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Role of Serum Levels of Zinc, Magnesium and Calcium Levels in Patients of Type 2 Diabetes Mellitus

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Abstract

Introduction

Diabetes mellitus is a chronic metabolic disorder that arises due to absolute or relative deficiency in insulin production by the beta cells of the pancreas. The Current classification of diabetes mellitus is mainly based on etiology. It comprises type 1 diabetes mellitus (T1DM) T2DM gestational diabetes mellitus and other types of DM. Most accurate predictor for occurrence of T2DM is obesity. Main focus has been laid on the role of macronutrients. These are mainly carbohydrates and fats but, micronutrients are also closely associated with DM. Trace metal elements are naturally occurring inorganic elements which play important role in improving metabolic disorders as they act as cofactors of many enzymes and prosthetic group of various proteins. Direct association of macro and trace elements with DM have been observed in many research studies. Role of insulin in reducing the blood glucose level has been reported to be enhanced by some elements such as chromium, magnesium, vanadium, zinc, manganese, molybdenum, and selenium.

Aims

It was to estimate the serum magnesium and serum zinc levels in type 2 diabetes mellitus (T2DM) patients and comparison normal healthy population. Serum calcium levels in patients of T2DM and comparison with normal healthy population (controls). In all the studies the basis of diagnosis HbA1c levels. 100 samples were taken in the present study. Patient was divided into two groups group 1 included 50 T2DM patients and group 2 included 50 normal healthy controls. age wise four groups were made on the basis of age. Group A included patients in age group A 30 to

40 years, group B 41 to 50 years group C 51 to 60 years and group D included 61 to 70 years. The lab investigation in the form of glucose, HbA1c, Zinc, Magnesium and calcium were estimated.

Results

Levels oF FB glucose (FBS) in group 1 <126 mg/dl with mean ± SD of 209.82 ± 65.75 mg/dl. whereas in group 2 FBG levels were in the range of 70-100 mg/dl with mean SD of 84.06 ± 6.86 mg/dl in HbA1c levels were foam to be <7.5%. While in group B the HbA1c levels 6.86 ± 0.26 %. With the increasing groups this level was enhanced. In group 1 Zinc levels 88.24 ± 10.32 µ/dl. While levels of zinc among T2DM patients were less than60 µ/dl with mean± SD of 59.16 ± 10.10 µ/dl. This difference was statically was highly significant (p=0.001). So, this suggested T2DM patients have significantly with mean level of zinc lower in T2DM as compare to normal healthy individuals. Low levels of zinc may contribute in the development of T2DM as it has been associated with impaired insulin release, insulin resistance and Glucose intolerance. Magnesium level in group 1 were 1.6 to 2.5 mg/dl. This difference between T2DM and controls was statically highly significant. In this study it was observed at magnesium levels have mean value 1.8 mg/dl with mean ± SD 2.13 or 0.27 mg/dl. While the magnesium levels in group 2 less than 1.6 g/dl with mean 1.70 ± 0.33 mg/dl.It differences between two groups are was statically highly significant (p=0.001). So, it was suggested that in T2DM patients have significantly lower level of magnesium. Levels of serum calcium were found to besignificantly lower serum calcium level as compare to healthy individuals.

Keywords

Chronic metabolic disorder, zinc, Magnesium, Calcium, T2DM, Glucose intolerance, β cells

Conclusion

From the present study it was confirmed that serum levels of zinc, magnesium and chloride are associated with patients of T2DM level. Lower levels of zinc yet to be ascertained that but its strong association with T2DM indicated the role played by magnesium and zinc in glucose homeostasis. Calcium is needed for release of insulin from β cells of pancreas.

Introduction of significant HbA1c and minerals

AS per the data by international diabetes Federation, around 493 million adults (age 80-82 Years) were living with DM.BY 2046 this will raise to more than 729 million. India have more than 32 million cases of DM. The number may rise up to more 87 million by years 2032.[2]

DM can be classified into under given types

1. T1DM is due to autoimmune β cells distraction, leading to complete deficiency of insulin.
2. T2DM occurs due to more loss of β cells insulin secretion owing to insulin resistance.
3. Gestational diabetes mellites (GDM) is diagnosed in second or third trimester of pregnancy otherwise patient is normal.
4. Many types of diabetes mellites are due to causes for example: monogenic diabetes syndrome such as neonatal and maturity on set of the young [MODY], diseases of the exocrine pancreas such as cystic fibrosis and pancreatitis and drug or hormone induces for example glucocorticoid.

