Thiamazole Pretreatment Lowers the ^{131}I Activity Needed to Cure Hyperthyroidism in Patients With Multinodular Goiter

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Multinodular goiter

- Prevalence

  Sex ratio: 1/6 for M/F

  Depending on population's **iodine sufficiency**

  ✓Framingham iodine sufficiency: **1%** population

  ✓Denmark mild iodine insufficiency**: 9,8%** palpation ---- **15%** echo

  moderate iodine insufficiency: **14,6%** palpation ----- **22,6%** echo

- Complications

  Hyperthyroidism (22% of longstanding MNG)

  Local compression

  Malignity

Treatment options for autonomous MNG

No official recommendations
Guided by local practice, patients' preferences, clinical presentation

	Surgery	^{131}I
Outpatient basis	-	+
Cost	+++	+
Histology	+	-
Volume reduction	+++	++ (40% at 1 year)
Recurrent laryngeal nerve paralysis	<2%	-
Hypoparathyroidism	<2%	-
Transient **hyperthyroidism**	-	~ 3%
Permanent **hypothyroidism**	+++	++ (15-20% at 1 year)
Autoimmunity induction	-	~ 5%

Radioiodine therapy

Efficiency:
depends on the thyroid **absorbed dose**

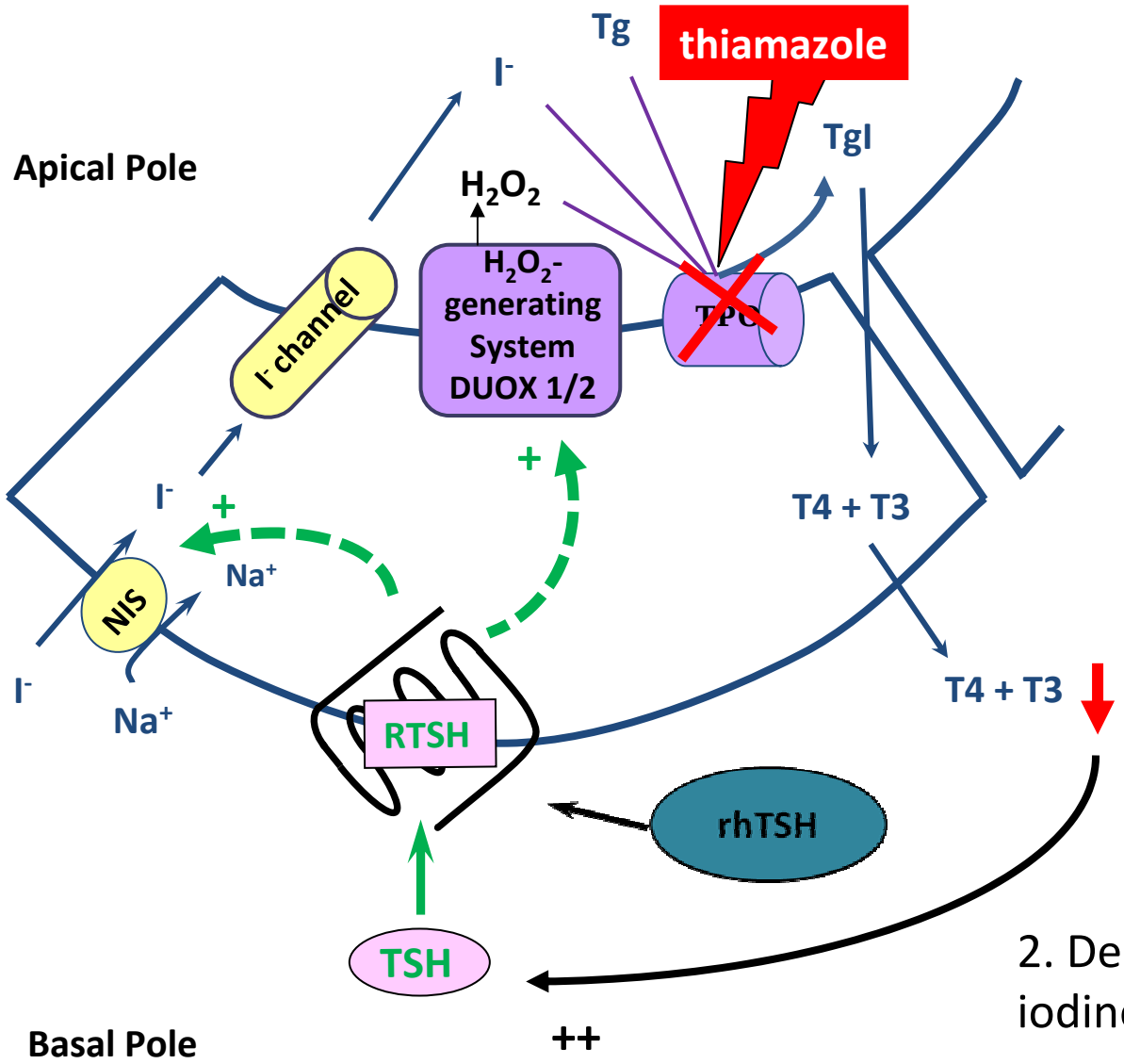
$$\text{Prescribed Dose } (\mu Ci) = \frac{\text{Mass of Gland } (g) \times \text{Desired Dose } (\mu Ci/g)}{\text{Uptake at 24 hours}} \times 100\%$$

