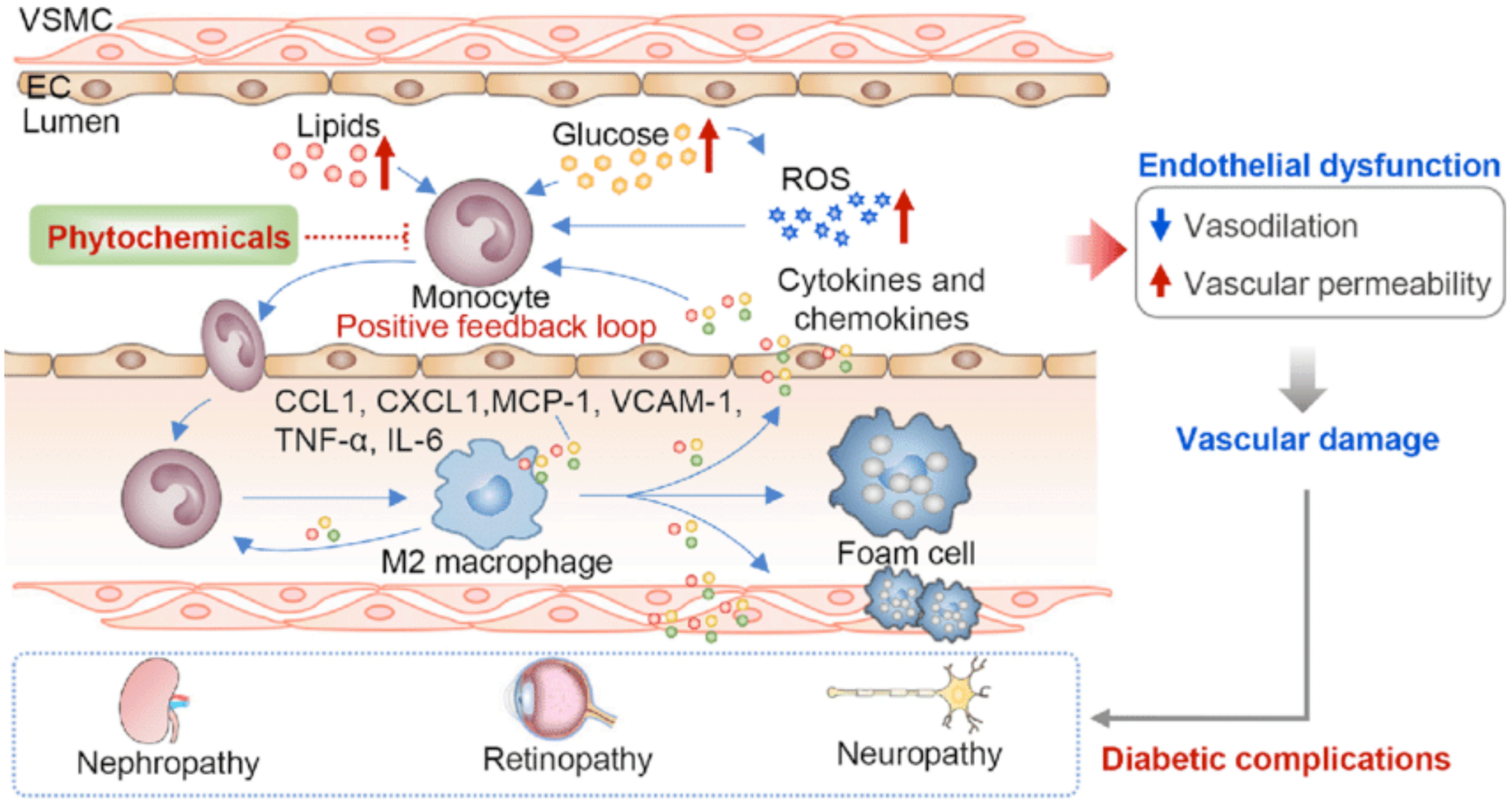
Inflammatory mechanisms of vascular damage in diabetes

Patients with poorly controlled blood sugar levels can prevent diseases such as plantar necrosis and hypertension through peripheral vasodilation.



