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Thyroid assessment in children & teenagers – when, why and how

WHAT DO WE KNOW ABOUT KIDS' THYROIDS?

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Kapelari et al.
Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. BMC Endocrine Disorders 2008, 8:15

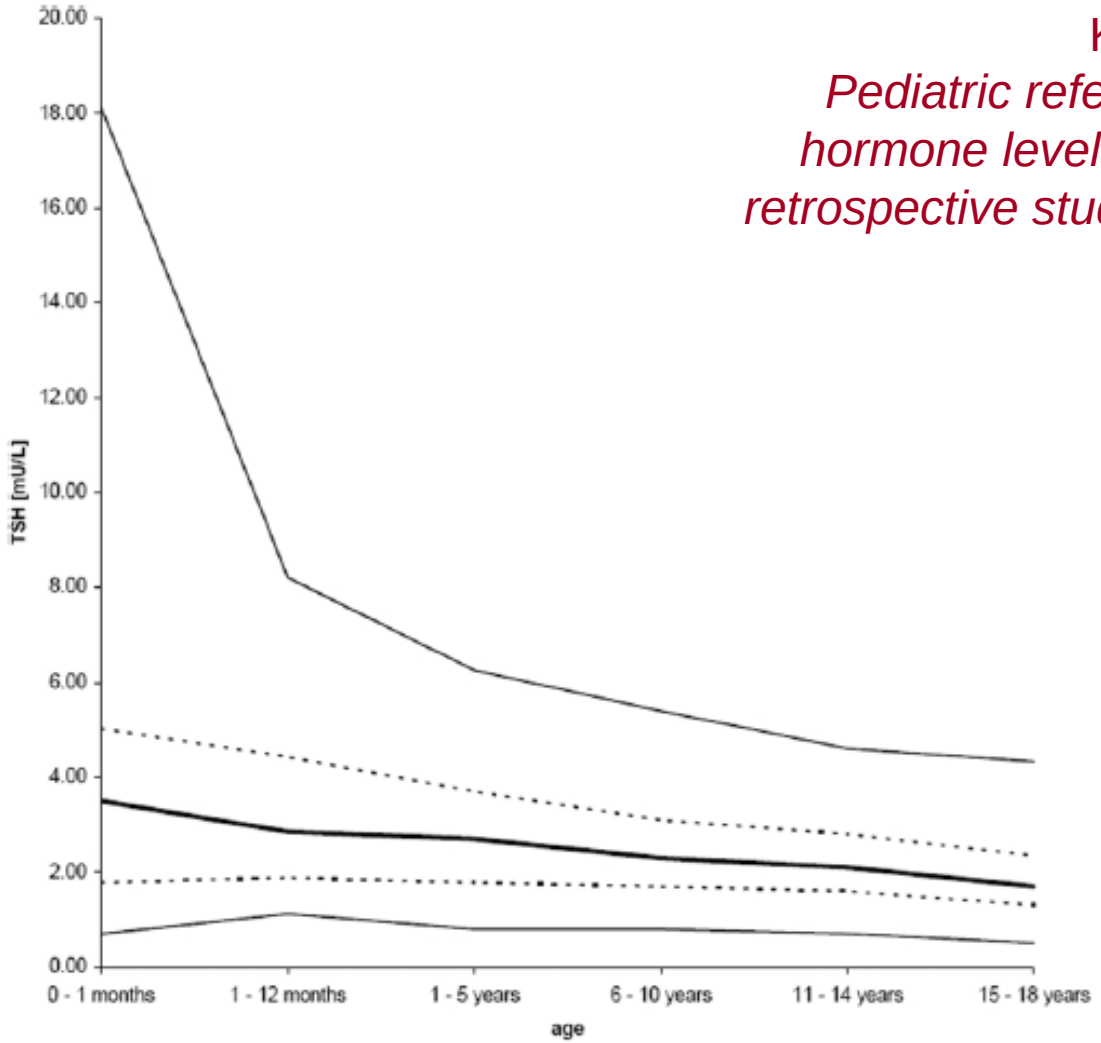

Figure 1
Reference intervals for TSH of age groups listed in table 2. The central 95% range (2.5th, 25th, 50th, 75th, and 97.5th percentiles) is shown.

