Brief Genetics Report

Altered Calcium Homeostasis Is Correlated With Abnormalities of Fasting Serum Glucose, Insulin Resistance, and β-Cell Function in the Newfoundland Population

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Alteration of extracellular calcium concentration may be involved in glucose metabolism in a number of pathways. The present study was designed to investigate the relationship between total serum calcium and *1*) fasting serum glucose, *2*) insulin, *3*) insulin resistance, and *4*) β-cell function in 1,182 healthy subjects from the province of Newfoundland and Labrador, Canada. All variables were $\log_{10}$ transformed, and confounding factors including age, trunk fat percentage, serum phosphorus, magnesium, 25-OH vitamin D, and parathyroid hormone were adjusted before analyses. Significant positive correlations between glucose and insulin resistance with calcium were found in both sexes, whereas an inverse correlation between β-cell function and calcium was found only in women. Similar results were found in medication-free women and men, as well as in pre- and postmenopausal women. Subjects with low calcium levels had the lowest concentration of glucose and the least insulin resistance, whereas subjects with high calcium levels had the highest concentration of glucose and insulin resistance in women but not in men. This relationship remained after calcium was adjusted for 25-OH vitamin D and parathyroid hormone. Our results suggest that alteration of serum calcium homeostasis is significantly correlated with the abnormality of glucose level, insulin resistance, and β-cell function. *Diabetes* 54:3336–3339, 2005

Worldwide, the number of people with diabetes is predicted to rise from 171 million in 2000 to 366 million in 2030 (1). Type 2 diabetes, which is characterized by hyperglycemia, accounts for ~90% of all diabetes cases worldwide (2). Recent studies have demonstrated that impaired fasting glucose is a useful predictor of type 2 diabetes (3).

Insulin resistance, a state in which increased concentrations of insulin are required to produce a given biological response, has been the focus of attention for a common link between several clinical disorders (4–6). However, the underlying biological basis for the clinical association remains unknown (7).

Calcium is a versatile intracellular messenger that is used throughout the life cycle of an organism to control diverse biological processes (8). It has been suggested that diabetes and cardiovascular disease are linked by a common defect of divalent cation metabolism, including calcium (9).

Since most research has focused on patients with diabetes and cardiovascular disorders, there is little data available on the relationship between fasting serum glucose, insulin, insulin resistance, β-cell function, and total serum calcium in people with normal fasting glucose and impaired fasting glucose. In the present study, we investigated the correlations between these variables in a large, healthy population taking into consideration other confounding factors.

RESEARCH DESIGN AND METHODS

A total of 1,182 subjects with a fasting serum glucose level <7.0 mmol/l were recruited from the province of Newfoundland and Labrador, Canada. Information regarding study design, criteria for participation, and body composition measurements can be found in a previous study (10).

Biochemical measurements. Serum concentrations of glucose, total calcium, phosphorus, magnesium, and albumin were measured using Synchron reagents performed on an LX20 (Beckman Coulter, Fullerton, CA). Serum total calcium concentration was corrected by serum albumin [calcium + 0.1 × (40 – albumin)/6]. Serum insulin was measured on an Immulite immunoassay analyzer, and parathyroid hormone (PTH) was measured using the IMMULITE 1000 Intact PTH kit (Diagnostic Products Corporation, Los Angeles, CA). 25-OH vitamin D was measured using a 25-Hydroxyvitamin D ^{125}I RIA Kit (DiaSorin, Stillwater, MN). Homeostasis model assessment was used to estimate insulin resistance and β-cell function (11).

Statistical methods. The results are expressed as means ± SE, except in Table 1, where means ± SD were used. Because of the skewed distributions, variables of serum glucose, insulin, phosphorus, magnesium, insulin resistance, and β-cell function were transformed using $\log_{10}$ before data analyses. Menopausal status in women, determined by a questionnaire, was also considered according to menopausal status (pre and post).

Confounding factor adjustments. In one-way ANOVA analyses, adjustments for the effects of covariates on serum calcium, glucose, insulin, insulin resistance, and β-cell function were carried out using a stepwise multiple regression procedure. The covariates for serum calcium and β-cell function were age, phosphorus, and magnesium; trunk fat percent was also included as a covariate in the analyses for serum glucose, insulin, and insulin resistance.

The analyses consisted of five parts:

Part 1. Partial correlation analyses were performed between the levels of

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PTH, parathyroid hormone.

