Association between thyroid hormone levels and frailty in the community-dwelling oldest-old: a cross-sectional study

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Abstract

Background: Changes in thyroid hormone levels are commonly recognized characters among the elderly, which were reported to potentially influence incident frailty. Therefore, we examined the cross-sectional associations of thyroid hormones (THs) with frailty as well as the five components characterizing frailty (fatigue, resistance, ambulation, number of illnesses, and loss of weight) among the oldest-old.

Methods: Four hundred and eighty-seven community-dwelling oldest-old from a local community in Haidian District, Beijing, participated in our recruitment campaign between April 2019 and May 2020. The primary outcomes were a definitive diagnosis of frailty according to the FRAIL scale (Fatigue, Resistance, Ambulation, Illnesses, Loss of weight) and a positive score for each frailty subdomain. Demographic information (age, sex, marital status, and educational status), comorbidities, and details on the participants' lifestyles were recorded. Serum THs including free triiodothyronin (fT3), triiodothyronine (T3), free thyroxine (fT4), and thyroxine (T4) and thyroid stimulating hormone (TSH) levels were also measured at the beginning of our study. Logistic regressions were conducted to screen for potential risk factors for frailty and its subdomains.

Results: Among the total 487 subjects at enrollment, 60 (12.23%) of them were diagnosed with subclinical hypothyroidism and 110 (22.59%) of the total population scored positive for frailty. Logistic regression analyses adjusted for all potential confounders, showed that frailty was significantly associated with the serum TSH concentration (odds ratio [OR]: 1.06), fT3 concentration (OR: 0.54), and subclinical hypothyroidism score (OR: 2.18). The association between fT4 and frailty was absent in our observational study. The fT3/fT4 ratio characterizing peripheral hormone conversion was also tested to be correlated with frailty.

Conclusion: Subclinical hypothyroidism, higher TSH level, lower fT3 level, and decreased fT3/fT4 ratio were all associated with frailty assessed by the FRAIL scale among the community-dwelling oldest-old, suggesting a relevant role of thyroid function in aging. Future longitudinal studies are warranted to determine the casual relationship between thyroid dysfunction and frailty in the oldest-old.

Keywords: Hypothyroidism; Frailty; Aging; Thyroid hormone; Oldest-old; Triiodothyronin; Thyroid stimulating hormone

Introduction

Frailty is a pathological status commonly observed alongside aging.[1] It is characterized by the culmination of biological reserve loss across multiple systems to a critical level, ultimately rendering the individual vulnerable to stressor and external impact, and causing a disproportionate rate in death, and hospitalization.[2-4] Currently, nearly 10% of the population aged >65 years suffers from frailty and the proportion is nearly tripled among those aged >85 years.[5] Modern society is affected by the greater longevity of people, with progressive aging commonly observed in most industrialized countries.[6] Taking into account the close relationship between frailty and aging, the prevalence of frailty is expected to rise further.[2] However, the underlying mechanism of frailty remains unclear, and may be complicated by the progress of aging.[7,8]

Changes in thyroid hormone levels have been well characterized among the elderly, and incident frailty is reported to be likely influenced by thyroid hormone fluctuations.[4] According to the National Health and Nutrition Examination Survey (NHANES) III report, subclinical hypothyroidism in the elderly is one of the most common endocrine malfunctions, occupying nearly 4.3% of the total hypothyroidism population.[9] Other thyroid dysfunctions such as iodine malabsorption, physical blunted

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002208

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Chinese Medical Journal 2022;135(16)

Received: 14-12-2021; **Online:** 28-09-2022 **Edited by:** Ningning Wang and Jing Ni

reaction to thyroid stimulating hormone (TSH), and elevated circulating TSH level in spite of thyroid condition are also commonly observed among the elderly.[4] Sarcopenia characterized by loss of viable muscle fiber was regarded as a key feature of the frailty phenotype.[10] Despite several precipitating factors, decline in anabolic hormones due to aging of the endocrine system might be the main cause of muscle insufficiency.[11] Thyroid hormones (THs), as an active participator in maintaining physical function and body composition, were also frequently implicated in sarcopenia development.[10]

