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Effect of Hyperglycemia on Impairment of Calcium Metabolism in T2DM

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ABSTRACT

Background: T2DM or type 2 diabetes mellitus is mostly related to the growing incidence of reduction in bone mineral density with increased porosity and susceptibility to fractures. Diabetes mellitus eventually compromise bone quality through production of advanced glycation products and misalignment of collagen fibrils, thereby culminating in reduction of bone strength. The underlying cellular mechanisms are related to suppression of osteoblast-induced bone formation and calcium accretion, as well as enhancement of osteoclast- induced bone resorption.
Objectives: The aim of the present study was to evaluate the effect of high glucose level on the impairment of calcium metabolism in diabetes mellitus patients and to study the inter- relationship between diabetes mellitus and calcium metabolism. The linked association between them would be helpful to support public health policy markers and practioners.
Materials and Methods: Total 100 samples were collected from Government Civil Hospital, Lopoke (Amritsar) with age group of 35-60 years having duration of diabetes more than 5 years. Blood and urine samples were analysed for biochemical parameters such as serum fasting glucose, alkaline phosphatase (ALP), albumin, vitamin D, phosphorus and calcium. Urine samples were also analysed to examine the excretion of phosphorus and calcium.
Results: Decreased levels of serum calcium, albumin, vitamin D in serum along with elevated urinary calcium were observed in type 2 diabetic patients.
Conclusion: From the study it has revealed that in the diabetic patients the calcium metabolism has been affected by the hyperglycemic state of the body. Hence, it is well established that effect of hyperglycemia on calcium metabolism is a risk factor for the development of osteoporosis in diabetic patients.

Keywords: Diabetes mellitus, Insulin, Osteoporosis, Calcium, Phosphorus, Vitamin D.

INTRODUCTION

T2DM or non-insulin-dependent diabetes mellitus is common form of diabetes, which accounts for 90–95 % of diabetic patients. It results from insulin resistance and relative insulin deficiency rather than absolute deficiency. Long term suffering from diabetes mellitus (DM) is mostly related to the growing incidence of bone related complications such as osteoporosis [1]. Diabetic patients frequently develop electrolyte related disorders. These patients are often potassium, magnesium, phosphate and calcium depleted, especially in context of diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar syndrome. Both types of DM eventually compromise bone quality through production of advanced

glycation end products and misalignment of collagen fibrils (so called matrix failure), thereby culminating in a reduction of bone strength. The underlying cellular mechanisms are related to suppression of osteoblast-induced bone formation and bone calcium accretion, as well as to enhancement of osteoclast- induced bone resorption [2]. Diabetes mellitus (DM) increases osteoclast function but decreases osteoblast function, thereby leading to the accelerated bone loss, osteopenia and osteoporosis. The mechanism is effected by insulin deficiency leads to IGF-1 deficiency and high glucose levels which inhibit osteoblast activity. Glycosuria elevate the Ca+ excretion and decrease serum Ca+ activates PTH that activates osteoclast avitivity [3].

Calcium metabolism is the movement and regulation of calcium ions (Ca^{2+}) *in* (via the gut) and *out* (via the gut and kidneys) of the body and between body compartments : the blood plasma, the extracellular and intracellular fluids and bone. Bone acts as a calcium storage center for deposits and withdrawals as needed by the blood via continual bone remodeling [4]. An important aspect of calcium metabolism is *plasma calcium homeostasis*, the regulation of calcium ions in the blood plasma within narrow limits [5]. The level of the calcium in plasma is regulated by the hormones parathyroid hormone (PTH) and calcitonin. It is imperative to study the status of calcium metabolism in the body in the state of hyperglycemia to study its possible effect so that further diabetic complications related to bone disorders can be controlled. Thus, the study was aimed to analyze the biochemical parameters viz, calcium, phosphorus, albumin, alkaline phosphatase and vitamin D in serum of diabetic patients.

