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Serum calcium is a novel parameter to assess metabolic syndrome in endometrial carcinoma

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ABSTRACT

Objectives: To investigate the distribution of serum calcium and the relationship between serum calcium and serum metabolic parameters in endometrial carcinoma (EC) patients.
Methods: Retrospective assessment of patients diagnosed with endometrial cancer from Peking University People's Hospital from 2004 to 2009. Clinical characteristics as well as pretreatment serum calcium, albumin, fasting plasma glucose (FPG), serum triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol (TC) value were extracted from patient records. Serum calcium was corrected for albumin. Unpaired t test and analysis of covariance were used to compare serum calcium among categorical variables. Simple correlation analyses and partial correlation analyses were used to assess the associations between serum calcium and continuous variables.
Results: Two-hundred twenty patients were included in this study. After adjusting for confounders, postmenopausal patients had higher total serum calcium (p=0.002) and albumin-corrected serum calcium (p=0.012) than premenopausal patients, endometrioid endometrial carcinoma (EEC) patients had higher total serum calcium than non-endometrioid endometrial carcinoma (NEEC) patients (p=0.037). Significant positive correlations were found between total serum calcium and FPG (p=0.017), TG (p=0.043), HDL (p=0.042), LDL (p<0.001), and TC (p<0.001) after adjusting for multiple variables, and the corrected serum calcium showed no significant correlation with metabolic parameters.
Conclusion: Total serum calcium might be a more sensitive parameter for metabolic syndrome in endometrioid endometrial cancer patients than lipids.

Keywords: Endometrial Neoplasms; Calcium; Metabolic Syndrome

INTRODUCTION

Endometrial carcinoma (EC) is one of the leading causes of malignancies in females. We previously found that ionized calcium (Ca^{2+}) influx to EC cells promotes their proliferation and migration, and the L-type Ca^{2+} channel subunit α1D was overexpressed in EC tissues compared to the level in benign controls [1]. Total serum calcium provides an important source of cytosolic Ca^{2+} [2], and it has been reported to be related to several malignancies. Higher albumin-corrected serum calcium distinguishes malignant pelvic masses from benign and borderline ones [3], is positively associated with an advanced stage of malignant

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Conflict of Interest
The authors declare that they have no conflict of interest.

Author Contributions
Conceptualization: L.Y., Z.J.; Data curation: L.Y., Z.J., C.L.; Formal analysis: L.Y.; Funding acquisition: W.J.; Investigation: L.Y., Z.J., C.L.; Methodology: L.Y., C.L.; Project administration: W.J.; Resources: C.L., X.Q., H.J.; Software: L.Y.; Supervision: W.J.; Validation: Z.J.; Visualization: L.Y.; Writing - original draft: L.Y., Z.J.; Writing - review & editing: Z.L., W.J.

melanoma [4], and is positively correlated with tumor volume in postmenopausal breast cancer [5]. However, to the best of our knowledge, the relationship between serum calcium and EC has not yet been reported.

Metabolic syndrome (MetS) is considered a well-established risk factor for EC. Hyperglycemia and dyslipidemia, 2 important components of MetS, have been reported to be closely related to endometrial cancer in several population-based epidemiological studies [6,7]. The relationship between fasting plasma glucose (FPG), lipid profiles and serum calcium remain controversial. Yamaguchi et al. [8] and Sun et al. [9] reported that serum calcium was independently positively correlated with FPG in diabetic and nondiabetic individuals. Albumin-corrected serum calcium was also found to be related to total cholesterol (TC) and high-density lipoprotein (HDL) in females [10]. However, no association between serum calcium and FPG, HDL or low-density lipoprotein (LDL) was found in another randomized controlled trial in females with excessive body mass index (BMI) and polycystic ovary syndrome [11].

The distribution of serum calcium among EC patients and whether it is related to FPG and serum lipids aroused our interest; we conducted a retrospective study to investigate these issues. We hypothesized that serum calcium positively correlated with FPG and serum lipids in EC patients. Combined with our previous findings, we assumed that cytosolic Ca^{2+} influx was one of the mechanisms by which serum calcium is involved in MetS-related EC.

