INTRODUCTION

The number of patients with diabetes mellitus (DM) increased from 108 million in 1980 to 422 million in 2014 and increasing day by day worldwide. The worldwide prevalence of DM in adult population is more than 8.5%. In Saudi Arabia, more than 3 million people (>16% of population) have DM. Most of the DM patients are classified as type 2 DM in adult population. The effect of insulin resistance and relative deficiency of insulin secretion leads to hyperglycemia. The chronic hyperglycemia increases oxidative stress by production of free radicals (oxidants) and reduction in antioxidant defense system. This leads to oxidative cellular injury damaging metabolism of lipid, proteins and DNA, resulting in cellular dysfunctions.

Zinc is a trace element that acts as co-factor for synthesis, storage and secretion of insulin by pancreas. The predominant effect of diabetes on zinc homeostasis is hypozincemia, which may be the result of hyperzincuria or decreased intestinal absorption of zinc or both. Zinc has an important role in the glucose utilization by muscle and fat cells. It is required as a co-factor for the function of intracellular enzymes that may be involved in protein, lipid and glucose metabolism.

Zinc may be involved in the regulation of insulin receptor-initiated signal transudation mechanism and insulin receptor synthesis. Zinc also plays a key role in the synthesis, storage, and secretions of insulin by pancreatic tissue, and it accounts for the conformation integrity of insulin in its hexameric crystalline form. Zinc may participate as an integral component of several antioxidant enzymes. Many of the complications of diabetes may relate to an increase in intracellular oxidant and free radicals associated with decrease in intracellular zinc and zinc dependent antioxidant enzymes.

Anderson et al. reported that 30% patients with DM found to be zinc deficient. Tripathy et al. had reported zinc depletion in type 2 DM. On the contrary, Mumza et al. reported high zinc level in type 2 DM patients. Therefore, this study was conducted to determine the serum zinc status and its relationship with age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood sugar (FBS), glycosylated hemoglobin (HbA1C) and lipid levels in type 2 DM patients.

METHODOLOGY

This cross-sectional study was done at Outpatient Department (OPD) of Dallah Hospital, Riyadh, Kingdom of Saudi Arabia, from May 2014 to June 2015. The sample size was calculated by using sample size calculating formula available on website by keeping 95% confidence level and 5% margin of error for population of 1,00,000. The minimum sample size was 383 subjects.
Patients above age of 20 years with type 2 diabetes for more than 2 years presented to Diabetic Clinic during study period from May 2014 to June 2015 and selected as randomly one in three till the sample size completed. The controls were selected on voluntary basis from the family of patients or other people who were not diabetic and matched with gender and age of patients. Patients with type 1 diabetes, pregnant patients, patients with chronic kidney disease stage 3 or less (creatinine clearance less than 30 ml/min/1.73m3), patients taking diuretics or vitamins or mineral supplements were excluded from the study. Informed consent was taken from all subjects and Hospital Ethical Committee approval was also acquired.

The age in years, gender, height in centimeter (cm), and weight in kilogram (kg) were recorded in patient's file by two OPD nurses in OPD triage room. The body mass index (BMI) was calculated by using the formula: BMI = Weight in kilogram divided by height in meter square. The blood pressure was recorded in both arms after five minutes of sitting and the higher one was recorded for data analysis. The 12-hour fasting blood sample was taken for lipid profile, FBS, HbA1c, and serum zinc level. The FBS was done by the enzymatic calorimetric method and HbA1c estimation was done by fast ion exchange resin method in the same hospital. Serum cholesterol and LDL were done by cholesterol oxidase method and serum triglyceride by glycerol peroxidase method on auto analyzer in the same hospital. Serum zinc was measured colorimetrically with 2-(5-Bromo-2-Pyridylazo)-5-(N-Propyl-N-Sulfopropylamino-) phenol by Bioscientia, Germany. The reference value of serum zinc was 70 mcg/dL to 120 mcg/dL. The groups were divided into normal zinc (>70 mcg/dL) and low zinc (<70 mcg/dL) levels. Another group division was diabetic and control subjects.

