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Association between uncarboxylated osteocalcin, blood glucose, and BMI among Saudi diabetic patients: an evaluation study

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Abstract. – OBJECTIVE: Uncarboxylated osteocalcin is an important osteocalcin enzyme found in the bloodstream and is a crucial protein for maintaining calcium binding in bones, controlling blood sugar levels, and balancing body minerals.

PATIENTS AND METHODS: Due to the lack of data, the current study intends to investigate the relationship between uncarboxylated osteocalcin levels and DM-II in Saudi patients. For 138 patients, case-control research was conducted in 2021-2023, with 69 type II diabetes mellitus patients and 69 matching healthy control participants. An enzyme immunoassay kit was used to quantify the levels of uncarboxylated osteocalcin in fasting blood samples, and an automated analyzer evaluated Hb1Ac, fasting blood glucose, enzymes, electrolytes, lipid, and kidney profiles. Data processing and analysis were carried out using GraphPad Prism statistical software.

RESULTS: According to our study, patients with type II diabetes mellitus had considerably lower levels of uncarboxylated osteocalcin than healthy controls. According to the correlation analysis, uncarboxylated osteocalcin and fasting blood sugar had a negative relationship. In the overweight BMI group, uncarboxylated osteocalcin was considerably higher in control subjects.

CONCLUSIONS: We concluded that, in Saudi type II diabetes mellitus patients, the compromised glucose level is associated with diminished serum uncarboxylated osteocalcin. This study has limitations, such as a small sample size and only measuring the uncarboxylated form of plasma osteocalcin. Future research is needed to understand how anti-diabetic drugs affect undercarboxylated osteocalcin's effect on metabolic control and provide more efficient techniques and resources in diabetes and osteoporosis prevention and care.

Key Words:
Osteocalcin, Uncarboxylated osteocalcin, Type II diabetes mellitus, Carboxylated osteocalcin.

Introduction

Elevated blood sugar levels and disturbances in insulin secretion or action are symptoms of a range of metabolic diseases known as diabetes mellitus[1]. Beta cell failure, decreased insulin, increased glucagon production, and elevated blood glucose levels are the major causes of type II diabetes mellitus[2]. Additionally, fat distribution in the body negatively affects insulin because fat secretes several molecules like leptin, tumor necrosis factor (TNF), resistin, and adiponectin, interfering with glucose metabolism and reducing insulin's effectiveness[2]. Also, some genes significantly influence type II diabetes mellitus illness susceptibility.

In the first third of the twenty-first century, diabetes mellitus prevalence is expected to increase by up to 2.5 times throughout the Middle East, Sub-Saharan Africa, Latin America, Asia, and India[3]. Diabetes is one of the significant health concerns in Saudi Arabia. Concerning the prevalence of diabetes, it is listed among the top 10 countries in the world[4].

Recent investigations[5] have found evidence that chemicals originating from bone affect glucose metabolism. The first molecule to be identified as a mediator between glucose and bone metabolism was osteocalcin (OCN)[5]. Osteocalcin, the most prevalent non-collagen protein in bone, is an essential part of the extracellular matrix of bone. In the 1970s, Hauschka and Price[5] initially isolated it from chicken and bovine bone and discovered that it bound to Ca^{2+} and included three-Gla residues. Uncarboxylated osteocalcin has been discovered[6] to improve adipocyte and β-cells synthesis and release of adiponectin, as well as insulin sensitivity and glucose tolerance in mice. When osteoclasts activate bone matrix-embedded osteocalcin and decarboxylate it, uncarboxylated osteocalcin is released into the bloodstream and

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stimulates the production of adiponectin in adipose tissue and insulin in the pancreas[7].

Several previous reports[7,8] indicate the effect of uncarboxylated osteocalcin on the ability to secrete insulin or control blood sugar. Therefore, we conducted an integrated assessment using a case-control approach to evaluate the correlation between uncarboxylated osteocalcin levels and type II diabetes mellitus (DM) in the Saudi population.

Patients and Methods

Study Subjects

The study comprised 138 participants: 69 participants were controls, and 69 had type II diabetes mellitus and were seen at the Diabetic Center in Almadina (King Fahd Hospital-Prince Abdelaziz Ben Maged) KSA.

Inclusion and Exclusion Criteria

Type II diabetes mellitus patients and healthy non-diabetic individuals of any age were included in the study.

Diabetes mellitus Type-I patients, women who were pregnant or breastfeeding due to a change in levels of the bone turnover mark, patients with osteoporosis or disease affecting bone metabolism, and patients with cardiovascular diseases and hyperthyroidism were excluded.