METHODS

1. Study design and patient selection
We conducted a retrospective study of serum calcium and clinical characteristics as well as metabolic profiles of newly diagnosed endometrial cancer patients using the medical records of patients diagnosed from January 2004 to December 2009. Patients were identified from the electronic medical database of Peking University People's Hospital (Beijing, China). Clinical characteristics, including age, BMI, history of diabetes and hypertension, menopause, and histological type, were obtained, and the patients were re-staged according to International Federation of Gynecology and Obstetrics (FIGO) 2009 staging. Pretreatment serum calcium, albumin, fasting glucose and serum lipids, including triglyceride (TG), LDL, HDL, and TC values, were extracted. This study was approved by the Institutional Review Boards of Peking University People's Hospital (2015PHB116-01).

The inclusion criteria included newly diagnosed and histologically confirmed endometrial cancer patients admitted to our hospital from January 2004 to December 2009. The exclusion criteria included the following: 1) EC patients with parathyroid disease or chronic kidney disease; 2) EC patients with a history of other malignancies; 3) patients with nonepithelial cancers of the uterus, such as carcinosarcoma; and 4) patient records missing data for serum calcium, albumin or metabolic parameters.

We estimated the biologically active fraction of serum calcium by a standard formula [12]:

$$\text{Corrected serum calcium (mmol/L)} = \text{total serum calcium (mmol/L)} + 0.2 \times [40 - \text{albumin (g/L)}]$$

2. Statistical analysis

Descriptive statistics are presented as percentages or means±standard deviation (SD). An unpaired t test was used to compare total serum calcium or corrected serum calcium between age groups, BMI groups, histologic subtypes, with or without a history of diabetes or hypertension, FIGO stages and whether menopause had occurred at the time of diagnosis. Multivariable analysis adjusted for confounders in menopause and histologic subtype were conducted with analysis of covariance. Simple correlation analyses were used to assess the relationship between total serum calcium or corrected serum calcium and metabolic profiles. Multiple variable analyses were conducted with partial correlation analyses and adjusted for age, menopause and subtype. All tests were performed as two sided, and a p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 20.0 software (IBM Corporation, Armonk, NY, USA).

RESULTS

1. Patient selection

Initially, we identified 278 patients with confirmed endometrial cancer in our hospital from 2004 to 2009. We excluded patients with parathyroid disease or chronic kidney disease (n=2), with a history of other malignancies (n=2), confirmed nonepithelial cancers of the uterus (n=4), or missing data for total serum calcium or albumin or metabolic parameters (n=50). Finally, 220 patients were included in this study (**Fig. 1**).

2. Demographic characteristics and metabolic parameters of included patients

A total of 220 patients with histologically confirmed endometrial cancer were included in this study, and the demographic characteristics and metabolic parameters are summarized
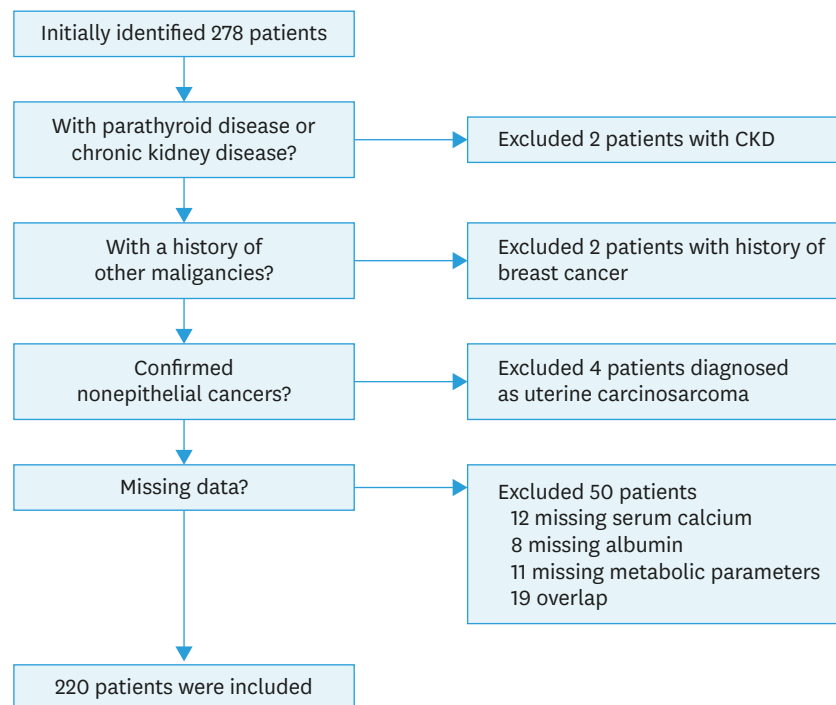

Fig. 1. Process of patient selection.

