Clinical Characteristics of ‘latent autoimmune diabetes in adults’ in Korea

경희의대 내분비대사내과

이 상 열

KNDP Korea National Diabetes Program

NECA 한국보건의료연구원 National Evidence-based Healthcare Collaborating Agency

본 발표와 관련된 이해관계

없 음

순서

- 정의
- 역학
- 병태생리
- 한국인 데이터
- 치료
- 생각해볼 문제
- 요약, 정리

순서

- 정의
- 역학
- 병태생리
- 한국인 데이터
- 치료
- 생각해볼 문제
- 요약, 정리

2. Classification and Diagnosis of Diabetes

Diabetes Care 2016;39(Suppl. 1):S13–S22 | DOI: 10.2337/dc16-S005

CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to β-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of insulin secretion on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS or after organ transplantation)

당뇨병의 분류

당뇨병은 1형, 2형, 임신성 당뇨병, 그리고 기타 다른 원인에 의한 당뇨병으로 분류된다(표 1)[1-5]. 당뇨병 형태에 따라 치료 전략이 다를 수 있다는 점에서 각각의 분류는 중요하나, 명확한 구분이 어려울 수 있다. 또한 감별에 항GAD(anti-glutamic acid decarboxylase) 항체 또는 항ICA(anti-islet cell antibody) 항체 같은 자가면역 지표가 도움이 되나, 진단적 가치는 확립되지 않았다[9,10]. 매우 낮은 C-펩티드 수치 역시 1형 당뇨병 감별에 도움이 될 수 있으나, 그 역할도 제한적일 수 있다.

너무 단순한 건 아닐까?

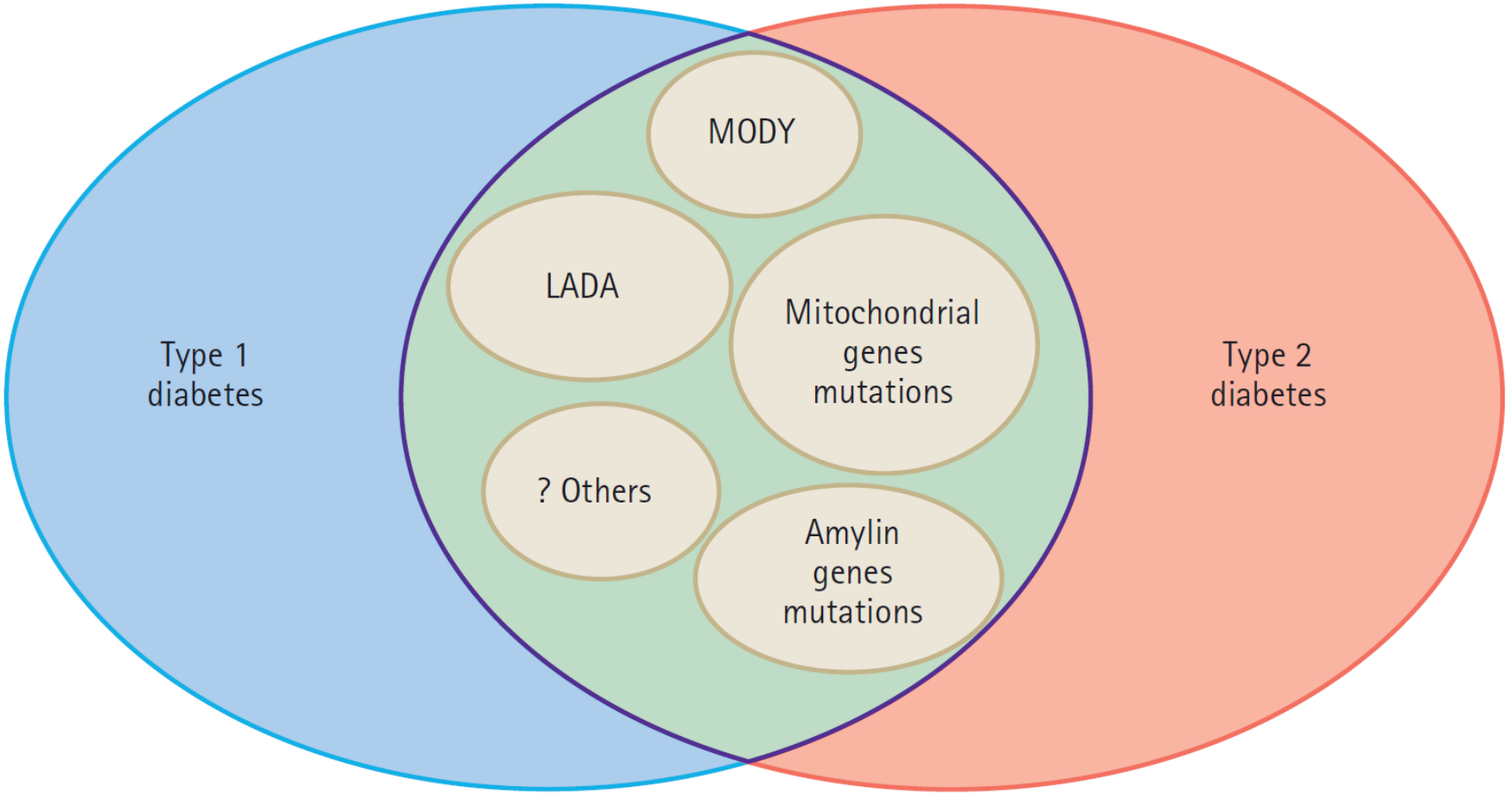
표 1 당뇨병 분류

- 1형 당뇨병은* 주로 췌장 베타세포 파괴에 의한 당뇨병이며, 케토산증 병력이 진단에 중요하다. 1형 당뇨병에는 자가면역에 의한 경우와 베타세포 파괴의 병인이 알려지지 않은 경우가 포함된다.
- 2형 당뇨병은 인슐린 저항성이 매우 높은 상태에서 상대적으로 인슐린 부족 상태를 보이는 경우부터 절대적으로 매우 낮은 인슐린 분비와 함께 인슐린 저항성을 보이는 범위까지 넓게 분포한다.
- 임신성 당뇨병은 임신 중 발생하거나 처음 진단된 내당능 장애다.
- 기타 형태는 유전학적으로 정의되는 당뇨병 및 다른 질병이나 약물 이용과 관계가 있는 비교적 흔하지 않은 다양한 상태가 포함된다.

* 췌장 베타세포의 면역 손상이 동반된 2형 당뇨병에 대한 용어인 잠재성 자가면역 당뇨병(latent autoimmune diabetes in adults, LADA)이 포함된다.

2형 당뇨병 임상연구센터 (KNDP). 한국인을 위한 당뇨병 임상 진료지침 2015.

Considerable overlaps between the phenotypes of T1DM and T2DM



Holt RIG, et al. Textbook of Diabetes,4th ed.

Definition of LADA

- No unified criteria exist for LADA
- but three criteria have often been used

- GAD antibody (+)
- ≥35 yrs at diagnosis
- no insulin therapy in the first 6–12 mo. after Dx.

Tuomi T et al. Lancet 383: 1084-1094, 2014.

A definition of LADA

- WHO classify LADA a Type 1 diabetes.

Study	Age	Antibody	Ketoacidosis[K]	Time to insulin
Agardh 2005	30-70	GAD	-	Not requiring insulin
Cabrera-Rode 2002	-	GAD and ICA	No K at 1 month	-
Kobayasahi 1996	-	ICA	No K	-
Maruyama 2003	-	GAD	No K	No insulin for 6 months
Zhou 2005	25+	GAD	No K within 6 months	-
Fourlanos 2006	30-75	GAD	-	No insulin for 6 months
Weslley Souza Rosario 2005	35+	GAD	-	No insulin for 1 year
Vatay 2002	35+	GAD or ICA	-	No insulin for 6 months
Isomaa 1999	35+	GAD	No K	-
Yang 2005	25+	GAD	No K for 6 months	-

Eponyms for autoimmune diabetes in adults

Eponym	Reference
Latent type 1 diabetes	Groop LC, et al. Diabetes, 1986.
Latent autoimmune diabetes in adults (LADA)	Tuomi T, et al. Diabetes, 1993.
Slowly progressive IDDM (SPIDDM)	Kobayashi, T et al. Diabetes Care, 1993.
Slow-onset IDDM	Lohmann, T et al. Diabetes Care, 1997.
Slowly progressive type 1 diabetes	Seissler J, et al. Diabetologia, 1998.
Type 1 1/2 diabetes	Juneja R, et al. Autoimmunity, 1999.
LADY-like	Lohmann T, et al. Diabetes Care, 2000.
Autoimmune diabetes not requiring insulin at diagnosis	Pozzilli P, et al. Diabetes Care, 2001.
LADA–type 1 and –type 2	Lohmann T, et al. Diabetologia, 2001.
Slowly progressive β-cell failure	Borg H, et al. JCEM, 2001.
Slowly progressive adult-onset type 1 diabetes	Hosszufalusi N, et al. Diabetes Care, 2003.
Antibody-positive phenotypic type 2 diabetes with obesity	Palmer JP, et al. Diabetes Care, 2003.
Latent autoimmune diabetes in children (LADC)	Aycan Z, et al. J Pediatr Endo Metab, 2004

순서

- 정의
- 역학
- 병태생리
- 한국인 데이터
- 치료
- 생각해볼 문제
- 요약, 정리

Global Epidemiology

	Study design	Frequency of GAD antibody positivity	Duration of diabetes	Number of patients with LADA (year of study if more than one group)	Number of patients with type 2 diabetes (year of study if more than one group)	Selection criteria for LADA			Measurement of β-cell function	Measurement of insulin resistance or metabolic syndrome	Measurement of high *vs* low concentrations of GAD antibody	Other auto-antibodies
						Age at diagnosis (years)	Time free from insulin therapy (months)	Auto-antibodies				
UKPDS (UK)[56–58]	Prospective	13·2%	<1 year	526 (1997);[56] 378 (2006–07)[57,58]	4545 (1997);[56] 400 (2006–07)[57,58]	25–65	≥3	Islet-cell antibody, GAD antibody	Treatment with insulin, HOMA-β	HOMA-IR, BMI	Yes	IA-2 antibody
Botnia (Finland)[59–62]	Cross-sectional	9·3%	Any	104 (1999);[59] 217 (2000);[60] 294 (2010–13)[61,62]	1122 (1999);[59] 744 (2000);[60] 648 (2010–13)[61,62]	>35*	≥6–12	GAD antibody	C peptide, oral glucose-tolerance test, (intravenous glucose tolerance test[60])	HOMA-IR, BMI, waist circum-ference, blood pressure, lipids, (normoglycaemic hyper-insulinaemic clamp[60])	Yes	Islet-cell antibody, IA-2 antibody, ZnT8 antibody, thyroidal antibody

Tuomi T et al. Lancet 383: 1084-1094, 2014.

Global Epidemiology

Castleden and colleagues (UK)[63]	Cross-sectional	7%	..	136	1923	>25	12	GAD antibody	Treatment with insulin	BMI	Yes	..
Fourlanos and colleagues (Australia)[64]	..	..	..	102	111	30–75	..	..	Treatment with insulin	BMI	..	..
ADOPT (USA, Canada, and Europe)[65]	Cross-sectional (drug intervention)	4·3%	<3 years†	174	3960	..	..	GAD antibody	Oral glucose-tolerance test	HOMA-IR, BMI, waist circumference, blood pressure, lipids‡	Yes	..
HUNT (Norway)[66,67]	Cross-sectional and prospective	10%	..	106–128	943–1134	≥20	12, or <12 if C-peptide concentration >150 pmol/L	GAD antibody	C peptide, treatment with insulin	BMI, waist circumference, blood pressure, lipids	Yes	IA-2 antibody, ZnT8 antibody
NIRAD (Italy)[68,69]	Cross-sectional and prospective	4·5%	6 months to 5 years	193 (2007);[68] 236 (2012)[69]	4057 (2007);[68] 450 (2012)[69]	..	..	GAD antibody, IA-2 antibody	Treatment with insulin	BMI, waist circumference, lipids	Yes	..

Tuomi T et al. Lancet 383: 1084-1094, 2014.