This depends upon level of HbA1c which is more than 7.0%.

Pre diabetes if the term used for individuals whose plasma glucose levels don't meet the diabetes mellitus but are very high to be considered normal. Patient with Pre-diabetes is not a clinical entity it may be associated with CVD, obesity, dislipidaemia with

high TG. The main factor considered for early incidence of T2DM in Indians. This may be due to life style of Indians[2].

Zinc is the second most abundant trace element essential for all living cells. It is a trace element essential for life. Zinc is essential for normal growth of the cells. It is a key component of structurer, catalytic and signaling process. Zinc finger motive was observed in the transcription[4].

The adult human contains >3 grams of insulin. Roughly skeletal muscle zinc is 60% and 30& in bones with 5& in liver and skin 5% with remaining 2-3% in bone of T2DM and other tissues. Zinc plays an important role in pathogenesis &physiology of carbohydrate of metabolism of carbohydrates[4]. Zinc plays an important role in insulin, storage, crystallization and secretion and action & translocation of insulin to the cells. Zinc stimulates glucose uptake of carbohydrates metabolism in insulin mimetic insulin sensitivity. Zinc is implicated in the suppression of proinflammatory cytokines e.g., interleukin-1β and another factor kβ, avoiding β cells. Destruction. and protecting insulin. Pancreatic β cells are cells. to contain relatively high concentration zinc as compared to various other cells[5]. Metallothionines, zinc importers and exporters. Nine zinc exporters and 14 zinc transporters (14ZIP) have been playing an important role in whole in zinc homeostasis at the cellular and subcellular levels[3]. These transporters act either collectively and in single specific manner. Zinc as whole is essential for the normal synthesis of insulin as well as its storage. Initially insulin mrna is translated into an inactive pre pro insulin molecule. Which comprises to chain that are coactive by c-peptide, with the signal peptide at the N-terminus pro inulin is forms pre pro insulin by signal peptide cleavage in the endoplasmic reticulum. Pro insulin folds into the final three-dimensional structure with formation of the correct disulphate bonds.

Magnesium

It is the fourth most abundant mineral and the second most abundant intracellular divalent cation. It is acting as a cofactor for more than 285 metabolic reactions in the body 15% magnesium in bone, 50% tissues and organs and less than 1% is in the blood. It imperative for protein synthesis, cellular energy production and storage, reproduction, DNA and RNA synthesis and stabilizing mitochondria membranes. It also plays an important role in maintaining normal nerve and muscle function[7]. Neuro muscular conduction, muscular contraction, vasomotor tone, normal blood pressure, bone integrity and glucose and insulin metabolism. Its deficiency is associated with migraine headaches Alzheimer's CVA, hypotension, CVD and T2DM. it plays important role in glucose and insulin metabolism through its impact on tyrosine kinase activity by transferring the phosphate from ATP to protein[8]. Magnesium plays an important role in auto phosphor relation of the β sub units of insulin receptors the insulin receptor tyrosine kinase is such that to magnesium ions can bind to the tyrosine kinase domain. The inflammatory environment is believed to the an important contribute to insulin resistance and is one of the main reasons that obesity is associated with T2DM[9]. the clinical evidence for role of Mg^{2+} in insulin secretion is limited and less understood than the effects of Mg^{2+} on insulin sensitivity but recent clinical study suggests that T2DM patient with hypomagnesemia have reduced insulin secretion. In patients without DM, low serum magnesium concentrations are associated with diminished secretion of insulin. There may exist a small cooperative effect of Magnesium attached to ATPon

