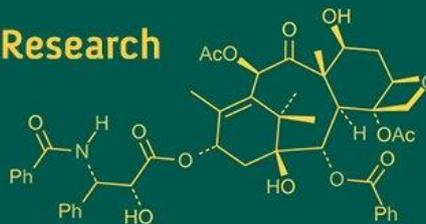
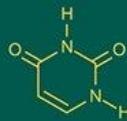
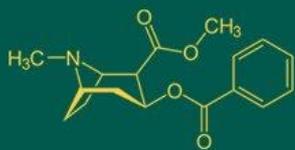


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Comparative study of serum calcium, serum phosphorus and alkaline phosphatase between prediabetes and type-2 diabetes mellitus

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Abstract

Background: Diabetes mellitus, a group of metabolic disorders with multiple etiologies is characterized by chronic hyperglycaemia, induced by deficiency of insulin production and insulin action. Prediabetes is a type of hyperglycemia in which glycemic indices are higher than normal but lower than the diabetes threshold.

Objective: This study aims to assess the impact of bone markers (serum calcium, phosphorus and alkaline phosphatase) on prediabetic and type 2 diabetes mellitus patients.

Material and Methods: This study was carried out in 2021 from January to December, in the Department of Biochemistry, Teerthanker Mahaveer Hospital, and Moradabad. Comparative levels of serum calcium, serum phosphorus and alkaline phosphatase between 65 Prediabetic and 65 Type2 diabetes mellitus patients were measured using an automated method.

Results: Serum ALP and serum phosphorus were significantly higher in the diabetic patients than that in the pre diabetic group ($p < 0.001$), whereas serum calcium was significantly lower in type 2 diabetes mellitus patients than that in prediabetes ($p < 0.001$).

Conclusion: Our findings depict variations in serum mineral levels are linked to prediabetes and these parameters can be considered as independent predictors for the diagnosis of type II diabetes mellitus, and their early diagnosis could be beneficial to prevent further complications.

Keywords: Alkaline phosphatase, calcium, phosphorus, prediabetes, type 2 diabetes mellitus

Introduction

Diabetes mellitus is the most common metabolic disease. It was initially reported 3000 years ago in Egyptian manuscripts and the distinction between type 1 and type 2 diabetes mellitus was established in 1936 [1, 2].

Diabetes mellitus is a worldwide pandemic disease that occurs in more than 150 million individuals. In 2030, globally the number of adults suffering from diabetes will reach to 439 million, with the majority of cases being type 2 diabetes mellitus. Diabetes mellitus is a one of the main cause of illness and mortality in the United States [3].

Diabetes mellitus refers to a group of metabolic disorder with a multiple etiologies that are defined by chronic hyperglycemia and includes lipid, protein and carbohydrate metabolic abnormalities induced by insulin production and insulin action [4].

Insulin, an anabolic hormone that causes metabolic irregularities in carbohydrate, lipids, minerals and a variety of others substances. Low insulin secretion, decrease glucose utilization and elevated glucose synthesis are all variables that contribute to hyperglycemia depending on etiology of diabetes mellitus [5, 6]. According to the ICMR INDIAB India had 62.4 million diabetic patients in 2011 and is anticipated to have 101.2 million by 2030 [7].

The American Diabetes Association proposed by the classical categorization of type 1 diabetes mellitus, type 2 diabetes mellitus & gestational diabetes mellitus and it is the most often used classification by the ADA [8].

Type1 diabetes characterized by inappropriate insulin secretion which is predominantly caused due to the loss of cells of the pancreas as well as destruction and tendency to ketoacidosis [9].

Type 1 diabetes affects 5-10% of diabetes patients and it is due to the loss of beta cells in the pancreas. In children & adolescents, it contributes for 80-90% of diabetes cases [10].

In 1988, type 2 diabetes mellitus was known as the primary component of metabolic syndrome. In 2011, 366 million people were expected to have diabetes mellitus by 2030 that number will have risen to 552 million [11, 12].

Non-insulin-dependent diabetes mellitus, also known as type 2 diabetes is a condition with elevated blood glucose levels (hyperglycemia) insulin resistance and may combined with a deficiency of insulin [13].

Insulin resistance and beta dysfunction characterized type 2 diabetes mellitus which affects 5.9% of adult worldwide and covering 8% of developing countries [14].

