Thyroid axis challenges in Leiden Longevity Study

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Chapter 8

English summary

This thesis covers the study design, primary outcomes and first secondary outcomes of the TSH and T3 challenges in participants from the Leiden Longevity Study (LLS).

In **Chapter 1** we emphasize the importance of understanding the mechanisms underlying healthy ageing, due to an increasing size of the older demographic locally as well as globally, and with it the corresponding rise of prevalence of age-related diseases. Moreover, we outline the impact of the thyroid axis on physiological processes and its potential role in healthy ageing.

In **Chapter 2** we report the study design and data collected throughout the TSH and T3 study. In total, there were 17 blood withdrawal moments in TSH study, among 30 participants, and 25 blood withdrawal moments in T3 study, among 27 participants. Other data such as peripheral blood mononuclear cells, continuous physiological monitoring, questionnaires and biobank samples were also obtained for further research.

Chapter 3 investigates and reports the results of a pilot study where thyroid parameters were determined at all 17 blood withdrawal moments during TSH study. Optimal measurements times are identified for a healthy, older population, with mean TSH concentration showing the greatest variation in the first 8 hours following rhTSH administration, mean T4, fT4, T3 and fT3 showing variation from 2 hours after rhTSH administration, and mean Tg only showing variation at later time points, namely 24, 48 and 72 hours after rhTSH administration.

Chapter 4 reports the primary outcomes of the TSH study: the TSH and thyroid hormone profiles following administration of 0.1mg i.m. rhTSH in offspring and controls from LLS. The area under the curve (AUC) fT4/AUC TSH ratio was significantly lower in offspring than in controls (estimated mean (95%CI) 1.6 (1.2-1.9) and 2.2 (1.9-2.6), respectively, p=0.01), as was the AUC Tg/AUC TSH ratio (median (IQR) 2.1 (1.4-3.6) and 3.2 (2.7-7.4), respectively, p=0.04). We observed the same trend with the AUC fT3/AUC TSH ratio, although the difference was not statistically significant (estimated mean (95%CI) 0.6 (0.4-0.7) and 0.7 (0.6-0.8), respectively,

p=0.07). Overall, we show that members of long-living families have a lower thyroid responsivity to TSH compared to controls.

Chapter 5 reports the primary outcomes of the T3 study: the thyroid hormone and TSH profiles following administration of 100mcg T3 in offspring and controls from LLS. The concentration of thyroid hormones was similar in offspring and controls following the challenge (T3 GLM p=0.11, fT3 GLM p=0.46), and the feedback on TSH was similar also (GLM p=0.08), as was the relative TSH decline (%). indicating that there are no apparent differences in thyroid hormone turnover between offspring and controls.

In **Chapter 6**, the first secondary outcomes of the TSH and T3 challenge are investigated by determining bone formation markers (P1NP) and bone resorption markers (CTX) in offspring and controls. We found that bone turnover markers were lower at baseline in offspring from long-lived families than in controls ($p<0.01$ for both) but that they increased similarly following an rhTSH challenge in both groups.

In **Chapter 7**, we reflect on our findings and suggest further research and innovation on TSH, the TSH receptor and other hormonal axes influencing the thyroid axis, as possibly important for differences in longevity and healthy aging between offspring and controls.