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Review Article

The role of zinc deficiency in endothelial dysfunction

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Abstract

Endothelial dysfunction is the key element for developing cardiovascular disease. The crucial role of endothelium mandate searching for possible reversible causes of its dysfunction. Zinc is one of trace elements and essential micronutrients and enters in the component of more than 300 metalloenzymes which have roles in the degradation of carbohydrates, lipids, proteins and nucleic acids. Moreover, Zinc exerts antioxidant properties through different mechanisms including the induction of potent antioxidant metallothionein. The zinc supplementation can prevent endothelial dysfunction via several mechanisms such as the inhibition of the increase in NF-κB-induced inflammatory markers, the induction of an increase in eNOS expression levels and NO availability, the activation of PPAR receptor and the inhibition of TNFα activation-induced apoptosis. Thus, screening for zinc deficiency in general population especially, people with chronic diseases and with nutritional problems is highly recommended. This review describes the role of zinc deficiency in endothelial dysfunction.

Keywords: Endothelial dysfunction, Zinc, antioxidant, NF-κB, apoptosis.

1. Introduction

The endothelium covers the whole entire wall of all vessels from the heart to small vessels. The endothelial cell ensures a large variety of functions: synthesis and secretion of various molecules, including vasodilator and vasoconstrictor factors, control of smooth muscle proliferation, exchanges of molecules between the plasma and interstitial fluid. The endothelial cells respond to physical and chemical stimuli such as pressure, shear stress, and pH [1] and respond also to other stimuli like microparticles and pro-inflammatory mediators. In response to stimuli, the endothelium has the capacity to regulate local vascular homeostasis by maintaining the balance between vasodilation and vasoconstriction [2]. Either endothelial cell dysfunction or activation plays a major

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role in the development and the progression of cardiovascular diseases. Indeed, the recruitment of inflammatory cell (leukocytes) by activated endothelial cells is one of the key events in disease progression [3]. Many risk factors are involved in activating endothelial cells including disturbed shear stress, reactive oxygen species and inflammatory mediators [4]. Zinc is one of the essential micronutrients and enters in the component of more than 300 metalloenzymes having roles in degradation of carbohydrates, lipids, proteins and nucleic acids as well as in the metabolism of other micronutrient [5, 6]. The human nutritional requirement for Zinc has been established, which come second to iron. The adult human body contains 2 grams of zinc [7]. Zinc is located relatively throughout the body, explains its outstanding biological value through its ability to participate in strong but readily exchangeable ligand binding [8]. The zinc incorporates into myriad biological systems via interaction with a wide range of organic ligands. The favouring feature of zinc ion (Zn++) which makes it a stable ion in a biological medium is the ability to not participate in redox reactions [9]. The biological role of zinc is well documented in structure and function of proteins, including enzymes, hormonal receptor sites, transcription factors and biologic membranes. Furthermore, it has crucial roles in DNA and RNA metabolism [10]. The outer most advances in our understanding the biological role of zinc was the identification of proteins that contain a zinc finger motif, a repeating pattern of amino acids with conserved residues of cysteine and histidine at the base to which zinc binds in a tetrahedral arrangement. Considering the fact that more than 3% of all identified human genes contain zinc finger domains, we can conclude that zinc plays a major role in gene expression [11]. The zinc has cytoprotective functions via suppressing major signalling pathways involved in apoptosis as well as via direct effects on apoptosis regulators triggered in response to a reduce in its intracellular concentrations [12].

2. Zinc as antioxidant agent

Zinc deficiency has been shown to be associated with inductive oxidative stress which ultimately can affect cell function, proliferation and survival via activates/inhibits oxidant-sensitive transcription factors leading to disease [13]. Zinc exerts its antioxidant properties through several mechanisms. It stabilizes macromolecules against radical-induced oxidation, competes with pro-oxidant metals (iron and copper) for binding sites, thus decreasing their ability to form free radicals and inhibits excess production of free radicals by biological systems. Zinc is an essential part of the intracellular and extracellular antioxidant enzyme superoxide dismutase (SOD) and it induces the potent antioxidant metallothionein, which is an efficient hydroxyl radical scavenger [13-15]. Metallothionein protein has a critical role in the homeostasis of essential metals such as zinc and copper, and detoxification of heavy metals such as cadmium and also protection against oxidative stress [16]. Based on its antioxidant properties and membrane-stabilizing properties, zinc appears to be crucial for the protection against cell-destabilizing agents such as polyunsaturated lipids and inflammatory cytokines. Eventually, zinc can provide antiatherogenic properties by preventing metabolic and physiologic derangements of the vascular endothelium [17]. Moreover, it has been suggested that zinc supplementation in humans may lead to reduced generation of tumor necrosis factor alpha and oxidative stress markers [18]. In the same context, zinc supplementation was shown to lead to downregulation of the inflammatory cytokines TNF-alpha and IL-1beta [19].

