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**Utility of the C-peptide/insulin molar ratio for distinguishing type A insulin
resistance syndrome from type 2 diabetes**

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Abstract

Objective:

Type A insulin resistance syndrome (IRS), characterized by impaired insulin receptor function due to variants of the insulin receptor gene, manifests as severe insulin-resistant diabetes. Differentiation of type A IRS from type 2 diabetes on the basis of hyperinsulinemia can be challenging. Given the association between insulin receptor dysfunction and reduced insulin clearance, we evaluated the potential of the circulating C-peptide reactivity (CPR)/immunoreactive insulin (IRI) molar ratio, a marker of insulin clearance, for distinguishing type A IRS from type 2 diabetes.

Methods:

We retrospectively analyzed CPR and IRI levels measured during a 75-g oral glucose tolerance test (OGTT) in 18 individuals with type A IRS and 126 with type 2 diabetes. Receiver operating characteristic (ROC) curve analysis was performed to determine the diagnostic performance of the CPR/IRI molar ratio and IRI levels.

Results:

IRI levels were significantly higher and the CPR/IRI molar ratio significantly lower in individuals with type A IRS compared with those with type 2 diabetes. The area under the ROC curve for the CPR/IRI molar ratio at baseline, 1 hour, and 2 hours after OGTT

71 initiation was 0.997 (sensitivity 100%, specificity 99.2%), 0.999 (sensitivity 100%,
72 specificity 97.6%), and 0.997 (sensitivity 100%, specificity 95.1%), respectively. The
73 CPR/IRI molar ratio demonstrated robust diagnostic performance regardless of body
74 mass index or hyperinsulinemia severity.

75 **Conclusions:**

76 The CPR/IRI molar ratio, both at baseline and during OGTT, exhibited higher
77 sensitivity and specificity than IRI levels alone for distinguishing type A IRS from type
78 2 diabetes. This ratio may serve as a reliable clinical marker for early and accurate
79 diagnosis of type A IRS.

Introduction

Insulin resistance syndrome (IRS), characterized by marked impairment of insulin action as a result of insulin receptor dysfunction, manifests as severe insulin resistance and treatment-refractory diabetes mellitus.(1, 2) This syndrome has been classically categorized as type A or type B, with the former being due to variants of the insulin receptor gene (*INSR*) and the latter to autoantibodies specific for the insulin receptor. (1, 2) Given that variants of genes related to insulin receptor signaling also give rise to phenotypes similar to type A IRS,(3, 4) a category of genetic IRS, which includes syndromes caused by variants of *INSR* or other such genes, has been recently proposed.(4)

Type A IRS has been thought to be a rare condition.(5) A recent nationwide survey in Japan estimated that at least 0.05% of the population (~0.7% of individuals with diabetes) harbor heterozygous *INSR* variants that can trigger type A IRS,(6) suggesting that, whereas the syndrome is indeed not common, there may be a considerable number of undiagnosed cases. Marked hyperinsulinemia, along with clinical manifestations such as acanthosis nigricans and polycystic ovary syndrome, is a common clue to the diagnosis of type A IRS.(4-6) However, such findings are not specific to type A IRS, being instead related to severe insulin resistance. Moreover,

some individuals with pathogenic heterozygous *INSR* variants do not manifest hyperinsulinemia.(7-9) Although the reasons for this absence of hyperinsulinemia remain unclear, they may include exhaustion of pancreatic beta cells as a result of long-term severe insulin resistance (10) as well as dysfunction of beta cells triggered directly by impaired insulin receptor signaling.(11)

Given that insulin clearance depends on receptor-mediated internalization, dysfunction of the insulin receptor can lead to reduced insulin clearance (12) and thereby contribute to hyperinsulinemia in type A IRS.(12, 13) Evidence suggests that the molar ratio of circulating C-peptide reactivity (CPR) to immunoreactive insulin (IRI) reflects insulin clearance, particularly by the liver.(14, 15) Consistent with this notion, previous studies have found that individuals with type A IRS manifest low values of the CPR/IRI molar ratio in the fasting state (16–18) or during an OGTT. (8, 17, 18) However, these previous studies evaluated only single cases of type A IRS, with no study having quantitatively assessed the utility of this parameter with a substantial number of individuals. It has therefore remained unclear whether the CPR/IRI molar ratio is able to distinguish between individuals with type A IRS and those with insulin-resistant type 2 diabetes.

To evaluate the potential of the CPR/IRI molar ratio to distinguish type A IRS

from type 2 diabetes, we retrospectively examined blood levels of CPR and IRI during an OGTT in 18 individuals with the former condition and 126 individuals with the latter. Our findings provide evidence that the CPR/IRI molar ratio is a better predictor of type A IRS than is IRI alone.

Methods

Study ethics

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki and its amendments and was approved by the Ethics Committee of Kobe University Hospital (approval no. B220103). Given that the study used existing data, the committee did not require written informed consent from individual participants, in accordance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects in Japan. Information about the study was made publicly available, giving participants the opportunity to opt out if they wished.

