Original Article

Comparison of Adults with Insulin Resistance (IR) in Latent Autoimmune Diabetes Versus IR in Glutamic Acid Decarboxylase Antibody-negative Diabetes

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Abstract

Introduction: Insulin resistance in latent autoimmune diabetes in adults (LADA) patients is controversial. The aim of this study was to evaluate insulin resistance and its related factors (metabolic syndrome parameters) among subjects with LADA and glutamic acid decarboxylase antibodies (GADA) negative diabetes, as well as the impact of these factors on insulin resistance. Materials and Methods: GADA levels were investigated in 1140 diabetic patients aged between 30 and 70 years. Insulin resistance and metabolic syndrome parameters were assessed in LADA and GAD-negative diabetic patients by general linear model. In addition, the impact of metabolic syndrome factors on insulin resistance was assessed in LADA and glutamic acid decarboxylase (GAD)-negative diabetic patients. Results: LADA was diagnosed in 33 subjects from 1140 Malaysian diabetic patients (prevalence = 2.9%). The results showed that LADA patients had higher insulin resistance and high density lipoprotein cholesterol (HDLc) ($P = 0.003$ and 0.00017 respectively) and lower body mass index (BMI) ($P = 0.007$) compared to GAD-negative diabetic patients. The HDLc was associated with decreased insulin resistance in LADA patients ($P = 0.041$), whereas HbA1c, triacylglycerides (TG) and waist were associated with increased insulin resistance in GAD-negative diabetic patients ($P = 3.6\times10^{-12}$, 1.01×10^{-5} and 0.004 respectively). HbA1c was highly associated with decreasing β-cell function in both LADA ($P = 0.009$) and GAD-negative diabetic subjects ($P = 2.2\times10^{-28}$). Conclusion: Insulin resistance is significantly higher in LADA than GAD-negative diabetic Malaysian subjects.

Ann Acad Med Singapore 2014;43:107-12

Key words: GAD-negative diabetes, Insulin resistance, LADA

Introduction

Latent autoimmune diabetes in adults (LADA) is a term used to describe the adult onset autoimmune diabetes, characterised by the presence of type 1 diabetes-associated antibodies but has a slower progression toward an absolute insulin requirement.[1] LADA is characterised by autoimmune destruction of pancreatic βcells with the presence of T-cell reactivity to circulating auto-antibodies, more frequently, glutamic acid decarboxylase antibodies (GADA).[2,3] GADA is the most sensitive marker for LADA.[4-6] Recent studies showed that GADA titers have a bimodal distribution in LADA and identify 2 subgroups of patients with distinct clinical, autoimmune and genetic features.[7] Patients with high GADA titers tend to be younger, leaner and have a lower prevalence of metabolic syndrome and its components, with more prominent traits of insulin deficiency (lower C-peptide, higher HbA1c) than individuals with lower GADA titers.[7,8] Epidemiological studies showed that LADA prevalence among T2D varies from 2% to 12%[9] and tends to be higher in Western countries compared to Asian countries.[10-13] Prevalence of LADA has not been studied in Malaysia, which has a multiethnic population including Malays (50.4%), Chinese (23.7%) and Indian (7.1%). These 3 ethnic groups represent the major portion of the population residents in Asia.[14]

LADA patients do not require insulin at diagnosis. However, insulin dependency occurs within a short period (ranging from months to years). The final clinical features of these patients include weight loss, proneness to ketosis, unstable blood glucose levels and an extremely diminished C-peptide reserve.[9] LADA patients may need treatment strategies different from that used for patients with T2D.[15] An appropriate therapeutic approach would be one that offers a good metabolic control that maintains the mass and function of residual β-cell mass.[7]

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Insulin resistance is a clear feature of T2D and is sometimes affected by age, body mass index (BMI), ethnicity, physical activity, and medication.[16,17] The role of insulin resistance and its contribution to the pathophysiology of LADA is controversial. Some studies showed that insulin resistance in LADA was lower than that in T2D and comparable to T1D.[1,18-20] However, recent studies found no differences in insulin resistance between LADA and GAD-negative diabetes.[17,21] The aim of this study was to evaluate insulin resistance and its related metabolic syndrome parameters, in LADA and GAD-negative diabetes, as well as study the impact of these factors on insulin resistance.

