Investigating the Effect of Oral Administration of Zinc Sulfate on Some Acute Phase Proteins of Serum Antioxidants and Thyroid Hormones in Women with Diabetes Type II and Comparing it with Animal Model (Rat)

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Abstract

Introduction Diabetes is a non-communicable disease that is very common and costly and it has been known as one of the major causes of death in the world, manifested in the form of gradual increase in blood glucose concentration and reduced blood content or disorder in insulin signaling pathway. In this regard, many researchers concluded that minerals play a significant role in controlling blood sugar and improving the general state of diabetic patients. Therefore, the effect of oral administration of zinc as a micronutrient that has the insulin-like properties and involved in the production, storage, and secretion of insulin with different doses was studied in both human and animal models (rats).

Methodology Human study includes four groups, in which one group was positive control group and three other groups received 25, 12.5, and 50 mg zinc on daily basis, and animal study included five groups including positive control group, negative control group, and three groups received 25, 12.5, and 50 mg zinc per kg of food. It should be stated that to create diabetes in rats, Streptozotocin drug with dose of 45 kg/mg and citrate buffer solvent injected in the form of IP were used. Results In a recent study, we concluded that study groups received different doses of zinc showed significant difference with control groups in both human and animal models, in other measured parameters such as acute phase proteins like CRP, total antioxidant capacity (TAC), malondialdehyde (MDA), and FT3 thyroid hormone FT3 in addition to the blood glucose reduction. Generally, it can be concluded that by taking zinc, acute phase protein reduced in these patients and by strengthening the body immune system through increasing the antioxidant capacity, it leads to reduced malondialdehyde.

Keywords: Diabetes disease, Human and rat, Acute phase protein, Total antioxidant capacity, Malondialdehyde. Thyroid hormone FT3- blood glucose.

Introduction

Minerals account for 2 to 5% of body weight, which 75 percent of this amount is in bones, 16 elements of minerals are involved in the metabolism of the body, known as essential minerals. These 16 elements are divided into two categories according to the density in the body:

Macro mineral

Micro mineral

Macro minerals in the body have greater density compared to micro minerals, and content of macro minerals are expressed based on percentage, and they include: sodium, chloride, calcium, phosphorus, potassium, magnesium and sulfur. The amount of micro minerals is low in the body and they are expressed based on PPM or μg / dl. This group includes iodine, iron, copper, selenium, molybdenum, cobalt, manganese and zinc [1]. Diabetes is a non-communicable disease that is very common and costly and causes numerous diseases and deaths in world. One of the most important of these diseases includes cardiovascular diseases that are the main cause of death in diabetics. Diabetes is one of the five leading causes of death in the world [2]. Zinc as a micronutrient is involved in the growth and development of the body, especially in the development and enhancement of the immune system and in metabolism of carbohydrates, fats, proteins, as well as...
reproduction, and mineralizing bone, and gene expression. In 1934, it was found for the first time that zinc is necessary for growth and health of rats so that zinc deficiency in all species caused severe loss of appetite, reduced growth, and reduced efficiency and reproductive activity and skin abnormalities (Mineral Nutrition; [3]. Body of a 70 kg man has about 3 to 2 grams of zinc that among the tissues, zinc has the lowest and prostate had the highest zinc. Zinc is found at very low level in plasma, but its concentration in tissues and cells is higher. Zinc plays an important role in the production, storage and secretion of insulin so that zinc in 1934 was considered as a component of the crystal insulin [4-8].

Zinc supplement can improve the blood sugar in diabetes (both type I and II). For this reason, it seems that it has insulin-like effects [9, 10]. It has been found for approximately 70 years that the concentration of zinc in the pancreas in diabetic patients is much lower than its concentration in the pancreas of healthy people and laboratory animals with lack of zinc have much less sensitivity to insulin (Cellular and Molecular). This sentence that zinc is emulorator of insulin means that incubation of cells and tissues with ion (Zn) has similar effects in glucose and fat metabolism, such as insulin effects [11].

