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Niacin and Oxidative Stress: A Mini-Review

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Abstract

Oxidative stress has been implicated in the pathogenesis of a variety of chronic diseases. One of the main factors involved in oxidative stress reduction is increased antioxidant potential. Several nutrients such as vitamin C, vitamin E and carotenoids are known to act as antioxidants; however, niacin is one of the neglected antioxidant nutrients that may have an antioxidant action both independently, and also as a component of the glutathione redox cycle. Thus, this study aimed to review the studies that have examined the antioxidant properties of niacin and its effect on oxidative stress reduction. The results of the reviewed studies confirm the antioxidant nature of niacin and indicate that this vitamin can protect the body against oxidative stress, specifically lipid peroxidation and reperfusion oxidative injury. The mechanisms by which niacin protects the body against oxidative stress can be attributed to the glutathione redox cycle and also to other possible roles such as decreasing NADH+H+/NADP+ ratio as well as increasing the NAD^+ content.

Keywords

Niacin, Lipid peroxidation, Reperfusion oxidative injury, Glutathione peroxidase

Introduction

Oxidative stress is a phenomenon that reflects an imbalance between the production of reactive oxygen species (ROS) and other oxidants, and their elimination through protective mechanisms. Antioxidative systems can detoxify the reactive intermediates, or repair the consequential damages causing toxic effects through the production of peroxides and free radicals that can destroy all cell components. Oxidative stress is thought to be involved in the development of atherosclerosis, neurodegenerative diseases such as Alzheimer's and Parkinson's disease, cancers, diabetes mellitus, inflammatory diseases, as well as psychological diseases and aging processes.

One of the main factors involved in oxidative stress reduction is increased antioxidant potential, that may be achieved by endogenous antioxidants, such as the enzymes Superoxide Dismutase (SOD), Catalase (CAT) and Glutathione Reductase (GR), and also, exogenous antioxidants like nutritional antioxidants including tocopherols, ascorbic acid, carotenoids, niacin, and trace elements such as chromium and selenium. There are also specific biological defense mechanisms that protect tissues against cellular damage. Niacin acts as a coenzyme of redox enzymes in Nicotinamide Adenine Dinucleotide (NAD) and Nicotinamide Mononucleotide (NMN) forms [1]. Many studies have examined the effects of niacin on various diseases such as anemia [2,3], hypertension [4], cardiovascular diseases (CVD) [5,6], liver diseases [7,8] and some cancers (esophageal, skin, breast, and lung) [9-11]. However, one of the roles through which niacin can have a potential effect on human health is that as an antioxidant, which has not been clearly investigated.

Compelling evidence from both *in vitro* and *in vivo* studies supported that Nicotinamide (NA) possesses potent antioxidant properties [12,13]. NA deficiency was associated with increased oxidative stress.

In this review, two aspects of the antioxidant properties of niacin are considered: (1) the role of niacin in the prevention of lipid peroxidation (LPO) and (2) the effect of niacin on the attenuation of reperfusion oxidative injury. Human and animal studies are summarized in table 1.

Niacin at a Glance

Niacin and its coenzymes NAD and Nicotinamide Adenine Dinucleotide Phosphate (NADP) have fundamental roles as a part of reduction/oxidation coenzymes involved in energy metabolism, amino acid metabolism, detoxification reactions for drugs and other substances as well as antioxidant protection (Figure 1) [14,15]. Niacin can be synthesized by the essential amino acid tryptophan. Even though this process is not efficient, dietary tryptophan intake seems crucial for the overall niacin status of the body. The Food and Nutrition Board (FNB) has recommended a daily intake of 2-4 mg niacin/day for infants, 6-8 mg niacin/day for children, 12-16 mg niacin/day for adolescents, and 14-18 mg niacin daily by mouth for adults. Considerable amounts of niacin have been found in a wide range of foods including lean meats, poultry, fish, peanuts, and yeasts.

Niacin deficiency can be caused by problems that affect absorption of niacin or tryptophan. Digestive disorders and prolonged treatment

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Table 1: Application of Niacin to inhibit oxidative stress and lipid peroxidation.