Materials and Methods

Ethics Statement

This study was approved by the Medical Ethics Committee of University Malaya Medical Centre (Reference No. 387.15) for data collection between 2009 and 2011.

Subjects and Data Collection

Malaysian diabetic patients aged between 30 and 70 years who attended the University Malaya Medical Centre (UMMC) Kuala Lumpur for treatment were invited to participate in this study. A total of 1140 diabetic subjects participated in this study. The subjects' height (in metre), weight (in kg) were measured using Seca scale (Seca gmbh & co. kg. Germany) and body mass index (BMI), defined as weight (kg)/height squared (m^2), was calculated. Waist circumference was measured halfway between the lower rib margin and the anterior superior iliac spine. The antidiabetic and antilipid medications of the diabetic patients were obtained from the patient records at UMMC. Fasting venous blood (10 mL) was collected from each participant after obtaining written consent.

Biochemical Analysis

Fasting plasma glucose (FPG), high density lipoprotein cholesterol (HDLc), and triacylglycerides (TG) were measured on Dimension® RxL Max® Integrated Chemistry System (Siemens Healthcare Diagnostics Inc., Deerfield, IL USA). Fasting plasma insulin (FPI) was measured by ADVIA Centaur XP Immunoassay System (Siemens Healthcare Diagnostics Inc., Deerfield, IL USA) while variant haemoglobin A1c reorder pack (Catalogue number 270-0003) (Bio-Rad, USA) was used for the measurement of glycosylated haemoglobin (HbA1c). The β-cell function (HOMA-β) and insulin resistance (HOMA-IR) were assessed by the Homeostasis Model Assessment (HOMA2) Calculator v2.2, which is available online from Diabetes Trials Unit (University of Oxfordwww.dtu.ox.ac.uk) according to Matthews et al.[22]

Immunological Analysis

GADA65 autoantibody was analysed by ELISA kit (RSR Limited, Cardiff, UK). The analysis was done manually according to the manufacturer's protocol. Plates were read at 450 nm using a microplate reader (BioRad, Calabasas, USA).

Statistical Analysis

Demographic and biochemical parameters were non-normally distributed, thus they were log-transformed before statistical analyses and then retransformed back and presented as geometric means. The statistical analyses were conducted using Social Package of Statistical Science (SPSS) 11.5 (LEAD Technologies; Inc. USA). Insulin resistance, β-cell secretion and metabolic syndrome parameters were assessed in LADA and GAD-negative diabetic patients by general linear model adjusted for age, gender, race, BMI, antidiabetes medications, and antilipid medications. The impact of metabolic syndrome factors on the insulin resistance, β-cell secretion among LADA patients and GAD-negative diabetes were evaluated by linear regression. The significance level was considered if $P < 0.05$.

Results

LADA was diagnosed in 33 subjects (2.9%) who had GADA titer above the cut-off point (5 u/ml) and did not require insulin at diagnosis of T2D for the previous 12 months. The demographic and biochemical parameters of the 2 groups are summarised in Table 1. Treatment data of diabetes revealed that 70% of LADA patients were insulin dependent while 43% of GAD-negative diabetic subjects were under insulin treatment ($P = 0.002$). Antilipid treatment data showed that 33% of LADA patients did not take any antilipid treatments versus 11% of GAD-negative diabetic patients ($P = 0.004$) (Table 2).

The general linear model (adjusted for age, gender, race, BMI, antidiabetes medications, and antilipid medications) showed that LADA patients had higher insulin resistance, fasting blood insulin and HDLc ($P = 0.003$; 0.015; 0.00017, respectively) and lower BMI ($P = 0.007$) compared to GAD-negative diabetic patients (Table 3). There were no differences between the 2 groups with respect to β-cell secretion, FPG, HbA1c, waist circumference and TG. HDLc was associated with decreased insulin resistance in LADA patients ($P = 0.041$), whereas, HbA1c, TG and waist were associated with increased insulin resistance in GAD-negative diabetic patients ($P = 3.6\times10^{-12}$; 1.01×10^{-5}; 0.004, respectively) (Table 4). HbA1c was highly associated with decreasing β-cell function in both LADA ($B = -17.466$, $P = 0.009$) and GAD-negative diabetic subjects ($B = -15.342$, $P = 2.2\times10^{-28}$).