Max legal threshold for outpatient ^{131}I administration in Belgium: **15mCi**

- **Low** radioiodine **uptake** (RAIU)
- **Heterogeneity** of ^{131}I uptake
- Large goiter **volume**

→ Can hamper ^{131}I treatment efficacy
Requiring ***very high activities*** of ^{131}I

Iodine uptake by thyrocyte



1. Increase TSH levels

Injection of rhTSH

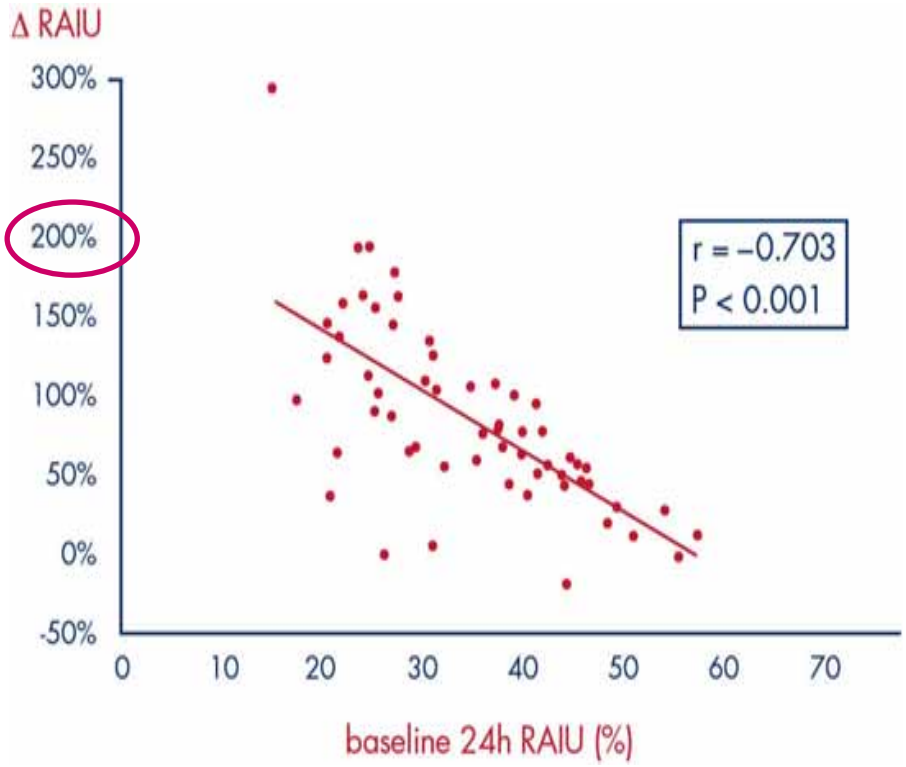
Endogenous TSH by AT drugs

2. Depletion of intrathyroid iodine pool

rh TSH in MNG treatment

- ✓ 0.01-0.9mg rh TSH
- ✓ **24**-76h prior to ^{131}I
- ✓ **2- 4 fold** increase in RAIU
- ✓ Baseline RAIU dependent