TABLE 1
Physical characteristics and biochemical measurements of subjects

	Women	Men
n	888–943*	217–238*
Age (years)	42.93 ± 9.98	39.47 ± 12.65†
Height (cm)	162.0 ± 5.8	174.83 ± 8.82†
Weight (kg)	68.60 ± 13.15	85.77 ± 16.48†
BMI (kg/m^2)	26.14 ± 4.87	28.83 ± 16.37†
Hip (cm)	101.9 ± 10.9	101.5 ± 9.5
Waist (cm)	89.6 ± 13.3	98.2 ± 12.5†
Hip-to-waist ratio	0.88 ± 0.07	0.97 ± 0.06†
Body fat percentage	37.19 ± 7.06	25.71 ± 7.51†
Trunk fat percentage	38.27 ± 8.15	30.46 ± 8.58†
Serum glucose (mmol/l)	4.93 ± 0.50	5.13 ± 0.56†
Serum insulin (pmol/l)	68.75 ± 44.59	79.7 ± 52.2‡
Serum calcium (mmol/l)	2.33 ± 0.12	2.36 ± 0.12‡
Serum calcium-C (mmol/l)§	2.31 ± 0.12	2.31 ± 0.12
Serum phosphorus (mmol/l)	1.20 ± 0.18	1.75 ± 9.21†
Serum magnesium (mmol/l)	0.98 ± 3.09	0.89 ± 0.09
Insulin resistance‖	2.14 ± 1.49	2.66 ± 1.94†
β-Cell function‖	151.0 ± 173.3	136.3 ± 140.2

Data are means ± SD. *Range of subjects; †P value <0.001; ‡P value <0.05 in the comparison between men and women using Student's t test; §calcium-C means total serum calcium corrected by albumin [Ca + 0.1 × (40 − albumin)/6]; ‖insulin resistance and β-cell function were estimated by the homeostasis model assessment (HOMA).

serum calcium and the levels of glucose, insulin, insulin resistance, and β-cell function within sex after controlling for the confounding variables.

Part 2. In women, all analyses were performed according to menopausal status. The following confounding factors were included in the partial correlation analyses: age, sex, smoking, percent BF-T, cholesterol, phosphorus, and magnesium.

Part 3. Subjects were categorized into three groups according to serum calcium levels: groups with low (bottom 33.3%), medium (middle 33.3%), and high (top 33.3%) calcium concentrations. One-way ANOVA was used to analyze the differences in serum glucose, insulin, insulin resistance, and β-cell function among the three groups, and P values were adjusted by the Bonferroni method.

Part 4. To exclude possible influences of various medications on the levels of variables, we selected only those subjects who were not taking any medications, including any nutritional supplements, at the time of the study (525 of 1,182 subjects) to perform the partial correlation analyses.

Part 5. To account for the influences of vitamin D and PTH, subjects from the "medication-free" group were ranked according to serum calcium concentration; 100 women (top 50 and bottom 50) were selected, and the serum concentrations of 25-OH vitamin D and PTH were measured. Total serum calcium levels were adjusted for the concentrations of 25-OH vitamin D and PTH using linear regression model before analysis. The levels of fasting glucose, insulin, insulin resistance, and β-cell function were then compared between the low and high calcium groups using a paired t test. All analyses were performed using the SPSS software for Windows, version 11.5.

RESULTS

The physical and biochemical characteristics of the subjects are shown in Table 1, and the results of the partial correlations are shown in Table 2. Significant positive correlations of serum glucose with calcium were found in women and men ($r = 0.31$ and $r = 0.22$, respectively; $P < 0.001$ for both). A significant positive correlation of serum insulin with calcium was found in women only, whereas positive correlations between insulin resistance and calcium were found in both sexes. Interestingly, significant inverse correlations were found between serum calcium levels and β-cell function in women but not in men. Age, percent trunk fat, and levels of serum phosphorus and magnesium were controlled.

The results presented in Table 3 show that, in women, those in the low calcium group had the lowest fasting glucose concentration and the least insulin resistance, those in the high calcium group had the highest glucose level and insulin resistance, and those in the medium calcium group had an intermediate glucose level and insulin resistance ($P < 0.001$ and $P = 0.009$ for glucose and insulin resistance).

Analyses, according to menopausal status, revealed significant positive correlations between glucose and insulin resistance and calcium for premenopausal ($r = 0.29$ and $r = 0.12$; $P < 0.001$ and $P = 0.01$) and postmenopausal women ($r = 0.26$ and $r = 0.13$; $P < 0.001$ and $P < 0.05$). Moreover, an inverse correlation was observed between β-cell function and calcium in premenopausal ($r = -0.18$ and $P < 0.001$) but not in postmenopausal women.