Table 1. Demographic Parameters Among LADA and GAD-negative Diabetes

Parameters	GAD-negative Diabetes (n = 1107) n (%)	LADA (n = 33) n (%)	*P* Value
Gender			
Male	748 (67.6)	21 (63.6)	
Female	359 (32.4)	12 (36.4)	
Race			
Malay	425 (38.4)	15 (45.5)	
Chinese	293 (26.5)	10 (30.3)	
Indian	389 (35.1)	8 (24.2)	
Age (years)	51.3 (50.8 – 51.9)	46.1 (42.8 – 49.6)	0.001
Weight (kg)	72.6 (71.5 – 73.7)	66.7 (59.2 – 75.3)	0.050
Height (m)	1.61 (1.60 – 1.61)	1.61 (1.57 – 1.65)	0.849
Insulin dependent	464 (43)	23 (70)	0.002
Antilipid medication	952 (89)	22 (67)	0.001

GAD: Glutamic acid decarboxylase; LADA: Latent autoimmune diabetes in adults

Note: The results presented represent geometric means (95% confidence interval of mean).

Table 2. Comparison of Antidiabetes and Antilipid Medications Among LADA and GAD-negative Diabetes

	GAD-negative Diabetes (n)%	LADA (n)%	*P* Value
Antidiabetes medications			
Non-treated	(42) 3.9%	0.00	-
Oral	(564) 52.7%	(10) 30.3%	0.038
Oral + insulin	(430) 40.2%	(18) 54.5%	0.173
Insulin	(34) 3.2%	(5) 15.2%	0.012
Antilipid medications			
Non-treated	(118) 11.0%	(11) 33.3%	0.004
Fibrates	(46) 4.3%	(1) 3%	0.704
Fibrates + statins	(165) 15.4%	(5) 15.2%	0.991
Statins	(741) 69.3%	(16) 48.5%	0.041

GAD: Glutamic acid decarboxylase; LADA: Latent autoimmune diabetes in adults

Table 3. Assessment of Insulin Resistance, Diabetic Parameters and Metabolic Syndrome Factors Among LADA and GAD-negative Diabetic Patients

Metabolic Syndrome Parameters	Univariate Model*			
	GAD-negative Diabetes	LADA	*P* Value	Eta Squared
HOMA-IR	2.44 (2.34 – 2.53)	3.47 (2.76 – 4.35)	0.003	0.8
HOMA-β	70.7 (67.4 – 74.2)	78.6 (59.3 – 104.1)	0.471	0.1
FPG (mmol/L)	7.88 (7.72 – 8.05)	8.63 (7.66 – 9.71)	0.145	0.2
FPI (pmol/L)	98 (94 – 102)	130 (104 – 164)	0.015	0.5
HbA1c (%)	7.98 (7.89 – 8.08)	8.41 (7.82 – 9.03)	0.167	0.2
BMI (kg/m^2)	27.4 (27.1 – 27.7)	25.2 (23.8 – 26.8)	0.007	0.6
Waist (cm)	96.1 (95.7 – 96.5)	95.5 (93.3 – 97.7)	0.592	0.01
TG (mmol/L)	1.56 (1.52 – 1.61)	1.39 (1.17 – 1.65)	0.183	0.2
HDLc (mmol/L)	1.09 (1.08 – 1.11)	1.27 (1.18 – 1.37)	0.00017	1.2

Note: The results presented represent geometric means and 95% confidence interval of the mean which evaluated by univariate (General Linear Model)

*adjusted for age, gender, race, BMI, antidiabetes and antilipid medications.

BMI: Body mass index; FPI: Fasting plasma insulin; FPG: Fasting plasma glucose; GAD: Glutamic acid decarboxylase; HOMA-β: β-cell function; HOMA-IR: Insulin resistance, LADA: Latent autoimmune diabetes in adults; TG: Triacylglycerides

