

Antiatherogenic Properties of Zinc: Implications in Endothelial Cell Metabolism

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Date accepted: 29 March 1996

ABSTRACT

Zinc is an essential component of biomembranes and is necessary for maintenance of membrane structure and function. There is evidence that zinc can provide antiatherogenic properties by preventing metabolic physiologic derangements of the vascular endothelium. Because of its antioxidant and membrane-stabilizing properties, zinc appears to be crucial for the protection against cell-destabilizing agents such as polyunsaturated lipids and inflammatory cytokines. Zinc also may be antiatherogenic by interfering with signaling pathways involved in apoptosis. Most importantly, we have evidence that zinc can protect against inflammatory cytokine-mediated activation of oxidative stress-responsive transcription factors, such as nuclear factor κ B and AP-1. It is very likely that certain lipids and zinc deficiency may potentiate the cytokine-mediated inflammatory response and endothelial cell dysfunction in atherosclerosis. Thus, the antiatherogenic role of zinc appears to be in its ability to inhibit oxidative stress-responsive factors involved in disruption of endothelial integrity and atherosclerosis. We discuss antiatherogenic properties of zinc with a focus on endothelial cell metabolism. *Nutrition* 1996;12:711–717

Key words: zinc, endothelial cells, lipids, cytokines, atherosclerosis

INTRODUCTION

Zinc is a critical component of biomembranes and is essential for proper membrane structure and function and the activity of numerous enzymes.¹ Factors implicated in the pathogenesis of atherosclerosis include chronic and cumulative metabolic alterations of the endothelium by certain lipids and inflammatory cytokines.^{2–4} Little is known about the requirements and functions of zinc in maintaining the integrity of the vasculature, particularly the vascular endothelium. Because zinc is required for normal cellular repair processes and because atherosclerosis is believed to begin with endothelial cell injury or dysfunction, a low zinc concentration in the plasma or vascular tissues may be involved in either initiation of cell injury, potentiation of oxidative stress and inflammatory response, or inadequate protection against apoptosis (Fig. 1). These events may have important implications during the inflammatory response in the pathogenesis of atherosclerosis⁵ and during times of infection and other stressors when plasma zinc is depressed because of possible redistributions of body zinc pools.

Part of the etiology of atherosclerosis involves damage to or dysfunction of the vascular endothelium.^{6–8} It is now widely recognized that the endothelium is not merely a passive blood-

compatible surface but that it plays an active role in the physiologic processes of vessel-tone regulation and vascular permeability. Endothelial cells are constantly exposed to the blood, which contains various kinds of cells, soluble components, vasoactive substances, toxic wastes, and factors involved in hemostasis, thrombosis, and immune reactions. Various circulating components, including “injurious” and “protective” nutrients, can interact with enzymes, receptors, and adhesion and transport molecules located on the luminal surface of endothelial cells, resulting in further “communication” between blood-borne cells and abluminal tissues. It is clear that maintaining an adequate and constant supply of protective nutrients to the tissues vulnerable to injury (e.g., the vascular endothelium) may make an important contribution to the protective mechanisms that prevent or reduce atherosclerosis. In general, while imbalance in certain blood lipids and inflammatory cytokines is implicated in the development of atherosclerosis, some selected vitamins and minerals, because of their physiologic functions as antioxidants and membrane stabilizers, may exhibit antiatherogenic properties.

