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Serum calcium is positively correlated with fasting plasma glucose and insulin resistance, independent of parathyroid hormone, in male patients with type 2 diabetes mellitus

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ABSTRACT

Patients with primary hyperparathyroidism have impaired glucose tolerance more often than do controls, and parathyroid resection sometimes improves this derangement. However, it is unclear whether serum calcium (Ca) or parathyroid hormone (PTH) is more strongly related to impaired glucose metabolism in subjects without primary hyperparathyroidism. In this cross-sectional study, we examined patients with type 2 diabetes mellitus (DM) (271 men and 209 women) and analyzed the relationships between serum concentrations of Ca or intact PTH and DM-related variables. Simple regression analyses showed that the level of serum Ca was significantly and positively correlated with the levels of fasting plasma glucose, immunoreactive insulin, and homeostasis model assessment insulin resistance in men ($P < .05$), but not in women. In contrast, intact PTH was not significantly correlated with DM-related parameters in either sex. Multiple regression analyses showed that the significant and positive correlations between serum Ca vs fasting plasma glucose and homeostasis model assessment insulin resistance in men still remained after adjustment for intact PTH as well as age, body weight, height, creatinine, albumin, phosphate, bone metabolic markers, and estradiol ($P < .05$). Serum Ca level is positively associated with impaired glucose metabolism, independent of PTH or bone metabolism, in men with type 2 DM.

1. Introduction

The near constancy of serum calcium (Ca) concentration (in the range of 1.1-1.3 mmol/L) in humans and other mammals ensures the availability of Ca ions for crucial extracellular roles, such as serving as a cofactor for adhesion molecules, clotting factors, and other proteins and regulating neuronal excitability [1]. Serum Ca also provides an important source of Ca for this ion's roles as a key second messenger and as a cofactor for various intracellular proteins and enzymes [2]. The extracellular Ca-sensing receptor (CaR) enables the parathyroid glands to sense alterations in the level of serum Ca and to negatively regulate secretion of parathyroid hormone (PTH), which functions to normalize the blood Ca concentration [3,4]. The CaR is also expressed in various cells [5] including human islets and human insulinoma cells [6]. It may participate in β-cell replication and differentiation and thus regulate nutrient-induced insulin secretion [6]. The C-terminus of CaR has been shown to interact with and inactivate inwardly rectifying K channels (Kir) [7]. The CaR can also interact spatially with the voltage-dependent Ca channel (VDCC) under high glucose conditions to allow control over Ca

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channel activity [8]. Because Kir and VDCC are involved in glucose-induced insulin secretion by β-cells, these findings suggest that serum Ca may modulate insulin secretion and glucose metabolism partly through stimulating CaR in pancreatic β-cells.

Clinically, patients with primary hyperparathyroidism (PHPT) tend to have impaired glucose tolerance more often than is observed in controls, and parathyroid resection sometimes improves this derangement. The prevalence of diabetes mellitus (DM) in PHPT is approximately 8%, which was about 3-fold higher than the expected prevalence in the general population; and approximately 40% of PHPT patients have impaired glucose tolerance [9]. Procopio et al [10] examined 105 consecutive PHPT patients and found that the prevalence of impaired glucose tolerance and undiagnosed DM was significantly higher in patients with PHPT than that in controls (40.7% vs 25.0%, $P < .03$, and 15.3% vs 5.0%, $P < .05$, respectively), although age and body mass index (BMI) were not significantly different (59.0 vs 57.0 years, and 25.0 vs 24.3 kg/m^2, respectively). Richards and Thompson [11] found that parathyroidectomy resulted in either stabilization or improved glucose control in 77% of PHPT patients with DM. Several other studies also showed improvement in DM after parathyroidectomy [12-14]. These findings suggest that high serum levels of either Ca or PTH may be associated with impaired glucose metabolism in PHPT patients.

In contrast, there are only a few studies that address whether high serum levels of Ca or PTH adversely affect glucose metabolism in subjects without PHPT. Sun et al [15] reported significant positive correlations of Ca with glucose and insulin resistance in 1182 healthy Canadian subjects. This relationship remained after the Ca concentration was adjusted for the concentrations of 25-OH vitamin D and PTH [15], suggesting that high serum Ca rather than PTH is involved in impaired glucose tolerance in healthy subjects. In contrast, Chiu et al [16] reported that the insulin sensitivity index was inversely correlated with serum PTH level in 52 healthy subjects after adjusting for age, sex, ethnicity, and waist-to-hip ratio. However, they did not present the data on serum Ca; nor did they adjust PTH levels for Ca concentrations in the study. Thus, further studies are needed to investigate whether Ca or PTH is more potently related to impaired glucose metabolism and whether Ca or PTH affects glucose levels, insulin secretion, or insulin resistance in subjects without PHPT.