Global Epidemiology

Sardinia (Italy)[70]	Cross-sectional	4·9%	<5 years	276	5292	..	..	GAD antibody	Treatment with insulin	BMI, waist circumference, blood pressure, lipids	Yes	IA-2 antibody, TPO antibody
Hungary[71]	Cross-sectional and meta-analysis	..	..	211	1297	>35	6	Islet-cell antibody, GAD antibody, IA-2 antibody, or insulin antibody	..	..	..	..
Action LADA (Europe)[72]	Cross-sectional	8·8%	<5 years	384	5558§	30–70	6	GAD antibody, IA-2 antibody, or ZnT8 antibody	Treatment with insulin	BMI, waist circumference, blood pressure, lipids	Yes	..
LADA China Study (China)[73]	Cross-sectional	5·9%	<1 year	287 (180 by genetic analysis)	4593 (174 by genetic analysis)	≥30	6	GAD antibody	..	..	Yes	..

GAD=glutamic acid decarboxylase. LADA=latent autoimmune diabetes in adults. HOMA-β=homoeostasis model assessment of β-cell function. HOMA-IR=homoeostasis model assessment of insulin resistance. BMI=body-mass index. IA-2=protein tyrosine phosphatase IA-2. ZnT8=zinc transporter 8. *No initial selection criteria for age but most patients were older than 35 years. †Untreated, fasting plasma glucose 7–10 mmol/L. ‡As defined by guidelines from the National Cholesterol Education Program Adult Treatment Panel. §114 patients had adult-onset type 1 diabetes, 24 had an intermediate phenotype (insulin started <6 months after diagnosis), and for 76 patients there was no information about time to insulin.

Tuomi T et al. Lancet 383: 1084-1094, 2014.

Epidemiology in Asia

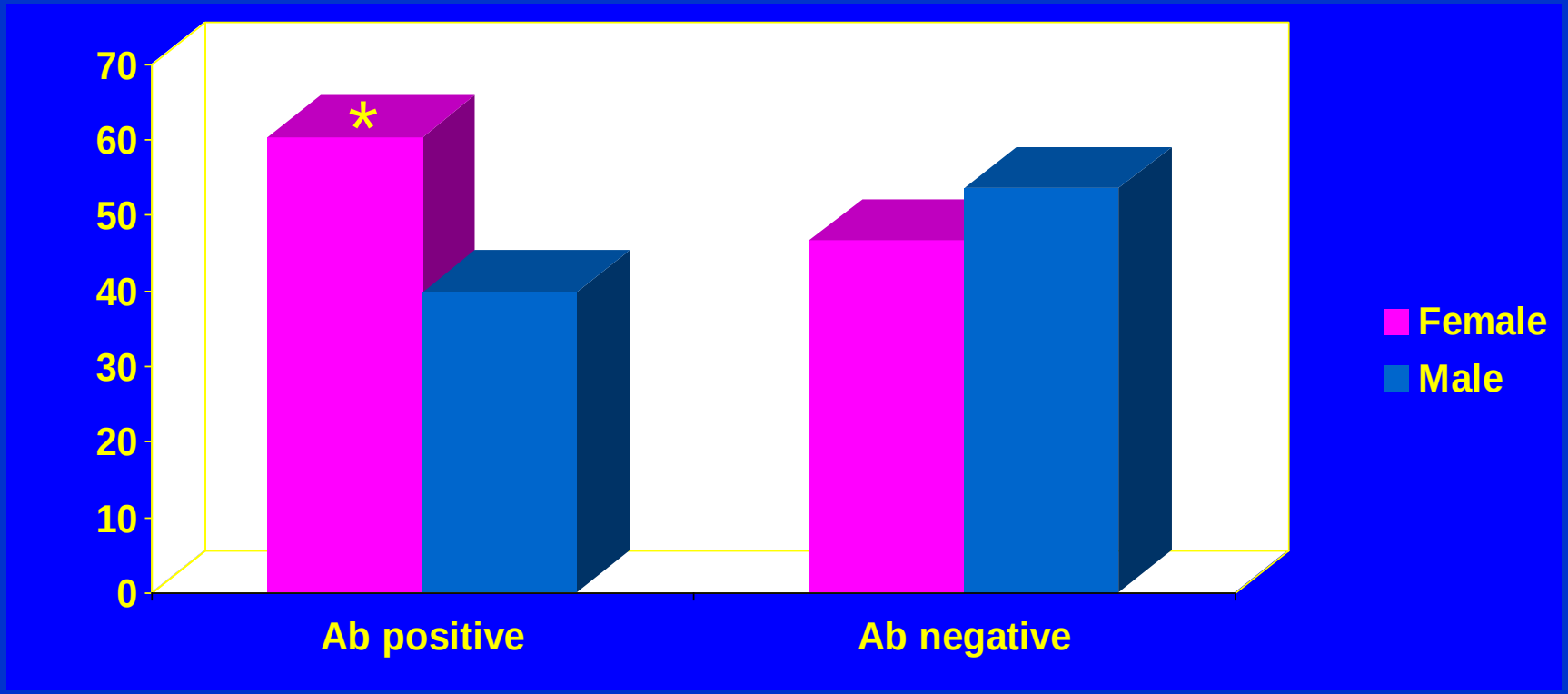
	n	Ethnicity	Age (yr)	Age at onset (yr)	Duration (yr)	BMI (kg/m^2)	GADA (+) (n, %)	ICA (+) (n, %)
Ko et al.	140 T1 and T2	Asian	30.8 ±5.8	25.9 ±7.2	4.6 ±4.7	25.6 ±5.1	**17 (12.1%)**	-
Thai et al.	168 T2	Asian	40.6 ±15.3	38.4 ±15.3	2.3 ±4.4	24.4 ±4.0	**27 (16.1%)**	8 (4.8%)
Tsuruoka et al.	680 T2	Asian	46.9 ±19.49	-	-	-	**29 (4.3%)**	-
Park et al.	121 New T2DM	Asian	57.4 ±12.5	-	-	25.2 ±3.8	**2 (1.7%)**	-
Huang et al.	40 T2	Asian	36.9 ±3.4	34.4 ±2.5	2.4 ±1.8	24.6 ±3.7	**2 (5.0%)**	1 (2.5%)

Modified Huang C.-Y. et al. Journal of Internal Medicine of Taiwan 15:12-18, 2004

순서

- 정의
- 역학
- 병태생리
- 한국인 데이터
- 치료
- 생각해볼 문제
- 요약, 정리

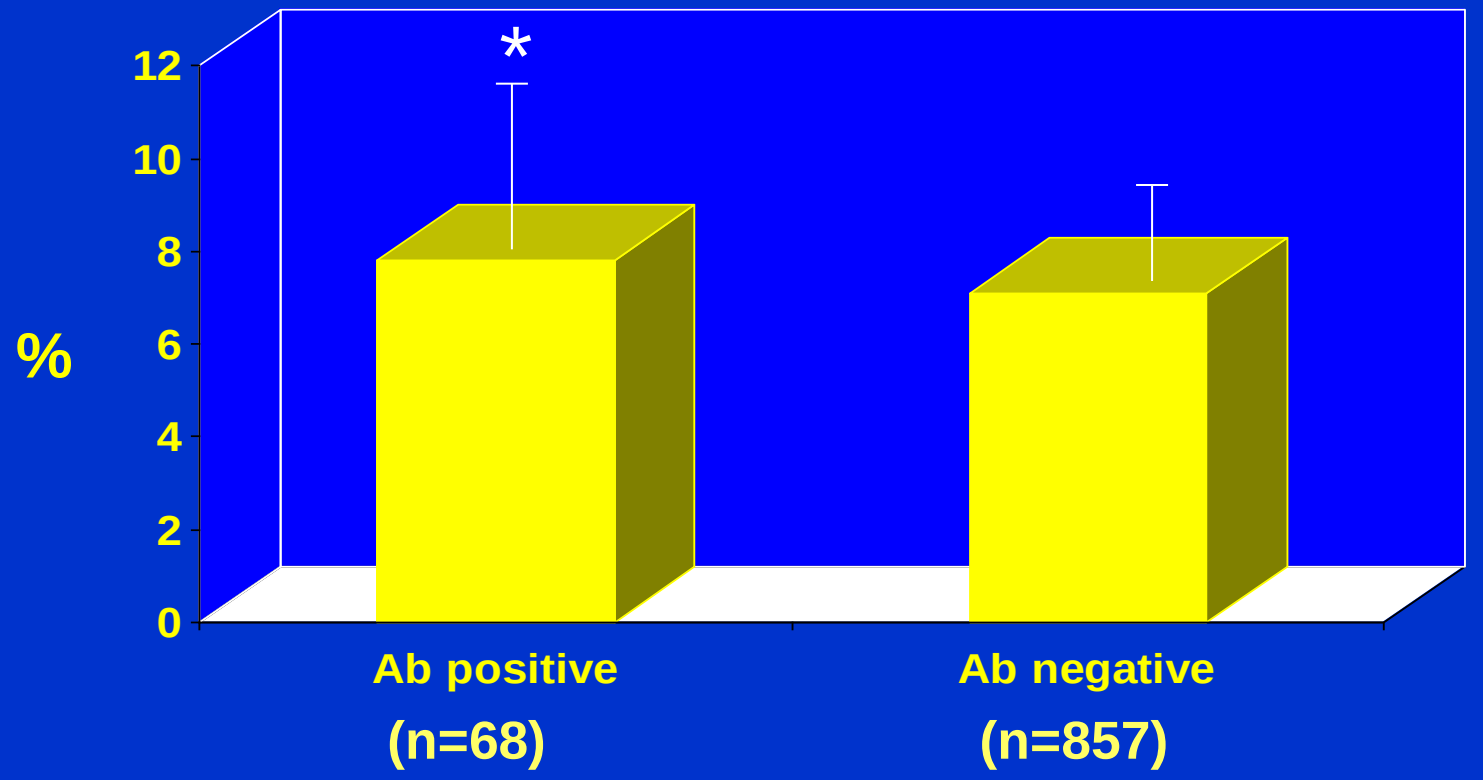
Gender distribution



* p=0.029 *vs* Ab negative

Genovese S, Pozzilli P et al. *Eur J Endocrinol 154:441-7, 2006*

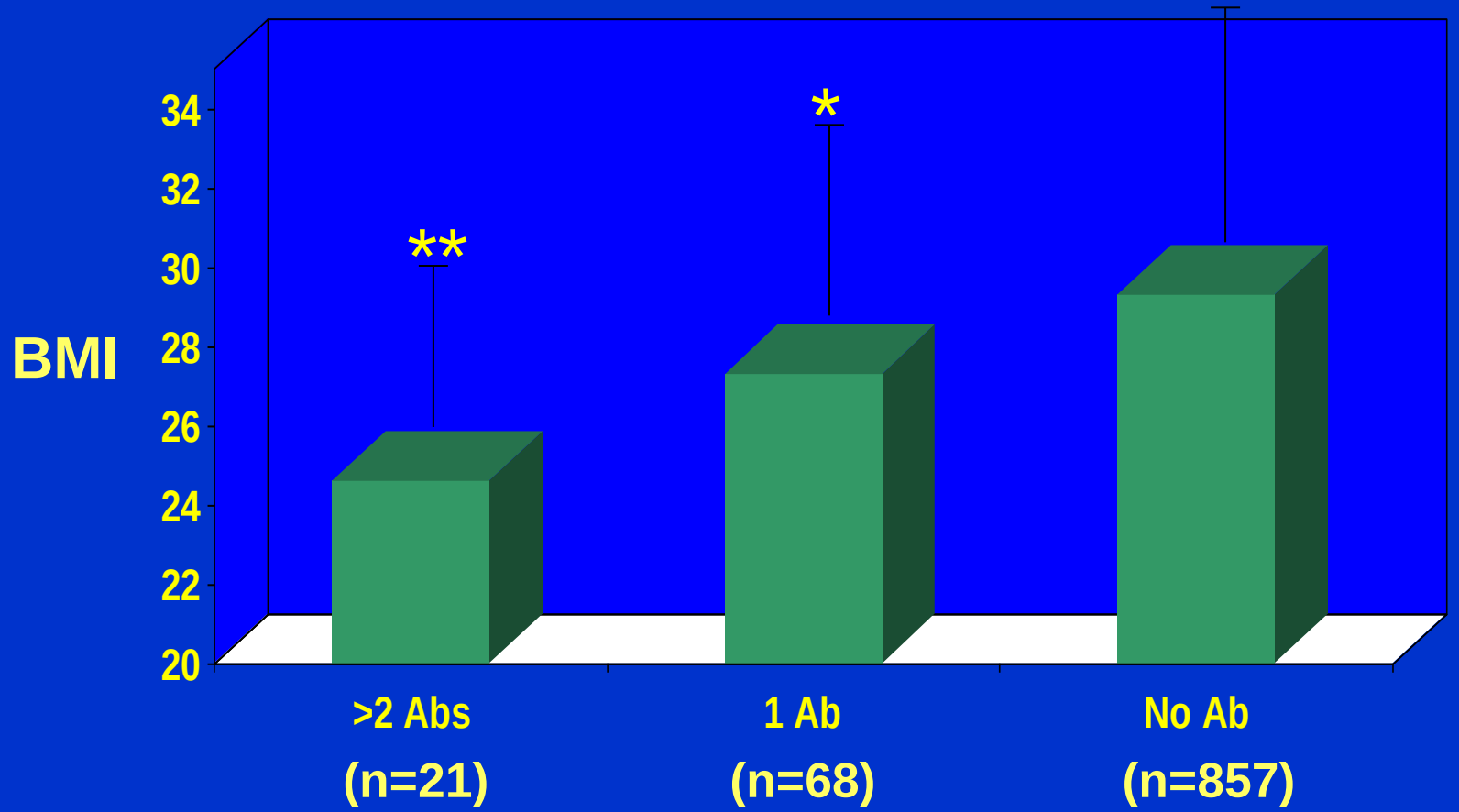
HbA1c values in screened patients according to antibody positivity