Several studies have examined the association between thyroid function and frailty. However, different principles for diagnosing frailty were used in these studies, and inconsistent results with regard to the risk estimates of thyroid dysfunction on frailty were reported, rendering debatable the involvement of THs in frailty.[3,4] Frailty is considered a modifiable condition with great potential for reversibility, rather than a definite consequence of aging,[12-14] and studies have demonstrated that even a slight deviation in THs among euthyroid subjects could cause differences in clinical parameters related to frailty.[7,15] Therefore, investigating the risk effects of thyroid function on frailty would help to identify a potentially modifiable factor so as to curb the development of frailty at an early stage, which may help patients to further enjoy social benefits.[4,16]

Therefore, we examined the cross-sectional association of commonly reported thyroid dysfunctions with frailty and its five subdomains according to the FRAIL (Fatigue, Resistance, Ambulation, Illnesses, Loss of weight) scale in an oldest-old subjects-based population.

Methods

Ethical approval

Our study was approved by the Research Ethics Committee of the Chinese People's Liberation Army (PLA) General Hospital (No. S2021-686-01) and strictly abided by the *Declaration of Helsinki* during the duration of the investigation. Written consent forms were also signed and retrieved from each participant.

Study design and population

Our study adopted a cross-sectional design, and we recruited over 500 community-dwellers aged ≥80 years who responded to our appeal. All the participants were from a local community in Haidian District, Beijing, and most of the residents were retired officials who had been working for the government since 1949. However, following initial recruitment, only those who fulfilled the following requirements were included in our study: (1) patients presenting with functional physical capacity and absence of intellectual impairment, allowing them to complete standard physical tests such as a gait speed test and answer face-to-face questionnaires; (2) having no history of thyroid disease, thyroid surgery, or treatment with radioactive iodine; and (3) capable of providing full and clear records on past medical history regarding the endocrine system. Furthermore, patients diagnosed with overt hypothyroidism or hyperthyroidism upon initial screening were excluded. A total of 487 subjects were enrolled in our study between April 2019 and May 2020.

FRAIL scale

As our primary interest, frailty was assessed according to the FRAIL scale, which was proposed by the International Association of Nutrition and Aging and showcased prominent effects in predicting mortality and disability.[17,18] The FRAIL scale set diagnosis of frailty according to five subdomains, namely fatigue, resistance, ambulation, number of illnesses, and unintentional weight loss. Participants were considered as frail when three or more of the criteria were met following thorough evaluation. The specific standards for each individual item of frailty are presented as the following: (1) patients who lost >5% of their total weight during the last year without knowing causes were scored positive for loss of weight; (2) patients who gave affirmative answers to questions such as "Do you feel tired or worn out?" or "Do you feel lack of energy?" were recorded as positive for fatigue; (3) patients having trouble in climbing one flight of stairs or walking >100 m scored positive on resistance and ambulation, respectively; and (4) the deficit for illness was predefined as having more than five of the common chronic conditions in elderly patients such as arthritis, Alzheimer's disease, dementia, or other comorbidities.[7]

Laboratory measurements

All the participants were asked to fast overnight before the biochemical tests. Blood samples were collected and prepared for examination of TSH, free thyroxine (fT4), thyroxine (T4), free triiodothyronin (fT3), and triiodothyronin (T3) levels. Thyroid hormone levels were assessed using chemiluminescence immunoassay kits (ElectroChemiLuninescence ImmunoAssay, Beijing, China) and the intra-assay and inter-assay coefficients were managed <5%; all the tests were performed in the lab of Chinese PLA General Hospital. TSH values between 0.35 and 4.94 mIU/L were adopted as reference. The reference ranges for fT4, T4, fT3, and T3 were as follows: (1) fT4: 9.01 to 19.05 pmol/L; (2) T4: 62.88 to 150.80 nmol/L; (3) fT3: 2.63 to 5.70 pmol/L; and (4) T3: 0.88 to 2.44 nmol/L.[19]

Potential covariates

Demographic information including age, gender, body mass index, marital status, and educational levels was collected through interviews and questionnaires. Information regarding physical comorbidities such as hypertension, coronary heart disease, cerebral artery diseases, chronic obstructive pulmonary disease, diabetes mellitus, cancer, and osteoporosis was gathered based on a self-reporting mechanism. Pertinent disease-driven habits such as drinking and smoking were also collected, the frequency of which were recorded.