Ethics Approval

The Institutional Review Board, General Directorate of Health Affairs in Madina (IRB#198-2021), and the Committee of Research Ethics, Deanship of Scientific Research, Qassim University, granted their ethical permission for this study (ethical approval #20-07-09).

Specimen Collection

After overnight fasting from all patients and controls, 3 mL of blood was drawn into plain/EDTA tubes. The Dimension X Pand, a clinical chemistry analyzer with automated processing (Siemens Healthcare Diagnostics Ltd. Frimley, Camberley, UK), was used for all analyses. Moreover, the samples were stored at -20°C until they were assayed for uncarboxylated osteocalcin.

Uncarboxylated Osteocalcin Measurements

For quantitative determination, the uncarboxylated osteocalcin assay is based on an *in-vitro* enzyme immunoassay (EIA) kit (MK118 from Takara Bio Inc.).

Biochemical Analyses

Aspartate aminotransferase (AST), alanine transaminase (ALT), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (AHDL), and glycated hemoglobin% (HbA1c%) were measured in serum samples, along with kidney function tests and electrolytes.

Statistical Analysis

GraphPad Prism 9 version (GraphPad Software, Dotmatics. CA, San Diego, USA) was used for statistical analysis; the distribution of measurable data was expressed as mean±SD. The relationship between the various parameters was analyzed by simple correlation analysis. Statistical significance was indicated by $p<0.05$. ANOVA test was utilized for analyzing the mean difference between the three studied groups of type II diabetes mellitus: patients with ucOC<1 ng/ml, patients with ucOC=1-2 ng/ml, and patients with ucOC>2 ng/ml.

Results

The biochemical parameters and the general characteristics of type II diabetes mellitus and controls are presented in Table I. Uncarboxylated osteocalcin levels in serum were measured in this investigation among people with type II diabetes mellitus (n=69) compared with controls (n=69) with a mean age of 53.26±8.97 and 39.6±7.7 years, respectively, were included in the final analysis.

Uncarboxylated osteocalcin levels were substantially lower in type II diabetes mellitus patients ($p<0.001$) than in control subjects; the levels were 2.51±0.85 ng/mL and 3.68±1.10 ng/mL, respectively. Regarding the BMI [body mass index (kg/m^2)] of diabetic patients, the mean BMI was 31.2±4.6 kg/m^2, which differed significantly from controls (BMI 28.4±3.8, $p<0.001$).

In addition, the data revealed that type II diabetes mellitus had considerably higher fasting blood glucose and glycated hemoglobin levels than controls ($p<0.001$). The lipid profile significantly differed in both groups ($p<0.001$), with type II diabetes mellitus characterized by increased triglyceride concentrations.

Regarding minerals and kidney function tests, the potassium and chloride in controls were more significant than in DM-II patients ($p<0.05$). In contrast, serum creatinine levels in type II diabetes mellitus patients were considerably higher than in controls ($p<0.001$). Also, serum aspartate

aminotransferase level was significantly higher in DM-II than in control subjects.

Figure 1 represents a statistically significant difference between DM-II and control concerning 2>ucOC, indicating that individuals with type II diabetes mellitus were substantially more likely to have 2>ucOC compared to controls.

Table II depicts the correlation related to uncarboxylated osteocalcin. A significant negative correlation with fasting blood glucose, creatinine, and LDL existed (r=-248, r=-0.262, and r=-0.325; p<0.05, p<0.01).

In contrast, a significant positive relationship existed between glycated hemoglobin and BMI (p<0.001). The correlation analysis related to lipid profile depicts a significant positive correlation in type II diabetes mellitus between low-density lipoprotein and total cholesterol and triglyceride (r=0.252, r=0.189; p<0.05, p<0.01, respectively).

Table I. The general characteristics and biochemical parameters in DM-II and control.

