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Intact proinsulin level is associated with insulin resistance but not insulin secretory capacity in subjects with abnormal glucose tolerance

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Introduction

Proinsulin is a propeptide of insulin and C-peptide during physiological insulin production and is increased in patients with type 2 diabetes. Increased proinsulin in peripheral blood indicates impairment of cleavage capacity to process insulin within the beta cell. Recently, chemiluminescence assays have been developed that are able to specifically measure uncleaved intact proinsulin in peripheral blood. In this cross-sectional study, we investigated the relationship between intact proinsulin and insulin resistance and secretion in Korean adults.

Materials and Methods

We performed standard 75g oral glucose tolerance test (OGTT) after an overnight fast in 388 subjects without history of diabetes. Glucose (0, 30, 60, 90, 120 min), insulin (0, 30, 60, 90, 120 min), C-peptide (0, 30 min), and fasting intact proinsulin were measured and insulin sensitivity and secretory indexes were calculated using the results of OGTT.

Results

Table 1 shows baseline characteristics of subjects in our study. Average age was 54.6 ± 11.8 years and 41.5% of the subjects were male.

Table 1. Baseline characteristics of the study subjects

	All (N=388)	NGT (N=33)	Prediabetes (N=153)	DM (N=202)	*P*-value
Age (yrs)	54.6 ± 11.8	49.1 ± 10.7	52.9 ± 10.9	56.9 ± 12.1	<0.001
Male [n (%)]	161 (41.5%)	6 (18.2%)	57 (37.3%)	98 (48.5%)	0.002
BMI (kg/m^2)	25.1 ± 3.3	23.8 ± 3.2	25.3 ± 3.4	25.1 ± 3.2	0.049
Fasting glucose (mg/dL)	125.8 ± 40.0	92.8 ± 5.2	106.7 ± 7.8	145.8 ± 46.6	<0.001
Fasting insulin (uIU/mL)	11.0 ± 4.9	8.99 ± 2.98	10.5 ± 3.7	11.7 ± 5.8	0.011
Fasting C-peptide (ng/mL)	2.45 ± 1.09	1.55 ± 0.61	2.28 ± 0.86	2.73 ± 1.20	<0.001
HbA1c (%)	6.64 ± 1.65	5.54 ± 0.33	5.78 ± 0.44	7.32 ± 1.90	<0.001
Intact proinsulin (pmol/L)	6.42 ± 5.67	2.96 ± 1.57	5.67 ± 5.44	7.56 ± 5.95	<0.001
HOMA IR	3.46 ± 2.17	2.07 ± 0.73	2.78 ± 1.04	4.21 ± 2.63	<0.001
HOMA beta	76.5 ± 38.0	111.1 ± 37.8	88.6 ± 31.2	61.7 ± 35.9	<0.001
Matsuda index	4.08 ± 1.96	6.08 ± 2.35	4.32 ± 1.85	3.57 ± 1.72	<0.001
Stumvoll index	6.72 ± 2.37	9.41 ± 1.29	7.46 ± 2.15	5.71 ± 2.11	<0.001
OGIS	349.8 ± 64.7	436.6 ± 44.7	380.2 ± 43.4	312.6 ± 54.6	<0.001
IGI	0.44 ± 0.54	0.91 ± 0.76	0.63 ± 0.66	0.21 ± 0.18	<0.001
Disposition index	1.67 ± 2.13	4.90 ± 3.50	2.32 ± 2.10	0.64 ± 0.48	<0.001

All data are presented as the means ± SD.
P-value was calculated using Kruskall-Wallis test or χ2 test.
BMI, body mass index; IGI, Insulinogenic index

Table 2. Spearman correlations of intact proinsulin with insulin resistance and sensitivity indexes (A) and with insulin secretory indexes (B)

(A)	HOMA-IR		Matsuda index		Stumvoll index		OGIS	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Intact proinsulin	0.504	<0.001	-0.445	<0.001	-0.449	<0.001	-0.399	<0.001

(B)	HOMA-beta		IGI		Disposition index	
	r	*P*	*r*	*P*	*r*	*P*
Intact proinsulin	0.008	0.880	-0.100	0.049	-0.297	<0.001

Intact proinsulin level was positively correlated with homeostasis model assessment insulin resistance (HOMA-IR) (*r*=0.504, *P*<0.001) and was inversely correlated with insulin sensitivity indexes (Matsuda index: *r*=-0.445, *P*<0.001; Stumvoll index: r=-0.449, *P*<0.001; OGIS: *r*=-0.399, *P*<0.001) (Table 2A, Figure 1). However, there were no significant correlations between intact proinsulin and insulin secretory indexes (HOMA-beta) (Table 2B).

