Dietary Fatty Acids and Vitamin B3: An Effective Treatment Strategy for the Metabolic Syndrome?

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Abstract

The metabolic syndrome (MS) may be defined as the constellation of cardiovascular disease (CVD) risk factors that comprises obesity, type 2 diabetes, dyslipidemia, and hypertension. Recent evidences suggest that, primarily due to its high monounsaturated fatty acids (MUFAs) content, olive oil and omega-3 polyunsaturated fatty acids (PUFAs) could be useful as a dietary approach for MS management, with relevance in the postprandial state. Vitamin B3, as a major substrate for nicotinamide phosphoribosyltransferase (NAMPT), also constitutes a nutritional intervention strategy for the treatment of MS. NAMPT has been shown to exert activities of central importance to cellular energetics and innate immunity. Within the cell, NAMPT is the rate-limiting step in a salvage pathway of nicotinamide adenine dinucleotide (NAD+) biosynthesis. NAMPT has been shown to correlate with triglycerides in the fasting plasma, and a potential regulatory role for fatty acids on NAMPT expression has been proposed. Whether different dietary fatty acids, including olive oil as a source of MUFA, play a role in NAMPT excursions and in the NAMPT-dependent regulation of glucose and lipid metabolism and inflammation states remains to be solved. In general, the mechanisms that alter NAD+ metabolism probably include multiple processes, but the understandings of these mechanisms are currently very unclear and a considerable effort in this area is required before we know how changes in NAD+ metabolism influence physiology of glucose and lipid metabolism and how NAD+ metabolism might be manipulated for healing benefit by specific dietary fatty acids as a therapeutic treatment for MS.

Keywords: Metabolic syndrome, cardiovascular diseases, dietary oleic acid, omega-3 PUFAs, niacin, NAMPT, NAD+

Introduction

Cardiovascular disease (CVD) is the first cause of death worldwide, with type 2 diabetes (T2D) making up about 90% of the cases [1,2]. Incorporating a cluster of metabolic abnormalities, the metabolic syndrome (MS) was advocated by several organizations as a major predictor of CVD and T2D [3-6]. MS is characterized by four major traits: increased abdominal fat, hypertension, hyperglycemia, and dyslipidemia [7]. Lacks of habitual physical activity combined with diet contribute to increase the risk of CVD, and the development of MS in particular. The core components of the dyslipidemia in the MS, which most likely initiate CVD, are the "lipid triad" of high plasma triglycerides (TG), low levels of high-density lipoproteins (HDL), and a preponderance of small, dense low-density lipoproteins (LDL) at fasting [8]. Abnormally elevated postprandial (non-fasting) TG levels are also recognized as an important component for atherosclerosis, as first suggested by Zilversmit [9]. More recently, several studies have described abnormalities during the postprandial state in patients with coronary artery disease (CAD) [10] and have shown that non-fasting TG levels are independent predictors of CAD in multivariate analysis [11], even after adjustment for fasting TG or HDL levels in normolipidemic men. Exacerbated non-fasting TG levels are often found in insulin-resistant subjects, denoting that hyperinsulinemia and/or decreased insulin sensitivity are involved in altered postprandial metabolism of dietary fats [12].

One of the current global recommendations to counteract disability and premature death resulting from CVD is to decrease the consumption of energy-dense diets, including high-fat foods enriched in saturated fatty acids (SFAs). The most effective replacement for SFAs in terms of risk factor outcomes for CVD is the monounsaturated fatty acids (MUFAs), and the polyunsaturated fatty acids (PUFAs) but

in much less importance [13]. In accordance, recent studies have demonstrated that olive oil, which is the only natural and most relevant source of MUFAs in the diet, when compared with butter, can postprandially limit TG excursions and buffer the pancreatic β-cell hyperactivity and peripheral insulin intolerance in subjects with normal [14] and high fasting [15] TG levels.

Dietary fatty acids have received considerable attention for their ability to regulate inflammatory gene expression and secretion. It has been proposed that dietary fatty acids affect insulin resistance and inflammatory processes through the modulation of transcription factors such as NFκB and peroxisome proliferator-activated receptor gamma (PPARγ) [16, 17].

There is general agreement that increasing dietary SFA intake, especially in overweight or obese individuals, is associated with raised inflammatory markers [18], predominately by activating the toll-like receptor 4 (TLR4) pathway. TLR4 is expressed in both subcutaneous (SAT) and visceral (VAT) adipose tissues. SFAs serve as ligands for TLR4, inducing inflammatory responses in both adipocytes and macrophages through an increase of adipocytokine gene expression and production [19,20]. Moreover, SFA is associated with NFκB activation [21] which is a fundamental component underlying chronic inflammatory diseases such as atherosclerosis, rheumatoid arthritis, and MS [22]. Conversely, unsaturated fatty acid have well known anti-inflammatory effects, which range from the inhibition of the lipoxygenase and cyclooxygenase pathways, inhibition of TLR4 signaling, and PPARγ activation [23,24]. Thus, MUFAs can reproduce a number of the anti-inflammatory effects of TLR4 or induce TNF-α inhibition [25], which suggest that dietary MUFAs constitute an attractive nutritional approach for the treatment of MS.