Study	Design	Outcome measure	Main findings
Arun*et al.* [2]	Cross-sectional	Various parameters of LPO and membrane stability of blood storage bags were compared with and without the presence of nicotinic acid.	In the presence of nicotinic acid, the concentration of MDA was lower, while, the GSH levels were higher.
Atac *et al.* [21]	Experimental	The effects of combined treatment with chromium and niacin on spleen, tongue and lens tissues in terms of LPO, GSH, CAT were compared between four groups of rats.	Niacin and chromium administration to hyperlipidemic rats increased tissue GSH levels and CAT activity and decreased tissue LPO levels compared with hyperlipidemic rats.
Benavente & Jacobson [9]	Cross-sectional	The levels of GSH, GSSG and the ratio of GSH/GSSG were compared between control group and niacin restricted human keratinocytes.	In the restricted group, the levels of GSH increased, whereas, GSSG levels and the ratio of GSH/GSSG were decreased.
Cho *et al.* [4]	Experimental	CAT activity and MDA levels were compared in niacin-treated and the control nephrectomized rats.	Niacin supplementation decreased MDA levels, and increased CAT abundance in remnant kidney pointing to the presence of antioxidant activity of niacin.
Doger *et al.* [25]	Experimental	The effect of the combination of niacin and chromium(III)-chloride on heart GSH, LPO levels, serum paraoxonase (PON), gamma-glutamyltransferase (GGT) activities and protein carbonyl contents(PCC) compared between four groups of one-year-old rats (fed with pellet chow, pellet chow+ lipogenic diet, lipogenic diet+ $CrCl_3$+niacin, pellet chow+$CrCl_3$+niacin).	The heart GSH levels increased and LPO (MDA) levels decreased significantly in rats treated with niacin compared with the hyperlipidemic groups. The activity of PON was increased where the activity of GGT and the serum levels of PCC decreased significantly.
Dou *et al.* [7]	Experimental	GPx and CAT activity, intracellular GSH/GSSG and total NAD contents were determined in male rats exposed to Lieber-De Carli liquid diet with or without NA supplementation.	Pretreatment with NA for 2 h prevented H_2O_2- induced GSH reduction and GSSG elevation, leading to almost complete recovery of GSH/GSSG ration and also increased the GPx and CAT activity.
Ganji *et al.* [12]	Cross-sectional	The effect of niacin on production of NADH, GSH, ROS and its effects on human aortic endothelial cells were determined activity.	In cultured human aortic endothelial cells, niacin increased NADPH levels and GSH/GSSG ratio, and inhibited ROS production.
Ghazi *et al.* [22]	Experimental	The effect of combination of niacin and captopril on oxidative stress in isolated perfused rat lung.	This treatment increased GSH and decreased LPO in the lung of rats.
Perumal *et al.* [14]	Experimental	Therapeutic efficacy of combination of niacin, riboflavin and coenzyme Q10 on mammary carcinoma bearing rats in terms of the mitochondrial LPO and antioxidants was investigated.	Administration of combinatorial therapy showed significant reduction in MDA levels and SOD, CAT and GPx activity and GSH levels restored to near the normal level.
Tang *et al.* [16]	Experimental	The effect of dietary niacin deficiency were examined on protein and DNA oxidation in bone marrow cells of Long-Evans rats.	There was no significant effect of niacin deficiency on total GSH levels in total or nucleated bone marrow population. Increased oxidant damage to DNA and protein occurs in niacin deficient bone marrow but is not a result of decreased NADPH or GSH level
Tupe *et al.* [20]	Experimental	The effect of dietary nicotinic acid supplementation on hepatic zinc uptake and oxidative stress in rats in 3 weeks treatment.	In comparison with normal control, dietary nicotinic acid supplementation increases the levels of SOD, CAT, GPx, glutathione and Zn, whereas, LPO values were lower for the intervention group.
Varella *et al.* [23]	Case-control	The effect of niacin supplementation was determined on intestinal permeability and oxidative stress in patients with alcoholic pellagra.	The plasma concentrations of vitamin E and GSH-Px activity were below normal values in the patients before treatment (Phase 1) and their increase after niacin treatment can be attributed to the ingestion of a balanced diet and to abstinence from alcohol during the period of hospitalization. MDA levels were also decreased
Yuvaraja *et al.* [11]	Clinical trial	The effect of combined modality of Co Q10, riboflavin and niacin with tamoxifen as an antioxidant on preventing breast cancer.	Plasma SOD level were unaffected by treatment showing that niacin may have antioxidant potential via inhibiting lipolysis and decreasing LPO.