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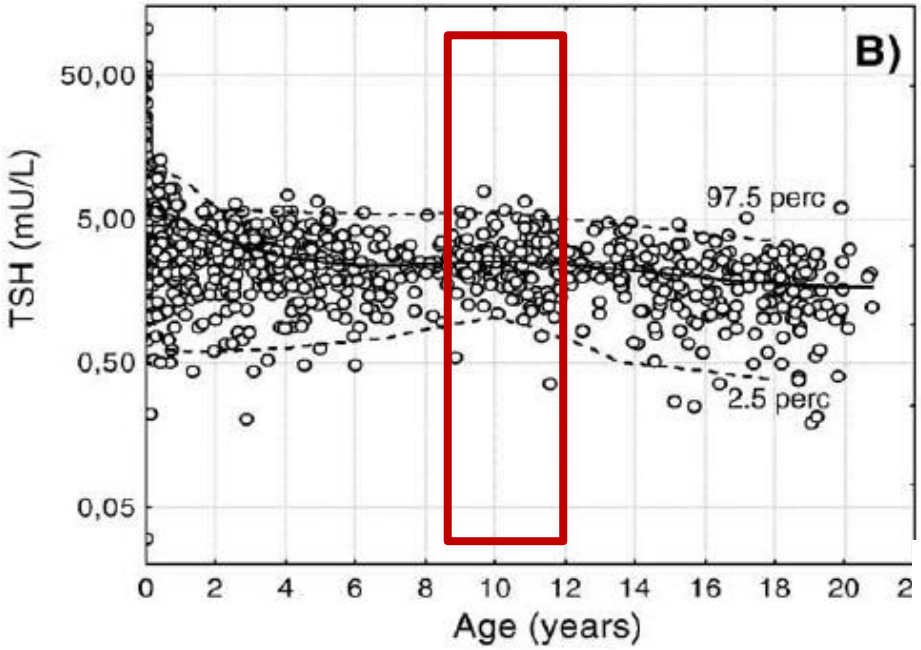
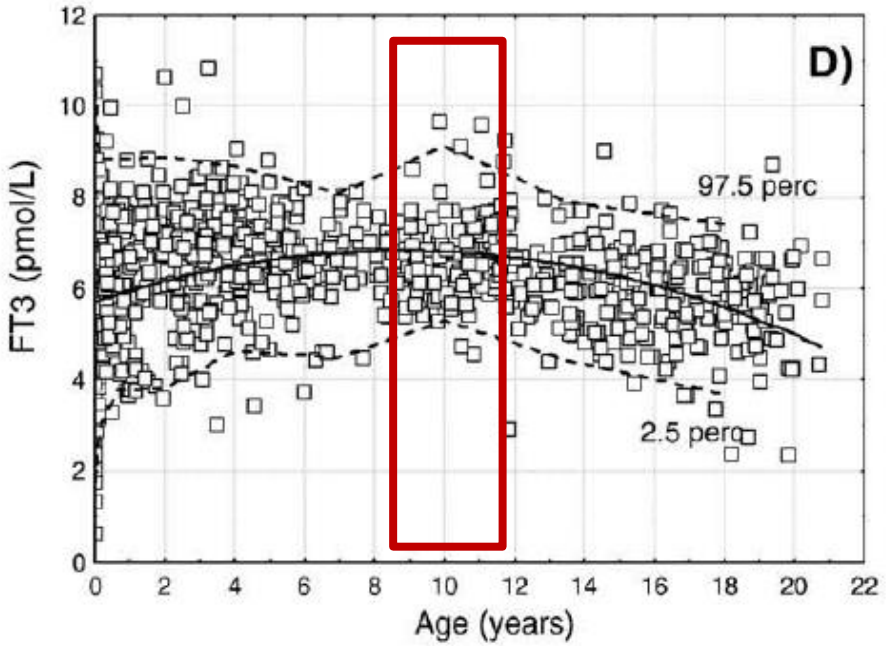


Kratzsch et al. 2008. Clinical Biochemistry 41 (2008) 1091–1098

Elevation in TSH/T3 levels between 9-11yrs in both genders – corresponds with growth spurt of the thyroid



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TSH Percentiles in Kids & Adolescents (Kapelari et al 2008)

Age	n	percentiles						
		2.5	10	25	50	75	90	97.5
0 – 1 months	22	0.70	1.00	1.78	3.50	5.03	9.34	18.10
1–12 months	42	1.12	1.53	1.88	2.85	4.43	6.81	8.21
1–5 years	218	0.80	1.30	1.78	2.70	3.70	4.80	6.26
6–10 years	315	0.80	1.20	1.70	2.30	3.10	3.80	5.40
11–14 years	355	0.70	1.10	1.60	2.10	2.80	3.60	4.61
15–18 years	233	0.50	0.94	1.30	1.70	2.35	3.30	4.33

T3 Percentiles in Kids & Adolescents

Table 2: Percentiles for fT3 (pmol/L) of children and adolescents in different age groups.

Age	Sex	n	percentiles						
			2.5	10	25	50	75	90	97.5
0 – 1 months	f	5	5.00	5.00	5.40	6.60	7.30	7.50	7.50
	m	9	4.60	4.60	5.70	6.30	6.90	10.10	10.10
1–12 months	f	14	4.30	4.50	5.63	6.15	7.03	7.50	7.60
	m	13	4.30	4.74	5.65	6.20	6.70	7.38	7.50
1–5 years	f	108	4.25	4.80	5.50	6.15	6.58	7.11	7.61
	m	111	3.96	5.32	5.70	6.30	6.70	7.48	8.14
6–10 years	f	163	4.21	5.10	5.50	6.20	6.60	7.00	7.58
	m	219	4.05	5.20	5.70	6.10	6.50	7.10	7.50
11–14 years	f	180	3.51	4.90	5.40	5.90	6.30	6.80	7.30
	m	252	4.63	5.20	5.60	6.00	6.40	6.80	7.20
15–18 years	f	98	3.50	4.48	4.80	5.30	5.83	6.50	6.90
	m	211	4.20	5.00	5.40	5.80	6.20	6.60	7.47

Median TSH Paediatrics (Kratzsch et al 2008)

Table 2
Reference intervals (2.5th –97.5th percentiles) for TSH, FT3 (a), FT4, T3 (b), T4 and T-uptal

A)	TSH (mU/L)		
	N	Median	Percentiles
1–6 days	70	6.88	0.71–57.2
	(63)	(7.10)	(0.71–57.2)
7–90 days	90	3.89	0.99–10.9
	(74)	(3.83)	(0.52–9.92)
3–12 months	113	3.42	0.61–10.7
	(104)	(3.48)	(0.73–10.7)
1–3 years	118	2.60	0.60–5.80
	(116)	(2.60)	(0.60–5.60)
3–5 years	129	2.57	0.63–5.63
	(128)	(2.58)	(0.63–5.63)
6–8 years	109	2.38	0.76–5.35
	(105)	(2.37)	(0.76–5.35)
9–11 years	132	2.54	1.04–5.61
	(122)	(2.53)	(1.04–5.61)
12–15 years	103	2.14	0.51–4.60
	(96)	(2.12)	(0.51–4.44)
16–20 years	127	1.66	0.38–3.47
	(116)	(1.67)	(0.36–3.83)