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M. Kong et al. Biomedicine & Pharmacotherapy 133 (2021) 110975

Reference

Original article

Niacin improves small artery vasodilatory function and compliance in statin-treated type 2 diabetic patients

Diabetes & Vascular Disease Research
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DOI: 10.1177/1479164110376206
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Sandra J Hamilton, Gerard T Chew, Timothy ME Davis, Gerald F Watts

Abstract

We investigated the effect of niacin (nicotinic acid prolonged release) on forearm vasodilatory function and arterial compliance in statin-treated type 2 diabetic patients with endothelial dysfunction. In a parallel group study, we randomised 15 subjects, with LDL-cholesterol ≤2.5 mmol/L, to niacin (dose titrated to 1500 mg/day over 8 weeks, then maintained for a further 12 weeks) or no additional treatment. Niacin increased maximal post-ischaemic forearm blood flow (mean ± SEM 6.4±2.4 *vs.* −2.3±1.2 ml/100 ml/min, $p = 0.001$) and small artery compliance (1.3±0.8 *vs.* −2.3±1.1 ml/mmHg, $p = 0.01$) compared with no additional treatment, but did not alter large artery compliance, blood pressure nor heart rate. Niacin decreased serum triglycerides by 47% ($p = 0.04$), with no change in LDL-cholesterol, HDL-cholesterol, apolipoprotein (Apo) B-100 nor ApoA-I ($p > 0.05$). Adding niacin to statin therapy improves small artery vasodilatory function and compliance in type 2 diabetes. This may relate to a decrease in serum triglycerides and/or a direct benefit of niacin on vascular biology.

Keywords

Arterial compliance, niacin, statins, type 2 diabetes, vasodilatory function

Introduction

Statin therapy decreases cardiovascular disease (CVD) events in type 2 diabetes mellitus (T2DM),[1] principally by reducing low-density lipoprotein (LDL) particle concentrations. However, a significant proportion of patients remain at high residual cardiovascular risk.[2] This may be due, at least in part, to inadequate management of dyslipidaemia.

Impaired forearm vasodilatory function and decreased small artery compliance have been consistently demonstrated in T2DM.[3–6] Forearm endothelial dysfunction and reduced small artery elasticity are both predictive of cardiovascular events.[7,8] Niacin (nicotinic acid prolonged release) improves brachial artery vasodilatory function and carotid atherosclerosis in statin-treated subjects with coronary artery disease (CAD) or risk equivalents.[9–12]

We aimed to test the hypothesis that niacin improves both forearm vasodilatory function and arterial compliance in statin-treated type 2 diabetic patients with endothelial dysfunction.

Methods

Type 2 diabetic patients (American Diabetes Association criteria)[13] aged 40–79 years on stable-dose statin therapy for ≥6 weeks were recruited. Inclusion criteria were serum LDL-cholesterol ≤2.5 mmol/L and endothelial dysfunction (defined as brachial artery flow-mediated dilatation <6.0%). Patients using other lipid-regulating therapies were excluded, as were those with a haemoglobin A_{1c} (HbA_{1c}) > 9.0%, blood pressure (BP) >150/90 mmHg and/or a history of gout.

In a parallel group study design, we randomised eligible subjects, single blind, to either additional therapy with niacin (nicotinic acid prolonged release, Alphapharm Pty Ltd, NSW, Australia) or no additional treatment (no niacin). Niacin was titrated to a maximum dose of 1500 mg/day over 8 weeks. If tolerated, this dose was maintained for a further 12 weeks. To prevent flushing, aspirin 100 mg/day was commenced in aspirin-naïve subjects (47%) at least

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Systematic Review and Meta-Analysis

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Effectiveness of niacin supplementation for patients with type 2 diabetes

A meta-analysis of randomized controlled trials

Dan Xiang, MM*, Qian Zhang, MM, Yang-Tian Wang, MM

Abstract

Background: Lipid profiles and glycemic control play a critical role in subsequent atherosclerotic cardiovascular disease for patients with type 2 diabetes mellitus (T2DM). This study aimed to evaluate the effectiveness of niacin supplementation on lipid profiles and glycemic control for patients with T2DM.

Methods: The PubMed, Embase, and the Cochrane Library databases were searched to identify randomized controlled trials (RCTs) that investigated the effects of niacin supplementation for patients with T2DM throughout December 2019. The weighted mean differences (WMDs) with 95% confidence intervals (CIs) were applied to calculate the pooled effect estimates using a random-effects model.