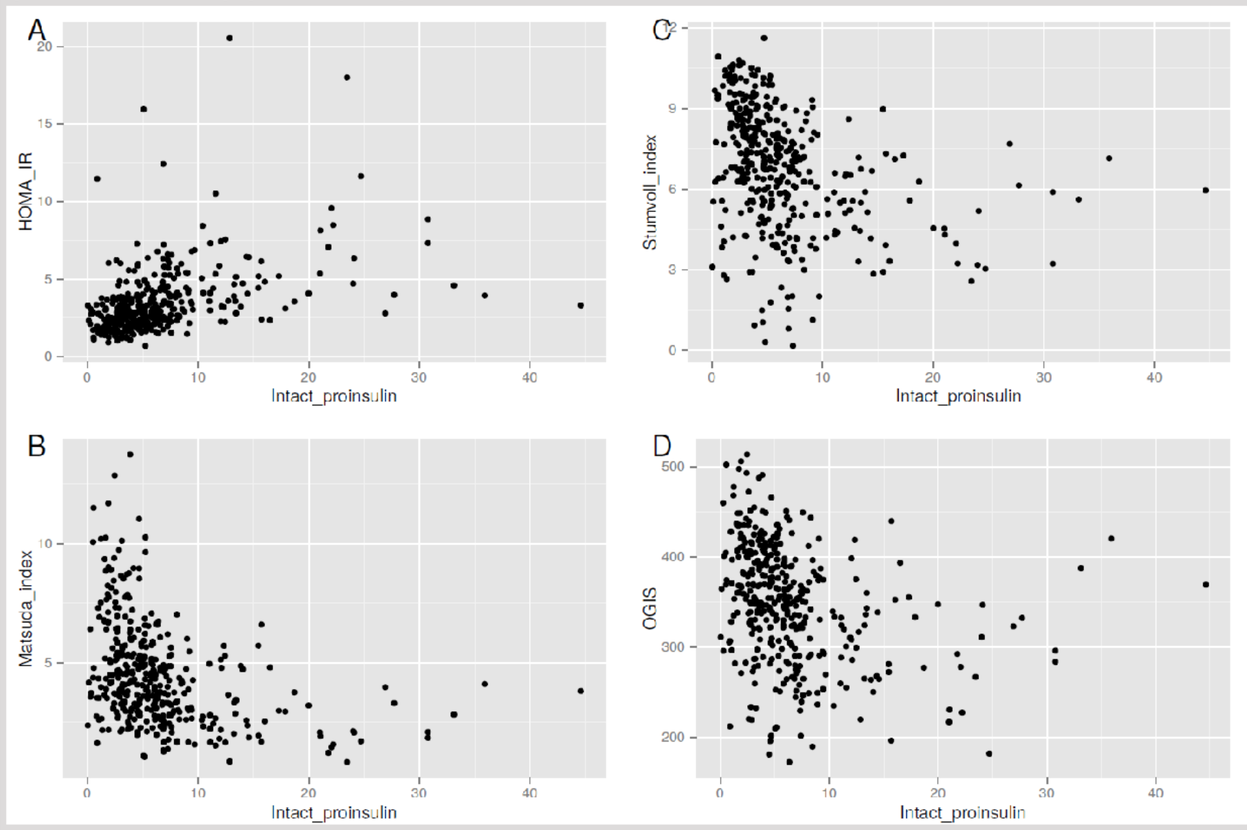

Figure 1. Correlation between intact proinsulin and insulin resistance or sensitivity indexes.

Total subjects were stratified by glucose tolerance status; normal glucose tolerance (NGT, n=33), prediabetes (impaired fasting glucose and/or impaired glucose tolerance, n=153), and diabetes mellitus (DM, n=202) (Table 1). Intact proinsulin level showed an increasing tendency with the deterioration of glucose tolerance (*P*<0.001, Table 1). In the NGT group, intact proinsulin level was not correlated with both insulin sensitivity and secretory indexes (Table 3). However, in the prediabetes and DM groups, intact proinsulin levels were inversely correlated with insulin sensitivity indexes (Matsuda index, Stumvoll index, and OGIS index) and positively correlated with insulin secretory index (HOMA-beta) (Table 3).

Table 3. Spearman correlations of intact proinsulin with insulin resistance and sensitivity indexes (A) and with insulin secretory indexes (B) in subgroups stratified by glucose tolerance status

(A)	HOMA-IR		Matsuda index		Stumvoll index		OGIS	
Intact proinsulin	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
NGT	0.193	0.282	-0.261	0.143	-0.212	0.237	-0.469	0.006
Prediabetes	0.405	<0.001	-0.389	<0.001	-0.400	<0.001	-0.231	0.004
DM	0.472	<0.001	-0.389	<0.001	-0.301	<0.001	-0.255	<0.001

(B)	HOMA-beta		IGI		Disposition index	
Intact proinsulin	*r*	*P*	*r*	*P*	*r*	*P*
NGT	-0.146	0.419	0.122	0.498	-0.077	0.669
Prediabetes	0.248	0.002	0.082	0.314	-0.134	0.098
DM	0.163	0.020	0.113	0.112	-0.105	0.139

Conclusions

Intact proinsulin level increases with the deterioration of glucose tolerance and is significantly correlated with insulin resistance indexes but not with insulin secretory indexes in subjects with abnormal glucose tolerance. Moreover, intact proinsulin partly reflects beta cell function.