A Whole LADA Love: Epidemiology, Overlap and Outcomes

Richard E. Pratley, M.D.

Samuel Crockett Chair in Diabetes Research
Medical Director, AdventHealth Diabetes Institute
Senior Scientist and Diabetes Program Head,
AdventHealth Translational Research Institute
Adjunct Professor, Johns Hopkins School of Medicine
Orlando, Florida

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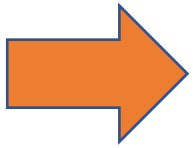
Disclosures

- Advisory Board/Consultant: AstraZeneca, GlaxoSmithKline, Glytec LLC, Janssen, Ligand, Lilly, Merck, Mundipharma, Novo Nordisk, Sanofi.
- Speaker: AstraZeneca, Novo Nordisk.
- Research Support: Lexicon, Ligand, Lilly, Merck, Novo Nordisk, Sanofi.



All honoraria directed toward a non-profit which supports education and research

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Who are these chaps?

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“Whole Lotta Love”

- Led Zeppelin's first US single
- Released in 1969 on their second album
- Their only US Top-10 hit
- Jimmy Page played the Blues riff on a Sunburst 1958 Les Paul Standard

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Willie Dixon

- Born: Jul 1, 1915 in Vicksburg, MS
- Studied music with a local carpenter
- Worked as a session musician with Muddy Waters
- Wrote a number of blues standards
- Sued Led Zepplin for copyright infringement over "Whole Lotta Love" and its resemblance to Dixon's "You Need Love."
- Developed diabetes, lost a leg
- Died Jan 29, 1992 in Burbank, CA

Key takeaway

When you dig deeper, it gets confusing…

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ADA Classification of Diabetes

- Type 1 diabetes
  - Autoimmune β-cell destruction
  - Thin children
  - Acute presentation
- Type 2 diabetes
  - Insulin resistance and insulin secretory defect
  - Heavy adults
  - Subacute
- Other specific types of diabetes
  - Genetic defects in β-cell function, insulin action
  - Diseases of the exocrine pancreas
  - Drug- or chemical-induced
- Gestational diabetes mellitus (GDM)

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S11.

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Case Presentation

- 55 y.o. male who self-referred for eval of DM
- FPG of 110 at annual physical
- SMBG 120-130 range
- No family history of DM
- Physical Exam
  - BMI 24 kg/m^2
  - BP 114/64
  - Otherwise normal
- Labs
  - FPG 130
  - A1c 7.2%
  - Normal TC, TG, HDL, LDL, LFTs and renal function
  - **GAD 2.7 (normal 0.0-0.02)**

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LADA Clinical Presentation

- Presents as “type 2 diabetes”
- Older than 30-35 y
- May be non-obese
- Initially diet-controlled or oral meds
- Progress relatively quickly to insulin requiring

Questions

- How is LADA defined?
- How common is LADA?
- How is LADA different from T1D?
- What's the natural history?
- What do we know about outcomes?

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LADA Definition – Immunology of Diabetes Society

- Age > 30 y
- Positive for at least 1 autoantibody
  - GAD65, IA-2, ICA, Insulin
- Not insulin requiring for at least 6 months after diagnosis

Palmer J, Hirsch I. Diabetes Care 26:536-538,2003

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Questions

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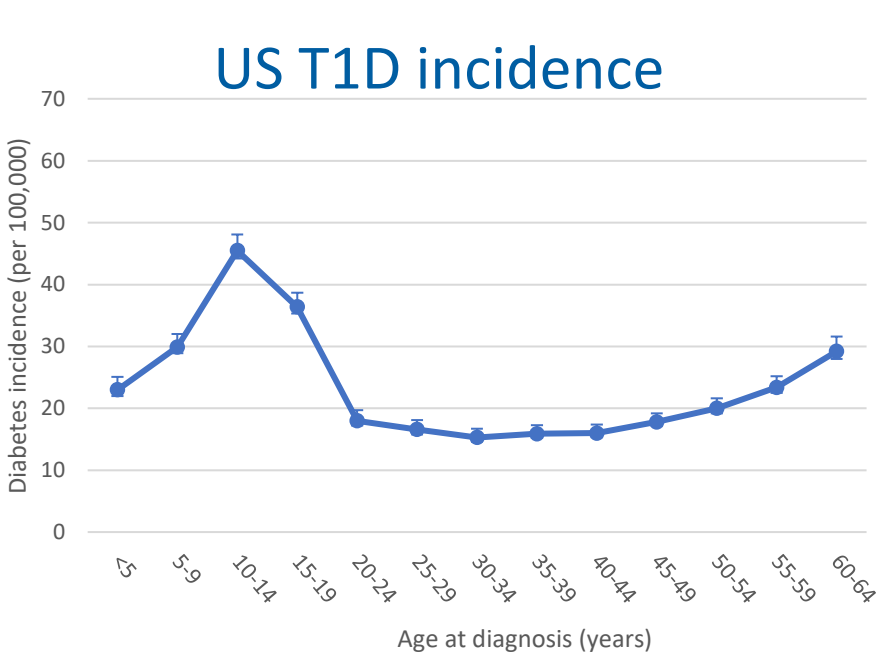
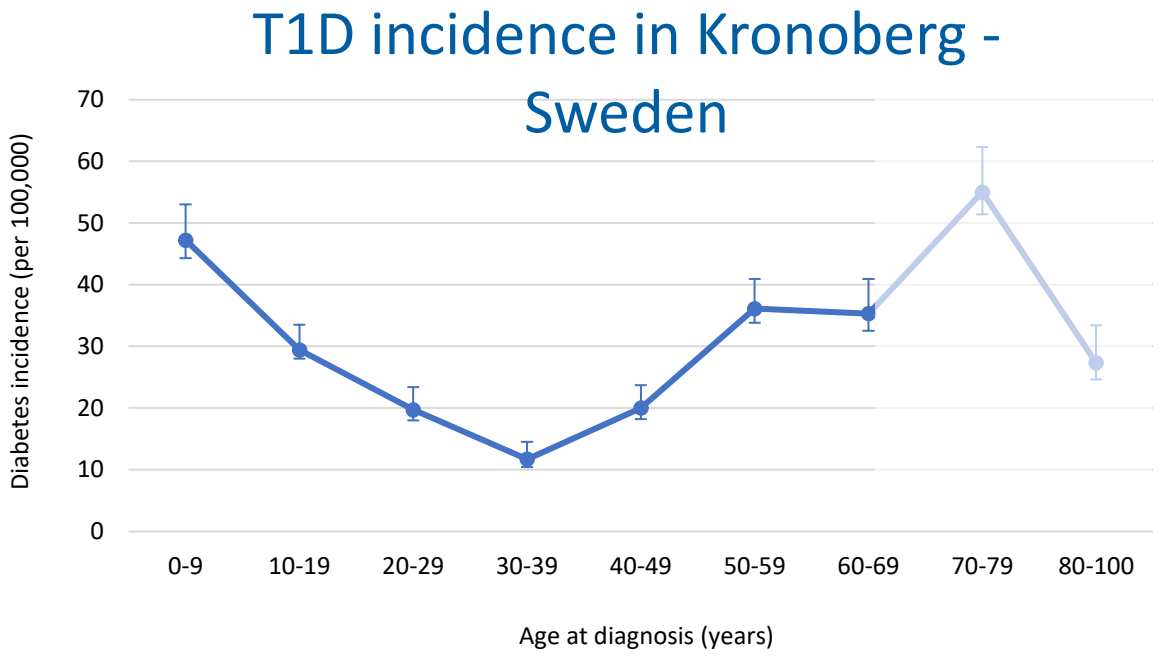
Autoimmune diabetes - epidemiology





Higher prevalence in Caucasians.
4.5-23% have DKA at onset.

M.A.M. Rogers et al. BMC Medicine 2017; 15: 199-208
M. Thunander et al. Diabetes Research and Clinical practice 82 (2008): 247-55

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Adult onset T1D - definition

Diagnostic criteria of LADA

- Age >30
- Not requiring insulin for 6-12 months (questionable as insulin treatment is proposed more often in those centers with GAD testing available – Brophy 2008)
- IAAb positive – usually GAD Ab
- C-peptide (if considered as a diagnostic criteria fasting levels >0.3nmol/l)

Location	Sample size	Ab Type	Age (years)	Ab positivity (%)
UK	3670	GAD IA-2	25-65	12
Finland	1122	GAD IA-2	28-83	9.3
US/Europe	4357	GAD IA-2	30-75	4.2
Italy	5330	GAD IA-2	30-75	4.5
Norway	1134	GAD	>20	10
Sardinia	5568	GAD	35-70	4.9
China	5324	GAD	>20	5.9
Europe	6810	GAD IA-2 ZnT8	30-70	9.7

Brophy S et al. Diabetes Care 2008; 31: 439-441
Buzzetti et al. Nature Rev Endo 2017

Adult onset (20-45 y) autoimmune DM– California

- Kaiser Permanente Southern California and Kaiser Permanente Northern California EMR
- Diabetes incidence in 2017 among patients aged 20-45 years followed by the KP system for at least 1 year.
- Islet autoantibody testing was offered to all the patients with a new diagnosis of diabetes.
- 7,862 newly diagnosed diabetes cases were identified. 2,063 consented to be tested for islet autoAbs.

Ab Type	Prevalence
GAD65 Ab	6.1%
IA-2 Ab	2.0%
ZnT8 Ab	1.7%
mIAA (less than 2 weeks from starting insulin treatment)	2.2%
ICD-10 T1D diagnosis	1.6%

N of Islet Abs	Prevalence
0	92.0%
1	5.6%
2	1.2%
3	1.2%
4	0.1%
Any	8.1%

J.M. Lawrence et al. Diabetes Research and Clinical Practice (2021) 171: 108624 PMID: 33338552

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Islet Autoantibody Positive Patients in “T2D” Studies

C-Peptide Levels in Latent Autoimmune Diabetes in Adults Treated With Linagliptin Versus Glimepiride: Exploratory Results From a 2-Year Double-Blind, Randomized, Controlled Study

Odd Erik Johansen,[1] Bernhard O. Boehm,[2,3] Valdemar Grill,[4] Peter A. Torjesen,[5] Sudipta Bhattacharya,[6] Sanjay Patel,[7] Kristiane Wetzel,[6] and Hans-Juergen Woerle[1]

Diabetes Care 2014;37:e11–e12 | DOI: 10.2337/dc13-1523

Latent autoimmune diabetes in adults (LADA) is a slowly progressing form of immune-mediated diabetes often misdiagnosed as type 2 diabetes because of its typical clinical presentation, i.e., an adult without weight loss or ketoacidosis not initially requiring insulin (1). Prior to insulin dependence, pharmacological options for reducing hyperglycemia comprise the oral glucose-lowering drugs used in type 2 diabetes; however, none has been established as the drug of choice in LADA because of the scarcity of evidence for or against the various agents (2).

This study was a prespecified, exploratory analysis of a large (n = 1,519) trial in which patients diagnosed

obtained at baseline and weeks 26, 52, and 104. Antibodies to GAD65 were detected using radioimmunoassay (Oslo University Hospital in-house assay using translation-labeled GAD); an antibody index of ≥0.05 was considered positive and provided a sensitivity of 82% and specificity of 99% (Diabetes Autoantibody Standardization Program 2010).

