ABSTRACT

This study was undertaken with the aim to determine Serum zinc and magnesium levels in patients with Type 2 Diabetes Mellitus without it's associated complications and Type 2 Diabetes mellitus patients with its various macro and micro vascular complications namely Coronary atherosclerosis, Peripheral vascular disease and retinopathy, nephropathy respectively. The study was conducted at diabetology out-patient department, Sree Balaji Medical college & Hospital, Chennai on total of 120 subjects of age group 40-70 years; of whom 20 were apparently healthy and served as control. Between control groups and retinopathy, a microvascular consequence of Type 2 Diabetes mellitus, there is no statistically significant reduction in serum magnesium. Overall, diabetic patients without comorbidities and microvascular consequences of Type 2 Diabetes mellitus, such as retinopathy and nephropathy, reveal a negative connection between serum magnesium and HbA1c. In diabetes patients without problems and microvascular consequences, such as nephropathy, serum zinc and HbA1c have a negative connection.

Keywords: Serum magnesium; hyperglycemia; diabetes mellitus; fasting plasma.

1. INTRODUCTION

Mineral elements constitute a minute part of the living tissues. Yet, they are important for the vital processes of life. They were difficult to measure in the past. Hence, they were mentioned as occurring in traces and thus originated the term "trace elements". This term has persisted though
they can now be estimated with great accuracy. The importance of the trace elements in living organisms was first shown over a century ago. The existence of a number of trace-metal-containing enzymes (metalloenzymes) of importance to the structural and functional integrity of the living cells [1].

Diabetes Mellitus is a group of metabolic disease which is characterized by hyperglycemia, resulting from defect in insulin secretion, insulin action or both [2]. Currently number of diabetic patients worldwide is estimated to be around 150 million, two third of which are residing in developing countries [3]. This number is predicted to double by 2025, with the greatest number of cases in India and china alone [4].

Many trace elements are important for human metabolic function. Numerous studies have demonstrated the essential role of trace elements like zinc, magnesium, chromium, vanadium, selenium, molybdenum and manganese in insulin action and carbohydrate metabolism [5]. The actual role of these trace elements in the pathogenesis and progress of diabetes is still unclear. The observed alterations in the status of these trace elements in diabetics have been attributed to hyperglycemia. In this study, it was observed that mean serum zinc levels was significantly low (p<0.05) in diabetics when compared to control subjects. Similar observations are reported by Al Maroof, who also observed significantly lower serum zinc levels in diabetics than in control subjects [6].

2. MATERIALS AND METHODS

This study was undertaken with the patients with Type 2 Diabetes Mellitus without its associated complication and Type 2 Diabetes mellitus patients with its various macro and micro vascular complications namely Coronary atherosclerosis, Peripheral vascular disease and retinopathy, nephropathy respectively.

The study was conducted at diabetology out-patient department, Sree Balaji Medical college & Hospital, Chennai on total of 120 subjects of age group 40-70 years; of whom 20 were apparently healthy and served as control. They were grouped as Category 1.

Remaining 100 subjects formed the study group (category 2 to 6). They are:

Category 2 - Type 2 DM without it's associated complication. Category 3 - Type 2 DM with coronary Atherosclerosis Category 4 - Type 2 DM with peripheral vascular disease Category 5 - Type 2 DM with Retinopathy Category 6 - Type 2 DM with Nephropathy

For the control group (category 1) the apparently healthy adults of 40 - 70 years were selected from staffs of Sree Balaji medical college and their relatives. For category 2 (Type 2 DM without any of its associated complication) patients were selected from outpatient’s clinic of Diabetology department who came there for monitoring of Type 2 DM and treatment. They were diagnosed as having DM - Type 2 based on American Diabetic Association criteria of fasting hyperglycemia of 126 mg/dl after an overnight fast of 8 hours. Those with inconsistent values of fasting glucose (110 mg/dl - 126 mg/dl) were diagnosed on the basis of OGTT. (WHO Criteria).

For Category 3 (Type 2 DM with coronary atherosclerosis) patients were selected based on history, clinical examination and Echocardiogram.

