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The Effect of Osteocalcin in Middle-Age Women With and Without Type2 Diabetes Mellitus

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Abstract

Background: Diabetes mellitus is a chronic disease that affects people of all ages. It's caused by deficiencies in insulin action and secretion, leading to long-term hyperglycemia. This can harm key organs such as the kidneys, heart, eyes, nerves, and blood vessels. Managing diabetes requires significant lifestyle changes and can impact both the patient and their family. Small and bone-specific, osteocalcin (OCN) is a non-collagen protein that is mostly present in bone. It is a sensitive marker of bone formation and primarily attaches to the extracellular matrix of bone after being carboxylated. Small amounts of OCN are also released into the bloodstream, where it aids in glucose and fat metabolism.

Objective: Our study aimed to examine the effect of Osteocalcin, Parathyroid hormone, Estrogen and HbA1c on middle-aged women who had type 2 diabetes compared to those who did not.

Patients and Methods: The study involved 90 middle-aged women, including 60 with type 2 diabetes, and 30 healthy women. The Sandwich enzyme-linked immunosorbent assay was used to measure OCN, PTH, and E2 hormone levels in women with and without type 2 diabetes. HbA1c levels were measured using the Cobos system. The statistical analysis was performed using SPSS software.

Results: In T2DM women, serum OCN, PTH, E2, and HbA1c levels were compared with non-diabetic women. T2DM women had significantly lower levels of serum OCN and PTH, and significantly higher levels of HbA1c than healthy women. Serum E2 levels were also significantly lower in T2DM women. OCN had a positive correlation with HbA1c and negative correlations with PTH and E2.

Conclusion: Significant change was detected in this study in the level of OCN, PTH and E2 between patients and controls. Investigations of serum OCN can be participated in the future as predictive marker for osteoporosis in diabetic women.

Keywords: Osteocalcin, parathyroid hormone, estrogen, Type2 diabetes mellitus.

Introduction

Elevated blood glucose levels are an indication of diabetes mellitus (DM), a long-term metabolic disorder that affects the kidneys, heart, eyes, nerves, and blood vessels gradually. The primary causes of the condition are either abnormal insulin production, insulin

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resistance, or most frequently both (1). Diabetes mellitus type 2(T2DM), also known as adult-onset diabetes, can affect individuals of any age, even children. Conversely, older and middle-aged adults are more likely to have T2DM. Obese and sedentary individuals are more likely to develop T2DM (2). The pathophysiology involves a complex interaction between environmental and genetic factors that results in the development of insulin resistance and β-cell failure (3). The molecular processes involved in the synthesis and release of insulin, as well as the insulin response in tissues, must be tightly controlled for insulin release and action to accurately correspond to the metabolic demand. Consequently, abnormalities in any of the underlying mechanisms may result in a metabolic imbalance and the development of T2DM (4). As the disease progresses, insulin secretion is unable to maintain glucose homeostasis, which results in hyperglycemia. Hyperglycemia is related to cellular oxidative stress through the production of advanced glycation end products, insulin resistance, dyslipidemia, and chronic inflammation (5) . Untreated hyperglycemia can cause serious, life-threatening complications such as kidney damage, eye damage, nerve damage, heart disease, and peripheral vascular disease (6). Hyperglycemia and the accumulation of advanced glycation end products are likely significant factors in the development of reduced bone strength, similar to other diabetic complications (7). To varying degrees, T2DM can affect osteocyte function and bone resorption, remodeling, and formation (8). Research has shown that prolonged high blood sugar levels can increase the levels of advanced glycation end products (AGEs) in bone collagen. This can affect osteoblasts' ability to bind to the collagen matrix, develop, and perform their regular functions (9).

Osteocalcin (OCN), or bone γ-carboxyglutamic acid (Gla) protein, is a circulating protein produced by osteoblasts. It contains three γ-carboxyglutamic acid residues at positions 13, 17, and 20 (10). OCN, which is derived from bone, controls parasympathetic tone, muscle mass, brain development and functions, testosterone synthesis, and glucose metabolism (11). Osteoblasts produce OCN, which is non-collagenous, exists in two forms: the carboxylated form, which binds calcium, and the uncarboxylated form, which is a circulating hormone, this hormone has been shown to improve beta-cell function, insulin responsiveness, and the secretion of adiponectin and insulin (12). The majority of OCN remains in bone tissue where it contributes to bone matrix formation, modifies hydroxyapatite and bone mineralization and binds to calcium and hydroxyapatite in the bone matrix (13). It has been demonstrated that OCN enhances insulin sensitivity in adipocytes by promoting adipocyte expression of adiponectin and increasing insulin synthesis in pancreatic β-cells from Langerhans islets (14). Low levels of OCN have been repeatedly associated with T2DM, elevated blood glucose, and insulin resistance, while higher levels have been linked to improved glucose tolerance and insulin sensitivity (15). OCN helps to increase the uptake and breakdown of glucose and fatty acids in muscles during exercise, promoting adaptation to physical activity, this can improve insulin secretion and sensitivity,