MATERIALS & METHODS

Biochemical investigation was done in diabetic subjects with age group of 35-60 years. Control group included both males and females of same age group without any systemic or endocrine disorder. Inclusion criteria involved the patients with type 2 diabetes mellitus with the duration of disease more than 5 years. Exclusion criteria included the cases having liver or cardiac problems, gestational diabetes, type 1 diabetes mellitus, thyroid dysfunctioning. Patient performa was structured and information regarding patient history for each individual subjects included in the study was obtained. Informed consents were taken from the patients and study protocol was approved by the Institutional Ethical Committee. Samples of the patients and controls were collected from Government Civil Hospital, Lopoke (Amritsar) and distributed in two groups viz. Group- I: healthy controls / non- diabetic persons and Group- II: type 2 diabetes mellitus patients. Blood and urine samples were collected and serum sample was separated by centrifugation at 1500 rpm for 15 minutes, and sample was preserved for further analysis. The level of glucose was analyzed by GOD- POD method [6]. Alkaline phosphatase was analyzed by PNPP Kinetic method [7]. Calcium was analyzed by OCPC method [8]. The level of phosphorus was determined by Molybdate U.V. method [9]. Albumin level was determined by BCG method [10]. The level of vitamin D was analyzed by ELISA method [11] using Microplate Reader [Alere, AM 2100] Biochemical investigation was performed on Semi-autoanalyzer (ERBA, Manheim Chem-5 Plus) Data was recorded in MS Excel. Data was analyzed on Statistical Package for Social Sciences (SPSS) version 25.0. One way ANOVA was applied to find the statistical relationship or differences in studied variables at 95% confidence interval and a P-value < 0.05 was considered significant. Descriptive statistics was used to measure mean and standard deviation for representation of data.

RESULTS & DISCUSSION

The mean age of the type 2 diabetic and healthy controls included in the study was comparative to each other. Mean age of healthy controls and type 2 diabetic subjects included in the study was 48.6±8.14 years and 51.3±7.49 years respectively. The elevated level of fasting glucose (171.2±35.5 mg/dl, $p<0.05$) was found in type 2 diabetic patients as compared to healthy controls included in the study. Diabetic patients had higher levels of glucose because of the body's inability to use glucose. There are so many factors encountered leading to diabetes and increased fasting blood glucose level in patients such as high familial aggregation, obesity, insulin resistance and lifestyle changes due to rapid urbanization [12]. Both the studied age groups of diabetic patients, showed high level of fasting glucose but 46–60 year age group had statistically significant increased levels (186.9±38.1 mg/dl, $p<0.05$) because with increased age, the pancreas produces less insulin which means blood sugar remains elevated for longer time. Although fasting glucose levels are generally known to increase with advancing age [13] and age specific associations of fasting glucose with all-cause mortality have rarely been examined. However it has been observed that both males and females did not showed any significant differences.

Table 1: Comparison of different biochemical parameters in controls and type II diabetic patients under study

S.No.	Biochemical parameters	Healthy controls	Type II Diabetic patients
1.	Fasting blood glucose (mg/dl)	90.3±9.41	171.2±35.5
2.	Alkaline phosphatase (U/L)	68.4±10.6	94.3±16.5
3.	Serum phosphorus (mg/dl)	4.13±0.41	5.75±0.85
4.	Urinary phosphorus (gm/24hr)	0.62±0.05	0.25±0.1
5.	Serum albumin (gm/dl)	4.07±0.37	3.14±0.56
6.	Serum calcium (mg/dl)	9.59±0.49	7.69±1.43
7.	Urine calcium (mg/24hr)	124.5±26.8	309.4±44.1
8.	Vitamin D (ng/ml)	45.8±5.21	30.0±9.32

*Data represented as mean ±S.D.

The alkaline phosphatase activity was significantly higher in type 2 diabetic patients 94.3±16.5 U/L ($p<0.05$) as compared to healthy controls 68.4±10.6 U/L which indicated a sign of bone condition as ALP isoenzyme is most abundant in the bones and liver. Females diabetic subjects had significantly higher ALP activity ($p<0.05$) than their male counterparts. However, no significant differences were observed in age groups. Serum phosphorus levels were high in diabetic subjects as compared to healthy controls, although urine excretion of phosphorus was significantly high in diabetic subjects. There were no age-wise and gender-wise significant differences encountered.

