

Comprehensive Screening Detects Undiagnosed Autoimmunity In Adult-onset Type 2 Diabetes

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The Changing Pattern Of Diabetes Development

Pre-1950s:

Persons With High-risk
Genes For Autoimmunity



Type-1 Or Juvenile Diabetes (Rare)

Older, Generally Overweight
Individuals



Type-2 Or Adult-onset Diabetes (Relatively Rare)

Now:

Persons With Low
Or Moderate-risk
Genes For
Autoimmunity



Environmental
Factors
Causing A Chronic
Inflammatory
State



Insulin
Resistance



Increased
Insulin Secretion
BY B CELLS

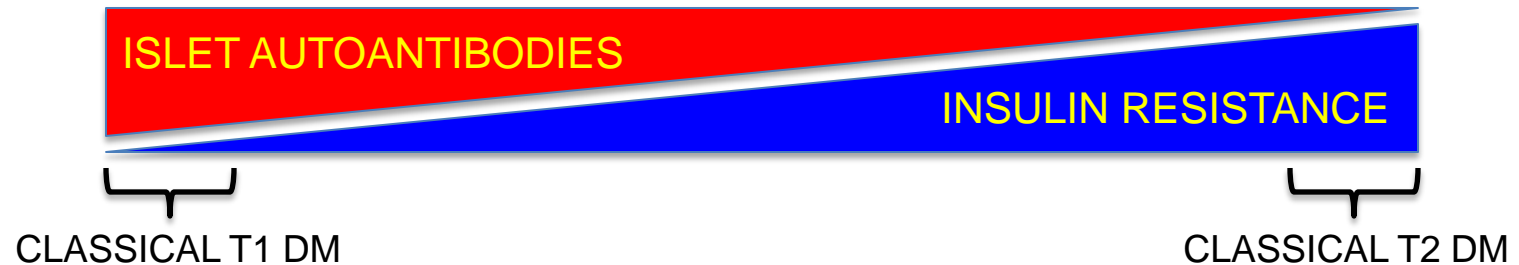


Development Of
Autoantibodies



B CELL DESTRUCTION
And Overt Diabetes

Diabetes As A Continuous Spectrum



Most patients, including children, now
Fall more in the middle of this spectrum

This intermediate class of diabetes has been
Called type-1.5, double diabetes, lada, etc.

Objective

- In a single setting perform a comprehensive autoimmune profiling to estimate the prevalence of islet, thyroid and celiac antibodies in type I and type II diabetes

Study questions:

What is relative extent of islet autoimmunity in classically-defined type-1 and type-2 diabetes?

What is the extent of thyroid and celiac autoimmunity typically associated with type-1 diabetes in a type-2 population ?

What are the associations between islet and thyroid and celiac autoimmunity?

Study Groups

T1DM

Analytic
population
N=298

T2DM

Analytic
population
N=318

Prediabetes
N=175

Type 2
Diabetes
N=143

Study Populations

- 320 Juvenile type 1 diabetics were recruited between October 2011 and September 2012 as part of the Changing Diabetes in Children (CDiC) program (Hyderabad, India).
- 318 newly diagnosed adult prediabetic/type 2 diabetic (pre-/T2DM) study population was obtained from a cross-sectional study of 1175 adults attending the same diabetes center (75-gram oral glucose tolerance test (OGTT)).

Methods

- Diabetes autoantibody standardization program (DASP) validated enzyme immunoassays were used for quantification of autoantibodies

	Sensitivity	Specificity
GAD65	92%	98%
IA-2 ALPHA	70%	99%
IAA	70%	98%
ZnT8	95th percentile of the control population	

ZnT8-directed antibodies were detected using recombinant ZnT8 comprised of the 74-amino acid N terminus fused to the 103-amino acid C terminus (with arginine at polymorphic residue 325).

Thyroid and Celiac Immunoassays

	Sensitivity	Specificity
Thyroid peroxidase (TPO)	94%	97%
Thyroglobulin (TG)	97%	97%
Tissue transglutaminase (tTG)	97%	95%

Aesku.Diagnostics (Oakland, CA).