glucose binding. Magnesium deficiency may therefore reduce glucose binding with glucokinase by slowing down metabolism and indirectly reducing insulin secretion[10]. It has been shown that magnesium increases synthesis of insulin at transcriptional level. Magnesium acts as an important regulator of protein synthesis and cell proliferation and may therefore regulate β-cell viability[11]. Although emphasized that DM may induce hypomagnesaemia, others have stressed that higher magnesium intake may decrease the onset of DM. In patients with T2DM, oral magnesium supplementation for 16-weeks period was suggested to improve insulin sensitivity and metabolic control. Calcium may play a key role in glucose homeostasis in many ways. Calcium regulates insulin-mediated intracellular processes in specific tissues that respond to insulin, participates in secretion of insulin from pancreatic beta cells and phosphorylation of insulin receptors[12]. Calcium also downregulates specific regulatory genes encoding proinflammatory cytokines that are involved in insulin resistance. Insulin secretion is a calcium-dependent process. There is a small range of intracellular calcium concentration needed for optimal insulin mediated functions. When there are changes in intracellular calcium concentration in insulin responsive tissues, insulin resistance increases. The role of VitaminD3 role in insulin secretion derives from its effects on Calcium influx, mobilization and buffering in pancreatic beta cells. There are oscillations in β pancreatic cells. These effects are independent of glucose levels. Patients with DM are at risk of getting renal failure due to volume depletion. In renal failure phosphorus can't be excreted, leading to hyperphosphatemia, which induces hypocalcemia. In addition, phosphate binds ionized calcium and removes calcium from the bloodstream.

Review

Al Maro of RA and L. Sharbati SS, in their study in 2006 reported that zinc levels in diabetes were lower as compared to control. They reported a strong reverse relationship between HbA1c levels of T2DM their level with with zinc and In T2DM.The first part of the study had shown that mean value of serum zinc was significantly lower in DM as compared to controls. It was 64±12.6 µg/dl in diabetes than 83.4±12.5 µg/dl. In 2013 the study was conducted by Saharia and Goswami, the serum zinc level was found to be very high than controls (79.86±13.4 vs. 109.74±9.72+µg/dl) with $p<0.001$ Study revealed inverse relation between HbA1c% serum zinc level in T2DM. In 2016 Atari-HajipirlooS observed higher levels of Cu and Fe as well as Cu/Zn and Fe/Zn ratios in patients of T2DM with the also observed in control. In T2DM group, a negative correlation between serum levels of HbA1c (r=--0.367, p= 0.01). The study conducted by Farooq DM et al in 2020 also observed that the mean Zn level was 11.7±1.5 in the control group whereas it was significantly low (9.3±1.6) in the diabetic group, while it was significantly low (p>1.6) in the diabetic group. The mean ages for the low zinc group and37.5±10.1and normal group were 40.9±12.5 respectively No substantial difference was noted in males and females. The clinical role for Mg evidence is less understand[13]. Some recent clinical studies have found that T2DM patients with hypomanesium have reduced insulin secretions. Hypomagnesemia has been found to occur in 13.5 to 45% on non-hospitalized patients with T2DM patients as compared to 2.5% to 15% in their counterparts. The wide range in the reported incidence of hypomagnesaemia, most likely reflects the difference in the definition of hypomagnesemia, techniques in measurement of magnesium levels and the