Study participants

Individuals with type A IRS diagnosed at Kobe University Hospital between 1997 and 2021, with the presence of pathogenic variants of *INSR* being confirmed by genetic

testing, were included in the study. Data were also collected for individuals with type A IRS in previously published studies. A literature search of PubMed was conducted with the key terms “type A insulin resistance,” “insulin resistance type A,” and the combination of “insulin receptor gene” or “INSR” with “mutation.” From the identified studies, those reporting individuals with type A IRS who underwent a 75-g OGTT with simultaneous measurement of CPR and IRI were selected.

Individuals diagnosed with type 2 diabetes according to the criteria of the Japan Diabetes Society (19) were included in the study if they met the following additional criteria: (1) they were admitted to the Department of Diabetes and Endocrinology at Kobe University Hospital between 1 February 2011 and 31 January 2021, (2) they were aged 18 years or older, and (3) they underwent a 75-g OGTT with simultaneous measurement of CPR and IRI. Individuals were excluded if (1) hemolysis was apparent in their blood samples, (2) they used basal insulin, (3) they had endocrine disorders other than diabetes, or (4) their eGFR was $<30 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$. If individuals underwent a 75-g OGTT on multiple occasions, only the data for the first test were collected.

Data collection and analysis

The collected data included individual demographics (age, sex, height, and weight); blood glucose, CPR, and IRI levels during the 75-g OGTT; laboratory data obtained closest to the date of the 75-g OGTT, including HbA_{1c} and eGFR values; and the absence or presence of insulin therapy or endocrine disorders. We evaluated the AUC of the receiver operating characteristic (ROC) curve for the CPR/IRI molar ratio and IRI levels both before and 1 and 2 h after initiation of the OGTT, which achieved optimal discrimination between type A IRS and type 2 diabetes. The CPR/IRI molar ratio was calculated according to the AMA Manual of Style (11th edition) with the following SI conversions: insulin, 1 μ IU/mL = 6.945 pmol/L; and C-peptide, 1 ng/mL = 0.331 nmol/L = 331 pmol/L.

Statistical analysis

The primary objective of this study was to evaluate the diagnostic performance of the CPR/IRI molar ratio in distinguishing type A insulin resistance syndrome (IRS) from type 2 diabetes using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) for CPR/IRI molar ratios and IRI levels was assessed at fasting, 1-hour, and 2-hour time points during the OGTT to determine their discriminatory ability. Comparisons of variables between type A IRS and type 2

diabetes groups were conducted according to descriptive statistics and the Mann-Whitney U test or chi-square test. Pearson's correlation coefficient was adopted to evaluate the relations among BMI, the fasting CPR/IRI molar ratio, and the fasting IRI concentration in both groups.

Post-hoc analyses were conducted to further investigate the diagnostic utility of CPR/IRI molar ratios for differentiating type A IRS from type 2 diabetes. These analyses included comparisons between institutional and literature-based type A IRS cases, evaluation of CPR/IRI molar ratios across functional classifications of insulin receptor variations, and comparisons of CPR/IRI molar ratios versus IRI alone using ROC curve analyses. Additional ROC curve analyses were performed for variables with significant differences between the two groups (age, BMI, HbA1c, and HOMA-R) to assess their diagnostic accuracy. The ROC curves were statistically compared using DeLong's test for the AUC, and McNemar's test was performed to evaluate differences in specificity. *P* value of <0.05 was considered statistically significant. All statistical analyses were primarily performed using JMP software (SAS Institute, Cary, NC, USA). ROC curve analysis, including comparisons of AUCs, was conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (20).

Results

Study Population

During the specified period, there were seven cases of type A IRS diagnosed at Kobe University Hospital (Fig. 1a). The literature search identified 349 articles, from which 6 studies reporting a total of 11 individuals with type A IRS who underwent a 75-g OGTT with simultaneous measurement of CPR and IRI were identified.(7–9, 17, 18, 21) The type A IRS group thus comprised 18 individuals (Fig. 1a). Clinical characteristics of the 18 individuals with type A IRS are summarized in Table 1, while genetic variants and their functional effects are detailed in Table S1 (22). Some of the cases diagnosed at our institution (Case 3 and Case 4 with her sister, Case 5) have been previously reported in the literature (23, 24).

A 75-g OGTT loading agent was prescribed 1457 times to individuals admitted to the Department of Diabetes and Endocrinology at Kobe University Hospital between 1 February 2011 and 31 January 2021 (Fig. 1b), with 342 of these prescriptions being repeats for individuals on more than one occasion. After exclusion of these duplicates, 718 individuals did not have a diagnosis of type 2 diabetes, 43 individuals did not undergo an OGTT, 56 individuals had hemolyzed samples, 154 individuals used basal

insulin, 16 individuals had endocrine disorders other than diabetes, and 2 individuals had an eGFR of $<30 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ and were therefore excluded, leaving a total of 126 individuals with type 2 diabetes to be included in the study (Fig. 1b).