Insulin-like properties of zinc are clearly seen in cell culture, in which zinc has been replaced by insulin (Cellular & Molecular; [9, 12]. Zinc is involved in insulin signaling pathway, in the phosphorylation of insulin receptor β subunit and in activating the Tyrosines [13, 14]. Zinc deficiency is the fifteenth major health risk in developing countries. Zinc deficiency is especially seen in people suffer recurrent infections or parasitic diseases. In general, the immune system of body requires zinc for its normal function as well as preventing infectious diseases such as diarrhea, pneumonia and malaria [15, 16].

The immune system of body uses two innate and adaptive response mechanisms to combat with pathogens. Zinc is necessary for the normal functioning of both defense mechanisms. In addition, zinc plays major role in production and increasing the effectiveness of the immune cells so that zinc makes connection between them (two defense mechanisms) as well as soluble factors such as cytokines [17, 18]. Lack of zinc is more characterized with damage to the immune system. In adult rats with zinc deficiency, thymus atrophy and reduced humoral immunity capacity have been reported (Mineral Nutrition). In rats where zinc deficiency was more sever, spleen macrophages were less able for mitogenesis of T facilitator cells. In addition, in rats with diet without zinc, there is evidence on decreased production of cytokines from T and B cells [19].

It has been found that zinc plays central role in the immune system and it is an essential in skin barrier, regulating gene lymphocytes, the immune system such as neutrophils and natural cell killer cells, and zinc deficiency creates problems for development of acquired immunity and the production of immunoglobulin G antibody. It also makes the production of macrophages, cytokines and phagocytosis non-regular. Zinc acts as an antioxidant and stabilizes the cell membrane [20]. Pancreas (endocrine and exocrine) requires zinc for its normal function. The highest concentration of vesicular zinc is found in β cells, and the amount of the zinc secreted from pancreatic exocrine is associated with the amount absorbed from intestine [21].

The zinc is necessary for production of proteolytic enzymes from the pancreas, so zinc inhibition could be a mechanism to control the pancreatic proteins secretion [22]. The effects of zinc on deficiency on the thyroid gland and its function by studying two hormones of T3 and T4 as well as studying on color, and sizes, as well as its histopathological study, changes such as atrophy and degeneration in follicles and reduced T3 and T4 and paleness (tendency to white color).

In general, researchers believe that there is a close correlation between zinc and the function of the thyroid gland because in case of hyperthyroidism the zinc amount is high in the blood and in hypothyroidism the amount of zinc is low in blood [23]. Diabetes is a set of clinical and genetic heterogeneous disorders in which blood glucose concentration raises abnormally in these patients [24]. Diabetes is a syndrome in which lack of insulin secretion or reduced sensitivity of tissues to insulin creates abnormalities in metabolism of carbohydrates, fats, and proteins [25]. There are two types of diabetes: 1) Type I (insulin-dependent) = result of autoimmune
Insulin plays an important role in storing excess energy in the body so that excess carbohydrates are converted into glycogen at the presence of insulin and they are stored in the liver and muscles. If excess carbohydrates are not converted to glycogen at the presence of insulin, they are converted into fat stored in the adipose tissue [25, 27, 28]. Insulin increases the consumption of carbohydrates to supply energy and at the same time reduces fat intake.

In contrast, if insulin is not available, fats become the main source of energy. The main factor to determine the source of energy in the body is blood sugar (glucose). When blood sugar levels drop, insulin secretion decreases and fats are used as a source of energy, when blood sugar level is high, by increasing insulin secretion, glucose in the blood is used by cells and insulin reaches the target tissues. Therefore, one of the important functions of insulin in the body is determining energy source of cells at any moment [25, 29].

The role of most of acute phase proteins is to reduce inflammatory lesions in tissues and thus due to the disposal of inflammation factor, removing and destroying damaged tissue pieces and ultimately tissue restoration. This protein is a component of the inherent immune system and begins working before specific safety and most of these proteins are glycoprotein and their main source is liver.