To clarify these issues, in this study we examined Japanese patients with type 2 diabetes mellitus (T2DM) and analyzed the relationships between serum levels of Ca or intact PTH and DM-related variables.

2. Subjects and methods

2.1. Subjects

The subjects in this study were 271 men and 209 women with T2DM (mean ages, 60.8 and 65.5, respectively; Table 1). We recruited consecutive subjects who visited Shimane University Hospital for education on, evaluation of, or treatment of T2DM.

Table 1 – Baseline characteristics of subjects

	Men	Women	P value
No. of subjects	271	209	
Age (y)	60.8 ± 13.0	65.5 ± 11.4	<.0001
Body weight (kg)	64.5 ± 15.3	56.1 ± 12.2	<.0001
Height (cm)	164.9 ± 7.1	150.2 ± 5.8	<.0001
BMI (kg/m^2)	23.6 ± 4.5	24.8 ± 5.0	.004
Alb (g/dL)	4.2 ± 0.5	4.1 ± 0.5	.138
Ca (mg/dL)	9.2 ± 0.4	9.2 ± 0.4	.217
Phosphate (mg/dL)	3.4 ± 0.5	3.7 ± 0.5	<.0001
ALP (IU/L)	252.1 ± 89.5	275.1 ± 96.0	.028
BUN (mg/dL)	15.4 ± 4.6	15.5 ± 5.0	.880
Cr (mg/dL)	0.81 ± 0.23	0.65 ± 0.28	<.0001
HbA_{1c} (%)	9.1 ± 2.4	9.0 ± 2.3	.650
FPG (mg/dL)	170 ± 61	168 ± 61	.619
IRI (μU/mL)	5.9 ± 5.5	7.6 ± 7.2	.007
Fasting C-peptide (ng/mL)	1.7 ± 1.0	1.6 ± 0.9	.312
HOMA-IR	2.4 ± 2.7	3.0 ± 3.2	.032
Intact PTH (pg/mL)	38.4 ± 16.7	44.5 ± 18.1	.0001
$1,25(OH)_2$ vitamin D (pg/mL)	46.8 ± 19.5	46.6 ± 20.9	.917
BAP (U/L)	26.4 ± 10.6	31.3 ± 12.1	<.0001
Osteocalcin (ng/mL)	5.0 ± 2.4	6.7 ± 3.1	<.0001
uNTX (nmol/L BC)/(mmol/L Cr)	34.7 ± 23.9	52.5 ± 30.8	<.0001
E_2 (pg/mL)	30.0 ± 11.0	17.0 ± 24.0	<.0001

We excluded patients who had higher than the reference range of serum creatinine (Cr) (reference range for women: 0.44-0.83 mg/dL, men: 0.56-1.23 mg/dL) or higher than 300 mg albumin (Alb) per gram urine Cr as a measure of urinary Alb excretion. One hundred eighty-nine women (90%) were postmenopausal. The majority of subjects were taking medication for the T2DM: 53 (20%), 98 (36%), 36 (13%), 39 (14%), and 17 (6%) men, as well as 60 (29%), 62 (30%), 47 (22%), 22 (11%), and 13 (6%) women, had been taking insulin treatment, sulfonylurea, metformin, α-glucosidase inhibitor, and thiazolidinedione, respectively. No subjects were taking drugs known to influence Ca metabolism, including vitamin D, bisphosphonate, and estrogen replacement therapy at the time of the present study. Ninety-one men (34%) and 83 women (40%) had diabetic retinopathy, and 179 men (66%) and 131 women (63%) had diabetic neuropathy. Fifty-eight men (21%) and 2 women (1%) were current smokers, and 92 men (34%) and 4 women (2%) consumed more than 1 U/d of alcohol. This study was cross-sectional and approved by the ethical review board of our institution and complied with the Helsinki declaration. All subjects agreed to participate in the study and gave informed consent.