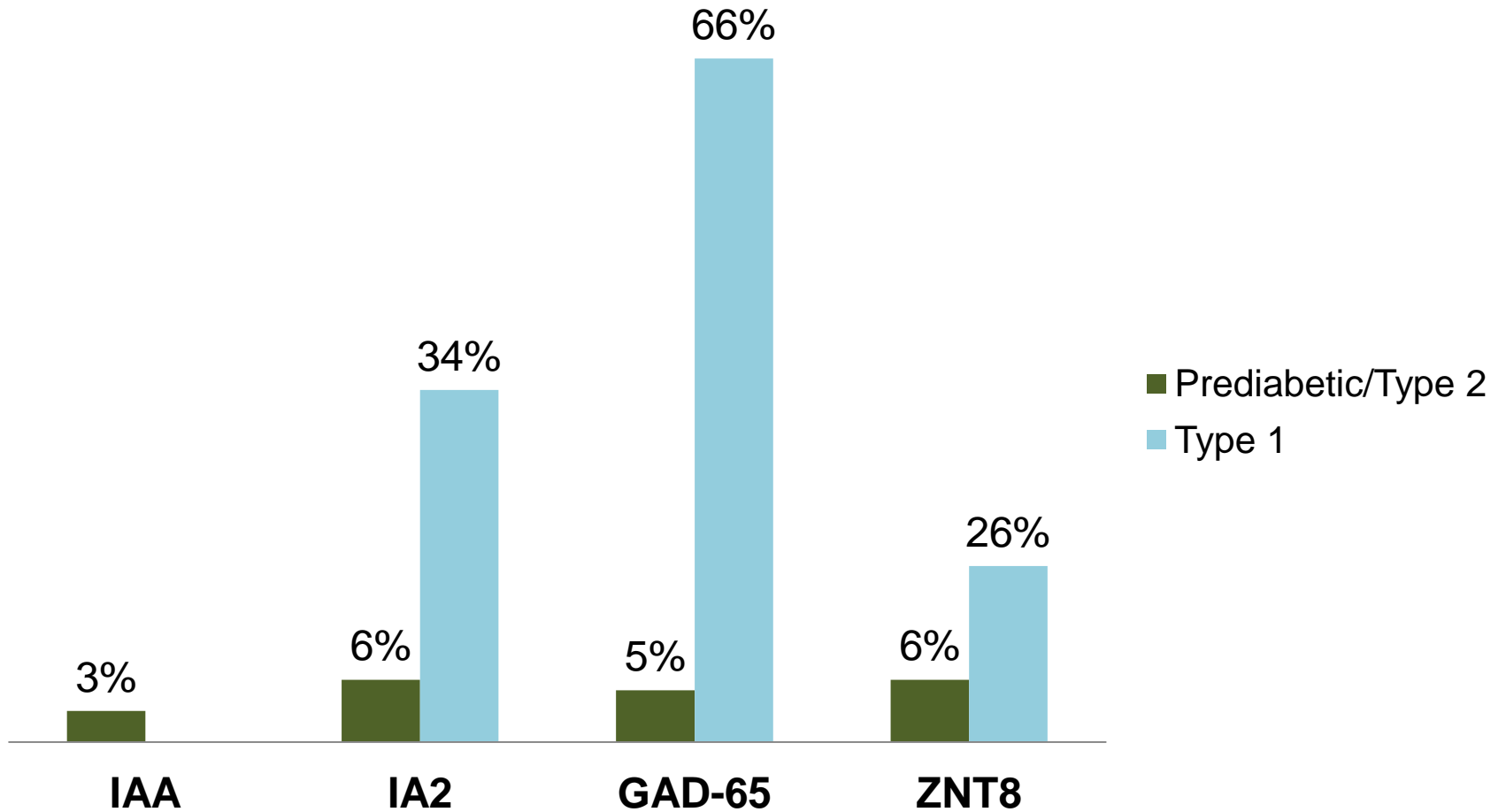
Statistical Analyses

- For continuous variables, tests of group differences by Islet Antibody Status or Number of Islet Antibodies were performed using t-tests and one-way analysis of variance (ANOVA).
- Categorical variables were analyzed using Chi-square tests and Fisher's exact tests.
- Crude and gender adjusted prevalence ratios (PR) and 95% confidence intervals (CI) for Number of Islet Antibodies and Islet Antibody Status by thyroid and celiac antibody positivity were obtained by Log-binomial regression using Poisson variance estimation