These two groups were analyzed by using the Statistical Package for Social Sciences (SPSS) version 22.0 for Windows from IBM. Chi-square test was done for qualitative data by using cross tab; and student's t-test was used to compare the means of zinc level, FBS, HbA1c, cholesterol, triglycerides, and LDL of diabetic subjects with their controls. Student's t-test was done to compare means on different variables between groups. The female to male ratio in diabetic group was 0.9:1, while in control group it was 1.3:1. The male to female ratio in low-zinc group was 1.3:1. There was no statistical significant difference found between the two groups regarding genderER

The mean age for type 2 DM group and control group was almost same and there was no significant statistical difference between the two groups (p=0.292, Table II). Age was categorized into two groups <50 years and >50 years, and had no statistically significant association with serum zinc level (p=0.506) and age group. The mean BMI for type 2 DM group and control group was 28.7 ± 5.88 Kg/m² and 29.0 ± 6.03 Kg/m²; and there was no significant difference noted in BMI between the two groups (p=0.506). The male to female ratio in diabetic group was 1.3:1. The male to female ratio in low-zinc group was 1.3:1. There was no statistical significant difference found between the two groups regarding gender (p=0.506). The mean BMI for diabetic group was 32.63 ± 5.88 Kg/m² and for control group 32.00 ± 6.03 Kg/m²; and there was no significant difference noted in diabetic and control groups (p=0.292); and there was no significant difference in low-zinc group (32.70 ± 6.31 mcg/dL) and normal-zinc group (31.99 ± 5.62 mcg/dL, p=0.242) regarding BMI in this study. The mean systolic and diastolic BP were significantly higher (p<0.001) in type 2 DM subjects and subjects with low zinc level as compared to the controls and normal zinc level subjects, respectively (Table II).

Mean serum zinc was significantly lower in diabetic patients (66.54 ± 11.328 mcg/dL) compared to healthy subjects (82.63 ± 12.194 mcg/dL, p < 0.001, Table II). The mean fasting blood sugar was 92.42 ± 7.82 mg/dL in healthy subjects and 146.66 ± 23.58 mg/dL in diabetic patients (p < 0.001, Table II). The mean FBS was 139.84 ± 30.68 mg/dL in low zinc level group in contrast to controls. Table I shows the frequency and distribution of demographic data with relation to low and normal zinc levels.

The mean age for type 2 DM group and control group was almost same and there was no significant statistical difference between the two groups (p=0.806, Table II). Age was categorized into two groups <50 years and >50 years, and had no statistically significant association with serum zinc level (p=0.739) and age group. The male to female ratio in diabetic group was 0.9:1, while in control group it was 1.3:1. The male to female ratio in low-zinc group was 0.9:1, and in normal-zinc group it was 1.3:1. There was no statistical significant difference found between the two groups regarding gender (p=0.082). The mean BMI for diabetic group was 32.63 ± 5.88 Kg/m² and for control group 32.00 ± 6.03 Kg/m²; and there was no significant difference noted in BMI between the two groups (p=0.506). Age was categorized into two groups <50 years and >50 years, and had no statistically significant association with serum zinc level (p=0.739) and age group. The male to female ratio in diabetic group was 0.9:1, while in control group it was 1.3:1. The male to female ratio in low-zinc group was 0.9:1, and in normal-zinc group it was 1.3:1. There was no statistical significant difference found between the two groups regarding gender (p=0.082).

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**RESULTS**

Among the 392 subjects, 51% (n=200) had type 2 DM while 49% (n=192) were age and gender matched...
Zinc deficiency is associated with poor glycemic control

**Table II:** Comparison of means of variables with normal and low zinc levels, diabetic and control and good and poor glycemic control.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low zinc level</th>
<th>Normal zinc level</th>
<th>p-value</th>
<th>Diabetic</th>
<th>Control</th>
<th>p-value</th>
<th>HbA1c&lt;7%</th>
<th>HbA1c&gt;7%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.9 ±10.5</td>
<td>52.8 ±10.2</td>
<td>0.408</td>
<td>52.3 ±10.3</td>
<td>52.5 ±10.4</td>
<td>0.806</td>
<td>52.5 ±10.9</td>
<td>52.2 ±10.2</td>
<td>0.857</td>
</tr>
<tr>
<td>BMI</td>
<td>32.7 ±6.3</td>
<td>31.9 ±5.6</td>
<td>0.242</td>
<td>32.6 ±5.8</td>
<td>32.0 ±6.1</td>
<td>0.292</td>
<td>32.5 ±6.8</td>
<td>32.6 ±5.5</td>
<td>0.869</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>174.9 ±26.5</td>
<td>133.9 ±26.3</td>
<td>&lt;0.001</td>
<td>185.1 ±11.6</td>
<td>119.5 ±7.5</td>
<td>&lt;0.001</td>
<td>186.1 ±11.8</td>
<td>184.7 ±11.6</td>
<td>0.474</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>100.9 ±13.1</td>
<td>83.5 ±13.1</td>
<td>&lt;0.001</td>
<td>105.7 ±6.7</td>
<td>76.8 ±5.3</td>
<td>&lt;0.001</td>
<td>105.1 ±6.4</td>
<td>106.1 ±6.4</td>
<td>0.025</td>
</tr>
<tr>
<td>FBS</td>
<td>139.5 ±30.6</td>
<td>104.6 ±26.1</td>
<td>&lt;0.001</td>
<td>148.6 ±23.5</td>
<td>92.4 ±7.8</td>
<td>&lt;0.001</td>
<td>146.1 ±24.1</td>
<td>149.4 ±23.4</td>
<td>0.397</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.9 ±2.1</td>
<td>5.7 ±2.3</td>
<td>&lt;0.001</td>
<td>9.7 ±1.1</td>
<td>4.5 ±0.3</td>
<td>&lt;0.001</td>
<td>6.7 ±0.2</td>
<td>10.1 ±4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>249.3 ±41.1</td>
<td>186.8 ±47.3</td>
<td>&lt;0.001</td>
<td>267.1 ±18.7</td>
<td>162.4 ±17.6</td>
<td>&lt;0.001</td>
<td>270.9 ±18.8</td>
<td>265.8 ±18.6</td>
<td>0.102</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>244.9 ±57.5</td>
<td>163.1 ±58.4</td>
<td>&lt;0.001</td>
<td>265.3 ±30.7</td>
<td>134.1 ±21.8</td>
<td>&lt;0.001</td>
<td>265.6 ±24.0</td>
<td>265.3 ±27.3</td>
<td>0.953</td>
</tr>
<tr>
<td>LDL</td>
<td>160.9 ±26.1</td>
<td>136.9 ±23.1</td>
<td>&lt;0.001</td>
<td>167.8 ±20.7</td>
<td>127.2 ±14.8</td>
<td>&lt;0.001</td>
<td>170.8 ±18.6</td>
<td>166.8 ±21.2</td>
<td>0.245</td>
</tr>
<tr>
<td>Zinc</td>
<td>62.3 ±5.4</td>
<td>84.9 ±10.7</td>
<td>&lt;0.001</td>
<td>66.5 ±11.3</td>
<td>82.6 ±12.2</td>
<td>&lt;0.001</td>
<td>73.8 ±9.5</td>
<td>67.6 ±10.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