2.2. Biochemical measurements

After the subjects fasted overnight, serum samples were collected in the morning before insulin or other drugs were administered. Serum concentrations of Ca, phosphate, alkaline phosphatase (ALP), and other markers were measured by automated techniques at the central laboratory of Shimane University Hospital as previously described [17] (reference range: Ca, 8.6-10.3 mg/dL; phosphate, 2.2-4.6 mg/dL; ALP, 110-340 IU/L). Serum Ca was corrected according to the following formula: corrected serum Ca concentration = 4 − serum Alb concentration + serum Ca concentration [18]. Intact PTH was

measured with an immunoradiometric assay (Allegro Intact PTH-radioimmunoassay kit; Nichols Institute Diagnostics, San Juan Capistrano, CA; reference range: 10-65 pg/mL) [19]. Hemoglobin A_{1c} (HbA_{1c}) was determined by high-performance liquid chromatography (reference range: 4.3%-5.8%). The homeostatic model assessment for insulin resistance (HOMA-IR) was calculated by the following formula: HOMA-IR = fasting plasma glucose (FPG) × fasting plasma insulin/405 [20]. Serum bone-specific ALP (BAP) and C-peptide immunoreactivities were measured by enzyme immunoassay kits (DS Pharma Biomedical, Suita, Japan, and TOSOH, Tokyo, Japan, respectively) (reference range: BAP, 13.0-33.9 U/L; C-peptide, 0.6-2.8 ng/mL). $1,25(OH)_2$ vitamin D and osteocalcin were measured by radioimmunoassay kits (TFB, Tokyo, Japan, and Mitsubishi Chemical Medience, Tokyo, Japan, respectively; reference ranges: $1,25(OH)_2$ vitamin D, 27.5-68.7 pg/mL; osteocalcin, 2.5-13.0 ng/mL). Urinary N-terminal cross-linked telopeptide of type-I collagen (uNTX) and estradiol (E_2) were measured with an enzyme-linked immunosorbent assay kit (Inverness Medical Japan, Tokyo, Japan) and an electrochemiluminescence immunoassay kit (Roche Diagnostics, Tokyo, Japan), respectively (reference ranges: uNTX, <40 (nmol/L BC)/(mmol/L Cr); E_2, 11-44 pg/mL). The coefficients of variation of these measurements were less than 15%.

2.3. Statistical analysis

All data are expressed as the mean ± SD for each index. Unpaired *t* tests were used to compare parameters between male and female subjects. Simple and multiple regression analyses were performed using the statistical computer program StatView (Abacus Concepts, Berkeley, CA). Simple regression analysis was used to assess the relationship between serum Ca or intact PTH levels and various confounders, including DM-related confounders. To evaluate the contribution of serum Ca or intact PTH levels to DM-related parameters, multiple regression analysis was performed after adjustment for age, body weight, height, Cr, Alb, phosphate, BAP, osteocalcin, uNTX, and E_2. $P < .05$ was considered to be significant. A cross-sectional study with 150 subjects would provide more than 80% power to detect a correlation coefficient of more than 0.2 at the conventional $\alpha = .05$ level. Thus, the number of subjects in this study fulfilled this requirement.

3. Results

3.1. Baseline characteristics of subjects

Table 1 compares the male and female T2DM patients with respect to demographic and biochemical parameters. Patient age, BMI, serum phosphate, ALP, immunoreactive insulin (IRI), HOMA-IR, intact PTH, bone formation markers such as BAP and osteocalcin, and the bone resorption marker uNTX were significantly lower in the male than in the female subjects (at least $P < .05$). In contrast, body weight, body height, Cr, and E_2 were significantly higher in the male than in the female subjects ($P < .0001$).

3.2. Simple regression analyses between serum Ca level vs Ca metabolism-related and DM-related parameters

In men, simple regression analyses showed that Ca was significantly and positively correlated with DM-related parameters such as FPG ($P = .0001$), IRI ($P = .019$), and HOMA-IR ($P = .002$), as well as height ($P = .005$), Alb ($P = .0002$), phosphate ($P < .0001$), BAP ($P = .014$), osteocalcin ($P = .041$), and uNTX ($P = .002$) and negatively correlated with age ($P < .0001$) and intact PTH ($P = .004$) (Table 2). In women, Ca was not correlated with any DM-related parameter, although it was significantly and positively correlated with Alb ($P = .003$) and negatively correlated with age ($P = .0006$) and intact PTH ($P = .004$) (Table 2).