For Category 4 (Type 2 DM with Peripheral Vascular Disease) patients were selected based on history, clinical examination and Doppler study.

For Category 5 (Type 2DM with Retinopathy) patients were selected based on Fundoscopic finding.

For Category 6 (Type 2 DM with nephropathy) patients were selected based on 24-hour urinary protein investigation. Excretion of more than 500 mg / day of total protein in the 24 hours urine in diabetic patients were considered to be because of nephropathy.

Patients having more than one complication together (e.g. Type 2 DM with coronary atherosclerosis as well as retinopathy) were grouped under both the categories respectively. While selecting subjects for the study group, following inclusion and exclusion criteria was adopted. For all the 120 subjects, 6 ml of peripheral venous blood was drawn under aseptic precaution from the antecubital vein; drawn blood was divided into 3 tubes as given below. Utmost care was taken to prevent hemolysis during the above procedure. Blood in Test Tube 2 (Plane) was allowed to stand for one
hour and Serum was separated by centrifugation after retraction of clot.

The separated serum was divided into 2 parts, 0.5ml of serum was stored in clean, acid washed, dried eppendorfs tube at - 20°C, which was used for Serum Zinc & Magnesium estimation within 3 weeks of collection. Remaining serum was utilized for estimation of parameters namely Blood Urea and Serum Creatinine on the same day of collection.

3. RESULTS

The levels of the analyzed descriptive statistics namely fasting plasma glucose, HbAlc, serum magnesium, serum zinc, blood urea, serum creatinine in 120 human subjects are tabulated in Table 1 and 2. The mean and standard deviation for each variable of different study groups (category 1 to category 6) which have been calculated are also shown in the respective tables (Table 1 & 2) and also depicted as histogram.

Statistically the levels of biochemical parameters of different study groups (category 2 to 6) are compared with the control groups (category-1) in Tables 3 to 7. Table 3 shows t-test to compare mean values between control groups and diabetic patients without complications. Table 4 shows t-test to compare mean values between control groups and diabetic patients with coronary atherosclerosis.

Table 5 shows t-test to compare mean values between control groups and diabetic patients with peripheral vascular disease. Table 6 shows t-test to compare mean values between control groups and diabetic patients with retinopathy. Table 7 shows t-test to compare mean values between control groups and diabetic patients with nephropathy.

Statistical significance between the levels of various biochemical parameters in all the comparison tables (Tables 3 to 7) was ascertained from the calculated 'p' value which was arrived using the student t-test. A p-value of< 0.05 was taken as significant. From statistical analysis, serum zinc levels were found to be significantly low (p<0.05) in type 2 diabetic groups irrespective of presence or absence of complications when compared to the control groups. Serum magnesium levels were also found to be significantly low ( p<0.05) in type 2 diabetic groups except in patients with diabetic retinopathy ( p = 0.021) when compared with the control groups.

To determine how far the serum zinc and magnesium levels varied with degree of control of disease, serum zinc and magnesium levels in the subjects irrespective of grouping and as well as with regard to grouping have been correlated with that of HbA1c in Table 8 and 9. Table 8 shows Karl Pearson Correlations co-efficient between HbA1C and Serum Magnesium (mg/dl) which shows positive correlation in controls and macro vascular complications like coronary atherosclerosis and peripheral vascular disease. Negative correlation is seen in overall groups, diabetic patients without complication and micro vascular complications namely retinopathy and nephropathy.

Table 9 shows Karl Pearson Correlations co-efficient between HbA1C and Serum zinc ( µg/dl) which shows positive correlation in overall groups, controls, macro vascular complications namely coronary atherosclerosis, peripheral vascular disease and micro vascular complication namely nephropathy. Negative correlation is seen in diabetic patients without complications and micro vascular complication namely nephropathy. Negative correlations between these trace elements and HbA1c can be attributed to loss of zinc and magnesium via urine due to osmotic diuresis in the presence of uncontrolled hyperglycemia.