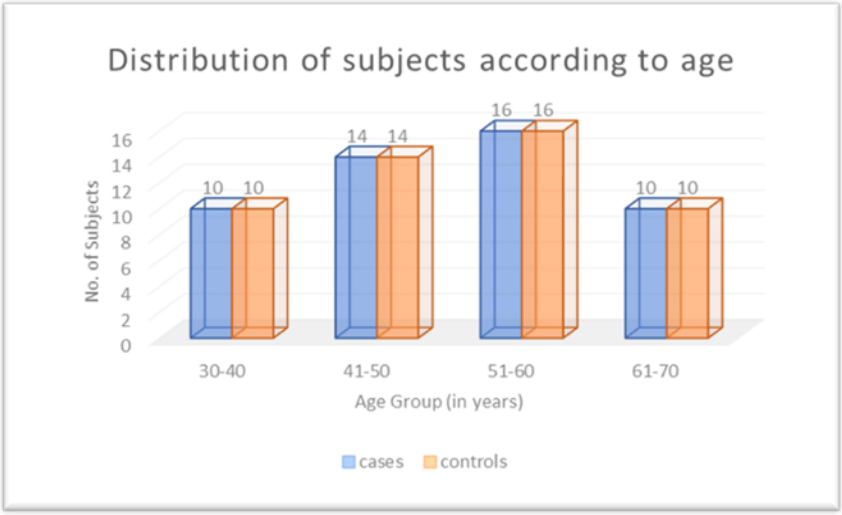
heterogeneity of the selected patient cohort[4]. This is seen higher in females than males in ratio of 2:1. In a 3 months prospective study conducted by Guerrero—Romero 60 participants were randomly assigned in a randomly assigned double blind manner to either 300mg/day of magnesium chloride or a placebo. The researchers found significant improvement in insulin sensitivity in magnesium supplemented group from baseline to the end of study ($p < 0.0001$). Researchers also found in serum magnesium concentrations from baseline to the end of intervention no change in placebo group ($p= 0.063$). In addition, calcitriol stimulates calcium via voltage dependent Ca channels. Pulsatol insulin release from pancreatic β is linked with frequency of calcium oscillations. In the same process insulin release oscillations are proportional to calcitriol.

Materials and Methods

The present study was conducted in Department of Biochemistry, Govt. Medical College, Amritsar in collaboration with Department of Medicine, Guru Nanak Dev Hospital, Amritsar. 100 samples of blood were taken in present study. Participants were divided into two groups: Group I include 50 T2DM patients and group 2 contains normal healthy controls. These were age group A of 30-40 years, Group B 41-50 years Group C had 51 to60 years and lastly Group D included 61 to 70 years. Biochemical investigations were done in all groups.

Exclusion Criteria

1. Patients more than 70 years and less than 30 years of age.
2. Patients on any kind of mineral supplements.
3. Patients with liver and kidney disease.



Graph - 1

Collection of blood sample

5 ml. of venous blood was taken from all subjects after 12 hours of overnight fasting in a dry disposable syringe under all aseptic conditions by venipuncture of the antecubital veinsunder all aseptic conditions.

Biochemical assays

Glucose: By GOD/POD Method.

HbA1c: By ion exchange method

Zinc: By colorimetric method by Nitro-PAPS Method.

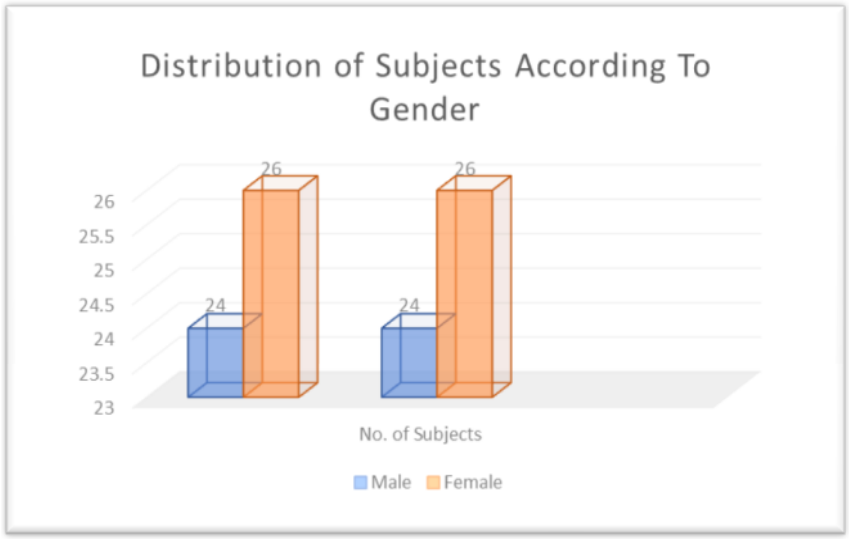
Magnesium: by Using calmagite method

Calcium: By O-Cresolphthalein Method

were estimated in serum in both the groups.