Plasma samples from 1,505, 862, 436, and 327 patients were tested for GAD, islet cell cytoplasm, IA-2A, and IAA, respectively, and 118 (7.8%) were identified as having LADA. GAD65 was the most prevalent autoantibody (99 patients, 6.5%). At baseline, GAD65-positive linagliptin patients

potential at decline in C-per els with linagliptin include a β-cell–protective effect through elevation of endogenous glucagon-like peptide 1 (GLP-1) (4), and/or non-GLP-1–related mechanisms through modulation

6.5% GAD65+

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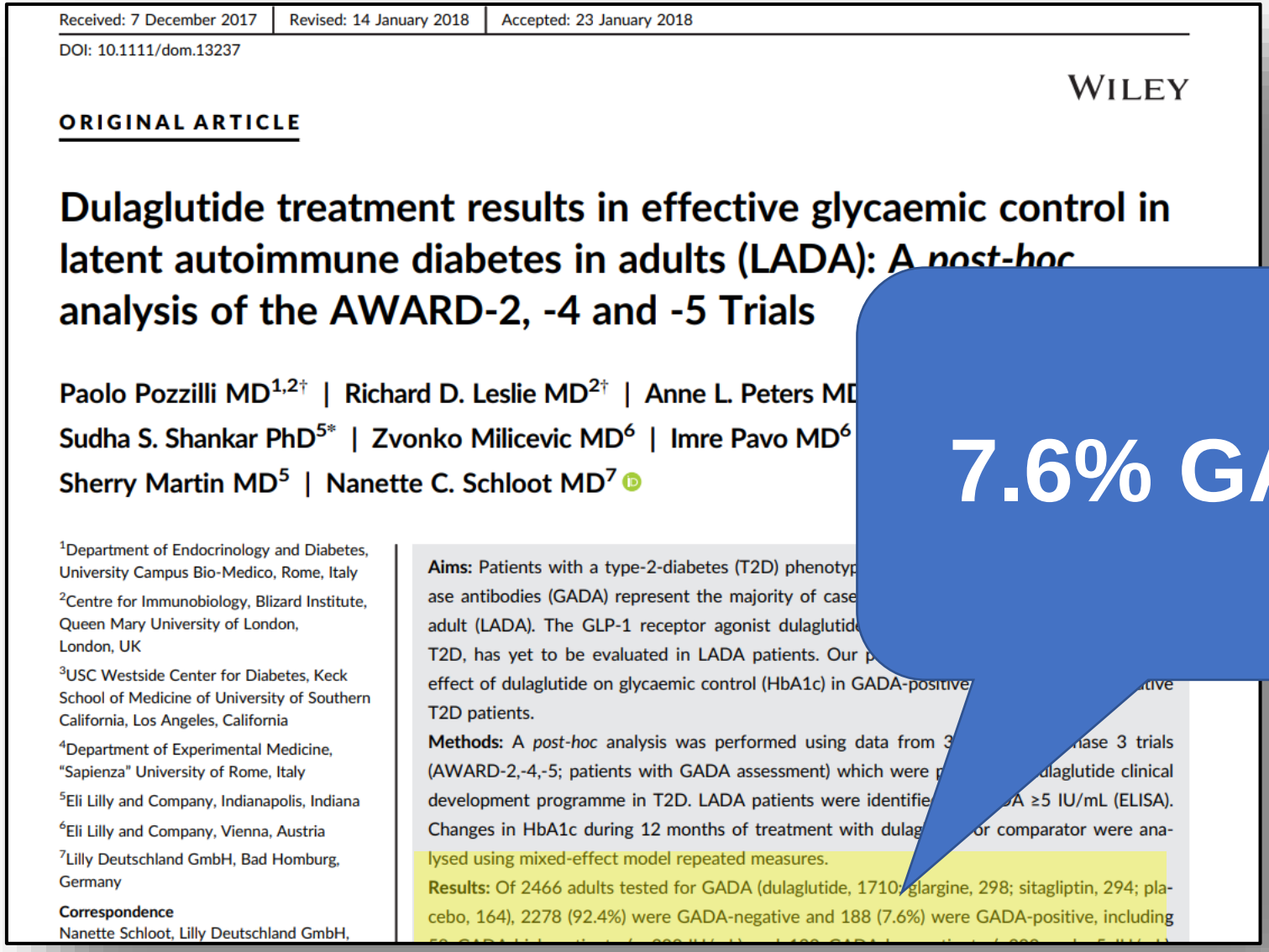
Islet Autoantibody Positive Patients in “T2D” Studies



Received: 7 December 2017 | Revised: 14 January 2018 | Accepted: 23 January 2018

DOI: 10.1111/dom.13237

WILEY

ORIGINAL ARTICLE

Dulaglutide treatment results in effective glycaemic control in latent autoimmune diabetes in adults (LADA): A *post-hoc* analysis of the AWARD-2, -4 and -5 Trials

Paolo Pozzilli MD[1,2†] | Richard D. Leslie MD[2†] | Anne L. Peters MD

Sudha S. Shankar PhD[5*] | Zvonko Milicevic MD[6] | Imre Pavo MD[6]

Sherry Martin MD[5] | Nanette C. Schloot MD[7]

[1]Department of Endocrinology and Diabetes, University Campus Bio-Medico, Rome, Italy

[2]Centre for Immunobiology, Blizard Institute, Queen Mary University of London, London, UK

[3]USC Westside Center for Diabetes, Keck School of Medicine of University of Southern California, Los Angeles, California

[4]Department of Experimental Medicine, “Sapienza” University of Rome, Italy

[5]Eli Lilly and Company, Indianapolis, Indiana

[6]Eli Lilly and Company, Vienna, Austria

[7]Lilly Deutschland GmbH, Bad Homburg, Germany

Correspondence
Nanette Schloot, Lilly Deutschland GmbH,

Aims: Patients with a type-2-diabetes (T2D) phenotyp
ase antibodies (GADA) represent the majority of case
adult (LADA). The GLP-1 receptor agonist dulaglutid
T2D, has yet to be evaluated in LADA patients. Our p
effect of dulaglutide on glycaemic control (HbA1c) in GADA-positive
T2D patients.

Methods: A *post-hoc* analysis was performed using data from 3
ase 3 trials (AWARD-2,-4,-5; patients with GADA assessment) which were p
dulaglutide clinical development programme in T2D. LADA patients were identifie
A ≥5 IU/mL (ELISA). Changes in HbA1c during 12 months of treatment with dulag
or comparator were analysed using mixed-effect model repeated measures.

Results: Of 2466 adults tested for GADA (dulaglutide, 1710; glargine, 298; sitagliptin, 294; placebo, 164), 2278 (92.4%) were GADA-negative and 188 (7.6%) were GADA-positive, including

7.6% GAD65+

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Questions

- How is LADA defined?
- How common is LADA?
- How is LADA different from T1D?
- What's the natural history?
- What do we know about outcomes?

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Genetics of LADA

- Increased prevalence of susceptibility haplotypes HLA DR3, DR4 DQb1*301 (similar to T1DM)
- Higher frequency of protective DR2 and DQb1*602 compared to T1DM
- Other associations (TNF-a and TCF7L2)

Genetics of LADA

Check for updates

First Genome-Wide Association Study of Latent Autoimmune Diabetes in Adults Reveals Novel Insights Linking Immune and Metabolic Diabetes

https://doi.org/10.2337/dc18-1032

Diana L. Cousminer,[1,2] Emma Ahlqvist,[3] Rajashree Mishra,[1,4] Mette K. Andersen,[5] Alessandra Chesi,[1] Mohammad I. Hawa,[6†] Asa Davis,[7] Kenyaita M. Hodge,[1] Jonathan P. Bradfield,[8] Kaixin Zhou,[9] Vanessa C. Guy,[1] Mikael Åkerlund,[3] Mette Wod,[10] Lars G. Fritsche,[11] Henrik Vestergaard,[5] James Snyder,[8] Kurt Højlund,[10] Allan Linneberg,[5] Annemari Käräjämäki,[12] Ivan Brandslund,[10] Cecilia E. Kim,[8] Daniel Witte,[10,13] Elin Pettersen Sørgjerd,[14] David J. Brillon,[15] Oluf Pedersen,[5] Henning Beck-Nielsen,[10] Niels Grarup,[5] Richard E. Pratley,[16] Michael R. Rickels,[17] Adrian Vella,[18] Fernando Ovalle,[19] Olle Melander,[3] Ronald I. Harris,[20] Stephen Varvel,[21] Valdemar E.R. Grill,[22,23] Bone Mineral Density in Childhood Study,[24*] Hakon Hakonarson,[8,25] Philippe Froguel,[26,27] John T. Lonsdale,[28] Didac Mauricio,[29] Nanette C. Schloot,[30] Kamlesh Khunti,[31] Carla J. Greenbaum,[7] Bjørn Olav Åsvold,[12,22] Knud B. Yderstræde,[10] Ewan R. Pearson,[9] Stanley Schwartz,[32] Benjamin F. Voight,[2,17,33,34] Torben Hansen,[5] Tiinamaija Tuomi,[35,36,37] Bernhard O. Boehm,[38,39] Leif Groop,[3,37] R. David Leslie,[6] and Struan F.A. Grant[1,2,8,17,25]

OBJECTIVE

Latent autoimmune diabetes in adults (LADA) shares clinical features with both type 1 and type 2 diabetes; however, there is ongoing debate regarding the precise definition of LADA. Understanding its genetic basis is one potential strategy to gain insight into appropriate classification of this diabetes subtype.

RESEARCH DESIGN AND METHODS

We performed the first genome-wide association study of LADA in case subjects of European ancestry versus population control subjects (n = 2,634 vs. 5,947) and compared against both case subjects with type 1 diabetes (n = 2,454 vs. 968) and type 2 diabetes (n = 2,779 vs. 10,396).

RESULTS

The leading genetic signals were principally shared with type 1 diabetes, although we observed positive genetic correlations genome-wide with both type 1 and type 2 diabetes. Additionally, we observed a novel independent signal at the known type 1 diabetes locus harboring *PFKFB3*, encoding a regulator of glycolysis and insulin signaling in type 2 diabetes and inflammation and autophagy in autoimmune disease, as well as an attenuation of key type 1–associated HLA haplotype frequencies in LADA, suggesting that these are factors that distinguish childhood-onset type 1 diabetes from adult autoimmune diabetes.

CONCLUSIONS

[1]Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA
[2]Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[3]Department of Clinical Sciences Malmö, Lund

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GWAS: Significant Signals Associated with LADA

Table 1—Genome-wide significant signals associated with LADA

SNP	Chromosome	Position (b37)	Reference/ other allele	Effect allele frequency (case/control subjects)	OR	95% CI	*P*	Gene
LADA (n = 2,634) vs. population control subjects (n = 5,947)								
rs9273368	6	32626475	A/G	0.50/0.28	3.115	2.855–3.398	7.87×10^{-143}	*HLA-DQB1*
rs2476601	1	114377568	A/G	0.159/0.102	1.717	1.539–1.915	7.21×10^{-22}	*PTPN22*
rs689	11	2182224	T/A	0.802/0.726	1.483	1.363–1.613	1.07×10^{-19}	*INS*
rs7310615	12	111865049	C/G	0.553/0.492	1.284	1.193–1.383	4.92×10^{-11}	*SH2B3*
LADA (n = 2,779) vs. case subjects with type 2 diabetes (n = 10,396)								
rs9273368	6	32626475	A/G	0.43/0.301	2.439	2.222–2.676	3.17×10^{-78}	*HLA-DQB1*
rs689	11	2182224	T/A	0.783/0.715	1.473	1.352–1.605	9.86×10^{-19}	*INS*
rs2476601	1	114377568	A/G	0.173/0.140	1.529	1.38–1.693	4.52×10^{-16}	*PTPN22*
rs3184504	12	111884608	C/T	0.544/0.52	1.24	1.151–1.336	1.77×10^{-8}	*SH2B3*
LADA (n = 2,454) vs. case subjects with type 1 diabetes (n = 968)								
rs9273368	6	32626475	A/G	0.415/0.65	0.335	0.256–0.385	8.46×10^{-40}	*HLA-DQB1*

We performed three genome-wide association approaches, first for LADA vs. population control subjects (top), then for LADA vs. type 2 diabetes (middle), and finally for LADA versus type 1 diabetes (bottom). ORs are given for the LADA risk allele, except for rs92773368 in LADA vs. type 1 diabetes, to illustrate that the type 1 diabetes risk allele was depleted in LADA.

The strongest genetic risk loci for LADA are shared with T1D, but established T2D loci also play a weaker role, as evidenced by the enrichment of established type 2 diabetes loci in LADA.