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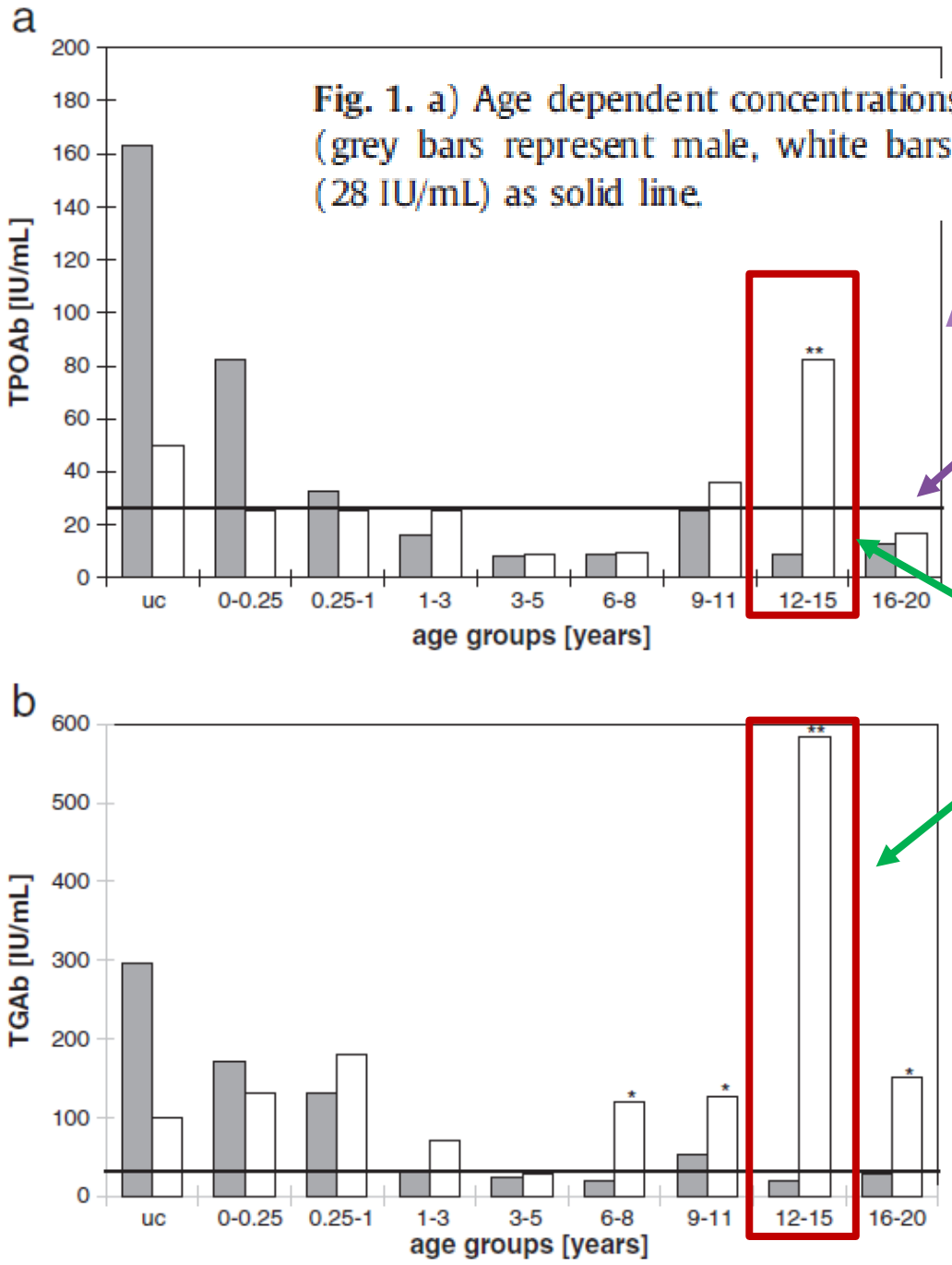

Fig. 1. a) Age dependent concentrations of TPOAb. Bars represent the 95th percentile, (grey bars represent male, white bars female values); the Roche cut-off for adults (28 IU/mL) as solid line.

Adult cut-off levels thyroid Abs

3.3%TPO Abs > adult ref range
13.3% TgAbs > adult ref range

Thyroid Abs levels jump especially in girls at puberty believed to be due to the immune activating effects of oestrogen

Taubner et al. Clinical Biochemistry 47 (2014) 3–7

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Rates of TPO Abs > 100mU/L in girls (grey) and boys (black)