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which helps prevent diabetes, according to studies done on animal models. OCN triggers the activation of GPCR6A, a member of the G protein-coupled receptor family, which then functions on β-cells and muscles. Osteoblasts, which produce and release OCN and have insulin receptors, are directly influenced by insulin (16).

The concentration of OCN in the blood changes with age as bone turnover changes (17), during infancy and adolescence, bone growth requires the highest activity of osteoblasts and a high rate of bone remodeling. Consequently, during these periods, the serum levels of OCN are higher. In adults, a meta-analysis revealed significant differences in total OCN serum concentrations between healthy subjects and those with T2DM (18).

The parathyroid gland secretes a hormone called parathyroid hormone (PTH) when the levels of calcium ions in the blood become low. When PTH binds to its receptor, PTHR1, which is mainly expressed in osteoblasts, it activates a G protein-family coupled receptor (GPCR) resulting in increased bone turnover, ultimately restoring the levels of calcium ions in the blood to normal (19). The unique effects of PTH on bone metabolism are due to its mechanism for regulating the balance of calcium and phosphorus. PTH can cause bone resorption when it is continuously stimulated, but it can also promote bone formation when the stimulation is intermittent, as per certain research findings (20). PTH plays a crucial role in regulating bone turnover by facilitating OCN production. The low bone turnover seen in T2DM patients may be due to the suppression of PTH, which impedes both bone formation and OCN production (21). The effect of OCN on middle-aged women with and without T2DM will be covered in this study, along with any relationships between PTH and E2 levels and whether OCN levels can be used as a predictor of osteoporosis in diabetic women

Patients and Methods

A case-control study at the Endocrinology and Diabetic Center and Al Mahmudyia General Hospital involved ninety Iraqi women in their 40s to 50s. Thirty of the ninety participants were healthy controls, and sixty of the women had been diagnosed with T2DM. All patient data, including height, weight, age, medical history, and any complications from diabetes, were recorded for the study. The research was conducted from November 29, 2023, to December 30, 2023.

For ten minutes, the blood samples were centrifuged at 4000 rpm. An ELISA (Enzyme Linked Immunoassay Analysis) analyzer was used to examine the serum sample of OCN, PTH and E2. OCN, PTH, and E2 were determined using human USA kits while HbA1c wsa estimated Roche\Germany kit using the Cobos C111 system.

ELISA Principle

ELISAs (Enzyme-Linked Immunosorbent Assays) are typically conducted in 96-well polystyrene plates. In this process, serum samples of (OCN, PTH or E2) are incubated in each well, with each well containing a different serum sample. Among the 96 samples, one well is reserved for a positive control serum, and another for a negative control serum. Antibodies or antigens present in the serum are captured by corresponding antigens or antibodies that are coated onto the solid surface of the wells.

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After the incubation period, the plate is washed to remove unbound serum, antibodies, or antigens using a series of wash buffers. To detect the bound antibodies or antigens, secondary antibodies that are conjugated to enzymes, such as peroxidase or alkaline phosphatase, are added to each well. Following another incubation period, any unbound secondary antibodies are washed away. Finally, a suitable substrate is added, and the enzyme reacts with it to produce a color change. This color change can be measured, providing a quantitative assessment of the antigens or antibodies present in the sample. The intensity of the color, measured at 450 nm, indicates the amount of antigen or antibody present.sent in serum are captured by corresponding antigen or antibody coated on to the solid surface. After some time, the plate is washed to remove serum and unbound antibodies or antigens with a series of wash buffer. To detect the bound antibodies or antigens, a secondary antibodies that are attached to an enzyme such as peroxidase or alkaline phosphatase are added to each well. After an incubation period, the unbound secondary antibodies are washed off. When a suitable substrate is added, the enzyme reacts with it to produce a color. This color produced is measurable as a function or quantity of antigens or antibodies present in the given sample. The intensity of color/ optical density is measured at 450nm. The intensity of the color gives an indication of the amount of antigen or antibody.

