

THYROID HORMONES INFLUENCE THE EXPRESSION OF TNF-RELATED APOPTOSIS-INDUCING LIGAND

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INTRODUCTION: Experimental evidence suggests that there is an association between thyroid hormones and TNF-related apoptosis-inducing ligand (TRAIL). TRAIL is in fact directly regulated by T3 in thyroid hormone receptors (TRs)-overexpressing hepatoma cell lines [1] and it is also upregulated by thyroid hormones in the skeletal muscle [2].

OBJECTIVES: The aim of this study was to investigate whether and how TRAIL levels change in patients with overt thyroid disorders and whether thyroid hormones influence such changes

METHODS: Patients under euthyroid (n=39), hyperthyroid (n=49, HYPER), and hypothyroid (n=28, HYPO) conditions were selected.

Circulating TRAIL was measured by ELISA in euthyroid, hyperthyroid, and hypothyroid patients at baseline (BEFORE) and after their respective treatments (AFTER). At the same time, TRAIL mRNA expression was quantified in peripheral blood mononuclear cells (PBMC) isolated from the same patients (data not shown). The stimulatory effect of T3 and T4 on TRAIL secretion was evaluated in the supernatant of PBMC isolated from healthy donors.

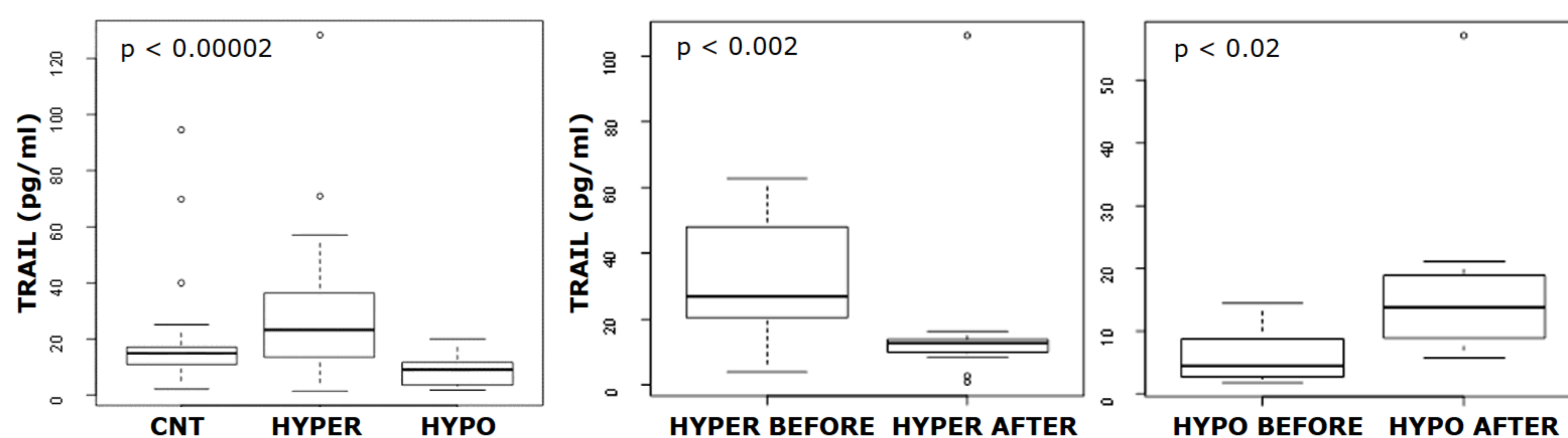
Comparisons of data between the groups were performed by one-way ANOVA (or Kruskal-Wallis test in case of non-parametric data). TRAIL levels before and after treatment were compared with the Wilcoxon-test for paired data. Spearman coefficient was calculated for the correlation between ft3, ft4 and TRAIL.

- RESULTS:**
1. TRAIL protein expression increases in hyperthyroidism and decreases in hypothyroidism. After euthyroidism restoration, TRAIL levels normalize in both hyperthyroid and hypothyroid patients.
 2. Circulating TRAIL is correlated to ft3 and ft4.
 3. T3 stimulates TRAIL release from human PBMC.