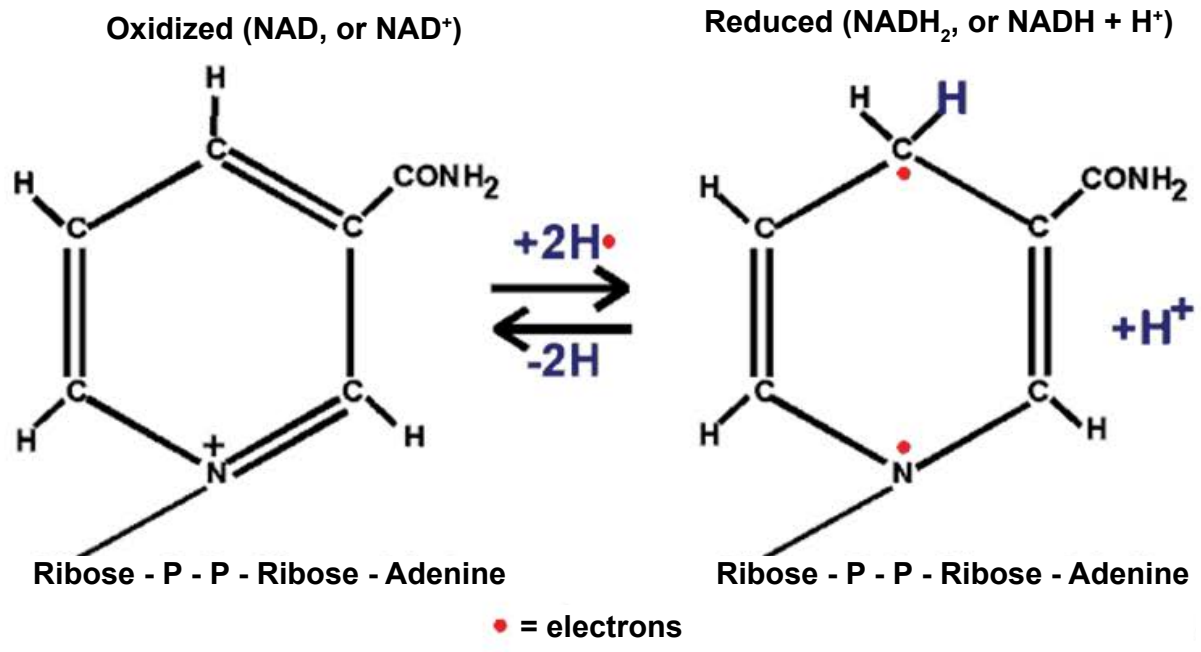

Figure 1: Conversion of NADH+H+ to the NAD+-a possible mechanism for its antioxidant nature [15].

