Is Zinc Deficiency an Independent Risk Factor in the Causation of Ischemic Heart Disease? A case Control Prospective Study to Estimate Serum Zinc Levels in Patients of Ischemic Heart Disease

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- Illustration 2
- Illustration 3
- Illustration 4
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Abstract

Background: Zinc deficiency can induce a state of endothelial activation which is characterized by a pro-inflammatory, proliferative and procoagulatory milieu that favors all stages of atherogenesis. Much less attention has been paid to micronutrients, and particularly to zinc. The aim of the study was to determine the alterations of serum zinc levels in patients of Ischemic heart disease and to correlate the variations with parameters of oxidative stress so as to determine the antioxidant potential of zinc in protection against atherosclerosis.

Research design: The study included 50 non diabetic chronic ischemic heart disease patients and 50 normal healthy individuals, in the age range of 40-75 years. All the subjects were evaluated for serum zinc, super oxide dismutase(SOD), malondialdehyde (MDA), total cholesterol, triglycerides, very low density lipoprotein (VLDL), low density lipoprotein( LDL) and high density lipoprotein (HDL) cholesterol estimations. The results obtained were statistically compared with the normal healthy control subjects.

Results and Discussion: As compared to the control group, the patient group showed lower serum zinc (p<0.001) and Superoxide dismutase levels (p<0.001) but higher serum MDA levels (p<0.001) signifying the underlying oxidative stress. Serum total cholesterol, triglycerides, VLDLc, LDLc, were significantly higher but the HDLc was lower highly significantly in the patient’s group as compared to normal control subjects. Statistically insignificant variations of serum zinc levels were observed with the age of the patients and the duration of the disease.

Conclusion and Recommendations: Zinc deficiency induces oxidative stress and can progress to atherosclerosis. A timely supplementation with the required amount of zinc can prevent the onset of oxidative stress induced endothelial dysfunction and its progression to atherosclerosis.

Introduction

Atherogenesis is a complex process involving mechanical, chemical and biological factors. [1] Recent insight into the basic mechanisms involved in atherogenesis indicate that deleterious alterations of endothelial physiology, also referred to as endothelial dysfunction, represents a key early step in the development of atherosclerosis and is also involved in plaque progression and the occurrence of atherosclerotic complications. Most, if not all risk factors that are related to atherosclerosis and cardiovascular morbidity and mortality, including traditional and nontraditional risk factors, are also found to be associated with endothelial dysfunction[2]. Many of these risk factors, including hyperlipidemia, hypertension, diabetes and smoking are associated with overproduction of reactive oxygen species or increased oxidative stress.[3] Hence increased oxidative stress is considered a major mechanism involved in the pathogenesis of endothelial dysfunction and may serve as a common pathogenic mechanism of the effect of risk factors on the endothelium.[4]

[Illustration-1] There is evidence that certain antioxidant nutrients and adequate antioxidant enzyme activities may protect against atherosclerosis by preventing metabolic and physiologic derangements of the vascular endothelium [5]. Of particular interest is zinc, because it may function as an antioxidant and membrane stabilizer [6]. Epidemiological studies suggest that in some population groups lower serum levels of zinc are inversely associated with coronary artery disease [7]. Mechanisms of the protective function of zinc in the pathogenesis of atherosclerosis, including vascular cell injury or dysfunction and the inflammatory response, are not yet clear[8]. Zn is required for structural and functional integrity of more than 2000 transcription factors and 300 enzymes. Therefore, almost every signaling and metabolic pathway is in some way dependent on at least one, and often several, Zn-requiring proteins [9]. There is evidence suggesting that zinc can act as an endogenous protective factor against atherosclerosis.
by inhibiting the oxidation of LDL by cells or transition metals [10]. Because of its antioxidant and membrane-stabilizing properties, zinc appears to be crucial for protection against cell destabilizing agents such as inflammatory cytokines and polyunsaturated lipids [11]. Because zinc is a micronutrient with indirect antioxidant activity, it might be relevant to assess its role in the Atherogenesis.

The objective of the present study was to determine

1. The variations of serum zinc levels in patients of Ischemic heart disease as compared to control subjects
2. The correlation between serum zinc levels and the degree of oxidative stress and
3. The potential use of serum zinc levels as predictors of underlying endothelial dysfunction in predisposed individuals.