Results: Eight RCTs comprised a total of 2110 patients with T2DM who were selected for final quantitative analysis. The patients' niacin supplementation was associated with lower levels of total cholesterol (WMD, −0.28; 95% CI, −0.44 to −0.12; $P = .001$), triglyceride (WMD, −0.37; 95% CI, −0.52 to −0.21; $P < .001$), and low-density lipoprotein (WMD, −0.42; 95% CI, −0.50 to −0.34; $P < .001$). Moreover, the level of high-density lipoprotein was significantly increased when niacin supplementation (WMD, 0.33; 95% CI, 0.21 to 0.44; $P < .001$) was provided. However, niacin supplementation produced no significant effects on plasma glucose (WMD, 0.18; 95% CI, −0.14 to 0.50; $P = .275$) and hemoglobin A1c (HbA1c) levels (WMD, 0.39; 95% CI, −0.15 to 0.94; $P = .158$).

Conclusions: This study found that niacin supplementation could improve lipid profiles without affecting the glycemic levels for patients with T2DM. Additional large-scale RCTs should be conducted to evaluate the long-term effectiveness of niacin supplementation.

Abbreviations: CIs = confidence intervals, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RCTs = randomized controlled trials, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglycerides, WMDs = weighted mean differences.

Keywords: diabetes Mellitus, glycemic Load, lipids, meta-Analysis, niacin, type 2

1. Introduction

Type 2 diabetes mellitus (T2DM) involves a group of disorders of intermediary metabolism and is characterized by glucose intolerance.[1] Patients diagnosed with T2DM have increased risk of death, cardiovascular disease, blindness, kidney, and lower-limb amputation.[2] Presently, there are >400 million adults with T2DM worldwide; this number is increasing rapidly and causing substantial economic costs.[3] The increased prevalence of T2DM is correlated with increased body fat and inactivity,[4] which often accompanies atherogenic dyslipidemia and is associated with high plasma triglycerides (TG) and lower high-density lipoprotein (HDL) concentrations.[5] Statins are widely used for improving lipid profiles and further reducing cardiovascular risk, while residual risk remains due to the modest effects of statins on plasma TG and HDL concentrations.[6] Therefore, additional management strategies should be identified to further improve lipid profiles in patients with T2DM.

Niacin is an essential B vitamin that plays an important role in increasing HDL, lowering plasma TG, and low-density lipoprotein (LDL).[7–9] Studies have already proven that niacin supplementation could regress coronary atherosclerosis and prevent risk of cardiac death.[10,11] However, whether niacin supplementation could produce additional clinical benefits in patients with dyslipidemia treated with statins remains controversial.[12–14] Clarifying the effects of niacin supplementation is particularly important in patients with T2DM because of the high prevalence of dyslipidemia in these patients, and because this concern has not yet been addressed. Therefore, this meta-analysis based on randomized controlled trials (RCTs) was conducted to

Editor: Jianxun Ding.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Endothelial-Vasoprotective Effects of High-Density Lipoprotein Are Impaired in Patients With Type 2 Diabetes Mellitus but Are Improved After Extended-Release Niacin Therapy

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Background—High-density lipoprotein (HDL)–raising therapies are currently under intense evaluation, but the effects of HDL may be highly heterogeneous. We therefore compared the endothelial effects of HDL from healthy subjects and from patients with type 2 diabetes mellitus and low HDL (meeting the criteria for metabolic syndrome), who are frequently considered for HDL-raising therapies. Moreover, in diabetic patients, we examined the impact of extended-release (ER) niacin therapy on the endothelial effects of HDL.

Methods and Results—HDL was isolated from healthy subjects (n=10) and patients with type 2 diabetes (n=33) by sequential ultracentrifugation. Effects of HDL on endothelial nitric oxide and superoxide production were characterized by electron spin resonance spectroscopy analysis. Effects of HDL on endothelium-dependent vasodilation and early endothelial progenitor cell–mediated endothelial repair were examined. Patients with diabetes were randomized to a 3-month therapy with ER niacin (1500 mg/d) or placebo, and endothelial effects of HDL were characterized. HDL from healthy subjects stimulated endothelial nitric oxide production, reduced endothelial oxidant stress, and improved endothelium-dependent vasodilation and early endothelial progenitor cell–mediated endothelial repair. In contrast, these beneficial endothelial effects of HDL were not observed in HDL from diabetic patients, which suggests markedly impaired endothelial-protective properties of HDL. ER niacin therapy improved the capacity of HDL to stimulate endothelial nitric oxide, to reduce superoxide production, and to promote endothelial progenitor cell–mediated endothelial repair. Further measurements suggested increased lipid oxidation of HDL in diabetic patients, and a reduction after ER niacin therapy.