Table 1. Descriptive statistics (overall group)

| Variables            | N   | Minimum | Maximum | Mean  | Std. Dev |
|----------------------|-----|---------|---------|-------|----------|
| FPG (mg/dl)          | 120 | 12.0    | 190.0   | 97.01 | 28.59    |
| HbAlC                | 120 | 4.4     | 10.4    | 6.09  | 1.15     |
| Serum Magnesium (mg/dl) | 120 | 1.2     | 2.7     | 1.75  | 0.38     |
| Serum Zinc (µg/dl)   | 120 | 12.0    | 118.0   | 66.81 | 15.94    |
| Blood Urea (mg/dl)   | 120 | 11.0    | 55.0    | 23.40 | 7.36     |
| Serum Creatinine (mg/dl) | 120 | 0.4     | 1.3     | 0.92  | 0.21     |
Table 2. T-Test to compare mean values between category 1 and category 2

| Variables            | Category | N  | Mean  | Std. Dev | t - Value | P - Value |
|----------------------|----------|----|-------|----------|-----------|-----------|
| FPG (mg/dl)          | Cat I    | 20 | 85.50 | 15.82    | 4.905     | <0.001    |
|                      | Cat II   | 20 | 123.60| 30.93    |           |           |
| HbA1C                | Cat I    | 20 | 5.21  | 0.47     | 5.088     | <0.001    |
|                      | Cat II   | 20 | 6.50  | 1.03     |           |           |
| Serum Magnesium (mg/dl) | Cat I | 20 | 2.10  | 0.30     | 3.944     | <0.001    |
|                      | Cat II   | 20 | 1.67  | 0.38     |           |           |
| Serum Zinc (µg/dl)   | Cat I    | 20 | 91.90 | 14.79    | 7.094     | <0.001    |
|                      | Cat II   | 20 | 65.60 | 7.49     |           |           |
| Blood Urea (mg/dl)   | Cat I    | 20 | 20.90 | 5.31     | 0.207     | 0.837     |
|                      | Cat II   | 20 | 20.60 | 3.70     |           |           |
| Serum Creatinine (mg/dl) | Cat I | 20 | 0.93  | 0.22     | 0.571     | 0.571     |
|                      | Cat II   | 20 | 0.97  | 0.17     |           |           |

Category 1 - Healthy and served as control; Category 2 - Type 2 DM without it's associated complication; Category 3 - Type 2 DM with coronary Atherosclerosis; Category 4 - Type 2 DM with peripheral vascular disease; Category 5 - Type 2 DM with Retinopathy; Category 6 - Type 2 DM with Nephropathy

Table 3. T-Test to compare Mean values between category 1 and category 3

| Variables            | Category | N  | Mean  | Std. Dev | t - Value | P - Value |
|----------------------|----------|----|-------|----------|-----------|-----------|
| FPG (mg/dl)          | Cat I    | 20 | 85.50 | 15.82    | 2.214     | 0.035     |
|                      | Cat III  | 20 | 103.15| 31.95    |           |           |
| HbA1C                | Cat I    | 20 | 5.21  | 0.47     | 4.592     | <0.001    |
|                      | Cat III  | 20 | 6.76  | 1.43     |           |           |
| Serum Magnesium (mg/dl) | Cat I | 20 | 2.10  | 0.30     | 4.980     | <0.001    |
|                      | Cat III  | 20 | 1.61  | 0.32     |           |           |
| Serum Zinc (µg/dl)   | Cat I    | 20 | 91.90 | 14.79    | 8.216     | <0.001    |
|                      | Cat III  | 20 | 58.80 | 10.29    |           |           |
| Blood Urea (mg/dl)   | Cat I    | 20 | 20.90 | 5.31     | 1.332     | 0.191     |
|                      | Cat III  | 20 | 23.20 | 5.61     |           |           |
| Serum Creatinine (mg/dl) | Cat I | 20 | 0.93  | 0.22     | 0.525     | 0.603     |
|                      | Cat III  | 20 | 0.90  | 0.21     |           |           |