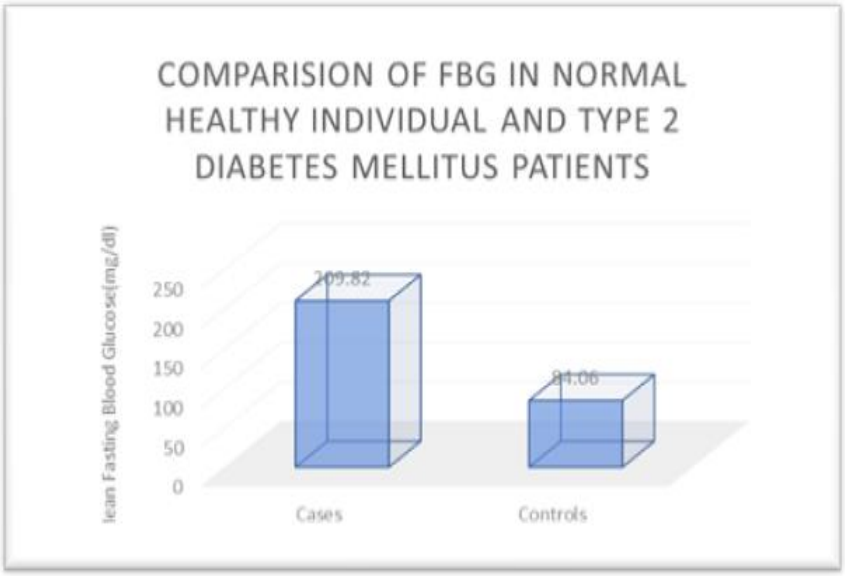
Observations

There was found similarity between the case and controls as it shows 52% females while males were 48% in both the cases and controls. So out of 50 cases and controls, 28 were females as well controls and 48 were males.



Graph – 2

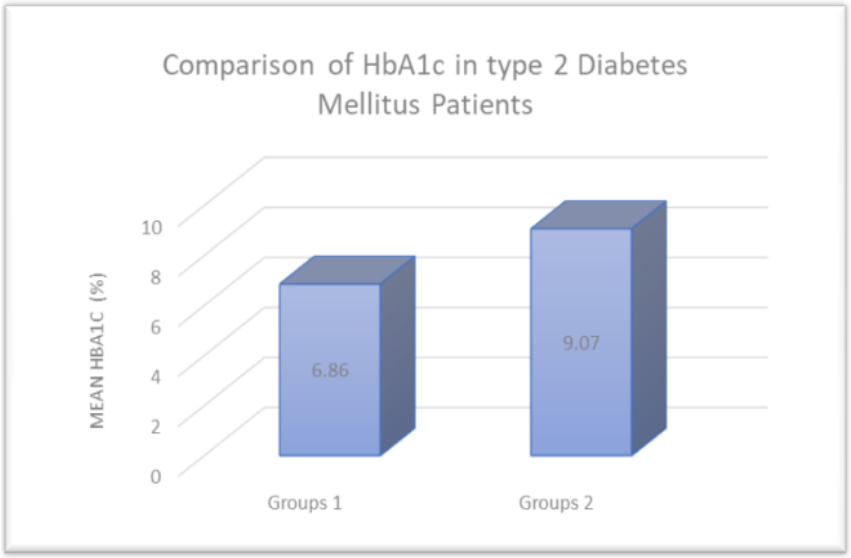
Levels of fasting blood glucose in controls was 70-100mg/dl with Mean± SD were 84.06±6.86 mg/dl and in cases it was >126 mg/dl with mean ± SD were 209.82±65.75. This was highly significant as p=0.001.