Clinical Characteristics

The clinical characteristics and biochemical parameters of the study participants are summarized in Table 2. Age, BMI, and HbA_{1c} level were significantly greater in the type 2 diabetes group than in the type A IRS group. IRI levels were significantly greater and the CPR/IRI molar ratio (normal level of fasting is $4.0 <$) (8) was significantly smaller in the type A IRS group than in the type 2 diabetes group both before and 1 and 2 h after initiation of the OGTT. HOMA-IR was significantly greater in the type A IRS group.

To address the potential variability within the Type A IRS group, post-hoc analyses were conducted. Comparisons between institutional cases ($n = 7$) and literature cases ($n = 11$) revealed no significant differences in age, BMI, HbA_{1c}, and OGTT-derived CPR/IRI molar ratios across fasting, 1-hour, or 2-hour measurements (Table S2) (22). Furthermore, no significant differences were observed in CPR/IRI molar ratios when individuals were classified based on the functional effects of *INSR* variants (25)

(Decreased receptor expression [n = 5] vs. Impaired tyrosine kinase activity[n = 12])
(Table S3) (22).

Diagnostic Performance

The CPR/IRI molar ratio demonstrated exceptional diagnostic performance in differentiating type A IRS from T2DM at all time points during the OGTT. The ROC curve analysis revealed that the AUC for the CPR/IRI molar ratio was 0.997 at fasting (cutoff: 5.96; sensitivity: 100%; specificity: 99.2%) (Fig. 2a), 0.999 at 1 hour (cutoff: 3.30; sensitivity: 100%; specificity: 97.6%) (Fig. 2b), and 0.997 at 2 hours (cutoff: 3.55; sensitivity: 100%; specificity: 95.1%) (Fig. 2c). At all time points, the CPR/IRI molar ratio demonstrated significantly higher diagnostic performance compared to IRI levels alone. Furthermore, the CPR/IRI molar ratio achieved 100% sensitivity across all time points, with specificity also being significantly higher than that of IRI alone during fasting, 1 hour, and 2 hours of the OGTT.

In addition, post-hoc ROC curve analyses were conducted for variables that showed significant differences between the two groups, including age, BMI, HbA1c, and HOMA-R. The AUC values for these parameters were all lower than those for the CPR/IRI molar ratio or IRI alone. These results are summarized in Table S4 (22).

BMI and CPR/IRI Molar Ratio Relationship

A scatter plot of BMI and the fasting CPR/IRI molar ratio revealed clear separation between individuals with type A IRS and those with type 2 diabetes regardless of BMI (Fig. 3a), suggestive of the diagnostic utility of this ratio. In contrast, the separation of the two conditions was less distinct in a scatter plot of BMI and fasting IRI levels, with some overlap apparent for type 2 diabetic individuals with a lower BMI (Fig. 3b). The fasting CPR/IRI molar ratio (correlation coefficient, -0.288 ; $p = 0.001$) and fasting IRI concentration (correlation coefficient, 0.612 ; $p < 0.001$) were significantly correlated with BMI in the type 2 diabetes group, whereas neither parameter was correlated with BMI in the type A IRS group (correlation coefficient of -0.029 , $p = 0.91$; and correlation coefficient of 0.059 , $p = 0.82$, respectively). A scatter plot of fasting IRI levels and the fasting CPR/IRI molar ratio also showed separation of the two conditions, albeit with some overlap for type 2 diabetic individuals with high IRI levels (Fig. 3c).

Discussion

We have here shown that the CPR/IRI molar ratio obtained during an OGTT is able to distinguish type A IRS from type 2 diabetes. Moreover, the CPR/IRI molar ratio is not

influenced by BMI, clearly separating the two conditions regardless of BMI. We demonstrated that the CPR/IRI molar ratio has significantly superior diagnostic performance compared to IRI alone at all OGTT time points. The current proposed diagnostic process for type A IRS is based on screening according to the fasting IRI level and, after ruling out other specific causes of insulin resistance such as obesity, confirmatory genetic testing.(2, 4) Genetic testing is costly and time-consuming, however, emphasizing the need for other means of efficient and accurate screening. Furthermore, some individuals with type A IRS are overweight or obese and are therefore excluded by the proposed criteria.(2, 4) The CPR/IRI molar ratio may therefore serve as a better screening tool for type A IRS regardless of BMI.

Another advantage of the CPR/IRI molar ratio is that it distinguishes type A IRS from type 2 diabetes regardless of the extent of hyperinsulinemia. Whereas marked hyperinsulinemia is a common trigger for suspicion of type A IRS, some cases show relatively low IRI levels.(7–9) Moreover, type A IRS can present with a wide range of phenotypes, from mild glucose intolerance to severe treatment-resistant diabetes.(3, 6) The individuals with type A IRS in the present study included individuals with mildly impaired or normal glucose tolerance, indicating that the CPR/IRI molar ratio remains a robust screening tool for the syndrome across various levels of hyperinsulinemia and

glucose intolerance.