104.88 ±26.12 mg/dL in normal zinc level group (p<0.001, Table II). The mean HbA1c was 4.502 ±0.383% in healthy subjects and 9.77 ±1.059% in diabetic patients (p<0.001, Table II). The mean HbA1c was 8.91 ±2.16% in low-zinc level group in contrast to 5.69 ±2.3 in normal zinc level group (p<0.001, Table II). High FBS and HbA1c were associated with diabetic and low zinc level groups (p<0.001). Serum cholesterol, LDL and triglyceride levels were significantly high in diabetic group and low-zinc level group compared to control group and normal zinc level group, respectively (p<0.001).

Good glycemic control (HbA1c <7%) was 23.5% in diabetic group. The results of sub-analysis of diabetic group in good glycemic control group (HbA1c <7%) and poor glycemic control group (HbA1c >7%) revealed that there was a significant difference between the two groups regarding zinc level, but no significant difference in age, BMI, blood pressure, and lipid levels (Table II).

The serum zinc level was negatively associated with BMI, age, cholesterol, HbA1c, Triglycerides, and LDL (Table II). There was no significant relationship between zinc level and other variables on Pearson correlation in control group (Table III).

**DISCUSSION**

This study revealed that diabetic subjects had significantly low mean zinc levels than control subjects (p<0.001). These results were consistent with the study done by Sahria and Goswami, which also showed low level of zinc in diabetic patients compared to their control (p<0.001). This finding also concurred with studies done by Saha-roy et al. and Naila et al., in which, serum zinc was found to be significantly lower in diabetic group. Al-Maroorf et al. also observed significantly lower serum zinc levels in diabetics than in control subjects. Marchesini et al. explained low zinc in the diabetic population was due to the decreased gastrointestinal absorption and increased urinary excretion. In one study, the zinc levels were reported similar in diabetic and control subjects. On the contrast, study done by Mumza et al. revealed high zinc levels in diabetic patients. The same finding was reported by Osman et al. that high concentration of zinc was associated with type 2 DM. The effect of zinc on insulin secretion is biphasic, that is, very high or very low zinc plasma concentrations impair insulin secretion.

There was no significant difference in zinc level regarding age of the subjects (p=0.408), as it was similar to the study done by Nair et al. In this study, there was no significant difference in male and female patients regarding zinc level (p=0.082), which was similar to previous studies done by Sahria and Goswami. In this study, there was no significant difference in zinc concentration regarding BMI of the subjects (p=0.242), although it was reported in a previous study that plasma zinc levels were lower in obese individuals.

It was observed that the mean fasting blood glucose in type 2 DM cases was found to be very significantly higher than that of the controls (p <0.001). The FBS was negatively correlated with serum concentration of zinc (r=0.478, p <0.001) which was not similar to the study done by Mumza et al. (p=0.334) and Nair et al. (p=0.81), where there was no relation of zinc concentration with FBS.