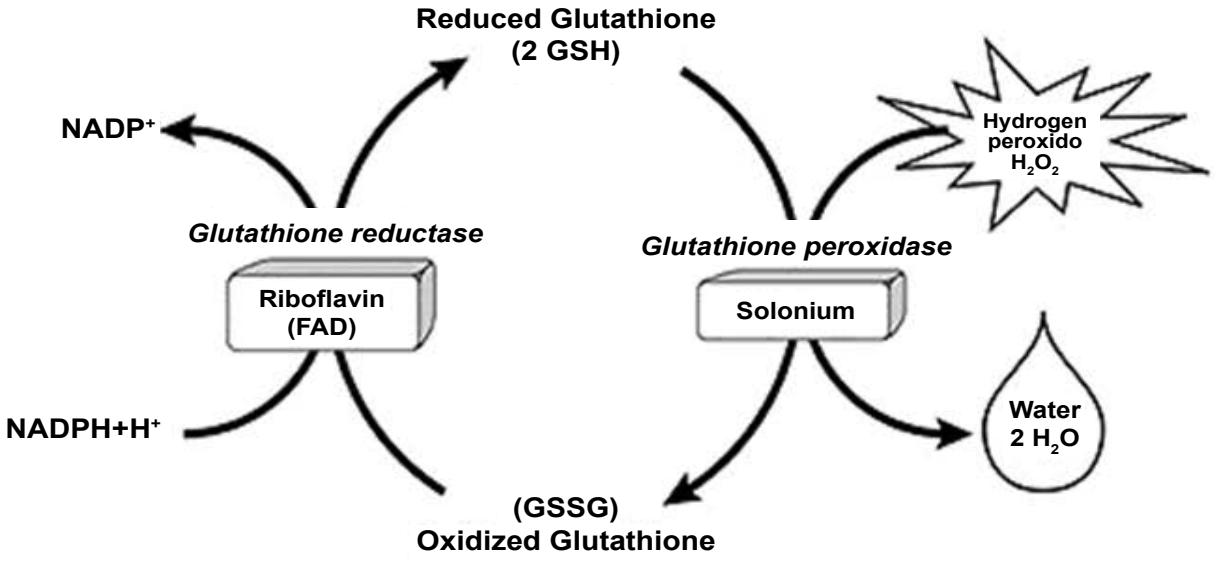

Figure 2: Conversion of oxidized glutathione (GSSG) to the reduced form (GSH) by Glutathione Reductase (GR) [19].

with the tuberculosis drug Isoniazid (Laniazid, Nydrazid) can be the risk factors of niacin deficiency. Additionally, alcoholism is regarded as the most common cause of this problem. Cases of niacin deficiency have been also found in patients suffering from Crohn's disease.

Generally, niacin has a low toxicity. High doses of niacin (1-2 g of NA three times per day) can be used in decreasing serum cholesterol. The upper limit (UL) of niacin suggested by the US Food and Nutrition Board is 35 mg/day. It can be suggested that a high dose of niacin could cause an imbalance in the antioxidant state of human body. However, there is not any strong evidence in this area, which recommends further investigations to clarify the possible adverse effects of niacin intake in high amounts.

Role of Niacin in the Prevention of Lipid Peroxidation

Niacin as the glutathione reductase coenzyme

NADPH is an important coenzyme of the GR, which converts oxidized glutathione (GSSG) to its reduced form (GSH) (Figure 2). GSH acts as a co-substrate for glutathione peroxidase (GPx) [16,17], an endogenous antioxidant in various cell types which deactivates ROS. Through its action, by converting this peptide to the oxidized form, it becomes deactivated. Thus, to recovering the antioxidant properties of glutathione, GSSG should be reduced again to GSH by GR. Intracellular NADPH, in turn, is generated through the reduction of $NADP^+$ by glucose-6-phosphate dehydrogenase, the first and rate-limiting enzyme of the pentose phosphate pathway, during the conversion of glucose-6-phosphate to 6-phosphogluconolactone. By generating NADPH, glucose-6-phosphate dehydrogenase is a critical determinant of cytosolic GSH buffering capacity (GSH/GSSG), therefore, it can be considered as an essential, regulatory antioxidant enzyme. It has been suggested that oxidative stress can be increased during niacin deficiency by the ability to regenerate GSH through the use of NADPH in the GR reaction [18]. NADPH adequately maintained by the pentose phosphate pathway, providing sufficient substrate for GSH regeneration in the GSH reductase reaction. This is supported by the lack of any GSH reduction during niacin deficiency [19].

One of the most important antioxidant activities of glutathione is the deactivation of peroxides such as hydroperoxide. This activity of glutathione is mediated by the action of GPx. GPx transfers a hydrogen ion from GSH to lipid peroxide and produces GSSG and alcohol [20]. Based on the aforementioned mechanisms, it is expected that niacin deficiency could increase LPO [21].

Effect of niacin status on glutathione content in tissues

The effect of niacin status on GSH content in tissue has been investigated in a limited number of studies. Benavente *et al.* [9] found that GSH was increased in restricted cells where GSSG and GSH/GSSG levels were decreased. NA supplementation either alone [4,7,22], or in a combination with other factors [14,23,24] has been shown to moderate the up-regulation of oxidative and inflammatory systems and increase the GSH levels.However, to our knowledge, there are a limited number of human studies that examined the effect of niacin on GSH status. Some human studies reported significant increase in GSH content with pharmacological doses of niacin [2,9,12].