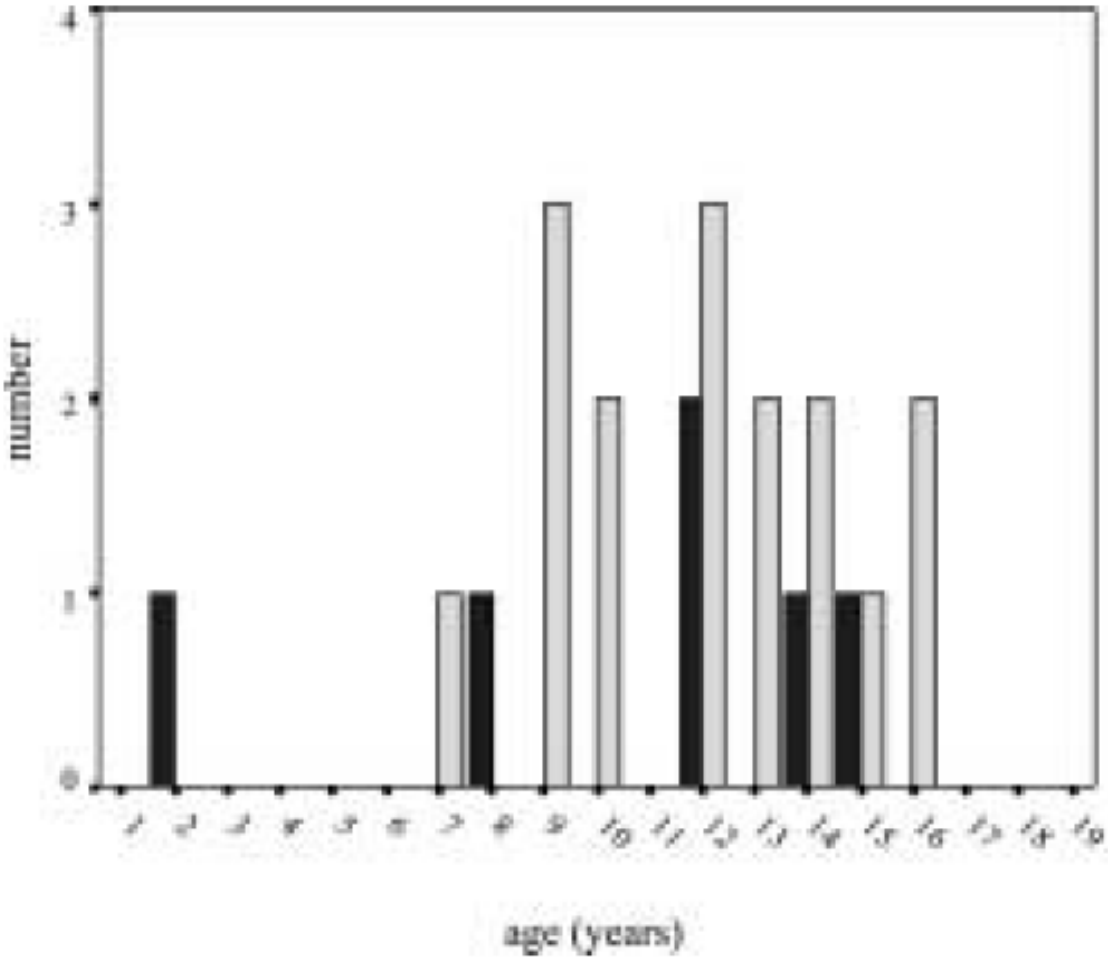

Figure 4 Age and sex distribution of the anti-TPO antibody positive probands. Dark grey bars, males; pale grey bars, females.

Kabelitz et al. The prevalence of anti-thyroid peroxidase antibodies and autoimmune thyroiditis in children and adolescents in an iodine replete area. European Journal of Endocrinology (2003) 148 301–307

How Should We Interpret Thyroid Abs in Kids?

- **Use of adult ref ranges for thyroid Ab titres is appropriate for TPO but not TgAbs which tend to be higher in kids**
- Typical trend described is the dominance of TgAbs in childhood – while not specifically pathological in thyroiditis – there is some suggestion that it represents the initial insult to the gland & secondary TPO ABs are then the one to watch?
- **Although several studies suggest that TPO titres >100mU/L should be the cut-off for concern/further investigation a Swedish study of adolescents found that 75% of these subjects had a diagnosable thyroid condition**

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How Should We Interpret Thyroid Abs in Kids?

- **It is reported that 3-8% of 'apparently healthy children' have thyroid Abs esp TPO (Segni et al 2014, Milakovic et al 2001)**
- Expect girls esp those entering puberty (ages 9-16yrs) to demonstrate a rise in thyroid Abs - ? Window of risk?
- **TPO Abs male:female in children has been reported to be 1:2.7**

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There is a general consensus that in kids…

(Bona et al 2013, Monzani et al 2013, Taubner et al 2014)

The initial presence of goitre and elevated Tg-Abs and a progressive increase in TPO-Abs and TSH values predict a progression toward overt hypothyroidism.

&

An initial TSH higher than 7.5 mIU/L and female gender are predictive factors for a sustained highly elevated TSH

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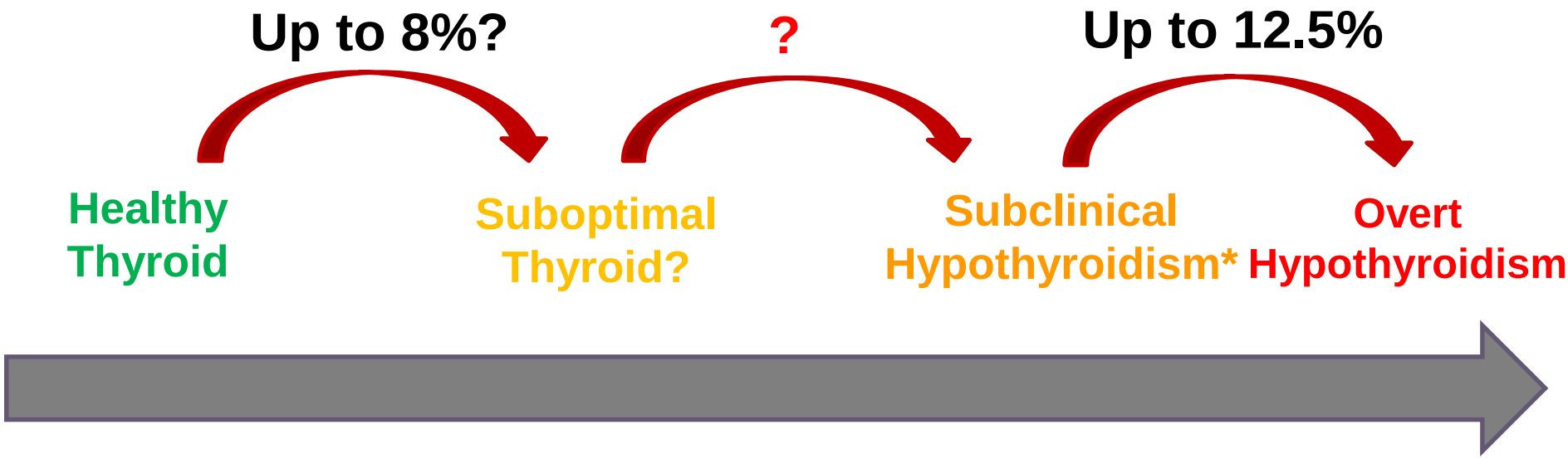
Kids' Thyroid Issues: A Spectrum or a Continuum?



