Endocrine and metabolic features of familial longevity : the Leiden Longevity Study

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Chapter 8: Low serum free triiodothyronine levels mark familial longevity: the Leiden Longevity Study

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Abstract

The hypothalamo–pituitary–thyroid axis has been widely implicated in modulating the aging process. Life extension effects associated with low thyroid hormone levels have been reported in multiple animal models. In human populations, an association was observed between low thyroid function and longevity at old age, but the beneficial effects of low thyroid hormone metabolism at middle age remain elusive. We have compared serum thyroid hormone function parameters in a group of middle-aged offspring of long-living nonagenarian siblings and a control group of their partners, all participants of the Leiden Longevity Study. When compared to their partners the group of offspring of nonagenarian siblings showed a trend towards higher serum thyrotropin levels (1.65 vs.157 mU/L, p=0.11) in conjunction with lower free thyroxine levels (15.0 vs. 15.2 pmol/L, p=0.045) and lower free triiodothyronine levels (4.08 vs 4.14 pmol/L, p=0.024). Compared to their partners, the group of offspring of nonagenarian siblings show a lower thyroidal sensitivity to thyrotropin. These findings suggest that the favorable role of low thyroid hormone metabolism on health and longevity in model organism is applicable to humans as well.

Introduction

The hypothalamo–pituitary–thyroid axis has been widely implicated in modulating the aging process. Life extension effects associated with low thyroid hormone levels have been reported in multiple animal models. In neonatal rats, induction of hypothyroidism results in a moderate extension of lifespan [1]. Similarly, low thyroid hormone levels are characteristic of murine pituitary mutants with delayed aging: long-lived Ames and Snell dwarf mice show traits that are hypothesized to be related to thyroid hormone deficiency, including hypothermia and delayed maturation [2, 3]. Administration of thyroid hormone during adulthood partly diminishes longevity in Snell dwarf mice [4]. Another very long-living mammal, the naked mole rat (*Heterocephalus glaber*) also has very low serum thyroxine levels [5].

In agreement with the findings in animals, various studies have shown an association between low thyroid function and improved longevity in elderly humans. In the general population of the oldest old, high levels of thyrotropin are associated with a prolonged life span [6, 7]. In contrast, low serum thyrotropin and higher serum free thyroxin levels are related to an increased risk of cardiovascular mortality [8]. These findings suggest a favorable effect of thyroid hypofunction on healthy aging in humans.

However, comparative cross-sectional studies involving long-lived subjects are hampered by the lack of proper controls. These studies remain inconclusive as to whether thyroid hypofunction in extreme old age represents an adaptive mechanism or is the result of selective survival of subjects with lifelong thyroid hypofunction. We designed the Leiden Longevity Study in order to identify familial determinants of healthy longevity in nonagenarian siblings and their offspring, who are enriched for heritable influences on morbidity and mortality.[9] The aim of this study was to assess whether low thyroid function observed in extreme old age is already present in middle-aged individuals with higher than average life expectancy. To this end we have compared thyroid hormone function parameters in a group of middle-aged offspring of long-living nonagenarian siblings and a control group of their partners of the Leiden Longevity Study.

Materials and methods

Leiden Longevity Study

In the Leiden Longevity Study, 420 families were recruited consisting of long-lived Caucasian siblings together with their offspring and the partners thereof. Families were recruited if at least two long lived siblings were alive and fulfilled the age-criterion of 89 years or older for males and 91 year or older for females. There were no selection criteria on health or demographic characteristics. For 2465 of the offspring and their partners, non-fasted serum samples taken at

baseline were available for the determination of endocrine and metabolic parameters. Between November 2006 and May 2008, for 2235 of the offspring and their partners, information on medical history was obtained from the participants' treating physicians (response: 90.7%). For 2255 of the offspring and their partners, information on the use of medication was obtained from the participants' pharmacist (response: 91.5%). For 2184 of the offspring and partners a general questionnaire containing information on lifestyle and self-reported height and weight was obtained (response: 89.0%). For the present study, for a total of 1738 of the offspring and their partners, serum as well as information on medical history and information on medication use and the general questionnaire were available (inclusion: 69.5%). The Medical Ethical Committee of the Leiden University Medical Centre approved the study and informed consent was obtained from all subjects.

