Insulin Sensitivity Is Inversely Correlated With Plasma Intact Parathyroid Hormone Level

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Abnormal glucose metabolism and a high prevalence of diabetes have been reported in patients with primary and secondary hyperparathyroidism. We hypothesize that plasma intact parathyroid hormone (iPTH) level is a determinant of either insulin sensitivity or β-cell function. The study included 52 normotensive, healthy subjects with glucose tolerance. Insulin sensitivity and β-cell function were assessed using a hyperglycemic clamp. Fasting plasma iPTH was determined. The relationships between its level and insulin sensitivity index and β-cell function were examined. Insulin sensitivity index was inversely correlated with plasma iPTH level ($r^2 = .104$, $P = .020$). The first phase insulin response was positively correlated with plasma iPTH level ($r^2 = .098$, $P = .023$), but no correlation existed with the second phase insulin response. After adjusting for age, gender, ethnicity, and waist-to-hip ratio, plasma iPTH level was an independent determinant of insulin sensitivity index ($P = .019$). However, no independent relationship between plasma iPTH level and β-cell function (the first phase and second phase insulin response) was found. In normotensive, glucose-tolerant, and healthy subjects, plasma iPTH level accounts for 10.4% of the variation in insulin sensitivity index. For each pg/mL increment in plasma iPTH level, there is a decrease of 0.247 μmol/L/m²/min/pmol/L in insulin sensitivity index. Although the molecular basis of this relationship is not clear, our results indicate that plasma iPTH level is inversely correlated with insulin sensitivity index.

GLUCOSE INTOLERANCE is one of the well-known consequences of chronic renal failure.[1] In uremic patients, parathyroid hormone (PTH) has been implicated to play a major role in glucose metabolism by either causing insulin resistance[2,3] or interfering with pancreatic β-cell function.[4] The association between elevated PTH levels and disturbance of glucose homeostasis has been described in nonuremic patients with parathyroid disorders.[5-7] Furthermore, a higher prevalence of diabetes has been detected in patients with primary hyperparathyroidism.[8,9] Although the effect of parathyroidectomy on glucose metabolism remains controversial,[8,10] there is evidence that parathyroidectomy could improve glycemic control in diabetic patients with hyperparathyroidism.[11-13]

However, the role of PTH on glucose homeostasis in healthy subjects has not been evaluated. This study was performed to evaluate the relationship of plasma intact PTH (iPTH) with insulin sensitivity and β-cell function in 52 normotensive, glucose-tolerant, and healthy subjects. We found that plasma iPTH level was an independent determinant of insulin sensitivity.

MATERIALS AND METHODS

Subjects

The study was approved by the Human Subject Protection Committee of the University of California, Los Angeles. A written informed consent was obtained from each participant before the study. Only healthy subjects who were currently receiving no medication were enrolled. All subjects underwent a standard oral glucose tolerance test (OGTT) with 75 g glucose and a brief physical examination after an overnight fast as described previously.[14,15] Subjects satisfying the following criteria were invited to return for the assessment of insulin sensitivity and β-cell function using a slightly modified hyperglycemic clamp technique[16]: fasting plasma glucose level less than 6.1 mmol/L, 2-hour postload plasma glucose level less than 7.8 mmol/L, interval plasma glucose level less than 11.1 mmol/L, and normal blood pressure (systolic blood pressure < 140 mm Hg and diastolic pressure < 90 mm Hg). The subjects come from different families, therefore they are not related biologically. An overnight stay with fasting in the General Clinical Research Center was required before the clamp study. To minimize the effect of smoking, the subjects ($n = 5$) were asked to refrain from smoking for at least 12 hours before the clamp. In the morning, subjects received a bolus of 50% dextrose solution based on their body surface (11.4 g of dextrose per square meter of body surface area) at $T = 0$ minute and continuous infusion with 30% dextrose solution starting at $T = 15$ minutes. The infusion rate was adjusted every 5 minutes based on the prevailing plasma glucose level to maintain it at 10 mmol/L toward $T = 180$ minutes. The first phase insulin response was the sum of plasma insulin levels at $T = 2.5$, 5, 7.5, and 10 minutes. The second phase insulin response was the average of plasma insulin levels during the last hour of the clamp ($T = 130$, 140, 150, 160, 170, and 180 minutes). Insulin sensitivity index was the average of the amount of glucose infused during the last hour of the clamp divided by the averaged steady-state plasma insulin level.