The involvement of zinc in the pathogenesis of atherosclerosis is not clear. A decrease in the zinc/copper ratio was observed in the plasma of atherosclerotic men,⁹ and serum zinc concen-

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trations were significantly decreased in rats with experimental atherosclerosis.¹⁰ In addition, zinc concentrations were significantly lower in aortas obtained from hypertensive patients with aortic aneurysms than in control patients or those with hypertensive occlusive tissues.¹¹ Finally, concentrations of serum zinc appear to decrease with age, especially in patients with atherosclerosis.¹² On the other hand, in subjects with significant coronary artery atherosclerosis, no correlation was found between plasma zinc or copper with serum lipids or lipoproteins.¹³ Also, higher levels of zinc have been reported in fibrous atherosclerotic plaques than in normal aortic tissues.¹⁴ A distinct basal expression of copper-zinc and extracellular superoxide dismutases was observed in normal aortic intima-medias, but no clear induction of these mRNAs was detected in atherosclerotic aortas.¹⁵ Even though the relationship between vascular concentrations of zinc, lipids, and the pathogenesis of atherosclerosis is not clear, zinc appears to have distinct protective properties during the inflammatory response in atherosclerosis.¹⁶ Evidence suggests that zinc can act as an endogenous protective factor against atherosclerosis by inhibiting the oxidation of low-density lipoprotein (LDL) by cells or iron.¹⁷ Intravenous injection of acetylated LDL or lipopolysaccharide (LPS) into mice induced a decrease in serum zinc levels, probably as a result of the release of interleukin-1 (IL-1).¹⁸ Interestingly, oral administration of probucol (a hypocholesterolemic agent with antioxidant properties) inhibited the LPS-induced fall in serum zinc levels.¹⁸ In another study, exposure to LPS resulted in a significant fall in plasma zinc and an increase in hepatic zinc concentrations in normal mice but not in mice lacking expression of metallothionein genes.¹⁹ This suggests that metallothionein synthesis is essential for endotoxin-induced liver zinc accumulation. However, plasma concentrations of metallothionein and superoxide dismutase appear not to be affected during zinc supplementation.²⁰ In cultured bovine aortic endothelial cells, zinc-induced tolerance to cadmium cytotoxicity also has been shown to occur without induction of metallothionein.²¹

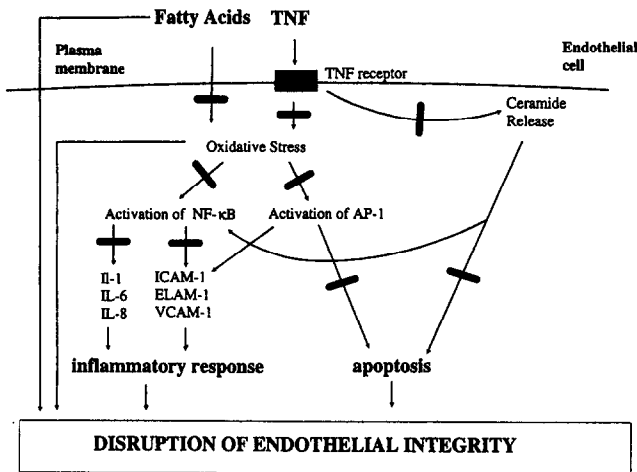


FIG. 1. A schematic diagram illustrating our hypothesis that certain lipids (e.g., fatty acids) can interact with and intensify inflammatory cytokine expression in vascular tissues, leading to disruption of endothelial integrity and contributing to atherosclerosis. We also postulate that zinc is an antiatherogenic nutrient by providing protection against lipid/cytokine-mediated endothelial cell dysfunction. Bold bars represent pathways possibly inhibited by zinc. TNF, tumor necrosis factor; IL, interleukin; ICAM-1, human intercellular adhesion molecule; ELAM-1, endothelial-leukocyte adhesion molecule.

The present review focuses primarily on recent research, which supports our hypothesis that zinc is a critical antiatherogenic nutrient by protecting and stabilizing vascular endothelial cells²² (Fig. 1). It is likely that certain lipids (e.g., fatty acids) will intensify cytokine expression in vascular tissues, leading to endothelial cell dysfunction and contributing to atherosclerosis. Recent evidence suggests that zinc may provide antiatherogenic properties by interfering with mechanisms of lipid/cytokine-mediated endothelial dysfunction (Fig. 1).