→ Inter individual variations
Off label use

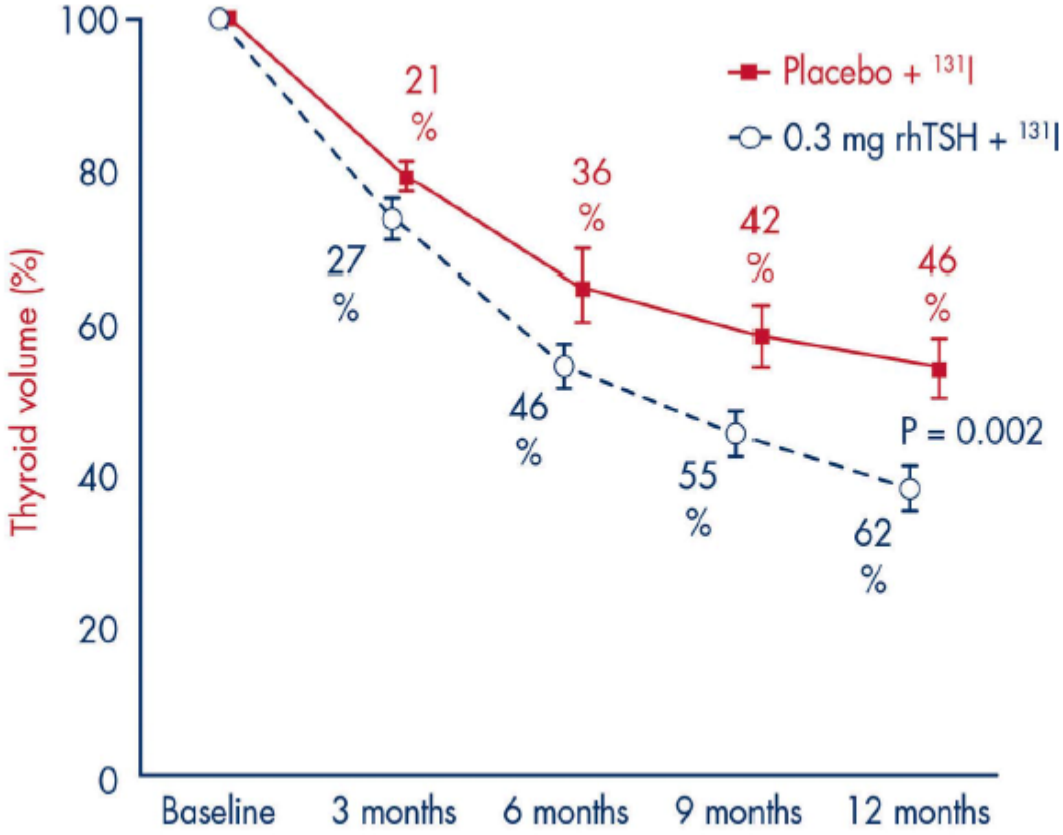


Fast S et al. J Nucl Med 2009

rh TSH in MNG treatment

- ✓ 0.01-0.9mg rh TSH
- ✓ **35-56% gain** in goiter volume reduction dose dependent

→ Inter individual variations
Off label use



Nielsen VE et al Arch Intern Med 2006

Objective of the study

Determine

Whether

✓ pretreatment with thiamazole (MTZ) could ***enhance 24h RAIU***

And

✓So ***decrease the ^{131}I activity*** needed to treat patients with subclinical hyperthyroidism and MNG

Patients and methods

Prospective, randomized controlled
patients referred for ^{131}I treatment
2006 -2013

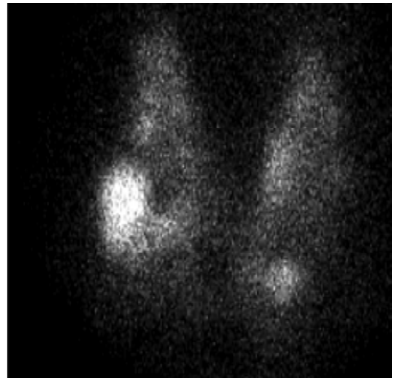
Inclusion criteria:

