

Autoantibodies in Thyroid Disease and Diabetes

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What's an Autoantibody?

- An autoantibody is an antibody manufactured by the immune system that is directed against one or more of the individual's own proteins

A List of a Few of the Medically Important Autoantibodies

- Antinuclear antibody (ANA)
- Anti-p62 antibodies in primary biliary cirrhosis
- Anti-sp100 antibodies in primary biliary cirrhosis
- Anti-glycoprotein210 antibodies in primary biliary cirrhosis
- antibody
- Anti-extractable nuclear antigen antibodies (Anti-ENA antibodies)
 - Anti-Ro antibody
 - Anti-La antibody
- Anti-PM/Scl (anti-exosome) antibody
- Anti-Scl 70 antibody (in sclerosis and scleroderma)
- Anti-topoisomerase antibodies
- Anti-centromere antibodies
- Anti-smooth muscle antibody
- Anti-transglutaminase antibodies
- Anti-tTG coeliac disease
- Anti-eTG dermatitis herpetiformis
- Anti-actin antibodies
- Anti-ganglioside antibodies
- Anti-GD3 (Guillain-Barré syndrome)
- Anti-GM1 (travellers diarrhoea)
- Anti-GQ1b
- Anti-gastric parietal cell antibody
- Anti-glomerular basement membrane antibody
- Anti-Hu antibody
- Anti-Jo 1 antibody
- Anti-liver/kidney microsomal 1 antibody (anti-LKM 1 antibodies)
- Anti-Ku antibody
- Anti-mitochondrial antibody
- Anti-neutrophil cytoplasmic antibody (ANCA)
- Rheumatoid factor
- Lupus anticoagulant
- Anti-thrombin antibodies
- etc, etc etc.....

Thyroid

The 2 Classic Autoimmune Thyroid Diseases

- Graves' disease – autoimmune hyperthyroidism
- Hashimoto's disease / thyroiditis – autoimmune hypothyroidism

	Females	Males
Hypothyroidism	4.1	0.6
Hyperthyroidism	0.8	<0.1

Incidence per 1000 per year

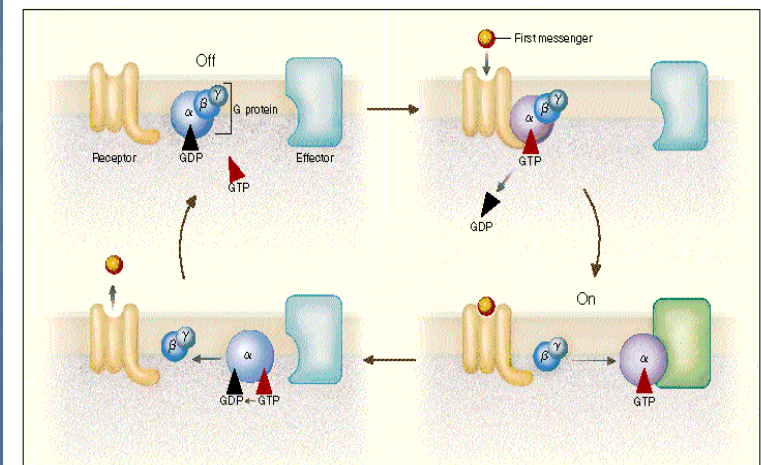
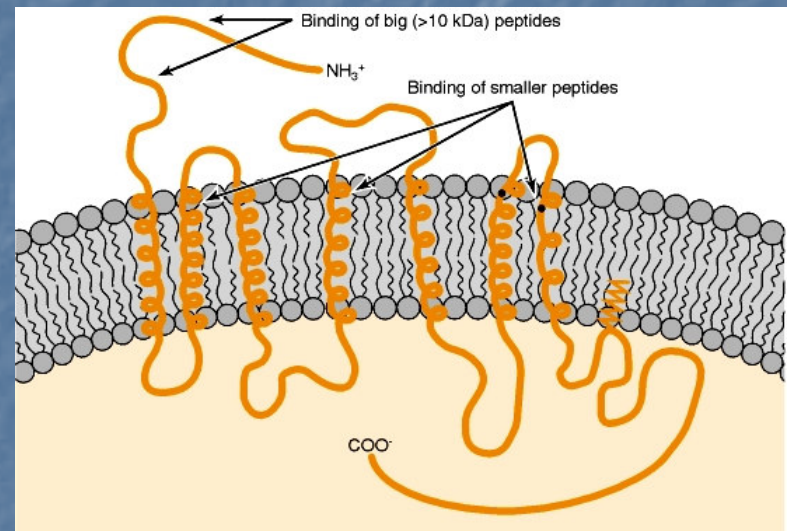
Vanderpump et al Clin Endo 1995;43:55-68

