

Original Article

Interrelationship between glucose metabolism and undercarboxylated osteocalcin: a cross-sectional study in a community-dwelling population

Shozo Yano MD^{1,2}, Toru Nabika PhD^{2,3}, Atsushi Nagai MD^{1,2}, Tsuyoshi Hamano PhD^{2,4}, Masayuki Yamasaki PhD^{2,5}, Minoru Isomura PhD^{2,3}, Kuninori Shiwaku PhD^{2,5}, Shuhei Yamaguchi MD⁶, Toru Yamaguchi MD⁷, Toshitsugu Sugimoto MD⁷

¹Department of Laboratory Medicine, Shimane University Faculty of Medicine, Shimane, Japan

²Shimane community-based health research and education (CoHRE), Shimane, Japan

³Department of Functional Pathology, Shimane University Faculty of Medicine, Shimane, Japan

⁴Organization for the Promotion of Project Research, Shimane University, Shimane, Japan

⁵Department of Environmental and Preventive Medicine, Shimane University Faculty of Medicine, Shimane, Japan

⁶Department of Internal Medicine 3, Shimane University Faculty of Medicine, Shimane, Japan

⁷Department of Internal Medicine 1, Shimane University Faculty of Medicine, Shimane, Japan

Objective: Undercarboxylated osteocalcin (ucOC) produced from the bone was recently found to play a regulatory role in the insulin and adiponectin secretion. We performed a cross-sectional study to investigate the relationship between ucOC and diabetes mellitus (DM). **Methods:** We included 1,870 subjects aged over 50 from participants of a health examination. According to the current medication and past history, 605 subjects had hypertension (HT), 316 had dyslipidemia (DL), and 182 had type 2 DM. Fasting blood samples were collected to measure concentrations of ucOC and the bone turnover marker, tartrate-resistant acid phosphatase 5b (TRACP5b) by ELISA. **Results:** The serum ucOC level was significantly lower in DM(+) than DM(-) in both men and women. In a logistic regression analysis, a low level of ucOC was significantly associated with the presence of DM in both men and women after adjusting for age, BMI, serum creatinine, triglyceride, and TRACP5b. Multiple regression analysis showed a negative association of ucOC with HbA1c and fasting plasma glucose, and a positive association with the insulin level. In contrast, no association was found between TRACP5b and the indices above, suggesting that the effect of ucOC on the insulin secretion and the glycemic status was independent of bone turnover. **Conclusions:** The present cross-sectional study showed a significant association between ucOC and glucose metabolism after correction with bone turnover in a community-dwelling population both in men and women, indicating that ucOC may play an important role in the pathogenesis of DM through the pathways independent of bone metabolism.

Key Words: undercarboxylated osteocalcin, glucose metabolism, diabetes mellitus, bone metabolism, TRACP5

INTRODUCTION

Recently, insulin and adiponectin were found to play a role in the regulation of bone metabolism in addition to the canonical regulatory roles on the glucose and lipid metabolism. Further, in a reciprocal manner, several hormonal substances controlling the bone metabolism was reported to regulate the secretion of insulin and adiponectin through the carboxylation of osteocalcin (OC).¹

OC produced in mature osteoblasts is known as a marker for the bone formation. In the generation of the mature form of OC, it becomes carboxylated at all three possible sites. OC is, however, often secreted as an insufficiently-carboxylated form, which is called the undercarboxylated OC (ucOC). Because this step depends on vitamin K, ucOC is clinically used as an indicator of the vitamin K insufficiency.² Through several animal studies,

ucOC was found to have a pivotal role in the glucose metabolism.^{3,4} OC-knockout mice showed an increased fat mass, high serum glucose and triglyceride levels and a decreased secretion of insulin and adiponectin,³ while administration of ucOC enhanced the insulin and adiponectin secretion and activated the glucose and lipid catabolism.⁴

Corresponding Author: Dr Shozo Yano, Shimane University Faculty of Medicine, Department of Laboratory Medicine, 89-1 Enya-cho, Izumo city, Shimane 693-8501, Japan.

