COMORBIDITY ASSESSMENT AND THYROID HORMONES IN INDEPENDENTLY-LIVING ELDERLY

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ABSTRACT

Background: the study was undertaken with an objective to study the spectrum of thyroid dysfunction in elderly and to correlate comorbidity with abnormal thyroid function.

Methods: a total of 246 subjects aged more than 60 years, admitted to General Medicine or attended the out-patient clinic who were presented with vague symptoms like easy fatigability and lethargy, were subjected to detailed clinical examination and thyroid function testing by biochemical means.

Results: a total of 246 patients were included in the study. Thyroid disorders were present in 51.2%. Clinical hypothyroidism in 8.13%, subclinical hypothyroidism in 4.88% cases, hyperthyroidism in 3.3% and Low tri-iodothyronine (T3) syndrome in about one third of our patients were noted. There were no correlation between the thyroid hormones and most of clinical and laboratory parametes. The prevalence of abnormal thyroid patterns were significantly high in patients with comorbidities in comparison to those without.

Conclusions: Elderly patients especially those with comorbidity have high prevalence of thyroid dysfunction. Clinical diagnosis is difficult to make because of vague symptomology and comorbid diseases. So, high clinical suspicion and thyroid function tests always helps in diagnosing the disease.

Key words: Comorbidity, thyroid hormones, elderly.
No conflict of interest

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INTRODUCTION

Thyroid hormones, tri-iodothyronine (T3) and thyroxin (T4) are secreted by the thyroid gland under the influence of its physiological regulator, the hypophysial thyrotrophic hormone, thyroid stimulating hormone (TSH) [1]. Under normal physiological conditions T4 is the main secretory product of the thyroid gland and about 80-90 µg of it is secreted per day. On the other hand the normal human thyroid secretes only 8 µg per day of T3 [2;3]. T3 is more active as compared to T4 because it has a very high affinity to enter the cellular thyroid hormone receptors [4]. Normally about 93% of T3 is produced by the peripheral conversion from T4 and only 7% is secreted by the thyroid gland itself [5]. Low T3 syndrome is a condition with impaired peripheral conversion of T4 to T3 [6].

Changing levels of several hormones in the aged compared with younger individuals have been reported. The role of multiple hormonal changes in the whole aging process is not clear. It is uncertain whether it is possible to alter the aging process markedly by giving one single hormone to gain the same levels as younger adults have, and whether the benefits would then exceed the risks. Overt and subclinical primary hypothyroidism is the most common pathological hormone deficiency [7].

Subclinical hypothyroidism is defined as a biochemical perturbation of TSH values with normal free T4 levels [8], irrespective of the presence or absence of symptoms [9]. The prevalence of subclinical hypothyroidism increases with age up to 20% in subjects older than 65 years of age [10]. Subclinical thyroid dysfunction has been associated with several adverse outcomes, such as cardiovascular disease [11], osteoporosis [12], and cognitive dysfunction [13]. Furthermore, subclinical thyroid dysfunction has also been associated

with decreased functional capacity [14] and neuromuscular abnormalities [15], but data are conflicting [16], and reliable evidence on the association between subclinical thyroid dysfunction and functional capacity in an older population is lacking.

Apparently easy to define if we were to consider the etymology of the word (prefix "co" = added, with "Morbus" = disease), comorbidity generates controversy both in meaning of the term, the effects it has over the patient and by the difficulty to measure it. Feinstein [17] described the term comorbidity as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study." Currently, the term comorbidity has two definitions. The first one indicates a medical condition existing simultaneously but independently with another condition in a patient (this is the older and more "correct" definition). A second definition indicates a medical condition in a patient that causes, is caused by, or is otherwise related to another condition in the same patient (this is a newer, nonstandard definition and less well-accepted). In psychiatry, comorbidity refers to the presence of more than one mental disorder occurring in an individual at the same time [18].

In a cross-sectional study design, we tried to explore thyroid hormone patterns in a series of elderly patients with comorbidity and to search for a possible relationship, if any, between these patterns and the extent of comorbid diseases, in terms of the number of diseases afflicted the patients and its nature.

METHODS

Patient Selection

We enrolled 246 consecutive patients attending the outpatient clinic of our hospital for follow up of their comorbid diseases, during the period from February 2014 to June 2015. Patients were considered eligible for enrollment if they were over 60 years of age. We excluded patients on medications that might interfere with thyroid hormone testing, for example: amiodarone, radioactive iodine, corticosteroids, etc. Before inclusion, an informed written consent was obtained from each patient after full explanation of the study protocol. The study protocol was reviewed and approved by our Local Institutional Human Research Ethical Committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002.

Thyroid Profile Assessment

Fasting serum samples were collected from all patients and processed within 30 minutes, after which they were kept frozen at -20 °C. We assayed the levels of free tri-iodothyronine (fT3), free T4 (fT4) using T3, T4 Accubind ELISA Microwells, respectively (Monobind, Inc. Lake Forest, CA (92630) USA). Values between 1.4 and 4.2 ng/dl, 0.8 and 2.5 ng/dl were considered normal for free T3 and free T4, respectively. Moreover, serum TSH was assessed using TSH Accubind ELISA Microwells (Monobind, Inc. Costa Mesa, CA (92627) and 0.45 and 5.6 mU/L were considered normal for TSH.