The American Diabetes Association, on the other side employs the same IGT cut off value (140 to 200 mg/dl) but has a reduced IFG cut-off value (100-125mg/dl) and incorporates additional hemoglobin A1C based criteria for the classification of prediabetes at a level of 5.7 to 6.4% [15].

Prediabetes is characterized by blood glucose concentration raised than average. However, the level is not high enough to be diagnosed with diabetes [16].

As a result, based on evidences that type 2 diabetes mellitus can lead to poor bone quality and bone loss. Also, few studies have suggested that various bone indicators levels were found to be such as serum calcium, serum phosphorus and serum alkaline phosphatase [17].

The hydrolytic enzyme alkaline phosphatase is found in the liver, bile duct, kidney, intestinal mucosa, and placenta among other places many diabetics may also have been shown to have elevated levels of serum alkaline phosphatase [18].

Calcium is found in bones and teeth, where it serves as a structural component of metabolism. Calcium is essential for insulin-mediated intracellular activities in insulin-responsive tissues such as skeletal muscle and adipose tissue, but only in a very limited range does insulin activity change. Calcium variations in the major insulin target tissue contribute to insulin action modifications [19].

Phosphorus is an essential nutrient and adult should consume between range from 550-700 mg per day with a tolerable top limit or 4000 mg per day. In recent years, phosphorus consumption has raised in the population, whereas type 2 diabetes incidences have increased alarmingly [20].

Hence, this study will be directed to determine the importance and to compare the levels of in serum calcium, phosphorus and alkaline phosphatase (ALP) between type 2 diabetes mellitus and prediabetic patients. This research will also look into the relationship between these factors and plasma fasting glucose and HbA1c level.

Material and Methods

Hospital based observational and comparative study was conducted in the Department of Biochemistry at TMMC &RC Moradabad. Total 130 patients were included in this study and were divided into two groups.

Group 1 (Cases): Consisted of 65 diagnosed case of diabetes mellitus attending the medicine OPD or admitted in emergency ward of the Teerthanker Mahaveer Hospital.

Group II (controls): Consisted of 65 pre-diabetic patients, who have fasting plasma glucose between 101 to 125mg/dl and HbA1c between 5.7-6.4%.

Exclusion criteria [21]

1. Smokers

2. Heavy alcoholics
3. Chronic infection affecting bone
4. Chronic renal failure
5. Bone tumours
6. Drugs that may affect bone metabolism

Statistical analysis

SPSS version 28.0 for data analysis and Microsoft Word and Excel for graph generation. Mean and standard deviation was assessed & comparison was done using student's t-test & Pearson's coefficient correlation (r-value).

Significant is evaluated as a p-value of less than 0.05. [S] Highly significant is described as a p-value of less than 0.001 [HS].

Results

This study included one hundred and thirty individuals divided into two groups: group I: prediabetic individuals (n=65) 42 (65%) males and 23 (35%) females. Their ages were ranged between 30 to 60 years with mean 43.72±7.39 years. Already diagnosed diabetic individuals (n=65) 37 (58.33%) males and 28 (41.66%) female was included in group II. Their ages were ranged 30to 60 years with mean 45.12±5.90 years.

Table 1: Comparison of age between prediabetic group and Diabetic group

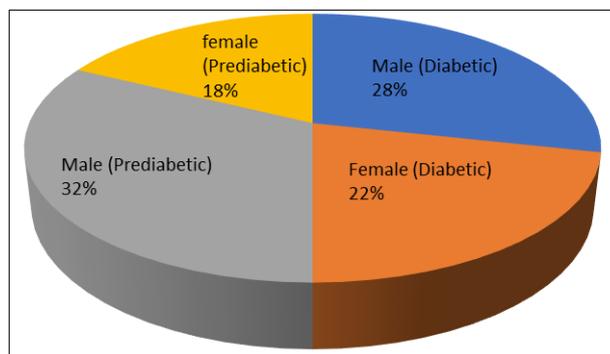
Parameter	Prediabetic group (n = 65)	Patients Suffering from Diabetes Mellitus (n = 65)	p-value
Age (year)	43.72±7.39	45.12±5.90	(p>0.05)

The independent Students t-test showed no statistically significant difference between mean ages of control group and patients with suffering from diabetes mellitus

Table 2: Comparison of percentage of gender between prediabetic group and patients suffering from diabetes mellitus group

Parameter	Prediabetic group (n = 65)		Patients suffering from diabetes mellitus (n = 65)	
	Male	Female	Male	Female
No of Individuals	42	23	37	28
Percentage	65%	35%	58.33%	41.66%

Patients suffering from diabetes mellitus is, 58.33% male and 41.66% female and in prediabetic group in 65% in male and 35% in female.