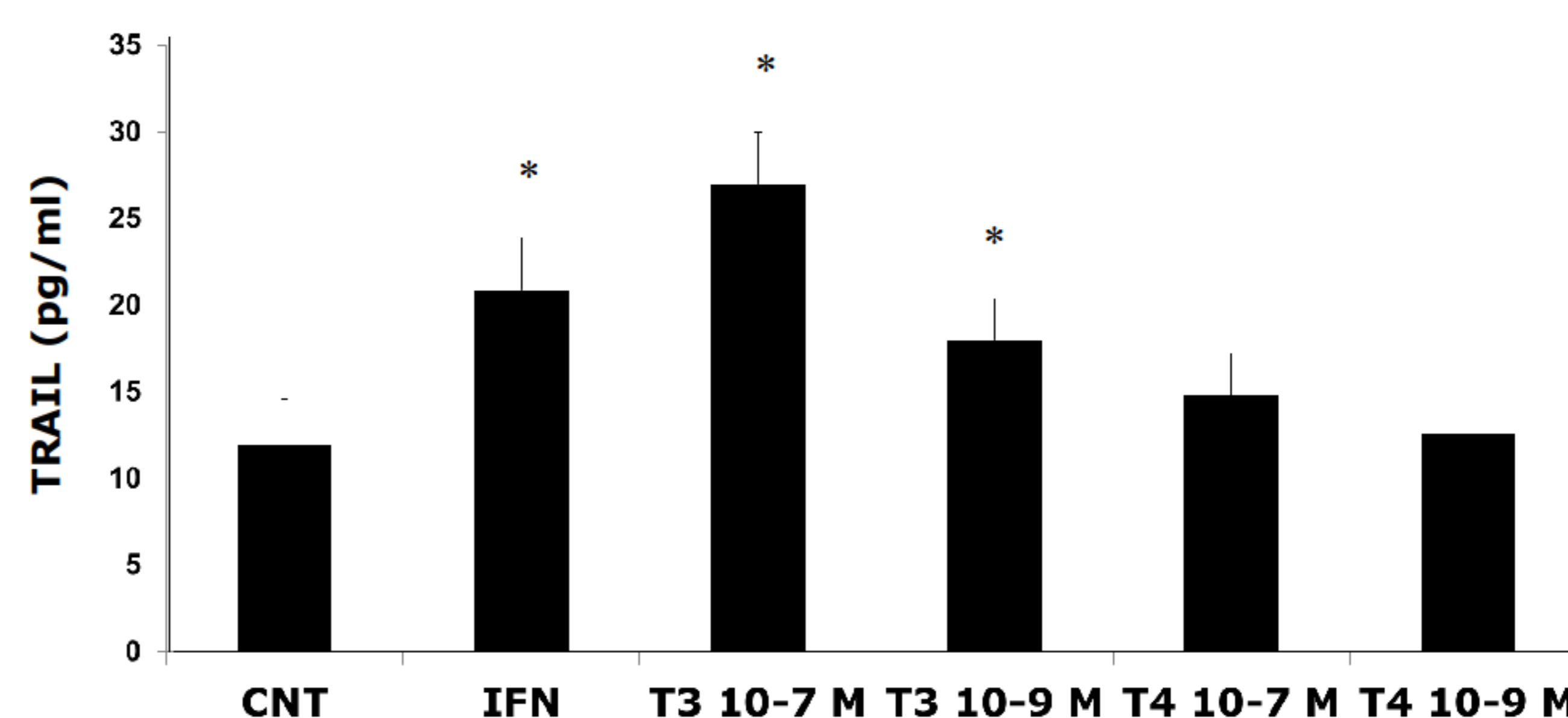
Patient characteristics

	CNT (n=39)	HYPER before (n=49)	HYPER after (n=22)	HYPO before (n=28)	HYPO after (n=19)
Age	54.8 ± 2.3	50.1 ± 2.5	=	61.9 ± 3.0 #	=
Sex (F/M)	29/10	39/10	17/5	23/5	14/5
TSH (μU/mL)	1.4 ± 0.1	0.0 ± 0.0 *	2.4 ± 0.3 †	68.2 ± 5.7 *#	2.8 ± 0.6 ‡
ft3 (pmol/L)	4.6 ± 0.1	16.7 ± 1.3 *	4.3 ± 0.1 †	2.8 ± 0.2 *#	4.2 ± 0.1 ‡
ft4 (pmol/L)	11.5 ± 0.5	43.6 ± 2.5 *	11.1 ± 0.8 †	4.1 ± 0.5 *#	13.6 ± 1.0 ‡

Circulating TRAIL in euthyroid, hyperthyroid and hypothyroid patients before and after their treatments