PPARγ is a fatty acid sensor that adapts β-cell mitochondrial function [26].

Unsaturated fatty acids enhance mitochondrial oxidation levels in insulin-secreting cells, which protects against β-cell dysfunction [27]. In line it has been demonstrated that NAMPT (also known as visfatin or PBEF) improves insulin sensitivity and exerts its hypocholesterolemic effects at least partially through upregulation of the tyrosine phosphorylation of IRS-1 protein and the mRNA levels of PPARγ and SREBP-2 [28].

NAMPT is considered as a multifunctional adipokine involved in the regulation of different pathophysiological conditions. NAMPT is the rate-limiting enzyme in the NAD+ biosynthetic pathway starting from nicotinamide and essential when the cellular NAD+ pool is depleted, for example through poly-ADP-ribosylation during DNA repair and NAD+-dependent protein deacetylase activity. Two forms of NAMPT exist (Figure 1), intracellular (iNAMPT) and extracellular (eNAMPT). While the function of iNAMPT as a NAD+ biosynthetic enzyme is well established, the physiological role of eNAMPT is still a matter of debate [29]. eNAMPT is positively secreted through a non-classical secretory pathway by fully differentiated human adipocytes and hepatocytes. It has been suggested that eNAMPT exhibits robust, even higher NAD+ biosynthetic activity compared to iNAMPT and that NAD+ biosynthesis mediated by iNAMPT and eNAMPT plays a critical role in the regulation of glucose-stimulated insulin secretion in pancreatic β-cells.

The observation that NAMPT has insulin-mimetic functions and is involved in the modulation of inflammation has raised the hypothesis that a dysregulation of the activity of this molecule may contribute to T2D and MS. Many research papers have been published on this topic, with controversial findings. Fasting NAMPT levels were found to be elevated in T2D patients, in women with gestational diabetes, and in extremely obese individuals (BMI >40), whereas fasting NAMPT levels were reduced by weight loss [30]. By contrast, other studies have failed to detect any correlation

between fasting NAMPT levels and body fat or insulin sensitivity [31]. In addition, NAMPT expression was not altered in a rodent model of the MS as compared with wild-type animals. Thus, the role of NAMPT in insulin resistance and diabetes is largely unknown and deserves further examination.

Niacin (NA) or Vitamin B3 is a major substrate for NAMPT. In doses large enough to produce pharmacological effects, NA is a potent lipid-modifying agent with a broad spectrum of effects, including those aimed at attenuating the risks associated with low HDL, high LDL and TG levels in fasting plasma [32]. It is interesting to note that fasting TG levels strongly and positively correlated, and represented an independent factor associated, with NAMPT levels in healthy subjects and patients with obesity and/or T2D [30]. Moreover, fasting TG levels positively correlated with NAMPT mRNA expression in the VAT of obese subjects [31]. In contrast, there is also evidence of positive correlation between NAMPT and HDL levels, and of negative correlation between NAMPT and TG levels in the fasting state in a cohort of subjects with genetic predisposition for dyslipidemia [33], suggesting that NAMPT may be an indicator of beneficial lipid profile. In support of this notion, oral administration of NA significantly increased cellular NAD+ levels and had the ability to reduce fasting TG and LDL, whereas raising HDL [34]. These findings raise questions regarding of whether NA administration and the type of dietary fatty acids might be harmful or helpful NAMPT modulators to influence lipid homeostasis. At this stage, it is possible to argue that exogenous NA and the type of fatty acids in plasma TG may regulate NAMPT metabolism and function. This assumption substantiates the thought that exogenous TG in postprandial TRL may evoke pro- or anti-inflammatory signals in a fatty acid-dependent fashion. Interestingly, a regulatory role for individual fatty acids, such as MUFAs (oleic acid), SFAs (palmitic acid), and omega-3 PUFAs (eicosapentaenoic

acid) on NAMPT gene expression has been described in 3T3-L1 murine adipocytes and monocytes [35,36]. In obese subjects, a recent cross-sectional study of associations between nutrient intake and fasting NAMPT levels has also demonstrated that MUFA intake, in the adjusted multivariate analysis, was the only independent predictor of fasting NAMPT levels [37].

Despite this considerable amount of data, whether different dietary fatty acids, including olive oil as a source of MUFAs and omega-3 PUFAs, play a role in NAMPT excursions and in the NAMPT-dependent regulation of glucose and lipid metabolism and inflammation in the fed and postprandial states remains to be solved.