Juvenile Type 1 Diabetic Population					
	Total	Number of Islet Antibodies ¹			p-value ²
	Population	0	1	2+	
n	298	49	148	80	
Age, years	12.0 ± 3.5	11.9 ± 3.8	12.1 ± 3.5	11.8 ± 3.6	0.85
Disease duration, years	3.6 ± 3.0	3.9 ± 3.5	3.3 ± 2.8	3.4 ± 3.0	0.56
Hemoglobin A1c, % (mmol/mol)	11.3 ± 2.8 (100 ± 31)	11.3 ± 3.1 (100 ± 34)	11.5 ± 2.7 (102 ± 30)	10.7 ± 2.6 (93 ± 28)	0.16
Hemoglobin, g/L	12.7 ± 1.8	13.1 ± 1.4	12.8 ± 1.5	12.2 ± 2.4	0.01
Thyroid stimulating hormone, µIU/ml	3.78 ± 3.35	3.19 ± 2.24	3.56 ± 2.87	4.90 ± 5.43	0.17
Albumin Creatinine Ratio, µg/mg	25 ± 58	24 ± 47	22 ± 49	37 ± 116	0.39
Female gender, n (%)	157 (53)	19 (39)	82 (55)	48 (60)	0.05
Thyroid-stimulating hormone, n (%) <0.5 or >4.00 µIU/ml	58 (20)	6 (12)	28 (19)	20 (25)	0.20
Adult Prediabetic/Type 2 Diabetic Population					
	Total	Islet Antibody Status ¹		p-value ²	
	Population	Negative	Positive		
n	318	232	53		
Age, years	47.2 ± 9.7	47.6 ± 9.6	45.2 ± 9.7	0.11	
Body mass index, kg/m ²	27.3 ± 4.1	27.3 ± 4.1	27.3 ± 3.2	0.95	
Fasting plasma glucose, mmol/L	6.3 ± 1.4	6.3 ± 1.4	6.1 ± 1.4	0.53	
Oral glucose tolerance test, mmol/L	11.2 ± 3.5	11.2 ± 3.6	10.8 ± 3.2	0.95	
Total cholesterol, mmol/L	4.83 ± 1.01	4.75 ± 0.98	5.07 ± 1.20	0.04	
Low density lipoprotein, mmol/L	3.08 ± 0.87	3.00 ± 0.83	3.29 ± 1.02	0.06	
High density lipoprotein, mmol/L	0.92 ± 0.19	0.92 ± 0.20	0.93 ± 0.18	0.84	
Triglycerides, mmol/L	1.78 ± 0.98	1.78 ± 1.03	1.86 ± 0.83	0.24	
Systolic blood pressure, mmHG	134 ± 18	135 ± 19	132 ± 14	0.31	
Waist-to-hip ratio					
Female	0.89 ± 0.06	0.89 ± 0.06	0.90 ± 0.06	0.71	
Male	0.95 ± 0.05	0.95 ± 0.05	0.95 ± 0.05	0.87	
Female gender, n (%)	102 (32)	67 (29)	22 (42)	0.07	
Diabetes condition, n (%)				0.16	
Prediabetes	175 (55)	124 (53)	34 (64)		
NDM	143 (45)	108 (47)	19 (36)		