Tel: +81-853-20-2312; Fax: +81-853-20-2409

Email: syano@med.shimane-u.ac.jp

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The secretion and bioactivity of ucOC seems to be inhibited by an enzyme called the osteostesticular protein tyrosine phosphatase (OST-PTP), which has the gene name Esp.³ Esp deficient mice showed increased sensitivity to insulin through increased phosphorylation of insulin receptor and the downstream, FoxO1.⁵ In addition, OST-PTP inhibited phosphorylation of insulin receptor in osteoblasts *in vitro*.⁵ Thus, insulin stimulates the ucOC secretion in the bone under a normal condition. By contrast, high fat diet inhibits the OC as well as the ucOC production and secretion because the high fat diet induces the insulin resistance.

Previous studies in humans demonstrated that the OC production was reduced in patients with diabetes mellitus (DM)⁶⁻⁹ and the ucOC level was inversely correlated with the HbA1c and the glucose level in patients with type 2 DM.¹⁰ In addition, most studies were performed only in men. Thus, we investigated a relationship between ucOC and glucose and/or lipid metabolism in community-dwelling population both in men and women, and further examined whether or not this relationship is independent of bone turnover or bone metabolism.

MATERIALS AND METHODS

Subjects

The participants in this study were 1,870 healthy subjects (774 men and 1,096 women, age range; 21-85 and 50-87 years; mean, 69.2 years and 68.7 years, respectively). We consecutively recruited subjects who took health examination performed in their community in Shimane prefecture between 2009-2010. All women except two who participated in this study were postmenopausal, and they were non-DM subjects. All were basically healthy and nobody had a serious disease such as heart failure, renal failure and liver cirrhosis. The presence of hypertension (HT), dyslipidemia (DL), or DM is assigned by the past diagnosis and current medication. In 605, 316, and 114 subjects, anti-hypertensives, statins or fibrates, and oral hypoglycemic agents (OHA), were prescribed respectively. None had insulin therapy.

This study was cross-sectional in design, approved by the ethical review board of our institution (#1555), and complied with the Helsinki Declaration. All agreed to participate in the study and provided written informed consent.

Biochemical measurements

Anthropometrical examination and written questionnaires about medical history, medications, smoking and exercise habits, and life style (standing or sedentary) were performed to make a database set. The present smoking habit was categorized into 2 groups (no: 0 and yes: 1), and exercise habits with 30 minutes-walk or the equal exercise (none: 0, sometimes: 1, and almost every day: 2) and life style (sedentary in daytime: 0, standing half of daytime: 1, standing almost whole day: 2) were into 3 categories, respectively.

After overnight fasting, blood samples were collected after we confirmed their consent. Biochemical laboratories including total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), albumin (Alb), high

sensitive C-reactive protein (CRP), immunoreactive insulin (IRI) and creatinine (Cr) were measured by standard enzymatic methods.

Serum concentration of tartrate-resistant acid phosphatase isoenzyme 5b (TRACP5b) were measured by fragments absorbed immunocapture enzymatic assay (FAICEA). Serum concentration of ucOC was measured by electrochemiluminescent immunoassay (ECLIA) (Sanko Junyaku Co., Ltd., Tokyo, Japan).¹¹ Estimated GFR was calculated by following equation: $eGFR = 194 \times Cr^{-1.094} \times Age^{-0.287}$ ($\times 0.739$, if female).¹²

Fasting plasma glucose (FPG) level was measured by electrode method. Hemoglobin A_{1c} (HbA_{1c}) was determined by high-performance liquid chromatography and expressed according to the National Glycohemoglobin Standardization Program (NGSP). HOMA-IR (Homeostasis model assessment-Insulin Resistance) was calculated by following equation: $HOMA-IR = IRI \times FPG / 405$.

Statistical analysis

Data were expressed as the mean±standard deviation (SD). Since ucOC and TRACP5b showed a markedly skewed distribution, logarithmic (log) transformation of these values was carried out before simple and multiple regression analysis. Statistical difference between two groups was determined by a Mann-Whitney U-test. All analysis was performed using the statistical computer program StatView (Abacus Concepts, Berkeley, CA). A *p* value less than 0.05 was considered to be statistically significant.

RESULTS

Serum ucOC levels in subjects with or without HT, DL and DM

Baseline data of the subjects were shown in Table 1. Serum ucOC and TRACP5b levels were significantly higher in women than men. Although serum Cr level was lower in women than men, there was no difference in eGFR.