To better understanding the role of zinc in the redox signalling pathway, we should know that the unique chemical nature of zinc determines its central position in the cellular redox signalling network. Indeed, to create a redox active environment, the zinc should binds to sulphur ligand, otherwise zinc by itself is redox inert. While the reduction in the oxidized sulphur ligand promotes zinc binding, the oxidation of the ligand mobilizes zinc. Thus the reversible oxidation of the sulfur ligand is coupled to the reversible zinc release from the protein, providing redox control over zinc availability. There are types of proteins that bind to zinc called “redox zinc swiches” which are controlled by cellular concentrations of both oxidants and zinc. The redox zinc swiches decide the ultimate function of zinc in the cell metabolism; both modulating enzymatic activity, molecular chaperone activity, and binding interactions or modulating signal transduction, metabolic energy generation, mitochondrial function, and gene expression. To maintain redox homeostasis, it is essential to keep tight control of zinc availability, because both inadequate and excessive cellular zinc will elicit oxidative stress [20].

3. Effect of zinc deficiency on vascular endothelial cell

Zinc deficiency leads to induction of vascular pro-inflammatory parameters accompanied with NF-κB and peroxisome proliferator activated receptor (PPAR) signalling pathway activation. *In vitro* and *in vivo* study has tested the hypotheses that zinc deficiency lead to inflammatory activation and vascular endothelial dysfunction [21]. It has been shown that cultured vascular endothelial cells subjected to zinc deficient state have increased oxidative stress and induction of COX-2 and E-selectin gene expression as well as monocyte adhesion [21]. Furthermore, the NF-κB Inhibitor significantly reduced the zinc deficiency-induced COX-2 expression, suggesting a main role of NF-κB signalling pathway [21]. The effect of PPAR alpha and gamma agonists on the TNFα-induced inflammatory response in zinc-deficient endothelial cells has been also evaluated [22]. In zinc-deficient cells, PPAR agonists tested were unable to decrease the TNF-alpha-induced inflammatory genes (VCAM-1 and IL-6). Interestingly, the addition of zinc to cultured endothelial cells enables PPAR agonists to reduce the TNF-alpha-induced inflammatory response indicating that that PPAR alpha and -

gamma DNA binding activity requires the presence of zinc [22]. Zinc has also shown to exert protective effect against upregulation of inflammatory cytokines and endothelial cell dysfunction by preventing cytokine-mediated (TNFα) activation of oxidative stress sensitive transcription factors (NF-κB and AP-1 binding) [23] . In the same context, zinc deficiency has been suggested to potentiate the pro-apoptotic effects of specific polyunsaturated fatty acids (linoleic acid) and pro-inflammatory cytokines (TNFα) and to be associated with activation of signal transduction leading to apoptosis via upregulation of caspase genes [24]. Furthermore, enhanced apoptosis was observed in metallothionein (potent antioxidant induced by zinc) null cell incubated with potent cytotoxic anticancer agents, like cytosine arabinoside, bleomycin, melphalan indicating that metallothionein acts as apoptotic regulator factor [25]. Zinc supplementation on endothelial cells subjected to pro-oxidation state (advanced glycation end products) significantly enhanced eNOS up-regulation, enzymatic activity and increased intracellular NO production and reduced NF-κB activation [26]. Recently, it has been shown that zinc finger transcription factor ZFP580 enhances the differentiation of endothelial progenitor cell into vascular endothelial cell. The apoptotic vascular endothelial cells as consequences of cell activation or dysfunction need to be replaced by healthy endothelial cell derived from endothelial progenitor cell in the bone marrow in the process named re-endothelialization. ZFP580, a zinc finger transcription factor has been found to enhance the differentiation of endothelial progenitor cells into healthy endothelial cells by upregulating the expression of eNOS and the bioavailability of nitric oxide as well as the vessel formation both in vitro and in vivo [27].

4. Conclusion

The cellular zinc state is very important for regular cell metabolism, growth and proliferation. The deficiency state leads ultimately to endothelial dysfunction through different mechanisms (Figure 1). However, it might be difficult to measure the exact cellular level of zinc *in vivo*, but taking into consideration the blood zinc level and general conditions including nutrition and metabolism rate of the individual we can justify the decision to start zinc replacement therapy and supplementation in majority of cases.

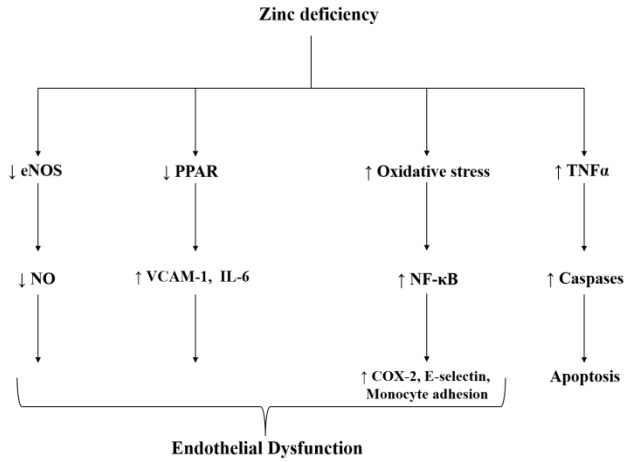

Figure 1. Schematic representation of the signalling pathways regulated by zinc deficiency leading to endothelial dysfunction.

Author contributions

R.KH. S and A.H equally contributed to the writing of this review. R.KH. S designed the figure.

Conflicts of Interest

The authors declare no conflicts of interest.

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