Research Design

The study included 50 non diabetic chronic ischemic heart disease patients and 50 normal healthy individuals, in the age range of 40-75 years. The subjects with family history of IHD, chronic smokers, known diabetics and the subjects with history of renal or liver disorder or any other chronic disease were not included in the study. All the subjects were evaluated for serum zinc, serum total cholesterol (TC), triglycerides(TG), high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C) and low density lipoprotein cholesterol and (LDL-C) concentrations. All the subjects were also evaluated for Superoxide dismutase enzyme and Malondialdehyde estimations to assess the degree of oxidative stress. The comparisons were made between the levels of healthy normal individuals and the ischemic heart disease patients.

All blood specimens were drawn at 8:00 A.M. after a 12-h fasting. Samples were centrifuged within 1 hour. The levels of serum total cholesterol, triglycerides and high density cholesterol (HDL) were estimated by Human Diagnostics Reagent (Max-Planck- Ring 21 D-65205 Wiesbaden Germany) adapted to 550 express plus auto analyzer (Ciba corning diagnostics corporation, 63 north street, Medfield, MA 02052-9990, USA). Low density cholesterol (LDL) was measured by enzymatic method[12].

The estimation of MDA in serum was done by the method of Kei Satoh. [13] The color produced by the reaction of thiobarbituric acid with MDA was measured at 530 nm with the help of spectrophotometer. The results were expressed as nmol/ml . SOD was assayed by the method of Marklund and Marklund [14] modified by Nandi et al . [15] This method is based on the ability of SOD to inhibit auto-oxidation of pyrogallol under specific conditions. Reading was taken at 420 nm and expressed as units/ml. Serum Zn measurement was performed by flame atomic absorption spectrophotometry with deuterium background correction (Perkin-Elmer model 5000) [16]. The case history and complete clinical examination of each of the subjects was recorded. All the results were compared with those of normal healthy individual and these results were expressed as mean ± SD. The comparisons were done by using student 'T' test on the number of variables for each parameter. The research protocol was approved by local ethical committee and informed consent was taken from all the subjects under study.

Results and discussion

In the present study majority of the patients (52%) were females and were in the age group of 61-70 years implying thereby that menopause opens the road to atherosclerosis. Serum zinc levels amongst patients were significantly lower (Illustrartion-2) as compared to control group (p<0.001). All the subjects were distributed in to three groups based on the age, Group I, II and III (Illustration-3). In both the study subjects serum zinc levels were found to be falling with the advancing age signifying thereby the decreased anti oxidant defense against oxidants and a rising predisposition for atherosclerosis even in the control subjects. Based on serum zinc level the study subjects were classified in to three groups, A, B and C with the values ranging between 30-50, 51-70 and above 71 µg/dl . Majority of the patients were having serum zinc level ranging between 51-70 ?g/dl, signifying the loss of protection with the onset of zinc deficiency. The least levels observed were between 30-50µg/dl in some of the patients (Illustration-2).

There are several mechanisms by which zinc might be capable of providing protection against atherogenesis. The enzyme superoxide dismutase, an endogenous antioxidant enzyme loses its functional potential upon loss of its zinc atom [17], zinc protects sulfhydryl groups against oxidation and inhibits the production of reactive oxygen by transition metals, in addition to its function as a membrane stabilizer [18]. Dietary zinc
deficiency is also reported to lower lymphatic absorption of vitamin E [19] and decrease concentrations of this vitamin in plasma [20] and selected organs [21], suggesting that dietary zinc deficiency may increase the nutritional requirement for vitamin E necessary to maintain adequate plasma and tissue concentrations thus predisposing more for oxidative stress induced cell injury.