ROLE OF ZINC IN MAINTAINING CELLULAR INTEGRITY

In addition to being an essential component of biomembranes,¹ zinc also participates extensively in protein, nucleic acid, carbohydrate and lipid metabolism, and in the control of gene transcription and other fundamental biologic processes.²³ For example, isolated lysosome membranes were protected from oxidative injury in the presence of zinc,^{24,25} and zinc deficiency resulted in oxidative damage to proteins, lipids, and DNA in rat testes.²⁶ Zinc is an essential component of copper zinc superoxide dismutase and is associated with metallothionein, a protein rich in thiolate groups.^{23,27} Zinc can also compete with copper and iron for membrane-binding sites, thus reducing the potential for hydroxyl radical formation via redox cycling. Recently, zinc has been demonstrated to decrease reperfusion injury in isolated rat hearts, presumably by its ability to suppress significantly hydroxyl radical formation after regional ischemia.²⁸ Therefore, in addition to its function as a membrane stabilizer, zinc may have a physiologic role as an antioxidant by protecting sulfhydryl groups against oxidation and inhibiting the production of reactive oxygen by transition metals.^{26,29} Furthermore, dietary zinc deficiency was reported to decrease plasma concentrations of vitamin E,³⁰ suggesting that dietary zinc deficiency may increase the nutritional requirement for vitamin E necessary to maintain adequate plasma concentrations.

Because of its unique properties, zinc may play a critical role in maintaining endothelial cell integrity. In our laboratory, we extensively studied methods to determine zinc deficiency in endothelial cells. These methods included cell culture in low-serum medium (where serum was the only source of zinc) and in media previously exposed to different types of chelating agents (1,10-orthophenanthroline or chelex). These techniques resulted in depletion of intracellular zinc levels and similar metabolic changes.³¹⁻³³

Zinc depletion and supplementation studies in cultured endothelial cells are usually complicated by the fact that most intra- and extracellular zinc is bound to proteins with varying degrees of affinity and that free zinc ion concentrations are very low. Thus, zinc levels used for supplementation studies (as well as deficiency studies, i.e., zinc transport or uptake and saturation into endothelial cells) will depend on the amount of serum in the culture media. For example, we found that when zinc is depleted by culture in 1% serum-containing media, cellular zinc levels can be replenished significantly by supplementation with 10 μ M zinc (Zn^{2+}). Zinc acetate appears to be the best tolerated zinc preparation with the highest levels of absorption after oral intake in human studies.³⁴ We also found that zinc acetate appears to be an effective form of zinc supplementation. Albumin also has been shown to modulate zinc transport into endothelial cells.³⁵ Endothelial cultures can also be supplemented with other divalent cations, such as calcium, magnesium, or cadmium, to demonstrate that zinc is unique in its protective function against lipid/cytokine insults. Cadmium has been shown to competitively inhibit zinc transport into endothelial cells, whereas equimolar concentrations of copper

and magnesium were ineffective.³⁶ Furthermore, zinc supplementation was capable of inducing a tolerance to cadmium cytotoxicity in cultured vascular endothelial cells.³⁷ Interestingly, cadmium and tumor necrosis factor (TNF) exhibited similar cytotoxicity,³⁸ suggesting that TNF-mediated signaling pathways may also be shared by cadmium or zinc.

Using several methodologies of zinc depletion and supplementation, we have shown that zinc is vital to endothelial integrity and that zinc deficiency causes a severe impairment of endothelial barrier function.^{32,33} In zinc-deficient endothelial cells, barrier function was significantly decreased compared with controls. Media supplemented with physiologic concentrations of zinc completely restored the cell integrity. Supplementation with calcium or magnesium, however, did not restore this function, suggesting a unique role of zinc in maintaining normal endothelial integrity. Our data suggest that in zinc deficiency, disruption of endothelial barrier function is related to a change in cell membrane characteristics secondary to altered cytosolic compositional changes. This in turn may cause alterations in the activity of membrane-bound enzymes, particularly the ones that are zinc dependent. Indeed, we showed that the activity of the membrane-bound zinc-dependent angiotensin-converting enzyme (ACE) decreased in zinc-deficient endothelial cell cultures.³² Furthermore, supplementation with zinc completely restored ACE activity. The observed decrease in ACE activity during zinc deficiency may be due to a total endothelial cell zinc loss or to a significant imbalance in the intracellular exchange among subcellular zinc pools.³⁹ Such a redistribution of intracellular zinc may be sufficient to alter activity of membrane-bound enzymes.