Conclusions—HDL from patients with type 2 diabetes mellitus and metabolic syndrome has substantially impaired endothelial-protective effects compared with HDL from healthy subjects. ER niacin therapy not only increases HDL plasma levels but markedly improves endothelial-protective functions of HDL in these patients, which is potentially more important.

Clinical Trial Registration—clinicaltrials.gov. Identifier: NCT00346970.

(*Circulation*. 2010;121:110-122.)

Key Words: diabetes mellitus ■ endothelium ■ free radicals ■ lipids ■ nitric oxide

Reduced levels of high-density lipoprotein (HDL) are a major risk factor for coronary disease[1,2] and are predictive of cardiovascular events in patients treated with statins who have low low-density lipoprotein (LDL) cholesterol levels.[3] Numerous recent studies have suggested that HDL exerts direct endothelial-protective effects, such as stimulating endothelial cell production of nitric oxide (NO)[4,5] and endothelium-dependent vasomotion,[4–7] exerting antioxidant effects,[8] and promoting endothelial progenitor cell (early EPC)–mediated endothelial repair.[9,10] Notably, however, these studies have been performed with the use of either HDL isolated from healthy subjects or reconstituted HDL. Given

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Increase NAD+

(Improvement of mitochondrial metabolism and Sirtuins)

V·THREE

- Aging is no longer a natural phenomenon. **Aging is a disease.**
  - WHO disease code assignment, 2018, LIFESPAN (David A. Sinclair, PhD), 2019

- **NAD^+** Anti-aging (Reverse Aging) Key Component

  - LIFESPAN (David A. Sinclair, PhD), 2019

- Niacin is a precursor of **NAD^+** and safely and effectively increases the concentration of **NAD^+** in the body.
  *- Int. J. Mol. Sci. **2019**, 20, 974*

- When the concentration of **NAD^+** increases, various metabolic diseases can be alleviated and treated.
  - J Nutr Health Aging, 2023;27(9):709-718

Cancer

(Cachexia)

V·THREE

Niacin supplementation in cancer patients

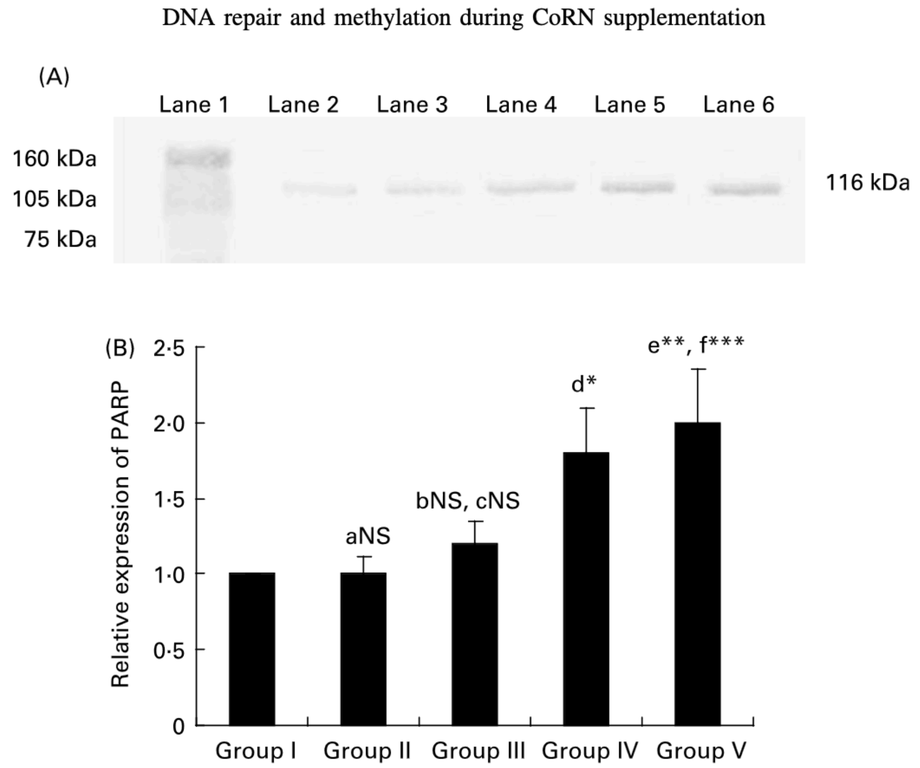
- **All patients in a small group of cancer patients were niacin deficient**