Assays

Plasma glucose concentrations were determined by a glucose oxidase method with a YSI glucose analyzer (YSI, Yellow Springs, OH). Plasma insulin concentrations were determined by radioimmunoassay as previously described.[17] The fasting values were the average of 3 measurements at $T = -15$, -10, and -5 minutes before the oral glucose load.

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Plasma iPTH concentration was determined retrospectively from the fasting plasma collected at T = −15 minutes as previously described.[18]

Statistical Analysis

The continuous variables, which failed the Normality test, were logarithmically transformed before analysis. The relationships between plasma iPTH level and insulin sensitivity index, first and second phase insulin response were analyzed by simple linear regression. A stepwise regression analysis using a backward stepwise option with α-to-enter of 0.100 and α-to-remove of .100 was used to adjust for differences in gender, age, body mass index, waist-to-hip ratio, blood pressure, and reported ethnicity. Statistical analyses were performed with SYSTAT version 8.0 of the SPSS (Chicago, IL). A nominal *P* value of less than .05 was considered significant.

RESULTS

Because either β-cell function or insulin sensitivity may be affected by abnormal glucose metabolism and/or various medications, only glucose-tolerant and healthy subjects were asked to participate in the study (Table 1). Only normotensive subjects were included because hypertension is known to be associated with insulin resistance.[19] As expected, there were wide interindividual variations in the first phase insulin response (16 times), the second phase insulin response (15 times), and also insulin sensitivity index (13 times).

Table 1. Clinical Features and Glycemic Parameters of the Study Subjects

Parameter	Mean (n)	Standard Error	Minimum	Maximum
No.	52			
Gender F/M	31/21			
Age (yr)	26	1	19	40
Body mass index (kg/m²)	24.50	0.63	17.58	35.61
Waist-to-hip ratio (cm/cm)	0.79	0.01	0.65	1.03
Systolic blood pressure (mm Hg)	114	2	92	137
Diastolic blood pressure (mm Hg)	67	1	51	83
OGTT				
Fasting plasma glucose (mmol/L)	4.69	0.06	3.30	5.51
Plasma glucose at 30 minutes (mmol/L)	7.30	0.16	5.58	9.33
Plasma glucose at 60 minutes (mmol/L)	7.35	0.18	4.57	10.05
Plasma glucose at 90 minutes (mmol/L)	6.60	0.18	3.62	9.55
Plasma glucose at 120 minutes (mmol/L)	6.08	0.16	3.48	7.77
Plasma iPTH (pg/mL)	40.11	1.74	15.74	71.09
Hyperglycemic clamp				
Fasting plasma glucose (mmol/L)	4.74	0.04	4.07	5.41
Fasting plasma insulin (pmol/L)	68	3	28	131
Clamped plasma glucose (mmol/L)	9.96	0.05	9.33	10.77
First phase insulin response (pmol/L)	1,896	176	465	7,415
Second phase insulin response (pmol/L)	500	40	104	1,567
Insulin sensitivity index (μm/m²/min/pmol/L)	6.59	0.54	1.39	17.99

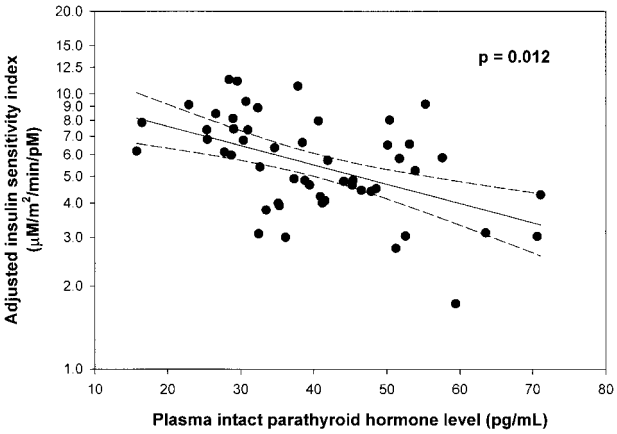

Fig 1. Relationship between adjusted insulin sensitivity index and plasma iPTH level in 52 glucose-tolerant and normotensive subjects. Regression lines (—) and 95% confidence intervals (----). Insulin sensitivity index was logarithmically transformed before analysis and was adjusted based on the stepwise regression analysis as shown in Table 2.