Analyses were also performed in "medication-free" subjects. Significant positive correlations were found for fasting glucose and insulin resistance with serum calcium in women ($r = 0.31$ and $r = 0.15$; $P < 0.001$ and $P = 0.004$) and men ($r = 0.18$ and $r = 0.18$; $P < 0.05$ and $P < 0.05$). An inverse correlation, however, was found for β-cell function

TABLE 2
Partial correlations between total serum calcium (mmol/l) and fasting serum glucose, insulin, insulin resistance, and β-cell function

	Women (n = 871–880)		Men (n = 213–217)	
	r	P	r	P
Glucose (mmol/l)	0.31	<0.001	0.22	0.001
Insulin (pmol/l)	0.07	<0.05	0.09	NS
Insulin resistance	0.13	<0.001	0.14	<0.05
β-Cell function	−0.17	<0.001	−0.09	NS

Confounding factors including age, trunk fat percentage, phosphorus, and magnesium were correspondingly controlled in analyses where applicable.

TABLE 3
Levels of fasting serum glucose, insulin, insulin resistance, and β-cell function among low, medium, and high serum calcium groups

	Calcium group	Women	Men
n		879–888	216–217
Glucose (mmol/l)	L	4.80 ± 0.03	5.12 ± 0.08
	M	4.92 ± 0.03	5.14 ± 0.06
	H	5.06 ± 0.03	5.15 ± 0.06
P value		<0.001	NS
Insulin (pmol/l)	L	64.5 ± 2.1	77.2 ± 6.1
	M	69.3 ± 3.0	74.9 ± 4.8
	H	72.4 ± 2.5	84.4 ± 7.4
P value		0.08	NS
Insulin resistance	L	1.95 ± 0.07	2.56 ± 0.24
	M	2.16 ± 0.10	2.41 ± 0.16
	H	2.30 ± 0.08	2.70 ± 0.24
P value		0.009*	NS
β-Cell function	L	160.1 ± 8.3	141.6 ± 10.0
	M	143.1 ± 6.2	150.6 ± 18.4
	H	150.0 ± 14.6	128.1 ± 18.9
P value		0.055	NS

Data are means ± SD unless otherwise indicated. Significance assessed by one-way ANOVA, corrected by Bonferroni method. *Significance difference between L and H. L, low calcium group; M, medium calcium group; H, high calcium group.

TABLE 4
Comparisons between low and high serum calcium groups of women adjusted for serum 25-OH vitamin D and PTH

	Low calcium group	High calcium group	*P*
n	50	50	
Glucose (mmol/l)	4.71 ± 0.06	5.23 ± 0.09	<0.001
Insulin (pmol/l)	61.1 ± 4.4	75.4 ± 6.8	NS
Insulin resistance	1.79 ± 0.13	2.55 ± 0.28	<0.05
β-Cell function	184.5 ± 33.2	144.1 ± 25.1	NS

Data are means ± SE of raw values. Significance assessed using Student's *t* test. Prior to analysis, total serum calcium was adjusted for 25-OH vitamin D and PTH, serum glucose for age, β-cell function for age, and 25-OH vitamin D using linear regression analysis.

with serum calcium levels in women only ($r = -0.14$ and $P = 0.001$).

Finally, the effects of 25-OH vitamin D and PTH were adjusted in a selected subgroup (100 women) (Table 4). Subjects with low serum calcium concentration had a significantly lower level of fasting glucose and insulin resistance compared with subjects with high calcium concentration ($P < 0.001$ and <0.05).

DISCUSSION

The common links among several clinical disorders including type 2 diabetes, hypertension, ischemic stroke, and coronary heart disease have been suggested in a number of studies (8). One of the most common clinical manifestations is insulin resistance (9,12). However, there is limited data available about the underlying molecular basis. The major findings made in the current study are the discovery of significant correlations between total serum calcium concentrations with fasting serum glucose, insulin resistance, and β-cell function in a large, healthy population. The results provide evidence that the variations in calcium metabolism, indexed by total serum calcium concentration, are related to measures of glucose metabolism.

Insulin secretion is a calcium-dependent biological process (13), and an elevation in calcium is required for both first- and second-phase insulin secretions (14). Type 2 diabetes is associated with a shift from biphasic to monophasic insulin release, which might result from a functional impairment of $Ca_V2.3$ Ca^{2+} channels (15). The threshold of blood glucose, which normally causes the sustained second-phase insulin release, is increased. An elevated level of serum calcium is the reflection of elevated extracellular calcium possibly in conjunction with the impairments of voltage-gated Ca^{2+} channels. Furthermore, there is evidence of a link between serum calcium levels and cellular function relating to cytosolic calcium. For instance, a previous study has showed that an increased serum calcium level led to an increased cytosolic calcium level, which induced muscle contraction in arterial smooth muscle (16).