3.3. Simple regression analyses between serum intact PTH levels vs Ca metabolism-related and DM-related parameters

Intact PTH only showed significant correlations with FPG in men ($P = .032$, negative correlation) and with fasting plasma C-peptide in women ($P = .005$, positive correlation) (Table 3). In men, intact PTH was positively correlated with blood urea nitrogen (BUN) ($P = .002$), Cr ($P < .0001$), and BAP ($P = .008$), and negatively correlated with Alb ($P = .030$), Ca ($P = .004$), and phosphate ($P < .0001$). In women, the hormone was positively correlated with age ($P = .010$), BMI ($P = .014$), BUN ($P = .005$), Cr ($P < .0001$), and osteocalcin ($P = .012$), and negatively correlated with Ca ($P = .004$) (Table 3).

3.4. Multiple regression analyses between serum Ca and DM-related parameters adjusted for multiple variables

We performed multiple regression analyses of serum Ca level vs DM-related parameters adjusted for intact PTH as well as age, body weight, height, Cr, Alb, phosphate, BAP,

Table 2 – Correlation coefficients between Ca and various parameters

	Men		Women	
	r	P value	*r*	P value
Age (y)	−0.281	<.0001	−0.235	.0006
Body weight (kg)	0.058	.343	−0.021	.766
Height (cm)	0.172	.005	0.112	.106
BMI (kg/m^2)	−0.008	.9016	−0.071	.308
Alb (g/dL)	0.224	.0002	0.207	.003
Phosphate (mg/dL)	0.266	<.0001	0.118	.089
ALP (IU/L)	0.129	.083	0.059	.488
BUN (mg/dL)	−0.007	.912	0.084	.228
Cr (mg/dL)	−0.070	.251	0.003	.969
HbA_{1c} (%)	0.156	.103	0.077	.271
FPG (mg/dL)	0.233	.0001	0.104	.133
IRI (μU/mL)	0.152	.019	−0.097	.195
Fasting C-peptide (ng/mL)	0.073	.234	−0.003	.964
HOMA-IR	0.200	.002	−0.061	.416
Intact PTH (pg/mL)	−0.174	.004	−0.200	.004
$1,25(OH)_2$ vitamin D (pg/mL)	−0.109	.128	−0.073	.403
BAP (U/L)	0.151	.014	0.011	.878
Osteocalcin (ng/mL)	0.130	.041	0.100	.175
uNTX (nmol/L BC)/(mmol/L Cr)	0.194	.002	0.062	.387
E_2 (pg/mL)	0.030	.683	−0.041	.585

Table 3 – Correlation coefficients between intact PTH and various parameters

	Men		Women	
	r	*P* value	*r*	*P* value
Age (y)	0.036	.557	0.177	.010
Body weight (kg)	0.035	.567	0.126	.068
Height (cm)	0.060	.323	−0.082	.238
BMI (kg/m^2)	0.015	.800	0.171	.014
Alb (g/dL)	−0.132	.030	−0.039	.580
Ca (mg/dL)	−0.174	.004	−0.200	.004
Phosphate (mg/dL)	−0.275	<.0001	−0.117	.094
ALP (IU/L)	0.122	.101	0.012	.892
BUN (mg/dL)	0.187	.002	0.193	.005
Cr (mg/dL)	0.247	<.0001	0.349	<.0001
HbA_{1c} (%)	−0.019	.750	0.009	.900
FPG (mg/dL)	−0.130	.032	0.009	.900
IRI (μU/mL)	−0.011	.870	0.112	.133
Fasting C-peptide (ng/mL)	0.095	.120	0.196	.005
HOMA-IR	−0.030	.648	0.089	.236
$1,25(OH)_2$ vitamin D (pg/mL)	−0.039	.585	−0.124	.157
BAP (U/L)	0.161	.008	0.103	.147
Osteocalcin (ng/mL)	0.071	.269	0.185	.012
uNTX (nmol/L BC)/(mmol/L Cr)	0.031	.621	−0.072	.312
E_2 (pg/mL)	0.012	.873	−0.065	.391

osteocalcin, uNTX, and E_2 (Table 4). In men, the significant and positive correlations of Ca with FPG and HOMA-IR were still observed after adjustment for these variables ($P = .004$ and $P = .025$, respectively). When we excluded patients undergoing insulin treatment and reanalyzed the data, Ca was significantly and positively correlated with HbA_{1c}, FPG, and HOMA-IR ($P = .028$, $P = .017$, and $P = .041$, respectively). In contrast, such significant correlations were not found in women, except for a significant and positive correlation between Ca and HbA_{1c} in women without insulin treatment ($P = .031$).