Statistical Analysis

Using SPSS, the data analysis was carried out. P-values <0.05 are regarded as significant, and P-value > 0.05 is considered non-significant.

Results

Demographic and clinical characteristics

This study involved a total of 90 participants, with 60 of them being patients and 30 controls. The study groups were carefully classified into subgroups based on age, duration of disease, and BMI, and the findings have been presented in Table 1. The results indicate that 46.6% of participants were aged between 48 and 50, while 26.7% of patients were aged between 40-43 and 44-47, and it is worth noting that the participants' BMI range was higher in comparison to other groups, at 61.67. As shown in Table 1, the majority of patients (52%) have been suffering from the disease for one to five years.

Table (1): Descriptive of the demographic characteristics of the study population (N=90).

Variable	Groups	Patient N=60	Control N=30
Age. Groups	40-43 Years	16%	13%
	44-47 Years	16%	8%
	48-50 Years	28%	9%
BMI. Groups	Normal weight	3%	15%
	Over weight	20%	10%
	Obesity	37%	5%
Duration of disease	Less than one years	5%	/
	1-5 Years	31%	/
	More than 5 Years	24%	/

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Examination the level of OCN in women with T2DM group compared to the control group.

Type 2 diabetes patients have lower OCN levels than healthy individuals, as per the results shown in Figure 1. The mean levels of OCN in patients were (4.29 ± 1.13) ng/ml, significantly lower than the Control group (8.21 ± 2.23) ng/ml, with a p-value of ≤ 0.001. Control group (8.21 ± 2.23) ng/ml, with a p-value of ≤ 0.001.

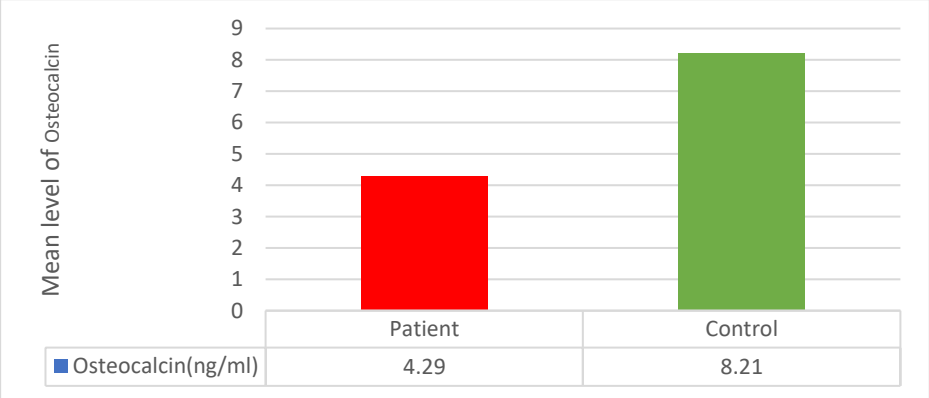

Figure (1): Results of the analysis of OCN in women with T2DM compared to control groups.

Examination the level of supporting parameters indices in women with T2DM for patients with control groups

In this study, we compared the T2DM indices of patients to healthy controls. HbA1c levels in the patient group were significantly higher than in the control group, while PTH and E2 levels were lower. All parameters showed high statistical significance (p<0.001) as seen in Figure 2.

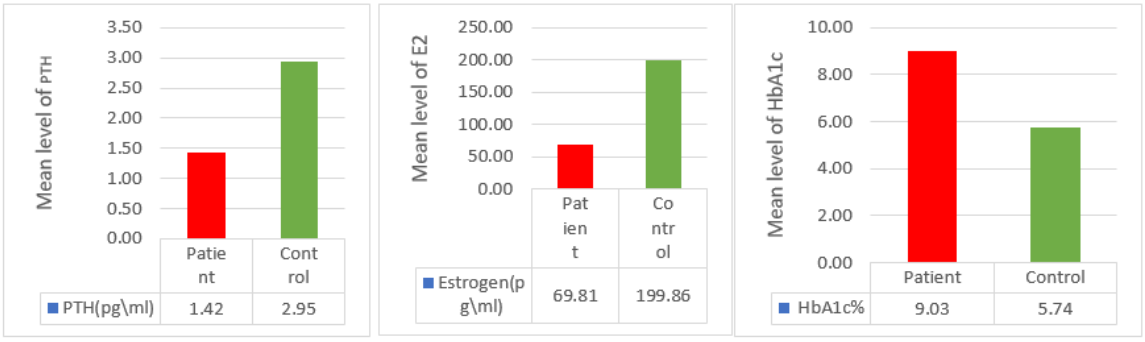

Figure (2): Results of the analysis of supporting parameters in women with T2DM compared to control.