Table 1. Demographic characteristics and metabolic parameters of included patients

Variables (n=220)	Values
Age (yr)	57.02±9.77
≤55	99 (45)
>55	121 (55)
BMI (kg/m²)	25.78±4.14
Missing	17 (7.72)
Normal (≤25)	102 (46.37)
Overweight (>25)	101 (45.91)
History of diabetes	
Yes	40 (18.18)
No	180 (81.82)
History of hypertension	
Yes	85 (38.64)
No	135 (61.36)
Menopause	
Missing	1 (0.45)
Yes	158 (71.82)
No	61 (27.73)
Stage	
Early stage (FIGO I/II)	178 (80.91)
Advanced stage (FIGO III/IV)	42 (19.09)
Histologic subtype	
EEC	165 (75)
NEEC	55 (25)
Metabolic parameters	
FPG (mmol/L)	6.05±1.66
TG (mmol/L)	1.46±0.74
HDL (mmol/L)	1.26±0.31
LDL (mmol/L)	3.02±0.87
TC (mmol/L)	4.95±0.99
Serum calcium	
Albumin (g/L)	45.01±4.22
Total serum calcium (mmol/L)	2.23±0.13
Corrected serum calcium (mmol/L)	2.20±0.11

Values are presented as number (%) or mean±SD.
BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; EEC, endometrioid endometrial carcinomal NEEC, non-endometrioid endometrial carcinoma; FPG, fasting plasma glucose; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; SD, standard deviation.

in **Table 1**. Newly diagnosed EC patients had a mean±SD age of 57.02±9.77 and a BMI of 25.78±4.14 kg/m². Of all the patients, 18.18% had a history of diabetes, 38.64% had a history of hypertension, and most of the patients were postmenopausal (71.82%). A total of 75% of the patients had a histological diagnosis of endometrioid endometrial carcinoma (EEC), 25% had confirmed non-endometrioid endometrial carcinoma (NEEC), and most of the cases (80.91%) had early stage disease based on 2009 FIGO staging. Metabolic parameters and serum calcium are presented as the mean±SD in **Table 1** as well.

3. Comparison of serum calcium in patients with different clinical characteristics

We compared serum calcium among patients with different clinical characteristics by unpaired t test. Total serum calcium was higher in patients who were >55 years old than those ≤55 years old (2.32±0.13 vs. 2.28±0.12 mmol/L; p=0.023). Postmenopausal patients had higher total serum calcium than premenopausal patients (2.31±0.14 vs. 2.26±0.12 mmol/L; p=0.009). And total serum calcium in EEC group was 2.31±0.14 mmol/L, which was significantly higher than NEEC group (2.26±0.17 mmol/L; p=0.044). We also performed comparisons on corrected serum calcium and found that corrected serum calcium was

Table 2. Comparison of serum calcium in patients with different clinical characteristics

Characteristics	Total calcium (mmol/L)	p	Corrected calcium (mmol/L)	p
Age (yr)		0.023*		0.002*
≤55	2.28±0.12		2.17±0.11	
>55	2.32±0.13		2.21±0.11	
BMI (kg/m²)		0.687		0.829
Normal (≤25)	2.30±0.12		2.20±0.11	
Overweight (>25)	2.29±0.13		2.19±0.12	
History of diabetes		0.111		0.088
Yes	2.33±0.14		2.23±0.11	
No	2.29±0.14		2.19±0.11	
History of hypertension		0.908		0.344
Yes	2.29±0.16		2.21±0.11	
No	2.30±0.13		2.19±0.11	
Menopause		0.009*†		<0.001*‡
Yes	2.31±0.14		2.22±0.10	
No	2.26±0.12		2.16±0.12	
Histologic subtype		0.044*§		0.801
EEC	2.31±0.13		2.20±0.11	
NEEC	2.26±0.17		2.20±0.11	
Stage		0.525		0.167
Early stage	2.30±0.13		2.19±0.11	
Advanced stage	2.31±0.13		2.22±0.11	