Graph 1: Percentage Distribution of Gender between Prediabetic and Diabetic group.

In this study, we observed that 28% of patients were male and 22% patients were female among diabetes mellitus and

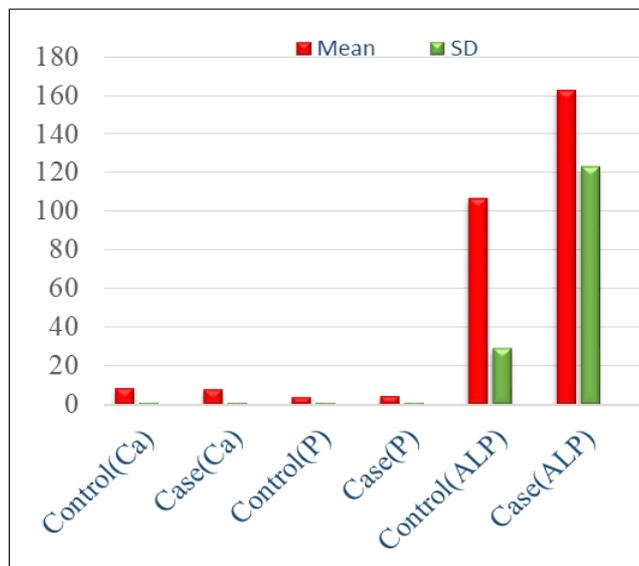
observed that 32% were male and 18% were female among prediabetic.

Table 3: Comparison of serum phosphorus serum ALP, Serum Ca between prediabetic group and patients suffering from diabetes mellitus group

Parameter	Prediabetic group (n = 65)	Patients suffering from diabetes mellitus (n = 65)	p - Value
Serum Phosphorus (mg/dl)	3.80±1.37	4.51±1.36	0.004
Serum Alkaline Phosphatase (ALP) (U/L)	107.30±29.40	163.15±123.07	0.001
Serum Calcium (mg/dl)	8.53±0.84	7.98±0.91	0.001

The mean value of serum phosphorus was higher in diabetes patients (4.5±1.36 mg/dl) then in prediabetic group (3.80±1.37 mg/dl) which was statically significant. It was found that higher level of serum phosphorus was present in serum of patients suffering from diabetes mellitus, which was found to statistically highly significant. ($p < 0.004$).

Comparable values of serum alkaline phosphatase (ALP) were obtained for prediabetic group and patients suffering from diabetes mellitus group and it was statistically highly significant. Mean value of serum alkaline phosphatase was higher in diabetes mellitus patents (163.15±123.07 IU/L) then in prediabetic group (107.30±29.40 IU/L) which was statically significant $p < 0.001$ Lower values of serum calcium were recorded for diabetes mellitus patients as compared to prediabetic group. These lower values of serum calcium in diabetes mellitus patients were found to be significant ($p < 0.001$) Mean value of serum calcium was lower in diabetes mellitus patients (7.98±0.91 mg/dl) than in prediabetic group (8.53±0.84 mg/dl) which was statically significant.

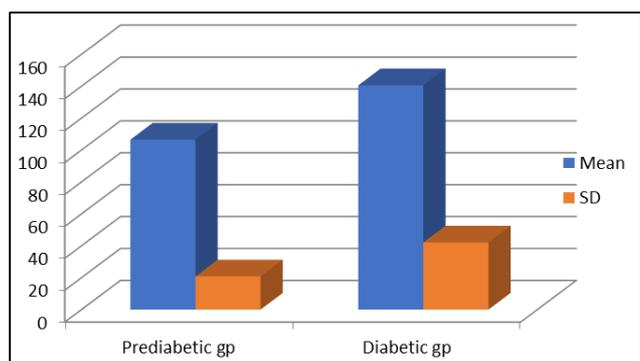


Graph 2: Shows Parameter in Cases and Controls

Table 4: Comparison of plasma glucose between prediabetic group and Diabetic group

Parameter	Prediabetic group (n = 65)	Patients Suffering from Diabetes Mellitus (n = 60)	p - Value
Plasma Glucose (mg/dl)	106.49±20.81	140.55±42.10	<0.001

There was a statistically significant difference ($p < 0.001$) found between prediabetic group and patients suffering from diabetes mellitus.