Correlation

The correlation coefficient was used for determining linear relationships with OCN for E2, PTH and HbA1c in women Patients with T2DM.

The results showed that there was a highly statistically significant correlation between OCN and others (p = <0.001), as shown in Figure (3).

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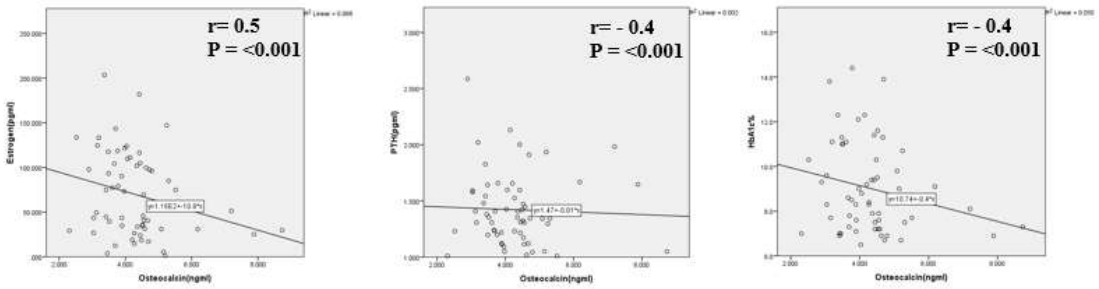

Figure (3): Simple linear regression between OCN and supporting parameters in women with T2DM.

Receiver Operating Characteristic Analysis

Results of the receiver operating curve (ROC) curve and area under curve (AUC) analysis for the OCN as diagnostic parameters were done OCN showed a good performance in predicting T2DM compared to the control group; data are presented in Table (2). For OCN levels: (sensitivity = 93.3 %, specificity 91.7%) at a level = 5.3595, the p-values of the AUC were <0.001 and highly statistically significant, as shown in table (2). The p-values of the AUC were <0.001 and statistically significant. Youden's J statistics for the parameters in Figure (4) confirm these results.

Table (2): The AUC, threshold, sensitivity, and specificity were determined using ROC curves in the study population.

Variable(s)	AUC	Sensitivity %	Specificity %	Youden index	Cut-off points	CI (95%)	PPV	NPV	P value
OCN (ng\ml)	91.70 %	93.30%	91.70%	0.85	5.3595	0.830-1.000	90%	88%	<0.001[S]

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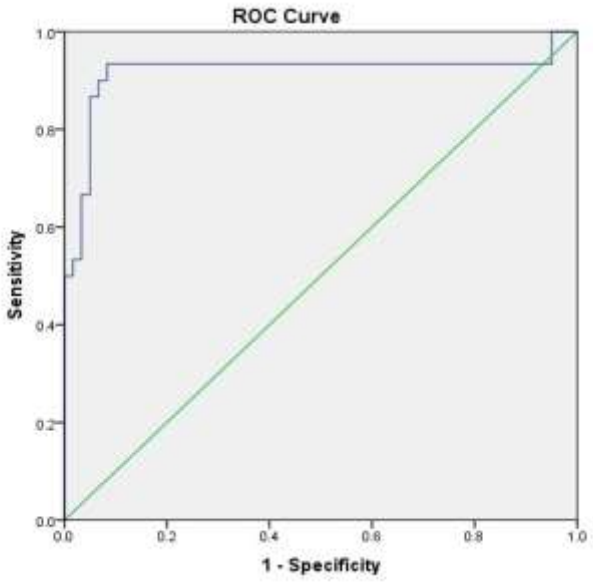

Figure (4): ROC curves for OCN in women with T2DM compared to the control group.