Values are presented as mean±SD.
BMI, body mass index; EEC, endometrioid endometrial carcinoma; NEEC, non-endometrioid endometrial carcinoma; SD, standard deviation.
*p<0.05; †Multivariable analysis adjusted for age and histologic subtype (p=0.002); ‡Multivariable analysis adjusted for age and histologic subtype (p=0.012); §Multivariable analysis adjusted for age and menopause (p=0.037).

significantly higher in older group(>55 vs. ≤55 years old, 2.21±0.11 vs. 2.17±0.11 mmol/L; p=0.002) and postmenopausal group(postmenopausal vs premenopausal: 2.22±0.10 vs. 2.16±0.12 mmol/L; p<0.001), but it was not significantly higher in EEC group (p=0.801). Both total calcium and corrected calcium showed no significant difference between patients with BMI less or over 25 kg/m², as well as between patients with and without diabetes or hypertension. No significant differences were found among FIGO stages. We were interested in the influence of menopause and histologic subtype, so multivariable analyses were performed. After adjusting for confounders, postmenopausal patients still had higher total calcium (p=0.002) and higher corrected calcium (p=0.002) than premenopausal patients, EEC patients still had higher total calcium than NEEC patients (p=0.037) (**Table 2**).

4. Simple correlation analyses between serum calcium and metabolic parameters

Total serum calcium showed significant and positive correlations with FPG (p=0.035), TG (p=0.011), HDL (p=0.002), LDL (p<0.001), and TC (p<0.001). And there were trends of increasing HDL (p=0.027), LDL (p=0.013), and TC (p=0.003) as corrected serum calcium increased, while trends of increasing FPG (p=0.638), TG (p=0.075) were not (**Table 3**).

Table 3. Correlation analyses between serum calcium levels and metabolic parameters

Parameters	Total calcium				Corrected calcium			
	r*	p*	r†	p†	r*	p*	r†	p†
FPG	0.143	0.035‡	0.170	0.017‡	0.032	0.638	−0.004	0.959
TG	0.173	0.011‡	0.146	0.043‡	0.121	0.075	0.069	0.341
HDL	0.215	0.002‡	0.146	0.042‡	0.150	0.027‡	0.119	0.099
LDL	0.336	<0.001‡	0.305	<0.001‡	0.169	0.013‡	0.126	0.080
TC	0.386	<0.001‡	0.295	<0.001‡	0.198	0.003‡	0.119	0.098

FPG, fasting plasma glucose; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.
*Pearson correlation coefficients between serum calcium and metabolic parameters; †Partial correlation coefficients between serum calcium and metabolic parameters, adjusted for age, menopause, and histologic subtype; ‡p<0.05.

5. Partial correlation analyses between serum calcium and metabolic parameters, adjusted for multiple variables

Then, we performed partial correlation analyses between serum calcium and metabolic parameters, adjusted for age, menopause, and histologic subtype. The significant and positive correlations of total serum calcium with FPG (p=0.017) and serum lipids (TG, p=0.043; HDL, p=0.042; LDL, p<0.001; TC, p<0.001) were still observed after adjustment for these variables. Regarding corrected serum calcium, there was no correlation between corrected serum calcium and FPG and serum lipids in the partial correlation analysis (FPG, p=0.959; TG, p=0.341; HDL, p=0.099; LDL, p=0.080; TC, p=0.098) (**Table 3**).

DISCUSSION

The present study suggests a direct, multivariable adjusted and positive correlation between total serum calcium and FPG as well as serum lipids in newly diagnosed EC patients. The correlation was not obvious when calcium was corrected for albumin. Postmenopausal patients had higher total and corrected serum calcium than premenopausal patients, and EEC patients exhibited higher total serum calcium than NEEC patients, but the difference was not found in albumin-corrected calcium.

Pretreatment Ca^{2+} was not provided in the medical records. We used total serum calcium rather than albumin-corrected calcium to evaluate Ca^{2+} because albumin corrects for the protein-bound serum calcium but not Ca^{2+} [12]. In the present study, total serum calcium rather than corrected calcium was positively correlated with metabolic parameters, indicating that calcium was likely to participate in metabolism disorder-related EC in ionized form.