According to the current medication and past history, we found 605 subjects (245 men and 360 women) with HT, 316 subjects (70 men and 246 women) with DL, and 182 subjects (98 men and 84 women) with type 2 DM. Serum ucOC level was not significantly different between HT(+) and HT(-) in both men and women (Figure 1a). However, it was significantly lower in DL(+) than DL(-) in women (5.4 vs 6.0 ng/mL), and it was significantly lower in DM(+) than DM(-) in both men (3.0 vs 3.9 ng/mL) and women (4.5 vs 6.0 ng/mL).

Serum TRACP5b levels in subjects with or without DM

On the other hand, serum TRACP5b level was also significantly lower in DM(+) than DM(-) in women (Figure 1b). However, no statistical difference was found in men. In a simple regression analysis, there was a positive correlation between TRACP5b and ucOC ($r=0.470$, $p<0.0001$) (data not shown).

Association between DM and ucOC

In logistic regression analysis, a low level of ucOC was significantly associated with the presence of DM in both men and women even after adjusting for covariates including age, BMI, serum Cr, HDL-C, TG, smoking, life

Table 1. Baseline data of this study

	Total n=1,870	Men n=774	Women n=1,096
Age (year)	68.9±7.3	69.2±7.7	68.7±7.1
Height (cm)	155±8.4	162±6.5	150±5.7
Body weight (kg)	54.5±9.5	60.1±9.1	50.5±7.5
BMI (kg/m ²)	22.6±3.0	22.8±2.8	22.3±3.0
SBP (mmHg)	131±17	131±17	131±18
DBP (mmHg)	78±11	80±10	76±11
Cr (mg/dL)	0.70±0.16	0.81±0.15	0.63±0.12
eGFR (mL/min/1.73m ²)	74.5±14.2	75.6±14.8	73.8±13.8
TC (mg/dL)	203±33	192±33	211±31
HDL-C (mg/dL)	62±16	59±16	64±16
TG (mg/dL)	107±63	110±72	105±55
Alb (g/dL)	4.3±0.3	4.2±0.3	4.3±0.2
CRP (IU/L)	0.09±0.25	0.11±0.28	0.08±0.21
HbA1c (%)	5.9±0.5	5.9±0.6	5.9±0.5
FPG (mg/dL)	98±16	100±20	96±12
IRI (IU/L)	4.9±5.1	5.1±5.8	4.8±4.5
HOMA-IR	1.3±1.7	1.4±2.1	1.2±1.5
TRACP5b (mU/dL)	484±182	434±172	519±180
ucOC (ng/mL)	5.0±3.5	3.8±2.6	5.9±3.7

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Cr: creatinine; eGFR: estimated glomerular filtration rate; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglyceride; Alb: albumin; CRP: C reactive protein; FPG: fasting plasma glucose; IRI: immunoreactive insulin; HOMA-IR: Homeostasis model assessment-Insulin Resistance; TRACP5b: tartrate-resistant acid phosphatase 5b; ucOC: undercarboxylated osteocalcin.