* p=0.008 *vs* Ab negative

Genovese S, Pozzilli P et al. *Eur J Endocrinol 154:441-7, 2006*

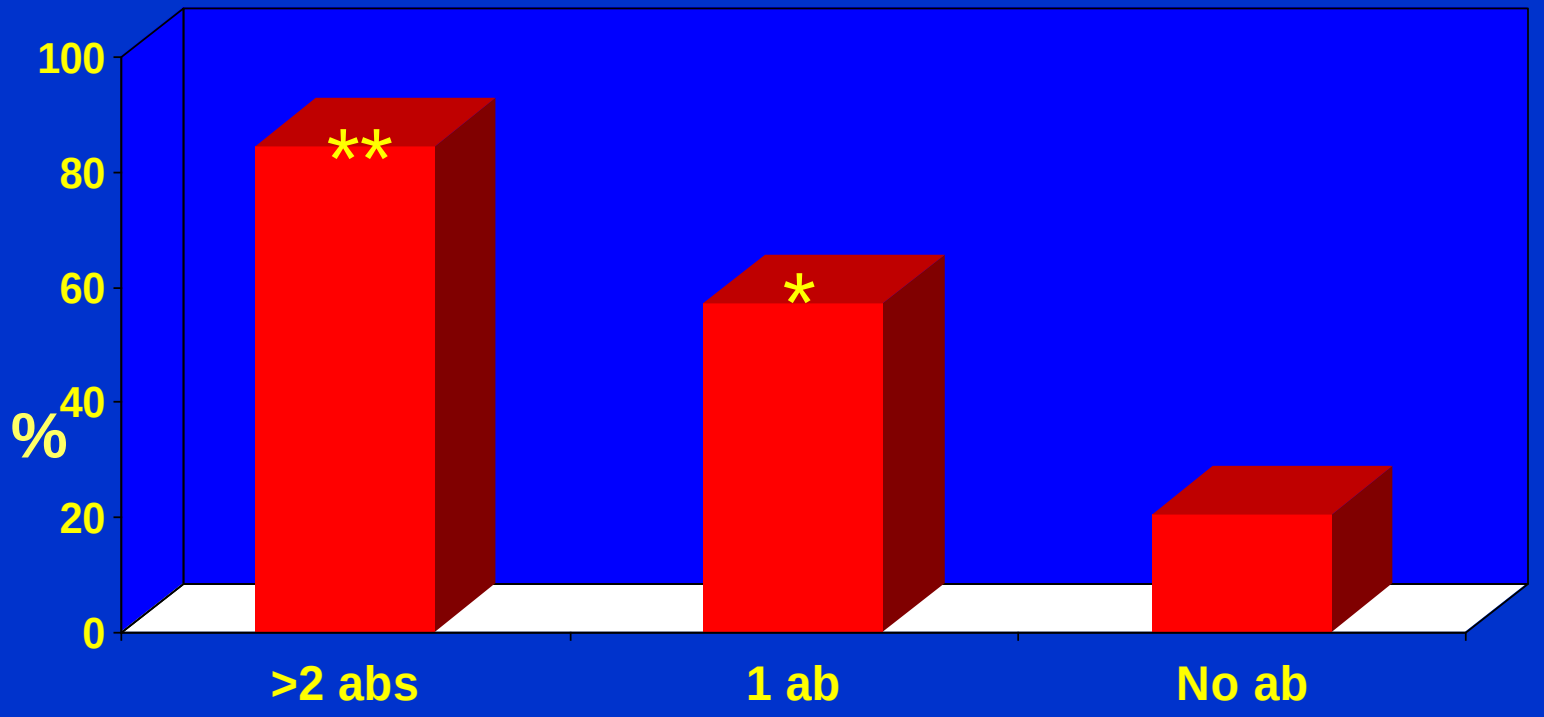
Body Mass Index in screened patients according to antibody positivity



** p=0.024 *vs* 1 Ab * p<0.001 *vs* No Ab

Genovese S, Pozzilli P et al. *Eur J Endocrinol 154:441-7, 2006*

Prevalence of patients treated with insulin according to antibody positivity

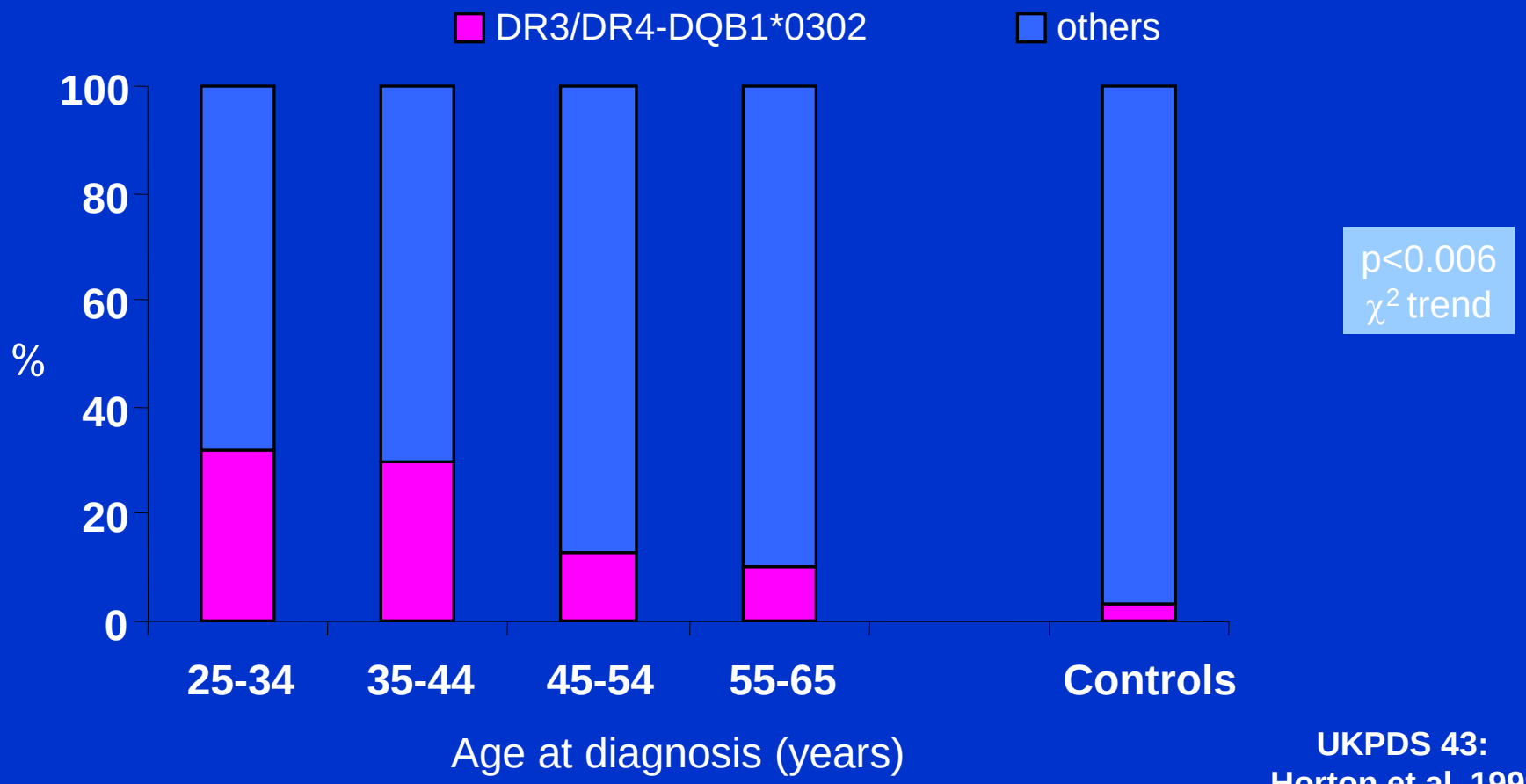


** p=0.036 *vs* 1 Ab * p<0.001 *vs* No Ab

Genovese S, Pozzilli P et al. *Eur J Endocrinol 154:441-7, 2006*

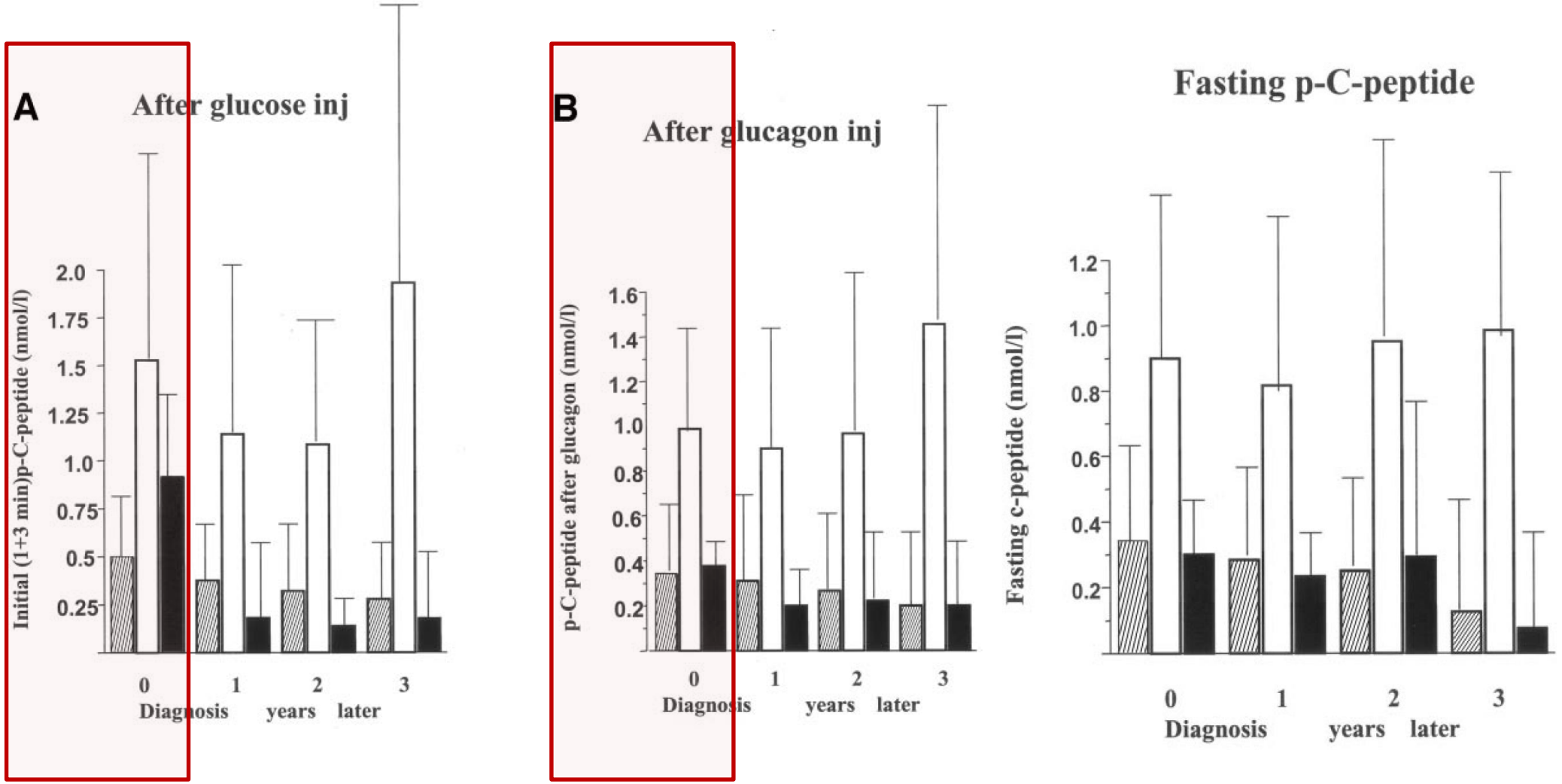
DRB1-DQB1 association is age-related in LADA