For the current study participants using thyroid medication were excluded from the analyses: 32 (2.7%) offspring using thyroid medication were excluded and 11 (2.0%) partners were excluded from the analyses. Thyroid hormone medication was defined as thyroid or anti-thyroid preparations (ATC code H03). Outliers were defined as serum thyroid parameters (thyrotropin, thyroxine and triiodothyronine) beyond three standard deviations below or above the standard error of the mean. Outliers were excluded from the analyses. 34 offspring with serum thyroid parameters beyond 3 standard deviations from the mean were excluded from the analyses, of which one individual was clinically hyperthyroid (thyrotropin <0.3 mU/L and free thyroxine > 24 pmol/L) and three individuals clinically hypothyroid (thyrotropin > 4.8 mU/L and free thyroxine < 10 pmol/L). 9 partners with serum thyroid parameters beyond 3 standard deviations from the mean were excluded from the analyses, of which 2 individuals were clinically hyperthyroid (thyrotropin <0.3 mU/L and free thyroxine > 24 pmol/L). In our laboratory, the reference values for thyrotropin were 0.3-4.8 mIU/L; free thyroxine: 10-24 pmol/L; and free triiodothyronine, 2.5-5.5 pmol/L.

Biochemical analysis

All serum measurements were performed with fully automated equipment. For thyrotropin, free thyroxine and free triiodothyronine, the Modular E170 was used from Roche, Almere, the Netherlands. The coefficients of variation of these measurements were all below 5 %.

Statistical analysis

Distributions of continuous variables were examined for normality and logarithmically transformed, when appropriate and used in all calculations. Geometric means (with 95% confidence intervals (CI)) are reported for thyrotropin. All differences between offspring and

partner categories were assessed with the use of linear mixed modeling, adjusted for age and correlation of sibling data. Differences in age and body mass index between the two groups of offspring and partners were tested using a Mann-Whitney rank sum test. Differences in smoking behavior and gender distribution between the group of offspring and the group of partners were calculated using a Chi-Square test. The Statistical Package for the Social Sciences (SPSS) program for Windows, version 16.0, was used for data analysis.

Results

Table 1 shows the baseline characteristics for the two study populations. In total, we used data on 1119 middle-aged offspring of nonagenarian siblings and 533 of their middle-aged partners. The group of female offspring was slightly older than the group of female partners, whilst the group of male offspring was younger than the group of male partners. No significant differences between the two groups were observed with regard body mass index and current smoking status.

Table 1. Baseline characteristics of study populations

	Offspring	Partners	P-value
Females – (n)	596	293	
Age (year)	58.9 (54.9 – 64.0)	57.4 (52.4 – 61.9)	*<0.001*
Height (cm)	166.8 (166.2 – 167.3)	167.0 (166.2 – 167.7)	0.62
Weight (kg)	69.6 (68.6 – 70.7)	70.8 (69.4 – 72.2)	0.17
Body Mass Index (kg/m^2)	25.0 (24.7 – 25.4)	25.4 (24.9 – 25.9)	0.20
Currently smoking (n, %)	75 (12.8%)	45 (15.4%)	0.30
Males – (n)	523	240	
Age (year)	59.4 (55.0 – 64.2)	61.4 (56.2 – 66.3)	*0.001*
Height (cm)	178.6 (178.0 – 179.3)	179.1 (178.3 – 180.0)	0.32
Weight (kg)	82.4 (81.3 – 83.4)	82.7 (81.1 – 84.2)	0.73
Body Mass Index (kg/m^2)	25.8 (25.5 – 26.1)	25.7 (25.3 – 26.1)	0.76
Currently smoking (n, %)	78 (15.1%)	37 (15.5%)	0.91

Age is presented as median age with interquartile range. Height, weight and body mass index are presented as estimated means with 95% confidence intervals. Results for weight, height and body mass index were adjusted for age.

Table 2 displays the mean serum levels of various thyroid function parameters in the group of middle-aged offspring of nonagenarian siblings as compared to the group of their middle-aged partners adjusted for age and body mass index. A trend was observed towards higher serum

thyrotropin levels in the group of offspring when compared to the group of partners (p=0.11). The free serum thyroxine levels were lower in the group of offspring than in the group of partners (p=0.045). Likewise, mean free serum triiodothyronine levels were lower in the group of offspring in comparison to the group of partners (p=0.024). Results were not materially different when analyses were adjusted for smoking behavior.