✓subclinical hyperthyroidism: TSH< 0.4mU/L , N FT3, FT4
✓24hRAIU< 50%

Exclusion criteria:

✓thyroid surgery
✓thiamazole within 6 months prior to enrollment
✓past ^{131}I treatment
✓Solitary autonomous nodule

Patients and methods



Day 0:

Thyroid ^{99m}Tc scintigraphy

SPECT CT/MRI (**volume** estimation)

Administration 10µCi for 24h RAIU

Day 1:

Low iodine diet, LID

Or

MTZ 30mg/d 42d

Day 01:

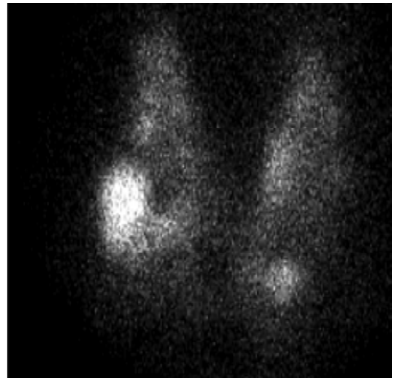
24h RAIU

If <50%

Serum TSH, FT4, FT3, Tg-Ab, TPO-Ab, UIC

Randomisation

Patients and methods



Day 43:

Stop MTZ

Day 48:

24h RAIU

Therapeutic ^{131}I activity calculation

Administration on outpatient basis

Day 47:

Serum TSH, FT4, FT3, UIC

Thyroid ^{99m}Tc scintigraphy

SPECT CT/ MRI

Administration 10µCi for RAIU

Patients and Methods

RAIU estimation

$$\frac{\text{Thyroid cpm (t)} - \text{Leg cpm (t)}}{\text{Standard cpm (t)} - \text{background (t)}}$$

cpm: counts per minute

^{131}I therapeutic activity calculation

$$\mu\text{Ci activity} = \frac{\text{R activity } \mu\text{Ci} \times \text{thyroid size}(\sqrt{\text{gr}})}{\text{24 h uptake (\%)}}$$

R (required) activity varied from 90-200 µCi/gr according to thyroid size

Roudebush C et al., Ann Intern Med. 1977

Results

Baseline clinical characteristics of LID and MTZ groups

Clinical characteristics		
	LID	**MTZ**
Nº of patients	**10**	**12**
Age	70.7±7	66.5±14
Sexe ratio (F:H)	8:2	10:2
TPO-Ab+/Tg-Ab+	0/0	0/0