Cousminer et al. Diabetes Care 2018

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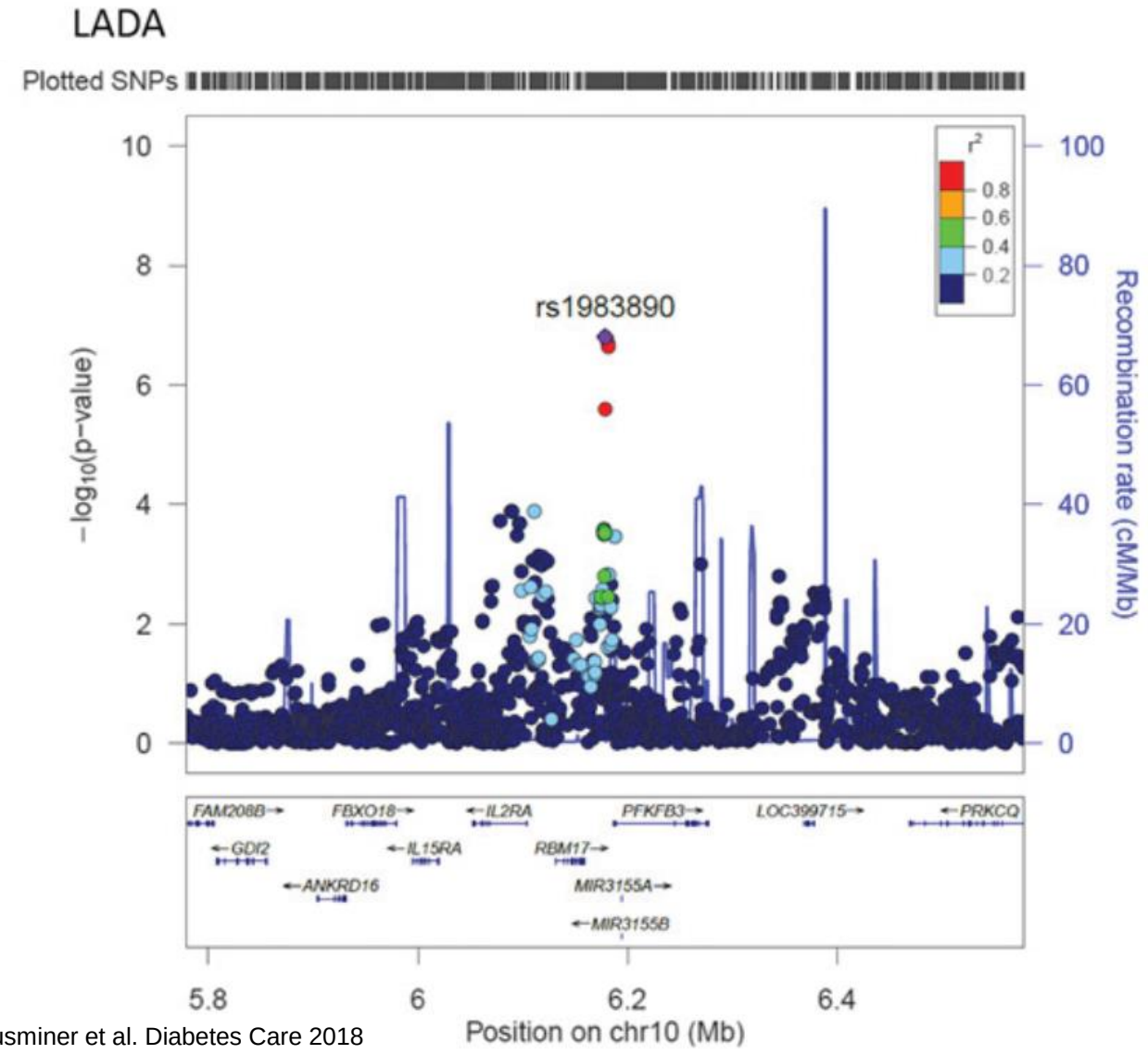
PFKFB3 Locus Associated with LADA



A novel strong signal at 10p15.1 between the two established type 1 diabetes loci at IL2RA and PRKCQ was described (rs1983890-C, odds ratio [OR] [95%CI] = 1.16 [1.14–1.32]; P = 3.02 x 10^{8}).

The gene encoding 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), was identified as the most likely functional candidate.

Cousminer et al. Diabetes Care 2018

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Circulating levels of pancreas-enriched miRNAs in subjects with different types of diabetes

Seyhan et al. Scientific Reports, 2016

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Clinical characteristics at “T1D” onset

T1D Exchange Registry and TrialNet

Age at diagnosis	<10	10-17	18-24	25-39	≥40	P-value
Underweight	16%	12%	14%	7%	6%	0.001
Normal weight	63%	65%	63%	55%	52%	
Overweight	9%	13%	14%	27%	27%	
Obese	12%	11%	9%	12%	15%	

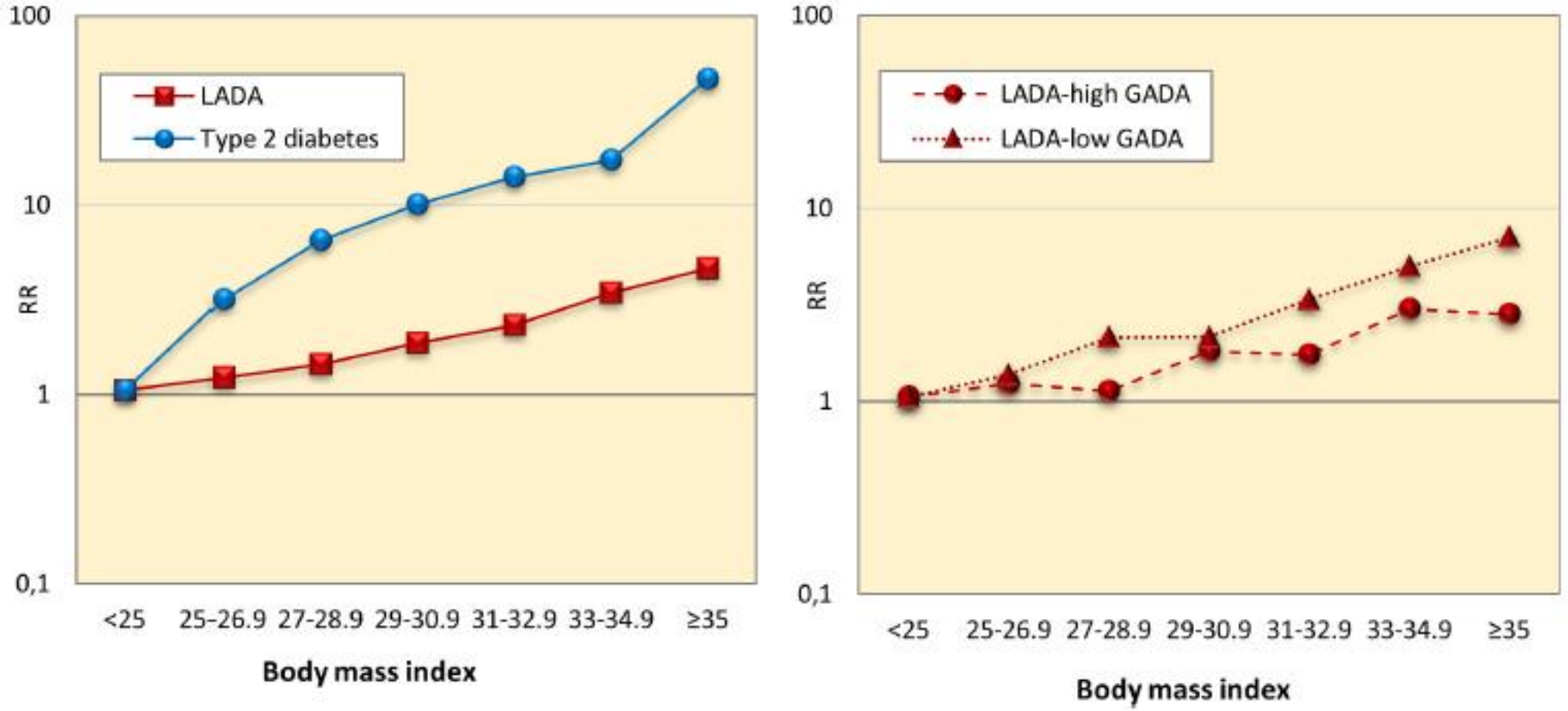
TrialNet PTP cohort 2-18 years
Overweight 14%
Obese 11%

TrialNet PTP cohort 20-50 years
Overweight 30%
Obese 30%

Casu A, et al. T1D Exchange Registry. Diabetes Medicine 2020
Ferrara CT et al. Diabetes Care (2017) 40: 698-701. Ferrara CT et al. J Clin Endocrinol Metab (2017) 102: 4596–4603

BMI and risk of LADA and T2D

Relative risk of LADA and T2D and LADA with high or low GADA levels in relation to BMI (HUNT and ESTRID studies)



Carlsson et al. Front Physiology 2019; Hijort et al. Diabetologia 2018

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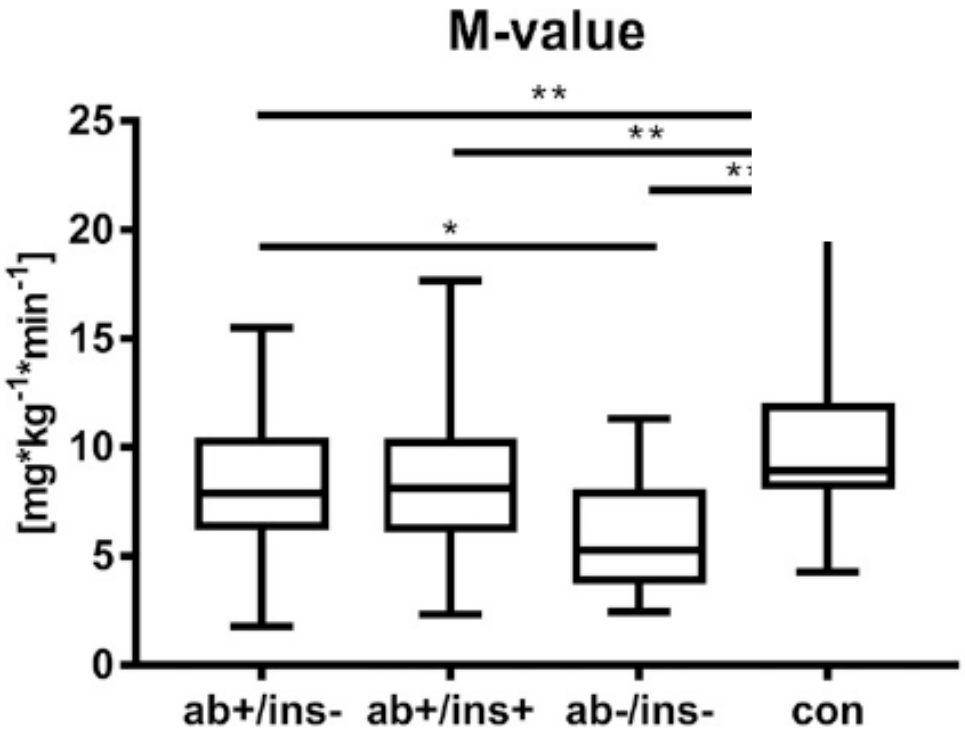
Insulin resistance in LADA

No differences in M value between IAAb+ requiring insulin (T1D) or not (LADA).



In the Action LADA study, no differences of insulin sensitivity measured with hyperinsulinemic euglycemic clamp were demonstrated between LADA and T2D once matched for BMI.

Subauste A et al. PLOSone 2014; Zaharia et al. JCEM 2018, Juhl et al. 2014

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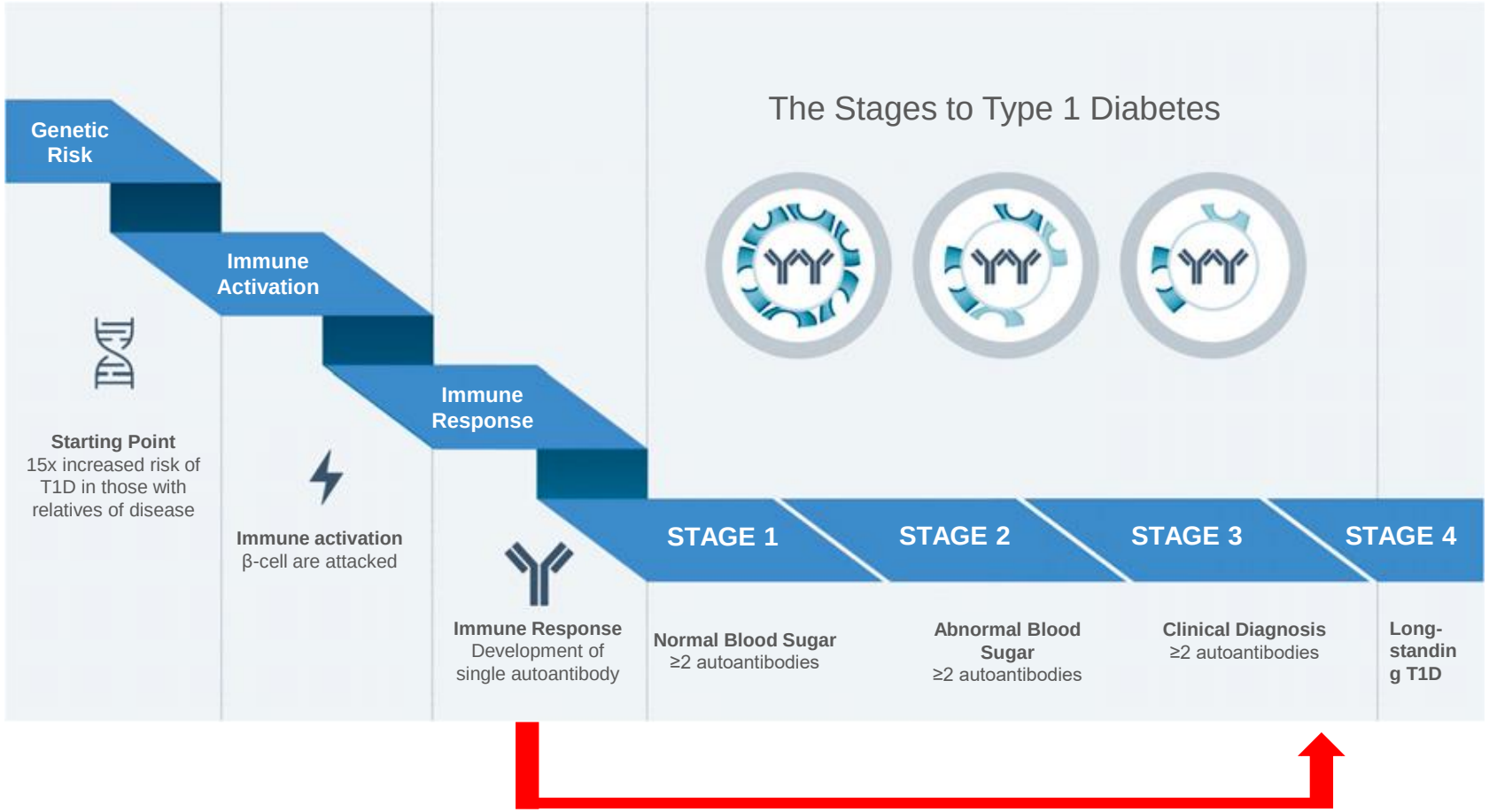
Adult onset T1D differs from childhood T1D

Attenuation of key T1D-associated HLA haplotype frequencies



LADA/AOnT1D does not fulfill the stages of progression to T1D defined for high risk subjects

Modified from Greenbaum C.J. et al. Diabetes 2018.