The Main Thyroid Antibodies

- Anti – TSH receptor antibodies (TRAb)
- Anti-thyroid peroxidase antibodies (TPO)
- (Anti thyroglobulin)

The TSH receptor

- The primary target for the autoantibody is the TSH receptor
- This is a classic glycopeptide 7 transmembrane G-protein linked receptor



Graves' Disease

- TSH receptor antibodies (TRAb) bind to the TSH receptor
- Activating the G-protein coupled mechanism
- Increasing cAMP and adenylate cyclase, triggering the intracellular signalling cascade
- Ultimately leading to the inappropriate secretion on thyroxine

Graves' Disease

- TSH receptor antibodies are present in 80-100% of all cases of Graves' – their presence is essentially diagnostic of Graves'
- Levels decrease with treatment
- Levels after treatment are predictive of relapse

Graves' Disease

- TRAb is usually stimulating
- They can occasionally be blocking – but these have no effect on the receptor
- They may be responsible for continuing pituitary TSH suppression despite normalisation of the fT4/fT3 levels with drugs / RAI / surgery

Anti TPO antibodies

- Far more commonly performed than TSH receptor antibodies
- But far less specific
- Useful as a diagnostic marker
- Is an indicator of thyroid injury – thus not a cause of the condition, but a result of the condition

Prevalence of Thyroid Autoantibodies

Group	TRAb (%)	TgAb (%)	TPOAb (%)
General population	0	5-20	8-27
Graves'	80-95	50-70	50-80
Hashimoto's	10-20	80-90	90-100
Relatives	0	40-50	40-50
Those with T1DM	0	40	40
Pregnant women	0	14	14