- Prevalence of the DR3/DR4-DQB1*0302 combination according to age of diagnosis in LADA (n= 255) and in controls (n= 200):



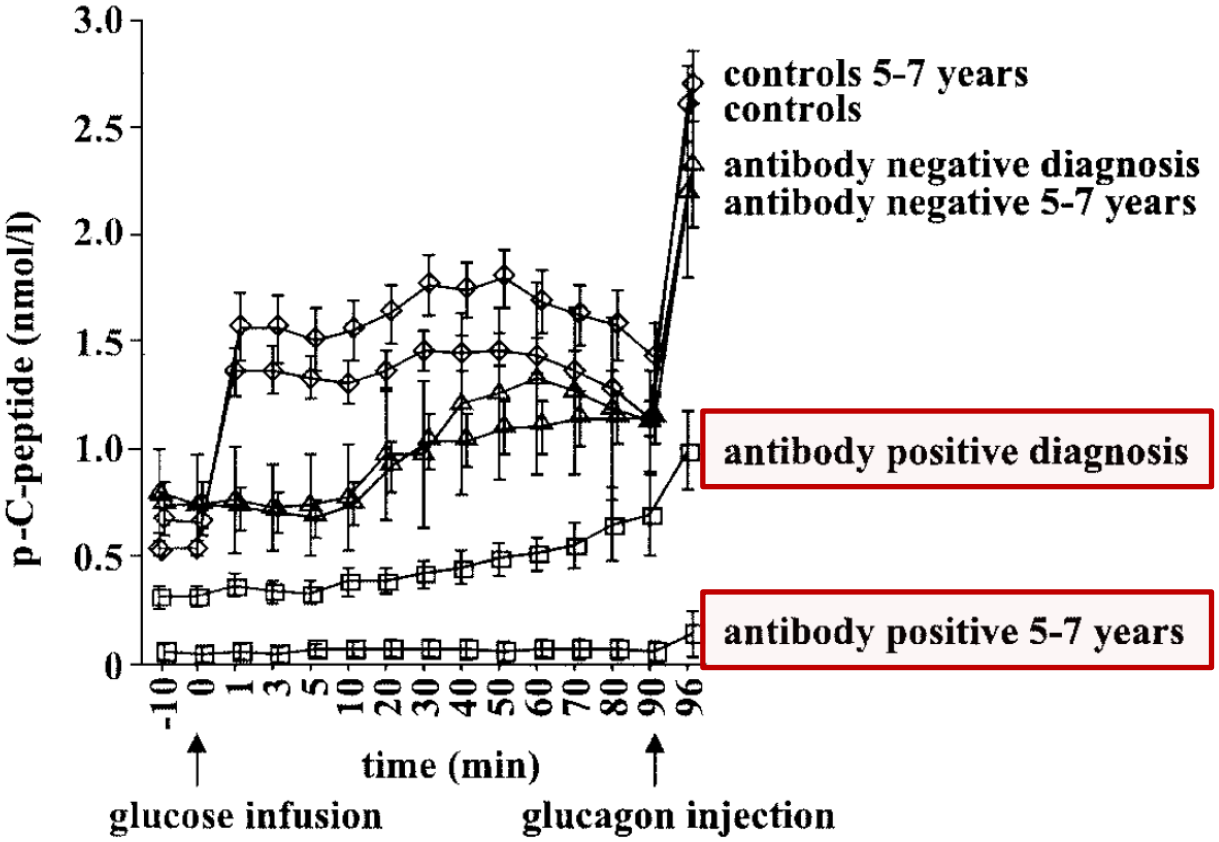
UKPDS 43:
Horton et al, 1999

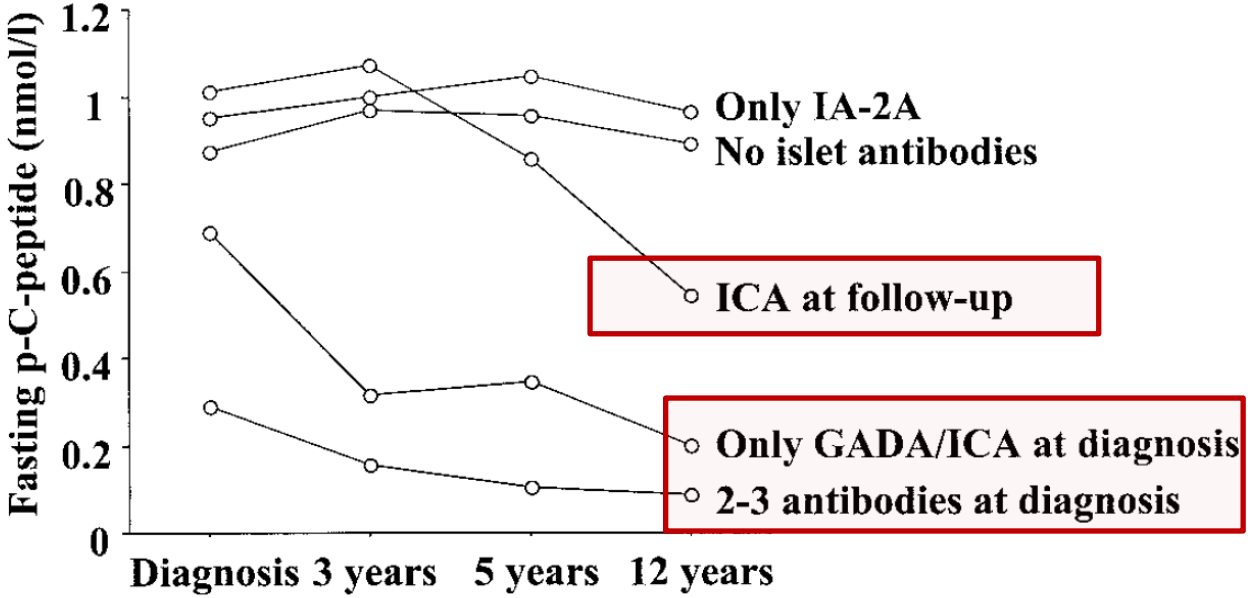
β-cell function in LADA



Stenström G et al. Diabetes 54: S68-S72, 2005.

β-cell function in LADA





Stenström G et al. Diabetes 54: S68-S72, 2005.

LADA, truly 'Latent'?

- Though not as severe as in classic type 1 diabetic patients, LADA patients have an early impairment in β-cell function. LADA is not a '**latent form**' of autoimmune diabetes.

- Hence, we favor the use of ADA (autoimmune diabetes in adults) rather than LADA for this type of patient in the future.

Stenström G et al. Diabetes 54: S68-S72, 2005.

순서

- 정의
- 역학
- 병태생리
- 한국인 데이터
- 치료
- 생각해볼 문제
- 요약, 정리

대한내과학회잡지 : 제40권 제 5 호

40세이하 한국인 당뇨병 환자의 임상적 양상

경희대학교 의과대학 내과학교실

손현석 · 윤현구 · 김성운 · 양인명
김진우 · 김영설 · 김광원 · 최영길

Son HS, et al. Korean J Med 40: 670-676, 1991.

4) ICSA 검사상 12.5%에서 양성 반응을 보였는데 이들은 모두 가족력이 없으나 비만도는 다양했으며 인슐린 분비능은 모두 증가되어 있어 이들은 아마도 인슐린 의존형 당뇨병의 초기 단계에 있는 당뇨병 환자일 것으로 생각된다.

결론적으로 15세에서 40세까지의 한국인 당뇨병 환자 중 전형적인 인슐린 비의존형과 의존형 당뇨병으로 분류될 수 있는 환자는 각각 15%, 14%이었으며 대부분의 분류하기가 어려웠던 환자에서 유전학적 연구를 포함한 더욱 자세한 연구가 필요할 것으로 생각된다.

Son HS, et al. Korean J Med 40: 670-676, 1991.

당뇨병 제 30 권 제 3 호, 2006

원 저

젊은 당뇨병환자의 원인에 따른 병형과 임상적 특징 및 경과

경희대학교 의과대학 내분비대사 내과[1], 내분비 연구소[2]

박미나[1] · 강양일[1] · 전 숙[1,2] · 오승준[1,2] · 우정택[1,2] · 김성운[2] · 김진우[1,2] · 김영설[1,2]

The Clinical Characteristics of Young Onset Diabetes According to Etiology Based Classification

Mina Park[1], Yang-Il Kang[1], Suk Chon[1,2], Seung-joon Oh[1,2], Jeong-taek Woo[1,2], Sung-Woon Kim[1,2], Jin-Woo Kim[1,2], Young-Seol Kim[1,2]

Department of Endocrinology and Metabolism[1], Endocrine Research Institute[2], College of Medicine, Kyung Hee University

Park M. et al. J Kor Diabetes Assoc 30: 190-197, 2006.

Table 1. Baseline Characteristics of Young Diabetic Patients (15~30 years) According to Etiology Based Classification

Characteristics	n = 85
M:F	40:45
Age (yrs)	24.1 ± 4.6
Disease duration (yrs)	6.8 ± 4.3
Age at diagnosis (yrs)	17.5 ± 5.3
BMI (kg/m^2)	21.7 ± 4.3
Normal (< 23)	50 (64.1%)
Overweight (23≤ <25)	10 (12.8%)
Obesity (≥ 25)	18 (23.1%)
HbA1c (%) at diagnosis	11.1 ± 2.5
Type of Diabetes Mellitus	
Type 1 DM	39 (45.9%)
Type 2 DM	20 (23.5%)
Unclassified	22 (25.9%)
Others	4 (4.7%)
Complication of Diabetes Mellitus	
Retinopathy	28 (32.9%)
Neuropathy	19 (22.4%)
Proteinuria	14 (16.4%)

* Data: mean ± SD or number (%), BMI: body mass index.

* Others: Diabetes after pancreatectomy (2) or gestational DM (2).

Park M. et al. J Kor Diabetes Assoc 30: 190-197, 2006.

Table 2. Clinical and Biochemical Characteristics of Young Diabetic Patients at Diagnosis

	T1DM(n=39)	T2DM(n=20)	Unclassified(n=22)	*P*-value
Age at diagnosis(yrs)	17.3 ± 5.7	17.9 ± 4.9	17.0 ± 4.9	ns
Family history	20 (52.6%)	12 (60%)	16 (76.2%)	ns
Disease duration(yrs)	6.48 ± 4.19	7.76 ± 4.65	5.5 ± 4.12	ns
BMI (kg/m^2)	19.9 ± 3.3	26.7 ± 3.6	20.4 ± 2.5	< 0.01
Autoantibody GADA	18 (66.7%)	1 (7.7%)	3 (21.4%)	< 0.01
IA-2A	9 (33.3%)	1 (7.7%)	3 (21.4%)	ns
ICA	1 (7.1%)	0 (0%)	2 (16.7%)	ns
C-peptide (nmol/L)	0.07 ± 0.06	0.80 ± 0.5	0.47 ± 0.23	< 0.01
ACR	0.53 ± 2.3	9.65 ± 11.6	7.04 ± 15.8	0.046
Insulinogenic index	0.02 ± 0.83	0.10 ± 0.11	0.10 ± 0.1	0.024
HbA1c (%)	11.3 ± 2.5	10.4 ± 2.3	11.7 ± 2.4	ns
T-cholesterol (mmol/L)	5.25 ± 1.73	5.44 ± 1.31	4.56 ± 1.27	ns
LDL (mmol/L)	2.81 ± 1.53	3.25 ± 1.53	2.63 ± 0.85	ns
HDL (mmol/L)	1.47 ± 0.45	0.98 ± 0.2	1.27 ± 0.45	0.02
TG (mmol/L)	1.81 ± 3.3	3.21 ± 3.0	1.25 ± 0.92	ns
Systolic BP (mmHg)	120.3 ± 16.1	123.5 ± 16.9	125.5 ± 22.6	ns
Diastolic BP (mmHg)	75.8 ± 10.2	83.5 ± 10.5	79.5 ± 13.9	ns

* Data: number (% within each type) or mean ± SD

* T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; BMI, body mass index; C-peptide, fasting C-peptide; ACR, acute c-peptide response to oral glucose (75 g) during first 30 min; Insulinogenic index, acute insulin response to oral glucose (75 g) during first 30 min; ns, not significant.

Park M. et al. J Kor Diabetes Assoc 30: 190-197, 2006.