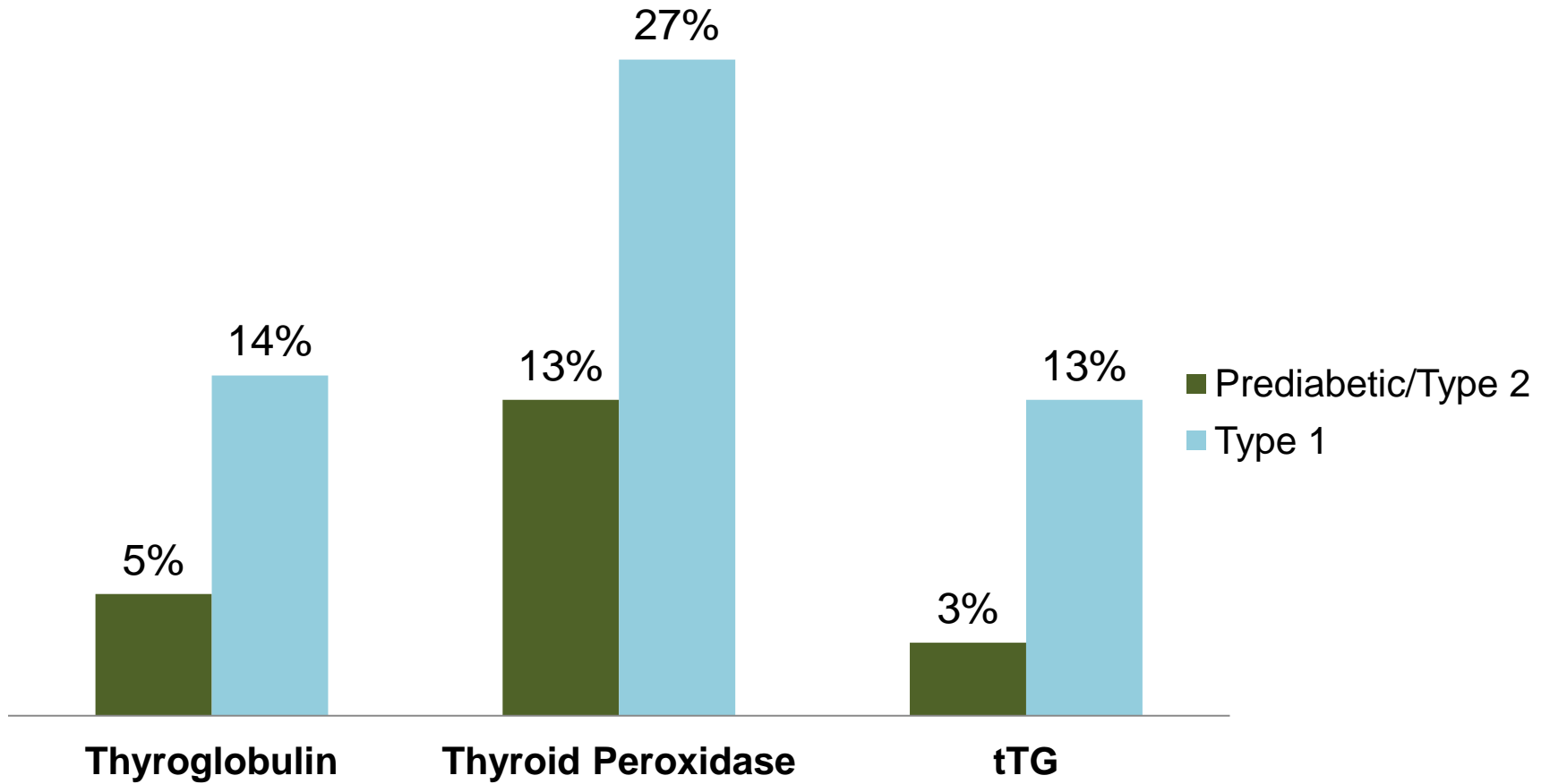
Prevalence Estimates

Islet Autoantibodies

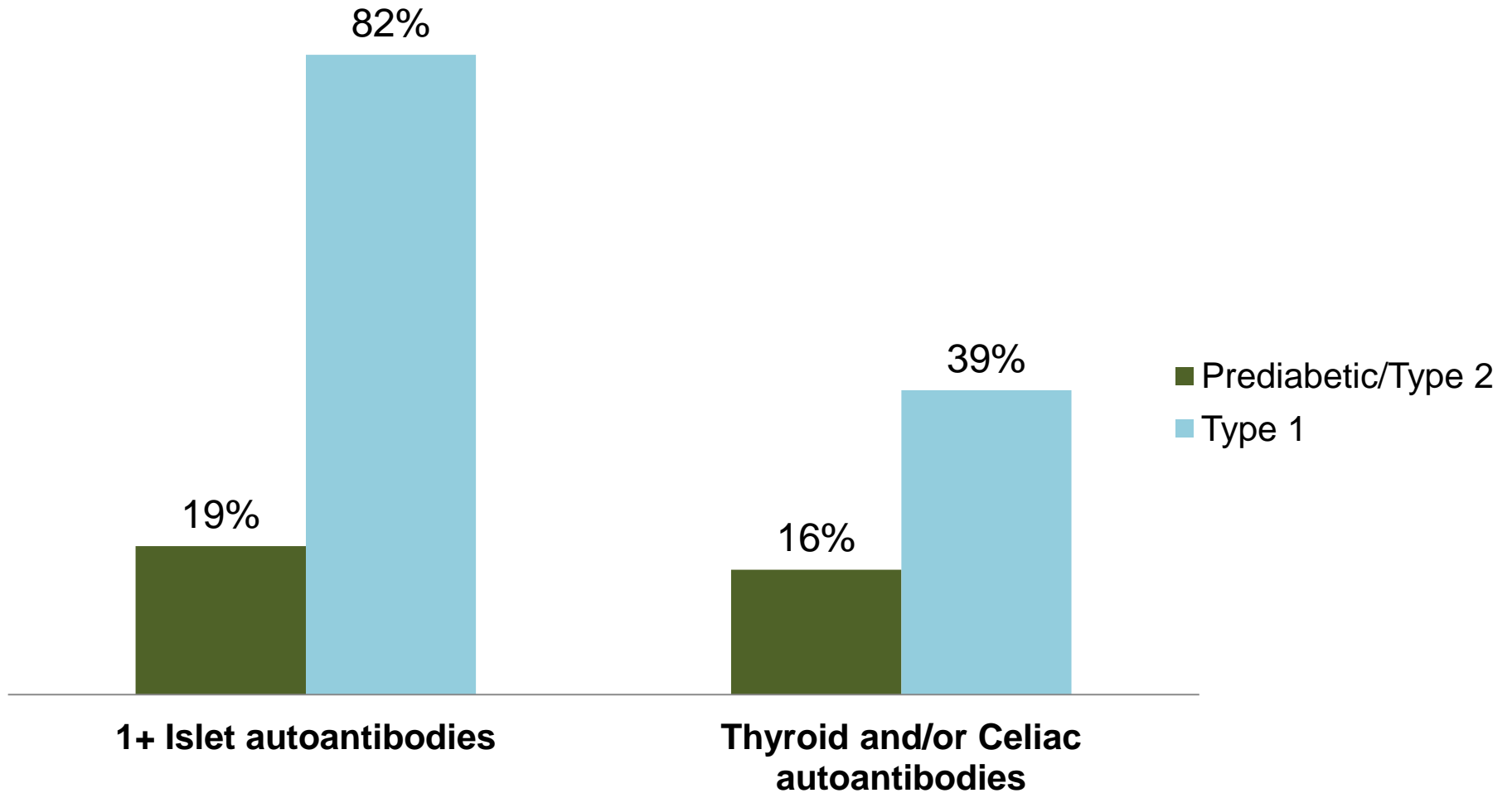


Prevalence Estimates

Thyroid And Celiac Autoantibodies

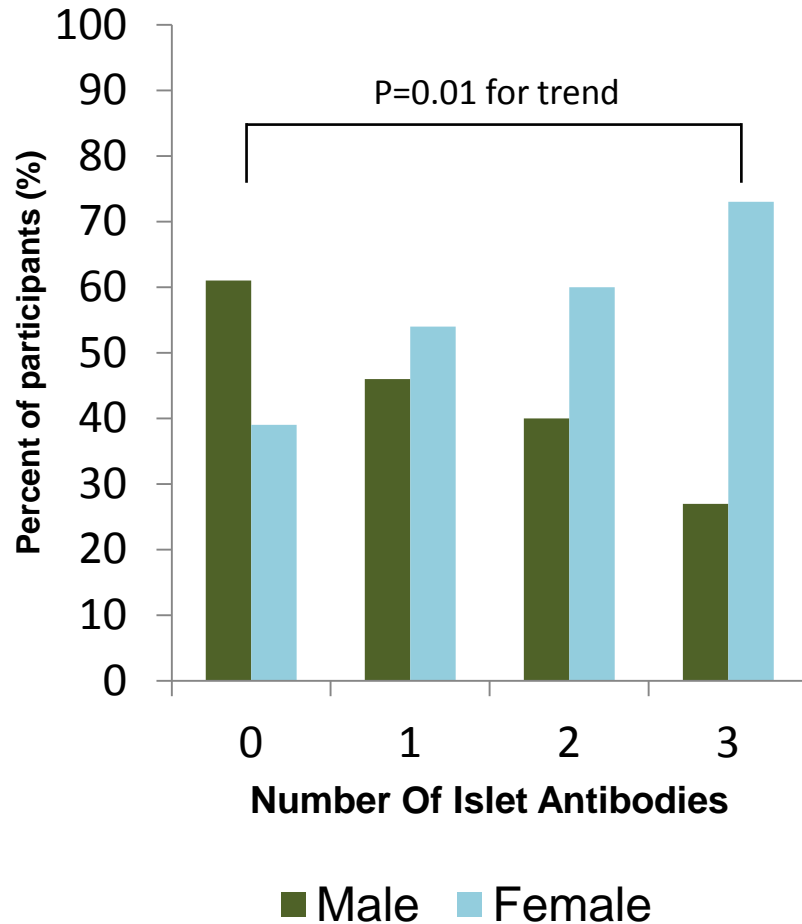


Frequency Of Autoimmunity

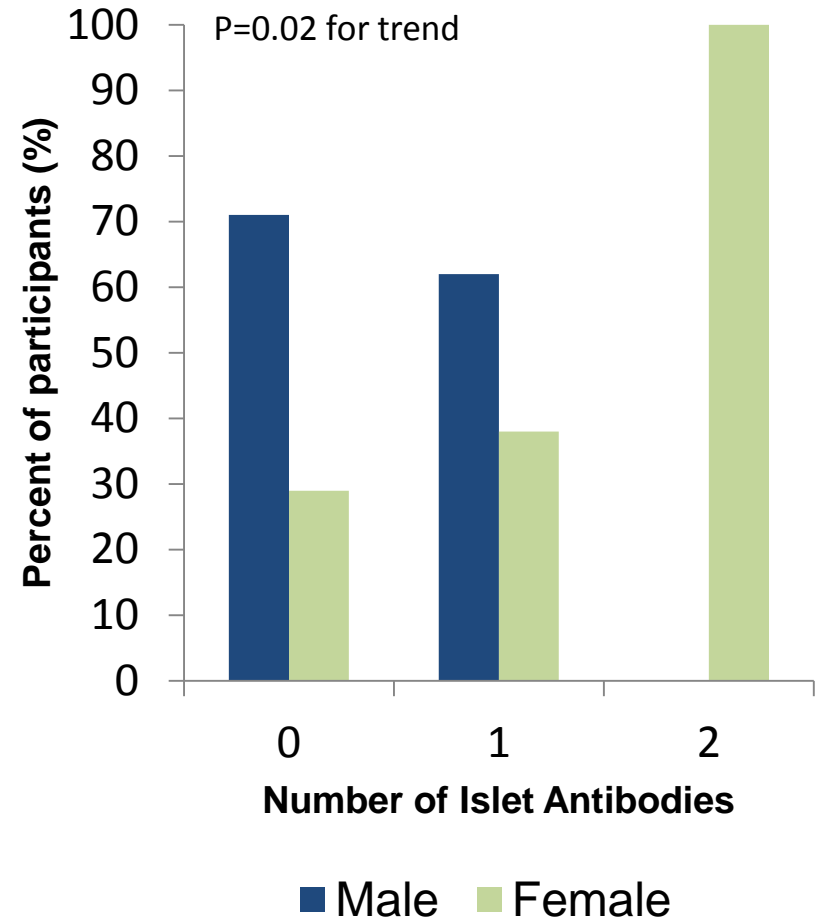


Gender Differences

Juvenile type 1 diabetes

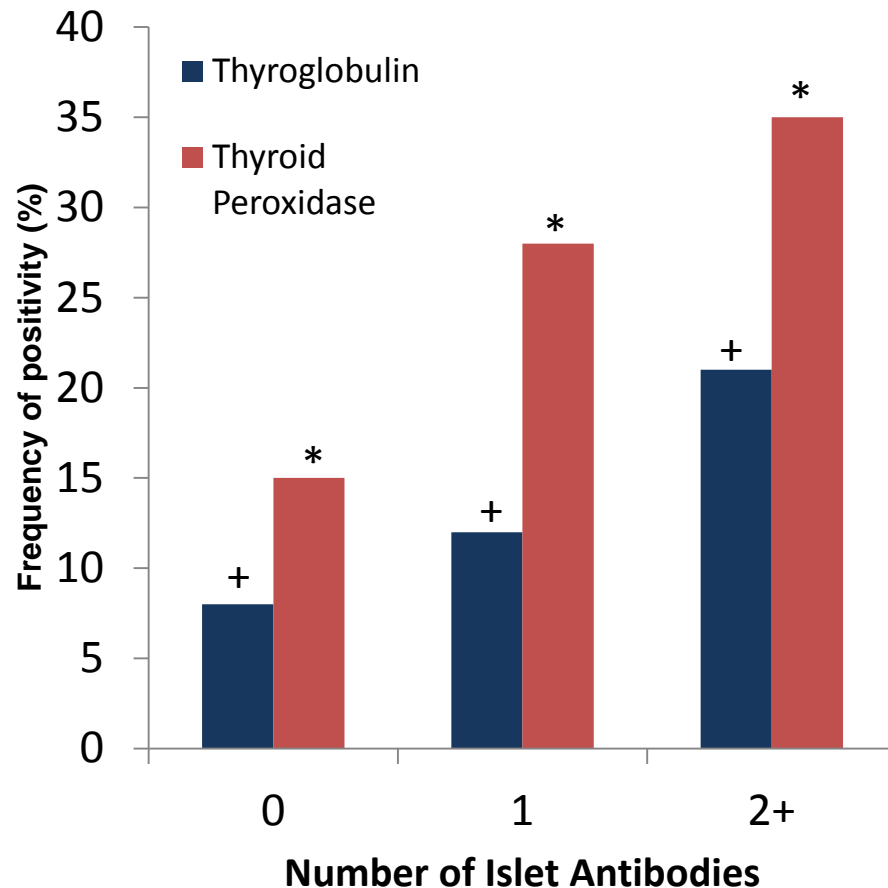