Secretion of APPs depends directly and indirectly to factors such as cytokines, T cells, and so on. Among the factors that produce and secrete APPs is end toxin of gram-negative bacteria. Additionally, cytokines of IL-1 and IL-6, and INF-α produced by macrophages leave effect on liver and cause production and secretion of APPs from liver cells. Among the acute phase proteins, we can refer to C reactive protein (CRP), protein, serum amyloid protein A, components of complement factor B, and components such as C2, C3, C4, C5 and C9. Emergence, increase, or decrease in the amount of each of the acute phase proteins vary during a disease in different and they are independent of each other. For example, CRP appears in serum 8-6 hours after a lesion and then reaches its maximum 72-48 hours and its amount remains still high during tissue lesion and immediately after tissue restoration, it decreases so that it cannot be measured in the serum. As CRP amount increases in the initial stages of tissue lesion and it decreases after improvement, it is the best factor to diagnose the tissue lesions. In addition, it seems that there is a relationship between tissue lesion and CRP level.

Therefore, in this study, we evaluated the effect of oral administration of zinc as a micronutrient that has insulin-like properties and involved in the production, storage, and secretion of insulin. It was examined in different doses in both human and animal (rat) models according to the classification mentioned later.

### Methodology

In this study, 32 females with type I diabetes who were under insulin treatment are used. These people were selected in such a way that all of them were in same range in terms of age, body weight, and dose of insulin treatment and after ensuring lack of any disease, females were grouped into 4 groups (n=8) as follows:

- Positive control group (treated only with insulin)
- Study group a (insulin treatment + taking one zinc capsule every 4 days (12.5 mg/kg))
- Study group b (insulin treatment + taking one zinc capsule every 2 days (25 mg/kg))
- Study group c (insulin treatment + taking one zinc capsule every day (50 mg/kg))

For the beginning of the study (day zero) in all 4 groups, blood glucose, insulin, CRP, HB, TSH, T3, T4, TAC, MDA,, TG and COL were measured and after 60 days and taking Zinc prescribed for groups A and B and C, all mentioned parameters were measured for each of the 4 groups. Additionally, in this study, 40 mature female rats were used, the selection of rats was in such way that all rats were in the same range in terms of age, weight and physical condition so that the difference in these parameters between different animals to be minimized. After selection of the rats, these animals were divided into 5 groups (n=8) as follows:

- Negative control group (only basic food)
- Positive control group (basic food + STZ)
• Study group a (basic food + STZ + Zinc at amount of 12.5 mg/kg
• Study group b (basic food + STZ + Zinc at amount of 50 mg/kg
• Study group c (basic food + STZ + Zinc at amount of 50 mg/kg

It should be noted that the after grouping, to pass the period of nutritional adaptation and environmental conditions adaptation, animals in each group received sulfate zinc for two weeks. Then, for 4 groups of positive control group, A, B and C, experimental diabetes was created intraperitoneally (IP) by streptozotcin drug with dose of 45 mg/kg. By measuring blood glucose after injection of drug, rats with blood glucose between 250 and 500 milligrams per deciliter were considered to be diabetic.

After completing the course of study and taking the blood sample of rats and sending them to laboratory, the considered parameters were measured. For sampling the rats, xylazine and ketamine drugs at a ratio of 1: 2 were used to produce anesthesia in rats. After induction of anesthesia, blood samples were prepared directly from heart of rats using disposable syringe. The blood amount of each rat was about 6 to 8 cc, and after sampling and conducting centrifuge, samples were sent to the laboratory at containers special for solution solving in the vicinity of dry ice and temperature - 20 °C. Finally, for the analysis of the data, SPSS16 software was used and significant difference in the tests was considered at level less than 0.05.

**Results**

The results of the study showed:

• There is a positive correlation between Glu and HSCRP (R = 0.385, P = 0.03) and FT3 (R = 0.404, P = 0.022) and TAC (R = 0.456, P = 0.009).
• There is a negative correlation between Ins and TAC (R = -0.464, P = 0.008)
• There is a positive correlation between HSCRP and TAC (R = 0.363, P = 0.041)
• There is a positive correlation between FT3 and FT4 (R = 0.386, P = 0.029)
• There is a positive correlation between TG with HSCRP (R =0.553, P = 0.001) and between CHOL with HSCRP (R = 0.395, P = 0.025).

