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Original Article

Relationship Between Serum Osteocalcin Levels and Glycosylated Hemoglobin in Type II Diabetes Patients

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ABSTRACT

Diabetic osteopathy is a complication of diabetes that elevates the risk of bone fractures and influences bone remodeling. Osteocalcin is a bone protein produced by osteoblasts that plays a role in the regulation of glucose and energy metabolism. **Objectives:** To explore the relationship between the level of glycosylated hemoglobin (HbA1c) and osteocalcin in diabetic patients. **Methods:** This cross-sectional analytical study was carried out at Hayatabad Medical Complex, Peshawar from January 2017 to February 2018. A total of 100 patients suffering from Type 2 Diabetes Mellitus (T2DM) were recruited. HbA1c and osteocalcin levels were measured by the enzymatic method and electrochemiluminescence immunoassay, respectively. SPSS was utilized for data entry and analysis; Pearson's correlation was performed to assess the relationship between variables while statistical significance was accepted at $p < 0.05$. **Results:** The mean (SD) age of participants was 50 (9.2), while 58% of the study population was female. The mean (SD) HbA1c and osteocalcin levels were 11.3 (8.8) and 13.1 (6.8), respectively. The results of the correlation analysis yielded a negative relationship between HbA1c and osteocalcin levels ($r = -0.099$), but the results were statistically non-significant (p-value =0.328). **Conclusion:** Our study suggested that osteocalcin level has a negative correlation with HbA1c level in Type 2 Diabetes Mellitus patients.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic ailment in which the body shows resistance to insulin where target cells are unable to react normally to insulin. Nutritional control and oral hypoglycemics are useful in treatment, but eventually, a patient needs insulin therapy [1]. According to data from 2010 studies, approximately 285 million individuals, constituting roughly six percent of the global population, were suffering from diabetes. Amongst them, 20% of the current diabetic population resides in Southeast Asia. The number of diabetics in developed countries is likely to triple by the year 2025 [2]. In 1980, approximately 108 million individuals were living with diabetes worldwide. However, this number increased to 422 million in 2014. Since 1980, the prevalence of diabetes in the general population has increased by nearly twofold, from 4.7% to 8.5%. This indicates a rise in risk factors like

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obesity and sedentary lifestyles. As per statistics of 2012, diabetes contributed to over one and half million fatalities. It is predicted that developing countries will endure the most of this epidemic in the 21st century [3]. Osteocalcin (BGLAP-bone gamma-carboxyglutamic acid-containing protein) is a non-collagen protein hormone found in dentin and bone because it has a Gla domain. Osteocalcin is encoded by the BGLAP gene and its receptors are GPRC6A [4]. Serum osteocalcin levels are a predictor of bone formation and its negative metabolic consequences. Various articles show an inverse association between adverse metabolic outcomes and serum osteocalcin, suggesting that osteocalcin levels should be maintained at normal levels in diabetic patients [5]. Recent studies conclude that serum osteocalcin has a positive role in glucose metabolism and fat accumulation. Osteocalcin works like a hormone in the human body, stimulating beta cells of the pancreas to secrete more insulin, and also direct fat cells to secrete the hormone adiponectin, which also increases its sensitivity to insulin. Osteocalcin alters insulin release and sensitivity, β-cell proliferation, and energy metabolism [6-7]. Uncarboxylated osteocalcin (ucOC) improves insulin sensitivity and enhances insulin release, which has been proven by clinical trials on animal models. Principally, human trials have shown that there is a decrease in total osteocalcin (TOC) values, which is linked with exacerbated glycemic control and insulin resistance [8-10]. This study was aimed to determine HbA1c and osteocalcin levels in diabetic (T2DM) patients and to find out if there were any potential relationships between them..

