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Serum Calcium Changes and Risk of Diabetes Mellitus

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Background

Western cohort studies have universally demonstrated that elevated serum calcium levels are associated with a greater risk of type 2 diabetes mellitus (T2DM). We examined the association between changes in serum calcium levels with the incidence of T2DM in apparently healthy South Korean subjects.

Methods

A retrospective longitudinal analysis was conducted with subjects who had participated in comprehensive health check-ups at least four times over a 7-year period (between 2006 and 2012). Initial data were obtained from 25,170 individuals over the age of 20). Among the data from each medical check-up conducted during the study period, those from the first visit served as baseline data. These subjects were categorized into tertiles based on changes in their albumin-adjusted serum calcium levels. Multivariate Cox regression models were fitted to assess the association between changes in serum calcium levels during follow-up and the relative risk of diabetes incidence.

Results

Overall, the participants were not obese, with a mean body mass index (BMI) of 23.7 ± 2.8 kg/m². The mean age of the participants was 51 years, and 57.4% were men. The mean follow-up period was 57.4 ± 14.7 months, during which the incidence of diabetes was 8.3%. There were significant differences in age, fasting glucose, HbA1c, triglyceride, HDL-C, LDL-C, systolic blood pressure (SBP), and alanine aminotransferase (ALT) levels among the tertiles of corrected calcium levels (**Table 1**).

Table 1. Baseline characteristics according to changes in albumin-adjusted serum calcium levels during the follow-up period					
	Changes in albumin-corrected serum calcium (mg/dL)				Total
	-2.54 - -0.22	-0.21 - 0.10	0.11 - 2.00	P value	
Number of subjects	7,450	7,842	7,639		22,931
Male, number (%)	4,171 (56.0)	4,621 (58.9)	4,366 (57.2)	0.001†	13,158 (57.4)
Age (years)	50.4 ± 8.2	50.7 ± 8.1	51.0 ± 8.2	<0.001*	50.7 ±8.2
BMI (kg/m²)	23.7 ± 2.8	23.6 ± 2.7	23.7 ± 2.8	0.352*	23.7 ± 2.8
Systolic BP (mmHg)	114.5 ± 15.6	112.8 ± 15.4	112.4 ± 15.6	<0.001*	113.2 ±15.5
Diastolic BP (mmHg)	71.1 ± 11.0	69.6 ±10.6	68.9 ± 10.7	<0.001*	69.9 ± 10.7
Fasting glucose (mg/dL)	90.2 ± 9.8	88.1 ± 9.3	87.8 ±9.8	<0.001*	88.7 ± 9.7
HbA1c (%)	5.37 ± 0.36	5.32 ± 0.36	5.32 ± 0.38	<0.001*	5.34 ± 0.37
Corrected calcium (mg/dL)	9.05 ± 0.29	8.77 ± 0.25	8.56 ± 0.27	<0.001*	8.79 ± 0.33
Triglycerides (mg/dL)	128.9 ± 76.8	123.6 ± 72.4	122.3 ± 74.1	<0.001*	124.9 ± 74.5
LDL-C (mg/dL)	125.7 ± 29.6	123.4 ±28.8	121.5 ± 27.8	<0.001*	123.6 ± 28.8
HDL-C (mg/dL)	57.0 ± 14.3	57.7 ± 14.2	57.8 ± 13.9	<0.001*	57.5 ± 14.1
ALT (U/L)	24.0 ± 15.8	23.4 ± 17.2	23.0 ± 15.8	<0.001*	23.5 ± 16.3
Change in corrected calcium	-0.45 ±0.20	-0.05 ± 0.09	0.36 ± 0.20	<0.001*	-0.05 ± 0.37

*by one way ANOVA for continuous variables. † by Chi-square test. by Chi-square test for linear by linear association. Data are means ± standard deviation or numbers (%). BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; ALT, alanine transaminase.

An increase in albumin-adjusted serum calcium levels during follow-up was related to an increased risk of T2DM, as shown in **Table 2**. After adjustment for potential confounders in the second model, the risk of diabetes was 1.8 times greater for subjects in the highest tertile of albumin-adjusted serum calcium level changes during follow-up than for those in the lowest tertile (HR 1.79, 95% CI 1.61-2.01, P <0.001, **Table 2**). This association was slightly attenuated but remained significant after additional adjustment for FPG, HbA1c and corrected serum calcium levels and other factors (HR 1.65, 95% CI 1.44-1.88, P <0.001, **Table 2**).

Table 2. Hazard ratios for incident diabetes mellitus based on tertiles of changes in albumin-adjusted serum calcium levels in non-diabetic subjects			
Variables	Changes in albumin-adjusted serum calcium (mg/dL)		
	-2.54--0.22	-0.21-0.10	0.11-2.00
Number of subjects	7,450	7,842	7,639
Number of subjects who developed diabetes (%)	552 (7.4)	533 (6.8)	820 (10.7)
Person-years of follow-up	33,488	38,625	37,667
Incident cases of DM per 1000 person-years (n)	16.5	13.8	21.8
Adjusted hazard ratio (95% CI)			
Multivariate model 1, P value*	1	0.80 (0.71-0.90), P<0.001	1.27 (1.14-1.41), P<0.001
Multivariate model 2, P value*	1	1.08 (0.96-1.22), P=0.214	1.80 (1.61-2.01), P<0.001
Multivariate model 3, P value*	1	1.03 (0.90-1.17), P=0.672	1.65 (1.44-1.89), P<0.001
Multivariate model 4, P value*	1	1.03 (0.91-1.17), P=0.642	1.66 (1.45-1.90), P<0.001

* by Cox proportional hazards model. Model 1: adjusted for age in years and sex. Model 2: additionally adjusted for fasting glucose, and HbA1c. Model 3: additionally adjusted for and albumin-adjusted serum calcium. Model 4: additionally adjusted for body mass index, systolic blood pressure, triglyceride, low-density lipoprotein cholesterol, and alanine aminotransferase levels. DM, diabetes mellitus; CI, confidence interval.

Conclusion

In conclusion, our results suggest that changes in albumin-adjusted serum calcium levels are associated with the risk of T2DM in an Asian population. Future studies are needed to define the clinical role of calcium and to assess calcium modulation as a potential intervention for the prevention and management of T2DM. Such studies will have significant public health implications, and these interventions could be implemented easily and inexpensively in clinical practice.

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