According to T-test test, there is a significant difference between tested groups in terms of TAC, HSCRP, GLU and MDA (P <0.05)

**Table 1: Mean ± standard error (SEM) ± factors examined in the studied human groups**

<table>
<thead>
<tr>
<th>Examined factors</th>
<th>GLU</th>
<th>INS</th>
<th>HSCRP</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive control Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non treatment</td>
<td>252.12 ± 33.32</td>
<td>3.48 ± 0.41</td>
<td>0.56 ± 0.04</td>
<td>2.57 ± 0.78</td>
</tr>
<tr>
<td>Treatment</td>
<td>237.5 ± 13.67</td>
<td>3.11 ± 0.18</td>
<td>0.5 ± 0.03</td>
<td>2.02 ± 0.36</td>
</tr>
<tr>
<td><strong>12.5 mg group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non treatment</td>
<td>206.5 ± 28.72</td>
<td>4.11 ± 0.74</td>
<td>0.55 ± 0.04</td>
<td>2.64 ± 0.6</td>
</tr>
<tr>
<td>treatment</td>
<td>183.37 ± 26.75</td>
<td>3.91 ± 0.61</td>
<td>0.41 ± 0.05</td>
<td>2 ± 0.31</td>
</tr>
<tr>
<td><strong>25 mg group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non treatment</td>
<td>241.5 ± 38.81</td>
<td>5.97 ± 1.02</td>
<td>0.59 ± 0.08</td>
<td>1.37 ± 0.39</td>
</tr>
<tr>
<td>treatment</td>
<td>194.75 ± 33.28</td>
<td>6.27 ± 0.92</td>
<td>0.51 ± 0.07</td>
<td>1.39 ± 0.54</td>
</tr>
<tr>
<td><strong>50 mg group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non treatment</td>
<td>201.12 ± 24.29</td>
<td>5.58 ± 0.76</td>
<td>0.43 ± 0.08</td>
<td>1.98 ± 0.6565</td>
</tr>
<tr>
<td>treatment</td>
<td>154.37 ± 22.2</td>
<td>6.36 ± 0.89</td>
<td>0.29 ± 0.05</td>
<td>1.47 ± 0.27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examined factor</th>
<th>Group</th>
<th>FT3</th>
<th>FT4</th>
<th>TAC</th>
<th>MDA</th>
<th>TG</th>
<th>CHOL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non treatment</td>
<td>3.3 ± 0.23</td>
<td>1.05 ± 0.06</td>
<td>2.51 ± 0.08</td>
<td>2/21 ± 0/08</td>
<td>165.12 ± 18.03</td>
<td>202.5 ± 33.73</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>3.2 ±0.16</td>
<td>1.2 ±0.03</td>
<td>2.41 ±0.13</td>
<td>2/22 ± 0/07</td>
<td>166.37 ± 18.85</td>
<td>200.12± 30.37</td>
<td></td>
</tr>
<tr>
<td><strong>12.5 mg group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non treatment</td>
<td>3.42 ±0.16</td>
<td>1.13 ±0.11</td>
<td>2.12 ±0.1</td>
<td>2/12 ± 0/05 a</td>
<td>156 ± 40.58</td>
<td>137.25 ± 25.7</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>3.64 ±0.19</td>
<td>1.09 ±0.05</td>
<td>2.17 ±0.14</td>
<td>1/96 ± 0/08 b</td>
<td>171 ± 38.47</td>
<td>135.62 ± 19.06</td>
<td></td>
</tr>
<tr>
<td><strong>25 mg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non</td>
<td>3.46 ±0.17</td>
<td>1.13 ±0.1</td>
<td>1.94 ±a0.11</td>
<td>2/23 ± 0/05 a</td>
<td>317.5 ± 68.52</td>
<td>200± 38.36</td>
<td></td>
</tr>
</tbody>
</table>
In each column, non-similar letters indicate significant difference between factors examined in treatment and non-treatments in test groups using Paired Samples Test with confidence level of 95% (p<0.05).