* No thyroid Abs after infancy
* Age appropriate TSH/T4/T3

*Presence thyroid Abs
*TSH/T3/T4 away from 50th percentile for age

*TSH > adult ref. range
*T4 levels still in range
* TPO Abs elevated

*TSH > adult ref range
*T4 < ref range
*Thyroid Abs

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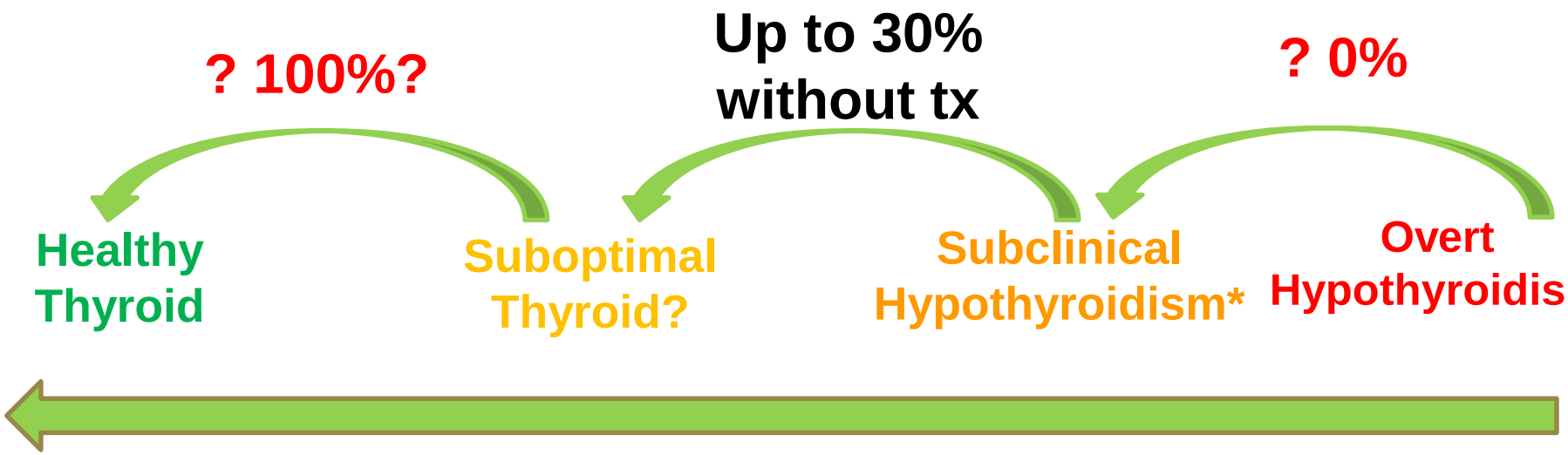
Kids' Thyroid Issues: A Spectrum or a Continuum?



* No thyroid Abs after infancy
* Age appropriate TSH/T3

- Presence thyroid Abs
- TSH/T3/T4 values outside age appropriate reference range

*TSH levels above adult ref. range((>4)
*T4 levels still in range
* TPO Abs elevated

*TSH > adult ref range (>10)
*T4 < ref range
*Thyroid Abs

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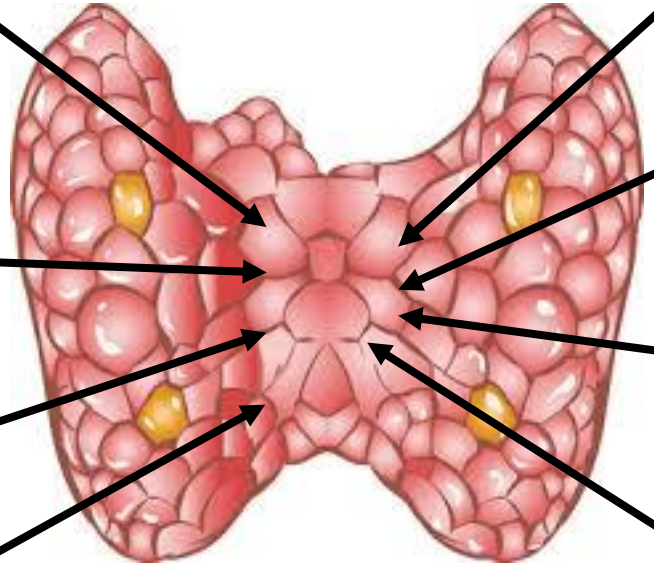
How Does the Child with Thyroid Problems Present?

Causes	Consequences	Concomitants*	Confounders
Genetics	Tired?	**Coeliac dx**	Stress
Female	**Weight gain?**	Anaemia	**Adrenal dx**
Age	Mood & memory	**Vitiligo**	Anaemia
Stress	**Hair loss**	T1DM	**Obesity**
Overweight?	Constipation?	**ANAs**	Mental health
Micronutrient deficiencies	**Arthralgias**	Pernicious anaemia	**Blood glucose imbalance**
Iodine ↑↓ (in utero →)			
Heavy metals			
Goitrogens			

Causes:
Attacks On The Thyroid Are Usually Multifactorial

Genetics – a first degree relative with a thyroid disorder

Being female



Heavy Metals

Iodine imbalance – in utero or any life-stage

Halogens

Selenium, iron, zinc, vitamin A, or D deficiency

Too much soy, raw cruciferous vegetables etc.