Statistical analyses

Continuous variables are presented as the mean with standard deviation or median with interquartile range

according to their distribution, and comparison of baseline population characteristics between the subclinical hypothyroidism and euthyroidism groups was made using independent Student's *t*-test. Categorical variables were presented as percentages and compared using the Pearson's chi-squared test. The backward stepwise logistic regression model was applied to identify potential covariates associated with frailty, with a *P* value <0.05 and >0.10 used as entry and removal criteria, respectively.

Multivariate logistic regressions were used to determine the association of each thyroid hormone level with overall frailty or each individual item. Only age and sex were included in Model 1 as the minimally adjusted model, while additional variables including education, marital status, smoking status, drinking status, and comorbidities were included in Model 2 as the fully adjusted models. All the statistical analyses were performed using the SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA), and a two-tailed *P* value <0.05 was considered as statistically significant.

Results

Characteristics of included participants

Of the 531 community-dwelling men aged >80 years, 30 were excluded for having a history of thyroid disease, thyroid surgery, or treatment with radioactive iodine, as were 14 for taking thyroid-related medications and 11 with missing data. Another 15 men with previously undiagnosed hyperthyroidism and 16 men with undiagnosed overt hypothyroidism were excluded, leaving 487 adults for the analysis.

The average age of the subjects was 86.0 ± 2.9 years. Of these, 60 (12.3%) were classified as having subclinical hypothyroidism and 427 (87.7%) as having euthyroidism. Baseline demographic data are shown in Table 1. Overall, 110 men were classified as being frail (22.5%).

Association between subclinical hypothyroidism and frailty

Subclinical hypothyroidism was not associated with frailty in Model 1 when adjusted for age and sex. The odds ratio (OR) for frailty was 1.66 (95% confidence interval [CI]: 0.90–3.08). However, after adjusting for full confounding factors (Model 2), subclinical hypothyroidism was significantly associated with frailty, with OR of frailty being 2.18 (95% CI: 1.09–4.37). Subclinical hypothyroidism was associated with none of the five subdomains of frailty both in Models 1 and 2 [Table 2].

Associations between thyroid hormone parameters and frailty

There was an inverse association between risk of frailty and fT3 (0.45, 95% CI: 0.30–0.68) or fT3/fT4 ratio (0.72, 95% CI: 0.57–0.90) after adjusting for age and sex. Furthermore, additional multivariate adjustment (full model) did not significantly attenuate the association. ORs for frailty were 0.54 (95% CI: 0.35–0.83) and 0.76 (95% CI: 0.57–0.97) with regard to fT3 and fT3/fT4, respectively.

Table 1: Characteristics of the community-dwelling oldest-old from a local community in Haidian District, Beijing (*N* = 487).