ZINC AND PROTECTION AGAINST LIPID-INDUCED ENDOTHELIAL INJURY OR DYSFUNCTION

The endothelium that lines the arterial wall is exposed to high concentrations of lipoproteins that are rich in triglycerides and cholesterol.⁴⁰ When these lipoproteins are elevated, hydrolysis of triglycerides by lipoprotein lipase occurs in proximity to the endothelial surface.⁴¹ Excessive local concentration of fatty acid anions may cause endothelial injury,^{42,43} allowing increased penetration of cholesterol ester-rich remnant lipoproteins, derived from chylomicrons or very-low-density lipoproteins, into the arterial wall. According to this hypothesis, the subsequent events leading to atherosclerotic lesion formation are initiated by the accumulation of these cholesterol-rich lipoprotein remnants in the arterial intima.⁴³

The effects of lipid (e.g., fatty acid) exposure on endothelial barrier function in culture can be expressed indirectly in terms of the movement of a macromolecule (e.g., albumin or LDL) across cultured endothelial cell monolayers.^{44,45} We investigated the effects of oleic acid (18:1n-9)⁴⁴ and other fatty acids on endothelial permeability to albumin.⁴⁶ Albumin-bound palmitic (16:0) and stearic acid (18:0) had little effect on endothelial permeability, but exposure of cell monolayers to linoleic acid (18:2n-6) produced an even greater increase in albumin transfer than did equal concentrations of oleic acid.⁴⁴ Endothelial cell exposure to linoleic acid also affects activities of membrane-bound enzymes, such as Ca^{2+} -ATPase,⁴⁷ induces peroxisomes,⁴⁸ stimulates oxidative stress, and depletes cellular glutathione levels.⁴⁹ In addition, oxidation derivatives of unsaturated fatty acids may be potent disruptors of endothelial barrier function. Indeed, the linoleic acid-mediated increase in transendothelial movement of albumin was greatly exacerbated in the presence of oxidation derivatives of unsaturated fatty acids.⁵⁰ In addition to a marked increase in albumin transfer, exposure of cells to linoleic acid hydroperoxide resulted in a rapid release

of lactate dehydrogenase into the culture medium. This suggests that oxidation of fatty acids significantly increases their cytotoxicity. We reported similar results with cholesterol and its oxidation derivatives.^{51,52} Pure cholesterol, even at high concentrations, did not decrease endothelial barrier function, whereas even small amounts of cholesterol oxidation derivatives, pure or incorporated into LDL, significantly increased endothelial permeability properties to albumin.^{51,52}

To test the hypothesis that zinc may protect endothelial cells against fatty acid-induced injury, we exposed endothelial cells to selected fatty acids using media with and without supplemental zinc. Injury to endothelial cells induced by 90 μM linoleic acid was prevented when culture media were supplemented with zinc but not with calcium or magnesium.⁵³ The mechanism of zinc protection is not clear and may be accounted for in part by its antioxidant property.