Results

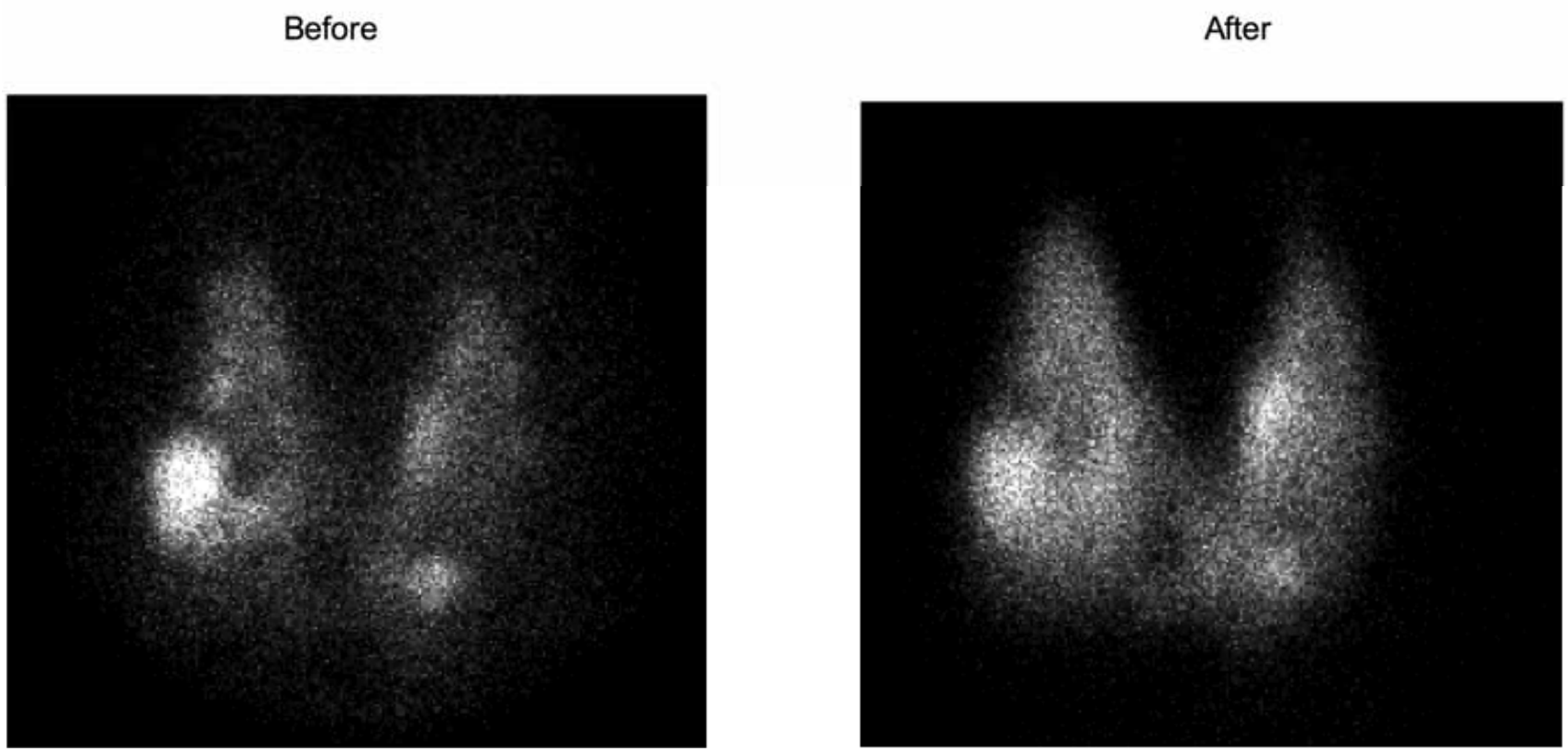
Thyroid function and thyroid volume before and after 42 days of LID or MTZ treatment

Baseline			**After treatment**	
	LID	**MTZ**	**LID**	**MTZ**
Nº patients	**10**	**12**		
TSH (N:0.4-4.0 mIU/l)	0.09 (0.04-0.17)	0.13(0.04-0.30)	0.09 (0.04-0.20)	**1.55(0.78-1.85)** [ab]
FT4 (N: 0.8-1.7 ng/dl)	1.27±0.20	1.25 ±0.20	1.25±0.16	**0.98 ±0.33** [ab]
FT3 (N:1.8-4.6 pg/ml)	3.60±0.50	3.30 ±0.60	3.40±0.70	**2.80 ±0.40** [ab]
Volume ml				
MRI	87 (45.7-184.5) [4]	55 (29-63) [7]	74 (46-180) [4]	58 (30-63) [7]
SPECT-CT	39 (31-56) [6]	44 (31.5-61) [5]	42 (35.5-61.3) [6]	50 (42.5-60.0) [5]

Data are expressed as median (25^{th}-75^{th} percentile) [number of cases] ± SEM

[a] different from baseline, $p<0.5$, [b] different from LID group after treatment, $p<0.5$