Graph - 3

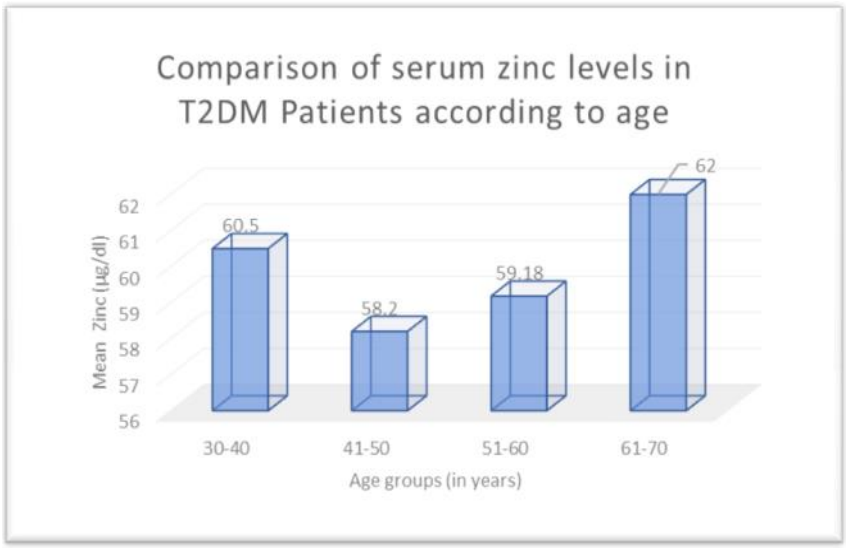
HbA1c levels in T2DM were divided into two groups. The group 1 (HbA1c<7.5%) type 2 cases and group 2 had been found (HbA1c>7.5%) with mean HbA1c ±SD of 9.07±1.36%. It was revealed highly

significant correlation between with p=0.001.In cases group 20% were found in the age group A, 20% (30-40), 28% (41-50 years) in group B, 32% in age group C (51-60) ,2o% age group D had age (61-70 years).



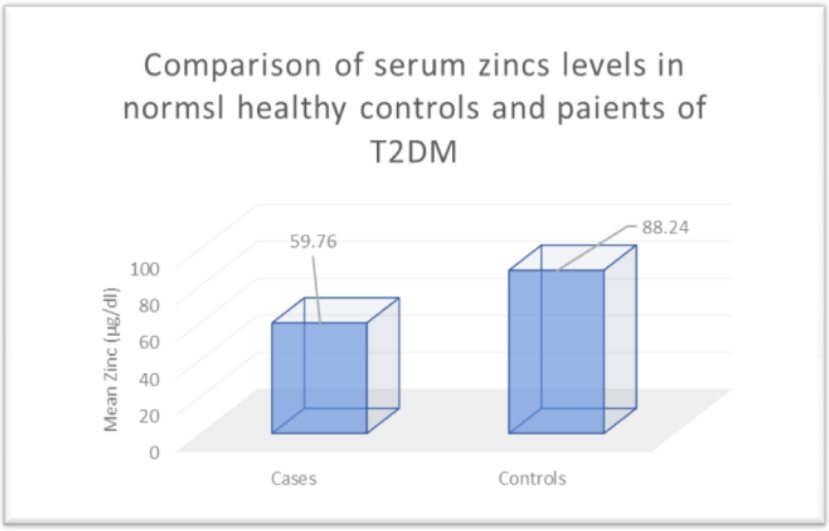
Graph - 4

Comparison of Zinc



Graph - 5

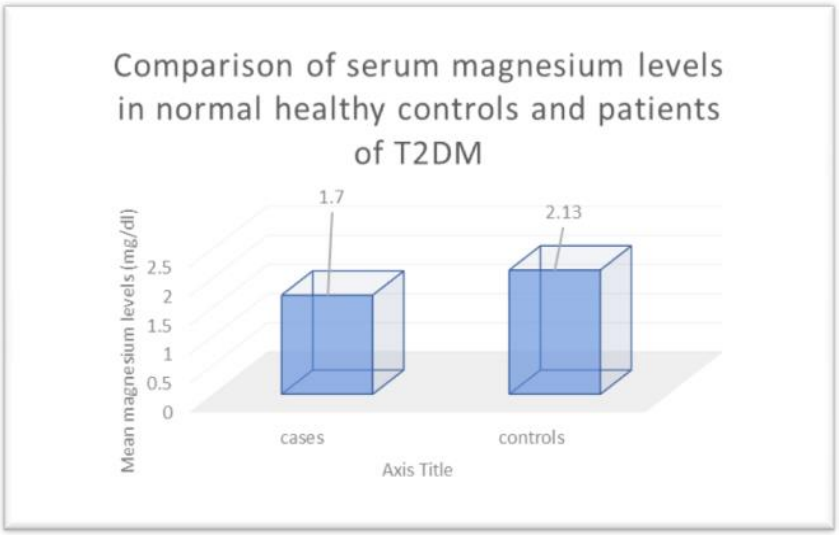
Serum zinc levels in the control group hadmean ± SD of 59.76±10.10 mg/dl. While the cases showed mean ±SD of 88.24±10.32. The difference between T2DM patients and control group showed highly significant (p=0.001). It was observed that levels of zinc were higher in group in cases as ± SD 64.48±8.42 µg/dl and there was very significant correlation between two groups (p=0.001).