Stress

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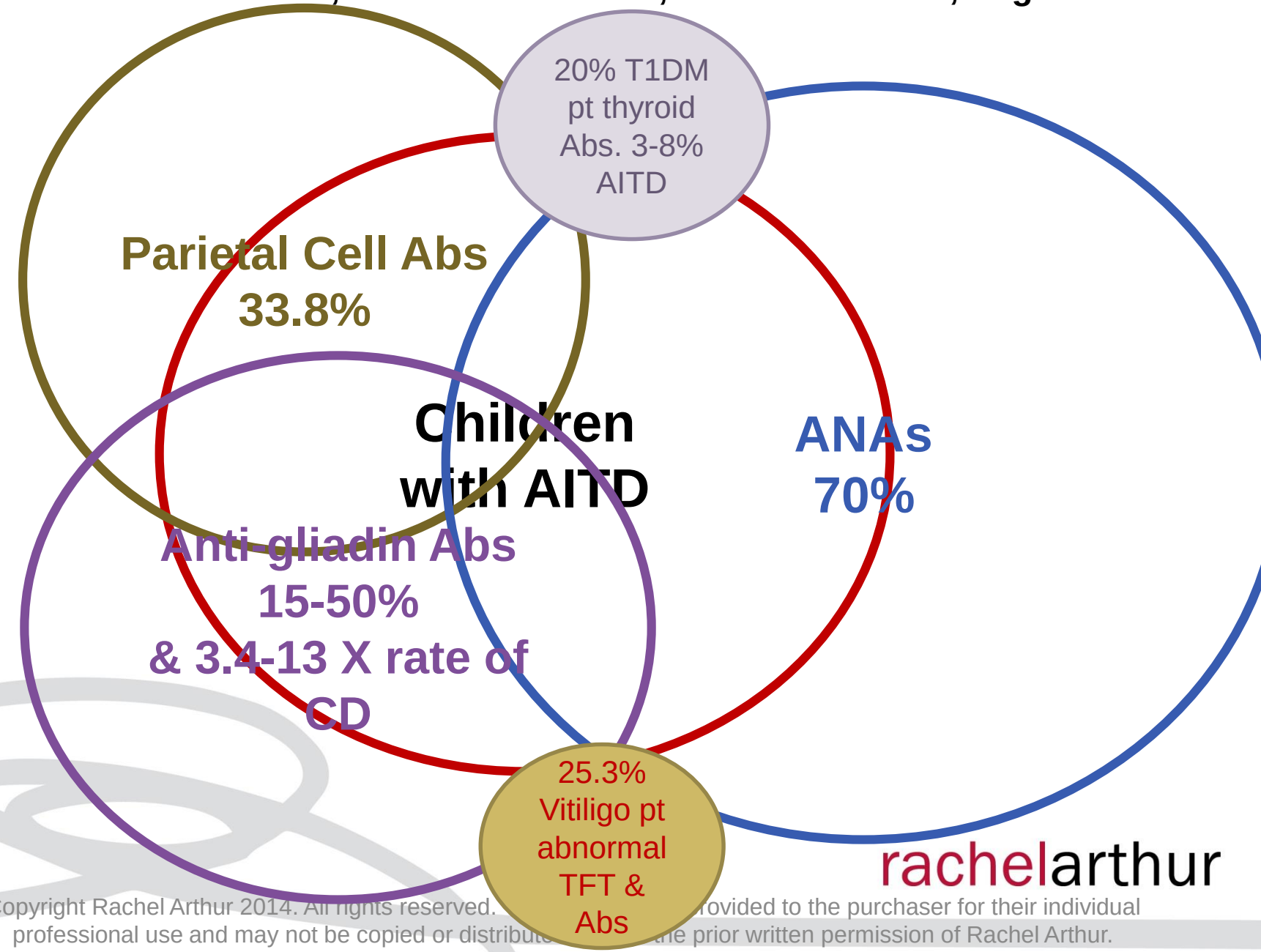
Kids with AITD - Possible Concomitants

Al-Mendalawi 2014, Daneshpazhooh et al 2014, Gerenova et al 2013, Kawicka et al 2015, Kroon et al 2013, Segni et al 2014



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Let's Talk About Gluten…

- **A higher percentage of AITD patients demonstrate gluten Abs but do not have CD (Jiskra et al 2003)**
  - EMA 1.18%
  - IgA tTG Abs 14.79%
  - IgA Anti-gliadin Abs 15.98%
  - IgG Anti-gliadin Abs 51.48%
- **I would encourage practitioners to perform thorough serology studies including total IgA & completely remove gluten in those instances where:**
  - Patients meet the CD criteria
  - There is any tTG or EMA Abs of significance
- **Consider minimising exposure in elevated AGA titres**

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THYROID ASSESSMENT
IN CHILDREN & TEENAGERS

Introducing the TTFT…
Thorough Thyroid Function Testing!

- Full thyroid function test (TSH, T4, T3*) and rT3**
- **Thyroid antibodies –TPO, TgAb & TRAb**
- Urinary iodine with urinary creatinine for correction
- **Plasma Selenium & Zinc**
- Iron studies
- **CRP – for correct interpretation of mineral results**
- Heavy metal assessment*
- **Coeliac serology with total IgA***
- Parietal cell antibodies*
- **Anti-nuclear antibodies***

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EARLY AUTOIMMUNE HYPOTHYROID?

11YO MATHEW HAIR LOSS

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Mathew 11yo

- **Reports excellent energy in spite of long hx onset insomnia**
- Rarely complains of tiredness or any unwellness – mum says not good at recognising signs or ‘saying no’
- **Nails consistently bitten and toenails picked at**
- Has been through significant stressful period over last 2y
- **Hair thick and good growth generally – but 10mo prior during period of marked stress – 20c size clump of bald patch appeared → 2-3 sections**
- Some reported loss of hair pigmentation as well
- **Severe white spots across all fingernails – long history & runs in family**
- Ferritin borderline at 28

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11yo Mathew with patches of severe hair loss

Date	11/06/13		
Time	08:58		
Lab No	63507790		
TSH	3.1	mU/L	(0.40-4.00)
free T4	14	pmol/L	(10-20)
aThyro'gb	< 10	U/mL	(< 60)
aPeroxase	37	U/mL	(< 60)

URINARY IODINE

Creatinine	14.4	mmol/L
Iodine	332	ug/L
Iodine	2.61	umol/L

Corrected Iodine = 204

WHO classification (2001) of iodine deficiency (Urine iodine ug/L):

> 100	Not iodine deficient
50-100	Mild iodine deficiency
20-49	Moderate iodine deficiency
< 20	Severe iodine deficiency

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TSH Percentiles in Kids & Adolescents

Table 1: Percentiles for TSH (mU/L) of children and adolescents in different age groups

Age	n	percentiles						
		2.5	10	25	50	75	90	97.5
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15–18 years	233	0.50	0.94	1.30	1.70	2.35	3.30	4.33

3.1

T4 Percentiles in Kids & Adolescents

Table 3: Percentiles for fT4 (pmol/L) of children and adolescents in different age groups.