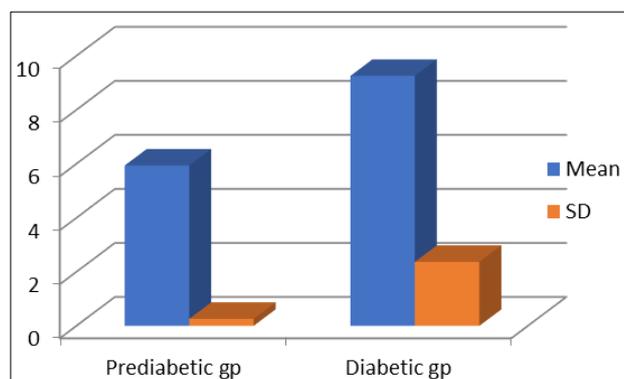


Graph 3: Comparison of mean and SD of plasma glucose between prediabetes group and diabetes group.

Table 5: Comparison of serum HbA1C between prediabetic group and diabetic group

Parameter	Prediabetic group (n = 65)	Patients suffering from diabetes mellitus (n = 65)	p - Value
HbA1C (%)	5.94±0.26	9.26±2.45	0.001

There was a significant difference ($p < 0.001$) found between prediabetic group & patients suffering from diabetes mellitus.



Graph 4: Comparison of mean and SD HbA1c between prediabetes group and diabetes group.

Discussion

Diabetes mellitus is a metabolic disorder. It is a group and various degrees of carbohydrate, lipid and protein metabolism impairment [22].

Diabetes mellitus can have a variety of causes and etiologies, but it usually involves aberrant insulin secretion & response at some point throughout the disease's evolution. Type 1 diabetes (autoimmune diabetes) and type 2 diabetes mellitus are the two most frequent types of diabetes mellitus both are characterized by hyperglycemia, insulin resistance and relative insulin shortage [13].

Therefore, this research was conducted to assess the impact of bone markers (calcium, phosphorus and alkaline

phosphatase) on prediabetic & Type 2 diabetes mellitus patients & also found a possible correlation of these bone markers with fasting blood sugar (FBS) and HbA1c in our study most patients were male & higher diabetic prevalence were seen in the age group of 30-60 years and patients suffering from diabetes mellitus female patients were about 22% of the total.

In table 1 we found that the comparison of age between prediabetic group and diabetic group were in the age group of 30-60 years & mean was 43.72 ± 7.39 in prediabetic group and 45.12 ± 5.90 mean in diabetic group. There were no significant changes in the age group of prediabetic and diabetic group.

In table 2 we have seen that the comparison of percentage of gender between prediabetic male was 42 (60%) and female was 23 (35%) and among include in our study diabetic group male was 37(58%) and female was 28 (41%) include in our study.

In figure 3 we compared overall gender distributions between prediabetic and diabetic group, in which male were 32% and female were 18% prediabetic group and 28% male and 22% female in diabetic group.

In table 3 we compared serum calcium level in prediabetes and diabetes mellitus patients. We found that the mean value of serum calcium (7.98 ± 0.91 mg/dl) in diabetes patients were significantly ($p < 0.001$) decreased when compared with prediabetes patients (8.53 ± 0.84 mg/dl). We found that the mean value of serum phosphorus (4.51 ± 1.36 mg/dl) in diabetes patients were highly significantly ($p < 0.001$) increased when compared with prediabetes group (3.80 ± 1.37 mg/dl). We found that the comparison of serum alkaline phosphatase level in prediabetic group (107.30 ± 29.40 IU/L) and diabetes mellitus group (163.15 ± 123.07 IU/L) were highly significant than the prediabetic patients.

In table 4 we compared plasma glucose in prediabetes and diabetes mellitus patients. We found that the value of glucose (140.55 ± 42.10 mg/dl) in diabetic patients were ($p < 0.001$) increased when compared with prediabetic individual (106.49 ± 20.81 mg/dl).