ZINC AND PROTECTION AGAINST CYTOKINE-MEDIATED ENDOTHELIAL INJURY OR DYSFUNCTION

Plasma levels of cytokines are elevated during inflammation, infection, or cell injury. In addition, inflammation is an integral part of the development of atherosclerosis. Therefore, inflammatory cytokines, in particular TNF- α , may play a critical role in atherogenesis. TNF has been detected in human atheroma, and increased TNF synthesis and accumulation of TNF have been reported in intimal thickening compared with normal intima.⁵⁴ TNF may act as a potent endothelial-activating factor, and the action of TNF, like those of other inflammatory cytokines (e.g., IL-1, IL-6, and IL-8), may serve to promote coagulation and inflammation.⁵⁵ TNF-activated endothelial cells show distinct time-dependent patterns for expression of various leukocyte adhesion molecules, and recent studies provide evidence of increased adhesion molecule expression in hyperlipidemic models of atherosclerosis. In addition, endothelial cell integrity may be directly compromised by TNF. TNF can directly injure endothelial cells and initiate events that result in increased endothelial permeability.⁵⁶ One of the mechanisms of endothelial barrier dysfunction may be via TNF-mediated induction of endothelial cell apoptosis.⁵⁷

Pathologic conditions related to increased activity of TNF, such as inflammation or infection, may significantly influence zinc metabolism. It is known that during inflammation or infection, there is an internal redistribution of zinc, with zinc being lost from some tissues, such as plasma, and accumulating in other tissues, such as liver. The endothelium may be one tissue from which zinc is lost during the acute-phase response. One may suggest that similar depletion of zinc in endothelial cells may occur in atherosclerosis. To support this hypothesis, it was demonstrated that zinc concentrations were significantly lower in atherosclerotic plaques of abdominal aortas of deceased patients with ischemic heart disease and acute myocardial infarction.⁵⁸ Moreover, our data indicate that there is a depletion of cellular zinc in association with TNF-mediated endothelial cell injury that may lead to disruption of normal membrane integrity.⁵¹

The nutritional status of the endothelium is likely to influence its response to TNF,^{16,59} and a marginal status of protective nutrients (e.g., zinc) may increase the susceptibility of the endothelial cell toward TNF-induced injury. In fact, we have evidence that a disruption of endothelial cell monolayer integrity by TNF can be prevented by pre-enriching cells with zinc.³¹ However, the specific target cells for zinc and mechanisms of action are still uncertain. For example, in different cell systems, zinc has been reported to both decrease and increase the expression of the adhesion molecule ICAM-1.^{60,61} Zinc also has been

shown to diminish the ability of human monocytes to be activated by LPS.⁶² Our data support the hypothesis that zinc may prevent TNF-induced endothelial cell dysfunction, at least in part, due to its antioxidant properties. TNF has been shown to induce endothelial cell oxidative stress and reduce intracellular reduced glutathione (GSH) levels.⁶³ Because many antioxidant systems work in concert, depletion of GSH may further compromise cellular antioxidant defense systems. For example, GSH has been shown to maintain α -tocopherol (vitamin E) levels through its regeneration from the tocopheryl radical.⁶⁴ Although this hypothesis requires further clarification, it is possible that supplementation with zinc can provide an adequate antioxidant protection and prevent oxidant- (such as TNF) mediated depletion of cellular antioxidants.

INHIBITION OF NUCLEAR FACTOR (NF- κ B) A NEW MECHANISM OF ANTIATHEROGENIC EFFECT OF ZINC

Mechanisms of lipid- and cytokine-mediated endothelial cell activation or dysfunction, adhesion molecule expression, and the relationship of these events to atherosclerosis are only speculative at the present time. However, one common mechanism of how diverse stimuli could activate stress-related genes in endothelial cells may be the generation of reactive oxygen intermediates. Lipid oxidation products cause endothelial cell injury,⁶⁵ and cytokines such as TNF can also induce the production of reactive oxygen species in endothelial cells.⁶⁶ Furthermore, biologically modified LDL increase the adhesive properties of endothelial cells.⁶⁷ A transcription factor implicated in many endothelial cell activation responses to injury and stress is NF- κ B.⁶⁸ Zinc may play a role in NF- κ B binding to DNA.⁶⁹ NF- κ B is a critical transcription factor in regulating the cytokine network and hence its activation may be a major consequence toward the pathogenesis of atherosclerosis. Many target genes in endothelial cells contain NF- κ B or NF- κ B-like sites on genes coding for adhesion molecules^{70,71} and inflammatory cytokines. Stimuli known to activate the NF- κ B complex include TNF, IL-1, and LPS, with the common denominator apparently being reactive oxygen species.⁷² We have exciting new evidence showing that certain lipids, such as linoleic acid, can activate NF- κ B.⁷³ A significant activation of NF- κ B by linoleic acid was achieved after a 6-h exposure to the fatty acid, which is the time point where we observed maximal depletion of cellular glutathione. This provides evidence that reactive oxygen intermediates may be important in the role of lipid- or inflammatory cytokine-mediated disruption of endothelial barrier function. Modulation of NF- κ B by antioxidants may have a significant impact on the overall inflammatory cytokine response and endothelial cell dysfunction. We now have evidence that zinc deficiency can activate NF- κ B in endothelial cells. In addition, zinc supplementation attenuated TNF-mediated activation of NF- κ B.⁷⁴