3.5. *Multiple regression analyses between intact PTH and DM-related parameters adjusted for multiple variables*

Multiple regression analyses adjusted for Ca, age, body weight, height, Cr, Alb, phosphate, BAP, osteocalcin, uNTX, and E_2 showed that serum intact PTH level was not associated with any DM-related parameters in either sex regardless of insulin treatment (Table 5).

4. Discussion

In this study, we found that the serum Ca concentration was significantly and positively correlated with FPG and HOMA-IR after adjustment for serum intact PTH and other variables in T2DM men. In contrast, the serum intact PTH level was not correlated with any DM-related parameters after adjustment for serum Ca in either sex. The results were similar when patients treated with insulin were excluded. These findings suggest that serum Ca, but not intact PTH, is potentially involved in the aggravation of hyperglycemia and insulin resistance in T2DM men. Thus, serum Ca may be more strongly related to glucose metabolism than serum PTH and may be linked to impaired glucose metabolism in T2DM men as well as PHPT patients. The present findings seem to be in accordance with those of Sun et al [15] who showed that serum Ca was significantly and positively correlated with glucose and insulin resistance in non-DM subjects after adjustment for 25-OH vitamin D and PTH.

Cytosolic Ca is known to modulate insulin secretion from β-cells in the pancreas as well as glucose uptake by skeletal muscle under insulin stimulation. Insulin secretion is a Ca-dependent biological process, and an elevation in cytosolic Ca is required for both first- and second-phase insulin secretions [21]. Cytosolic Ca also plays a critical role in glucose uptake in skeletal muscle, a major site for insulin resistance, by influencing the affinity of the insulin receptor and its sensitivity to insulin after insulin binds to muscle cells [22]. The CaR is expressed in various tissues including pancreatic β-cells [6] and muscle cells [23] and evokes an elevation in cytosolic Ca by sensing extracellular Ca [3,5]. The elevation of cytosolic Ca subsequently activates its signaling pathway as well as cause the interaction of CaR with Kir and VDCC on β-cells [7,8]. Aoki and Miyagawa [24] suggested that an increased serum Ca level is linked to Ca influx into arterial muscle and increased cytosolic Ca because intravenous Ca infusion induced vasoconstriction and blood pressure elevation in normotensive men. Thus, the positive correlations between serum Ca and both FPG and HOMA-IR found in our study might be because serum Ca positively affects cytosolic Ca in both pancreatic β-cells and muscle, partly via CaR, which results in hyperinsulinemia, reduced glucose uptake, and insulin resistance. However, the current findings were provided by a cross-sectional study, rather than by prospective or mechanistic investigations. Thus, it is also possible that Ca

Table 4 – Partial correlation coefficients between Ca and DM-related parameters adjusted for age, body weight, height, Cr, Alb, phosphate, intact PTH, BAP, osteocalcin, uNTX, and E_2

Independent variables	Men				Women			
	All		No insulin		All		No insulin	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
HbA_{1c} (%)	0.144	.055	0.189	.028	0.124	.112	0.226	.031
FPG (mg/dL)	0.215	.004	0.263	.017	0.118	.123	0.140	.197
IRI (μU/mL)	0.137	.079	0.135	.121	−0.045	.562	0.015	.895
Fasting C-peptide (ng/mL)	0.078	.254	0.038	.710	0.032	.668	0.071	.513
HOMA-IR	0.184	.025	0.167	.041	−0.026	.748	0.029	.789

Table 5 – Partial correlation coefficients between intact PTH and DM-related parameters adjusted for age, body weight, height, Cr, Alb, phosphate, Ca, BAP, osteocalcin, uNTX, and E_2

Independent variables	Men				Women			
	All		No insulin		All		No insulin	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
HbA_{1c} (%)	−0.040	.595	−0.071	.404	0.072	.403	0.075	.471
FPG (mg/dL)	−0.042	.573	−0.012	.888	0.055	.518	0.016	.876
IRI (μU/mL)	−0.030	.694	−0.032	.707	0.068	.409	0.086	.420
Fasting C-peptide (ng/mL)	−0.043	.530	−0.058	.597	0.152	.068	0.094	.366
HOMA-IR	−0.003	.974	−0.004	.963	0.058	.499	0.031	.773

levels could simply be associated with insulin resistance without any causality.