In general, the mechanisms that alter NAD+ metabolism probably include multiple processes, but the understandings of these mechanisms are currently very unclear and a considerable effort in this area is required before we know how changes in NAD+ metabolism influence physiology of glucose and lipid metabolism and how NAD+ metabolism might be manipulated for healing benefit by specific dietary fatty acids.

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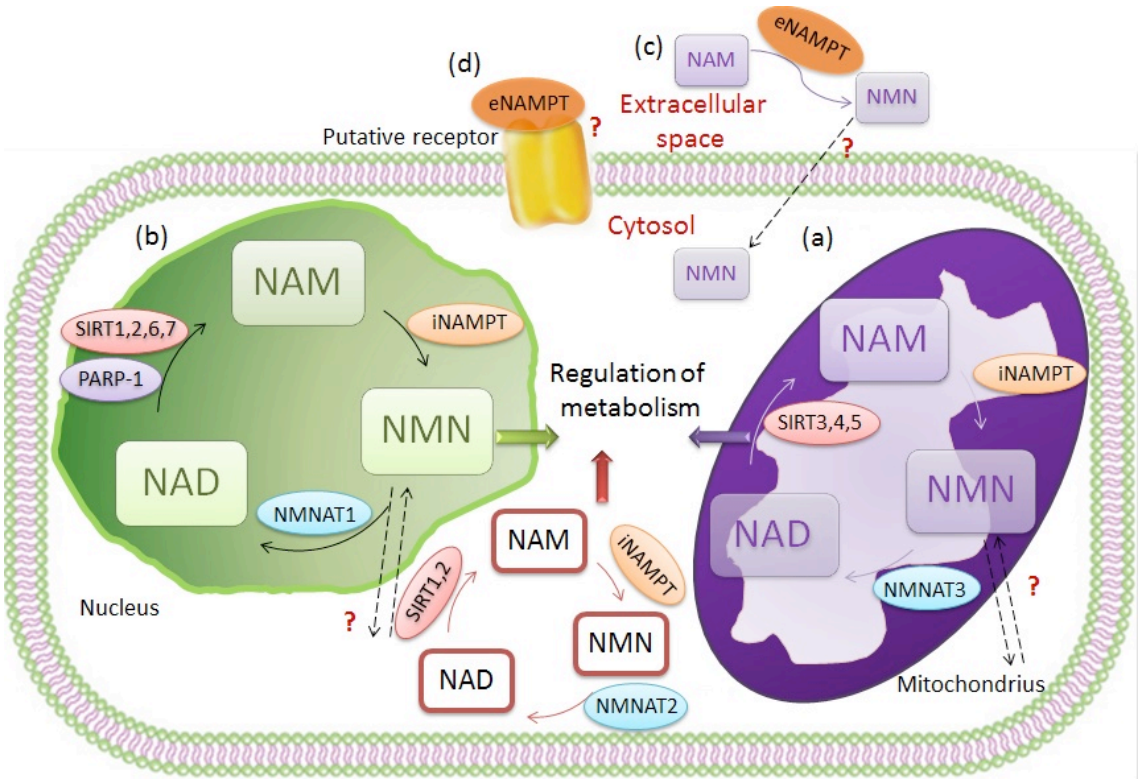
Legend to Figure

Figure 1. Model of putative modes of action for NAMPT to affect cell metabolism adaptaed from *Garten et al.* [29]. NAMPT functions as an intra- and extracellular NAD+ biosynthetic enzyme. NAMPT catalyzes the formation of nicotinamide mononucleotide (NMN) from nicotinamide (NAM). NMN is subsequently converted to NAD+ by three organelle-specific isoforms of nicotinamide mononucleotide adenylyltransferase (Nmnat1–3). Intracellularly, NAMPT has been shown to be located in different cellular compartments. It affects the function of NAD+-degrading enzymes by raising cellular NAD+ levels and consequently influences the regulation of metabolism and stress resistance through sirtuins (Sirt1–7) and other NAD+-consuming enzymes, such as poly(ADP-ribose)polymerase-1 (PARP-1). The NAD+ metabolism of (a) mitochondria and (b) nucleus is possibly influenced by transport of NAD+ metabolites from and to the cytoplasm. (c) Extracellularly, NAMPT produces nicotinamide mononucleotide (NMN), which might act in an autocrine/paracrine fashion and/or be transported to other target tissues, where it acts on glucose-stimulated insulin secretion in pancreatic β-cells and potentially elicits other biological responses. (d) Possibly, NAMPT also functions as a cytokine by binding to and activating an unidentified receptor.


(d)
eNAMPT
Putative receptor
?
(c)
NAM
eNAMPT
NMN
Extracellular space
?
Cytosol
NMN
(b)
NAM
iNAMPT
SIRT1,2,6,7
PARP-1
NMN
NAD
NMNAT1
Nucleus
?
SIRT1,2
Regulation of metabolism
NAM
iNAMPT
NMN
NAD
NMNAT2
(a)
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SIRT3,4,5
NMN
NAD
NMNAT3
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Mitochondrius