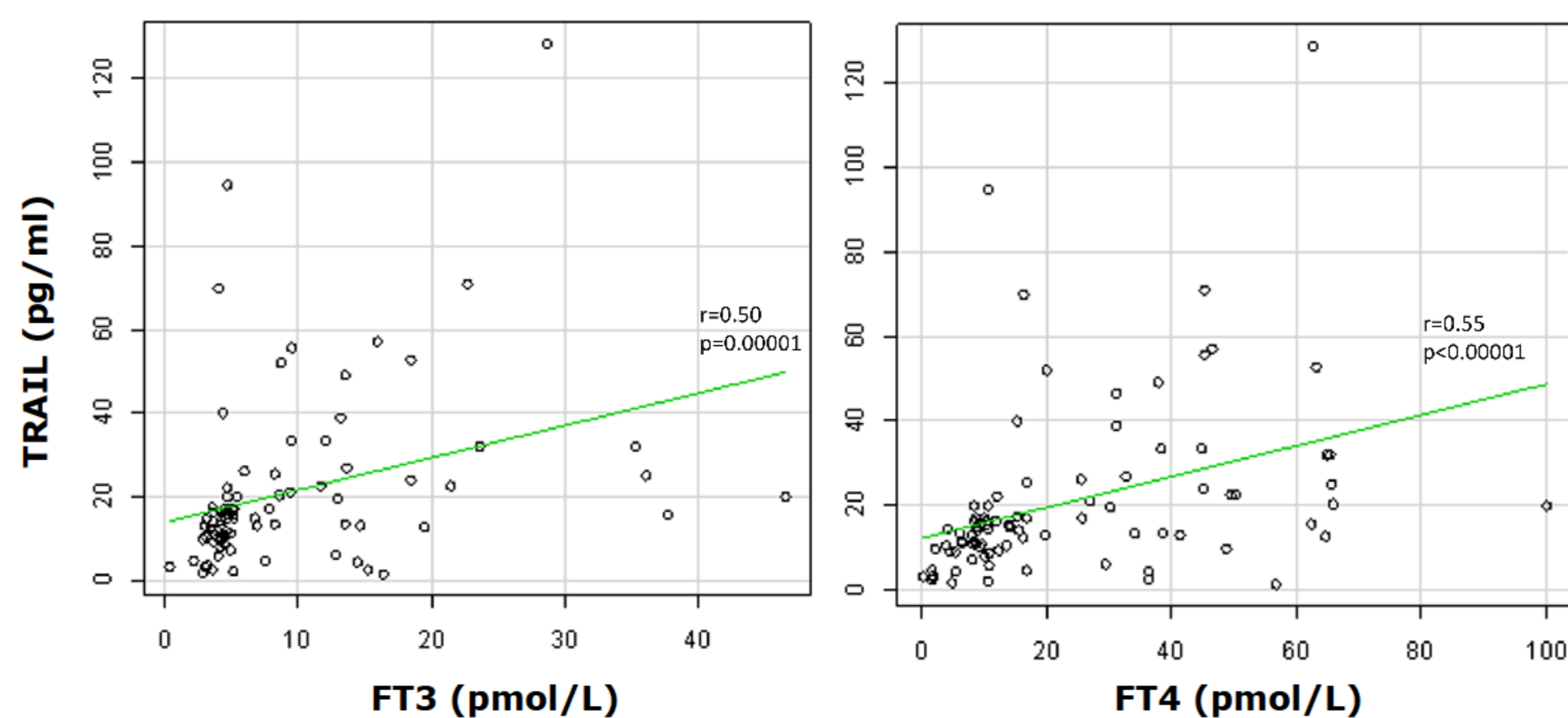


T3-induced TRAIL release from human PBMC



*p<0.05 vs CNT;
#p<0.05 HYPO before vs HYPER before;
† p<0.05 HYPER after vs HYPER before;
‡ p<0.05 HYPO after vs HYPO before

Correlation between thyroid hormones and circulating TRAIL



CONCLUSIONS: There is a significant direct correlation between thyroid hormones and TRAIL, which is likely to be due to thyroid hormone stimulatory effect. Given the overlap between the metabolic actions of thyroid hormones and TRAIL [3], this work sheds light on the possibility that TRAIL might mediate some of thyroid hormones peripheral effects.

- REFERENCES:** [1] Chi HC et al, Cell Death and Differentiation 2012;19:1802-1814
[2] Visser WE et al, The Journal of Clinical Endocrinology and Metabolism 2009;94:3487-3496
[3] Bernardi S et al, Clinical Science 2012;123:547-555