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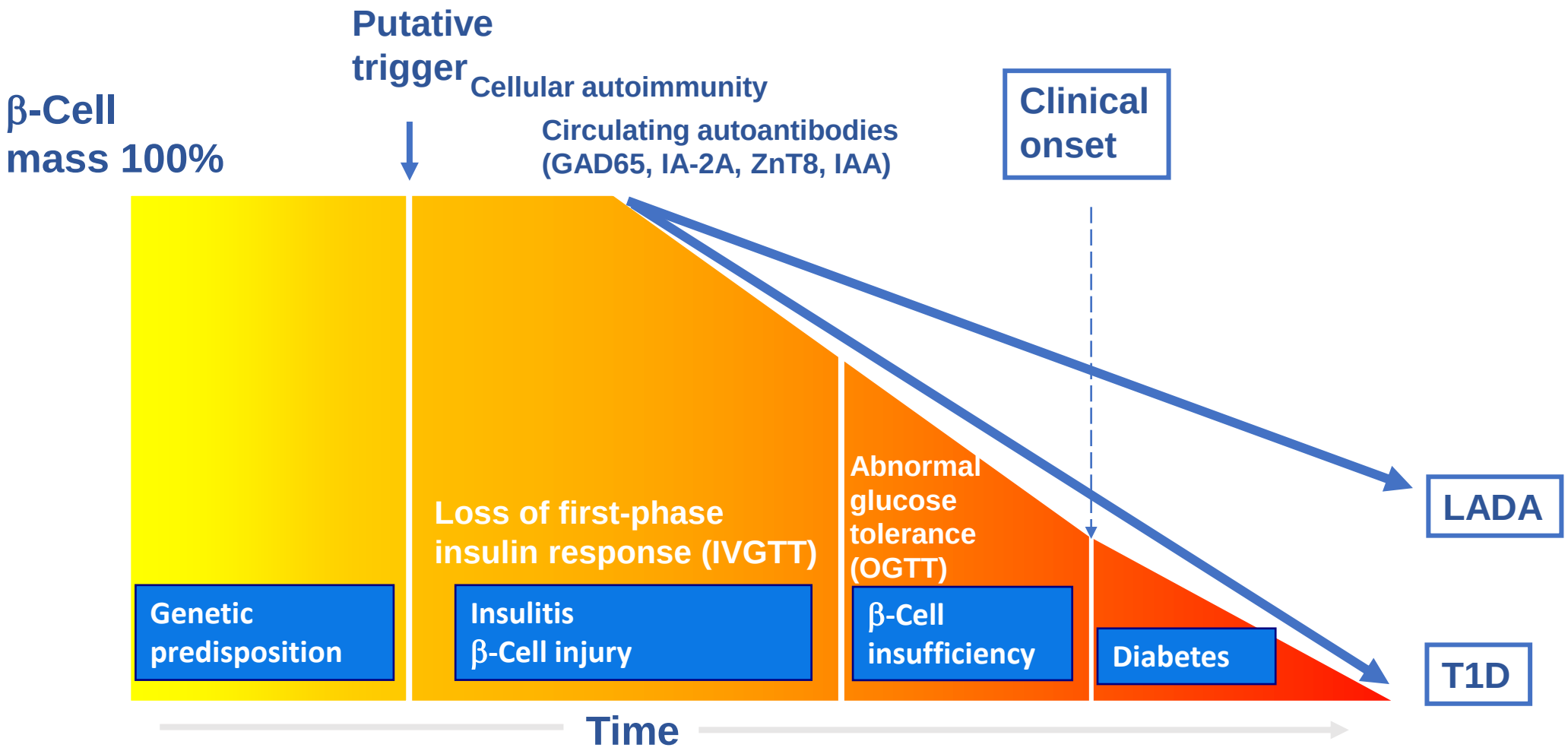
Natural history of autoimmune diabetes



Eisenbarth GS. *N Engl J Med*. 1986;314:1360-1368

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Subtypes of diabetes

Diabetes Volume 66, February 2017

Jay S. Skyler,[1] George L. Bakris,[2] Ezio Bonifacio,[3] Tamara Darsow,[4] Robert H. Eckel,[5] Leif Groop,[6] Per-Henrik Groop,[7,8,9] Yehuda Handelsman,[10] Richard A. Insel,[11] Chantal Mathieu,[12] Allison T. McElvaine,[4] Jerry P. Palmer,[13] Alberto Pugliese,[1] Desmond A. Schatz,[14] Jay M. Sosenko,[15] John P.H. Wilding,[16] and Robert E. Ratner[4]

Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis

Diabetes 2017;66:241–255 | DOI: 10.2337/db16-0806

The American Diabetes Association, JDRF, the European Association for the Study of Diabetes, and the American Association of Clinical Endocrinologists convened a research symposium, "The Differentiation of Diabetes by Pathophysiology, Natural History and Prognosis" on 10–12 October 2015. International experts in genetics, immunology, metabolism, endocrinology, and systems biology discussed genetic and environmental determinants of type 1 and type 2 diabetes risk and progression, as well as complications. The participants debated how to determine appropriate therapeutic approaches based on disease pathophysiology and stage and defined remaining research gaps hindering a personalized medical approach for diabetes to drive the field to address these gaps. The authors recommend a structure for data stratification to define the phenotypes and genotypes of subtypes of diabetes that will facilitate individualized treatment.

Though therapeutic algorithms for diabetes encourage individualization of approaches (1), they are often broadly applied in treatment and reimbursement decisions, reinforcing the "one-size-fits-all" approach (2). However, if individualized approaches are successful (if they improve morbidity/mor… effective), health care systems are… them. For example, better insights… iology of different types of cancer h… agnostic tools and therapies, whi… improved outcomes (3). A similar… realized for diabetes.

Many different paths, driven by… environmental factors, result in th… β-cell mass (4,5) and/or function (6… ically as hyperglycemia. Once hyper… ple with all forms of diabetes are … the same complications (Fig. 1), tho… sion may differ. The present challe… the many paths to β-cell dysfun… identify therapeutic approaches t… path. By reviewing the current evi… remaining research gaps, we aim to… diabetes that may be associated wit… progression and differential risks … personalized approach to intensive… or treat specific complications may … den of diabetes complications, pa… highest risk.

[1]Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, FL. [2]The University of Chicago Medicine, Chicago, IL. [3]Technische Universität Dresden, Dresden, Germany. [4]American Diabetes Association, Arlington, VA. [5]University of Colorado Anschutz Medical Campus, Aurora, CO. [6]Lund University, Skåne University Hospital, Malmö, Sweden. [7]Abdominal Center Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. [8]Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland. [9]Baker IDI Heart and Diabetes Institute, Melbourne, Australia. [10]Metabolic Institute of America, Tarzana, CA. [11]JDRF, New York, NY. [12]Katholieke Universiteit Leuven, Leuven, Belgium. [13]University of Washington and VA Puget Sound He… [14]University of Florida College of Medicine, Gaine… [15]University of Miami Miller School of Medicine, … [16]University Hospital Aintree, Liverpool, U.K.

Corresponding author: Allison T. McElvaine, amce…

Received 1 July 2016 and accepted 23 Novembe…

This article contains Supplementary Data online a… .diabetesjournals.org/lookup/suppl/doi:10.2337/db…

Novel subgroups of adult-onset diabetes and their associat… with outcomes: a data-driven cluster analysis of six variabl…

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki*, Mats Martinell*, Mazhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B P… Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Olle Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop

Summary

Background Diabetes is presently classified into two main forms, type 1 and type 2 diabetes, but type 2 diab… particular is highly heterogeneous. A refined classification could provide a powerful tool to individualise tre… regimens and identify individuals with increased risk of complications at diagnosis.

Methods We did data-driven cluster analysis (k-means and hierarchical clustering) in patients with newly dia… diabetes (n=8980) from the Swedish All New Diabetics in Scania cohort. Clusters were based on six va… (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA_{1c}, and homoeostatic model assessment 2 es… of β-cell function and insulin resistance), and were related to prospective data from patient records on devel… of complications and prescription of medication. Replication was done in three independent cohorts: the … Diabetes Registry (n=1466), All New Diabetics in Uppsala (n=844), and Diabetes Registry Vaasa (n=348… regression and logistic regression were used to compare time to medication, time to reaching the treatment g… risk of diabetic complications and genetic associations.

Findings We identified five replicable clusters of patients with diabetes, which had significantly differen… characteristics and risk of diabetic complications. In particular, individuals in cluster 3 (most resistant to insul… significantly higher risk of diabetic kidney disease than individuals in clusters 4 and 5, but had been pre… similar diabetes treatment. Cluster 2 (insulin deficient) had the highest risk of retinopathy. In suppor… clustering, genetic associations in the clusters differed from those seen in traditional type 2 diabetes.

Interpretation We stratified patients into five subgroups with differing disease progression and risk of … complications. This new substratification might eventually help to tailor and target early treatment to patien… would benefit most, thereby representing a first step towards precision medicine in diabetes.

Funding Swedish Research Council, European Research Council, Vinnova, Academy of Finland, Novo N… Foundation, Scania University Hospital, Sigrid Juselius Foundation, Innovative Medicines Initiative … Underwaking, Vasa Hospital district, Jakobstadsnejden Heart Foundation, Folkhälsan Research Foundation, … Foundation, and Swedish Foundation for Strategic Research.

Introduction

Diabetes is the fastest increasing disease worldwide and a substantial threat to human health.[1] Existing treatment strategies have been unable to stop the progressive course of the disease and prevent development of chronic diabetic complications. One explanation for these shortcomings is that diagnosis of diabetes is based on measurement of only one metabolite, glucose, but the disease is heterogeneous with regard to clinical presentation and progression.