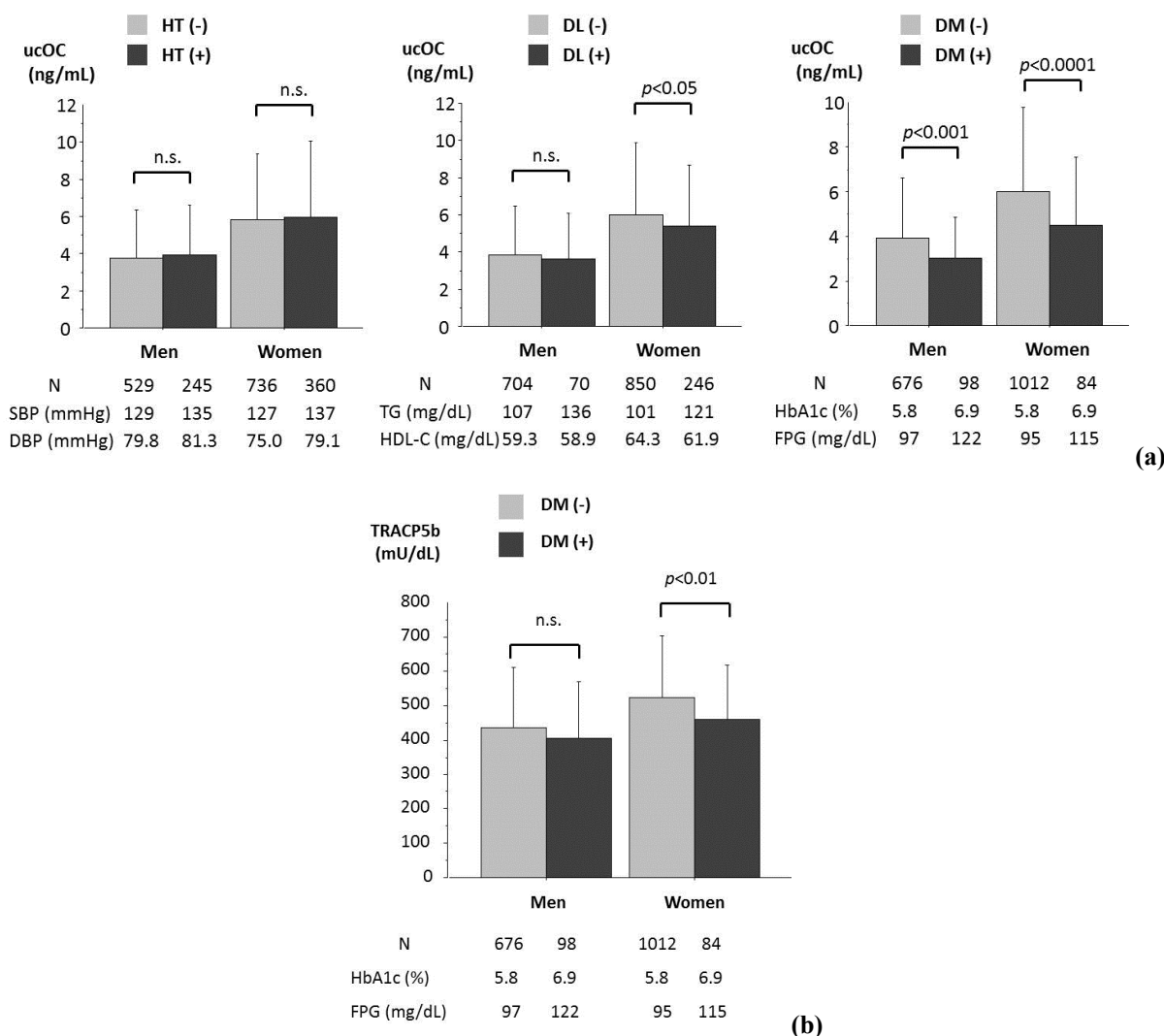


Figure 1. Serum ucOC and TRACP5b levels according to disease status. (a) Serum ucOC levels in patients with and without hypertension (HT), dyslipidemia (DL), or diabetes (DM) are shown. (b) Serum TRACP5b levels are compared between DM and non-DM patients.

Table 2. Logistic regression analysis predicting the presence of diabetes mellitus

	Men			Women		
	Odds ratio	95% CI	<i>p</i>	Odds ratio	95% CI	<i>p</i>
Log(ucOC) crude	0.26	0.12-0.55	0.0005	0.18	0.08-0.39	<0.0001
Log(ucOC) adjusted for #1	0.26	0.12-0.56	0.0006	0.18	0.08-0.39	<0.0001
Log(ucOC) adjusted for #2	0.26	0.12-0.58	0.0009	0.14	0.06-0.32	<0.0001
Log(ucOC) adjusted for #3	0.28	0.12-0.64	0.0028	0.16	0.06-0.41	0.0001

#1: age and BMI

#2: #1, serum Cr, HDL-C, TG, smoking, lifestyle, and exercise

#3: #2, and Log(TRACP5b)

Table 3. Multiple regression analysis for HbA1c and fasting plasma glucose

	HbA1c			FPG		
	Standard β	t	<i>p</i>	Standard β	t	<i>p</i>
BMI	0.13	5.39	<0.0001	0.12	5.21	<0.0001
Age	0.02	0.98	0.33	0.04	1.85	0.065
Sex	0.04	1.41	0.16	-0.1	-3.51	0.0005
Cr	-0.0002	-0.009	0.99	-0.06	-2.01	0.045
Log(ucOC)	-0.13	-4.94	<0.0001	-0.12	-4.61	<0.0001
Log(TRACP5b)	-0.003	-0.12	0.91	-0.02	-0.62	0.53

FPG: fasting plasma glucose.