Parameter	Controls N=69 Mean ± SD	Patients N=69 Mean ± SD	p
Age (years)	39.6±7.7	53.2±8.9	<0.001**
Weight (kg)	74.1±11.8	76.6±13.2	0.2535
Height (cm)	159.2±20.5	156.3±6.5	0.2821
Body mass index (kg/m^2)	28.4±3.8	31.2±4.6	<0.001**
Fasting blood glucose (mmol/L) (4.1-5.9)	5.17±0.42	9.83±3.50	<0.001**
Glycated Hemoglobin (%) (4.5-6.2)	5.23±0.39	8.98±2.3	<0.001**
Aspartate aminotransferase (U/L) (10-50)	18.1±4.8	26.2±13.6	<0.001**
Alanine transaminase (U/L) (0-41)	27.3±8.1	26.8±12.6	0.7925
Triglyceride (mmol/L) (0.17-11.3)	1.00±0.31	1.76±0.87	<0.001**
High-density lipoprotein (mmol/L) (1-1.5)	1.03±0.46	1.2±0.59	0.3130
Low-density lipoprotein (mmol/L) (0-3.7)	2.66±0.96	2.76±1.32	0.619
Sodium (mmol/L) (136-145)	138.2±2.7	137.5±3.4	0.2108
Potassium (mmol/L) (3.5-5.1)	4.3±0.3	4.2±0.48	0.0207*
Chloride (mmol/L) (98-107)	101±2.04	100±2.8	0.0142*
Calcium (mmol/L) (2.12-2.52)	2.3±0.07	2.29±0.13	0.0549
Uric acid (µmol/L) (155-428)	241±53.2	262.7±74.9	0.0541
Blood urea nitrogen (mmol/L) (2.5-8.3)	4.3±1.27	4.6±2.3	0.3033
Creatinine (µmol/L) (52.2-91.9)	57.3±12.01	69.08±22.5	<0.001**
Uncarboxylated osteocalcin ng/ml (0.25-8)	3.68 ±1.10	2.51±0.85	<0.001**

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.001 level (2-tailed).

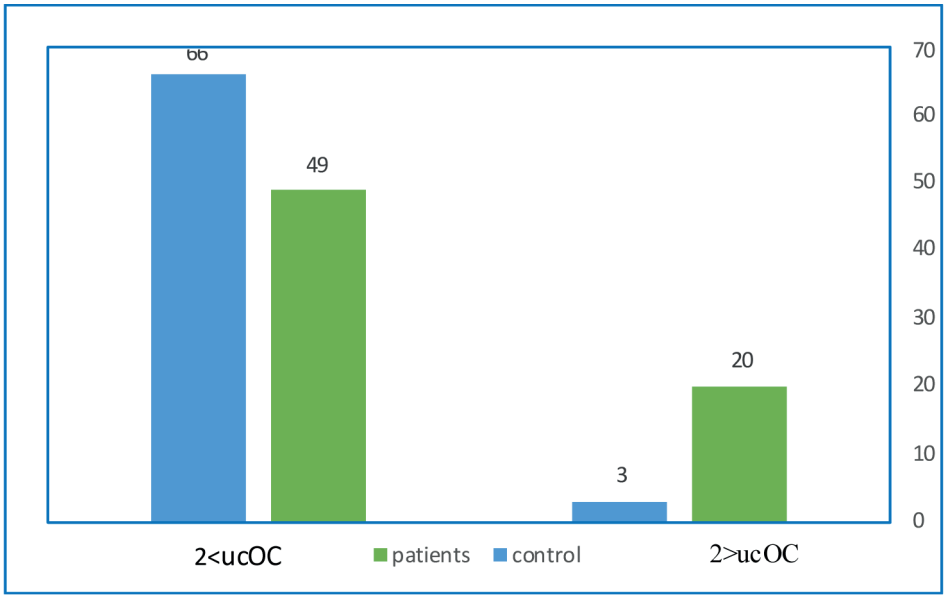

Figure 1. Histogram represents the frequency of 2 ng/ml>ucOC and 2 ng/ml<ucOC in diabetic patients and controls.

Table II. Correlation analysis between different variables in Type II diabetes mellitus patients.

Pearson's Statistical Correlation									
Variables	**BMI**	**FBG**	**HbA1C**	**TG**	**CHOL**	**ucOC**	**LDL**	**CREAT**	**UA**
BMI			*p*=0.001* r=0.798						
FBG					*p*=0.01* r=0.297	*p*=0.04** r=-248			*p*=0.005* r=-0.333
HbA1C	*p*=0.001* r=0.798				*p*=0.04** r=0.247				*p*=0.002* r=-0.363
TG					*p*=0.008* r=0.189		*p*=0.03** r=0.252		
CHOL		*p*=0.01* r=0.297	*p*=0.04** r=0.247	*p*=0.008* r=0.189					
ucOC		*p*=0.04** r=-248					*p*=0.006* r=-0.325	*p*=0.02** r=-0.262	
LDL				*p*=0.03** r=0.252		*p*=0.006* r=-0.325			
CREAT						*p*=0.02** r=-0.262			
UA		*p*=0.005* r=-0.333	*p*=0.002* r=-0.363						

The variables include BMI (body mass index), FBG (fasting blood glucose), HbA1C (glycated hemoglobin), TG (triglyceride), CHOL (total cholesterol), ucOC (uncarboxylated osteocalcin), CREAT (creatinine), UA (uric acid), with the correlation significant for 2-tailed analyses at the 0.01 and 0.05** levels.