Diabetes classification into type 1 and type 2 diabetes relies primarily on the presence (type 1 diabetes) or absence (type 2 diabetes) of autoantibodies against pancreatic islet β-cell antigens and age at diagnosis (younger for type 1 diabetes). With this approach, 75–85% of patients are classified as having type 2 diabetes. A third subgroup, latent autoimmune diabetes in adults (LADA; affecting <10% of people with diabetes), defined by the presence of glutamic acid decarboxylase antibodies (GADA), is phenotypically indistinguishable from type 2 diabetes at diagnosis, but becomes increasingly similar to type 1 diabetes over time.[2] With the introduction … sequencing in clinical diagnostics, several rare mon… forms of diabetes were described, including m… onset diabetes of the young and neonatal diabetes.[3]

Existing treatment guidelines are limited by … they respond to poor metabolic control when … developed, but do not have means to predic… patients will need intensified treatment. I… suggests that early treatment is crucial for prever… life-shortening complications because targe… seem to remember poor metabolic control decad… (so-called metabolic memory).[5,6]

A refined classification could provide a powerfu… identify at diagnosis those at greatest risk of compli… and enable individualised treatment regimens … same way as genetic diagnosis of monogenic … guides clinicians to optimal treatment.[7] With th… we present a novel diabetes classification ba… unsupervised, data-driven cluster analysis of st… monly measured variables and compare it meaab…

Articles

Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study

Oana P Zaharia, Klaus Strassburger, Alexander Strom, Gidon J Bönhof, Yanislava Karusheva, Sofia Antoniou, Kálmán Bódis, Daniel F Markgraf, Volker Burkart, Karsten Müssig, Jong-Hee Hwang, Olof Asplund, Leif Groop, Emma Ahlqvist, Jochen Seissler, Peter Nawroth, Stefan Kopf, Sebastian M Schmid, Michael Stumvoll, Andreas F H Pfeiffer, Stefan Kabisch, Sergey Tselmin, Hans U Häring, Dan Ziegler, Oliver Kuss, Julia Szendroedi, Michael Roden, for the German Diabetes Study Group*

Lancet Diabetes Endocrinol 2019; 7: 684–94

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See Comment page 659

*Members listed in the appendix

Institute for Clinical Diabetology (O P Zaharia MD, A Strom PhD, G J Bönhof MD, Y Karusheva MD, S Antoniou MD, K Bódis MD, D F Markgraf PhD, V Burkart PhD, K M Müssig MD, J-H Hwang PhD, D Ziegler MD, J Szendroedi MD, M Roden MD), and Institute for Biometrics and Epidemiology (K Strassburger PhD, O Kuss PhD), German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany; German Center for Diabetes Research, Munich, Germany (J Seissler MD, P Nawroth MD, S Kopf MD, S M Schmid MD, M Stumvoll MD, A F H Pfeiffer MD, S Kabisch MD, S Tselmin MD, H U Häring MD, O P Zaharia, K Strassburger, A Strom, G J Bönhof, Y Karusheva, S Antoniou, K Bódis, D F Markgraf, V Burkart, K M Müssig, J-H Hwang, D Ziegler, O Kuss, J Szendroedi, M Roden); Division of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany (S Antoniou, K Bódis, D Ziegler, J Szendroedi, M Roden); Genomics, Diabetes and Endocrinology, Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden (O Asplund MSc, L Groop MD, E Ahlqvist MD); Medizinische Klinik und Poliklinik IV, Klinikum der Ludwig Maximilians Universität, and Clinical Cooperation Group Diabetes, Ludwig Maximilians Universität München, and Helmholtz Zentrum München, Munich, Germany

Summary

Background Cluster analyses have proposed different diabetes phenotypes using age, BMI, glycaemia, homoeostasis model estimates, and islet autoantibodies. We tested whether comprehensive phenotyping validates and further characterises these clusters at diagnosis and whether relevant diabetes-related complications differ among these clusters, during 5-years of follow-up.

Methods Patients with newly diagnosed type 1 or type 2 diabetes in the German Diabetes Study underwent comprehensive phenotyping and assessment of laboratory variables. Insulin sensitivity was assessed using hyperinsulinaemic-euglycaemic clamps, hepatocellular lipid content using magnetic resonance spectroscopy, hepatic fibrosis using non-invasive scores, and peripheral and autonomic neuropathy using functional and clinical criteria. Patients were reassessed after 5 years. The German Diabetes Study is registered with ClinicalTrials.gov, number NCT01055093, and is ongoing.

Findings 1105 patients were classified at baseline into five clusters, with 386 (35%) assigned to mild age-related diabetes (MARD), 323 (29%) to mild obesity-related diabetes (MOD), 247 (22%) to severe autoimmune diabetes (SAID), 121 (11%) to severe insulin-resistant diabetes (SIRD), and 28 (3%) to severe insulin-deficient diabetes (SIDD). At 5-year follow-up, 367 patients were reassessed, 128 (35%) with MARD, 106 (29%) with MOD, 88 (24%) with SAID, 35 (10%) with SIRD, and ten (3%) with SIDD. Whole-body insulin sensitivity was lowest in patients with SIRD at baseline (mean 4·3 mg/kg per min [SD 2·0]) compared with those with SAID (8·4 mg/kg per min [3·2]; p<0·0001), MARD (7·5 mg/kg per min [2·5]; p<0·0001), MOD (6·6 mg/kg per min [2·6]; p=0·0011), and SIDD (5·5 mg/kg per min [2·4]; p=0·0035). The fasting adipose-tissue insulin resistance index at baseline was highest in patients with SIRD (median 15·6 [IQR 9·3–20·9]) and MOD (11·6 [7·4–17·9]) compared with those with MARD (6·0 [3·9–10·3]; both p<0·0001) and SAID (6·0 [3·0–9·5]; both p<0·0001). In patients with newly diagnosed diabetes, hepatocellular lipid content was highest at baseline in patients assigned to the SIRD cluster (median 19% [IQR 11–22]) compared with all other clusters (7% [2–15] for MOD, p=0·00052; 5% [2–11] for MARD, p<0·0001; 2% [0–13] for SIDD, p=0·0083; and 1% [0–3] for SAID, p<0·0001), even after adjustments for baseline medication. Accordingly, hepatic fibrosis at 5-year follow-up was more prevalent in patients with SIRD (n=7 [26%]) than in patients with SAID (n=5 [7%], p=0·0011), MARD (n=12 [12%], p=0·012), MOD (n=13 [15%], p=0·050), and SIDD (n=0 [0%], p value not available). Confirmed diabetic sensorimotor polyneuropathy was more prevalent at baseline in patients with SIDD (n=9 [36%]) compared with patients with SAID (n=10 [5%], p<0·0001), MARD (n=39 [15%], p=0·00066), MOD (n=26 [11%], p<0·0001), and SIRD (n=10 [17%], p<0·0001).

Interpretation Cluster analysis can characterise cohorts with different degrees of whole-body and adipose-tissue insulin resistance. Specific diabetes clusters show different prevalence of diabetes complications at early stages of non-alcoholic fatty liver disease and diabetic neuropathy. These findings could help improve targeted prevention and treatment and enable precision medicine for diabetes and its comorbidities.

Funding German Diabetes Center, German Federal Ministry of Health, Ministry of Culture and Science of the state of North Rhine-Westphalia, German Federal Ministry of Education and Research, German Diabetes Association, German Center for Diabetes Research, Research Network SFB 1116 of the German Research Foundation, and Schmutzler Stiftung.

Introduction

Findings of a Swedish cohort study published in 2018 have challenged the current paradigm of classifying patients with adult-onset diabetes mellitus;[2] patients were allocated into five clusters based on different pathophysiological and genetic profiles.[2] This analysis comprised an unbiased cluster allocation[3] using common variables such as autoimmunity, age at diagnosis, BMI,

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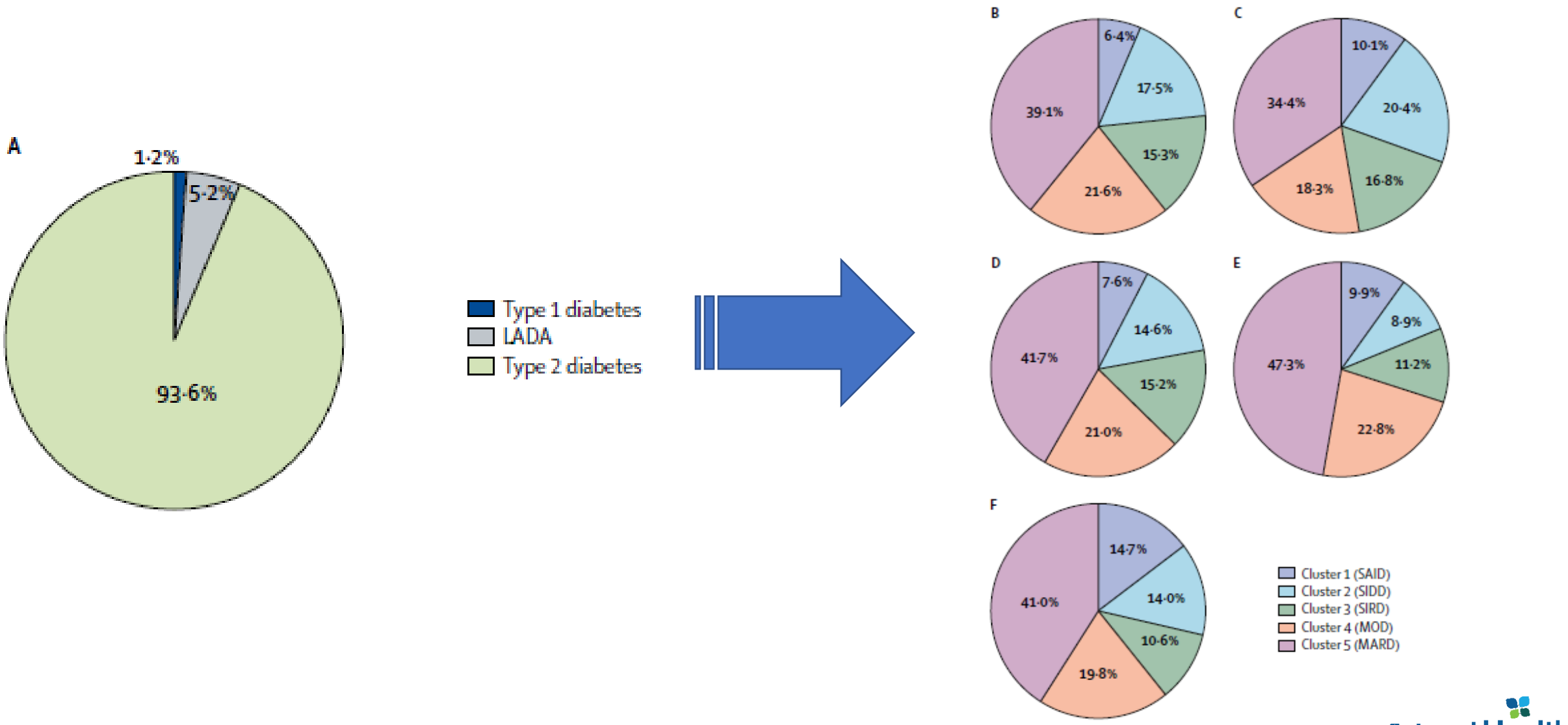
Subtypes of diabetes



Ahlqvist et al Lancet Diabetes and Endocrinology, 2019

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Questions

- How is LADA defined?
- How common is LADA?
- How is LADA different from T1D?
- What's the natural history?
- What do we know about outcomes?

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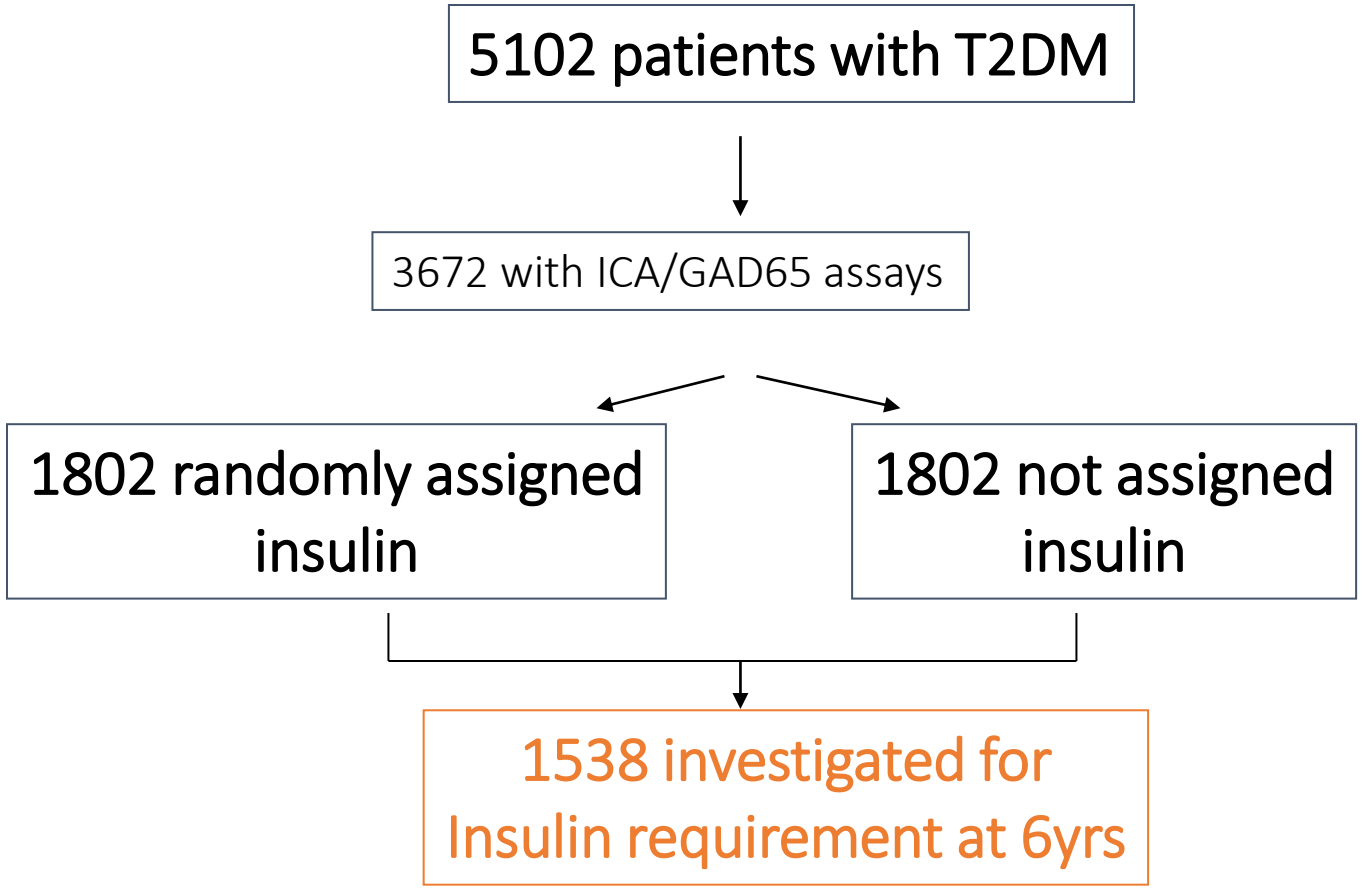
LADA in UKPDS