In the present study, it was observed that the mean HbA1C concentration in type 2 DM cases had an inverse

**Table III:** Pearson correlation of zinc level with other variables.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pearson</th>
<th>Age</th>
<th>BMI</th>
<th>SPB</th>
<th>DBP</th>
<th>FBS</th>
<th>HbA1C</th>
<th>Cholesterol</th>
<th>Triglycerides</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc in control group (N=192)</td>
<td>p-value</td>
<td>-0.043</td>
<td>-0.083</td>
<td>-0.111</td>
<td>0.153</td>
<td>-0.93</td>
<td>0.159</td>
<td>0.108</td>
<td>0.066</td>
<td>0.1040</td>
</tr>
<tr>
<td>Zinc in diabetic group (N=200)</td>
<td>p-value</td>
<td>0.557</td>
<td>0.254</td>
<td>0.126</td>
<td>0.034</td>
<td>0.198</td>
<td>0.027</td>
<td>0.138</td>
<td>0.365</td>
<td>0.150</td>
</tr>
<tr>
<td>Zinc in all subjects (N=392)</td>
<td>p-value</td>
<td>0.094</td>
<td>0.124</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
relation with serum zinc concentration. The zinc level was significantly low in patients with poor glycemic control compared to patients with good glycemic control; that means having lower values of HbA1C have higher values of serum zinc concentration and vice versa. The Pearson correlation coefficient 'r' is found to be -0.527 which also established the strong negative correlation between these two parameters (p<0.001).

Sahria and Goswami also reported negative relationship between HbA1c and zinc concentration with 'r' value of -0.804. Tripathy et al. found a significant negative correlation between serum zinc and HbA1C percentage with 'r' value of -0.408; and diabetic subjects of the study were found to have lower levels of zinc in serum as compared with healthy controls. The findings of the present study were also consistent with Al-Marooof et al., who showed significant negative correlation between serum zinc concentration and HbA1c% value in the diabetic group and found correlation coefficient 'r' to be -0.33. In view of the above, it may be concluded that there is significant reduction of serum zinc in type 2 DM patients; although it is still not clear which came first, the effects of DM and hyperglycemia on zinc metabolism or the effects of alterations in zinc homeostasis on carbohydrate metabolism. There are evidences that hyperglycemia interferes with the active transport of zinc back into the renal tubular cells leading to more urinary excretion of zinc. Moreover, zinc also increases insulin sensitivity by increasing the binding ability of insulin to its receptors.

In this study, the low serum zinc level was associated with high cholesterol, triglycerides, and LDL levels (p<0.001). The study done by Seo et al. revealed that serum zinc levels in men were negatively associated with elevated FBS and positively associated with elevated triglycerides. On the other hand, there was no significant relationship found in women regarding serum zinc level and triglycerides. On the other hand, Seo et al. found a negative association between serum zinc and HDL cholesterol levels in both men and women. In this study, the data of HDL was not available, therefore no statistical correlation done. The effect of zinc on lipid profile and blood pressure was documented also in some other studies. One study revealed that zinc supplementation decreases triglycerides, cholesterol, LDL, and BP after 12 weeks of therapy. The issue whether serum zinc levels are associated with change in plasma lipids is controversial. Ghasemi et al. found a positive correlation between serum zinc levels and triglycerides in Iranian men, whereas no association was observed between serum zinc concentrations and lipid profiles in Lebanese population.

In this study, the systolic and diastolic blood pressures were negatively correlated with serum zinc level (SBP 'r' value -0.561, DBP 'r' value -0.511, p <0.001). This was consistent with other study done on type 2 diabetic patients to see the effect of vitamin/minerals (including zinc) on blood pressure, which revealed there was significant improvement in blood pressure after vitamin/mineral supplements.

There are some limitations of this study results. First, it was cross-sectional study so cause and effect relationship between diabetes and low zinc level cannot be established. Second, in this study other minerals not done concurrently with zinc level (like magnesium, chromium or copper) to know the influence of these trace elements on serum zinc level. Therefore, low zinc level could be due to some effects of alteration of other minerals, especially copper. Third, the level of HDL was not available to make the statistical relationship with zinc level. Although these were the limitations but this is one of the few studies done in the Middle East population and could be first study from Kingdom of Saudi Arabia. This study not only showed the relationship of FBS and HbA1C, but also revealed relationship of LDL and TG levels.

CONCLUSION
Patients with type 2 DM had significantly low level of zinc that could be the cause of development of diabetes or may be a contributing factor. There was a negative relationship among serum zinc and FBS; and HbA1C LDL cholesterol, triglycerides and blood pressure. Further investigations are warranted to confirm the association between serum zinc levels, type 2 DM and lipid profiles.

REFERENCES
Zinc deficiency is associated with poor glycemic control