However, some animal studies did not report any changes in GSH content. In an experimental study conducted by Tang *et al.* [18] no diet-induced change was observed in GSH concentration in total or nucleated bone marrow population in rats, which would indicate that shifts in thiol-dependent transcriptional activity, can play a role in niacin deficiency [18]. The authors reported that measurements of GSSG were elevated, especially in the total cell population. Taken together, these results showed that the reductive roles in oxidant defense were not compromised and increased level of oxidant stress in niacin-deficient bone marrow cells resulted from other events [18].

Effect of niacin status on the activity of antioxidant enzymes

An experimental study indicated that niacin can increase SOD and GPx activities in hepatic tissue in rats [22]. Another study that investigated the effects of dietary niacin on antioxidant defense mechanism of rats, reported a significant increase in levelsof SOD, CAT, GPx, glutathione and zinc, while, LPO level was lower in the intervention group [22]. Several studies have reported similar findings on the positive effects of niacin on SOD [14], GPx [7,14,25] and CAT [7,14,23] activities, although, some studies did not observe any association between niacin status and antioxidant enzyme activity [26].

In conclusion, studies indicated that niacin status could affect the activity of several antioxidant enzymes; however, some studies did not attain the similar findings. Furthermore, as studies have been limited to animals, further investigations are warranted in human populations to clarify the role of niacin in the activity of antioxidant enzymes.

Effect of niacin status on lipid peroxidation

Animal studies: Several animal studies indicated that not only niacin deficiency could adversely affect LPO, but also, niacin administration had inhibitory effects on it [4,14,22-24,27]. Studies in which niacin deficiency was induced in animals through a niacin-deficient diet, LPO in different tissues was found to be significantly increased compared to the control groups [4,22,27]. Other studies

reported that niacin administration could reduce the production of LPO biomarkers such as malondialdehyde (MDA) in rats [4,22].

Human studies: A limited number of human studies investigated the effects of niacin status on LPO. Arun *et al.* [2] investigated the effect of nicotinic acid added to the Citrate-Phosphate-Dextrose-Adenine (CPDA) solution on LPO and integrity of red cells. The authors reported that MDA levels decreased, while, concentrations of GSH and vitamin E increased by adding nicotinic acid [2]. In another study, the effects of 27 days of niacin supplementation on intestinal permeability and oxidative stress were investigated in patients suffering from alcoholic pellagra. The study indicated that lipid and protein peroxidation biomarkers had a significant decrease ($P < 0.05$) after 27 days of niacin supplementation [25]. In the same line with these studies, Hamoud *et al.* [28] addressed the effects of 3-month niacin supplementation (1 g/day in the first month, followed by 2 g/day for the second and third months) in patients with hypercholesterolemia and low HDL-C levels and in healthy control subjects (received no intervention). The authors reported that niacin treatment in hypercholesterolemic patients led to a significant reduction in oxidative stress, as measured by a significant decrease in the serum concentration of thiobarbituric acid reactive substances, and also, paraoxonase 1(PON1) activity was significantly increased after niacin treatment for 12 weeks, compared with the initial levels. The study also indicated that serum interleukin-6 level significantly decreased following the niacin intervention. However, it should be noted that serum level of C-reactive protein (CRP) was not affected by niacin supplementation. Similarly, findings from a prospective cohort study [29] indicated that plasma oxidized LDL was inversely correlated with dietary niacin intake ($r = -0.23$, $P < 0.05$) and was lower in participants with above 22mg/day vs. below-average niacin intake .Moreover, Ganji *et al.* [6] investigated the effect of niacin on human hepatocyte fat accumulation, ROS production, and inflammatory mediator interleukin-8 secretion. The authors reported that niacin (at 0.25 and 0.5 mmol/L doses for 24 h) decreased hepatocyte ROS production, palmitic acid-induced interleukin-8 levels and it also inhibited NADPH oxidase activity. However, these findings were not fully supported by all studies. Taylor *et al.* [30] assessed the changes PON1 activity and concentration after single aerobic exercise sessions conducted before and after 6 weeks of niacin supplementation in men with metabolic syndrome (MetS). Niacin dosage was titrated by 500 mg/week from 500 to 1500 mg daily and maintained at 1500 mg daily for the last 4 weeks. PON1 activity, PON1 concentration, myeloperoxidase (MPO), and ox-LDL had no change following the independent effects of exercise and niacin ($P > 0.05$ for all). However, PON1 activity increased by 6.1% ($P = 0.037$) and PON1 levels increased by 11.3% ($P = 0.015$) with the combination of exercise and niacin. The authors concluded that exercise and niacin works synergistically to enhance PON1 activity and concentration with little or no changes in markers of lipid oxidation.