Items	Thyroid function		
	Subclinical hypothyroidism (*n* = 60)	Euthyroidism (*n* = 427)	*P* value
Age (years)	86 (84–88)	86 (84–89)	0.526
Female	35 (58.3)	274 (64.2)	0.379
BMI (kg/m^2)	24.4±3.2	24.0±3.3	0.411
Marital status			0.173
Widowed/not married/ divorced	29 (48.3)	167 (39.1)	
Spouse alive	31 (51.7)	260 (60.9)	
Education level			0.782
≤Elementary school	5 (8.3)	45 (10.5)	
Primary school	11 (18.3)	71 (16.6)	
High school	17 (28.3)	100 (23.4)	
≥College	27 (45.0)	211 (49.4)	
Smoking status			0.547
Never	49 (81.7)	350 (82.0)	
Former	9 (15.0)	70 (16.4)	
Current	2 (1.6)	7 (1.6)	
Drinking frequency in the past year			0.844
Never	54 (90.0)	378 (88.5)	
<once per week	4 (6.7)	26 (6.1)	
≥once per week	2 (3.3)	23 (5.4)	
Chronic conditions			
Hypertension	43 (71.7)	305 (71.4)	0.969
CHD	35 (58.3)	217 (50.8)	0.275
Stroke/TIA	19 (31.7)	122 (28.6)	0.621
COPD	13 (21.7)	79 (18.5)	0.558
DM	21 (35.0)	131 (30.7)	0.499
CKD	3 (5.0)	60 (14.1)	0.050
Cancer	8 (13.3)	86 (20.1)	0.211
Osteoarthritis	19 (31.7)	182 (42.6)	0.107
Osteoporosis	27 (45.0)	244 (57.1)	0.076
MNA scores	13±12	14±12	0.494
Frailty	18 (30.0)	92 (21.5)	0.143
Fatigue	16 (26.7)	81 (19.0)	0.162
Resistance	38 (63.3)	252 (59.0)	0.523
Ambulation	22 (36.7)	138 (32.3)	0.502
Illness	23 (38.3)	170 (39.8)	0.826
Loss of weight	9 (15.0)	35 (8.2)	0.085

Data are presented as odds ratio (95% confidence interval). BMI: Body mass index; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease; DM: Diabetes mellitus; MNA: Mini-Nutritional Assessment; TIA: Transient ischemic attack.

In addition, higher thyroid-stimulating hormone levels were associated with increasing OR of frailty both in Model 1 (1.05, 95% CI: 1.01–1.10) and Model 2 (1.06, 95% CI: 1.00–1.11) [Table 3].

Association of thyroid hormone parameters with individual components of frailty

After adjusting for full confounding factors (Model 2), higher fT3 levels were associated with lower risks of fatigue (OR = 0.51, 95% CI: 0.32–0.79), resistance (OR =

Table 2: Associations between subclinical hypothyroidism and frailty and components of frailty.

Items	Model 1	Model 2
Frailty	1.66 (0.90–3.08)	2.18 (1.09–4.37)*
Fatigue	1.66 (0.89–3.12)	1.85 (0.92–3.69)
Resistance	1.25 (0.71–2.19)	1.41 (0.76–2.60)
Ambulation	1.30 (0.73–2.30)	1.54 (0.83–2.86)
Illness	0.88 (0.50–1.57)	1.29 (0.49–3.41)
Loss of weight	2.14 (0.96–4.78)	1.96 (0.78–4.96)

Data are presented as odds ratio (95% confidence interval). * indicates $P<0.05$. Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, education level, marital status, smoking status, drinking status in the past year, BMI, MNA scores, and chronic conditions (hypertension, CHD, stroke/transient ischemia attack, COPD, DM, CKD, cancer, osteoporosis, and osteoarthritis). BMI: Body mass index; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease; DM: Diabetes mellitus; MNA: Mini-Nutritional Assessment.

Table 3: Associations between thyroid hormone parameters and frailty.

Item	Model 1	Model 2
fT3	0.45 (0.30–0.68)*	0.54 (0.35–0.83)*
T3	0.23 (0.10–0.54)*	0.35 (0.14–0.86)*
fT4	1.00 (0.92–1.08)	0.99 (0.91–1.08)
T4	0.99 (0.98–1.00)	0.99 (0.98–1.00)
TSH	1.05 (1.01–1.10)*	1.06 (1.00–1.11)*

Data are presented as odds ratio (95% confidence interval). * indicates $P < 0.05$. Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, education level, marital status, smoking status, drinking status in the past year, BMI, MNA scores, and chronic conditions (hypertension, CHD, stroke/transient ischemia attack, COPD, DM, CKD, cancer, osteoporosis, and osteoarthritis). BMI: Body mass index; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease; DM: Diabetes mellitus; MNA: Mini-Nutritional Assessment; TSH: Thyroid stimulating hormone.