Regarding the treatment of Type A IRS, the effectiveness of metformin has been reported (26,27). Recently, clinical trials have demonstrated the efficacy and safety of SGLT-2 inhibitors in treating insulin-resistant diabetes, including Type A IRS (28,29). These drugs, which lower blood glucose levels independently of insulin signaling, are considered effective for Type A IRS (28). As more effective treatment options become available for managing diabetes in Type A IRS, early detection and accurate diagnosis become increasingly crucial.

The ROC curve analysis revealed that the CPR/IRI molar ratio at baseline as well as 1 and 2 h after initiation of the OGTT had a sensitivity of 100% for differentiation of type A IRS from type 2 diabetes, although the specificity was <100%. The lower specificity was attributable to one individual with type 2 diabetes who showed a low CPR/IRI molar ratio. This individual had a BMI of 44.4 kg/m² and a fasting IRI concentration of 70 µIU/mL. It is thus possible that severe obesity may lower the CPR/IRI molar ratio independently of *INSR* variants.

This study has several limitations. First, the type 2 diabetes group did not undergo genetic testing, and we cannot exclude the possibility that individuals with pathogenic *INSR* variants were included. Second, the study was conducted at a single

center and utilized a retrospective design, which could limit the generalizability of the findings. Third, the type A IRS and type 2 diabetes groups differed significantly in age, BMI, and HbA1c levels, which could influence insulin clearance and potentially affect the study results. However, our findings suggest that the CPR/IRI molar ratio provides superior diagnostic performance regardless of these differences. Fourth, the T2DM group consisted exclusively of Japanese individuals, reflecting the typical BMI and demographic characteristics of this population. For example, the median BMI of the T2DM group (25.9 kg/m²) aligns with values commonly observed in Japanese individuals with type 2 diabetes (30) but is lower than those reported in Western populations. Further studies involving diverse ethnic groups are warranted to validate these findings. Fifth, this study did not include healthy control individuals. Future studies incorporating healthy controls are warranted to evaluate the diagnostic utility of the CPR/IRI molar ratio in identifying individuals with milder phenotypes within non-diabetic populations. Such research would provide additional insights into the broader applicability of this diagnostic tool.

In conclusion, the CPR/IRI molar ratio, both at baseline and during a 75-g OGTT, showed higher sensitivity and specificity compared with the current diagnostic criterion of fasting IRI concentration for distinguishing type A IRS from type 2 diabetes.

Whereas type A IRS is relatively rare, recent estimates suggest its prevalence is at least 0.7% of individuals with diabetes,(6) suggesting the existence of a considerable number of undiagnosed cases. The CPR/IRI molar ratio might therefore prove useful for identification of such undiagnosed cases.

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Data availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Conflict of Interest Disclosure

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conflict of interest.

Author contributions

S.N. and Y.H. conducted the research and analyzed data, contributed to discussion, and wrote the first draft of the manuscript. W.O. reviewed and edited the manuscript.

Tomofumi Takayoshi, K.Y., Takehito Takeuchi, T.H., M.U. and A.Y. contributed to discussion and reviewed and edited the manuscript. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kobe University Hospital (approval no. B220103). As this was a retrospective study using existing data, the committee did not require written informed consent.

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482

Figure Legends

Fig. 1 Flowcharts for individual selection in the type A insulin resistance syndrome (a) and type 2 diabetes (b) groups. CPR, C-peptide reactivity; IRI, immunoreactive insulin.