Also, a significant positive association was observed in DM-II patients between total cholesterol, glycated hemoglobin, and fasting blood glucose. However, no association existed between LDL and HDL. A significant negative association was also observed between glucose, glycated hemoglobin, and uric acid.

The characteristics of DM-II patients based on uncarboxylated osteocalcin levels were determined by the analysis of variance using the ANOVA test, revealing a significant difference in the means between the three studied groups of type II diabetes mellitus: patients with uncarboxylated osteocalcin lower (ucOC<1 ng/ml), patients with uncarboxylated osteocalcin middle (ucOC=1-2 ng/ml) and patients with uncarboxylated osteocalcin upper (ucOC>2 ng/mL) (Table III). Additionally, Table IV displays the clinical features of type II diabetes mellitus and its relationship with uncarboxylated osteocalcin. Uncarboxylated osteocalcin levels in type II diabetes mellitus were inversely connected with fasting blood glucose, according to a correlation analysis between those levels and glucose status ($p<0.001$, $r=-0.24$). Uncarboxylated osteocalcin and triglyceride also had a strong adverse relationship ($p<0.001$, $r=-0.102$). The mean concentrations of uncarboxylated osteocalcin according to BMI in type II diabetes mellitus patients and healthy control subjects are represented in Table V.

Regarding the BMI of type II diabetes mellitus and healthy control subjects, the mean BMI was 31.2±4.6 kg/m^2, which differed significantly from the control BMI (28.4±3.828). In the overweight BMI group, uncarboxylated osteocalcin was found to be considerably higher ($p<0.001$) in control subjects (3.51±1.15 ng/ml) compared to DM-II patients (2.46±0.77 ng/ml). Additionally, uncarboxylated osteocalcin levels were substantially higher in controls (4.08±0.23 ng/mL) in the obese group than in type II diabetes mellitus (2.58±0.15 ng/mL) ($p<0.001$).

Discussion

Circulating osteocalcin is a conventional indicator of bone turnover commonly used to diagnose and manage metabolic bone disorders[8]. Moreover, recent research[9] suggests that uncarboxylated osteocalcin may regulate energy metabolism. Our research focused on the relationship between ucOC and levels and diabetes mellitus type II. Compared to healthy control

Table III. Characteristics of type II Diabetes Mellitus based on uncarboxylated osteocalcin.

Parameter	unOCN<1 Mean ± SD N=6	unOCN (1-2) Mean ± SD N=14	unOCN>2 Mean ± SD N=49	p
Age (years)	59.33±7.39	54.28±7.63	52.22±9.16	0.167
Body Mass Index	32.70±4.94	29.84±6.89	31.5±3.83	0.371
Fasting blood glucose	10.01±3.47	9.11±3.03	9.64±3.46	0.883
Glycated hemoglobin	8.7±1.76	8.60±1.73	9.60±3.02	0.407
Aspartate aminotransferase	24.33±4.36	25.71±18.86	26.60±9.56	0.919
Alanine transaminase	24.5±9.73	28.07±15.32	26.81±10.05	0.114
Albumin	38.33±4.03	33.92±7.13	31.93±8.87	0.181
Triglyceride	1.88±0.49	1.67±0.96	1.75±0.88	0.887
Total cholesterol	4.20±1.13	4.17±1.27	4.49±1.12	0.593
HDL	0.90±0.25	1.10±0.32	1.28±0.67	0.246
LDL	3.32±1.32	3.53±1.69	2.44±1.16	0.928
Sodium	138.5±3.61	137.78±1.88	137.36±3.75	0.723
Potassium	4.15±0.27	4.25±0.36	4.22±0.53	0.906
Chloride	100.3±4.92	100.21±2.63	100.0±2.59	0.944
Calcium	2.26±0.04	2.30±0.09	2.30±0.15	0.802
Uric acid	265.1±61.95	255.27±65.44	264±80.67	0.918
Blood urea nitrogen	4.45±1.10	4.41±1.11	4.73±2.66	0.883
Creatinine	67.1±10.88	72.79±10.96	68.2±26.07	0.787
Uncarboxylated osteocalcin	0.67±0.22	1.69±0.21	2.9±0.41	<0.001*

*Correlation is significant at the 0.001 level.