In terms of Glu factor, there is a significant difference between 25 mg and 50 mg groups (P <0.05).

In terms of HSCRP factor, there is significant difference only in group 50 mg (p<0.05).

In terms of MDA factor, there is significant difference in all three groups (p<0.05).

According to the results of Tukey test: In terms of Glu factor, there is significant difference among all three groups, except for between 12.5 mg and 50 mg (p<0.05). In terms of HSCRP factor, there is significant difference among groups, except for the difference between control group and 50mg group (p<0.05). In terms of FT3, there is significant difference 25 mg and 50 mg groups and other groups (p<0.05). In terms of TAC, there is significant difference between control groups and 25 mg and 50 mg groups. In addition, there is significant difference among control group and 12.5 mg group and 25 mg and 50 mg groups.

In terms of MDA, there is significant difference between control groups and 25 mg and 50 mg groups (p<0.05).

**In addition**

- There is a positive correlation between Glu and HSCRP (R=0.441, p=0.015)
- There is a negative correlation between HSCRP and FT3 (R=0.0421, p=0.020)
- There is a positive correlation between MDA and FT3 (R=0.517, p=0.003)
- There is a positive correlation between TG and Glue (R=0.412, p=0.024)
- There is a positive correlation between CHOL and Glu (R=0.517, p=0.001)
- There is a negative correlation between FT3 and TAC (R=-0.713, p=0.0001)
- There is a negative correlation between MDA and TAC (R=-0.621, p=0.0001)

In terms of Gle factor, there is significant difference between 12.5 mg, 25 mg, and 50 mg groups and positive control group (p<0.05).

Mean ± standard error (Mean ± SEM) ± of examined factors in studied groups of rats

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### Table 3: The mean ± standard error (Mean ± SEM) ± of examined factors in studied groups of rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>GLU</th>
<th>INS</th>
<th>HSCRP</th>
<th>TSH</th>
<th>FT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg group</td>
<td>Treatment</td>
<td>3.57 ± 0.15</td>
<td>1.15 ± 0.05</td>
<td>2.12 ± b0.1</td>
<td>2/07 ± 0/07 b</td>
<td>315.87 ± 66.46</td>
</tr>
<tr>
<td></td>
<td>non</td>
<td>3.4 ± 0.22</td>
<td>1.13 ± 0.12</td>
<td>1.67 ± a0.08</td>
<td>2/16 ± 0/04 a</td>
<td>230.12 ± 65.35</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>3.56 ± 0.16</td>
<td>1.28 ± 0.08</td>
<td>2.02 ± b0.06</td>
<td>1.9 ± b0.05</td>
<td>224.5 ± 62.38</td>
</tr>
</tbody>
</table>

Continuation of Table 2: The mean ± standard error (SEM) of factors examined in the studied groups of rats

<table>
<thead>
<tr>
<th>Examined factor Group</th>
<th>FT4</th>
<th>TAC</th>
<th>MDA</th>
<th>TG</th>
<th>CHOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive control</td>
<td>1.59 ± 0.12</td>
<td>3.31 ± 0.08</td>
<td>3 ± ab0.51</td>
<td>189.66 ± 47.82</td>
<td>92.5 ± b5.19</td>
</tr>
<tr>
<td>Negative control</td>
<td>1.12 ± 0.14</td>
<td>3.08 ± 0.09</td>
<td>2.33 ± a0.42</td>
<td>114.16 ± 22.14</td>
<td>68.33 ± ab4.15</td>
</tr>
<tr>
<td>12.5 mg group</td>
<td>1.7 ± 0.19</td>
<td>2.98 ± 0e0.07</td>
<td>4.33 ± ab0.66</td>
<td>102.33 ± 11.85</td>
<td>78.66 ± ab3.28</td>
</tr>
<tr>
<td>25 mg group</td>
<td>1.57 ± 0.15</td>
<td>2.43 ± a0.16</td>
<td>6.5 ± b1.68</td>
<td>111.83 ± 10.94</td>
<td>81.16 ± ab5.11</td>
</tr>
<tr>
<td>50 mg group</td>
<td>1.42 ± 0.22</td>
<td>2.63 ± ab0.13</td>
<td>6.16 ± b0.83</td>
<td>148.5 ± 18.88</td>
<td>80.33 ± ab4.84</td>
</tr>
</tbody>
</table>

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• In each column, non-similar letters indicate significant difference in ANOVA analysis test and Turkey test with confidence level of 95% (p<0.05).