METHODS

This cross-sectional study was conducted at Hayatabad Medical Complex (HMC), a public tertiary care hospital situated in Peshawar, Pakistan. The study duration was one year (January 2017 to February 2018), and ethical approval was granted by the Post Graduate Medical Education department, Khyber Girls Medical College (Ref No. 1831/PGMED/KGMC). A total of 100 participants were selected, who were presented to the Medical and Endocrinology department of HMC. Patients already diagnosed with T2DM were included in the study. The criteria for T2DM were based on the American Diabetes Association guidelines, which stated that diabetes was diagnosed when fasting plasma glucose was 7.0 mmol/L, or 2-hour oral glucose tolerance test (OGTT) was 11.1mmol/L, or HbA1c was 6.5%. However, any patient who was suspected or diagnosed with a disease that could potentially alter bone metabolism was excluded. Patients with cushing syndrome, acromegaly, thyroid disease, osteoporosis, ankylosing spondylitis, rheumatoid arthritis, hyperparathyroidism, liver failure, chronic kidney disease, and other similar conditions were deemed ineligible for the study. Patients who were on corticosteroids, synthetic hormones, or bisphosphonates were also excluded from the study. A detailed history and clinical examination were performed, and the patient's files were reviewed in detail to strictly meet the inclusion criteria. Participants were informed about the nature and purposes of the study, and a written consent form was also signed. All participants were assured of their confidentiality and were given the option to withdraw from the research at any time. Furthermore, no monetary remuneration was provided to individuals for their participation in the study. Fasting blood samples were collected, centrifuged, and stored at -25° C until analysis. The blood specimens were then sent to the Pathology Department at Rehman Medical Institute (RMI), Peshawar because of the availability of standard kits and laboratory services needed for the present study. Glycosylated hemoglobin A1c (HbA1c) was measured utilizing EDTA (Ethylenediamine tetraacetic acid) tubes through an enzymatic method using ARCHITECT ci8200 (Abbott®, Abbott Park, Illinois, U.S.A) while serum osteocalcin concentration was measured using an electrochemiluminescence immunoassay (Cobas 601, Roche Diagnostics). SPSS version 22.0 (SPSS Inc., Chicago, IL) was used for data entry and analysis. Data entry was performed by research assistants and was cross-checked by other members for any potential errors. Where appropriate, descriptive statistics were presented as means, standard deviations, and percentages. Pearson's correlation test was performed to find out any potential relationship between study variables. For statistical significance, a p-value of < 0.05 and a 95% confidence interval were considered significant.

RESULTS

There were 100 participants in the present study. The mean (SD) age of the study subjects was 50 (9.2) (range: 40-65 years). 28% of patients were in the age range of 40–45 years; 32% of patients were in the age range of 46–55 years; and 40% of patients were in the age range of 55–65 years. Gender wise, 58% of the participants were female and 42% were male.

Variable	Total	Male	Female
Age	50 ± 9.2 years	48 ± 6.3	52 ± 7.6
Duration of T2D	9.76 ± 4.2 years	9.2 ± 3.8	9.98 ± 4.8
MBMI	28.56 ± 3.1	28.11 ± 3.2	28.96 ± 2.9
Comorbidities			
Hypertension	62	27	35
Cardiovascular disease	34	16	18
Obesity	73	34	39
Osteoporosis	16	3	13

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Medications			
Sulfonylureas	46	20	26
Metformin	67	30	37
Insulin	33	21	12

Table 1: Baseline characteristics of study population

The mean (SD) and median serum osteocalcin levels were found to be 13.13 (6.8) ng/mL and 11.7 ng/mL, respectively (range: 5.0-7.0 ng/mL). The mode value of serum osteocalcin levels was 9 ng/mL, indicating that the majority of the patients presented with 9 ng/mL of serum osteocalcin levels. The normal of data were skewed towards the lower extreme, demonstrating that osteocalcin levels decreased during disease. The mean (SD) HbA1c was 11.36 (range; 6%-86%) while the median was 10.05%, indicating that 50% of the patients had an HbA1c level above 10.05%. The normal curve shows that the HbA1c of diabetic patients is more skewed toward the highest value, implying that HbA1c is a good predictor of the chronic effect of diabetes. HbA1c levels were 6.5%–8.0% in 26% of patients, 8.1%–10% in 28% of patients, 10.1%–15% in 42% of patients, and more than 15.1% in 4% of patients, respectively (Table 2).

Variable	Total	Male	Female
Mean Osteocalcin levels	13.13 ng/mL	12.24 ng/mL	13.98 ng/mL
Mean HbA1C levels	11.36 %	11.16 %	11.45 %
Median Osteocalcin levels	11.7 ng/mL	11.2 ng/mL	11.7 ng/mL
Median HbA1C levels	10.05%	10.80%	10.01%

Table 2: Mean and median of variables

As indicated from the descriptive statistics, the mean serum osteocalcin and HbA1c levels were 13 (6.8) ng/L and 11% (8.8%) respectively. Pearson's correlation analysis revealed that there was a weak inverse relationship between serum osteocalcin and HbA1c levels; however, the results were statistically non-significant (r = -0.099, p-value = 0.328) (Figure 1). However, BMI and Age were positively correlated with the HbA1c as shown in (Table 3).

Variable	Total		Male		Female	
	r	p-value	r	p-value	r	p-value
Serum Osteocalcin	-0.099	.328	-0.121	.541	-0.091	.046
BMI	0.324	.046	0.312	.061	0.341	.048
Age	0.181	.112	0.172	.213	0.189	.096

Table 3: Shows correlation between HbA1c and other variables.