Treatment Modality

Table 3. Treatment Modality According to the Type of DM

	Type 1 DM	Type 2 DM	Unclassified	*P*-value
Initial treatment				
Insulin	31 (86.1%)	2 (20.0%)	11 (73.3%)	
OHA	0 (0%)	3 (30.3%)	2 (13.3%)	< 0.01
Combined	5 (13.9%)	5 (50.0%)	2 (13.0%)	
Current treatment				
Insulin	25 (92.6%)	7 (38.9%)	13 (81.3%)	
OHA	0 (0%)	1 (5.6%)	2 (12.5%)	< 0.01
Combined	2 (7.4%)	10 (55.6%)	1 (6.3%)	

Park M. et al. J Kor Diabetes Assoc 30: 190-197, 2006.

The Low Prevalence of Immunogenetic Markers in Korean Adult-Onset IDDM Patients

RESULTS — The overall prevalence of anti-GAD antibodies was 1.7% (2 of 121) in patients with previously undiagnosed NIDDM, whereas 1 of 100 control subjects had a positive test for antibodies. Among those who tested positive, titers of antibodies to GAD were not high. No statistically significant differences in the distributions of either mean levels of anti-GAD antibodies or DQA1 and DQB1 alleles were found comparing NIDDM patients with control subjects. Interestingly, the frequency of DQB1*non-Asp-57 and DQA1*Arg-52 alleles in the Korean adult control population was similar to that in the U.S. white population (DQB1*non-Asp-57: 0.431 vs. 0.475; DQA1*Arg-52: 0.492 vs. 0.463).

CONCLUSIONS — The low prevalence of anti-GAD antibodies and HLA-DQA1 and DQB1 susceptibility alleles among recent-onset NIDDM patients, which was similar to observations in control subjects, suggests that diabetes in Korean adults is unlikely to have an autoimmune component to its pathogenesis.

Park YS et al. Diabetes Care 19: 241-245, 1996.

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Brief report

Identifying latent autoimmune diabetes in adults in Korea: The role of C-peptide and metabolic syndrome

Seung-Hwan Lee, Hyuk-Sang Kwon, Soon-Jib Yoo, Yu-Bai Ahn, Kun-Ho Yoon, Bong-Yun Cha, Kwang-Woo Lee, Ho-Young Son *

Division of Endocrinology and Metabolism, Department of Internal Medicine, The Catholic University of Korea, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 14 October 2008
Received in revised form
14 October 2008
Accepted 20 November 2008

ABSTRACT

We aimed to establish the prevalence and characteristics of latent autoimmune diabetes in adults (LADA) and compare it with type 2 diabetes in 1370 Korean patients. The prevalence of LADA was 5.1%. Low C-peptide level and absence of metabolic syndrome were variables independently associated with the diagnosis of LADA.

Lee SH et al. DRCP 83: e62-e65, 2009.

Table 1 – Baseline characteristics and their comparison between LADA and T2DM.

	LADA (n = 70)	T2DM (n = 1200)	p value
Age	59.7 ± 12.5	60.3 ± 14.0	0.763
Age at diagnosis	48.6 ± 10.2	48.5 ± 13.4	0.914
Sex (M/F) (%)	44.3/55.7	47.8/52.2	0.573
DM duration (months)	134.7 ± 105.7	142.1 ± 116.3	0.603
Current insulin treatment (%)	42.9	28.2	0.009
Time to insulin treatment (months)	107.1 ± 72.1	115.4 ± 101.5	0.439
Hypertension (%)	40.0	52.1	0.048
Family history of diabetes (%)	45.5	45.0	0.946
History of DKA (%)	1.6	0	0.288
Acute signs (%)*	39.1	26.0	0.017
Hypothyroidism (%)	5.5	3.0	0.208
BMI (kg/m^2)	23.1 ± 3.7	23.9 ± 3.7	0.100
Waist (cm)	85.6 ± 9.9	88.7 ± 10.3	0.032
Waist–hip ratio	0.92 ± 0.07	0.94 ± 0.08	0.021
Diabetic retinopathy (%)	33.9	42.8	0.170
Diabetic nephropathy (%)	41.4	43.7	0.714
Diabetic peripheral neuropathy (%)	30.0	35.1	0.377
HbA1c (%)	9.5 ± 2.3	9.4 ± 2.4	0.670
Fasting C-peptide (ng/mL)	1.16 ± 1.33	1.64 ± 1.48	0.009
Stimulated C-peptide (ng/mL)	2.35 ± 2.28	3.46 ± 2.73	0.001
GAD antibody (u/mL)	1.43 (0.04, 83.89)	0.07 (0.01, 1.35)	0.0004
IA-2 antibody (u/mL)	0.13 (0.01, 20.19)	0.07 (0.00, 1.28)	0.012
Total cholesterol (mg/dL)	175.1 ± 51.9	178.3 ± 45.9	0.581
Triglyceride (mg/dL)	123.9 ± 76.1	163.0 ± 128.4	0.0001
HDL-cholesterol (mg/dL)	46.5 ± 13.0	43.4 ± 13.4	0.060
LDL-cholesterol (mg/dL)	104.1 ± 47.7	103.9 ± 37.4	0.978
Metabolic syndrome (%)	47.1	72.9	<0.0001

Values are expressed as means ± SD or percentage except for GAD and IA-2 antibody, which is median (minimum, maximum). LADA: latent autoimmune diabetes in adults, T2DM: type 2 diabetes, DM: diabetes mellitus, DKA: diabetic ketoacidosis, BMI: body mass index, GAD: glutamic acid decarboxylase, IA-2: insulinoma-associated protein 2, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

* Polyuria/polydipsia or acute weight loss at the time of diagnosis.

Lee SH et al. DRCP 83: e62-e65, 2009.

Table 2 – The relationship of variables with the diagnosis of LADA using logistic regression analysis.

		Odds ratio (95% CI)*	*p* value
Simple logistic regression	Age at diagnosis	1.001 (0.983, 1.019)	0.932
	Current insulin treatment	1.912 (1.171, 3.120)	0.010
	Time to insulin treatment	0.999 (0.996, 1.002)	0.564
	Hypertension	0.612 (0.374, 1.001)	0.050
	Acute signs†	1.826 (1.107, 3.011)	0.018
	Waist	0.971 (0.944, 0.998)	0.034
	Waist–hip ratio	0.030 (0.001, 1.043)	0.053
	BMI	0.943 (0.880, 1.011)	0.099
	HbA1c	1.022 (0.924, 1.130)	0.673
	Fasting C-peptide	0.721 (0.568, 0.916)	0.007
	Stimulated C-peptide	0.805 (0.707, 0.917)	0.001
	Log(IA-2 antibody)	2.099 (1.714, 2.572)	<0.0001
	Log(GAD antibody)	9.508 (6.217, 14.542)	<0.0001
	Triglyceride	0.996 (0.992, 0.999)	0.009
	HDL-cholesterol	1.016 (0.999, 1.033)	0.060
	Metabolic syndrome	0.353 (0.215, 0.580)	<0.0001
Multiple logistic regression	Age at diagnosis	1.015 (0.995, 1.036)	0.152
	Acute signs†	1.625 (0.956, 2.763)	0.073
	BMI	1.003 (0.928, 1.085)	0.933
	Stimulated C-peptide	0.841 (0.734, 0.964)	0.013
	Metabolic syndrome	0.438 (0.249, 0.771)	0.004

BMI: body mass index, IA-2: insulinoma-associated protein 2, GAD: glutamic acid decarboxylase, HDL: high-density lipoprotein.

* Odds ratio for classifying diabetes as LADA compared with T2DM.

† Polyuria/polydipsia or acute weight loss at the time of diagnosis.

Lee SH et al. DRCP 83: e62-e65, 2009.

Acta Diabetol (2013) 50:129–134
DOI 10.1007/s00592-010-0228-y

ORIGINAL ARTICLE

The prevalence and characteristics of latent autoimmune diabetes in adults (LADA) and its relation with chronic complications in a clinical department of a university hospital in Korea

Mi-Oh Roh · Chan-Hee Jung · Bo-Yeon Kim · Ji-Oh Mok · Chul-Hee Kim

Received: 18 June 2010 / Accepted: 29 September 2010 / Published online: 16 October 2010

Roh M, et al. Acta Diabetol 50: 129-134, 2013.

Table 3 Characteristics and prevalence of diabetes chronic complications in subgroups

	T1DM (n = 37)	LADA (n = 17) 5.2%	T2DM (n = 268)	P value
Age (years)	29.0 ± 10.7	40.2 ± 14.0	48.7 ± 16.1	<0.001
BMI (kg/m^2)	20.5 ± 4.4	21.5 ± 6.2	24.7 ± 3.7	<0.001
GAD Ab titer (U/ml)	0.08 (0.01–91.9)	6.0 (1.5–114.85)	0.07 (0.01–1.41)	<0.001
Onset age (years)	26.1 ± 11.4	32.8 ± 8.1	44.6 ± 13.8	<0.001
Duration of DM (years)	0.5 (0–19)	4 (0–17)	1 (0–43)	0.160
Systolic BP (mmHg)	119.8 ± 15.3	129.0 ± 20.7	131.4 ± 16.3	0.004
Diastolic BP (mmHg)	73.5 ± 10.6	78.5 ± 13.7	83.0 ± 11.7	0.001
Fasting plasma glucose (mg/dL)	200.9 ± 82.0	193.5 ± 59.5	180.9 ± 79.0	0.430
HbA1C (%)	12.3 ± 3.0	10.4 ± 2.8	9.4 ± 2.5	<0.001
Total cholesterol (mg/dL)	186 (55–586)	163 (79–245)	183 (78–439)	0.264
Triglyceride (mg/dL)	111 (29–464)	94 (43–173)	139 (52–511)	0.175
HDL-C (mg/dL)	50.0 ± 17.8	43.4 ± 13.2	44.0 ± 16.1	0.218
LDL-C (mg/dL)	109.1 ± 51.7	88.3 ± 23.8	107.1 ± 41.7	0.300
Microalbumin (μg/ml)	9.71 (0.8–174.8)	6.20 (1.86–100.86)	8.93 (0.04–382)	0.666
C-Peptide (fasting) (ng/ml)	0.33 (0.01–2.13)	0.39 (0.01–9.67)	2.18 (0.01–14.3)	<0.001
C-Peptide (stimulated) (ng/ml)	0.83 (0.01–7.22)	0.62 (0.01–8.64)	5.33 (0.01–28.2)	<0.001
Nephropathy [n(%)]	5 (14.3)	2 (13.3)	51 (21.0)	0.527
Neuropathy [n(%)]	13 (44.8)	7 (58.3)	73 (42.4)	0.557
Retinopathy [n(%)]	7 (20.0)	3 (20.0)	48 (25.5)	0.720

Values are expressed as mean ± SD, median (IQR), or percentage

GADA glutamic acid decarboxylase antibody, *BMI* body mass index, *HDL-C* high-density lipoprotein-cholesterol, *LDL-C* low-density lipoprotein-cholesterol

Roh M, et al. Acta Diabetol 50: 129-134, 2013.

Table 4 The relationship of variables with the low remaining beta cell function using logistic regression analysis

	Odds ratio (95% CI)	*P* value
GADA positivity	6.99 (1.89–25.82)	0.004
Duration of DM	1.034 (0.96–1.11)	0.394
Onset age	0.967 (0.93–1.00)	0.082
HbA1C	1.28 (1.04–1.59)	0.022
BMI	0.88 (0.78–0.99)	0.028

GADA glutamic acid decarboxylase antibody, *BMI* body mass index

Roh M, et al. Acta Diabetol 50: 129-134, 2013.