Adult Pre- and Type 2 diabetes

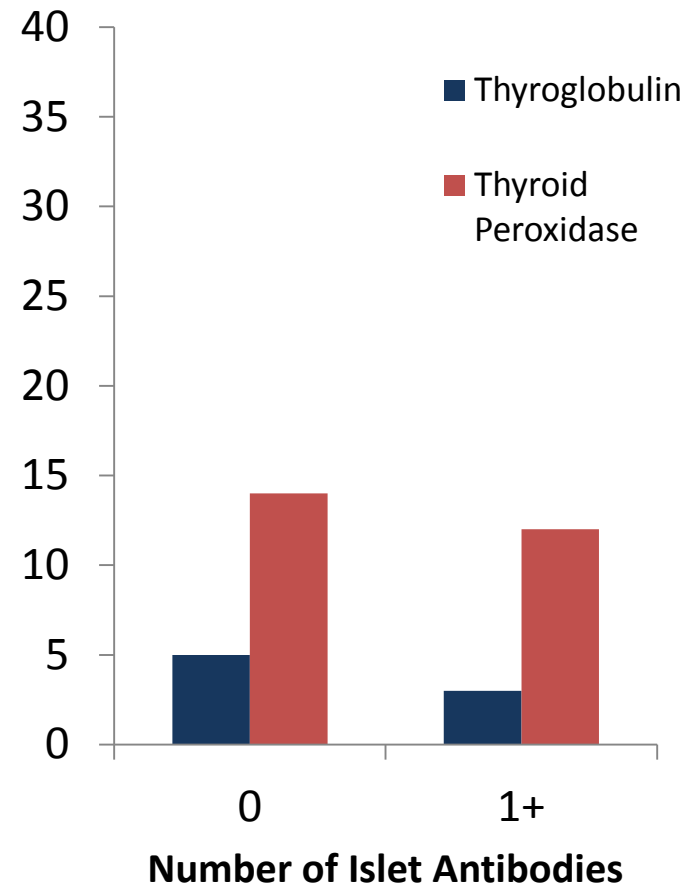


Frequency Of Thyroid Autoantibodies By Number Of Islet Autoantibodies

Juvenile Type 1 diabetes



Adult Pre- and Type 2 diabetes



* p=0.02 for trend + p=0.04 for trend

Juvenile Type 1 Population					
	0 Islet Antibody	1 Islet Antibody		2+ Islet Antibody	
		PR (95% CI)	p-value	PR (95% CI)	p-value
Thyroid Peroxidase Antibody					