0.73, 95% CI: 0.59–0.90), and loss of weight (OR = 0.45, 95% CI: 0.23–0.89). In addition, T3 levels demonstrated an inverse association with ambulation (OR = 0.38, 95% CI: 0.17–0.82), illness (OR = 0.32, 95% CI: 0.11–0.95), and loss of weight (OR = 0.09, 95% CI: 0.02–0.42). Higher TSH level was marginally associated with a higher chance of fatigue (OR = 1.05, 95% CI: 1.01–1.09). These details are shown in Table 4.

Discussion

People aged >85 years, who are regarded as the "oldest old," constitute a growing group normally comorbid with many age-associated diseases and present phenotypic frailty.[20] Though several common molecular mechanisms such as inflammation or metabolic disorder were revealed as the "pillar" of integrated perspective of aging, the oldest-old still showed great heterogeneity.[21] During aging, endocrine system experiences great changes, and the changes in thyroid gland are of great importance since thyroid functions are implicated in physical adjustment and many aspects of metabolism. Recently, the concept of

Table 4: Associations between thyroid hormone parameters and components of frailty.

Item	Model 1	Model 2
fT3		
Fatigue	0.47 (0.31–0.71)*	0.51 (0.32–0.79)*
Resistance	0.56 (0.40–0.78)*	0.73 (0.59–0.90)*
Ambulation	0.74 (0.53–1.03)	0.77 (0.53–1.11)
Illness	0.66 (0.47–0.91)*	0.88 (0.50–1.54)
Loss of weight	0.44 (0.25–0.77)*	0.45 (0.23–0.89)*
T3		
Fatigue	0.45 (0.19–1.06)	0.68 (0.27–1.70)
Resistance	0.81 (0.44–1.49)	0.83 (0.41–1.71)
Ambulation	0.35 (0.16–0.73)*	0.38 (0.17–0.82)*
Illness	0.23 (0.11–0.49)*	0.32 (0.11–0.95)*
Loss of weight	0.11 (0.03–0.40)*	0.09 (0.02–0.42)*
fT4		
Fatigue	1.02 (0.94–1.10)	0.98 (0.90–1.07)
Resistance	0.99 (0.93–1.06)	0.96 (0.90–1.04)
Ambulation	1.01 (0.94–1.08)	1.01 (0.94–1.09)
Illness	0.97 (0.91–1.03)	1.01 (0.89–1.14)
Loss of weight	0.96 (0.85–1.08)	0.90 (0.79–1.04)
T4		
Fatigue	0.99 (0.98–1.00)	0.99 (0.98–1.00)
Resistance	1.00 (0.99–1.01)	1.00 (0.98–1.01)
Ambulation	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Illness	1.00 (0.99–1.01)	1.00 (0.98–1.01)
Loss of weight	0.98 (0.96–0.99)*	0.97 (0.95–0.99)*
TSH		
Fatigue	1.04 (1.00–1.09)*	1.05 (1.01–1.09)*
Resistance	1.06 (0.99–1.13)	1.07 (0.99–1.15)
Ambulation	1.03 (0.99–1.07)	1.03 (0.99–1.08)
Illness	1.02 (0.99–1.06)	1.02 (0.93–1.11)
Loss of weight	1.00 (0.95–1.06)	1.01 (0.94–1.09)

Data are presented as odds ratio (95% confidence interval). * indicates $P < 0.05$. Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, education level, marital status, smoking status, drinking status in the past year, BMI, MNA scores, and chronic conditions (hypertension, CHD, stroke/transient ischemia attack, COPD, DM, CKD, cancer, osteoporosis, and osteoarthritis). BMI: Body mass index; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease; DM: Diabetes mellitus; MNA: Mini-Nutritional Assessment; TSH: Thyroid stimulating hormone.