Inculet RI et al., JPEN J Parenter Enteral Nutr 1987;11:243-9

- Increased mitochondrial metabolism
- Activation of Sirtuins by increasingNAD+
- Chemotherapy worsens nutritional status, and niacin deficiency has been observed in several studies.

Stevens HP, et al., Br J Dermatol 1993;128:578–80

S Dreizen et al. Postgrad Med. 1990 Jan;87(1):163-7, 170.



DNA repair and methylation in breast cancer patients

V·THREE

Vummidi Giridhar Premkumar et al. British Journal of Nutrition (2008), 100, 1179–1182

Niacin in breast cancer patients

Decreased DNA repair and DNA methylation due to niacin administration in breast cancer patients receiving tamoxifen treatment

- increase poly(ADP-ribose) Polymerase
- Decrease (RASSF1A) DNA methylation
  - Prevention of metastasis and relapse
- Prevention of cachexia
- Treatment of hyperlipidemia with tamoxifen

Niacin treats hyperlipidemia and inhibits metastasis in breast cancer patients receiving tamoxifen

British Journal of Nutrition (2008), 100, 1179–1182
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Short Communication

Co-enzyme Q_{10}, riboflavin and niacin supplementation on alteratio repair enzyme and DNA methylation in breast cancer patients und tamoxifen therapy

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In the present study, eighty-four breast cancer patients were randomized to receive a daily supplement of 100 mg co-enzyme Q and 50 mg niacin (CoRN), one dosage per d along with 10 mg tamoxifen twice per d. A significant increase in poly(ADP-ribose) and disappearance of *RASSF1A* DNA methylation patterns were found in patients treated with supplement therapy along with ta to untreated breast cancer patients and tamoxifen alone-treated patients. An increase in DNA repair enzymes and disap methylation patterns attributes to reduction in tumour burden and may suggest good prognosis and efficacy of the treatment.

DNA repair: Methylation: Breast cancer: Tamoxifen: Co-enzyme Q_{10}: Riboflavin: Niacin

Tamoxifen (TAM) is a non-steroidal anti-oestrogen drug, which has led to an increase in both disease-free and overall survival of breast cancer patients after primary surgery[1]. A complicating factor is the relapse in breast cancer patients during tamoxifen therapy and in this subset of patients, treatment is only palliative and the recurrent breast cancer is incurable[2]. Endometrial cancer and other serious side-effects of therapy have been reported in tamoxifen-treated patients and TAM-induced DNA adducts were found in leucocyte DNA from breast cancer patients[3].

Poly(ADP-ribose) polymerase (PARP) is a highly conserved, abundant protein, with three functional domains identified within the PARP polypeptide by limited proteolysis[4]. PARP protein and associated poly(ADP-ribonyl)ation reactions are thought to play a number of roles in different biological processes such as DNA repair, recombination, apoptosis, p53 function and maintenance of genomic stability[5].

In recent years, changes in the status of DNA methylation, known as epigenetic alterations, have turned out to be one of the most common molecular alterations in human neoplasia including breast cancer[6]. Muller *et al.* [7] detected the prognostic value for *RASSF1A* methylation in pre-therapeutic sera of patients with breast cancer. The present study h to evaluate the effect of nutritional supple enzyme Q_{10}, riboflavin and niacin (CoRN) DNA repair enzyme PARP and *RASSF1A* DNA tern in breast cancer patients undergoing tamo

Materials and methods

Study patients

Patients were recruited from the Medical O ment of the Government Royapettah Ho India, via their physicians according to the by the Institutional Human Ethical Review a single blinded study. They were aged bet years with histopathology-confirmed breast with diabetes mellitus, renal and hepatic excluded from the study.