In summary, although there are discrepant findings regarding the niacin and LPO, the majority of literature indicated that niacin intake/ status is negatively associated with LPO and ROS production.

Effect of niacin on the attenuation of reperfusion oxidative injury

Reperfusion injury is the tissue damage that occurs when blood flows into the tissue after a period of ischemia. It has been shown that free radicals [16,17] and inflammatory cytokines [31] have a key role in the reperfusion injury process. Tai *et al.* [32] showed that treatment with niacin, as a precursor of NADH and an effective antioxidant, improved kidney I/R-induced cardiac dysfunction and the severity of myocardial LPO through maintaining myocardial peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a) expression to a level comparable to that of the sham group. The authors also reported that niacin led to a reduction in kidney injury. Niacin is commonly used in treating dyslipidemia because of its ability to decrease lipolysis and the production of very-low-density lipoprotein, and also, it increases the production of high-density lipoprotein [33]. Previously, Brown *et al.* [34] showed that niacin is effective in reducing myocardial I/R injury in patients with dyslipidemia, potentially through reducing plasma lipid. Furthermore, Lamping *et al.* [35] showed that the cardiac protective effects of niacin may be independent of the systemic lipids, and associated with a reduction in free fatty acids uptake and utilization of triglyceride. Additionally, Trueblood *et al.* [33] showed that niacin treatment effectively reduced the cytosolic NADH/NAD^+ ratio during myocardial I/R injury, which helps to sustain mitochondrial respiration function and ATP production.

In the study by Thirunavukkarasu *et al.* [36] the effects of 90 days oral administration of niacin-bound, chromium-based energy formula (40 mg·kg body wt^{-1}·day^{-1}) on the cardiovascular and pathophysiological functions in an isolated rat heart model were investigated in male and female rats. The authors reported that aortic flow, maximum first derivative of developed pressure, left ventricular developed pressure, and infarct size were significantly improved following the niacin formulation comparison with the control group. Energy formula, which includes niacin-bound chromium and D-ribose, might activate adenosine monophosphate-activated protein kinase (AMPK), cause an increase in ATP levels by triggering the ATP-generating pathways and decreasing the energy demand through reducing the ATP consuming process that regulates the cellular energy status, causing cardio protective effects.

Energy formula (EF) supplementation increases the expression of heat shock proteins (HSPs) like HSP-70, -32, and -25. HSP-70 is found to protect cardiac cells against simulated ischemia or thermal stress *in vitro* [37] as well as in a model of ischemia-reperfusion injury via the suppression of inflammatory cytokines [38]. Additionally, Sammut *et al.* [39] reported that HSP-70 upregulation may protect the mitochondrial energy metabolism in the injured heart by repairing the ion channels under stress conditions. HSP-25 (also called as HSP-27) is relatively higher in heart tissue [40] and known to play a role in retaining the redox balance, and also, has a regulatory role in muscle contraction [40]. In addition, the results of functional recovery of EF-treated animals after ischemia might be its amino acids contents which are precursors of important molecules like glutathione that may be responsible for ischemic myocardial protection [41].

Future Directions and Conclusion

The role of niacin as an antioxidant micro-nutrient has been established in a variety of research. The mechanisms through which niacin protects the body against oxidative stress can be retaining the glutathione redox cycle, and also, decreasing NADPH/total NADP+ ratio as well as increasing the NAD+ content. However most of the investigations in this area are limited to experimental studies, these mechanistic studies can be useful for further clinical development of niacin and niacin-related compounds for the treatment of oxidative stress and its complications.

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Conflict of Interest

None

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