Age	n	percentiles						
		2.5	10	25	50	75	90	97.5
0 – 1 months	23	8.50	8.98	13.50	20.10	24.70	28.48	30.50
1–12 months	45	9.17	13.10	14.00	15.50	17.20	19.22	25.28
1–5 Years	229	10.45	12.80	14.15	15.70	17.90	19.70	22.35
6–10 Years	327	10.60	12.80	14.40	15.80	17.30	18.90	20.90
11–14 Years	364	10.40	12.15	13.40	15.20	16.80	19.05	21.36
15–18 Years	233	10.57	11.74	13.50	15.20	16.90	18.80	22.62

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Kapelari et al 2008 Full reference

Mathew 11yo – Mum says ‘Should I take him off Gluten?’

Coeliac Disease Autoantibodies

Tissue Transglutaminase IgA Abs	<1	U/mL	(<7)
Gliadin (deamidated) IgG Abs	<1	U/mL	(<7)
Immunoglobulin A (Total IgA)	2.26	g/L	(0.52 - 2.53)

Comments on Lab Id: 587869027

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Mathew

- Although Mathew's TSH falls within range the 50th percentile value for kids of his age is 2.1 mU/L
- **His TSH value places him almost on the 90th percentile**
- **Presence of TPO antibodies**

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Mathew's treatment

- **Selenium 200mcg/d**
- Zinc elemental 15mg X 2/d
- **Combination powder including:**
  - **Magnesium equivalent 300mg/d**
  - **Vitamin C equivalent to 1g/d**
  - **Tyrosine 1g/d**

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11yo Mathew follow up TFT after 1 month of treatment with Selenium, tyrosine etc.

Date	02/04/12	29/07/13		
Time	0841	0925		
Lab Id.	587869027	592754794	Units	Range
Free T4	15.6	15.5	pmol/L	(9.0-19.0)
Free T3		5.7	pmol/L	(3.0-7.0)
TSH	2.2	1.7	mIU/L	(0.3-5.3)

with Se @ 200mcg

- Rapid reduction of TSH values has brought them back under the 50th percentile
- **Both T4 and T3 levels look good according to percentiles**
- Hair loss slowing with possible regrowth → full regrowth within 3 months

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ANOTHER EARLY AUTOIMMUNE HYPOTHYROID?

13YO CLAIRE VITILIGO & FATIGUE

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13yo Claire

- Ongoing fatigue duration 12mo
  - 12months ago developed severe tonsillitis
  - Emergency tonsillectomy
  - Undiagnosed concomitant glandular fever
  - Treatment with multiple antibiotics → severe reaction emergency admission – patient entered a coma Patient experienced significant trauma & anxiety following on from this period
  - Patient started psychotherapy & treatment with Lovan (both for 10months)

- Fatigue currently presents as (did not experience any of these prior to 12months ago)
  - Might have to lie down during busy days
  - Napping during the day after a sleepover at friend's
  - Tired after most school days
  - Mother has restricted sporting and extra-curricular activities significantly
  - Sleep pattern 'appears' healthy

- Physicals
  - BP 90/60 reports occasional dizziness on standing
  - Urinalysis in clinic
    - Significant proteinuria
    - Trace bilirubin
  - BMI 21 → 75th percentile for age/gender
  - Perifollicular hyperkeratosis – mild
  - Recent white spots on nails
  - Conjunctiva good colour
  - Weak nails with some ridging

- Skin problems – all appeared in last 12mo
  - **Vitiligo**
    - Confirmed by pediatrician
    - All over but especially on abdomen
  - **Eczema**
    - Occurs in flexures
    - Tx cortisone cream
  - **Red petechiae (no diagnosis)**
    - On abdomen and tops of thighs

13yo Claire

THYROID FUNCTION TESTS

Thyroid Stimulating Hormone	1.1 mU/L	(0.40-4.00)
free Thyroxine (fT4)	13 pmol/L	(10-20)
Anti-Thyroglobulin Ab	32 U/mL	(< 60)
Anti-Thyroid Peroxidase Ab	48 U/mL	(< 60)

Euthyroid levels.

These antibody levels are not suggestive of autoimmune Thyroid inflammation.

Tests Completed:THYROID TISSUE AB, TSH, FREE T4, SE E/LFT
Tests Pending :SE IMMUNOGLOBULINS, IRON STUDIES, TTG, GLIADIN AB, FBC, RBC FOLATE
Tests Pending :SERUM VITAMIN B12, ESR

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13yo Claire

COELIAC DISEASE SEROLOGY

Anti Gliadin IgA	6 U/ml	(0-19)
Anti Gliadin IgG	8 U/ml	(0-19)
Anti Tissue Transglutaminase IgA	< 5 U/mL	(0-6)

Negative serology makes the diagnosis of untreated coeliac disease unlikely. Falsely negative coeliac disease serology may occur if the patient is on a gluten free diet at the time of testing.
If a strong clinical suspicion for coeliac disease exists, definitive diagnosis is by small bowel biopsy.