Category 1 - Healthy and served as control; Category 2 - Type 2 DM without it's associated complication; Category 3 - Type 2 DM with coronary Atherosclerosis; Category 4 - Type 2 DM with peripheral vascular disease; Category 5 - Type 2 DM with Retinopathy; Category 6 - Type 2 DM with Nephropathy

Table 4. T-Test to compare Mean values between category 1 and category 4

| Variables            | Category | N  | Mean  | Std. Dev | t - Value | P - Value |
|----------------------|----------|----|-------|----------|-----------|-----------|
| FPG (mg/dl)          | Cat I    | 20 | 85.50 | 15.82    | 1.768     | 0.085     |
|                      | Cat IV   | 20 | 94.20 | 15.29    |           |           |
| HbA1C                | Cat I    | 20 | 5.21  | 0.47     | 3.670     | <0.001    |
|                      | Cat IV   | 20 | 6.22  | 1.13     |           |           |
| Serum Magnesium (mg/dl) | Cat I | 20 | 2.10  | 0.30     | 3.502     | <0.001    |
|                      | Cat IV   | 20 | 1.72  | 0.38     |           |           |
| Serum Zinc (µg/dl)   | Cat I    | 20 | 91.90 | 14.79    | 6.741     | <0.001    |
|                      | Cat IV   | 20 | 63.00 | 12.20    |           |           |
| Blood Urea (mg/dl)   | Cat I    | 20 | 20.90 | 5.31     | 0.680     | 0.500     |
|                      | Cat IV   | 20 | 22.15 | 6.27     |           |           |
| Serum Creatinine (mg/dl) | Cat I | 20 | 0.93  | 0.22     | 1.003     | 0.322     |
|                      | Cat IV   | 20 | 0.86  | 0.23     |           |           |

Category 1 - Healthy and served as control; Category 2 - Type 2 DM without it's associated complication; Category 3 - Type 2 DM with coronary Atherosclerosis; Category 4 - Type 2 DM with peripheral vascular disease; Category 5 - Type 2 DM with Retinopathy; Category 6 - Type 2 DM with Nephropathy
### Table 5. T-Test to compare Mean values between category I and category V

| Variables             | Category | N  | Mean  | Std. Dev | t - Value | P - Value |
|-----------------------|----------|----|-------|----------|-----------|-----------|
| FPG (mg/dl)           | Cat I    | 20 | 85.50 | 15.82    | 1.058     | 0.297     |
|                       | Cat V    | 20 | 78.60 | 24.50    |           |           |
| HbAIC                 | Cat I    | 20 | 5.21  | 0.47     | 3.177     | 0.003     |
|                       | Cat V    | 20 | 5.80  | 0.67     |           |           |
| Serum Magnesium (mg/dl) | Cat I | 20 | 2.10  | 0.30     | 2.406     | 0.021     |
|                       | Cat V    | 20 | 1.83  | 0.39     |           |           |
| Serum Zinc (µg/dl)    | Cat I    | 20 | 91.90 | 14.79    | 7.687     | <0.001    |
|                       | Cat V    | 20 | 61.60 | 9.59     |           |           |
| Blood Urea (mg/dl)    | Cat I    | 20 | 20.90 | 5.31     | 1.249     | 0.219     |
|                       | Cat V    | 20 | 23.15 | 6.05     |           |           |
| Serum Creatinine (mg/dl) | Cat I | 20 | 0.93  | 0.22     | 1.043     | 0.303     |
|                       | Cat V    | 20 | 0.86  | 0.21     |           |           |

Category 1 - Healthy and served as control; Category 2 - Type 2 DM without it's associated complication; Category 3 - Type 2 DM with coronary Atherosclerosis; Category 4 - Type 2 DM with peripheral vascular disease; Category 5 - Type 2 DM with Retinopathy; Category 6 - Type 2 DM with Nephropathy