Table 2: Age-wise differences in levels of different parameters of diabetic patients under study.

S.No.	Biochemical parameters	Age group (35-45 years)	Age group (46-60 years)
1.	Fasting blood glucose (mg/dl)	128.7±23.3	186.9±38.1
2.	Alkaline phosphatase (U/L)	95.26±15.9	94.04±21.4
3.	Serum phosphorus (mg/dl)	5.37±1.41	5.89±1.89
4.	Urinary phosphorus (gm/24hr)	0.28±0.25	0.24±0.20
5.	Serum albumin (gm/dl)	3.28±0.36	3.12±0.37
6.	Serum calcium (mg/dl)	8.05±1.51	7.67±1.41
7.	Urine calcium (mg/24hr)	303.7±37.9	309.1±40.8
8.	Vitamin D (ng/ml)	24.3±7.86	31.7±10.9

*Data represented as mean ±S.D.

The level of calcium in blood serum of diabetic subjects has been found to be reduced as compared to healthy control ($p<0.05$). However, females and higher age group individuals had lesser serum calcium but no significant differences were found as compared to their male counterparts and lower age group patients, respectively. The

urinary excretion of calcium in diabetic patients was found to significantly higher ($p<0.05$) as compared to controls, although no age-wise and gender-wise differences were observed statistically. Albumin levels in serum of healthy controls were higher in comparison to diabetic subjects, although no significant differences were observed among both studied age groups and genders.

It has been observed that vitamin D levels were significantly lower in diabetic patients as compared to healthy controls ($p<0.05$), although subjects were not deficient, but normal. However, levels were quite low as compared to healthy counterparts. Also, female diabetic patients were found to be more affected as compared to males. The level of vitamin D was higher in patients of 35-45 years of age as compared to the patients of 46-60 years of age.

Table 3: Determination of levels of biochemical parameters in type II diabetic patients based on gender distribution

S.No.	Biochemical parameters	Males	Females
1.	Fasting blood glucose (mg/dl)	174.6±36.7	168.7±34.3
2.	Alkaline phosphatase (U/L)	86.41±2.31	100±8.12
3.	Serum phosphorus (mg/dl)	5.56±0.64	5.89±0.99
4.	Urinary phosphorus (gm/24hr)	0.24±0.21	0.26±0.22
5.	Serum albumin (gm/dl)	3.22±0.44	3.09±0.32
6.	Serum calcium (mg/dl)	7.72±1.59	7.66±1.33
7.	Urine calcium (mg/24hr)	310.8±14.8	311.3±15.2
8.	Vitamin D (ng/ml)	44.95±4.32	30.87±4.56

*Data represented as mean ±S.D.

Table 4: Differences in biochemical parameters of diabetic patients on different medications

S.No	Biochemical parameters	Metformin Hydrochloride	Glimepiride	Metformin Hydrochloride and Calcium Supplements	Ayurvedic
1.	Fasting blood glucose (mg/dl)	191.4±53.9	179.2±50.3	183.6±40.6	182.2±40.7
2.	Alkaline phosphatase (U/L)	94.99±23.5	99.90±19.4	95.80±17.4	81.43±13.0
3.	Serum phosphorus (mg/dl)	6.51±1.85	6.41±1.71	4.50±0.49	5.37±1.47
4.	Urinary phosphorus (gm/24hr)	0.19±0.07	0.20±0.16	0.64±0.25	0.17±0.06
5.	Serum albumin (gm/dl)	3.13±0.27	3.38±0.53	3.01±0.42	3.02±0.26
6.	Serum calcium (mg/dl)	6.77±0.83	7.51±1.29	8.85±1.27	7.38±1.30
7.	Urine calcium (mg/24hr)	335.8±54.03	328.9±57.33	236.3±37.5	307.3±36.4
8.	Vitamin D (ng/ml)	26.27±10.1	23.46±5.27	28.39±11.4	26.97±6.24

*Data represented as mean ±S.D.