Table 4. Multiple regression analysis for insulin and HOMA-IR

	Insulin (IRI)			HOMA-IR		
	Standard β	t	<i>p</i>	Standard β	t	<i>p</i>
Log(FPG)	0.43	15.4	<0.0001	0.58	22.6	<0.0001
BMI	0.23	8.14	<0.0001	0.152	5.91	<0.0001
Age	-0.10	-0.34	0.73	-0.008	-0.31	0.76
Sex	0.11	2.97	0.003	0.087	2.66	0.008
Cr	0.11	3.14	0.002	0.093	2.91	0.004
Log(ucOC)	0.07	2.09	0.04	0.048	1.63	0.10
Log(TRACP5b)	-0.05	-1.56	0.12	-0.038	-1.30	0.20

HOMA-IR: Homeostasis model assessment-Insulin Resistance.

style, exercise and TRACP5b (Table 2). No significant association was found between ucOC and the presence of DL after adjusting for HbA1c (data not shown). These findings suggest that the presence of DM, but not DL, had an strong association with low serum ucOC level even if bone turnover was considered.

Association between ucOC and glycemic indices

Next, multiple regression analysis showed that glucose control (HbA1c and fasting plasma glucose) had negative and positive associations with ucOC and BMI, respectively, while no association was found with TRACP5b (Table 3). Serum ucOC had a positive association with insulin level, whereas TRACP5b had no association (Table 4). There was no significant association between ucOC and HOMA-IR, an indicator of insulin resistance.

In order to correct effects of OHA on the results above, we performed additional analysis in subjects with or without these medications. We observed a positive association between ucOC and glycemic status in subjects not taking OHA whereas no significant association was found in 114 DM patients with OHA (data not shown). Taken together, a strong relationship was present between high level of ucOC and better glycemic status as well as increased insulin secretion.

DISCUSSION

Our findings suggest the presence of strong interrelationship between ucOC and glucose metabolism in community-dwelling healthy Japanese people. High ucOC level had a positive and negative correlation to endogenous secretion of insulin and low plasma glucose level, respectively, whereas low ucOC level was correlated with the presence of DM. Serum ucOC level was significantly lower in DL(+) than DL(-) in women, indicating ucOC may be associated with lipid metabolism. However, this may be indirect action mediated by insulin action and glucose metabolism, because multiple logistic regression analysis showed that marginal significant association between ucOC and the presence of DL disappeared after adjusting for HbA1c.

In animal studies, ucOC has been found to play critical roles in glucose metabolism. Ferron et al showed that recombinant ucOC stimulates insulin and adiponectin expression in beta cells and adipocytes, respectively, and affects the development of metabolic diseases, obesity, and type 2 diabetes in wild-type mice.⁴ On the other hand, previous clinical studies showed that serum OC level was associated with plasma glucose and adiponectin levels, fat mass, and atherosclerosis parameters in humans.⁶⁻⁹ We have previously shown that serum OC level was negatively correlated with plasma glucose level and atherosclero-

sis parameters in patients with type 2 DM.⁶ Pittas et al have shown that OC levels were associated with change in fasting plasma glucose in prospective analyses.⁹ These experimental and clinical findings suggest that bone metabolism and glucose/fat metabolism are associated with each other through the action of ucOC or OC.