Study design

Forty-two socio-economically and age-matc healthy controls were recruited in group

Abbreviations: CoRN, co-enzyme Q_{10}, riboflavin and niacin; PARP, poly(ADP-ribose) polymerase; TAM, tamoxifen; Tris, 2-ami 1,3-propanediol.
* **Corresponding author:** Professor P. Sachdanandam, fax +91 44 24926709, email psachdanandam2000@yahoo.co.in

NS British Journal of Nutrition

Research article

Mitochondrial complex I activity and NAD+/NADH balance regulate breast cancer progression

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Despite advances in clinical therapy, metastasis remains the leading cause of death in breast cancer patients. Mutations in mitochondrial DNA, including those affecting complex I and oxidative phosphorylation, are found in breast tumors and could facilitate metastasis. This study identifies mitochondrial complex I as critical for defining an aggressive phenotype in breast cancer cells. Specific enhancement of mitochondrial complex I activity inhibited tumor growth and metastasis through regulation of the tumor cell NAD+/NADH redox balance, mTORC1 activity, and autophagy. Conversely, nonlethal reduction of NAD+ levels by interfering with nicotinamide phosphoribosyltransferase expression rendered tumor cells more aggressive and increased metastasis. The results translate into a new therapeutic strategy: enhancement of the NAD+/NADH balance through treatment with NAD+ precursors inhibited metastasis in xenograft models, increased animal survival, and strongly interfered with oncogene-driven breast cancer progression in the MMTV-PyMT mouse model. Thus, aberration in mitochondrial complex I NADH dehydrogenase activity can profoundly enhance the aggressiveness of human breast cancer cells, while therapeutic normalization of the NAD+/NADH balance can inhibit metastasis and prevent disease progression.

Introduction

Despite advances in clinical therapy, metastasis is still the leading cause of death in breast cancer patients (1). A clearer understanding of molecular mechanisms that drive metastasis will help to develop more effective therapies (2). Our present study focused on metabolism as an essential driver of tumor growth and metastasis, potentially common to all breast cancer types. Normal cells primarily use mitochondrial oxidative phosphorylation (OXPHOS) for energy production, whereas cancer cells depend on aerobic glycolysis (the Warburg effect) to generate energy and glycolytic intermediates for enhanced growth (3, 4). Tumor cells also generate high levels of reduced forms of NAD^+, NADH, and NADPH as important cofactors and redox components (4, 5). These altered metabolic activities can be linked to mitochondrial dysfunction that inhibits OXPHOS, increases ROS, promotes uncontrolled growth, and causes DNA damage that further supports a metastatic phenotype (6, 7). Mitochondrial dysfunctions can be caused by mutations in mitochondrial DNA (mtDNA) or nuclear genes encoding mitochondrial proteins (6, 8) that are essential for the respiratory chain/OXPHOS system. Due to the lack of protective histones and limited DNA repair (8), mtDNA mutations occur at high rates and were found in tumors including breast cancer (6, 9–14), which suggests that defects in OXPHOS might contribute to tumorigenesis.

By combining the nuclear genome of a recipient cell with the mitochondrial genome of a donor cell using cybrid technology, mitochondria from the triple-negative aggressive breast cancer cell lines MDA-MB-435 (15) and MDA-MB-231 facilitated tumor progression and metastasis in nonmetastatic tumor cells (7, 10). The donor cell lines harbor mtDNA mutations in tRNAs, in the noncoding D-loop region (9, 10), and in mitochondrial complex I subunit genes (10). These defects suggest a role of mtDNA mutations and complex I in tumor progression. Therefore, these cell lines are excellent models for defining a specific role of complex I activity in tumor growth and metastatic aggressiveness.

Complex I is the gatekeeper of the respiratory chain and catalyzes the first step of NADH oxidation. It elevates the NAD^+/NADH ratio and translocates protons across the inner mitochondrial membrane, which ultimately leads to energy production. mtDNA mutations in genes encoding complex I subunits are found in malignancies including breast cancer (6, 11–14, 16). However, it is largely unknown how alterations in complex I and the cellular NAD^+/NADH redox balance affect tumorigenesis and metastasis.