Graph - 6

Magnesium

Magnesium levels among control were <1.6mg/dl. In cases it was found as I.6±2.5 mg/dl. In healthy age group was found to be 2.13±0.27mg/dl. In control group it was found to be <1.70±0.33 mg/dl. The difference between T2DM patients and controls was statistically



Graph - 7

highly significant (p=0.001) with the mean level of magnesium lower in T2DM patients as compared to normal healthy individuals. Levels of magnesium were higher in group 1(HbA1c >7.5%) with mean 0f ±1.82 SD of 1.82±o-28 mg/dl. It had decreased value in group

2 with mean of 1.60±0.35 mg/dl. There was significant difference between two groups regarding magnesium

levels (p=0.002 A). The mean level of serum magnesium in group A was 1.80±0.22 mg/dl while in group B it was 1.57±0.39 mg/dl. In group C it was highest in group C and lowest in group B, the difference was statistically insignificant. (P>0.05)

Calcium

Comparison of serum calcium shows calcium levels 8.7 t0 11.0 mg/dl with mean ±SD of 8.77±0.59 mg/dl in normal healthy individuals. While levels in DM patients levels of calcium among were <8.7 mg/dl and mean ± SD of 8.55±0.36 mg/dl. The difference between controls and T2DM controls and T2DM patients was significant statistically (p=0.035). It was observed that mean level of (HbA1c <7.5%) was 8.52±0.38 mg/dl. In group 2 of cases (HbA1c > 7.5%) was 8.59±0.36 mg/dl. There was insignificant difference between two groups regarding calcium levels (p>0.05). It was observed that the mean level of calcium in in group A subjects was 8.44±0.35 mg %, In group B it was 8.6±0.37 mg/dl. The mean level in group C and D were 8.58±0.37 mg/dl and 8.53±0.38. The difference between serum calcium levels among different age groups was no significant (p>0.05).There was correlation positive correlation of zinc, magnesium and calcium in T2DM and controls. The zinc was positively correlated with magnesium and calcium in cases having coefficient value of correlation 0.122 and 0.041 respectively. Magnesium was negativelycorrelated with calcium in both cases and controls having value of coefficient of correlation 0.100 and -0.049 respectively. However, the results were insignificant among all parameters with p=0.05.