Discussion

The presented case-control study included 60 women (40-50) years of age with T2DM compared to 30 healthy control women. The serum OCN level was highly significantly decreased in patients compared to control women ($p<0.001$). The study findings indicate that osteocalcin (OCN) is associated with the glycemic state in patients with type 2 diabetes mellitus (T2DM). This aligns with previous research that revealed a negative correlation between OCN levels and the progression of T2DM as well as glycosylated hemoglobin (HbA1c) (22) .

Our research indicated that the average HbA1c levels measured in the patient group were significantly higher than those of the healthy control group, and that there was a strong statistical correlation between OCN and HbA1c ($r=-0.4$, $p<0.001$), This is consistent with earlier studies showing that higher HbA1c levels correlate with lower serum vitamin D3 and OCN concentrations (23). This suggests that poor glucose management negatively affects bone growth, leading to an imbalance in bone metabolism which results in increased resorption and a higher risk of osteoporosis. Previous study revealed that patients with poorly controlled blood glucose levels had lower levels of OCN compared to those with well-controlled blood glucose levels (24). The presented study also revealed a significant negative correlation between OCN and HbA1c, indicating a relationship between worsening glucose metabolism and lower OCN levels. This aligns with previous research, revealed that the level of OCN did not show any significant difference between the pre-diabetes and normal glucose tolerance (NGT) groups, however, the pre-diabetes group had a slightly higher level of OCN than the NGT group, suggesting that the plasma OCN levels remain unchanged until diabetes develops (25). During the pre-diabetes state, when more insulin is initially secreted in pancreatic β-cells, osteoblasts may secrete more OCN to overcome a given level of insulin resistance.

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However, when insulin resistance becomes more severe, the osteoblast is unable to release enough OCN, which ultimately leads to the development of diabetes as insulin secretion decreases. Previous study demonstrated that elevated OCN levels enhance insulin sensitivity and glucose homeostasis through their effect on beta-pancreatic cells (26). Bone turnover is a significant factor affecting bone quality, and it can be identified through bone metabolic markers. Studies have revealed that individuals with T2DM have lower levels of OCN, a biochemical marker of bone formation, in their serum as compared to those without T2DM, this suggests that bone formation is suppressed in T2DM patients in comparison to non-T2DM controls (27). A previous study observed low bone turnover in patients with T2DM, which could be attributed to low levels of PTH, responsible for the production of OCN and bone formation (21). Our study also supports these findings as we observed a significant decrease in both OCN and PTH levels. PTH plays a vital role in regulating bone turnover by supporting OCN production. Previous studies have shown that individuals who have T2DM and poor glycaemic control tend to have lower levels of PTH in their serum, which can negatively impact the activity of osteoblasts and lead to demineralization of bones (28). This suggests that there is a correlation between HbA1c levels and PTH levels in diabetic patients. There is a relationship between T2DM and the hormone called 17β-estradiol (estradiol), which is E2 hormone. Estradiol helps to protect β-pancreatic cells from apoptosis during hormone reproduction, which in turn helps to prevent insulin insufficiency. As a result, women have a lower incidence of diabetes because female sex steroids, rather than male hormones, protect against pancreatic β-cell injury. A previous study found that women over 46 years old had higher levels of estradiol compared to those under 45 (29). According to the presented study, women with T2DM have significantly lower levels of E2 than healthy women ($p<0.001$), this finding aligns with prior research, indicating that reduced levels of estradiol due to aging are a significant contributor to osteoporosis in older women (30). Since E2 deficiency can lead to bone loss, which is the primary cause of osteoporosis, hormone therapy has been considered an optional treatment for postmenopausal women to prevent osteoporosis.

E2 plays a crucial role in regulating the expression of hormones that affect bone metabolism. This includes increasing the secretion of calcitonin and enhancing the levels of vitamin D_3 (due to increased renal 1 alpha-hydroxylase and 25-hydroxylase activity). Additionally, E2 can prevent the secretion of PTH by lowering the level at which it responds to blood calcium. Any malfunctions in these regulatory factors can lead to abnormal mineralization or bone structure, which may result in conditions like osteoporosis or fractures (31). The presented study shows a significant correlation ($r=0.5$, $p<0.001$) between OCN and E2 levels. This can be attributed to the impact of low E2 on OCN-secreting bone osteoblasts. It was

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previously thought that while androgens promote bone formation, E2 inhibit it, giving men a higher bone density than women. Because E2 regulates the expression of its receptors, T2DM is associated with a decrease in E2 receptors (ERs), which may lead to impaired bone metabolism. Research has indicated that postmenopausal women may experience gradual deterioration of glucose tolerance, a decline in bone mass density, and an increase in bone turnover due to E2 deficiency (32).