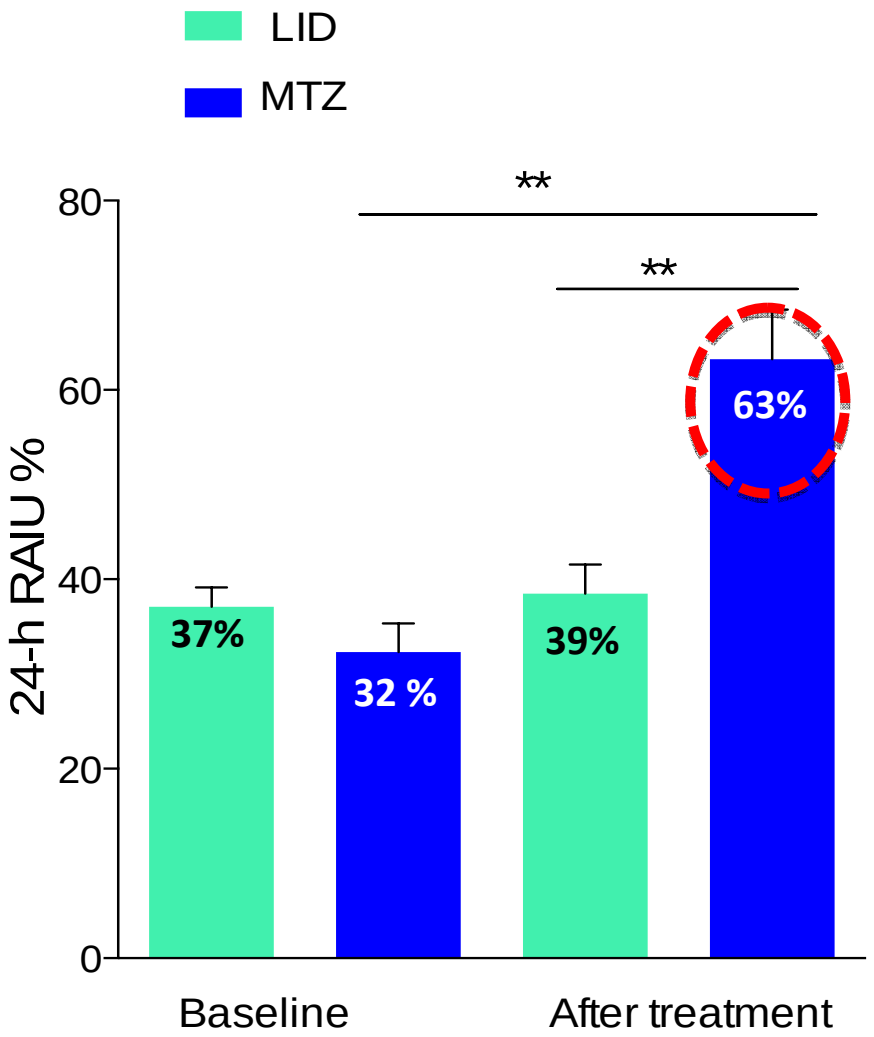
MTZ modified regional thyroid ^{99m}Tc uptake



Previously ‘resting’ tissue surrounding hyper functioning areas ----- ***REACTIVATED*** as a result of the MTZ induced TSH increase