As an antioxidant, zinc has membrane-stabilizing properties and is said to preserve endothelial function [22] . Zinc can protect endothelial cells against tumor-necrosis-factor-? (TNF-?)-induced cell injury [23], and one of the underlying mechanisms could be the ability of zinc to down-regulate oxidative stress-sensitive transcription factors. The fact that zinc can also in part block genes encoding for inflammatory cytokines, such as IL-6 or IL-8, in endothelial cells strongly supports the hypothesis that adequate zinc nutrition may protect against inflammatory diseases such as atherosclerosis by inhibiting the activation of oxidative stress-responsive transcription factors, as well as expression of inflammatory cytokines. [24]

In the present study, an inverse relationship was observed between the severity of the disease and the serum zinc levels . Although statistically insignificant but certain variations were also observed in terms of decreasing serum zinc levels and increasing duration of the disease, implying the loss of protective effects of zinc with the progression of the disease. Serum superoxide dismutase (SOD) level was found to be lower in the patient as compared to control subjects. Age related variations were also observed. The difference was significant statistically in group I and II while it was statistically insignificant in group – III subjects (Illustration-3). This might be due to advancing age, since as the age advances the oxidative stress also increases.

Superoxide dismutase (SOD) is the most important antioxidant enzyme synthesized in response to oxidative stress. It protects the cells from damages caused by superoxide anion (O2-) and H2O2[25]. The decrease in activity of SOD could be due to decreased Zinc levels and this explains the indirect antioxidant role of zinc [17]. The lowered serum SOD activity amongst such patients could also be explained by the fact that initial increased SOD activity leads to excessive production of H2O2 which is inhibitory to the activity of SOD. H2O2 rapidly reduces Cu (in Cu-Zn-SOD) at the active site and then more slowly inactivates the reduced enzyme [26]. Statistically insignificant variations of serum SOD levels were observed amongst males and females of study subjects; signifying the equal predisposition of each group against oxidative stress.

Hydroxyl radicals produced as a result of metal catalyzed reactions are highly reactive and can oxidize lipids giving rise to lipid peroxidation. Malondialdehyde (MDA) is a major end product and an index of lipid peroxidation. A significant increase in serum MDA level (p<0.001) was observed in patients as compared to controls (Illustration-2). The increase in MDA levels observed could be due to increased oxidative stress or decrease in anti oxidant defense mechanisms.[27] The serum SOD was falling but serum MDA levels were found to be rising amongst both the study groups (controls as well as patients) with advancing age. The maximum concentration was observed in group III (of the age range of 61-70 years) suggesting that oxidative stress increases with the advancing age. Upon comparison, the difference between the levels of serum SOD and MDA in age matched normal individuals and patients was statistically highly significant (p<0.001) (Illustration 3).

An inverse relation of serum SOD activity was observed with serum MDA levels. With the fall in serum SOD, serum MDA levels were found to be rising signifying excessive production or decreased quenching of free radicals. Zn levels were found to be positively related with SOD levels. In the subjects with low zinc levels , levels of SOD were also lower but levels of MDA were higher indicating the presence of oxidative stress.

All the patients were having statistically higher serum total cholesterol, high serum triglycerides, high serum VLDLc and LDLc but lower serum HDc levels in comparison to the control subjects. (Illustration-4 and 5).The ratios of Serum total cholesterol/serum HDLc and Serum triglyceride/ serum HDLc were also significantly higher in the patient group as compared the normal control subjects. Dyslipidemia is also well-known accelerating risk factors for atherosclerosis. [28] .This compromised state of oxidative stress in the presence of zinc deficiency produces low resistance to chemically induced oxidant injury, and produces high vulnerability of lipoproteins to oxidation thereby enhancing the risk for I.H.D.

Conclusion & Recommendations

Although it is difficult to prove whether zinc deficiency
is a cause or a consequence but it can be said based on the observations that zinc deficiency is certainly correlated with oxidative stress which is the main culprit behind the pathogenesis of atherosclerosis. The administration of antioxidants would be expected to be a reasonable strategy to treat this disorder. A timely supplementation with the required amount of zinc will prevent the onset of oxidative stress induced endothelial dysfunction and its progression to atherosclerosis. The screening of the predisposed or high risk individuals can be done by the set of Serum Zinc, SOD and MDA levels. These investigations could be considered the early markers of oxidative stress and the related endothelial dysfunction. A close attention is required to be paid to this ‘mineral of life.’