Regression analyses showed that plasma iPTH level was inversely correlated with insulin sensitivity index ($P = .02$, $r^2 = .104$) and positively correlated with the first phase insulin response ($P = .023$, $r^2 = .098$). Plasma iPTH level was not associated with the second phase insulin response ($P = .111$). Because there were differences in gender, age, ethnicity, body mass index, waist-to-hip ratio, and blood pressure, these factors were considered as covariates and evaluated using a stepwise regression analysis as described above. Furthermore, in the glucose-tolerant subjects we recruited for this study, β-cell function compensated for the prevailing insulin resistance to maintain glucose homeostasis ($P < .001$, $r^2 = .343$ for first phase insulin response and $P < .001$, $r^2 = .451$ for second phase insulin response). Therefore, insulin sensitivity index was also considered as a covariate for β-cell function. We found that plasma iPTH level was an independent determinant for insulin sensitivity index (Fig 1, $P = .012$) after adjusting for gender, age, waist-to-hip ratio, and ethnicity. However, body mass index and blood pressure had no impact on insulin sensitivity index. Also, the plasma iPTH level along with these 3 covariates could explain 50.9% of the variation in insulin sensitivity index (Table 2). Conversely, after adjusting for insulin sensitivity, the plasma iPTH level had no impact on either first phase insulin response ($P = .253$) or second phase insulin response ($P = .943$).

In addition, we also examined the role of plasma iPTH level on obesity. Plasma iPTH level correlated with body mass index poorly ($r^2 = .060$, $P = .080$). No correlation was found between plasma iPTH level and waist-to-hip ratio ($r^2 < .0001$, $P = .944$). Regression analysis confirmed that the influence of plasma iPTH level on insulin sensitivity index was independent of the influence of obesity (waist-to-hip ratio as shown in Table 2). Therefore, we concluded that plasma iPTH level was not a surrogate for obesity.

Table 2. Regression Analysis Using a General Linear Model

Dependent Variable	Covariate Entered	r^2	P
ISI*	iPTH	.104	.020
ISI*		.509	
	iPTH		.012
	Waist-to-hip ratio*		<.001
	Age*		.001
	Gender		.002
	Ethnicity		.075
	Covariate Removed		**P**
	Body mass index*		.283
	Systolic blood pressure		.728
	Diastolic blood pressure		.199

*The variables were logarithmically transformed before analysis.

DISCUSSION

In the present study, we observed that plasma iPTH level was inversely correlated with insulin sensitivity index and accounted for 10.4% of its variation in normotensive glucose-tolerant and healthy subjects (Fig 1). Because there is no frozen serum available to measure serum vitamin D, calcium, and phosphorous levels, we cannot exclude the possibility that some of the studied subjects had hyperparathyroidism. Nevertheless, we observed this relationship throughout the entire spectrum of plasma iPTH levels, including normal and low plasma iPTH levels. Therefore, to our knowledge, this is the first report describing this relationship in apparently healthy subjects. This finding is in agreement with those observed in patients with primary or secondary hyperparathyroidism.

Our finding of inverse relationship between plasma iPTH level and insulin sensitivity is consistent with various reports suggesting that hyperparathyroidism is a risk factor for diabetes. Although no large-scale epidemiologic data are available to date, it has been shown that the prevalence of diabetes is increased in patients with hyperparathyroidism. Cheung et al[12] reported a 3.08-fold increase in the prevalence of diabetes among patients with primary hyperparathyroidism compared with the general population. Taylor[9] reported that the prevalence of diabetes was 7.8% in patients with primary hyperparathyroidism, while it was 3.0% in control patients. Similarly, Ljunghall et al[8] reported a 3-fold increase, and Werner et al[20] reported a 4-fold increase in the prevalence of diabetes in patients with primary hyperparathyroidism. These cumulative data support the notion that the prevalence of diabetes in patients with hyperparathyroidism is increased by 2- to 4-fold.

In rats, continuous infusion of PTH decreases the effect of insulin on glucose utilization by 14%.[21] In addition, insulin resistance, one of the key features of type 2 diabetes, has been shown in patients with primary hyperparathyroidism.[3,22] Furthermore, in diabetic patients with primary hyperparathyroidism, parathyroidectomy has been shown to improve glycemic control.[12,13,22,23] Kautzky-Willer et al[22] used frequently sampled intravenous glucose tolerance tests to evaluate patients with primary hyperparathyroidism before and after parathyroidectomy. Severe impairment in insulin sensitivity with reduced glucose effectiveness and a 2-fold elevation of insulin secretion has been observed in patients with primary hyperparathyroidism when compared with control subjects.[22] However, only insulin sensitivity improved significantly after parathyroidectomy.[22] Additional evidence relating PTH to insulin resistance stems from data that patients with primary hyperparathyroidism were noted to have an increased risk of death from coronary artery disease by 1.71 to 1.85 times.[24] This result suggests that primary hyperparathyroidism is associated with insulin resistance (or decreased insulin sensitivity), as the notion between coronary artery disease and insulin resistance is well established.[25] Therefore, our observation is consistent with these reports describing the association between plasma PTH and insulin resistance.