One of the main reason of elevated fasting blood glucose level is ignoring the diet chart eat more junk food and lack of physical acitivity. According to the Centers for Disease Control and Prevention (CDC), men are more likely to receive a diagnosis of diabetes than women. Having overweight or obesity is considered a primary risk factor for diabetes. Some research suggests that women are more proactive than men about managing their type 2 diabetes. In addition, the androgen hormone 'testosterone' is vital in male puberty. This is particularly worrying as $1/6^{th}$ of all males have low testosterone, which leads to increased fat storage and dramatic increase in diabetes risk. The relationship between alkaline phosphatase and type II diabetes have been examined, and the levels were higher than healthy controls. Many things may cause increases of ALP activity in serum, the most common being obstructive liver disease and metabolic bone disease. Bone specific alkaline phosphatase isoenzyme is elevated as a result of increased osteoblastic activity. The enzyme activity, which is localized in the plasma membrane of osteoblasts before extracellular release, correlated with the extent of the disease. The high ALP was generally observed in women who were at menopausal stage. Ageing and menopause, which leads to decline in estrogen and progesterone production has been implicated

in the increased levels of alkaline phosphatase in postmenopausal women. Thus, high levels of ALP in elderly women suggest the presence of osteoporosis. Many women experience osteoporosis after menopause [14]. Inverse relationship of serum calcium and phosphorus has been diagnosed in subjects under study. As levels of phosphorus in the blood rise, levels of calcium in the blood fall because phosphorus binds to calcium reducing the available free calcium in the blood [15]. However, decreased level of urinary phosphorus in type II diabetic patients was found because when serum phosphorus level increases and the filtered load of phosphorus increases and causes net urinary loss of phosphorus occurs because of the transcellular shift, and reduced renal phosphate reabsorption [16]. The mean level of serum phosphorus was higher in the age group of 46-60 years due to hypocalcemic levels and uncontrolled diabetes. Although, in some people with certain kidney disease, high phosphorus levels cause calcium levels in the blood to drop. Although older age group people had slightly lower levels than other group and it happens when the body has low levels of this vital mineral. In case of diabetic females, they had slightly inclined level of serum phosphorus as compare to males. As vitamin D is known to increase the absorption of calcium and phosphorus in human gut, in order to maintain the calcium homeostasis [17]. Thus, due to calcium and vitamin D deficiency in females, diabetic females had slightly higher serum phosphorus than diabetic male group. Phosphorus homeostasis includes regulation of intestinal absorption from diet, bone turnover, and urinary excretion and it is regulated by combined actions of parathyroid hormone and vitamin D [18].

Decreased level of serum albumin in diabetic patients was due the reason that more than 50% of the plasma calcium is bound to albumin. In diabetes, albumin synthesis and secretion is decreased due to insulin deficiency. Therefore, it is expected that albumin levels decrease in diabetes and may affect plasma protein glycation and glycosylated hemoglobin (HbA1c) is a measure of high glucose levels [19]. The elderly age group (46-60 years) people have slightly decreased and the most common causes might be vitamin D deficiency, malnutrition or other conditions. Low levels of albumin are associated with difficulty in recovery after acute pathologies and it's level decreases continuously with the aging [20]. Similarly, diabetic females also had slightly lower levels and the most common causes might be vitamin D deficiency, malnutrition or other conditions Also, calcium in serum is bound to proteins, principally albumin. As a result, majority of body calcium is bound to albumin for strong bones. Incidence of hypoalbuminemia increased parallel with age from 1.2% to 4.1% in males and 0.6% to 6.6% in females [21].