Table 4. Impact of Metabolic Syndrome Factors, on the HOMA-β and HOMA-IR

Parameters	GAD-negative Diabetes		LADA	
	HOMA-β B (*P* Value)	HOMA-IR B (*P* Value)	HOMA-β B (*P* Value)	HOMA-IR B (*P* Value)
Waist Circumference (cm)	1.313 (0.001)	0.041 (0.004)	– 5.126 (0.116)	– 0.012 (0.914)
BMI (kg/m^2)	0.416 (0.639)	0.059 (0.073)	12.876 (0.088)	0.077 (0.767)
Glycosylated HbA1c (%)	– 15.342 (2.2×10^{-28})	0.350 (3.6×10^{-12})	– 17.466 (0.009)	0.257 (0.242)
High Density Lipoprotein (mmol/L)	– 12.905 (0.204)	– 0.636 (0.091)	– 72.143 (0.152)	– 3.806 (0.041)
TG (mmol/L)	– 0.911 (0.686)	0.369 (1.01×10^{-5})	11.791 (0.641)	0.637 (0.484)

Note: The results are presented as unstandardised coefficients; B and (*P* value) the impact of each parameter on β-cell function and insulin resistance was assessed by linear regression controlled for the other parameters in addition to gender, race and age. The positive sign of the coefficient implies a direct relationship, and the negative sign implies an inverse relationship.

BMI: Body mass index; GAD: Glutamic acid decarboxylase; HOMA-β: β-cell function; HOMA-IR: Insulin resistance; LADA: Latent autoimmune diabetes in adults; TG: Triacylglycerides

Table 5. Assessment of Insulin Resistance, Diabetes Parameters and Metabolic Syndrome Factors Among LADA and GAD-negative Diabetic Patients

Metabolic Syndrome Parameters	1st Univariate Model*				2nd Univariate Model†			
	GAD-negative Diabetes	LADA	*P* Value	Eta Squared	GAD-negative Diabetes	LADA	*P* Value	Eta Squared
HOMA-IR	2.44 (2.35 – 2.54)	3.68 (2.93 – 4.63)	0.001	1.1	2.44 (2.35 – 2.54)	3.39 (2.71 – 4.25)	0.005	0.7
HOMA-β	70.5 (67.2 – 73.9)	76.0 (57.5 – 100.4)	0.602	0.02	70.8 (67.5 – 74.3)	76.4 (57.8 – 101.1)	0.596	0.3
FPG (mmol/L)	7.90 (7.74 – 8.06)	8.91 (7.91 – 10.04)	0.052	0.3	7.88 (7.72 – 8.05)	8.67 (7.70 – 9.76)	0.122	0.2
FPI (pmol/L)	97.8 (94.1 – 101.8)	136.4 (108.7 – 171.2)	0.005	0.7	97.9 (94.2 – 101.8)	127.7 (101.9 –160.0)	0.023	0.4
HbA1c (%)	7.97 (7.87 – 8.07)	8.77 (8.13 – 9.46)	0.015	0.5	7.98 (7.89 – 8.08)	8.39 (7.81 – 9.01)	0.183	0.1
BMI (kg/m^2)	27.5 (27.2 – 27.7)	24.7 (23.3 – 26.3)	0.001	0.9	27.4 (27.1 – 27.7)	24.9 (23.5 – 26.5)	0.002	0.8
Waist (cm)	95.9 (95.6 – 96.3)	95.4 (93.2 – 97.6)	0.642	0.01	96.1 (95.7 – 96.5)	95.2 (93.1 – 97.4)	0.431	0.02
TG (mmol/L)	1.58 (1.53 – 1.63)	1.28 (1.07 – 1.52)	0.020	0.5	1.57 (1.52 – 1.62)	1.31 (1.10 – 1.56)	0.051	0.3
HDLc (mmol/L)	1.09 (1.08 – 1.10)	1.27 (1.17 – 1.37)	0.0001	1.2	1.09 (1.08 – 1.11)	1.28 (1.19 – 1.38)	7.03×10^{-5}	1.3

Note; The results presented represent geometric means and 95% confidence interval of the mean which were evaluated by univariate (General Linear Model)

*adjusted for age, gender, race and BMI

†adjusted for age, gender, race, BMI and antidiabetes medications

BMI: Body mass index; FPI: Fasting plasma insulin; FPG: Fasting plasma glucose; GAD: Glutamic acid decarboxylase; HOMA-β: β-cell function; HOMA-IR: Insulin resistance; LADA: Latent autoimmune diabetes in adults; TG: Triacylglycerides

Discussion

The prevalence of LADA among Malaysian diabetic patients was 2.9%. This prevalence tends to be lower than that seen in Western countries and similar to that found in Asian countries. This finding was in agreement with previous reports[11,12,23-25] in Japan and Korea.