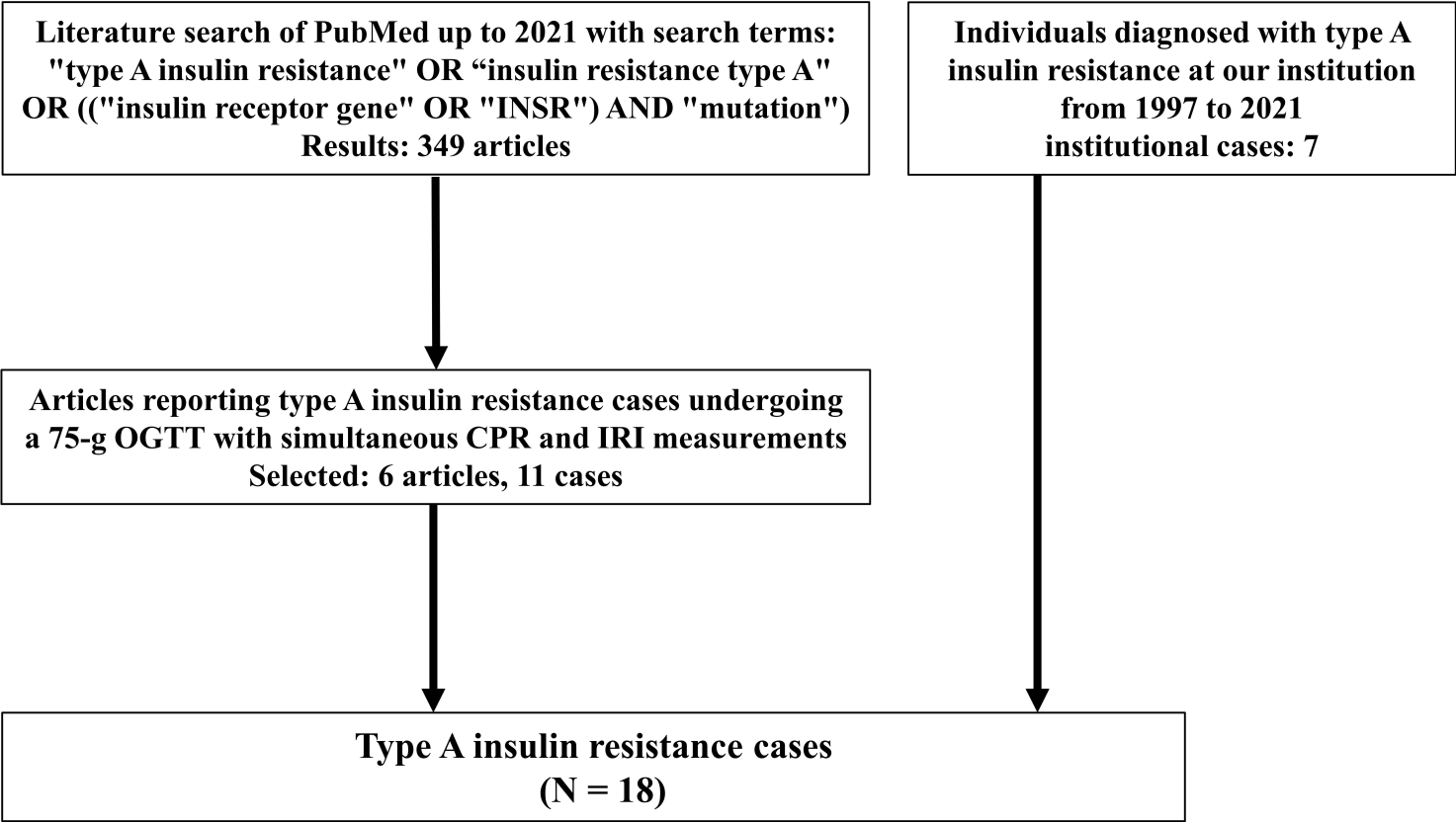
Fig. 2 Receiver operating characteristic (ROC) curves comparing the diagnostic performance of the immunoreactive insulin concentration (IRI, solid lines) and the C-peptide reactivity/immunoreactive insulin molar ratio (CPR/IRI, dashed lines) for differentiating type A insulin resistance syndrome from type 2 diabetes. ROC curves are shown for measurements taken at fasting (a), 1 hour after glucose ingestion (b), and 2 hours after glucose ingestion (c) during a 75-g oral glucose tolerance test (OGTT). The area under the curve (AUC) for each ROC curve was compared using DeLong's test. Specificity was compared using the McNemar test, while sensitivity was 100% for CPR/IRI, making statistical testing for sensitivity impossible.

Fig. 3 Scatter plots illustrating: (a) the relationship between the fasting C-peptide reactivity (CPR)/immunoreactive insulin (IRI) molar ratio and BMI, (b) the relationship between fasting IRI concentration and BMI, and (c) the relationship between the fasting

501 CPR/IRI molar ratio and fasting IRI concentration. Data are shown for individuals with
502 type A insulin resistance syndrome (IRS) and type 2 diabetes. These plots highlight the
503 distinct separation between the two groups, emphasizing the diagnostic utility of the
504 CPR/IRI molar ratio.