We used a unique approach to define contributions of complex I activity to breast cancer progression, based on expression of the yeast NADH dehydrogenase Ndi1 in human tumor cells. Ndi1 encodes a single protein that faces the inner mitochondrial matrix and oxidizes NADH from the Krebs cycle. Unlike mammalian complex I, Ndi1 is rotenone insensitive (17). Ndi1 contains 26 N-terminal residues for mitochondrial import (17), can be functionally expressed in mammalian cells (18, 19), and does not cause an immune response (20). Ndi1 restores complex I function (18) in diseased cells, *e.g.*, in neurons of Parkinson's disease (21) and optic neuropathy (22); protects cardiomyocytes from ischemic reperfusion injury (23); and increases lifespan in *Drosophila* (24). Recently, it was shown that Ndi1 expression in complex I–deficient tumor cells can reduce soft agar colony formation (25).

We used Ndi1 to investigate a cause-and-effect relationship between aberrant mitochondrial complex I activity and malignant progression in breast cancer. Moreover, we analyzed metabolic alterations caused by mitochondrial complex I malfunction and translated the information gained into a novel therapeutic approach against breast cancer progression.

Conflict of interest: The authors have declared that no conflict of interest exists.
Citation for this article: *J Clin Invest.* 2013;123(3):1068–1081. doi:10.1172/JCI64264.

British Journal of Nutrition (2008), 100, 1179–1182

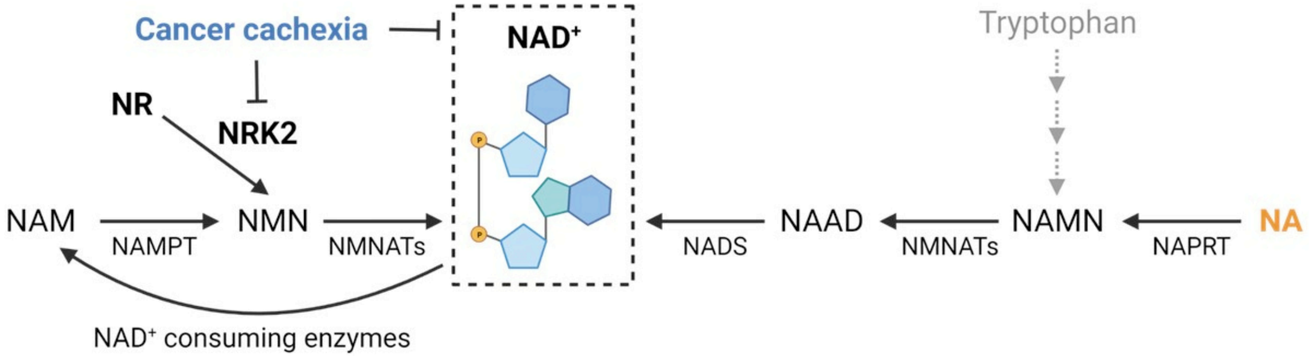
Santidrian AF et al, The Journal of clinical investigation. 2013; 123:1068–1081

V·THREE

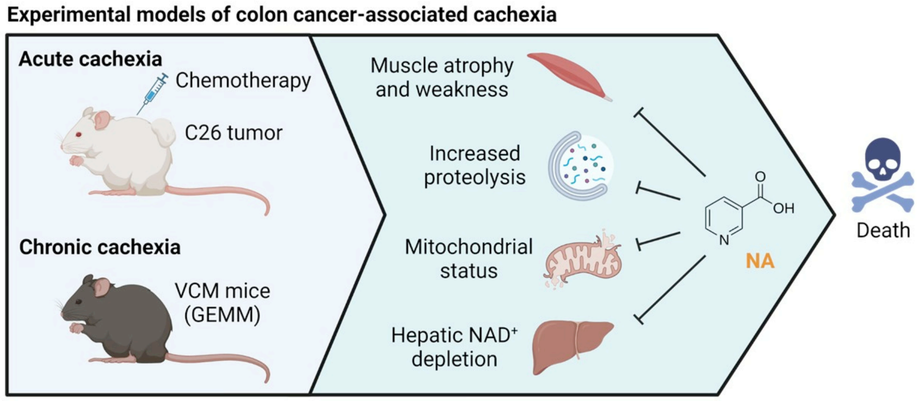
Cachexia and Niacin

- Confirming the effect of NAD^+ supplementation in tumor mice (a mouse model of cancer cachexia)
- Confirming that NAD^+ loss in muscle is a common feature of experimental cachexia, particularly induced by colon and pancreatic cancer
- Transcripts for the NAD^+ biosynthetic enzyme nicotinamide riboside kinase 2 (Nrk2) were consistently reduced in all models examined

In humans, we also demonstrated NRK2 loss and impaired energy metabolism in skeletal muscle of patients with colon and pancreatic cancer.