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2011; **27:** 975–979.
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/dmrr.1278

RESEARCH ARTICLE

LADA prevalence estimation and insulin dependency during follow-up

Yongsoo Park[1]*
Sangmo Hong[1]
Leejin Park[1]
Jungtaek Woo[2]
Sehyun Baik[3]
Munsuk Nam[4]
Kwanwoo Lee[5]
Youngseol Kim[2] and on behalf of The KNDP collaboratory Group

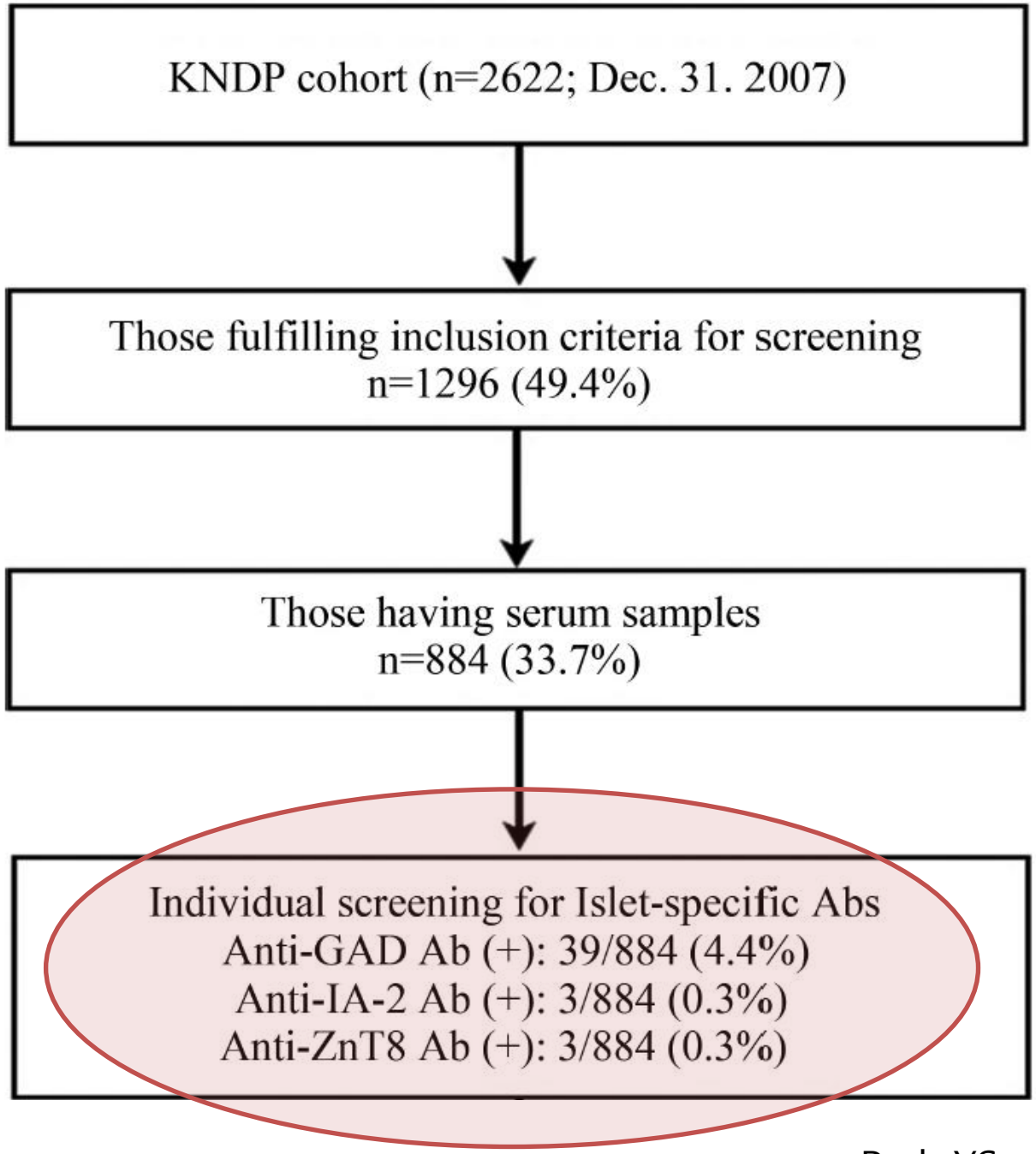
[1]*Department of Internal*

Abstract

Background Latent autoimmune diabetes in adults (LADA) is a form of autoimmune-mediated diabetes in adults, usually defined by GAD autoantibody positivity. Few epidemiological surveys on LADA in Asians did not come to a conclusive answer regarding prevalence and incidence, because of different criteria used in patient ascertainment.

Methods We estimated LADA prevalence in a recent type 2 diabetes cohort by the positivity of circulating autoantibodies to pancreatic islet cell antigens (GAD, IA-2 and zinc transporter 8 (ZnT8)) applying a comparable Caucasian criteria. We then observed the development of insulin dependency prospectively for 36 months.

Park YS et al. DMRR 27: 975-979, 2011.



Park YS et al. DMRR 27: 975-979, 2011.

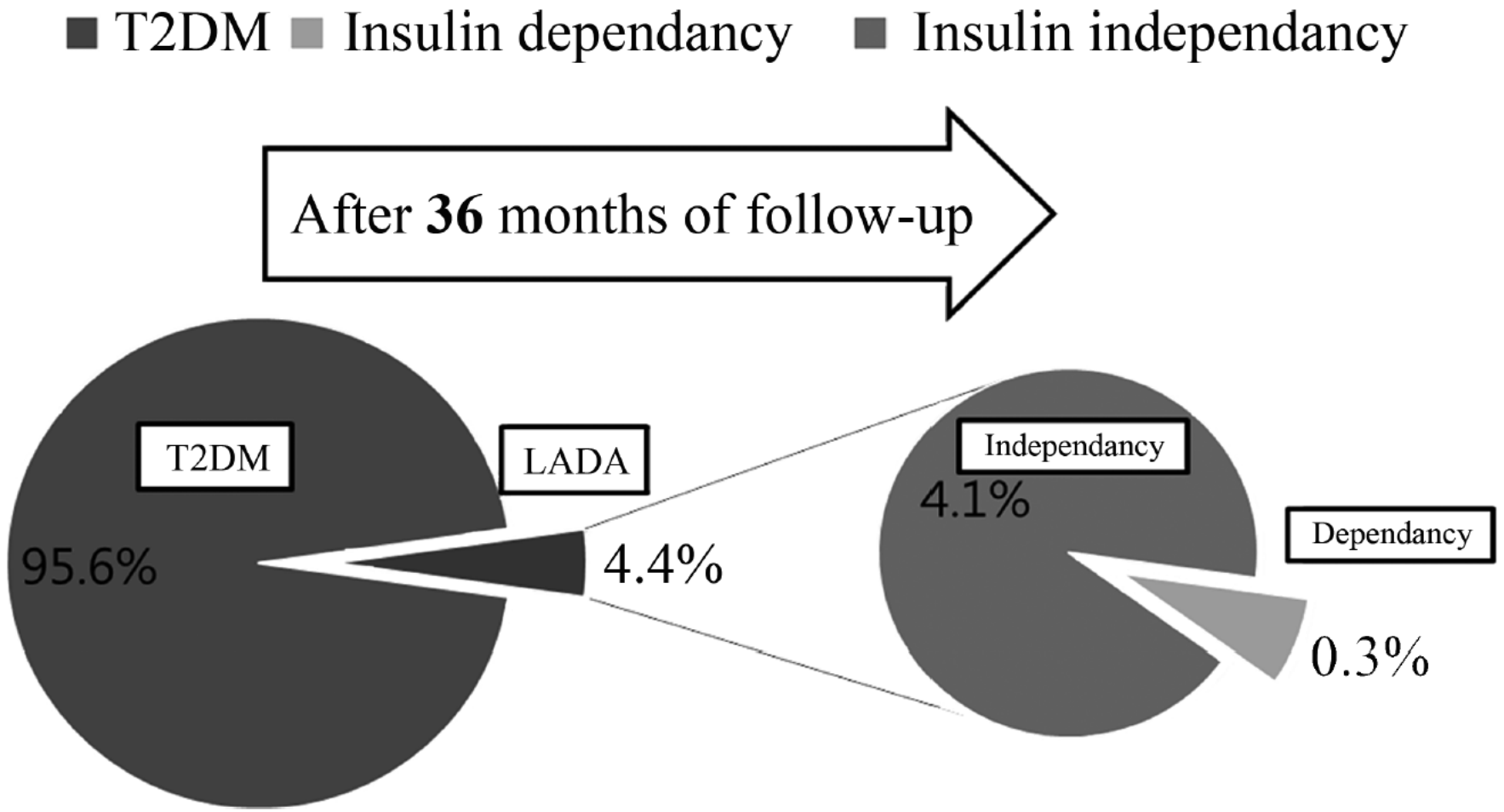
Table 1. The comparisons between the latent autoimmune diabetes in adults patients and type 2 diabetes patients

	Latent autoimmune diabetes in adults (+)	Latent autoimmune diabetes in adults (−)	*p*-value
Number	39	845	
Sex (male/female)	(19/20)	(543/392)	ns
Age (years)	51.9 ± 7.9	52.3 ± 8.7	ns
Duration (years)	1.83 ± 1.75	2.08 ± 1.77	ns
Body mass index (kg/m^2)	25.3 ± 3.1	25.3 ± 3.1	ns
Waist hip ratio	1.12 ± 0.76	1.10 ± 0.83	ns
Systolic blood pressure (mmHg)	123.4 ± 17.8	123.4 ± 14.0	ns
Diastolic blood pressure (mmHg)	77.9 ± 10.3	78.5 ± 11.9	ns
Fasting blood sugar (mg/dL)	126.1 ± 29.6	142.9 ± 49.7	0.005
Haemoglobin A1c (%)	6.9 ± 1.0	7.5 ± 1.9	0.003
Total cholesterol (mg/dL)	194.9 ± 29.3	188.5 ± 40.6	ns
Family history of diabetes (%)	50	44	ns
Oral hypoglycaemia agent medication (%)	75.7	73.7	ns
Cardiovascular risk factors (%)	74.3	64.5	ns
Aspartate transaminase	25.9 ± 13.2	27.2 ± 22.9	ns
Alanine transaminase	27.5 ± 20.3	31.0 ± 28.8	ns
Gamma-glutamyl transpeptidase	45.4 ± 44.0	58.5 ± 125.9	ns
High-sensitivity C-reactive protein	0.7 ± 0.73	4.1 ± 27.9	0.004
Insulin (μg/dL)	9.3 ± 5.9	8.9 ± 13.4	ns
Homeostatic model assessment of insulin resistance	2.95 ± 2.15	3.19 ± 5.37	ns

ns, not significant

Park YS et al. DMRR 27: 975-979, 2011.

LADA Prevalence Estimation and Insulin Dependency



Park YS et al. DMRR 27: 975-979, 2011.

Insulin dependency and Auto-Ab titer

Table 2. Comparison of the mean titres of islet-specific antibodies between those who progressed into insulin dependency and those who did not during follow-up

	GAD	Zinc transporter 8 antibody	IA-2
Insulin dependency ($n = 3$)	0.071 ± 0.032	0.070 ± 0.047	0.100 ± 0.031
Insulin independency ($n = 36$)	0.029 ± 0.022	-0.007 ± 0.023	-0.001 ± 0.025
p-Value	0.036	0.011	0.005

Park YS et al. DMRR 27: 975-979, 2011.

한국인 특성?

- 비 비만형 phenotype, 큰 차이 없음
- Prevalence of Autoantibodies
- Insulin dependency ↓
- Prevalence 증가 예상

순서

- 정의
- 역학
- 병태생리
- 한국인 데이터
- 치료
- 생각해볼 문제
- 요약, 정리

General treatment strategy

- Diet treatment in LADA is similar
- Obese LADA patients benefit
  - calorie restriction and increased physical activity.
- Issues from glibenclamide
  - promote the autoimmune process ??
- Thiazolidinediones seem to prevent diabetes