Fig.1

a



b

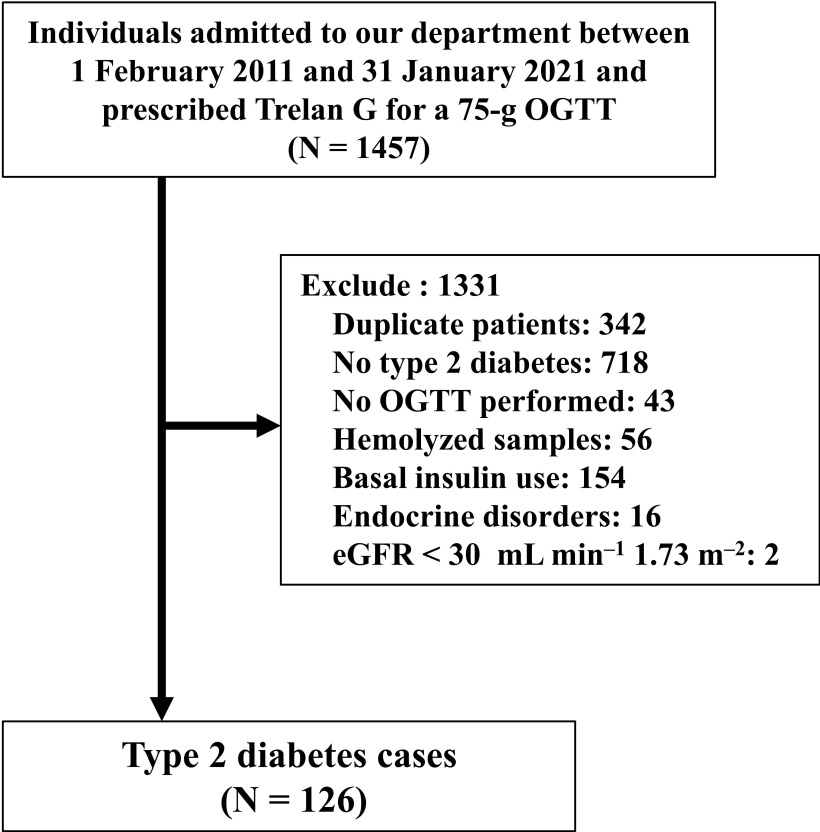
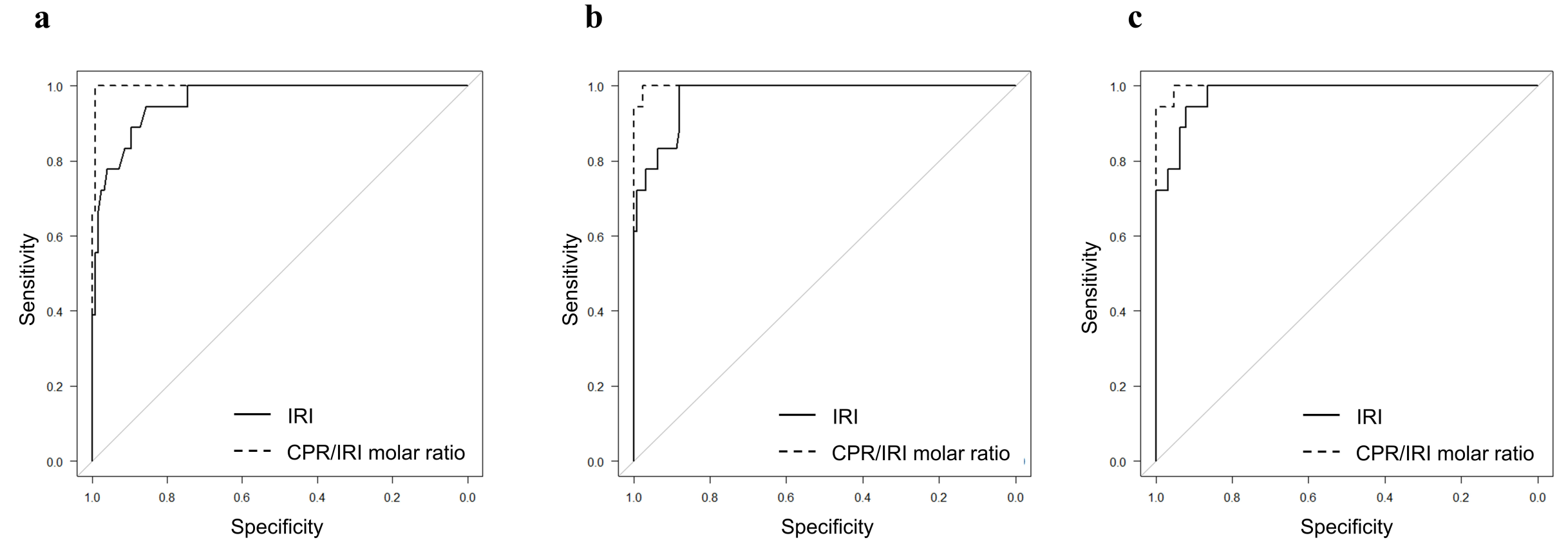


Fig.2



	Fasting IRI	Fasting CPR/IRI molar ratio	<i>P</i> value
AUC	0.962	0.997	< 0.05
Sensitivity	94.4%	100%	N/A
Specificity	85.7%	99.2%	< 0.001
Cutoff	15.00 μ IU/mL	5.96	

	1-h IRI	1-h CPR/IRI molar ratio	<i>P</i> value
AUC	0.974	0.999	< 0.05
Sensitivity	100%	100%	N/A
Specificity	88.1%	97.6%	< 0.01
Cutoff	100.5 μ IU/mL	3.30	