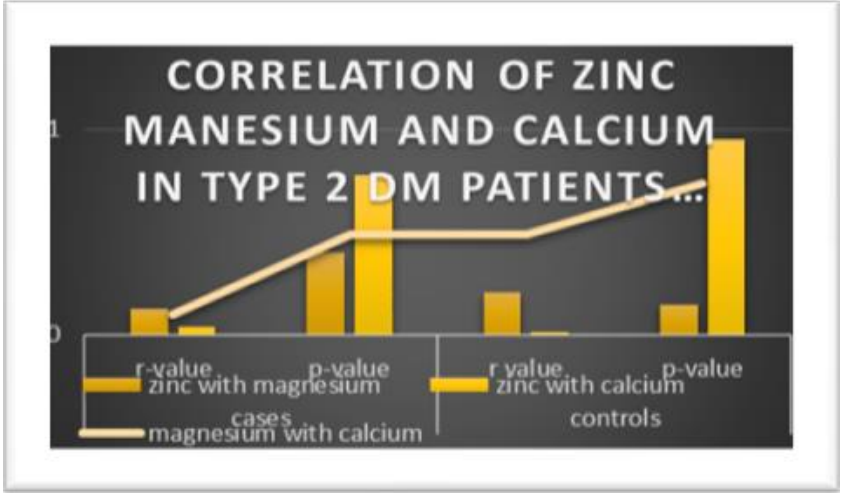
Discussion

In the present study, the males Were the ratio of males and females of study group, females were dominant in both the groups i.e., study and control group (48% males & 52% Females)[5]. Fasting blood Glucose levels in group 1 was equal to equal or more than 126 mg/dl with mean ±SD of 209.82±65 while in controls Normal FBG levels were in the range of 70-100 mg/dl with mean ±84.06±6.86 mg/dl. According to American diabetes association recommendation, a goal of reasonable HbA1c for many nonpregnant adults is <7% (Good glycemic[2]. The study by control) in females and for those having diabetic like symptoms it was >7.5% (poor glycemic control). Study conducted by Farooq DM et al showed similar results[3]. Mean serum levels of zinc in serum in group A was 60. 50±11.While in group B it was 88.24±10.32 µg/dl while the levels of zinc T2DM were <60 µg/dl in 24 subjects. and between 60-120µg/dl in 26 subjects with mean ±SD of 5976±10.10 µg/dl. The difference between T2DM and controls was highly significant (p=0.001) and mean level of zinc lower in T2DM as compared to controls[5]. So T2DM patients showed significantly lower zinc level as compared to healthy adults. This is in line with conducted by Atari-Hajipirloo S et al who found lower level of zinc in patients of T2DM as compared to healthy adults. In fact, zinc levels have been associated with impaired insulin release[6]. Thus, the present study depicts that those patients of T2DM with poor glycemic control have significantly lower levels of Zinc[7]. Farooq DM et al[9]. It was found that magnesium levels among normal healthy were <1.6mg/dl in two cases while in rest 48 patients ±SD of 2.13±0.27mg/dl. The magnesium levels in T2DM levels were 1.6-2.5 mg/dl and in 37 patients ±SD 1.70±0.33 mg/dl. The difference between T2DM levels and normal healthy individuals was highly significant with p=0.001. Thus, the present study suggests that type 2 diabetics serum magnesium levels were high in the patients. This is in line with the study done by Jayaraman SMT et al and Woledo AD et

al. Low levels of magnesium may be due to loss of magnesium in diarrhea, malabsorption, increased renal loss or lower levels of magnesium may act as factor leading to onset of diabetes. Mean serum levels were higher in group 1 (HbA1c<7.5%) with mean± SD of 1.80 ± 0.22 when compared to group 2 (HbA1c<7.5%) with mean of ±SD of 1.60±0.35 mg/dl. There was significant difference between magnesium level of two groups (p=0.002). It was observed that calcium levels were <8.7 mg/dl in 27 subjects and between 8.7 to 11.0 mg/dl. Among normal healthy subjects mean± SD of 8.7±0.59. In the patients under study, it was 8.55±0.36 mg/dl subjects between 8.7 to 11.0 mg/dl. The difference between controls and patients was statistically significant (p=0.035) with the mean level of calcium lower in T2DM patients as compared to normal healthy individuals. So the present study shows significantly lower levels of calcium in T2DM as compared to normal. This in line with study conducted by Najeeb Q et al[12]. Lower levels of calcium may be due to the fact that patients with diabetes mellitus have an increased levels of developing acute Renal Failure. Advanced renal may be associated with hypocalcemia or lower level of vitamin D[6]. The mean level of serum calcium in patients of group A 8.44±0.37mg/dl while in B it was 8.63±0.37mg/dl. Mean levels of group 3 and 4 were 8.58±0.37 and 8.53±0.38 mg/dl. Mean level of serum calcium was maximum in group B and minimum in group A.

Conclusion

It can be concluded from the study that serum zinc, magnesium and calcium are associated with associated to patients of T2DM. Low levels of magnesium and decreased levels of zinc is the cause or consequence diabetes mellitus is yet to be ascertained but its association with T2DM indicates the role played by magnesium and zinc in glucose homeostasis. Calcium is needed for release of insulin from β cells of pancreas. The association of zinc, magnesium and calcium estimation should be a part of the screening panel in the risk detection of T2DM patients. Supplementation with these minerals may be considered when the status of zinc, magnesium and calcium is poor in T2DM patients and for those subjects that are at risk of developing type 2 diabetes mellitus. Further study with more sample sizes is needed to correlate these associations.



Graph - 8

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