Patients with DM have latent hypoparathyroidism with immunoreactive PTH comparatively lower than that of non-DM controls [25,26]. A clinical study showed that intact PTH rose less obviously in DM patients than in non-DM controls when phosphate was administered and ionized Ca concentrations were reduced [27]. Indeed, the significant and inverse correlations between Ca and intact PTH seem modest in this study (r = −0.179 in men, and r = −0.200 in women; Table 2). High glucose and advanced glycation end products (AGEs) directly inhibited PTH secretion from cultured parathyroid cells [28,29], suggesting that hyperglycemia and accumulating AGEs may play a pivotal role in the pathogenesis of hypoparathyroidism in DM patients. In the current study, however, neither FPG nor HbA_{1c}, which clinically reflects hyperglycemia and circulating AGEs, respectively, was correlated with intact PTH in either sex after adjustment for Ca (Table 5). These findings suggest that their direct inhibitory effects on PTH, if any, would be minimal. In contrast, FPG and HOMA-IR were significantly and positively correlated with Ca independent of intact PTH in T2DM men (Table 4). Because Ca was significantly and inversely correlated with intact PTH by simple regression analysis (Table 2), the present findings suggest that hyperglycemia and insulin resistance are associated with high serum Ca concentration, which, in turn, may lower the serum intact PTH level and cause latent hypoparathyroidism in T2DM men.

In this study, we examined the relationships between serum Ca or intact PTH and DM-related parameters separately in each sex because bone and mineral metabolism is known to be markedly affected by estrogen deficiency in postmenopausal women [30]. Indeed, we found a sex difference in the correlations between serum Ca and DM-related parameters. Because most women enrolled in this study were postmenopausal, these differences might have been due to sex hormone differences between the groups. In this study, E_2 levels were lower in women than men, with subsequent increases in bone metabolic markers (Table 1). This high bone turnover status induced by low estrogen might dominantly affect Ca metabolism and obscure the relationship between serum Ca and DM-related parameters in women. However, this explanation seems unlikely because the sex difference in the relationship between serum Ca and DM-related parameters still remained after adjustment for bone markers and E_2 (Table 4). We also found in previous studies that the associations of serum pentosidine, insulin-like growth factor I, and adiponectin levels with the presence of prevalent vertebral fractures differed between men and women. The associations of pentosidine and insulin-like growth factor I with fractures were significant only in postmenopausal women [31,32], whereas the association between adiponectin and fractures was significant only in men [33]. Thus, sex differences seem to be frequently observed in studies on bone and minerals, although we are unable to explain what mechanisms underlie these observations.

This study has some limitations. First, the study was cross-sectional, although the sample size was fairly large. Second, we analyzed only subjects who visited Shimane University Hospital, a tertiary center, for evaluation or treatment of T2DM. Therefore, the patients enrolled in this study might have relatively severe T2DM and might not be representative of other Japanese patients with the disorder. Third, we did not measure serum 25-OH vitamin D, which is the best available index of vitamin D nutrition, because the cost of its measurement is not financially supported by the health insurance system in Japan. Low amounts of vitamin D are known to be associated with T2DM [34], and the observations in this study may reflect an underlying association with vitamin D. Fourth, the subjects in this study were Japanese; and there are differences in PTH dynamics between races and ethnic groups. Black women have lower 25-OH vitamin D and higher PTH than white women [35]; and the thresholds of serum 25-OH vitamin D to prevent the elevation of PTH have been reported to be different between black, white, and Japanese subjects (37, 59, and 70 nmol/L, respectively) [35,36]. Thus, the influence of such racial differences should be considered in interpreting the current findings. Finally, we did not exclude subjects who underwent pharmaceutical therapies for T2DM, including insulin, sulfonylurea, metformin, and thiazolidinedione. Because these drugs are known to affect insulin secretion or insulin resistance, the present data might not reflect intrinsic insulin activities in the subjects. We also did not evaluate intrinsic insulin secretion precisely with the insulin clamp technique in each patient.

In conclusion, we found that serum Ca level was significantly and positively correlated with FPG and HOMA-IR independent of intact PTH or bone metabolic markers in T2DM men, but not in women. Our study is the first to show that high serum levels of Ca are adversely related to glucose metabolism in T2DM men without PHPT and suggests that serum Ca rather than PTH is associated with insulin resistance and impaired glucose metabolism in the population. Further prospective and mechanistic studies are needed to

look into the hypotheses raised by the current observations and to clarify the underlying mechanisms, including the involvement of CaR in pancreatic β-cells and muscle, as well as the reason for the sex difference in the findings.

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