	2-h IRI	2-h CPR/IRI molar ratio	<i>P</i> value
AUC	0.979	0.997	< 0.05
Sensitivity	100%	100%	N/A
Specificity	86.5%	95.1%	< 0.01
Cutoff	110.5 μ IU/mL	3.55	

Fig.3

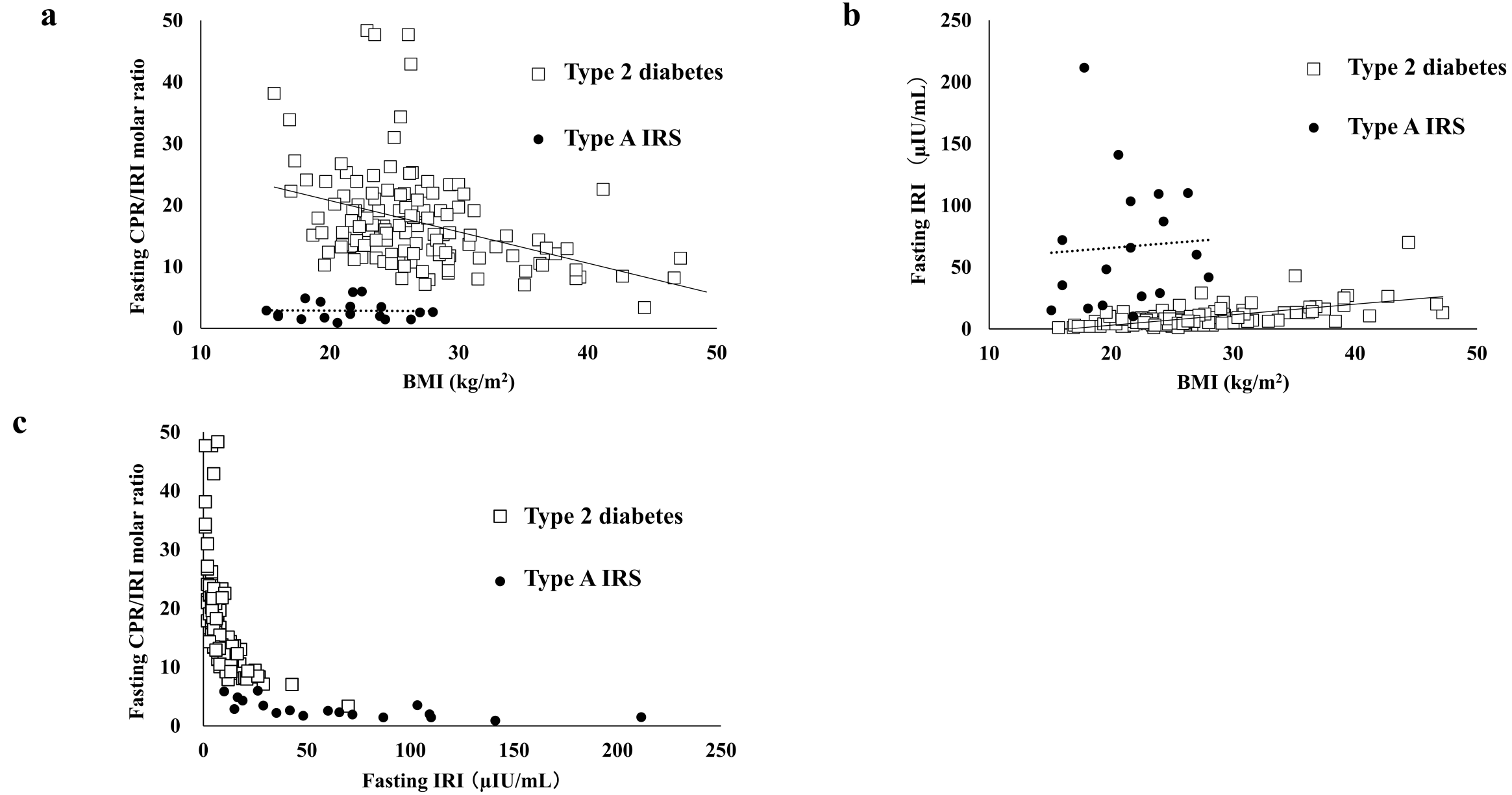


Table 1 Details of the study participants with type A insulin resistance syndrome