Table IV. Correlation analysis between clinical characteristics of type II diabetes mellitus and uncarboxylated osteocalcin.

Parameters	Uncarboxylated osteocalcin		
Type II diabetes mellitus indicators (mmol/L)	Mean ± SD	p	r
FBG	9.83±3.50	<0.001	-0.24
TG	1.76±0.87	<0.001	-0.102
LDL	2.76±1.32	0.24	-0.325

Table V. Comparison of BMI and uncarboxylated osteocalcin in type II diabetes mellitus and healthy control subjects.

Variables	Underweight		Normal weight		Overweight		Obese	
ucOC	DM-II	Control	DM-II	Control	DM-II	Control	DM-II	Control
Mean ± SD	-	-	1.8±0.20	3.33±0.49	2.46±0.77	3.51±1.15	2.58±0.15	4.08±0.23
p	-		<0.001		<0.001		<0.001	

patients, people with diabetes mellitus type II had considerably lower serum levels of uncarboxylated osteocalcin (Table I). This finding aligns with the research by Sanchez-Enriquez et al[10], who reported a decreased amount of uncarboxylated osteocalcin in type II diabetes mellitus patients than in control persons.

Uncarboxylated osteocalcin significantly reduced blood glucose levels, increased insulin production, and improved insulin resistance, which aligns with our findings and animal research[11,12]. A strong association between uncarboxylated osteocalcin and skeletal metabolism in type II diabetes mellitus patients was also observed[13].

It is generally recognized[14] that diabetes weakens mature osteoblastic cells due to aberrant glucose metabolism, affecting bone integrity. Therefore, it is hypothesized[15] that specific humoral substances generated from bones, such as uncarboxylated osteocalcin, may trigger beta cells to enhance aberrant glucose metabolism.

Moreover, by restoring normal glucose metabolism through ucOC-induced insulin production, ucOC protects against bone deterioration brought on by disturbance in glucose metabolism[16]. Experiments[9] on osteocalcin-deficient mice revealed that the effects of uncarboxylated osteocalcin control bone mineralization and limit bone formation. However, subsequent experiments demonstrated that the uncarboxylated form of osteocalcin affects energy metabolism by stimulating insulin production in beta-cell islets of Langerhans and adiponectin in adipocytes[6,11].

Our study suggests that the fasting glucose levels of type II diabetes mellitus patients with 2 ng/ml>ucOC were substantially higher than DM-II patients with 2 ng/ml<ucOC, indicating a significant difference between the two types of the disease (Figure 1). In diabetic patients, higher levels of uncarboxylated osteocalcin were linked to decreased fasting plasma glucose levels and improved glycemic control[17]. Higher serum osteocalcin was significantly correlated with improved insulin sensitivity using HOMA-IR[18].

Pearson's statistical correlation between variables DM-II patients depicts a significant adverse connotation observed among uncarboxylated osteocalcin and triglyceride. Additionally, it also showed evidence of a considerable inverse relationship between triglyceride levels and osteocalcin[19].

Fernandez-Real et al[20] observed that in obese non-diabetic females, serum osteocalcin did not correlate with triglyceride levels at baseline; however, this relationship changed after a nutritional and resistance-training intervention. According to findings from animal research by Kim et al[21], uncarboxylated osteocalcin and triglyceride have a negative association.

Our results support the existing research demonstrating a negative relationship between uncarboxylated osteocalcin levels and blood glucose in type II diabetes mellitus. For instance, one study[22] found that removing osteoblasts in adult mice impacted their glucose metabolism. Like uncarboxylated osteocalcin deficiency, partial resection of these cells led to hyperglycemia, hypoinsulinemia, decreased insulin sensitivity, and glucose intolerance; however, after treatment with uncarboxylated osteocalcin, the mice's glucose intolerance improved, and their blood glucose and insulin levels returned to normal[22]. In another investigation[23], intermittent osteocalcin administration in mice effectively regulated glucose metabolism and delayed the onset of type II diabetes mellitus. A negative relationship between glycated hemoglobin, fasting plasma glucose, and osteocalcin was also discovered[24,25].

Cross-sectional longitudinal investigations[26] showed a negative correlation between fasting plasma glucose and fasting insulin, two indicators of insulin resistance, and serum total osteocalcin levels. Osteocalcin and fasting glucose were found to be negatively correlated[27]. Low blood osteocalcin levels at baseline were independently associated with an augmented risk of developing type II diabetes mellitus[28].