Table 2. Serum levels of thyroid hormone axis parameters for offspring and partners

	Offspring	Partners	p-value
All			
Thyrotropin (0.3 - 4.8 mU/L)	1.65 (1.59 - 1.71)	1.57 (1.49 - 1.66)	0.11
Free thyroxine (10 - 24 pmol/L)	15.0 (14.9 - 15.2)	15.2 (15.0 - 15.4)	*0.045*
Free triiodothyronine (2.5 - 5.5 pmol/L)	4.08 (4.04 - 4.12)	4.14 (4.09 - 4.20)	*0.024*
Ratio triiodothyronine thyroxine	0.28 (0.27 - 0.28)	0.28 (0.27 - 0.28)	0.84
Females			
Thyrotropin (0.3 - 4.8 mU/L)	1.72 (1.63 - 1.80)	1.64 (1.52 - 1.76)	0.28
Free thyroxine (10 - 24 pmol/L)	14.8 (14.6 - 14.9)	15.1 (14.8 - 15.3)	*0.034*
Free triiodothyronine (2.5 - 5.5 pmol/L)	3.89 (3.84 - 3.94)	4.00 (3.93 - 4.07)	*0.007*
Ratio triiodothyronine thyroxine	0.27 (0.26 - 0.27)	0.27 (0.26 - 0.27)	0.48
Males			
Thyrotropin (0.3 - 4.8 mU/L)	1.60 (1.52 – 1.69)	1.53 (1.42 - 1.65)	0.26
Free thyroxine (10 - 24 pmol/L)	15.2 (15.0 - 15.4)	15.5 (15.2 - 15.7)	0.12
Free triiodothyronine (2.5 - 5.5 pmol/L)	4.26 (4.20 - 4.31)	4.34 (4.26 - 4.42)	*0.048*
Ratio triiodothyronine thyroxine	0.28 (0.28 - 0.29)	0.28 (0.28 - 0.29)	0.95

Data are presented as estimated means with 95% confidence intervals. Results for all were adjusted for age, sex and body mass index. Results for males and females separately were adjusted for age and body mass index. Reference values are given between parentheses.

Discussion

The secretion of thyroid hormone from the thyroid gland is regulated by thyrotropin, which in turn is controlled by the hypothalamic derived thyroid-releasing-hormone. The main thyroid hormone produced in the thyroid gland is thyroxine (3,5,3',5'-tetraiodothyronine), which has a low affinity for thyroid hormone receptors in target tissues. Thyroxine can be converted peripherally to the more biologically active free 3,5,3'-triiodothyronine or the inactive reverse

triiodothyronine (3,3′,5′-triiodothyronine). When compared to their partners the group of offspring of nonagenarian siblings showed a trend towards higher serum thyrotropin levels in conjunction with lower free thyroxine levels and lower free triiodothyronine levels. These findings indicate a lower thyroidal sensitivity to thyrotropin in the group of offspring of nonagenarian siblings.

In middle aged human populations the effect of low thyroid hormone metabolism on health is unclear. At middle age, overt hypothyroidism is considered a risk factor for the development of atherosclerosis and myocardial infarction [10, 11]. Paradoxically, in euthyroid middle-aged subjects, lower triiodothyronine serum levels are associated with a beneficial cardio-metabolic profile [12, 13]. In the current study we demonstrate lower thyroid hormone levels in a middle-aged population which was previously shown to have a lower prevalence of cardiovascular disease [14]. These data suggest that selective survival of subjects with a lifelong thyroid hypofunction may contribute to the association between decreased thyroidal sensitivity to thyrotropin and a longer life span [6, 7].

Our results agree with observations in several several animal studies showing that lower activity of the thyroid hormone axis is beneficial during the aging process [1, 3, 15]. Active triiodothyronine primarily regulates the basal metabolic rate of cells, thereby increasing thermogenesis and the production of free radicals [16]. Data from model organisms show that low triiodothyronine is associated with lower production of reactive oxygen species (ROS) and ROS inflicted genomic damage [17]. The more efficient transport of electrons through the respiratory chain under conditions of low triiodothyronine might reduce the production of ROS and slow aging. Additionally, previous studies in euthyroid subjects have shown an association between higher levels of thyroid hormones and higher serum glucose levels, higher serum insulin levels as well as increased serum triglyceride levels in males [18, 19]. Furthermore higher triiodothyronine levels have been associated higher blood pressure. Increases in heart rate, cardiac output, myocardial contractility, and blood volume possibly underlie this association between triiodothyronine levels and blood pressure [20].

In conclusion, our data demonstrate that the middle-aged offspring of nonagenarian siblings have lower serum free triiodothyronine levels as compared to their middle-aged partners. These findings hint at a role of the thyrotroph axis in the regulation of human health and longevity.

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