Anti TPO antibodies

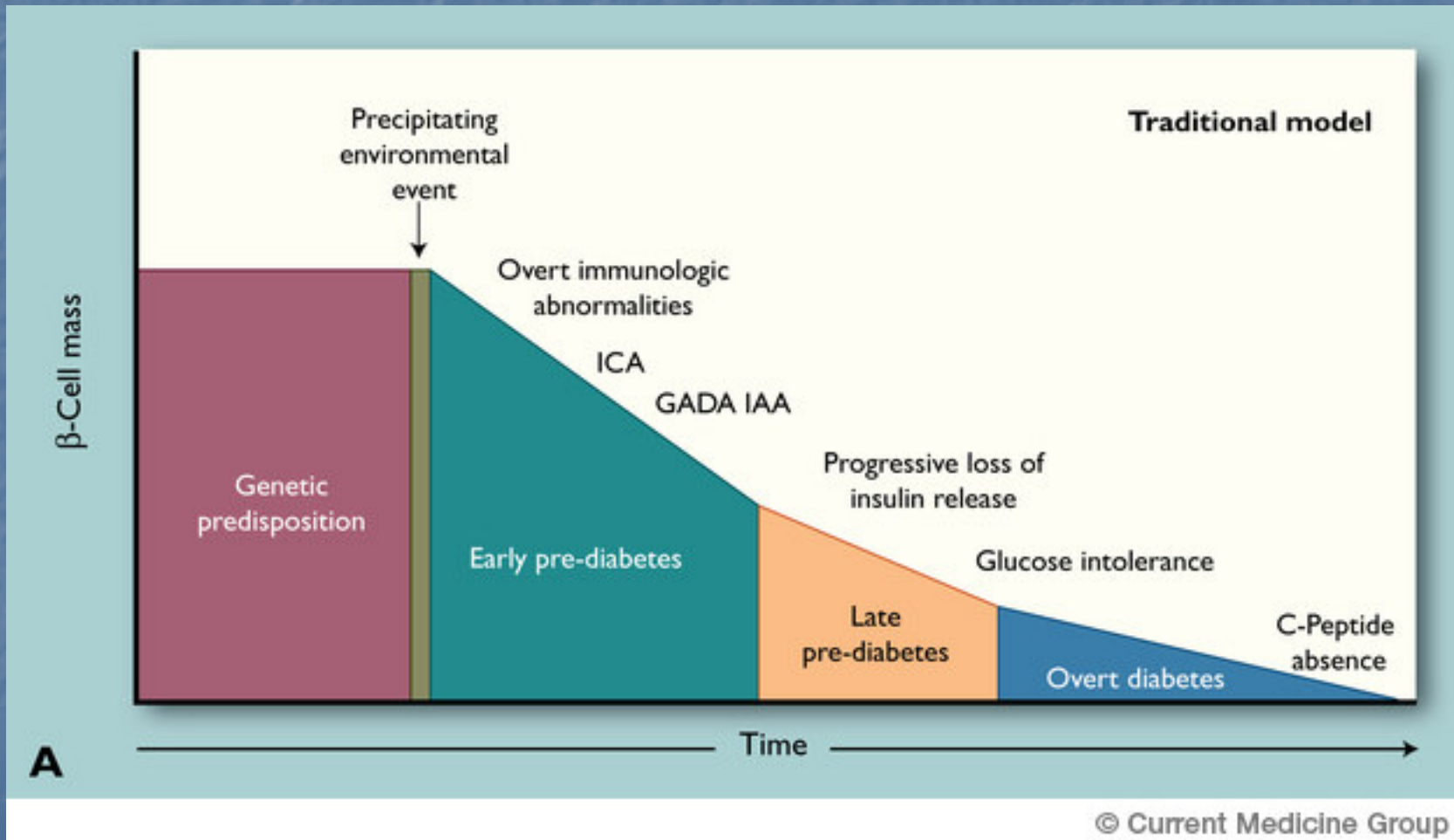
- High titres in subclinical disease (i.e. raised TSH but normal fT4/fT3) are more likely to be associated with the development of overt hypothyroidism over time (3-5% per year)

Anti-thyroglobulin antibodies

- Very rarely done at the N&N. The only time this is really useful is in patients with thyroid cancer
- Thyroid cancer releases thyroglobulin, and is thus a maker for tumour bulk
- Post surgery / RAI is it is measured to assess tumour recurrence
- High levels of AntiTg negates the Tg report, and disease progression needs to be made clinically / using imaging

Diabetes

The Classic Model of the Pathogenesis of T1DM



Autoantibodies in Type 1 Diabetes

- There are 3 main autoantibodies
 - Anti islet cell (ICA512/IA-2)
 - Anti glutamic acid decarboxylase (GAD65)
 - Anti-insulin (IAA)

Autoantibodies in Type 1 Diabetes

- In relatives of people with established T1DM, over 90% of people who go on to develop T1DM have one or both of these antibodies
- It is thus a reasonable predictor to see if someone is at risk of developing the condition
- The more antibodies present simultaneously, the greater the risk