Insulin resistance mainly arises from the insensitivity of liver, muscle, and/or adipose tissue to insulin. Muscle is one of the major sites responsible for insulin resistance. Calcium plays a critical role in muscle contractions and in glucose uptake after insulin binds muscle cells. Furthermore, calcium influences the affinity of insulin receptor and sensitivity to insulin (17), whereas calcium and glucagon affect the liver plasma membrane Ca^{2+} pump, which is thought to extrude cytosolic calcium of the cell (18). Skeletal muscle is considered the major organ responsible for glucose uptake under insulin-stimulated conditions (19) and is a major site for insulin resistance (20). Cytosolic Ca^{2+}, Ca^{2+}-dependent enzymes, and Ca^{2+} channels are closely involved in glucose uptake by muscle cells (21,22).

The regulation of blood glucose and insulin involve many hormonal and physiological factors. Consequently, when trying to reveal true associations between total serum calcium and any variable of interest, it is critical to exclude possible confounding factors. In the current study, age was accountable for a gradual increase in fasting glucose and insulin, along with a gradual decrease in β-cell function. Men had higher levels of glucose, insulin, and insulin resistance compared with women, which are consistent with other previous reports (23). Age and sex were controlled throughout analyses in the present study.

Adiposity is the strongest factor in terms of influence on fasting glucose, insulin, insulin resistance, and β-cell function (24). Most previously reported studies have used BMI, ratio of hip-to-waist circumference, or bioimpedance analysis to correct the possible confounding influence. However, the accuracies of these field methods to clarify body fat percent are low (10,25). Thus, an inaccurate estimation of body composition using field methods might mask the effort to reveal the relationship between the complex biological networks of glucose metabolism. We resolved this by using dual-energy X-ray absorptiometry, an accurate method to measure body composition, and found that trunk fat percent is superior to all others, whereby it is a constant and strong confounding factor.

Significant correlations between phosphorus and serum calcium, insulin resistance, and β-cell function were found in women. Corresponding adjustments were made to exclude the effects of this confounding factor. A previous study has indicated that magnesium deficiency is a characteristic of type 2 diabetes (26). Weak, but significant, negative correlations between serum magnesium and calcium, glucose and β-cell function were found in men. Consequently, magnesium was included in the analysis as a confounding factor.

In women, menopausal status may have an influence on the association between serum calcium and glucose metabolism. We performed complete analyses according to menopausal status. Significant positive correlations of glucose, and insulin resistance with serum calcium levels were found, whereas an inverse correlation of β-cell function with serum calcium was found regardless of menopausal status. Similar positive correlations were also found in postmenopausal women, which indicates that the menopausal status is not likely a strong factor on these correlations in our study.

Various medications taken by subjects were of concern since they may affect the levels of total serum calcium and other variables. However, similar results were obtained in the selected "medication-free" group, further supporting our findings.

Vitamin D may have a direct effect on insulin sensitivity and β-cell function (27). 25-OH vitamin D is the predominant circulating form of vitamin D in the normal population and is the most reliable index of vitamin D status (28). Serum calcium levels are regulated by the action of PTH, and evidence from many studies suggest possible interactions between PTH and glucose metabolism (29) and PTH and insulin sensitivity (30). In the present study, serum calcium levels were adjusted for 25-OH and PTH before

analysis in "medication-free" women. The adjustment did not change the significant correlations between calcium and fasting glucose and insulin resistance.

The limitations of the present study should be mentioned. With any association study, the results of the present study require confirmation in other cohorts and populations. Furthermore, because of the design and large size of the current study, we used serum measurements of glucose as an indication of glucose metabolism rather than the oral glucose tolerance test, which is a more precise method of glucose tolerance.

In summary, the correlations of fasting serum glucose, insulin, insulin resistance, and β-cell function with total serum calcium levels, corrected by albumin, were analyzed in 1,182 healthy subjects from the Newfoundland population. Fasting serum glucose and insulin resistance were positively correlated with serum calcium levels in women and men, whereas β-cell function was negatively correlated in women only. The significant correlations are independent of age, sex, percent trunk fat, phosphorus, magnesium, medications, 25-OH vitamin D, and PTH.

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