Crude	1.00	2.04 (0.92, 4.53)	0.08	2.44 (1.11, 5.39)	0.03
Gender-Adjusted	1.00	1.91 (0.86, 4.25)	0.11	2.21 (1.00, 4.90)	0.05
Thyroglobulin Antibody					
Crude	1.00	1.08 (0.37, 3.18)	0.89	2.20 (0.80, 6.04)	0.13
Gender-Adjusted	1.00	0.98 (0.33, 2.87)	0.97	1.88 (0.69, 5.12)	0.21
Tissue Transglutaminase Antibody					
Crude	1.00	3.61 (0.88, 14.80)	0.08	2.93 (0.70, 12.37)	0.14
Gender-Adjusted	1.00	3.48 (0.84, 14.46)	0.09	2.77 (0.66, 11.72)	0.17
Adult Pre-T2DM Population					
	Islet Antibody Negative	Islet Antibody Positive			
		PR (95% CI)	p-value		
Thyroid Peroxidase Antibody					
Crude	1.00	0.91 (0.45, 1.88)	0.80		
Gender-Adjusted	1.00	0.85 (0.41, 1.74)	0.65		
Thyroglobulin Antibody					
Crude	1.00	0.58 (0.13, 2.51)	0.46		
Gender-Adjusted	1.00	0.53 (0.11, 2.52)	0.42		