• In terms of Glu factor, there is a significant difference between all studied groups and + control group.

• In terms of HSCRP factor, there is significant difference between 12.5 mg and 25 mg groups and positive control group (p<0.05).

• In terms of FT3 factor, there is significant difference between 12.5 mg and 25 mg groups and positive control group (p<0.05).

• In terms of TAC factor, there is significant difference between 12.5 mg and 25 mg groups and positive control group (p<0.05).

• In terms of FT3 factor, there is significant difference between 12.5 mg and 25 mg groups and positive control group (p<0.05).

• In terms of FT3 factor, there is no significant difference between 12.5 mg group and negative control group (p<0.05).

• In terms of CHOL factor, there is significant difference between positive control and negative control groups (p<0.05).

• According to ANOVA test, there is significant difference among the studied groups in terms of mean values of GLU, HSCRP, FT3, TAC, MDA, and CHOL factors (p<0.05).

Discussion and Conclusion

Diabetes that is now one of the most important diseases of the modern world appears in the body in the form of gradual increase in blood glucose levels or reduced insulin in blood or reduced insulin function in the body. The development of new therapies to improve glycemic management and protection from the effects of the disease has been interested by many researchers. Hence, many of the researchers have suggested that the mineral compounds could have beneficial effects in the pathogenesis and disorders caused by this disease and the idea of using mineral ions for the treatment of diabetes results the report in the year 1899. In this regard, the important effects of zinc, we can refer to these points: In terms of presence in insulin compound, zinc has an important role in the synthesis, storage and secretion of insulin. It seems that zinc activity is due to increases activity of Insulin-dependent glucose carriers that can do it by protecting sulfhydryl group against oxidation and contribution in control of production of free radicals.

In this study, according to the results of data analysis in terms of mean blood glucose in both human and animal models, it was found that there is a significant difference in the groups studied and comparing the groups showed that blood glucose reduction in the group received zinc in the human model (50mg group) and animal model (25 mg group) per kg diet is more than that that other groups.

In this regard, suggested that zinc is effective in the production, storage and secretion of insulin and increased activity of insulin-dependent glucose carriers is effective in reducing blood glucose content in laboratory diabetic animals.

Omotayo O. Erejuwa et al [30] conducted a study in the year entitled honey as new antibiotic agent. In this study, they believed that honey for the sake of having some minerals including zinc and copper can increase insulin sensitivity leading reduced blood glucose. Additionally, Shen Huiyun et al in a study in believe that by discharge of zinc from body in terms of effect on insulin and glucose metabolism, significant changes occur in the blood glucose level of body.

In terms of hs-CRP, according to the results of the data analysis, its mean values in the blood of both human and animal models showed a significant difference in the tested groups. It should be explained that it has the lowest level in human model in the group received 50 mg zinc, while the control group had the highest level of hs-CRP. In the animal model, its lowest value was found in the group received 50 mg zinc, while the highest value was obtained in positive control group.

In this regard, In a study conducted by F. Hümayra Yerlikaya et al [31]. The amount of acute phase protein hs-CRP in obese diabetic women was more than that in non-obese diabetic women. Examining serum values of zinc in the studied sample, they
reported that there is a negative correlation between zinc and hs-CRP value. They also believed that micronutrients and minerals are effective in the pathogenesis of obesity and diabetes and involvements resulting from it, especially in development of per oxidation and inflammation.

However, the study conducted by Alaa. A. Adbulkadir and Imad A- J Thanon [32] to compare the effect of Glibendamide and Metformin on CRP and oxidant and antioxidant status in patients with type II diabetes mellitus, while it was found that CRP is a biomarker increases in patients with diabetes and many inflammatory diseases, these drugs used commonly to treat diabetes cannot reduce the acute phase proteins.