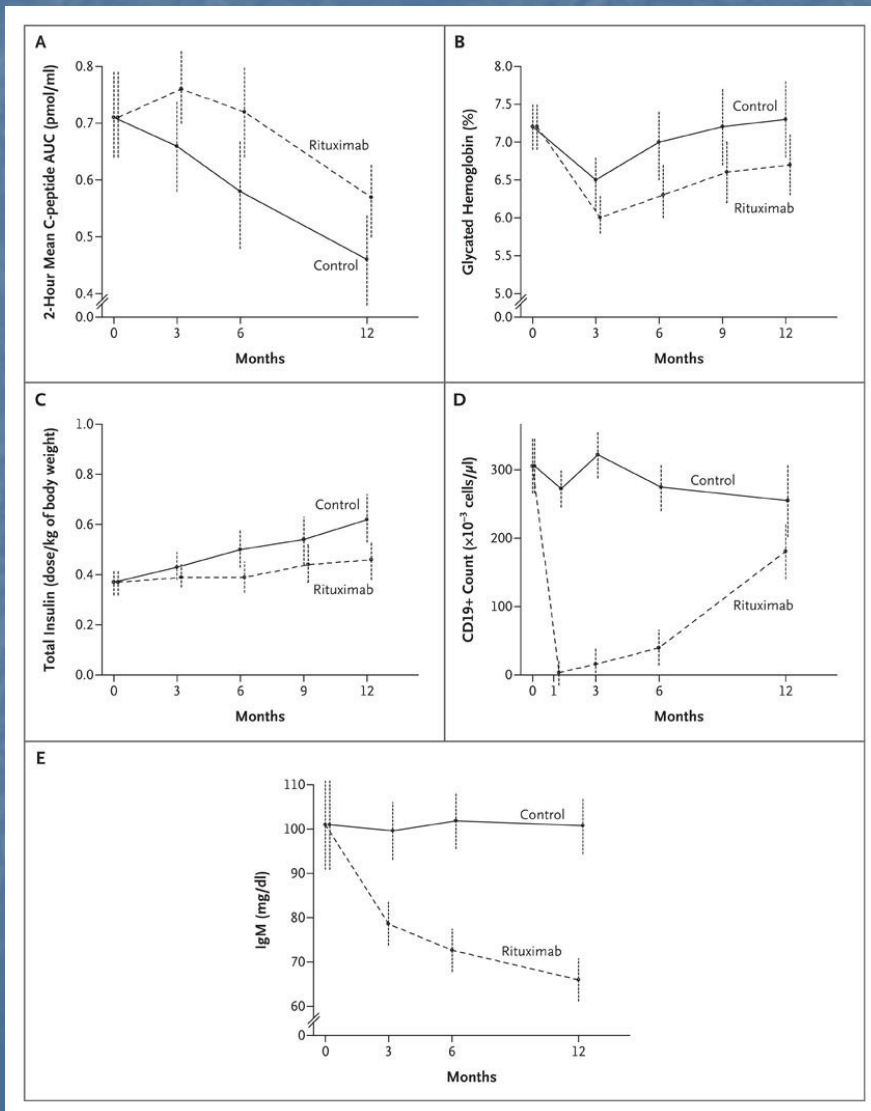
However

- Up to 3% of the population has these antibodies, and 90% of children who develop T1DM do not have a family member with the condition

Prevalence of GAD

Group	Autoantibody Frequency (%)
Healthy control group	0.3–0.6
First-degree relatives of patients with type 1 diabetes	3–4
Patients with other autoimmune endocrine disorders	1–2
Patients with newly diagnosed type 1 diabetes	55–85
Patients with type 2 diabetes	10–15
Patients with gestational diabetes	10

Hope with Rituximab?



- 87 people with newly diagnosed type 1 diabetes
- Given 4 doses of rituximab over 3 weeks
- Followed up for a year

Thyroids and Diabetes are Related

- If a person presents with one, look out for the same person having another autoimmune disease, or for one of their family to have something else

	Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED)		
	PAS I	PAS II(A) (Schmidt's syndrome)	PAS IIB (or III)
Central Clinical Feature:	Autoimmune adrenal failure (Addison's disease)	Autoimmune adrenal failure (Addison's disease)	Autoimmune thyroid disease (Hashimoto, Graves)
Other clinical features (one or more):	Hypoparathyroidism	Autoimmune thyroid disease (Hashimoto, Graves)	Pernicious anaemia
	Chronic candidiasis	Pernicious anaemia	Vitiligo
	Gonadal failure	Vitiligo	Alopecia
	Hypopituitarism	Alopecia	Immune mediated diabetes (T1DM)
	Coeliac disease	Immune mediated diabetes (T1DM)	Coeliac disease
	Pernicious anaemia	Coeliac disease	Gonadal failure
	Vitiligo	Gonadal failure	
	Alopecia		
	Immune mediated diabetes (T1DM)		
	Autoimmune thyroid disease		
Genetics:	Autosomal recessive	Likely to be an autosomal dominant, with variable expression	Likely to be an autosomal dominant, with variable expression
	Defect of AIRE gene	CTLA-4 gene HLA-DR3 and/or HLA-DR4 haplotypes, chromosome 6	CTLA-4 gene HLA-DR3 and/or HLA-DR4 haplotypes, chromosome 6
Prevalence:	Rare	More common	More common
Onset:	Childhood onset	Adult onset	Adult onset

Thank you for your attention