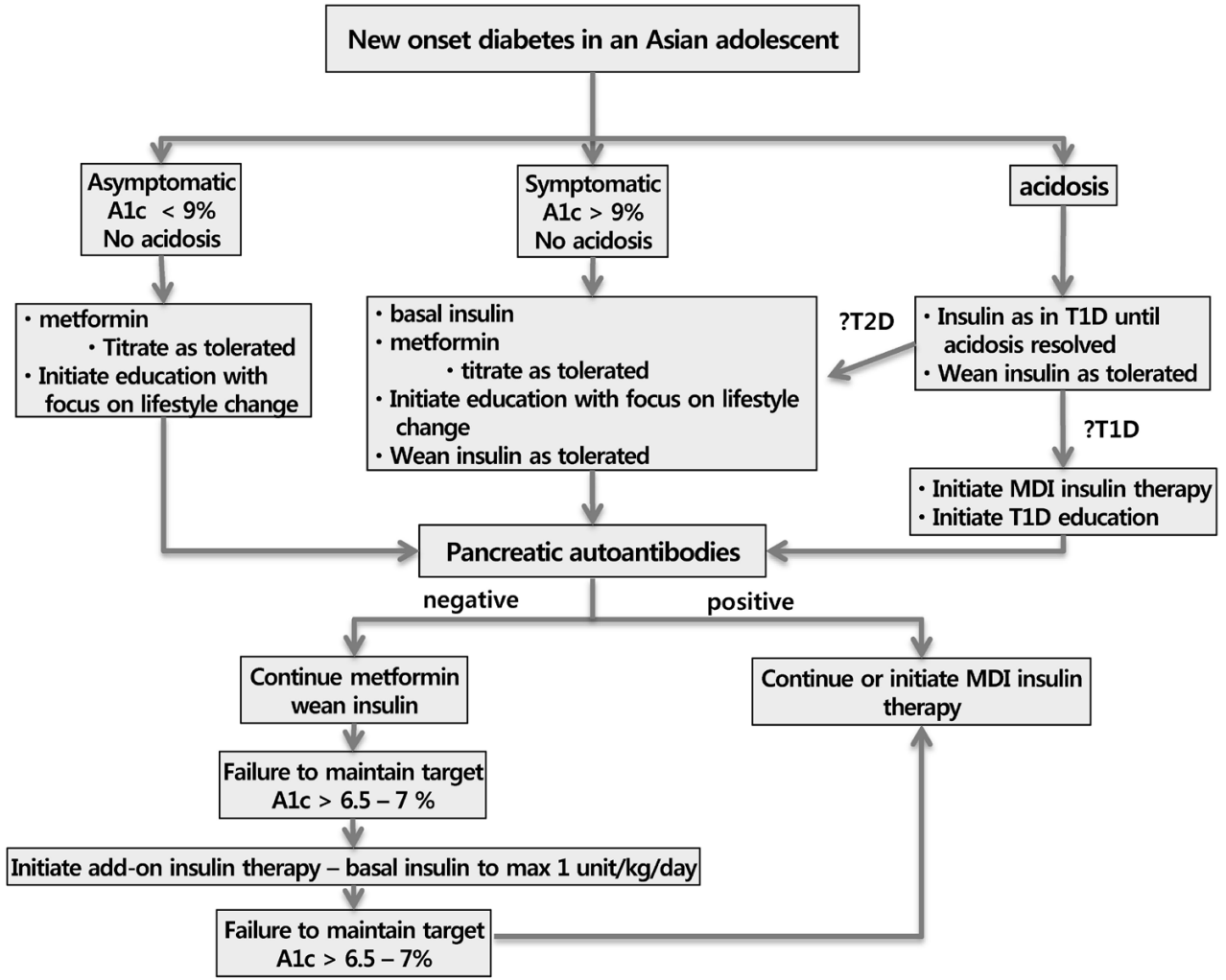
Stenström G et al. Diabetes 54: S68-S72, 2005.

General treatment strategy

- Metformin is probably useful
  - Esp. in obese patients.
- Insulin therapy is the treatment of choice.
  - β-cell function is impaired at diagnosis of LADA patients, irrespective of the clinical phenotype.
  - Early insulin treatment may improve β-cell dysfunction
  - no reason to postpone the commencement of insulin

Stenström G et al. Diabetes 54: S68-S72, 2005.

Approach to the treatment of the Asian adolescent with diabetes



Park YS. J Korean Diabetes 15: 190-195, 2014.

Antigen-specific intervention trials in T1DM

Table 59.6 Antigen-specific intervention trials in T1DM. Adapted from Staeva-Vieira *et al.* [94].

Trial name	Agent	Type of trial	Description	Outcome
DiaPep77 (HSP60)	Subcutaneous peptide heat shock protein 60	R, PC, DB, PA, ET	An immunomodulatory peptide proposed to protect internal production of insulin through halting β-cell killing	Preserved β-cell over 12–18 months in adults. No similar effect in children Phase III (DIA-AID) is ongoing NCT00615264
Alum-GAD (Diamyd®)	Alhydrogel-formulated GAD65 20 μg s.c.	R, PC, DB, PA, ET	Immuno-modulation effect in LADA (Phase IIa) and 10–18 years old with new-onset T1DM (Phase IIb)	Preserved β-cell and C-peptide levels in patients with <6 months onset Phase III ongoing NCT00723411
NBI-6024	Altered peptide ligand insulin B:9–23 vaccine s.c.	R, DB, PC, PA, ET	Multinational trial used a genetically engineered peptide in adolescents (10–17 years) and adults (18–35 years) with new onset T1DM	Completed NCT00873561
BHT-3021	Pro-insulin-based DNA vaccine weekly i.m. inj./12 weeks	R, DB, PC, OL, CO	Assesses safety in ≥18-year-old patients with T1DM: 12 months blinded treatment, 12 months cross-over and 12 months follow-up	Ongoing NCT00453375

CO, cross-over; DB, double blinded; ET, efficacy trial; i.m. inj., intramuscular injection; LADA, latent autoimmune diabetes of adults; OL, open label; PA, parallel assignment; PC, placebo controlled; R, randomized; RC, randomized controlled; s.c subcutaneous.
For further details, see clinical trial identifier: http://www.clinicaltrials.gov/ct2/search.

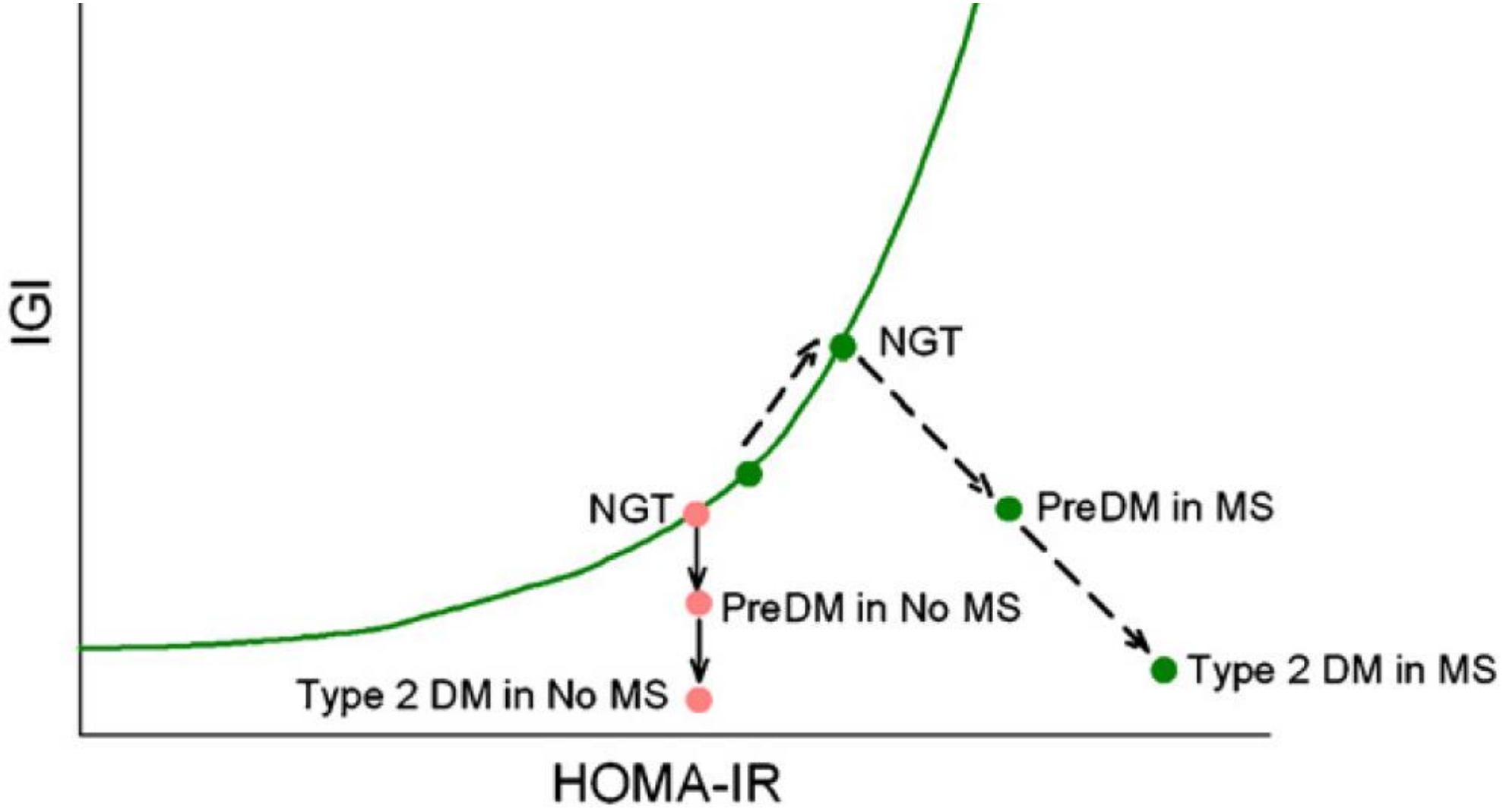
Holt RIG, et al. Textbook of Diabetes,4th ed.

순서

- 정의
- 역학
- 병태생리
- 한국인 데이터
- 치료
- 생각해볼 문제
- 요약, 정리

인슐린 분비 감소가 당뇨병 발생에 가장 중요

Korean Data (n=322)



Rhee SY et al. DRCP 76: 397-403, 2007.

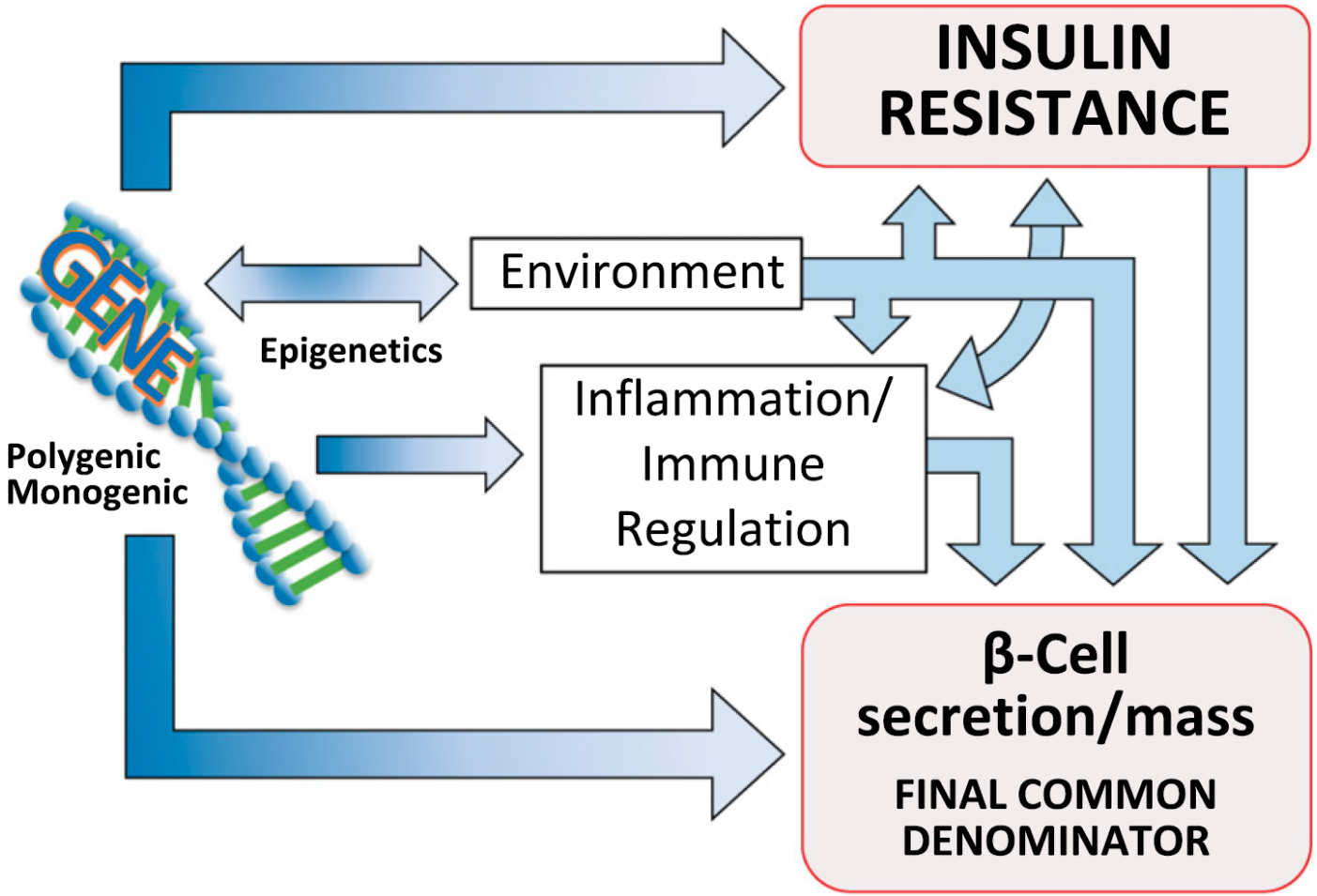
The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-Cell–Centric Classification Schema