However, in this study in both animal and human models, particularly in the animal model in which no anti diabetic drug was used, with an increase in the zinc in food, hs-CRP reduced significantly compared to positive control group. In addition, conducted a study in which they found that hs CRP that is acute phase protein emphasized in diabetes increased significantly in healthy people compared to diabetic people.

Additionally, Chin Hung Guo and Chia Liang Wang [33] conducted a study in on the effects of zinc supplementation on age, oxidative stress, and immunological status of hemodialysis patients. They believe that zinc supplementation increases serum value of zinc and increases catabolic value of protein. It also increases LDL and cholesterol concentration and increases plasma value of CRP that is a biomarker for inflammation. In addition, reports of different studies are in line with results of the current study. Antioxidants in the present research were examined in both human and animal TAC and MDA models, and results of the statistical analysis suggest that in the initial and final results of the study course in groups received 25 mg and 50 mg zinc, there is significant difference in all three groups in terms of TAC and MDA.

In this regard, Duzauner and Kaya conducted a study in 2007 to examine the impact of zinc sulfate in rabbits with diabetes. They concluded that zinc sulfate significantly reduces the plasma concentration of MDA and it increases the activity of antioxidant enzymes SOD, CAT, and GSH-PX significantly.

In addition, in a study conducted by Chia Liang Wang and Chih Hug Guo[33] in hemodialysis patients, they concluded that MDA plasma values in hemodialysis patients increases compared to that in healthy individuals, leading to reduced SOD in erythrocyte of these patients. They also observed after use of zinc supplementation in these patients, oxidative products reduces significantly and SOD increases in these patients compared to control group patients.

In the group received zinc supplementation, positive correlation was found between copper plasma ratio and MDA concentration. According the results of the studies on TAC and MDA, they are in line with findings of the current study. In general, the study data analysis suggests that using zinc supplementation by diabetic patients reduced the acute phase proteins CRP and by increasing the total amount of antioxidants serum (TAC), malondialdehyde (MDA) amount reduced. In the case of thyroid hormones, results of the statistical analysis showed significant difference only in animal models in Ft3 and Turkey test showed this difference among groups received 25mg and 50mg zinc compared to other groups.

In this regard, during a study conducted by Zhang liqun et al in 2001, they found that concentration of Free Thyroxine in diabetic patients reduces and in the present study, investigation serum value of different groups showed that Ft3 value is in its lowest level in positive control group, while its highest value was found in the group received 25 mg zinc that is approximate to serum level of Ft3 in the negative control group, and it is in line with result of the current study as FT3 reduces in diabetes. However, on the influence of sulfate zinc on the rate of thyroid hormones in rats, no study has been published and it could be considered as base study.

Finally, with regard to what was said above, it can be concluded that studied conditions in human and animal models could not quite identical and nutritional conditions were not identical in human models and animal models. However, in the case of many considered factors in this study, similar results were observed. In comparing human and animal models, the best effect of sulfate zinc was seen in human model in the group.
received 50 mg zinc. In animal model, these conditions were seen more in group received 25 mg on kg food was and another point was that in terms of CRP factor, while these conditions could not be identical in human and animal models completely, the results have been quite similar and consistent with other studies. It can be suggested that using zinc supplementation along with common diabetes treatments and evaluation of serum level of hs-CRP can be used as a diagnostic biomarker to evaluate the process of response to therapy in diabetic patients.

**Recommendations**

- Since the present study was considered as a base study, by increasing the number of samples in different groups and using larger population, more accurate studies can be conducted.

- It is recommended all the parameters examined in the present investigation to be examined in type II diabetics.

- In the present study, the effect of zinc sulfate supplementation was examined in diabetic patients, but the effects of other minerals such as CU (copper) separately in complex zinc can be studied.

- By prescribing vitamins C and E (as antioxidants) and minerals, a study can be conducted in the area of TAC and MDA and their impact on acute phase proteins can be examined.

- For accurately investigation of the study, it is recommended that in the case of human study, the subjects to be placed in nutritional and environmental quarantine [34-72].

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