Results

Change in mean RAIU after 42 days of LID, MTZ treatment

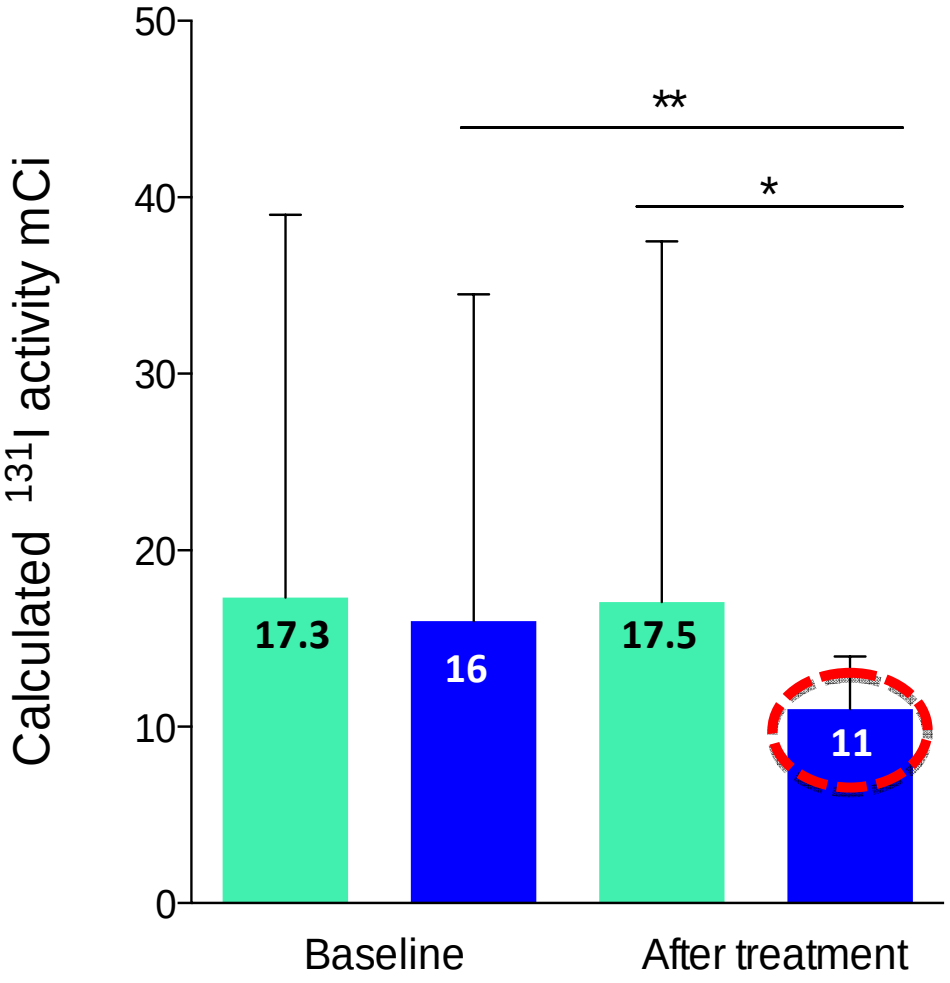


24h RAIU increased by **2 fold** after ^{131}I treatment preceded by MTZ

Data are expressed as mean ± SEM

Results

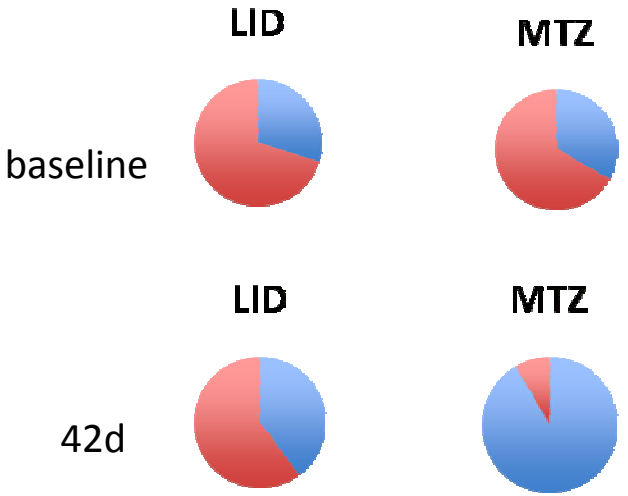
Changes in calculated 131I activity after LID, MTZ