The current study showed that LADA patients are younger and leaner than GAD-negative diabetes which is in agreement with Tuomi et al.[26] However, this is not in agreement with Zinman et al study.[20] LADA subjects showed poor glycaemic control, elucidated by the HbA1c levels, which is in agreement with Roh et al.[12] Furthermore, compared to GAD-negative diabetes, a large ratio of LADA patients were insulin-dependent. This finding which is in agreement with Lee et al[11] may be indicative of the progression of pancreatic β-cell decline and insulin dependency in LADA patients. Currently there are no specific treatment guidelines for LADA patients, even though early insulin treatment may have beneficial effect. Early diagnosis of LADA and initiation of insulin treatment may maintain the function of residual β-cell mass.

The insulin resistance was higher in LADA patients compared to GAD-negative diabetes patients even when controlled for most confounders (age, gender, race, BMI, antidiabetes and antilipid medications). This finding is in contrast to the findings of Behme et al[19] and Chiu et al.[17] This variation might be due to differences in treatment profile between the current study subjects and subjects of Behme et al and Chiu et al which may affect insulin resistance. However the known metabolic syndrome parameters such as waist and TG that were associated with metabolic syndrome in T2D were not associated with increased insulin resistance

Table 6. Comparison of Fasting Plasma Glucose, Fasting Plasma Insulin and Insulin Resistance Between LADA Patients Subgroups According to the Diabetic Treatment

Parameters	LADA Subjects Under Oral Diabetic Treatment Only (n = 10)	LADA Subjects Under Oral and Insulin Treatment (n = 18)	LADA Subjects Under Insulin Treatment Only (n = 5)	*P* Value
Fasting Glucose (mmol/L)	9.77	9.71	7.49	0.59
Fasting Insulin (pmol/L)	132	119	122	0.96
HOMA-IR	3.47	3.48	3.20	0.99

Note: The results are presented as non-adjusted means.
HOMA-IR: Insulin resistance; LADA: Latent autoimmune diabetes in adults

in LADA patients. The HDLc was higher in LADA subjects than GAD-negative diabetes subjects and was unexplainably associated with insulin resistance among LADA patients. HbA1c was higher in LADA subjects compared to GAD-negative diabetes patients (Table 5), and was associated with decreased β-cell function in both LADA and GAD-negative diabetes. HbA1c reflect glycaemic control and on the other hand it indirectly reflects irreversible protein glycosylation inside the body. Abnormal and irreversible pancreatic β-cell damage caused by prolonged exposure of β-cell to supraphysiological glucose results in decreased insulin gene expression and is characterised by a decrease in insulin synthesis and secretion.[27] Once hyperglycaemia becomes apparent, β-cell function gradually deteriorates[28] and culturing of human islet with supraphysiological glucose induces β-cell apoptosis.[29] The mechanism responsible for the deleterious effect of chronic exposure to high glucose on islet cells is unclear. However, this effect may be mediated by increasing protein glycosylation (so-called advanced glycosylation end products or AGEs) and oxidative stress, which causes cell damage and ultimately cell death.[30] Hyperglycaemia increases production of reactive oxygen species (ROS) and ROS is thought to mediate glucose toxicity of β-cell and induce of β-cell apoptosis.[31] It is still unclear whether LADA is a distinct entity and what the degree of its insulin resistance is.[11,32] The limitations of the current study are that it is a hospital-based study and small sample size of T2D resulted in 33 subjects with LADA. Another potential weakness of this study using insulin test instead of C-peptide in comparison between LADA and GAD-negative diabetes in which the result may be affected by insulin treatment as 70% LADA patients were under insulin treatment. However, fasting insulin for LADA patients on insulin therapy was not higher than those on oral therapy (Table 6) suggesting that any spillover effect from the previous day's treatment is negligible. In conclusion, LADA patients were more insulin resistant than GAD-negative in diabetic Malaysian subjects. High HDLc is associated with decreased insulin resistance in LADA patients. Early detection of LADA and initiation of insulin treatment may delay the decline of pancreatic β-cell function.

Acknowledgments

We thank all the participants of this research and all nursing and medical staff at UMMC for their dedication in this study. The authors wish to thank University of Malaya for supporting this study with the research grants, UM RG350/11HTM and PV029/2012A.

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