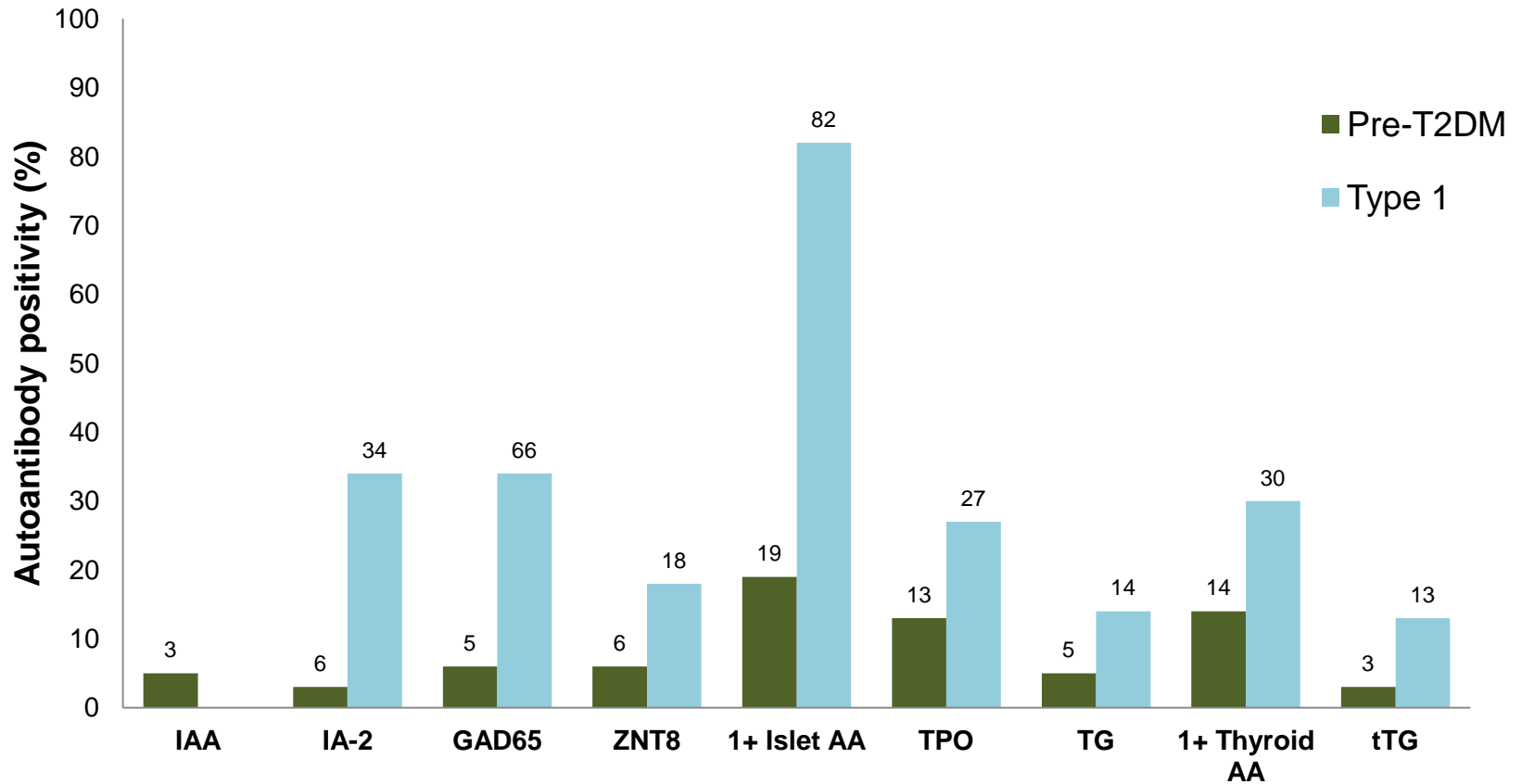
Thyroid Autoantibodies

In type 1 diabetes, the frequency of thyroid peroxidase (TPO) and thyroglobulin (TG) autoantibodies increased as the number of islet autoantibodies increased (p for trend=0.01 and 0.04, respectively).

TPO and TG were significantly associated with TSH values outside the range of 0.50-5.00 μ IU/mL (p<0.001 and p=0.0003, respectively).

TPO exhibited higher frequencies of positivity in both Type 1 and pre/type-2 groups. TG was rarely positive in the absence of TPO positivity.

SUMMARY OF AUTOANTIBODY FREQUENCIES



Conclusions

Islet autoantibodies are present in a significant proportion of newly diagnosed subjects with pre- as well as frank type 2 diabetes.

Thyroid and celiac autoantibodies known to be associated with type 1 diabetes are also present in a significant proportion of individuals with pre- and type 2 diabetes.

These data suggest that a more comprehensive assessment of autoimmunity may be warranted in evaluation of patients with pre- or type 2 diabetes.

Acknowledgements

Supported in part by grant 1R43DK096956-01 to SRN