Turner R et al, Lancet 1997, 350, 1288, 1997

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Progression to insulin requirement in UKPDS

	No insulin	Insulin	P
N	1644	237	
Age	53.	48.5	<0.0001
BMI	29.5	27.6	<0.0001
ICA (%)	2.9	26.2	<0.0001
Anti-GAD (%)	5.3	38	<0.0001

Turner R et al, Lancet 1997, 350, 1288, 1997

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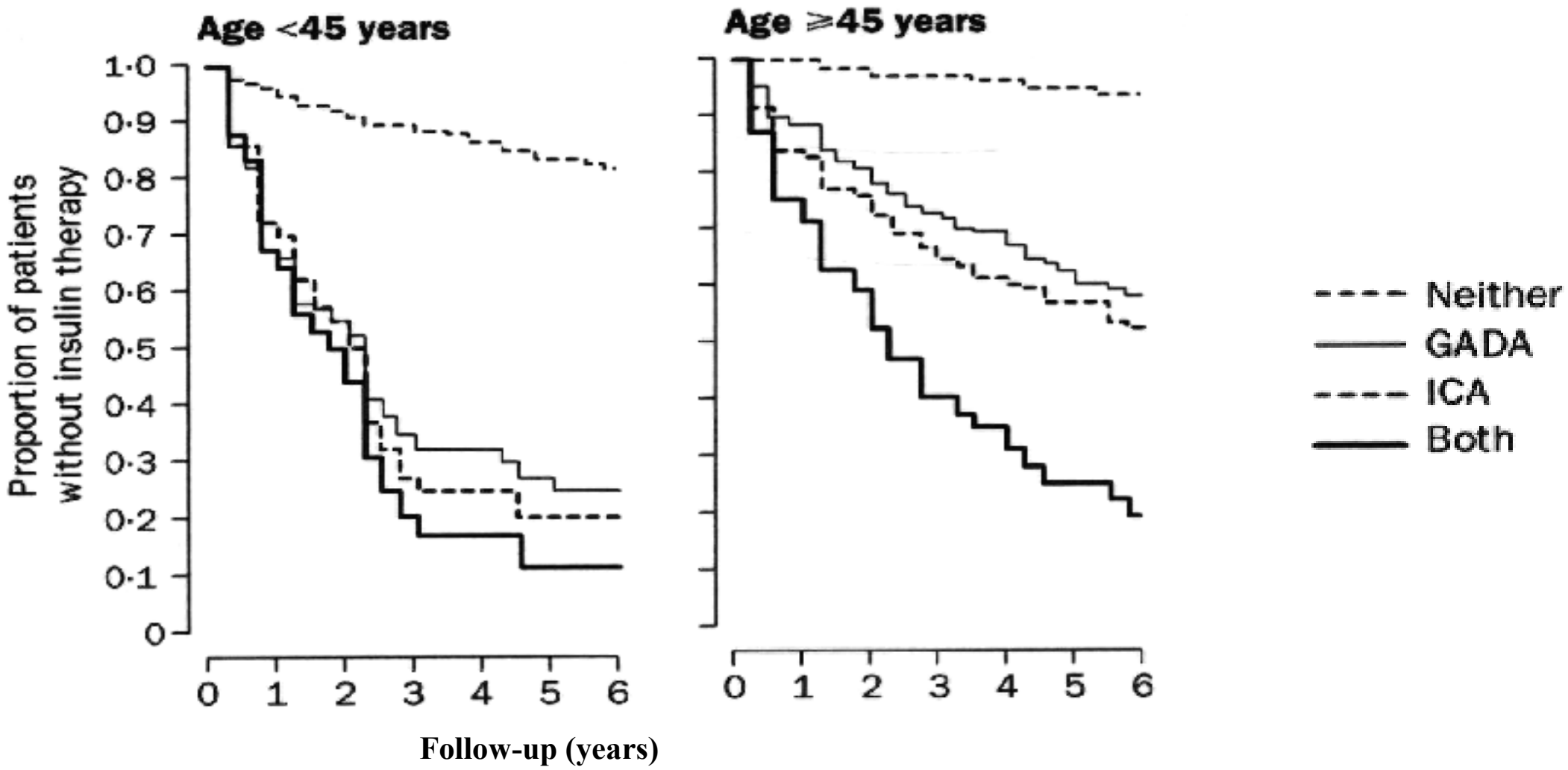
Predictive value of GAD and ICA in UKPDS



Turner et al, Lancet 1997, 350 :1288

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Questions

- How is LADA defined?
- How common is LADA?
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Complications in T2D, LADA and T1D

Table 3—*Chronic complications in patients with type 2, LADA, and type 1 diabetes*

	Type 2 diabetes	LADA	Type 1 diabetes
n (M/F)	59 (26/33)	59 (26/33)	111 (67/44)
Distal neuropathy	27	29	13*
Biothesiometer >10.3 V	83	79	41†
Biothesiometer >25 V	41	45	13†
Microalbuminuria (AER > 20 μg/min)	29	27	24
Retinopathy			
None	44	49	24*
Mild	39	28	55
Moderate	12	14	
Severe	5	9	21‡
Macular edema	7	12	ND
CHD	58	56	4.5†
ABI <0.9	27	27	5†

Data are %, unless otherwise indicated. For type 1 diabetic patients, mild and moderate retinopathy are grouped together. *$P < 0.05$ vs. LADA or type 2 diabetes; †$P < 0.001$ vs. LADA or type 2 diabetes; ‡$P < 0.05$ vs. type 2 diabetes.

- Cross-sectional study
- T1D patients younger but had longer duration of DM
- Similar microvascular complications
- CHD/PVOD similar to T2D

Isomma et al Diabetes Care 1999

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Carotid Intimal Medial Thickness in LADA

Hernández et al. Cardiovasc Diabetol (2017) 16:94
DOI 10.1186/s12933-017-0576-9

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Preclinical carotid atherosclerosis in patients with latent autoimmune diabetes in adults (LADA), type 2 diabetes and classical type 1 diabetes

Marta Hernández[1,2,3], Carolina López[2,3], Jordi Real[4,5], Joan Valls[3,6], Emilio Ortega-Martínez de Victoria[7], Federico Vázquez[8], Esther Rubinat[2], Minerva Granado-Casas[2,8], Nuria Alonso[8], Teresa Molí[9], Angels Betriu[3,9], Albert Lecube[1,2,3], Elvira Fernández[9], Richard David Leslie[10] and Didac Mauricio[3,8*]

Abstract

Background: LADA is probably the most prevalent form of autoimmune diabetes. Nevertheless, there are few data about cardiovascular disease in this group of patients. The aim of this study was to investigate the frequency of carotid atherosclerotic plaques in patients with LADA as compared with patients with classic type 1 diabetes and type 2 diabetes.

Methods: Patients with LADA were matched for age and gender in different proportions to patients with type 2 diabetes, and classic type 1 diabetes. None of the patients had clinical cardiovascular disease. All subjects underwent B-mode carotid ultrasound to detect atheroma plaques. Demographics were obtained from all subjects.

Results: We included 71 patients with LADA, 191 patients with type 2 diabetes and 116 patients with type 1 diabetes. Carotid atherosclerosis was more frequent in patients with LADA compared with type 2 diabetes (73.2% vs. 56.9%, $P = 0.0018$) and classic type 1 diabetes (57.1%, $P = 0.026$); these changes occurred despite healthier macrovascular risk profiles in the former. Age ($P < 0.001$), smoking ($P = 0.003$) and hypertension ($P = 0.019$) were independently associated with carotid atherosclerosis. Multiple plaques were also more frequent in patients with LADA as compared with classic type 1 diabetes and type 2 diabetes (45.1% and 33.6% vs. 27.2%, respectively, $P = 0.022$). The frequency of carotid plaques increased with increasing diabetes duration in LADA patients compared with type 2 diabetes (85.7% vs. 58.8%, inverse OR 5.72 [1.5–21.8]; $P = 0.009$).

Conclusions: LADA patients do not present with less carotid atherosclerosis than patients with type 1 and type 2 diabetes. Their macrovascular risk occurs despite a healthier macrovascular risk profile than those patients with type 2 diabetes.

Keywords: Carotid plaque, Atherosclerosis, Late onset autoimmune diabetes, LADA, Type 1 diabetes, Type 2 diabetes

Background

Macrovascular disease is the leading cause of morbidity and mortality in patients with both type 1 diabetes and type 2 diabetes [1]. Latent autoimmune diabetes of the adults (LADA), that is patients with adult-onset autoimmune diabetes who do not initially require insulin, represent 4–14% of subjects previously diagnosed with type 2 diabetes [2]. LADA can be estimated to have a higher prevalence than classic type 1 diabetes in both children and adults. Notwithstanding its clinical relevance, data about cardiovascular events and mortality in patients with LADA are limited. It could be anticipated that

*Correspondence: didacmauricio@gmail.com
[8] Department of Endocrinology and Nutrition, CIBER of Diabetes and Associated Metabolic Diseases, Health Sciences Research Institute & University Hospital Germans Trias i Pujol, Carretera Canyet S/N, Badalona 08916, Spain
Full list of author information is available at the end of the article

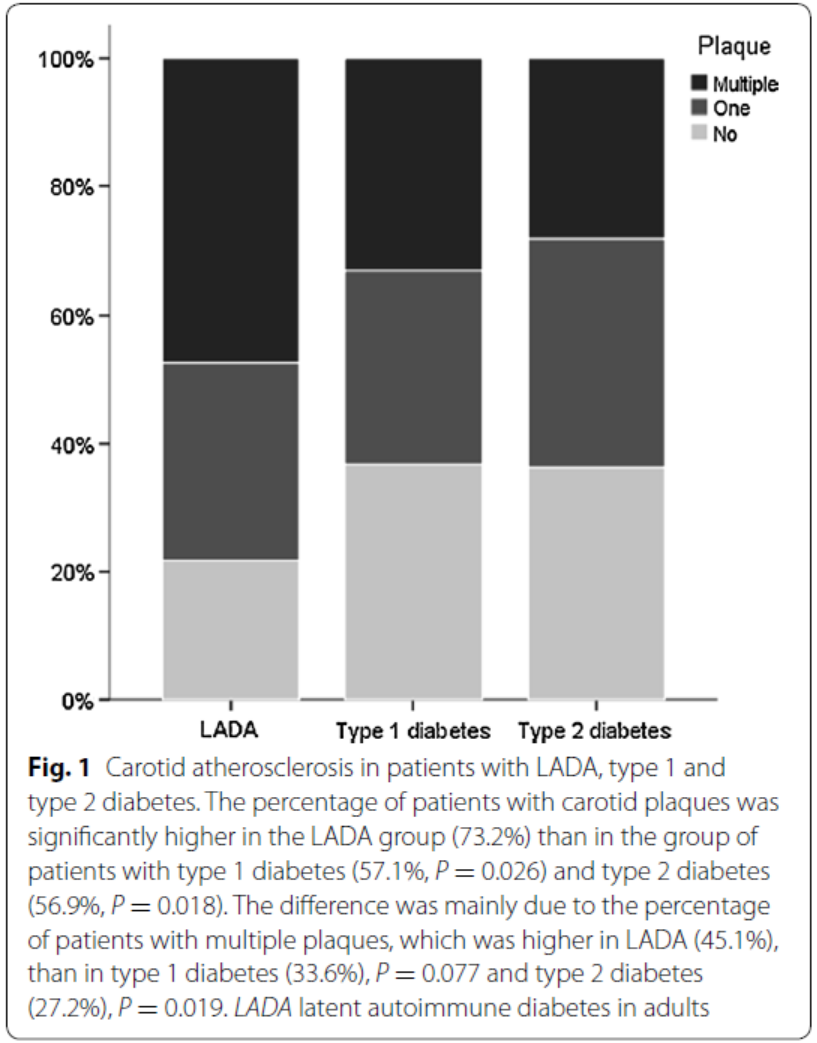

Fig. 1 Carotid atherosclerosis in patients with LADA, type 1 and type 2 diabetes. The percentage of patients with carotid plaques was significantly higher in the LADA group (73.2%) than in the group of patients with type 1 diabetes (57.1%, $P = 0.026$) and type 2 diabetes (56.9%, $P = 0.018$). The difference was mainly due to the percentage of patients with multiple plaques, which was higher in LADA (45.1%), than in type 1 diabetes (33.6%), $P = 0.077$ and type 2 diabetes (27.2%), $P = 0.019$. *LADA* latent autoimmune diabetes in adults