In the present study, we showed inverse and positive associations of ucOC with plasma glucose and insulin levels, respectively, even when adjusted for TRACP5b, suggesting ucOC may be important in glucose metabolism independent of bone metabolism. These findings are in line with previous reports conducted in men with type 2 diabetes,¹⁰ elderly men,¹³ and hemodialysis patients.¹⁴ However, it remains uncertain whether or not carboxylated OC also plays a role in glucose metabolism. According to the previous report, carboxylated OC rather than ucOC may be potent for insulin resistance.¹⁵ Although we did not find significant association between ucOC and HOMA-IR, this is compatible with findings in general population¹⁵ and type 2 diabetic patients.¹⁶ Decrease in ucOC levels and increase in carboxylated OC levels induced by an administration of vitamin K2 increased insulin sensitivity.¹⁷ This is compatible with association between vitamin K intake and insulin sensitivity in a cross-sectional study¹⁸ and an interventional study.¹⁹ In addition, changes in insulin sensitivity were associated with changes in carboxylated OC but not ucOC.¹⁷ Since vitamin K status and bone metabolism is responsible for ucOC concentration, ucOC would be more potent if severe vitamin K deficiency was absent.²⁰

A recent report in a 5-year follow-up study showed that low concentrations of carboxylated OC or ucOC were involved in the development of DM.²¹ Low OC (ucOC) levels in diabetic patients are thought to result from suppressed activity of mature osteoblasts. We found high concentrations of glucose and advanced glycation end products inhibited OC production by osteoblastic cells in *in vitro* study.²² The action of ucOC, in turn, is suppressed at the insulin receptor level in diabetic condition.⁵ Administration of ucOC ameliorated glucose metabolism through insulin and adiponectin secretion in an animal study.⁴ Therefore, ucOC may be a therapeutic target for metabolic disorders such as DM, DL and obesity.

Finally, this study has several limitations. We did not assess dietary vitamin K intake, although it might affect gamma-carboxylation and serum ucOC levels. This is one of shortcomings in the present study. In addition, the study design was cross-sectional, and neither adiponectin nor total OC were measured. However, we measured TRACP5b to adjust for bone metabolism and found a significant interrelationship of ucOC and glucose metabolism in both men and women in community-dwelling subjects. This observation is in line with previous findings and it adds to the evidence concerning bone and glucose/lipid endocrine loop.

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AUTHOR DISCLOSURES

All authors declare no conflicts of interest.

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¹Department of Laboratory Medicine, Shimane University Faculty of Medicine, Shimane, Japan

²Shimane community-based health research and education (CoHRE), Shimane, Japan

³Department of Functional Pathology, Shimane University Faculty of Medicine, Shimane, Japan

⁴Organization for the Promotion of Project Research, Shimane University, Shimane, Japan

⁵Department of Environmental and Preventive Medicine, Shimane University Faculty of Medicine, Shimane, Japan

⁶Department of Internal Medicine 3, Shimane University Faculty of Medicine, Shimane, Japan

⁷Department of Internal Medicine 1, Shimane University Faculty of Medicine, Shimane, Japan

葡萄糖代謝與未羧化骨鈣素之相關：一個社區族群的橫斷性研究

目的：近期，骨頭生成的未羧化骨鈣素（ucOC）被發現扮演胰島素及脂聯素分泌的調節角色。我們執行一個橫斷性研究以探討 ucOC 與糖尿病的相關性。**方法：**此研究納入 1870 名大於 50 歲來自健康檢查的參與者。根據目前藥物治療及過去病史，605 名研究對象有高血壓（HT）、316 名有血脂異常（DL）及 182 名有第 2 型糖尿病。收集禁食血液樣本以 ELSA 測量 ucOC 及骨轉換標記、抗酒石酸磷酸酶 5b（TRACP5b）濃度。**結果：**男女性糖尿病患者比起非糖尿病患者都有顯著較低的血清 ucOC 濃度。以羅吉斯迴歸分析，校正年齡、BMI、血清肌酸酐、三酸甘油酯及 TRACP5b 後，發現男女性低濃度的 ucOC 與糖尿病有顯著相關。複迴歸分析顯示 ucOC 與 HbA1c、禁食血糖為負相關，與胰島素濃度則為正相關。反之，並未發現與 TRACP5b 以及上述指標的相關性，意指 ucOC 對胰島素分泌及血糖狀態的影響是獨立於骨轉換。**結論：**此橫斷性研究顯示在社區的男女性，校正骨轉換後，ucOC 及葡萄糖代謝的顯著相關性，這顯示 ucOC 可能透過獨立於骨代謝的途徑扮演糖尿病致病重要的角色。

關鍵字：未羧化骨鈣素、葡萄糖代謝、糖尿病、骨代謝、TRACP5