For enquiries, contact Dr David Heyworth-Smith (ph 07 31214444)

Tests Completed:THYROID TISSUE AB, TSH, FREE T4, SE IMMUNOGLOBULINS, IRON STUDIES, TTG
Tests Completed:GLIADIN AB, FBC, RBC FOLATE, SERUM VITAMIN B12, SE E/LFT, ESR
Tests Pending :

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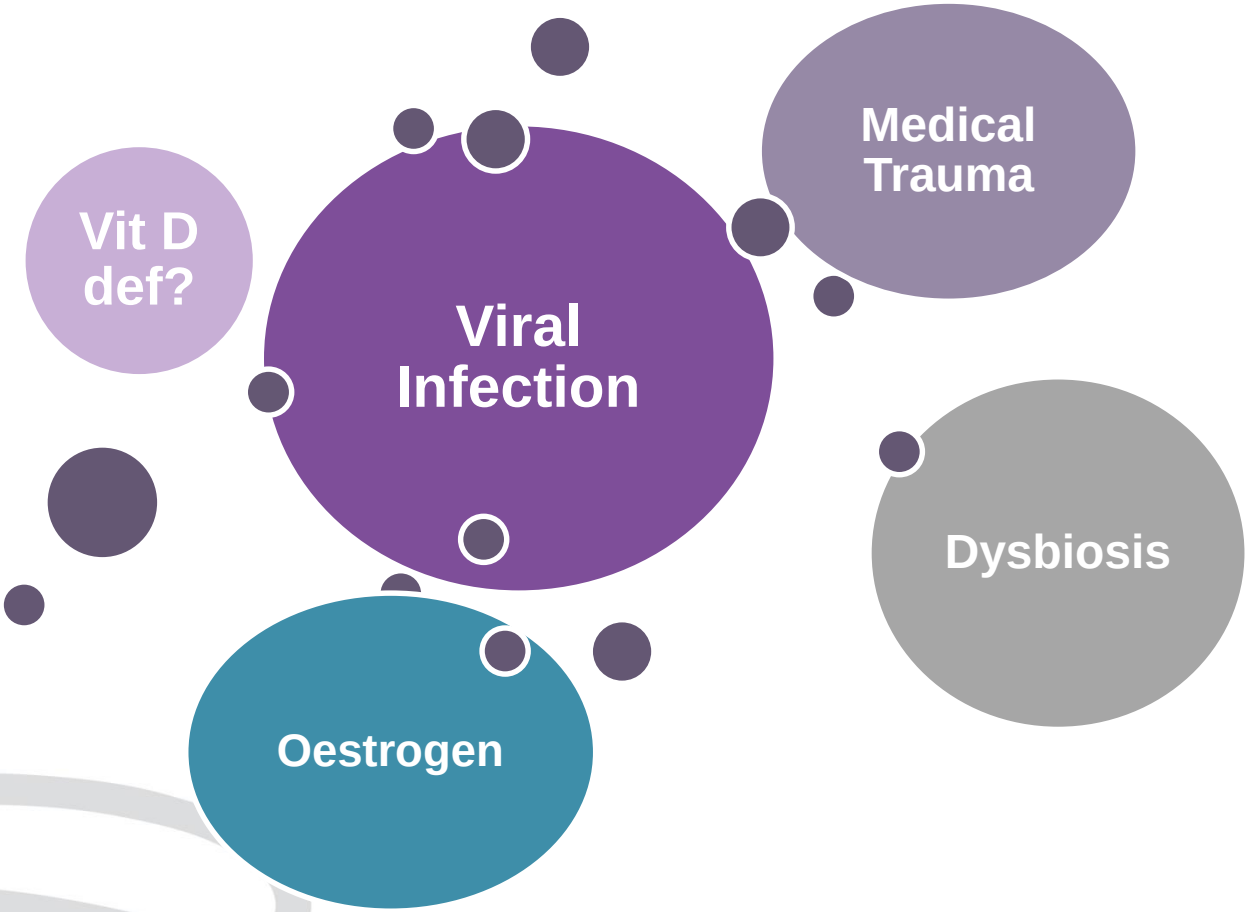
Pathology results show

- **Evidence of ongoing physiological effects of glandular fever**
  - Raised IgM EBV antibodies
  - Presence of atypical lymphocytes
  - Low white blood cell counts
- **Evidence of emergent autoimmunity/risk**
  - Thyroid / anti-gliadin antibodies

Claire's Cumulative Risks for Autoimmunity



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Claire's Treatment objectives

- **Support adrenals**
- **Modulate & ease burden on immune system**
  - Improve GIT flora
  - Remove reactive foods, support with immune nutrients
- **Correct deficiencies**
  - General dietary imbalances (Fe/Ca/Protein)
  - Immune nutrients (Se/Zn/Vitamin D/Vitamin A)
  - Secondary deficiencies due to cortisol/adrenal issues
- **Minimise stressors**
  - Psychological
  - Physical

Treatment Summary

- **Low reactive diet including gluten removal**
- Selenium 180mcg/d
- **Cod liver oil to provide high dose Vitamin A (≈ 5000 IU) and medium dose D (≈ 1000 IU)**
- Zinc 30mg/d
- **Combination high dose Mg/Tyrosine/Vitamin C for adrenal support**
- Herbal adaptogens
- **Probiotics for addressing dysbiosis**

Follow up to initial treatments – 3mo

- **All skin rashes have improved – no evidence of vitiligo!**
- Marked improvement in energy levels & mood
  - No need for daytime naps on busy days
  - Still sleeping full 10hrs+ at night
- Mother reports improved body shape
  - Increased lean tissue

What About Teenagers' Thyroids?

"It is our experience that doctor's delay in diagnosing of hyper- or hypothyroidism may be considerable in schoolchildren. The reason for this seems to be that symptoms of thyroid disease are often misinterpreted as problems associated with adolescence and teenager life style."

Milakovic et al. Screening for thyroid disease of 15-17year old schoolchildren in an area with normal iodine intake. Journal of Internal Medicine 2001; 250: 208-212

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