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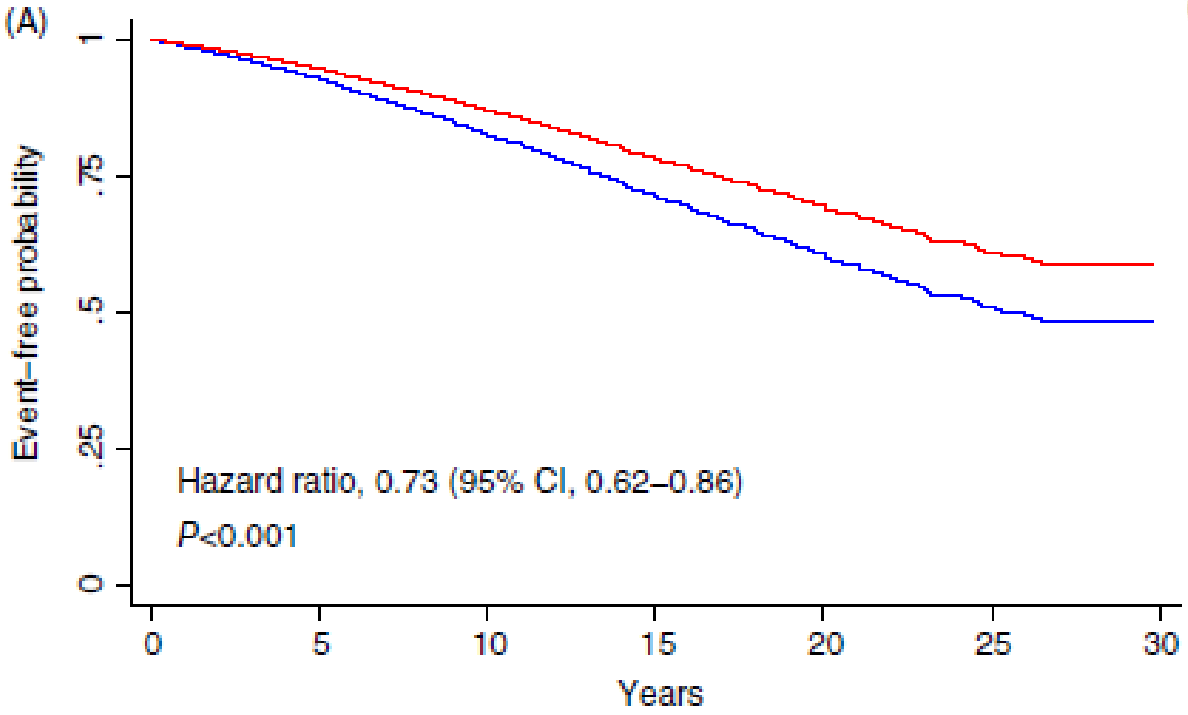
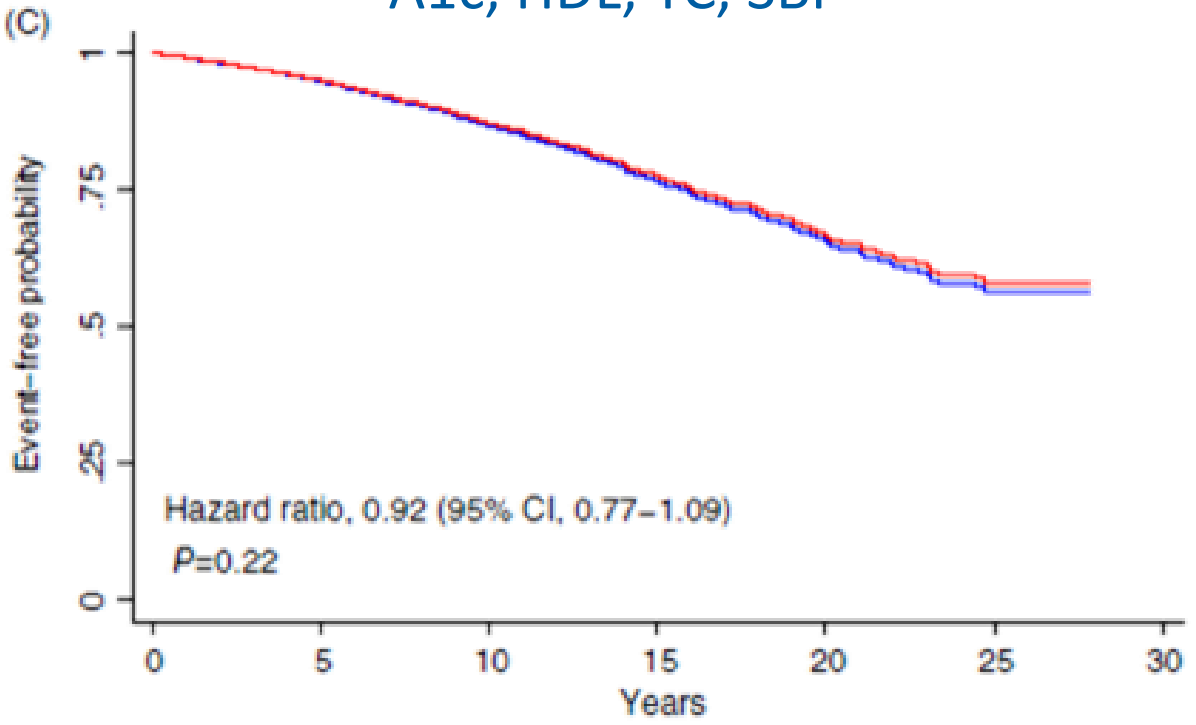
MACE in LADA and T2DM - UKPDS

Median follow-up 17.3 y

Unadjusted



Adjusted for age, BMI, A1c, HDL, TC, SBP



—— LADA (N = 157/567)
—— T2DM (N = 1544/4495)

Maddaloni et al. DOM 2019

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Incidence rate and hazard ratios for macrovascular outcomes

TABLE 2 Incidence rate and hazard ratios of macrovascular outcomes

	Incidence rate per 1000 person-years (95% CI)				
	LADA	T2D	HR (95% CI)	Age-adjusted HR (95% CI)	Fully adjusted HR
MACE	17.4 (14.9–20.3)	23.5 (22.4–24.7)	0.73 (0.62–0.86)	0.86 (0.73–1.02)	0.92 (0.77–1.09)
Cardiovascular death	11.8 (9.8–14.2)	15.0 (14.2–16.0)	0.77 (0.64–0.94)	0.93 (0.77–1.13)	0.97 (0.79–1.18)
Fatal MI	9.0 (7.3–11.1)	10.9 (10.1–11.7)	0.81 (0.65–1.01)	0.98 (0.79–1.23)	1.01 (0.81–1.28)
Fatal stroke	1.5 (0.9–2.5)	2.7 (2.3–3.1)	0.54 (0.31–0.92)	0.68 (0.39–1.16)	0.77 (0.44–1.32)
Sudden death	1.0 (0.5–1.8)	0.9 (0.7–1.2)	1.02 (0.51–2.05)	1.12 (0.56–2.26)	1.09 (0.53–2.25)
Unknown death	0.3 (0.1–1.0)	0.4 (0.3–0.6)	0.72 (0.22–2.35)	0.79 (0.24–2.60)	0.75 (0.22–2.54)
Non-fatal MI	4.7 (3.5–6.3)	7.5 (6.8–8.1)	0.63 (0.46–0.86)	0.70 (0.51–0.96)	0.73 (0.53–1.00)
Non-fatal stroke	2.7 (1.8–4.0)	4.7 (4.2–5.2)	0.56 (0.38–0.85)	0.68 (0.45–1.02)	0.73 (0.48–1.11)

Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

Consensus - JDRF Expert Panel 2021

Diabetes Care Volume 44, November 2021 2449

Adult-Onset Type 1 Diabetes: Current Understanding and Challenges

Diabetes Care 2021;44:2449–2456 | https://doi.org/10.2337/dc21-0770

R. David Leslie,[1] Carmella Evans-Molina,[2,3] Jacquelyn Freund-Brown,[4] Raffaella Buzzetti,[5] Dana Dabelea,[6] Kathleen M. Gillespie,[7] Robin Goland,[8] Angus G. Jones,[9] Mark Kacher,[4] Lawrence S. Phillips,[10] Olov Rolandsson,[11] Jana L. Wardian,[12] and Jessica L. Dunne[4]

Recent epidemiological data have shown that more than half of all new cases of type 1 diabetes occur in adults. Key genetic, immune, and metabolic differences exist between adult- and childhood-onset type 1 diabetes, many of which are not well understood. A substantial risk of misclassification of diabetes type can result. Notably, some adults with type 1 diabetes may not require insulin at diagnosis, their clinical disease can masquerade as type 2 diabetes, and the consequent misclassification may result in inappropriate treatment. In response to this important issue, JDRF convened a workshop of international experts in November 2019. Here, we summarize the current understanding and unanswered questions in the field based on those discussions, highlighting epidemiology and immunogenetic and metabolic characteristics of adult-onset type 1 diabetes as well as disease-associated comorbidities and psychosocial challenges. In adult-onset, as compared with childhood-onset, type 1 diabetes, HLA-associated risk is lower, with more protective genotypes and lower genetic risk scores; multiple diabetes-associated autoantibodies are decreased, though GADA remains dominant. Before diagnosis, those with autoantibodies progress more slowly, and at diagnosis, serum C-peptide is higher in adults than children, with ketoacidosis being less frequent. Tools to distinguish types of diabetes are discussed, including body phenotype, clinical course, family history, autoantibodies, comorbidities, and C-peptide. By providing this perspective, we aim to improve the management of adults presenting with type 1 diabetes.

Clinically, it has been relatively easy to distinguish the acute, potentially lethal, childhood-onset diabetes from the less aggressive condition that affects adults. However, experience has taught us that not all children with diabetes are insulin dependent and not all adults are non-insulin dependent. Immune, genetic, and metabolic analysis of these two, apparently distinct, forms of diabetes revealed inconsistencies, such that insulin-dependent and immune-mediated diabetes was redefined as type 1 diabetes, while most other forms were relabeled as type 2 diabetes. Recent data suggest a further shift in our thinking, with the recognition that more than half of all new cases of type 1 diabetes occur in adults. However, many adults may not require insulin at diagnosis of type 1 diabetes and have a more gradual onset of hyperglycemia, often leading to misclassification and inappropriate care. Indeed, misdiagnosis occurs in nearly 40% of adults with new type 1 diabetes, with the risk of error increasing with age (1,2). To consider this important issue, JDRF convened a workshop of international experts in November 2019 in New York, NY. In this Perspective, based on that workshop, we outline the evidence for

[1]Centre for Immunobiology, Blizard Institute, Queen Mary University of London, London, U.K.
[2]Departments of Pediatrics and Medicine and Center for Diabetes and Metabolic Diseases, Indiana University School of Medicine, Indianapolis, IN
[3]Richard L. Roudebush VA Medical Center, Indianapolis, IN
[4]JDRF, New York, NY
[5]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy
[6]Lifecourse Epidemiology of Adiposity & Diabetes Center, Colorado School of Public Health, and Departments of Epidemiology and Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO
[7]Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, U.K.
[8]Naomi Berrie Diabetes Center, Columbia University, New York, NY
[9]Institute of Biomedical and Clinical Science, University of Exeter, Exeter, U.K.
[10]Atlanta VA Medical Center and Division of Endocrinology, Metabolism, and Lipids, Department of Medicine, Emory University School of Medicine, Atlanta, GA
[11]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[12]College of Medicine, University of Nebraska Medical Center, Omaha, NE

Corresponding author: Carmella Evans-Molina, cevansmo@iu.edu, or R. David Leslie, r.d.g.leslie@qmul.ac.uk

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- Half of all cases of T1D are diagnosed in adults
- Frequently misdiagnosed
- Progression slower
- Genetics overlaps with T1D
- Understanding of pathophysiology and natural history not well understood

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Adult-onset autoimmune diabetes: knowledge gaps

Table 1—Knowledge gaps

Area of focus	Description
Eliminating cultural bias in order to understand what impacts disease development	Most large-scale studies of adult type 1 diabetes have been done in Europe, North America, and China. There is a pressing need to extend these studies to other continents and to diverse racial and ethnic groups. Such studies could help us identify and understand the nature and implications of diversity, whether in terms of pathogenesis, cultural differences, or health care disparity. In addition, prospective childhood studies of high-risk birth cohorts could be extended into adulthood and new studies initiated to better understand mechanisms behind disease development and whether there is a differentiation in the disease process between young and adult type 1 diabetes.
Population screening	At present, universal childhood screening programs are being developed in many countries. Research will be needed to develop strategies for the follow-up of autoantibody-positive populations throughout adulthood.
Disease-modifying therapies in early-stage disease	Trials of disease-modifying therapies have generally shown better efficacy in children (12). There are likely to be important differences in agent selection between adult and pediatric populations, and these differences require study.
Diagnosis and misclassification	There is a need to build a diagnostic decision tree to aid in diabetes classification. Tools are needed to estimate individual-level risk.
Adjunctive therapies	There is a need to better understand the benefits and risks of using therapies that are adjunctive to insulin in adult-onset type 1 diabetes. To this end, large-scale drug trials need to be performed, and therapeutic decision trees are required to help health care professionals and endocrinologists select such therapies.
Post-diagnosis education and support	Improving education and support post-diagnosis is vital and should include psychosocial support, health care provision, and analysis of long-term outcomes (including complications) in adult-onset type 1 diabetes. Current knowledge is limited with respect to complications, especially related to the complex mechanisms contributing to macrovascular disease in adult-onset type 1 diabetes. Surveillance efforts based on larger and representative cohorts of patients with clear and consistent case definitions are needed to better understand the burden and risk of diabetes-related chronic complications in this large population.