Conclusions

It has been found that middle-aged women with T2DM are more prone to developing osteoporosis as compared to healthy women. This is because of lower levels of OCN, E2, and PTH, all of which have a significant impact on bone health. T2DM leads to a decrease in circulating OCN concentration due to a negative correlation between HbA1c and OCN. This suggests that patients with T2DM have less bone turnover and remodeling.

Recommendations

It was recommended to measure OCN levels of women in various stages of life, such as pre-menopause, menopause, and post-menopause, and measure the level of adiponectin. In addition, it is important for the future study to be done on a larger sample size to give results that are more accurate.

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Ethical Clearance: Official approval has been obtained to use data and data were analyzed without the names to protect privacy. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2024HIJ837).

Conflict of Interest: Non

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تأثير الاوستيوكالسين في النساء متوسطات العمر المصابات وغير المصابات بالسكري النوع الثاني

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الملخص

خلفية الدراسة: مرض السكري هو مرض مزمن يصيب الاشخاص في جميع الاعمار وينجم عن قصور في عمل الانسولين و افرازه مما يؤدي الى ارتفاع السكر في الدم على المدى الطويل. مرض السكري ممكن يضر الاعضاء الرئيسية مثل الكلى والقلب والعينين والاوعية الدموية. تتطلب السيطرة على مرض السكري تغييرات كبيرة في نمط الحياة وممن ان تؤثر على المرض وعائلته. الاوستيوكالسين هو بروتين غير كلايكوجيني صغير مختص بالعظم ويوجد غالبا فيها.وهو علامة حساسة لتكوين العظام ويرتبط بشكل اساسي بالمصفوفة الخارجية لخلايا العظم بعد كاربوكسليته, كما يتم اطلاق كميات صغيرة من هذا البروتين في الدم حيت يساعد في ايض السكريات والدهون.

اهداف الدراسة: هدفت دراستنا إلى فحص تأثير Osteocalcin و Parathyroid hormone و Estrogen و HbA1cعلى النساء في منتصف العمر المصابات بداء السكري من النوع ٢ مقارنة بأولئك اللاتي لم يعانين منه.

المرضى والطرائق: أجريت دراسة الحالات والشواهد على تسعين امرأة في منتصف العمر (٤٠-٥٠) وستين امرأة مصابة بداء السكري من النوع ٢ (ن = ٦٠)، وثلاثين امرأة صحية (ن = ٣٠) ليس لديهن مرض السكري من النوع ٢ ، ٤٥,٨٨ كان المستوى المتوسط لعمر المشارك في هذه الدراسة. بالمقارنة مع النساء الأصحاء وغير المصابات بالسكري، قامت الدراسة بقياس مستويات OCN و PTHو E2لدى النساء في منتصف العمر المصابات أو غير المصابات بداء السكري من النوع ٢. تم تقدير مستوى OCN و PTHو E2في المصل بواسطة مقايسة الامتصاص المناعي المرتبط بإنزيم ساندويتش بينما تم تقدير HbAlc بواسطة نظام Cobos C111 .تم إجراء الفحص الإحصائي بواسطة برنامجSPSS

النتائج: في النساء المصابات بمرض السكري النوع الثاني, تمت مقارنة مستويات OCN و PTHوE2 و HbA1c في الدم مع النساء الاصحاء غير المصابات بالسكري. كان لدى النساء المصابات بالسكري النوع الثاني مستويات قليلة من OCN وPTH وE2 في الدم, ومستويات عالية من HbA1c مقارنة بالنساء الاصحاء. كان لل OCNعلاقة ايجابية مع HbA1c وارتباطات سلبية مع PTH و E2.

الاستنتاجات: تم الكشف عن تغير كبير في هذه الدراسة في مستوى OCN، PTH وE2 بين المرضى والمجموعة الضابطة. يمكن المشاركة في تحقيقات مصل OCN في المستقبل كعلامة تنبؤية لهشاشة العظام لدى النساء المصابات بالسكريز

الكلمات المفتاحية: الاوستيوكالسين, هرمون الغدة الجارادرقية, الاستروجين, مرض السكري النوع الثاني

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