Our study's Pearson correlation analysis (Table II) of creatinine showed a negative correlation with uncarboxylated osteocalcin. Creatinine is a by-product of muscle metabolism, converted from creatine non-enzymatically to creatinine. Since the total body creatine content is constant, there is continuous creatinine production and excretion in the urine[29].

Several potential processes[30] explain the correlation between uric acid concentrations and osteocalcin. First, because of its antioxidant properties, uric acid may directly contribute to the etiology of type II diabetes mellitus and osteoporosis.

Our results in the present study showed that serum uric acid levels had no significant correlation with uncarboxylated osteocalcin. Our investigation of the inverse correlation of uric acid in HbA1c and blood glucose showed an inverse relationship between uric acid and HbA1c[31]. Additionally, several studies[31,32] have discovered an inverse relationship between uric acid and blood glucose levels in type II diabetes mellitus.

Our results show a negative correlation analysis of low-density lipoprotein with uncarboxylated osteocalcin in the lipid profile. However, no significant correlation existed between total cholesterol and uncarboxylated osteocalcin or between high-density lipoprotein and uncarboxylated osteocalcin. This aligns with the findings of Bao et al[33], who reported no significant relationship between high-density lipoprotein and uncarboxylated osteocalcin levels in their study. In addition, their study found no association between total cholesterol and uncarboxylated osteocalcin levels.

In the present study, total cholesterol positively affected fasting blood glucose and glycated hemoglobin, suggesting that high cho-

lesterol levels could affect insulin secretion. In addition, another study revealed a significant association between total cholesterol and glycated hemoglobin[34].

Characteristics of type II diabetes mellitus based on uncarboxylated osteocalcin levels were determined by analysis of variance using the ANOVA test (Table III). In our study, there was a significant difference between type II diabetes mellitus patients with 2 ng/ml>ucOC level and DM-II patients with 2<ucOC level regarding fasting glucose levels, as the first ones with 2 ng/ml>ucOC showed significantly higher fasting glucose levels. Higher levels of uncarboxylated osteocalcin were associated with better glycemic control and lower fasting plasma glucose levels in persons with diabetes.

Clinical characteristics of DM-II patients and the associations of uncarboxylated osteocalcin are depicted in Table IV. In the current investigation, uncarboxylated osteocalcin and fasting blood glucose were strongly negatively correlated.

Uncarboxylated osteocalcin was inversely linked with fasting blood glucose, which levels were substantially higher in all individuals in the decrease-ucOC group compared to the increase-ucOC group[35]. The negative correlation between plasma glucose and osteocalcin might further support our findings[36].

The diagnosis of type II diabetes mellitus has been linked to low ucOC concentration[35]. Higher levels of ucOC are linked to improved beta-cell activity and insulin sensitivity, greater insulin secretion, better glycemic management, and lower fasting plasma levels[13].

BMI and uncarboxylated osteocalcin levels in DM-II and healthy control subjects (Table V) show that in the overweight Body Mass Index group, uncarboxylated osteocalcin was significantly higher in control subjects as compared to DM-II[37,38]. Other research[39] has linked higher vitamin K intake to a lower risk of type II diabetes mellitus. However, it does not support uncarboxylated osteocalcin as a mediator of enhanced insulin sensitivity, as vitamin K administration lowers uncarboxylated osteocalcin levels without any link to unfavorable metabolic outcomes[39].

Limitations

This study has limitations, such as a small sample size and only measuring the uncarboxylated form of plasma osteocalcin.

Conclusions

Uncarboxylated osteocalcin is an essential factor in type II diabetes mellitus, associated with low serum levels. Future research is needed to understand how anti-diabetic drugs affect undercarboxylated osteocalcin's effect on metabolic control and provide more efficient techniques and resources in diabetes and osteoporosis prevention and care.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

All participants provided informed consent for participation in the study.

Ethics Approval

The Institutional Review Board, General Directorate of Health Affairs in Madina (IRB#198-2021), and the Committee of Research Ethics, Deanship of Scientific Research, Qassim University, granted their ethical permission for this study (#20-07-09).

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Authors' Contributions

Corresponding Author, Conceptualization, Methodology, Validation & Formal analysis, Taghreed AlAmari; Critical review & Co-Supervision, Fahad A. Alhumaydhi; Supervision & Funding acquisition, Afshan Zeeshan Wasti. All authors have read and agreed to the published version of the manuscript.

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Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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