The type II diabetic patients showed lower levels of serum calcium. Both type I and type II also diabetes mellitus (TIDM and T2DM) are associated with profound deterioration of calcium and bone metabolism, partly from impaired intestinal calcium absorption, leading to reduction in calcium uptake into the body. However, both types of DM eventually compromise bone quality through production of advanced glycation end products and misalignment of collagen fibrils (so- called matrix failure), thereby culminating in a reduction of bone strength. Whereas, slightly higher levels of urine calcium was observed in diabetic patients because in the kidneys, DM and resultant hyperglycemia lead to calciuresis and hypercalciuria in human beings [22]. Renal dysfunction might occur following hyperglycemia with subsequent vitamin D deficiency which is very important in calcium homeostasis and in bone metabolism [23]. The elderly age group (46-60 years) also

showed lower levels of serum calcium due to increased blood sugar levels inhibit bone-forming cells from building strong bones by lowering the calcium level. As ageing progresses, due to decreased dietary uptake and reduced absorption, calcium homeostasis is altered. The most common cause of hypocalcemia is hypoalbuminemia in old diabetic people. Besides this, diabetic duration, vitamin D deficiency, alcoholism, low estrogen in women, dietary intoleranc caused low calcium in body in elderly people. Also, mildly elevated levels of urinary calcium was observed in both the age groups. These findings suggest that increased urinary calcium excretion is observed during poor blood glucose control, and may be one of the factors leading to reduced bone mass in diabetes mellitus [24]. The decreased level of serum calcium was observed in female than males diabetic group indicated women are more prone to calcium deficiency, especially, with age group 46 to 60 years old, who are going through menopause. This is because of the change in female hormone estrogen at the menopause which directly affect the bone density and plays a important role in calcium metabolism. Estrogen inhibits osteoblasts activity by reducing their number [25]. However, other causes for calcium deficiency include vitamin D deficiency, not getting enough calcium in diet, gut disorders, abnormal magnesium, high phosphorus levels [26]. Both males and females diabetic group showed slightly higher level of urinary calcium. High calcium excretion is associated with vitamin D deficiency, reduced calcium absorption are the causes of hypercalciuria in bones and increases chances and may predispose to trabecular bone loss [27].

The level of vitamin D was lower in diabetic patients as compared to healthy controls. Vitamin D is a well- known vitamin responsible for bone and calcium metabolism and is responsible for regulating blood glucose levels. Also, calcium has also similar relationship to vitamin D, which means that when vitamin D declines, calcium levels also falls down and hence calcium is not stored in the bones. The younger age group had decreased level than older age group. The high prevalence of vitamin D deficiency in younger individuals may be explained by their lower consumption of vitamin D-containing foods and insufficient exposure to sunlight [28]. The levels of vitamin D level were also low in females as compare to diabetic males. Vitamin D deficiency was present in 88% of women. There is a high prevalence of hypovitaminosis D among women of reproductive or postmenopausal age. These women may possibly have higher risk of development of osteoporosis and other complications in future life [29]. Vitamin D deficiency is most common cause of hypocalcemia in diabetic patients.

Diabetic patients on different medications were also analyzed for biochemical parameters and it has been observed that patients taking glimepiride had higher calcium levels as compared to patients on metformin hydrochloride and on ayurvedic medicines. Moreover, maximum level was found in patients on combination of metformin hydrochloride and calcium supplements. Also, urinary calcium excretion and serum phosphorus level was reduced in those patients.

CONCLUSION

The levels of calcium, albumin and vitamin D were reduced in type II diabetes mellitus subjects under study. However, the levels of phosphorus and alkaline phosphatase activity was found elevated in diabetic subjects. Further, it has been observed that studied parameters were more altered in female diabetic patients as compared to male counterparts. Hypovitaminosis D was more pronounced in females as compared to males. Moreover, aged subjects (46- 60 years) were more affected obviously due to prolonged disease duration and hyperglycemic state.

Further, it has been observed that levels of vitamin D were reduced in age group of 35-45 years as compare to diabetic patients of age group 46-60 years. Also, parameters were compared in diabetic patients taking different medications and it has been observed that calcium and phosphorus levels were less affected with the combination of metformin and calcium supplements in studied subjects. In diabetes, renal dysfunction might occur following hyperglycemia with subsequent vitamin D deficiency which is very important in calcium homeostasis and in turn bone metabolism. Lower level of insulin and high blood glucose concentration and high plasma phosphorus concentration which in turn might lead to reduction in serum calcium and elevation of plasma alkaline phosphatase following bone reabsorption. More investigation should be done to elucidate the exact mechanism by which bone disease appeared in patients with high level of blood glucose.

Conflict of Interest: None

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