"thyroid biography" was proposed by Franceschi *et al*[20], indicating lifestyle and environmental factors being involved in individual thyroid aging, which might account for the vast heterogeneity of overall aging. Frailty is regarded as the manifestation of aging and showed great heterogeneity as well.[2,19] Therefore, comprehensively evaluating the thyroid status and exploring the relationship between thyroid hormone concentrations and frailty among the oldest-old might help uncover the intricate pathogenesis of aging. Therefore, our study investigated the correlation between each thyroid hormone with frailty diagnosed by FRAIL scale among a group of community-dwelling oldest-old. The FRAIL scale is a convenient instrument in identifying frail subjects but yields comparable results with other screening tools, and it was also a firm predictor of mortality and disability in the long run.[18,22]

In our research, we investigated the associations of subclinical hypothyroidism and thyroid hormone levels

with frailty and the five individual components of the FRAIL scale. The statistics showed that subclinical hypothyroidism was associated with higher risk of frailty. In line with subclinical hypothyroidism, TSH concentration was also positively correlated with prevalent frailty. In addition, fT3 and fT3/fT4 ratio emerged as predictors of frailty (assessed by the FRAIL scale) whereas fT4 showed no correlation with frailty or either of its components.

In our study, after adjusting for full confounding factors, subclinical hypothyroidism was significantly associated with frailty (OR = 2.18; 95% CI: 1.09–4.37). However, results from numerous other studies have suggested otherwise. Yeap *et al*[7] reported a null association between subclinical hypothyroidism and frailty based on a population comprising 3943 male subjects, while Virgini *et al*[23] found that subclinical hyperthyroidism, rather than subclinical hypothyroidism, was associated with increased odds of prevalent frailty among community-dwelling older men. In our study, although subclinical hypothyroidism appeared as a risk factor for frailty, it presented no correlation with either of the components in the FRAIL scale. Subclinical hypothyroidism may simply be a derivative of the naturally shifting TSH levels in conjunction with increasing age, and its risk effect on frailty might be a pure reflection of aging.[19,24] In addition, it was reported that though replacement therapy with levothyroxine was confirmed to bring benefits to elderly patients with overt hypothyroidism, the clinical benefits of levothyroxine supplementation among those with subclinical hypothyroidism was absent.[25,26] Therefore, the predictive value of subclinical hypothyroidism on frailty among the elderly should be treated with discretion, and the degree of TSH deviation and the presence of autoimmune markers should also be taken into consideration.

We observed that TSH levels were correlated with prevalent frailty and fatigue. Our result was thus in agreement with others that a higher TSH concentration was associated with frailty in both male and female patients.[19,27,28] The possible explanation of the role of TSH on frailty is that high TSH levels may contribute to overt and subclinical hypothyroidism, all of which may precipitate the development of overall metabolic reduction, cardiovascular decompensation, and neuromuscular abnormalities.[29-32] Common symptoms such as tiredness and fatigue would arise from these pathological processes and serve as the underpinning of frailty. Our study reinforced that TSH may be a potential marker of frailty since even minor changes of TSH within the normal limit could interfere with homeostasis.[28]

Lower levels of fT3 were associated with not only higher risk of frailty but also increased ORs of fatigue, resistance, and loss of weight. However, associations between fT4 and frailty or its components were absent in our observational study. Our results were in accordance with two other studies which also investigated the relationship between fT3 and frailty.[27,33] Xiu *et al*[33] determined that low fT3 levels, rather than fT4 and TSH, were associated with a significantly higher chance of frailty among type 2 diabetes mellitus elder inpatients, while Bano *et al*[40] also determined an inverse relationship between fT3 levels and frailty based on a cohort of 62 inpatients with hip fracture and 50 controls. Our study suggests that although the participants were free from a history of thyroid diseases or any treatments related to the thyroid, THs were still subjected to the influence of nonthyroidal illness syndrome (NTIS) in community-dwelling old adults. NTIS is referred to as a disorder of thyroid hormone levels due to extrinsic acute or chronic illnesses,[34] normally characterized by reduced fT3 levels in combination with slightly deviated fT4 and TSH levels.[35] Because no patients with acute illness were included in our study, the NTIS may be triggered by chronic comorbidities that activate the inflammatory process causing bunted conversion from T4 to T3.[36-38] A decrease in fT3 levels could compromise myosin expression, which is a key regulator of skeletal muscle relaxation and contraction rates.[3,39] Therefore, lowered fT3 levels are associated with the loss of muscle mass and strength, further causing restricted movement and reduced gait speed.[33,40]