As it was mentioned above, activated NF- κ B can stimulate adhesion molecule expression or inflammatory cytokine production and thus potentiate the overall inflammatory response within the endothelium. Therefore, zinc-mediated inhibition of this transcription factor could attenuate an inflammatory reaction associated with cell injury and thus preserve endothelial cell integrity.

ZINC AND PROTECTION AGAINST ENDOTHELIAL CELL APOPTOSIS

Even though the influence of zinc on apoptosis in several cell systems has been reviewed recently,⁷⁵ little is known about the effect of zinc on apoptotic events in vascular endothelial cells. It is likely that zinc may be antiatherogenic by interfering

with signaling pathways involved in apoptosis. TNF-induced oxidative stress can activate oxidative stress-responsive genes of the immediate early gene family, such as c-jun and c-fos. The Fos and Jun proteins, products of the c-jun and c-fos genes, create another potent transcription factor, AP-1. The role of c-fos, c-jun, and AP-1 in endothelial cell metabolism is not fully understood, but they may be involved in TNF-mediated expression of adhesion molecules, such as ICAM-1⁷⁶ and TNF-induced apoptosis.⁷⁷ Recent investigations also indicate that the ceramide pathway (i.e., sphingomyelin hydrolysis to ceramide by a sphingomyelinase) is a critical signal transduction pathway in TNF-mediated apoptosis.^{76,78,79} Internucleosomal DNA fragmentation, which can lead to apoptosis, was induced by a synthetic cell-permeable ceramide analogue and inhibited by zinc ion.⁸⁰ Two agents known to inhibit TNF-mediated cytotoxicity, zinc and 3-aminobenzamide, were also shown to inhibit TNF-induced apoptosis in U937 tumor cells.⁸¹ Furthermore, zinc has been shown to significantly inhibit TNF cytotoxicity as well as DNA fragmentation in L929 target cells.⁸² On the basis of this information, one may suggest that TNF-mediated endothelial barrier dysfunction may be in part due to initiation of endothelial cell apoptosis. Interestingly, recent evidence suggests that apoptosis is also involved in the regulation of aortic intimal thickening during atherosclerosis.⁸³ We now have preliminary evidence that supplementation of cultured endothelial cells with zinc can inhibit TNF-induced AP-1 expression (unpublished data). Therefore, zinc-induced inhibition of AP-1 can be a critical mechanism that explains how zinc protects against programmed cell death and, possibly, against disruption of endothelial integrity.