### Table 6. T-Test to compare Mean values between category I and category VI

| Variables             | Category | N  | Mean  | Std. Dev | t - Value | P - Value |
|-----------------------|----------|----|-------|----------|-----------|-----------|
| FPG (mg/dl)           | Cat I    | 20 | 85.50 | 15.82    | 1.612     | 0.115     |
|                       | Cat VI   | 20 | 97.00 | 27.71    |           |           |
| HbAIC                 | Cat I    | 20 | 5.21  | 0.47     | 2.649     | 0.014     |
|                       | Cat VI   | 20 | 6.03  | 1.29     |           |           |
| Serum Magnesium (mg/dl) | Cat I | 20 | 2.10  | 0.30     | 5.398     | <0.001    |
|                       | Cat VI   | 20 | 1.61  | 0.27     |           |           |
| Serum Zinc (µg/dl)    | Cat I    | 20 | 91.90 | 14.79    | 7.492     | <0.001    |
|                       | Cat VI   | 20 | 59.95 | 12.04    |           |           |
| Blood Urea (mg/dl)    | Cat I    | 20 | 20.90 | 5.31     | 3.464     | 0.002     |
|                       | Cat VI   | 20 | 30.40 | 11.06    |           |           |
| Serum Creatinine (mg/dl) | Cat I | 20 | 0.93  | 0.22     | 0.856     | 0.397     |
|                       | Cat VI   | 20 | 0.99  | 0.19     |           |           |

Category 1 - Healthy and served as control; Category 2 - Type 2 DM without it's associated complication; Category 3 - Type 2 DM with coronary Atherosclerosis; Category 4 - Type 2 DM with peripheral vascular disease; Category 5 - Type 2 DM with Retinopathy; Category 6 - Type 2 DM with Nephropathy

### Table 7. T-Test to compare Mean values between category I and category VI

| Variables             | Category | N  | Mean  | Std. Dev | t - Value | P - Value |
|-----------------------|----------|----|-------|----------|-----------|-----------|
| FPG (mg/dl)           | Cat I    | 20 | 85.50 | 15.82    | 1.612     | 0.115     |
|                       | Cat VI   | 20 | 97.00 | 27.71    |           |           |
| HbAIC                 | Cat I    | 20 | 5.21  | 0.47     | 2.649     | 0.014     |
|                       | Cat VI   | 20 | 6.03  | 1.29     |           |           |
| Serum Magnesium (mg/dl) | Cat I | 20 | 2.10  | 0.30     | 5.398     | <0.001    |
|                       | Cat VI   | 20 | 1.61  | 0.27     |           |           |
| Serum Zinc (µg/dl)    | Cat I    | 20 | 91.90 | 14.79    | 7.492     | <0.001    |
|                       | Cat VI   | 20 | 59.95 | 12.04    |           |           |
| Blood Urea (mg/dl)    | Cat I    | 20 | 20.90 | 5.31     | 3.464     | 0.002     |
|                       | Cat VI   | 20 | 30.40 | 11.06    |           |           |
| Serum Creatinine (mg/dl) | Cat I | 20 | 0.93  | 0.22     | 0.856     | 0.397     |
|                       | Cat VI   | 20 | 0.99  | 0.19     |           |           |

Category 1 - Healthy and served as control; Category 2 - Type 2 DM without it's associated complication; Category 3 - Type 2 DM with coronary Atherosclerosis; Category 4 - Type 2 DM with peripheral vascular disease; Category 5 - Type 2 DM with Retinopathy; Category 6 - Type 2 DM with Nephropathy
Table 8. Karl Pearson Correlations co-efficient between HbAl C and Serum Magnesium

| Category   | N  | Correlation | P- Value |
|------------|----|-------------|----------|
| Overall    | 120| -0.161      | 0.079    |
| Cat I      | 20 | 0.165       | 0.488    |
| Cat II     | 20 | -0.294      | 0.208    |
| Cat III    | 20 | 0.495       | 0.027    |
| Cat IV     | 20 | 0.223       | 0.344    |
| Cat V      | 20 | -0.072      | 0.763    |
| Cat VI     | 20 | -0.513      | 0.021    |