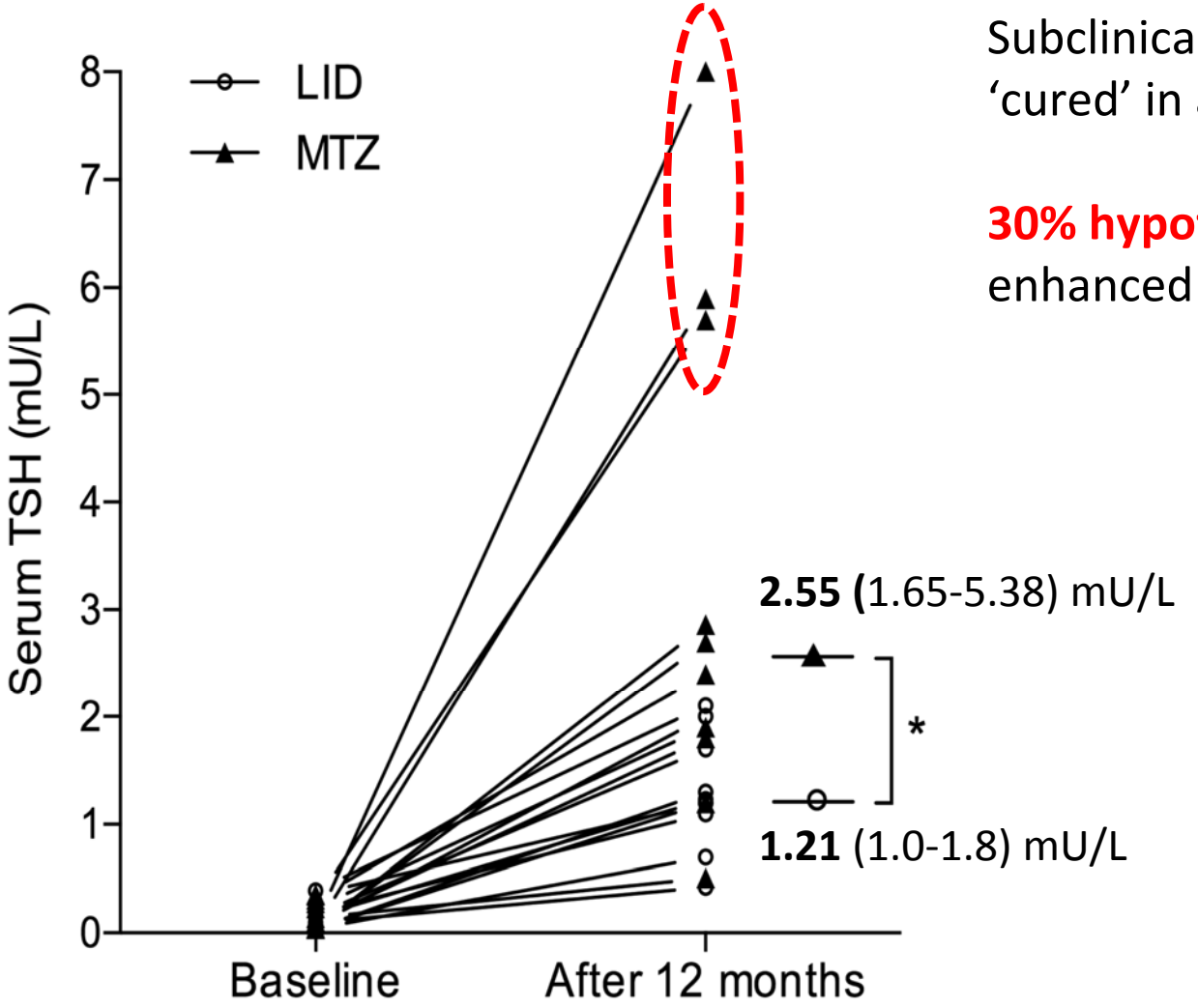
Data are expressed as median (25th-75th percentile)

MTZ enhanced RAIU led to **31% decrease** in ^{131}I activity needed to treat the patients

Exceeding 15mCi outpatient 131I threshold



12 months follow up



Subclinical hyperthyroidism was ‘cured’ in all patients

30% hypothyroidism post MTZ enhanced RAIU

In comparison

MTZ

- Gradual and **slight TSH** increase
- **No** thyroid swelling
- **FT3, FT4 normalized** or reduced
- **Volume** long term?

- **30%** hypothyroidism after 1 year ---- long term?

- **Modifies** regional ^{99m}Tc uptake

≠

rh TSH

- Acute **supra normal TSH** peak
- Thyroid gland **swelling**
- Transient hyperthyroidism **high FT3, FT4**
- **Volume reduction** gain 30-65% after 1 year
- **50%** hypothyroidism after 5 years
- **Cost**
- **Modifies** regional ^{131}I uptake

Conclusions

- Thiamazole (MTZ) pretreatment induced an average *2 fold increase in 24h RAIU*
- MTZ *lowered the ^{131}I activity* needed to treat subclinical hyperthyroidism in MNG patients
- MTZ is easy, low cost with few secondary effects
- MTZ did **not** modify ^{131}I efficacy
- MTZ enhanced ^{131}I treatment resulted in *30% hypothyroidism* (further reduction of ^{131}I activity possible)
- Thyroid volume reduction needs to be evaluated

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