Stanley S. Schwartz,[1] Solomon Epstein,[2] Barbara E. Corkey,[3] Struan F.A. Grant,[4] James R. Gavin III,[5] and Richard B. Aguilar[6]

Diabetes Care 2016;39:179–186 | DOI: 10.2337/dc15-1585

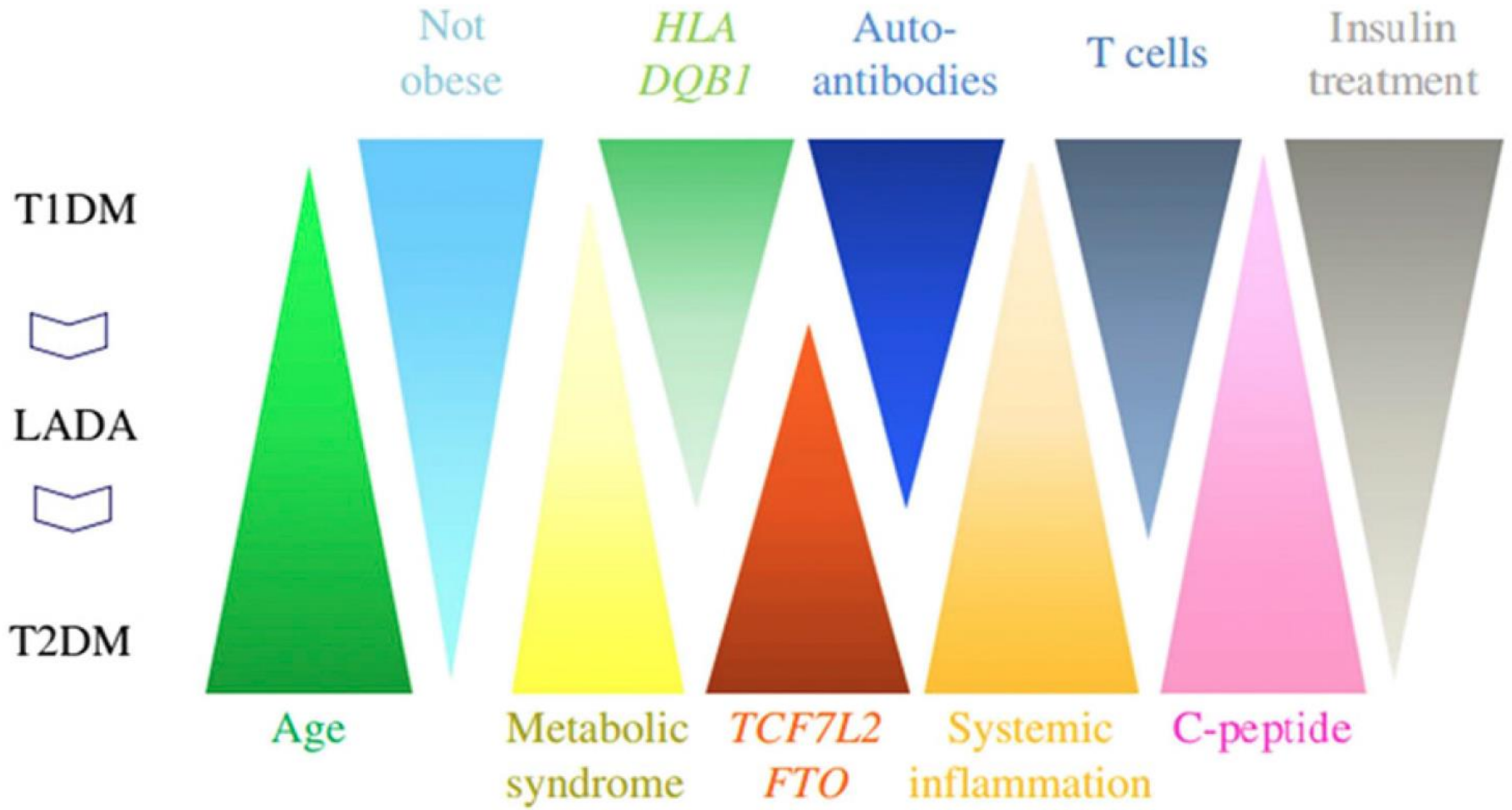
SS Schwartz, et al. Diabetes Care 39: 179-186, 2016.

Dysfunctional β-cell: the final common denominator in all DM



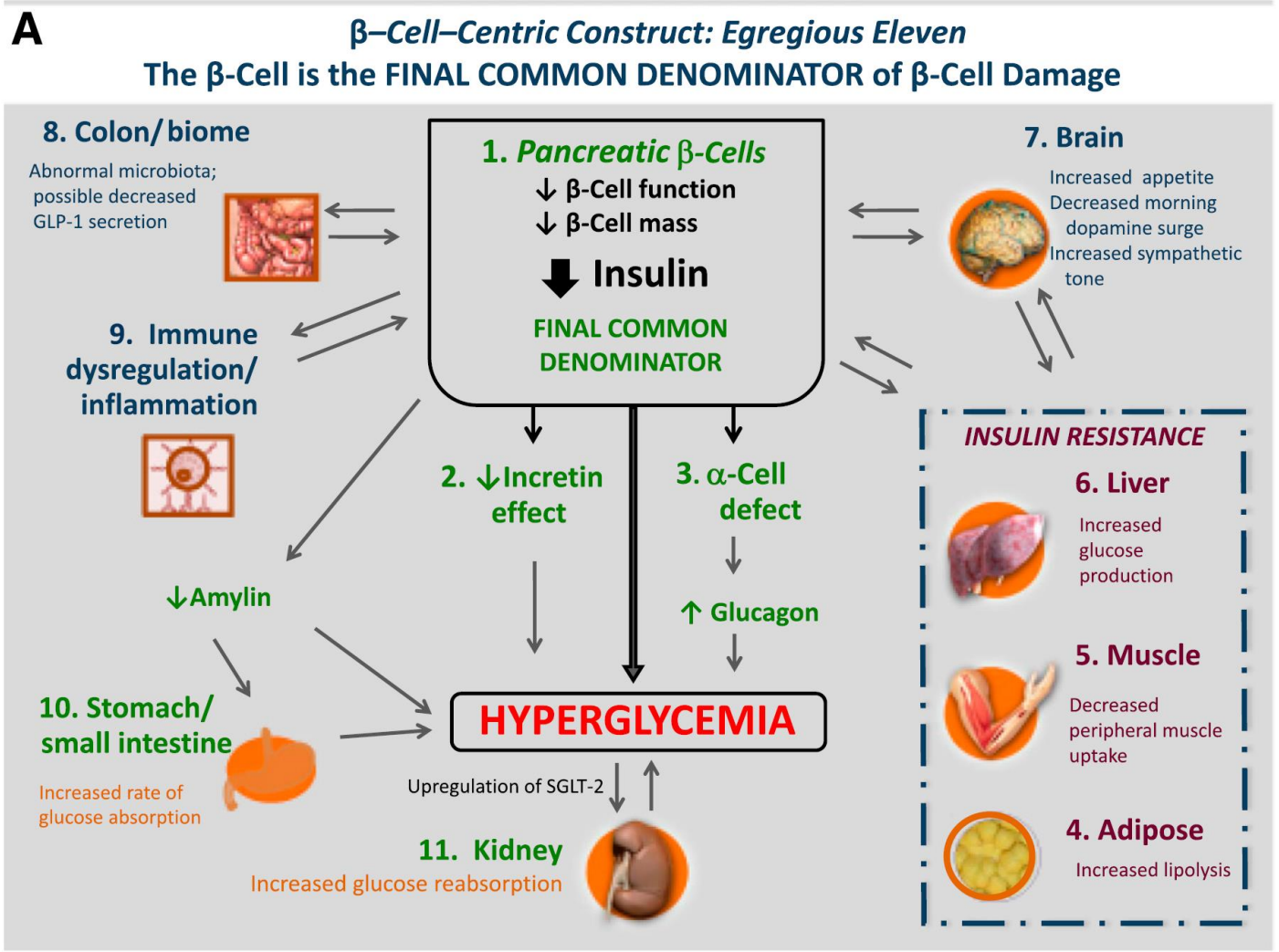
SS Schwartz, et al. Diabetes Care 39: 179-186, 2016.

Spectrum of factors associated with different forms of DM



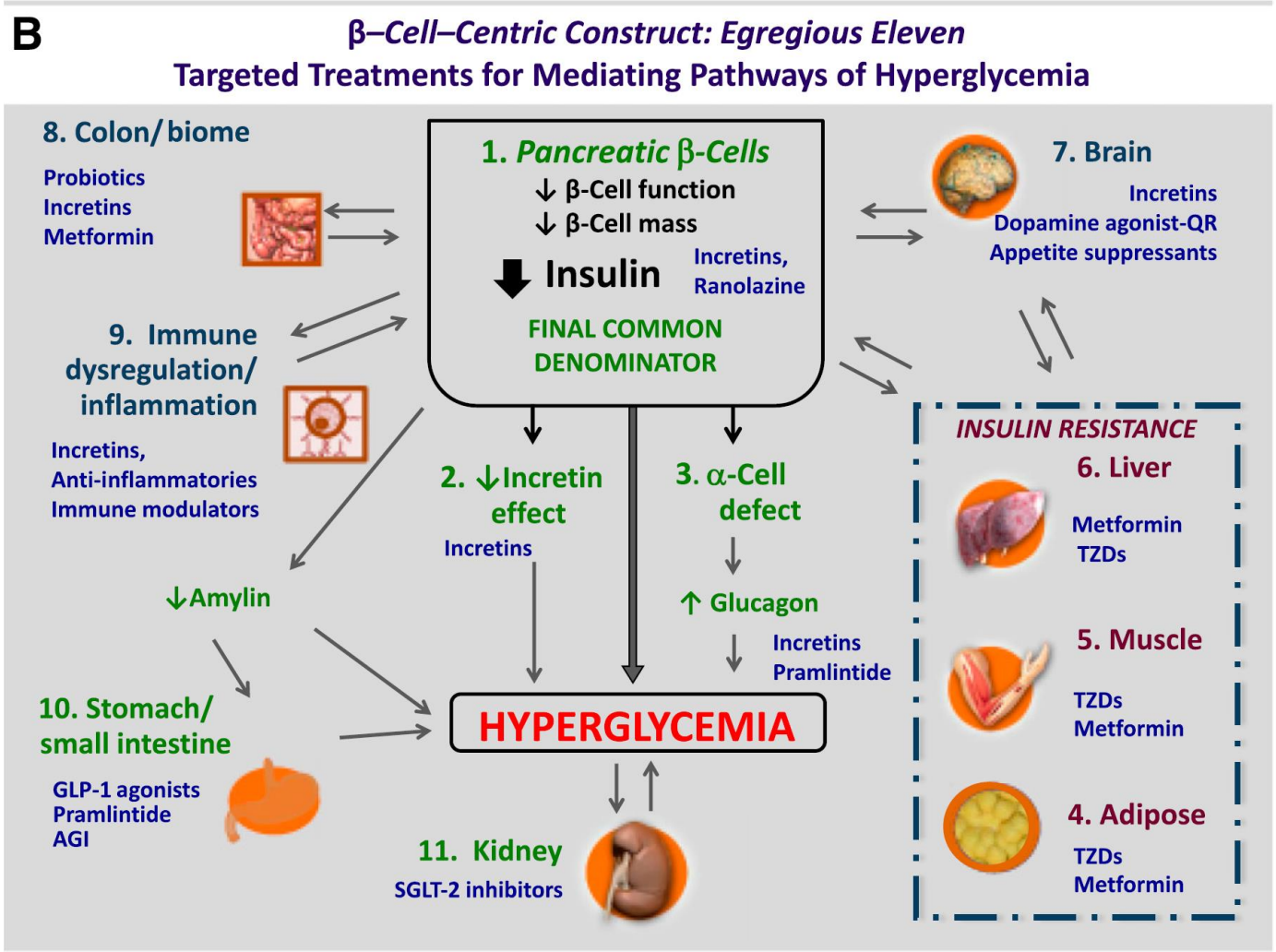
SS Schwartz, et al. Diabetes Care 39: 179-186, 2016.

Egregious Eleven



SS Schwartz, et al. Diabetes Care 39: 179-186, 2016.

Targeted Treatment Strategy



SS Schwartz, et al. Diabetes Care 39: 179-186, 2016.

요약 및 정리

- 정의
- 역학
- 병태생리
- 한국인 데이터
- 치료
- 생각해볼 문제


경청해주셔서 감사합니다