Category 1 - Healthy and served as control; Category 2 - Type 2 DM without it's associated complication; Category 3 - Type 2 DM with coronary Atherosclerosis; Category 4 - Type 2 DM with peripheral vascular disease; Category 5 - Type 2 DM with Retinopathy; Category 6 - Type 2 DM with Nephropathy

Table 9. Karl Pearson Correlations co-efficient between HbAl C and Serum Zinc (µg/dl)

| Category   | N  | Correlation | P- Value |
|------------|----|-------------|----------|
| Overall    | 120| 0.655       | <0.001   |
| Cat I      | 20 | 0.543       | 0.013    |
| Cat II     | 20 | -0.285      | 0.223    |
| Cat III    | 20 | 0.405       | 0.077    |
| Cat IV     | 20 | 0.212       | 0.370    |
| Cat V      | 20 | 0.131       | 0.582    |
| Cat VI     | 20 | -0.333      | 0.151    |

Category 1 - Healthy and served as control; Category 2 - Type 2 DM without it's associated complication; Category 3 - Type 2 DM with coronary Atherosclerosis; Category 4 - Type 2 DM with peripheral vascular disease; Category 5 - Type 2 DM with Retinopathy; Category 6 - Type 2 DM with Nephropathy

4. DISCUSSION

The possible explanation of hypozincemia observed in diabetics can be hyperzincuria and decreased gastrointestinal absorption of zinc. Some other studies have also reported lower serum zinc levels in diabetics. Magnesium is an essential ion involved in multiple levels in insulin's secretion, its binding and its activity, and it is also a critical cofactor of many enzymes in carbohydrate metabolism. In this study, serum magnesium was significantly low in diabetics (p<0.05) when compared to control subjects. Similar observations are reported by Diwan et al, who also observed significantly lower serum magnesium levels in diabetics than in control subjects [7].

Lower serum magnesium levels in diabetics than in controls were also reported by Tripathy et al. In contrast to these results, Walter et al reported a study which showed no difference in serum magnesium levels between diabetics and control subjects [8].

Though serum magnesium levels may not accurately reflect the level of total body magnesium stores; persistent glycosuria with osmotic diuresis leads to magnesium wasting and likely contributes to high frequency of hypomagnesaemia in poorly controlled diabetics. The statistical lowering of serum magnesium level is absent in diabetic patients with retinopathy when compared with control subjects. In contrast to these results, Sharma reported a strong association with retinopathy and inverse correlation between serum magnesium level and poor glycemic control. HbA1c was included in the study which is a reliable marker of diabetes control and uncontrolled. Higher the value of HbA1c may be attributed to the more complication of the patient in the study group [9].

When the Karl Pearson correlation coefficient is analyzed between serum magnesium and HbA1c, it is seen that there is negative correlation in overall groups, diabetic patients without complications and micro vascular complications namely retinopathy and nephropathy. Similarly, when the Karl Pearson correlation coefficient is analyzed between serum zinc and HbA1c, it is seen that there is negative correlation in diabetic patients without complications and micro vascular complication namely nephropathy. In contrast to these results, Manal Kamal et al. also reported negative correlation between trace elements and HbA1c [10-12].
5. CONCLUSION

From the analysis of the results obtained, in controls, Type 2 diabetic patients without complication and Type 2 Diabetic patients with various macro and micro vascular complication selected for the study. There is definite hypomagnesaemia and hypozincemia in Type 2 Diabetic patients irrespective of the presence or absence of complication of Type 2 Diabetes mellitus, when compared to control groups. The statistical lowering of serum magnesium is absent between control groups and micro vascular complication of Type 2 Diabetes mellitus namely retinopathy. Serum Magnesium and HbA1c shows negative correlation in overall groups, diabetic patients without complications and micro vascular complication of Type 2 Diabetes mellitus namely retinopathy and nephropathy. Serum zinc and HbA1c shows negative correlation in diabetic patients without complications and micro vascular complication namely nephropathy.

CONSENT AND ETHICAL APPROVAL

Informed consent was obtained from all subjects. Study was approved by ethical committee. Detail history and clinical examination was done.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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