In table 5 we compared of serum HbA1c in prediabetes and diabetes mellitus were found that the value of HbA1c ($9.26 \pm 2.45\%$) in diabetic patients were ($p < 0.001$) increased when compared with prediabetic group ($5.95 \pm 0.26\%$). In this study we found that plasma glucose & HbA1c level is increased significantly in case then healthy controls.

This agrees with study done by Kanchana N, *et al.* 2014 [19] they observed that serum level of calcium with mean value of (9.4 ± 0.38 mg/dl) was significantly decreased in type 2 diabetes mellitus patients then controls and also found a negative correlation between fasting plasma glucose and serum calcium concentration, that prove increased glucose levels was associated with decreased calcium levels. Our study also correlated with above finding with mean value of serum calcium (7.98 ± 0.91 mg/dl) in diabetic patients and (8.53 ± 0.84 mg/dl) in prediabetic patients that shows a significant decrease, we were also observed a negative correlation between fasting plasma glucose level and serum calcium level $r = -0.249$.

According to the researcher Abdulrehman Ibrahim H, *et al.* 2019 [23] they found that serum level of calcium with mean value (7.54 ± 1.21 mg/dl) in case of type 2 diabetes mellitus patients when compared with mean of reference value (9.45 mg/dl) and were shown on the mean value of Random blood

glucose was (273.40 ± 126.08) with mean of reference value (170 mg/dl), their study concluded that the level of serum calcium was reduced among diabetic patients. In our study also correlated with these finding with mean value of serum calcium (7.98 ± 0.91 mg/dl) in diabetic patients and (8.53 ± 0.84 mg/dl) in prediabetic patients that shows a significant decreased.

Ruaa, *et al.* 2020 [24] who reported raised level of serum alkaline phosphatase with mean (90.36 ± 30.37 IU/L) in case significantly increased as compared to (78.76 ± 25.87 IU/L) healthy controls. In our study we found that the mean value of serum alkaline phosphatase in prediabetic group (107.30 ± 29.40 IU/L) and diabetes mellitus group (163.15 ± 123.07 IU/L) in this study it is concluded that ALP level is higher in diabetic patients as compared with healthy or prediabetic subjects.

According to the Butola LK, *et al.* 2020 [25] in the year 2020 found that the level of serum calcium in diabetic patients (6.41 ± 1.18 mg/dl) and healthy individuals (9.26 ± 0.59) the level of serum phosphorus was (1.68 ± 0.6) and (3.65 ± 0.48) in type 2 diabetic group and normal healthy individuals, these study showed a significant decrease in serum calcium and serum phosphorus level. Our study also correlated with above finding with the mean value of serum calcium (7.98 ± 0.91) in diabetic patients and (8.53 ± 0.84) in prediabetic that shows a significant decrease we found that the mean value of serum phosphorus (4.51 ± 1.36) in diabetes patients were highly significantly ($p < 0.001$) increased when compared with prediabetes group (3.80 ± 1.37).

Raikou VD, *et al.* 2020 [26] observed that the mean levels of serum phosphate was (4.2 ± 0.4 mg/dl) and controls was (3.2 ± 0.3 mg/dl) and serum calcium mean value was (9.5 ± 0.6 mg/dl) with controls (9.5 ± 0.5 mg/dl). They determined the differences between diabetics and non-diabetics individuals and observed high serum phosphate then compared controls and observed similar serum calcium levels.

Conclusion

Diabetes mellitus is the century's epidemic and diabetes will continue to rise unless effective diagnostic procedures are developed at an early stage.

The current study indicated that the most effective diagnostic methods and criteria for diagnosing prediabetes and diabetes are focused on the type of diabetes and its criteria, as well as the types of diabetes and their criteria.

Prediabetes is a type of hyperglycemia that is intermediate in severity.

Diabetes and type 2 diabetes mellitus are metabolic diseases that can be avoided by changing one's lifestyle, controlling overweight and dieting, and avoiding obesity.

The results of this study revealed alterations in parameters of diabetes mellitus. Serum calcium was decreased, whereas Serum P and Serum ALP were increased in patients of diabetes mellitus. However, these parameters do not show any significant change in the prediabetic condition.

Hence this study observed that these parameters can be considered as independent predictors for the diagnosis of diabetes, and their early treatment could be beneficial to prevent further complications.

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