LIPID/CYTOKINE-MEDIATED ENDOTHELIAL CELL INJURY OR DYSFUNCTION: A NEW AREA TO STUDY CELLULAR EFFECTS OF ZINC

Endothelial cell injury mediated by selected lipids (e.g., fatty acids) may increase the production and circulating concentrations of cytokines involved in the atherosclerotic disease process. Thus, certain diet-derived lipids (pure or oxidatively modified) may cause endothelial cell injury or dysfunction that may lead to adhesion molecule activation and monocyte recruitment. These events may potentiate the overall inflammatory response to injury by increasing cytokine release in proximity to the endothelium, which may further disrupt endothelial barrier function. Recent evidence has suggested a direct link between generation and release of free fatty acids and TNF- α synthesis. It was shown that lipoprotein lipase, an enzyme associated with the luminal site of endothelial cells, can induce expression of the TNF gene and TNF production in macrophages.^{84,85} This suggests that the release of free fatty acids during lipoprotein lipase-mediated hydrolysis of triglyceride-rich lipoproteins may be accompanied by increased production of TNF. Thus, endothelial cells can be exposed simultaneously to high levels of free fatty acids and TNF.

Certain lipids and cytokines can independently, but more markedly in concert, induce cellular dysfunction that leads to a disruption of endothelial barrier function.⁸⁶ These events may be associated in part with an increase in oxidative stress or perturbation of calcium homeostasis. Our data suggest that when presented for 6 h to endothelial cells, linoleic acid alone, and especially in concert with TNF, can contribute to increased oxidative cellular stress.⁸⁶ These data provide evidence that certain lipids and cytokines may synergistically increase the generation of reactive oxygen species. Similar results were observed when studying the effect of lipids and cytokines on intracellular calcium changes.⁸⁶ Even though either linoleic acid

or TNF exposure alone caused a significant increase in intracellular calcium, the combination of linoleic acid plus TNF most markedly increased intracellular calcium. These data suggest that perturbations in calcium homeostasis are important events that lead to endothelial barrier dysfunction. Little is known about the possibility that zinc may be antiatherogenic by acting as a calcium antagonist. However, our findings about lipid/cytokine-mediated increases intracellular calcium and the fact that zinc can protect against lipid/cytokine-mediated endothelial cell dysfunction supports this hypothesis. The cytoprotective protective property of zinc, possibly as a calcium antagonist, has been demonstrated in other cell systems.⁸⁷⁻⁸⁹ Selected lipids, such as linoleic acid, also can affect TNF-mediated endothelial cell programmed cell death. Although linoleic acid alone did not stimulate apoptosis in cultured endothelial cells, this fatty acid potentiated TNF-induced apoptotic cell death.⁹⁰

These findings suggest that zinc could be a crucial nutrient for the protection against cell-destabilizing agents such as cytokines and polyunsaturated lipids (Fig. 1). Zinc exerts both antioxidant and membrane-stabilizing properties and has been shown to attenuate programmed cell death. Moreover, zinc protects endothelial cells against both fatty acid- or TNF-induced injury.^{31,53} However, the effectiveness of zinc in maintaining endothelial integrity against combined effects of selected fatty acids and TNF remains to be determined.

CONCLUSION

Damage to or dysfunction of endothelial cells is considered to be a critical event in the causes of atherosclerosis. The vascular endothelium plays an active role in the physiologic processes of vessel-tone regulation, inflammatory responses, and vascular permeability. Endothelial cell dysfunction may disturb the normal communication of these cells with plasma components, blood-borne cells, and abluminal tissues. There is evidence that zinc is vital to endothelial integrity and that zinc can protect endothelial cells against lipid- or inflammatory cytokine-mediated insults (Fig. 1). These observed protective properties may be due in part to the ability of zinc to act as an antioxidant and a membrane stabilizer. Most of all, zinc may have specific antiatherogenic properties by inhibiting oxidative stress-responsive transcription factors that are activated during an inflammatory response in atherosclerosis. Thus, the continued discoveries of the unique properties of zinc as an antioxidant, membrane stabilizer, and inhibitor of signaling pathways involved in inflammatory response and apoptosis warrant further research in the role of zinc in endothelial cell metabolism and atherosclerosis.

ACKNOWLEDGMENT

Supported in part by grants from the National Institutes of Health (1P01 HL36552), the Veterans' Administration, the General Clinical Research Center (MO1 RR02602-08), and the Kentucky Agricultural Experiment Station.

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