Nicotinamide riboside kinase 2 (NRK2) inhibition in cancer cachexia



NAD^+ supplementation via niacin improves cancer cachexia

Nature Communications volume 14, Article number: 1849 (2023)

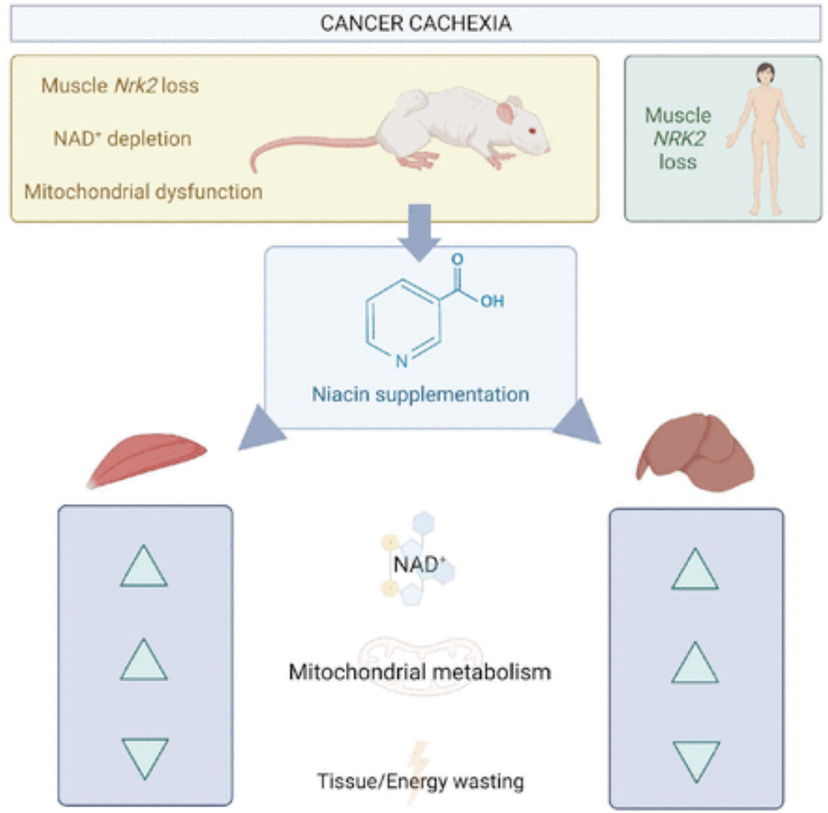
V·THREE

Cachexia and Niacin

- **Loss of Nrk2 and NAD⁺ is a common feature of cachexia in cancer patients**

NAD⁺ supplementation with niacin improves energy homeostasis in tumor-bearing animals and is effective in treating cachexia

<u>Use of niacin can improve survival and quality of life in cancer patients by reversing the vicious cycle of cachexia and treatment non-responsiveness.</u>



Beneficial effects of niacin on NAD⁺ content, mitochondrial homeostasis, and energy metabolism were generalized despite model-specific variations

Nature Communications volume 14, Article number: 1849 (2023)

V·THREE

Niacin in cancer treatment

V-THREE INJ. Recap

- **It is the only injectable product containing 50 mg of niacin as its main ingredient.**
- **Niacin restores mitochondrial metabolism by increasing NAD^+.**
- **It can be used for numbness in the hands and feet, cold extremities, frostbite, and chilblains due to its peripheral vasodilation effect.**
- **Niacin inhibits breast cancer metastasis and improves cachexia.**
- **Niacin improves diseases associated with aging by increasing NAD^+, a key anti-aging substance.**

END

V·THREE