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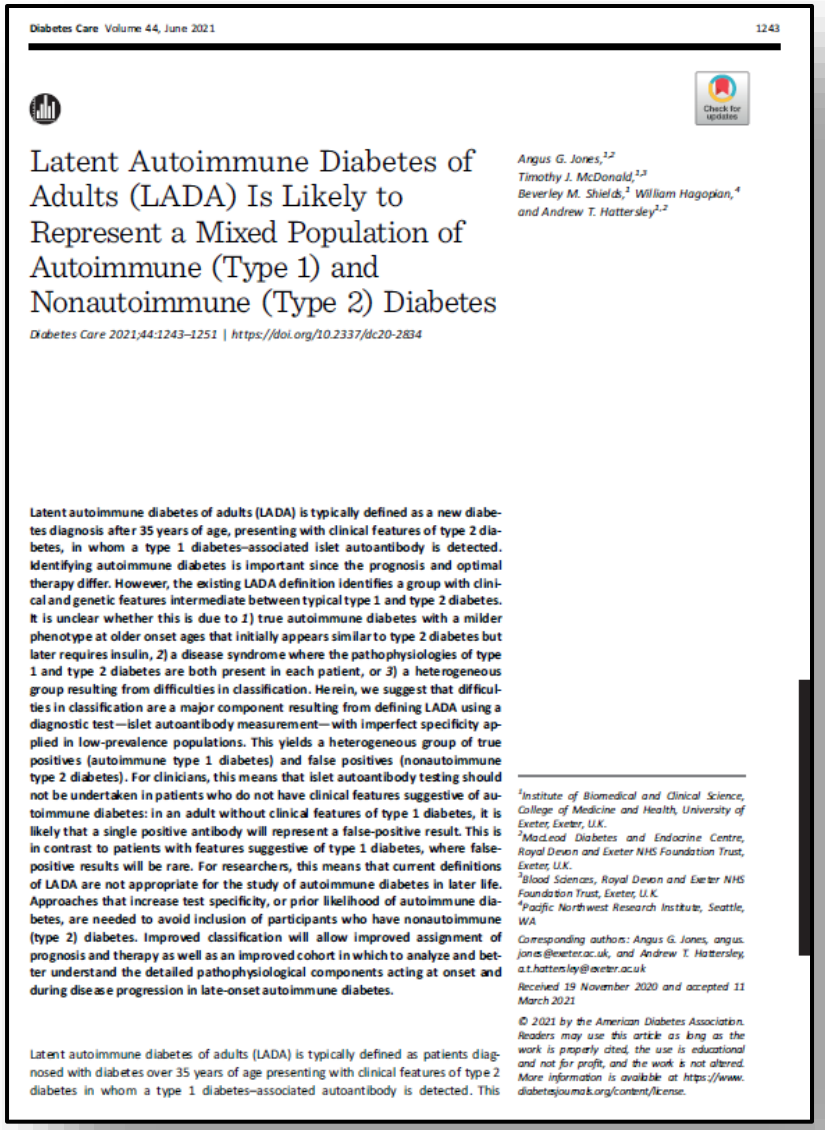
Or maybe not?



Diabetes Care Volume 44, June 2021 1243

Latent Autoimmune Diabetes of Adults (LADA) Is Likely to Represent a Mixed Population of Autoimmune (Type 1) and Nonautoimmune (Type 2) Diabetes

Angus G. Jones,[1,2] Timothy J. McDonald,[1,3] Beverley M. Shields,[1] William Hagopian,[4] and Andrew T. Hattersley[1,2]

Diabetes Care 2021;44:1243–1251 | https://doi.org/10.2337/dc20-2834

Latent autoimmune diabetes of adults (LADA) is typically defined as a new diabetes diagnosis after 35 years of age, presenting with clinical features of type 2 diabetes, in whom a type 1 diabetes–associated islet autoantibody is detected. Identifying autoimmune diabetes is important since the prognosis and optimal therapy differ. However, the existing LADA definition identifies a group with clinical and genetic features intermediate between typical type 1 and type 2 diabetes. It is unclear whether this is due to *1*) true autoimmune diabetes with a milder phenotype at older onset ages that initially appears similar to type 2 diabetes but later requires insulin, *2*) a disease syndrome where the pathophysiologies of type 1 and type 2 diabetes are both present in each patient, or *3*) a heterogeneous group resulting from difficulties in classification. Herein, we suggest that difficulties in classification are a major component resulting from defining LADA using a diagnostic test—islet autoantibody measurement—with imperfect specificity applied in low-prevalence populations. This yields a heterogeneous group of true positives (autoimmune type 1 diabetes) and false positives (nonautoimmune type 2 diabetes). For clinicians, this means that islet autoantibody testing should not be undertaken in patients who do not have clinical features suggestive of autoimmune diabetes: in an adult without clinical features of type 1 diabetes, it is likely that a single positive antibody will represent a false-positive result. This is in contrast to patients with features suggestive of type 1 diabetes, where false-positive results will be rare. For researchers, this means that current definitions of LADA are not appropriate for the study of autoimmune diabetes in later life. Approaches that increase test specificity, or prior likelihood of autoimmune diabetes, are needed to avoid inclusion of participants who have nonautoimmune (type 2) diabetes. Improved classification will allow improved assignment of prognosis and therapy as well as an improved cohort in which to analyze and better understand the detailed pathophysiological components acting at onset and during disease progression in late-onset autoimmune diabetes.

Latent autoimmune diabetes of adults (LADA) is typically defined as patients diagnosed with diabetes over 35 years of age presenting with clinical features of type 2 diabetes in whom a type 1 diabetes–associated autoantibody is detected. This

[1]Institute of Biomedical and Clinical Science, College of Medicine and Health, University of Exeter, Exeter, U.K.
[2]MacLeod Diabetes and Endocrine Centre, Royal Devon and Exeter NHS Foundation Trust, Exeter, U.K.
[3]Blood Sciences, Royal Devon and Exeter NHS Foundation Trust, Exeter, U.K.
[4]Pacific Northwest Research Institute, Seattle, WA

Corresponding authors: Angus G. Jones, angus.jones@exeter.ac.uk, and Andrew T. Hattersley, a.t.hattersley@exeter.ac.uk

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It is unclear whether LADA is:

1) true autoimmune diabetes with a milder phenotype at older onset ages that initially appears similar to type 2 diabetes but later requires insulin

2) a disease syndrome where the pathophysiologies of type 1 and type 2 diabetes are both present in each patient

3) a heterogeneous group resulting from difficulties in classification.

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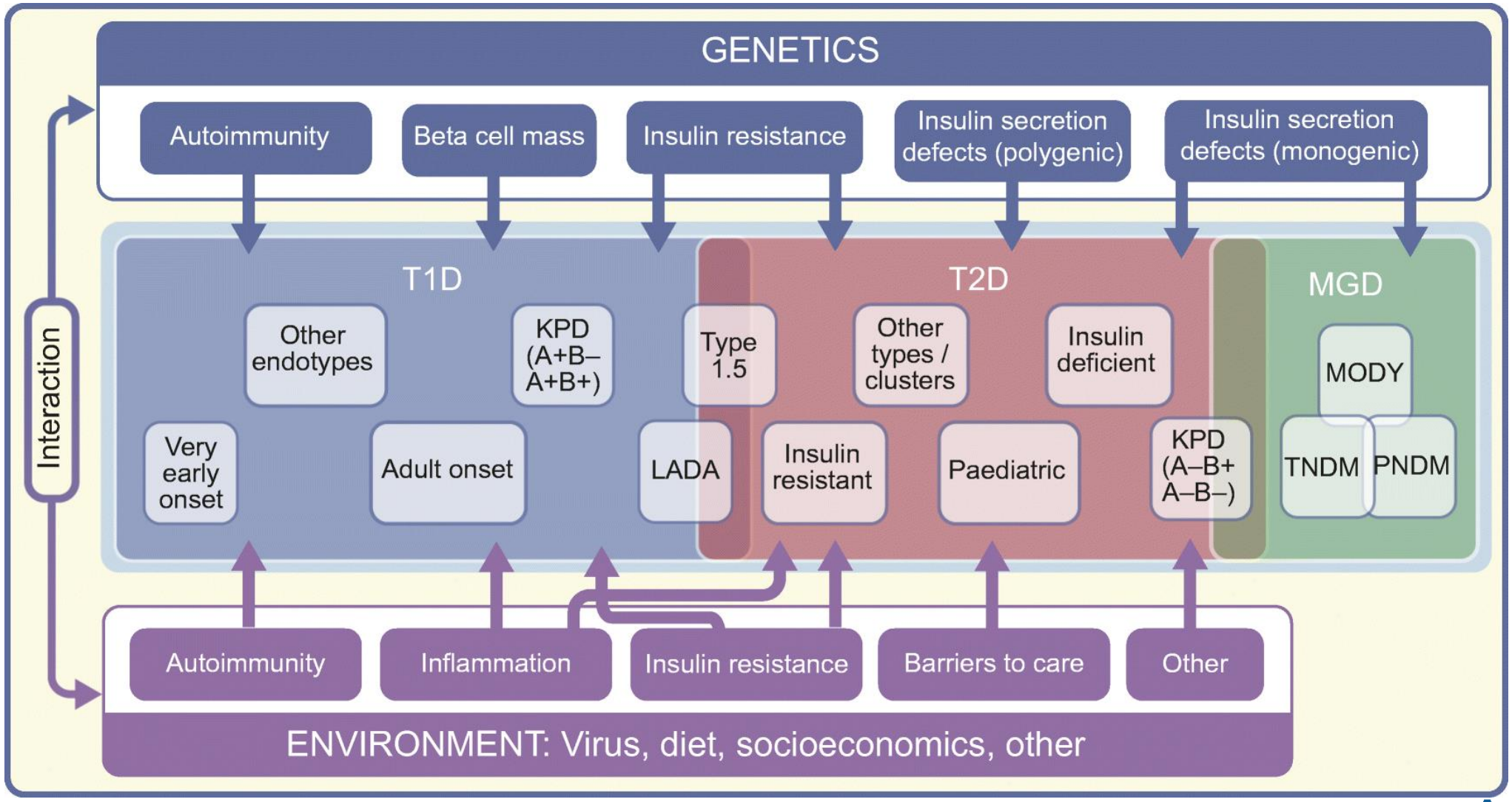
Pathophysiologic Classification of Diabetes



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Summary

- LADA patients have several features of classic type 1 diabetes in addition to islet cell antibody positivity, including high rates of HLA-DR3 and DR4.
- Patients with LADA share obesity and insulin resistance with type 2 diabetic patients but display a more severe defect in maximally stimulated [beta]-cell capacity.
- Adults with non-insulin-requiring diabetes who are positive for GAD and/or islet cell antibodies (ICA) require insulin treatment significantly earlier after diagnosis than ICA- patients.
- Considerable knowledge gaps remain:
  - What is the best treatment?
  - What is risk for CVD and microvascular complications?
  - Role of therapies adjunct to insulin?

“Whole LADA Love” from the AdventHealth Translational Research Institute

Questions?

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Connect!

Email:

Richard.Pratley.MD@adventhealth.com

Websites:

www.tri-md.com

www.adventhealthdiabetes.com

@RpratleyMD

Richard Pratley

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