Case	Age (years)	Sex	BMI (kg/m ²)	HbA _{1c} (%)	Fasting glucose (mg/dL)	Fasting CPR (ng/mL)	Fasting IRI (μIU/mL)	Fasting CPR/IRI molar ratio	1-h CPR/IRI molar ratio	2-h CPR/IRI molar ratio
Case 1	39	F	18.1	5.6	90	1.69	16.6	4.85	2.63	2.38
Case 2 (Case 1 father)	74	M	22.5	6.0	103	3.29	26.3	5.96	2.19	2.00
Case 3 Hashimoto <i>et al</i> (2012)	28	F	20.6	6.0	80	2.60	141.0	0.88	0.89	1.34
Case 4 Ogawa <i>et al</i> (2009)	16	F	16.0	5.6	64	2.91	72.0	1.93	1.07	0.84
Case 5 (Case 4 sister) Ogawa <i>et al</i> (2009)	19	F	19.3	5.8	73	1.71	19.0	4.29	1.88	1.45
Case 6	31	M	27.0	5.4	99	3.23	60.2	2.56	1.14	0.98
Case 7	64	F	21.6	5.7	136	7.64	103.4	3.52	1.92	1.45
Takahashi <i>et al</i> (2010) proband	12	F	21.6	9.2	124	3.18	65.7	2.31	1.74	1.64
Takahashi <i>et al</i> (2010) father	40	M	21.8	4.7	88	1.24	10.1	5.85	3.30	3.55
Huang <i>et al</i> (2009) proband	16	F	17.8	N/A	N/A	6.53	211.5	1.47	0.55	1.19
Huang <i>et al</i> (2009) father	43	M	23.9	N/A	N/A	4.50	109.3	1.96	0.76	0.41
Huang <i>et al</i> (2009) twin 1	8	M	16.0	N/A	N/A	1.63	35.3	2.20	0.62	0.65
Saito-Hakoda <i>et al</i> (2018)	12	F	24.0	5.5	75	2.10	29.0	3.45	1.61	1.41
Nakashima <i>et al</i> (1992)	17	F	26.3	12.8	266	3.30	110.0	1.43	1.62	1.36
Kuroda <i>et al</i> (2015) case 2	34	M	28.0	6.7	82	2.30	41.8	2.62	1.52	1.06
Kuroda <i>et al</i> (2015) case 2 son	9	M	15.1	5.9	79	0.90	15.0	2.86	2.00	1.71
Preumont <i>et al</i> (2017) case 1	16	F	24.3	N/A	61.3	2.60	87.0	1.42	1.75	1.46
Preumont <i>et al</i> (2017) case 2	43	F	19.6	N/A	86.5	1.72	48.2	1.70	0.90	0.86

Cases 1 to 7 were from our institution, with the remaining cases being derived from the literature search as

indicated. Fasting, 1-h, and 2-h glucose, C-peptide reactivity (CPR), and immunoreactive insulin (IRI) concentrations were measured during a 75-g OGTT. N/A, not available.

Table 2 Characteristics of the type A insulin resistance syndrome (IRS) and type 2 diabetes groups

Characteristic	Type A IRS (<i>n</i> = 18)	Type 2 diabetes (<i>n</i> = 126)	<i>p</i> value
Age (years)	23.5 [15.0-40.8]	62.0 [51.0-68.0]	<0.001
Sex (male/female)	7/11	79/47	0.07
BMI (kg/m ²)	21.6 [18.0-24.1]	25.9 [22.7-29.2]	<0.001
HbA _{1c} (%) / (mmol/mol)	5.8 [5.6-6.4] / 39.0 [36.5- 7.3 [6.6-8.4] / 56.0 [48.0-45.5]	68.0]	<0.001
Fasting plasma glucose (mg/dL)	86.5 [75.0-103.0]	94.5 [86.8-108.3]	0.09
Fasting CPR (ng/mL)	2.6 [1.7-3.3]	2.1 [1.6-3.1]	0.23
Fasting IRI (μIU/mL)	54.2 [24.5-104.9]	6.1 [4.0-10.6]	<0.001
HOMA-IR	10.3 [3.7-20.1]	1.5 [0.9-2.6]	<0.001
Fasting CPR/IRI molar ratio	2.4 [1.6-3.7]	15.5 [11.9-21.1]	<0.001
75-g OGTT 1-h plasma glucose (mg/dL)	220.0 [134.0-263.0]	212.0 [171.0-249.0]	0.78
75-g OGTT 1-h IRI (μIU/mL)	436.2 [182.0-695.2]	34.0 [19.0-63.8]	<0.001
75-g OGTT 1-h CPR/IRI molar ratio	1.6 [0.9-1.9]	7.8 [6.0-10.2]	<0.001
75-g OGTT 2-h plasma glucose (mg/dL)	172.0 [122.0-262.0]	217.0 [159.3-262.0]	0.29
75-g OGTT 2-h IRI (μIU/mL)	551.6 [263.7-969.1]	43.0 [26.8-71.4]	<0.001
75-g OGTT 2-h CPR/IRI molar ratio	1.4 [0.9-1.7]	9.1 [6.7-12.1]	<0.001

With the exception of sex, data are presented as median [interquartile range]. The *p* values for comparisons between the two groups were determined with the Mann-Whitney U test, with the exception of sex (chi-square test). Fasting, 1-h, and 2-h glucose, C-peptide reactivity (CPR), and immunoreactive insulin (IRI) concentrations were measured during a 75-g OGTT.