Acknowledgements

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References

23. Hennig B, Wang Y, Ramasamy S, McClain CJ:


Illustrations

Illustration 1

Showing the central role of oxidative stress in the causation and progression of Atherosclerosis
TABLE 1: Distribution of patients into groups as per serum zinc levels and correlation of serum SOD and MDA levels among patient groups.

Range of Serum zinc levels in different patient groups-

Group A = 30 to 50 µg/dl, Group B = 51 to 70 µg/dl and Group C = >70 µg/dl.

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum Zn Level (µg/dl) Mean ± SD</th>
<th>Serum SOD Levels (U/ml) Mean ± SD</th>
<th>Serum MDA Levels (U/ml) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 50)</td>
<td>99 ± 8.3</td>
<td>4.08 ± 0.31</td>
<td>2.39 ± 0.13</td>
</tr>
<tr>
<td>Patient Group A</td>
<td>42.9 ± 7.87*</td>
<td>2.83 ± 0.38*</td>
<td>5.84 ± 1.72*</td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Group B</td>
<td>62.5 ± 4.88*</td>
<td>2.78 ± 0.47*</td>
<td>5.47 ± 1.58*</td>
</tr>
<tr>
<td>(n = 30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Group C</td>
<td>77.3 ± 5.19*</td>
<td>2.67 ± 0.36*</td>
<td>5.14 ± 1.75*</td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p value is < 0.001 highly significant.
Illustration 3

TABLE 2: Comparison of serum ZINC, SOD and MDA levels according to age groups

<table>
<thead>
<tr>
<th>Group</th>
<th>ZINC Levels (µg/dl)</th>
<th>SOD Levels (U/ml)</th>
<th>MDA Levels (U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>(Age in years)</td>
<td>(n = 4)</td>
<td>(n = 10)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>Group – I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(40 to 50)</td>
<td>118 ± 8.1</td>
<td>76.4 ± 11.1*</td>
<td>4.39 ± 1.36</td>
</tr>
<tr>
<td></td>
<td>(n = 4)</td>
<td>(n = 10)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>Group – II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(51 to 60)</td>
<td>96 ± 9.2</td>
<td>63.8 ± 8.4*</td>
<td>4.09 ± 0.99</td>
</tr>
<tr>
<td></td>
<td>(n = 18)</td>
<td>(n = 19)</td>
<td>(n = 18)</td>
</tr>
<tr>
<td>Group – III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(61 to 70)</td>
<td>83 ± 6.5</td>
<td>58.4 ± 7.6*</td>
<td>3.77 ± 0.40</td>
</tr>
<tr>
<td></td>
<td>(n = 28)</td>
<td>(n = 21)</td>
<td>(n = 28)</td>
</tr>
</tbody>
</table>

*P < 0.001
Illustration 4

TABLE 3: Comparison of lipid profile in different study subjects

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Lipid profile</th>
<th>Control (Range)</th>
<th>Control (Mean ± SD)</th>
<th>Patients (Range)</th>
<th>Patients (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Serum total cholesterol (mg/dl)</td>
<td>155-210</td>
<td>177.4±16.98</td>
<td>172-275</td>
<td>226.4±20.42*</td>
</tr>
<tr>
<td>2</td>
<td>Serum Triglycerides (mg/dl)</td>
<td>110-162</td>
<td>142.7±11.48</td>
<td>109-240</td>
<td>174.29±25.22*</td>
</tr>
<tr>
<td>3</td>
<td>Serum VLDL (mg/dl)</td>
<td>22-32.4</td>
<td>28.5±2.26</td>
<td>21.8-48</td>
<td>35.2±7.07*</td>
</tr>
<tr>
<td>4</td>
<td>Serum LDL (mg/dl)</td>
<td>67.9-115</td>
<td>96.9±14</td>
<td>99-204</td>
<td>150±22.8*</td>
</tr>
<tr>
<td>5</td>
<td>Serum HDL (mg/dl)</td>
<td>40-58</td>
<td>52.1±6.09</td>
<td>33.5-55</td>
<td>40.76±4.8*</td>
</tr>
</tbody>
</table>

*p<0.001 (Highly significant)
Illustration 5

Comparison of Mean values of lipid parameters

Comparison of Mean values of lipid parameters

![Graph showing comparison of lipid parameters](image)
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