Higher Ca^{2+} concentrations [13] and Ca^{2+} channels [1] were found in endometrial cancer tissues compared to those in benign samples, indicating that endometrial tumorigenesis may require a high Ca^{2+} microenvironment and more active Ca^{2+} entry into cells. Cellular research has found that glucose and lipids directly and indirectly regulate cytosolic Ca^{2+} and Ca^{2+}-mediated signaling in cancer cells. For example, Ca^{2+} entry through membrane channels is considered to be one of the mechanisms by which glucose and lipids promote cancer progression [14,15]. The influence of glucose control and lipid-lowering drugs on endometrial cancer and cytosolic Ca^{2+} has also been investigated. We previously found that metformin improved the outcome of grade I endometrial cancer in fertility-sparing treatment with increasing HbA1C [16]. And long-term use of statins lowered the risk [17] and improved the survival of endometrial cancer [18]. Basic research found that antitumor effect of these drugs may performed by Ca^{2+}. For example, metformin inhibits pancreatic cancer growth by abrogating the insulin-stimulated increase in Ca^{2+} signaling [19], and simvastatin activates calcium-dependent apoptosis in leiomyoma cells [20]. We assumed that serum calcium plays a role in metabolism-impaired EC via cytosolic Ca^{2+}. Further fundamental studies are needed to prove this hypothesis.

Another interesting finding is that postmenopausal patients had higher total and corrected serum calcium than premenopausal patients. Postmenopausal individuals usually suffer from estrogen deprivation, which increases the risk of osteoporosis due to calcium resorption from bone [21]; this may be one of the reasons that our postmenopausal patients had higher serum calcium than the premenopausal group. We assumed that the difference was consistent in metabolic parameters. Thus, we compared metabolic parameters between pre- and postmenopausal individuals and found that TC, LDL, and TG were significantly higher in

postmenopausal patients, while FPG and HDL were not (**Supplementary Table 1**). Population-based studies revealed that the postmenopausal state was significantly and independently associated with impaired glucose metabolism [22,23]. Postmenopausal females had higher TC, TG than premenopausal females [24].

Interestingly, the present study suggested that EEC, the subtype that accounts for the majority of type I EC, had higher serum calcium than NEEC, the more likely type II cancer. Type I EC is well recognized as MetS related in classic Bokhman classification [25], so the elevated total serum calcium was likely to be related to rising FPG and serum lipids in the EEC group. Unfortunately, we did not find higher FPG or lipids (**Supplementary Table 2**) or a higher portion of diabetic or hypertensive subjects (**Supplementary Table 2**) in the EEC group in the present study. On one hand, our patients might have controlled their abnormal glucose and lipids with medicine before being diagnosed with EC, unfortunately we could not trace back the complete medication history. On the other hand, as a single institutional study involving 220 patients, selection bias was inevitable, and an enlarged sample size or multicenter research may correct the distribution of MetS components in EEC and NEEC.

To our knowledge, this is the first study demonstrating the relationship between serum calcium and EC. We searched PubMed, Web of Science, and Embase and did not find research focusing on serum calcium in EC patients as of July 31, 2018. The present study has some limitations. First, this was a retrospective analysis, and selection bias could not be avoided. We tried to control the bias by executing exclusion criteria, ensuring that the same laboratory methods were used in all involved cases and restaging patients with FIGO 2009 staging as the reference. Additionally, there were some clinical characteristics that were not included in the study, such as myometrial invasion and lymph node status. We missed some important variables, such as histological grade and menopausal age, which may be confounders of the analysis. What is more, if we could control history of medication as a confounder in multivariate analyses, we would make our results more convincing. Another study may be conducted in the near future focusing on these variables, while the present study concerns MetS-related factors.

For the first time, we found a positive correlation between serum calcium and FPG as well as serum lipids in EC patients. Serum calcium, but not FPG or lipids, was higher in EEC than NEEC, which indicated that serum calcium might be a novel and more sensitive parameter that should not be ignored when investigating the effect of MetS on endometrioid endometrial cancer. Large-scale clinical studies and more in-depth fundamental researches are needed to prove this finding.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Comparison of metabolic parameters between pre- and postmenopausal patients

Click here to view

Supplementary Table 2
Distribution of metabolic factors in EEC and NEEC

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