Although the molecular mechanism of this association is unclear, some insights have been gained from studies in uremic patients. Insulin resistance almost always presents in uremic patients as a result of secondary hyperparathyroidism.[1,2,26,27] De Fronzo et al[27] examined tissue sensitivity to insulin with the euglycemic insulin clamp technique in 17 chronically uremic and 36 control subjects. They found that suppression of hepatic glucose production by physiologic hyperinsulinemia was not impaired by uremia; insulin-mediated glucose uptake by the liver is normal in uremic subjects; and peripheral insensitivity to insulin is the primary cause of insulin resistance in uremia with a 47% reduction in insulin sensitivity.[27] Mak et al[28] studied glucose metabolism in a group of adolescents and young adults with uremia using the hyperglycemic clamp technique. They found that the glucose metabolic rate correlated negatively with PTH levels, and uremic patients with secondary hyperparathyroidism had decreased glucose metabolic rates and reduced insulin sensitivity compared with normal subjects.[28] After parathyroidectomy, the glucose metabolic rate improved by 47%, and plasma insulin concentrations during hyperglycemia increased by 37%, whereas insulin sensitivity did not change significantly.[28] It was suggested that the underlying mechanism for insulin resistance in primary hyperparathyroidism may not be the same as in secondary hyperparathyroidism, because in the latter patients, parathyroidectomy failed to improve insulin sensitivity.

Secondary hyperparathyroidism could be corrected, at least in part by administration of 1,25-dihydroxyvitamin D_3.[29] Using a glucose clamp technique, Mak[29-31] showed that intravenous 1,25-dihydroxyvitamin D_3 treatment in uremic patients improved insulin sensitivity. However, administration of 1,25-dihydroxyvitamin D_3 had no affect on insulin-mediated glucose uptake in healthy subjects.[32] Similarly, in rats, continuous infusion of PTH decreased insulin sensitivity by 12.5%,[33] while continuous infusion of vitamin D had no affect on glucose disposal.[21] The data from the studies of vitamin D administration in normal subjects and rats indicate that the influence of PTH on insulin sensitivity is not mediated through vitamin D.

We observed that plasma iPTH level had a positive correlation with the first phase insulin response ($r^2 = .098$, $P = .023$) and a marginal influence on the second phase insulin response ($P = .111$). However, these correlations were no longer significant after adjusting for insulin sensitivity index ($P = .253$ for first phase insulin response and $P = .943$ for second phase insulin response) because, as we also showed in this study, β cells of glucose-tolerant subjects compensate for the prevailing insulin resistance to maintain glucose homeostasis. In contrast, there was ample evidence indicating that β-cell dysfunction

occurred in uremic patients with secondary hyperparathyroidism[34] and in uremic dogs[4] and uremic rats.[35-37] It was attributed, at least in part if not all, to abnormal calcium metabolism[35,38] via a protein kinase C pathway.[39] Furthermore, β cell dysfunction was only observed in uremic patients with secondary hyperparathyroidism and in uremic rats, but not in patients with primary hyperparathyroidism. On the contrary, overexpression of parathyroid hormone-related protein in pancreatic islets of transgenic mice caused islet hyperplasia, hyperinsulinemia, and hypoglycemia.[40] Therefore, further studies are required to examine the role of iPTH on β-cell function.

In summary, this study indicates that plasma iPTH level is inversely correlated with insulin sensitivity index and for each pg/mL increment in plasma iPTH level, there is a decrease of 0.247 μmol/L/m^2/min/pmol/L in insulin sensitivity index. Comparison of those to the lowest and highest quartiles of plasma iPTH levels showed that those with the lowest quartile were 3.8 times more insulin sensitive than those with the highest quartile (11.482 ± 0.123 *v* 3.041 ± 0.137 μmol/L/m^2/min/pmol/L, $P = .002$) after adjusting for age, gender, waist-to-hip ratio, and ethnicity. Therefore, we conclude that plasma iPTH level is an independent determinant of insulin sensitivity index in normotensive, glucose-tolerant, and healthy subjects, and it accounts for 10.4% of the variation in insulin sensitivity index. Further studies are required to define the molecular basis of this relationship.

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