The relationship between fT3/fT4 ratio representing the degree of thyroxin peripheral conversion and frailty were also tested in our research, and the ratio was found to be an effective predictor of frailty. Our result was in line with findings in several previous studies. Pasqualetti *et al*[41] stratified 619 hospitalized patients aged >65 years according to fT3/fT4 ratio and observed reduced comorbidity burden along with improved nutritional status, physical reserve, and cognitive capacity in the highest quartile of fT3/fT4 ratio. Ostan *et al*[42] researched on 672 centenarians and semi-supercentenarians found that fT3/fT4 ratio showed a marked reduction with age and a negative association with functional status and mortality. Arosio *et al*[43] recommended fT3/fT4 as the best marker of frailty (diagnosed by Frailty index) in comparison with other THs, especially in the long-lived group. T3 is the bioactive form of thyroid hormone which was converted from T4 peripherally depending on 5′-deiodinases activity.[44] Above all, though a reduction in thyroxin deiodination was witnessed alongside aging even in fit centenarians and previously regarded as an energy-saving response,[45] compensatory increase in 5′-deiodinases' activities to counterbalance the decreasing fT3 level was crucial to the preservation of endocrine stability.[44] Deiodinase downregulation could play the role as a precursor in the development of frailty,[41] and a normal fT3/fT4 ratio might be relevant in the natural aging process and longevity.[43]

To our knowledge, this is a population-based study in China exploring the comprehensive relationship between thyroid function (including subclinical hypothyroidism, each hormone level and fT3/fT4 ratio) with frailty according to the FRAIL scale among community-dwelling oldest-old. The latter represents a well-validated measurement that is considered useful for evaluating frailty over time. Only fT3 level was proved to be associated with not only the overall frail status but also three subdomains of frailty, indicating that fT3 might be a potentially effective marker for early detection and a target for instant prevention on frailty. Several limitations should be mentioned. First, considering the observational nature of our study, the causality should only be confirmed by

longitudinal prospective cohort studies. Second, the association between subclinical hyperthyroidism and frailty was not investigated in our study because of its low prevalence. Third, as important mediators in both thyroid dysfunction and frailty development, the level of systemic inflammation, patients' nutritional statuses, and autoimmune comorbidities were not assessed in the models. Fourth, even though we checked the medical history of each patient, information on the history of medication taken was collected based on a self-reporting mechanism. Medications such as amiodarone, lithium carbonate, and corticosteroids might confound our results.

Conclusion

Subclinical hypothyroidism, higher TSH level, lower fT3 level, and decreased fT3/fT4 ratio were all associated with frailty assessed by the FRAIL scale among the community-dwelling oldest-old, suggesting a relevant role of thyroid function in aging. The large heterogeneity in the aged population might project on their thyroid status. Monitoring the overall thyroid function might help identify subjects at risk of frailty. Future longitudinal studies are still warranted to confirm our results.

Funding

This research was funded by grants from NCRCG-PLAGH-2022004, and the Military Healthcare Research Program (No. 21BJZ26, 18BJZ32).

Conflicts of interest

None.

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How to cite this article: Guan B, Luo J, Huang X, Tian F, Sun S, Ma Y, Yu Y, Cao J, Fan L. Association between thyroid hormone levels and frailty in the community-dwelling oldest-old: a cross-sectional study. Chin Med J 2022;135:1962–1968. doi: 10.1097/CM9.0000000000002208