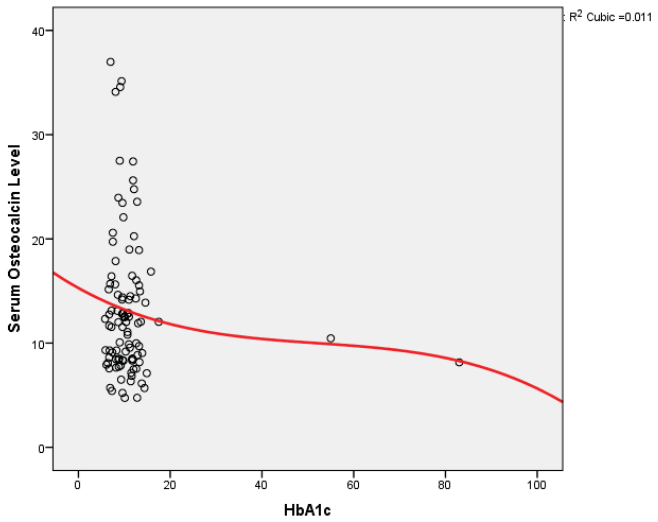

Figure 1: Correlation between serum osteocalcin levels and HbA1c levels

DISCUSSION

It is generally acknowledged that Type II diabetes mellitus is a complicated metabolic disorder driven by the combination of several factors, including hereditary, ecological, and life-style factors. In multiple studies, researchers have suggested that in individuals with Type II diabetes mellitus, serum osteocalcin was linked with glucose tolerance [10-11]. Osteopathy related to diabetes is one of the most crucial problems and needs prompt intervention as it may lead to an increased risk of bone fracture and ill adaptation of bone metabolism. Osteocalcin is one of the bone proteins that plays an important role in bone metabolism and maintains bone density and integrity. From a metabolic perspective, osteoblasts produce osteocalcin, which was involved in glucose metabolism and produces energy in the form of Adenosine Tri-Phosphate (ATPS). However, in diabetes, the deranged metabolism leads to a decrease in the osteocalcin levels [12]. HbA1c levels may represent the possible role of osteocalcin in glucose metabolism in patients with type 2 diabetes mellitus. Maddaloni et al., reported that diabetes and osteoporosis are two very common diseases with a great socio-economic impact [13]. Patients with Type-2 diabetes mellitus have altered bone density and have an increased risk of bone fractures. The results of osteoporosis treatment in patients with diabetes are not satisfactory [14]. An HbA1c of 48 mmol/mol (6.5%) is considered as the cut-off point for diagnosing diabetes. HbA1c less than 48 mmol/mol (6.5%) necessitates additional testing, such as oral glucose tolerance tests (OGTT) [15]. The results indicate that the mean serum osteocalcin level was 13. 13 ± 6.899 ng/ml (reference values for > 18 years: 9–38 ng/mL) while the mean HbA1c 11.36 ± 8.862% (reference value > 6.5%),

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indicating that almost all of them have chronic diabetic conditions. While the mean osteocalcin level was within an acceptable range, the median of data showed that 50% of the samples had osteocalcin levels greater than 15 ng/ml, indicating increased bone turnover. John et al., revealed that in cases of type 2 diabetes, osteoblastic activities of the bone forming cells/tissue are impaired, but the reabsorption remains normal or improved [16]. The osteocalcin level in the present study also supports this mechanism as shown from the range which comes under the reference range. However, most of the results are skewed toward the upper border of the reference ranges. HbA1 was found to be inversely related to osteocalcin ($r = 0.099$, $p = 0.328$). Bao et al., which demonstrates a raised osteocalcin level in serum ($p = 0.014$), while parameters identified with glucose variability, the standard deviation of plasma glucose values, and mean adequacy of glycemic expedition (MAGE), diminished fundamentally ($p < 0.001$) after treating patients for 8 weeks [17]. At standard, the connection between homeostatic model appraisal of β-cell capacity ($P = 0.048$) and fasting C-peptide levels and serum osteocalcin levels ($p = 0.004$) was positive. However, the relationship between serum osteocalcin levels and 24 h mean blood glucose ($P < 0.001$), HbA1c ($p = 0.020$) and fasting plasma glucose ($p = 0.023$) was negative. It was concluded that serum osteocalcin foci expanded with enhanced glucose control. Gundberg et al., reported that changes in glucose variability (controlling glucose) by hypoglycemic agents were linked with early high levels of osteocalcin (i.e., maintaining serum osteocalcin level) [18]. This indicates that osteocalcin could be used to enhance the glucose-related metabolism aspect of energy regulation. Previous research found that osteocalcin was strongly linked to carbohydrate metabolism due to changes in pancreatic cell (β -cell) proliferation and increased insulin sensitivity [19]. In Gu et al., study animal model has shown similar results and reported cognitive impairment in subjects with decreased serum osteocalcin levels [20]. However, a proper clinical trial on an animal model is required to see the effect of osteocalcin therapy among diabetic subjects. The current results cannot be generalized; however, they can be used as a basis for further research.

CONCLUSIONS

The present study suggested that osteocalcin level has a negative correlation with HbA1c level in Type 2 Diabetes Mellitus patients. The poor control of diabetes can significantly lead to diabetic osteopathy, and patients can experience different bone disorder, including bone deformity, frequent fractures, and limited bone turnover.

Conflicts of Interest

The authors declare no conflict of interest

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