Definitions of Thyroid Hormone Patterns

Clinical hypothyroidism was defined as a serum TSH concentration above the defined upper limit of normal with serum fT4 concentration below the lower limit of normal. Subclinical hypothyroidism was defined as a serum TSH concentration above the defined upper limit of normal with serum fT4 concentration within the reference range. Clinical hyperthyroidism was defined as a serum TSH level below the defined lower limit of normal with increased serum levels of both fT4 and fT3. Subclinical hyperthyroidism was defined as a serum TSH concentration below the defined lower limit of normal with both serum fT4 and fT3 concentrations within the reference ranges. Sick euthyroid syndrome was defined as any abnormal result not matching the above definitions.

Comorbidity Evaluation

Comorbidity was assessed at entry of the study, based on both the number of diseases known to the patient or detected by clinical and laboratory evaluation and the Geriatric Index of Comorbidity (GIC), which takes into account the number of diseases as well as the

occurrence of very severe diseases, assuming that both are determinants of health [19]. In computing the GIC, each of the 15 more prevalent clinical conditions (ischemic or organic heart diseases, primary arrhythmias, heart diseases with a non-ischemic or – organic origin, hypertension, stroke, peripheral vascular diseases, diabetes mellitus, anemia, gastrointestinal diseases, hepatobiliary diseases, renal diseases, respiratory diseases, parkinsonism and nonvascular neurologic diseases, musculoskeletal disorders, malignancies) is graded on a 0 to 4 disease severity scale on the basis of the following general framework: 0 = absence of disease, 1 = asymptomatic disease, 2 = symptomatic disease requiring medication but under satisfactory control, 3 = symptomatic disease uncontrolled by therapy, and 4 = life-threatening or the most severe form of the disease.

The GIC classifies patients into four classes of increasing somatic comorbidity. Class 1 includes patients who have one or more conditions with a disease severity grade equal to or lower than 1. Class 2 includes patients who have one or more conditions with a disease severity grade of 2. Class 3 includes patients who have one condition with a disease severity of 3, other conditions having a disease severity equal to or lower than 2. Class 4 includes patients who have two or more conditions with a disease severity of 3 or one or more conditions with disease severity of 4.

STATISTICAL ANALYSIS

Quantitative variables are presented as the means ± standard deviation, and the qualitative variables are presented as proportions. The level of significance was set to 5%. Statistical analysis was conducted using SPSS version 18 (Statistical Package for Social Science). Chi square test was used to calculate difference between qualitative variables. Independent T test was used to calculate difference between quantitative variables in normally distributed data in two groups. Mann Whiteny test was used to calculate difference between quantitative variables in not normally distributed data in two groups. Spearsmann and Pearson correlation coefficient used to calculate correlation between quantitative variables.

RESULTS

In this study, 246 elderly patients who were attending our hospital due to complaints either related to their comorbid diseases or not; were evaluated in detail with clinical examination and laboratory investigations (table 1).

Table 1: Clinical and laboratory results of all studied patients presented as means ± STD.

Parameter	Means ± STD	Minimum – maximum
Sex (m/f)	118/128	Percentage (48% and 52%)
Age (in years)	69.56 ± 6.26	61 – 90
Creatinine (mg/dl)	1.29 ± 1.04	0.4 - 6
Geriatric index of comorbidity	2.6 ± 1	1 - 4
Barthel Index	90.41 ± 9.25	70 - 100
Thyroid stimulating hormone (mU/L)	3.86 ± 5.66	0.1 - 34
Free T4 (ng/dl)	1.55 ± 0.666	0.2 – 4.6
Free T3 (ng/dl)	1.91 ± 1.56	0.22 - 6
Hemoglobin (gm/dl)	12.6 ± 1.3	8 - 15
White blood cells ($x10^3$/ml)	6.87 ± 2.15	8 – 15.5
Platelets ($x10^3$/ml)	308.99 ± 82	164 - 660
Bilirubin (mg/dl)	0.71 ± 0.16	0.37 – 1.1
Albumin (mg/dl)	4.3 ± 0.42	3 – 5.5
Total cholesterol (mg/dl)	201.51 ± 34.43	120 – 312
Triglyceride (mg/dl)	149.2 ± 37.93	78 – 300
Low density lipoprotein (mg/dl)	127.63 ± 37.45	58 - 220
High density lipoprotein (mg/dl)	42.42 ± 7.81	27 - 56

STD, standard deviation

The prevalence of any thyroid dysfunction was very high (51.2%) in all studied patients and increased significantly in patients with comorbidity (68.5%) in comparison to those without comorbidity (37.7%). In particular, 120 (48.8%) participants had euthyroidism, 20 (8.13%) had clinical hypothyroidism, 12 (4.88%) had subclinical hypothyroidism, 8 (3.3%) had clinical hyperthyroidism, and almost one third [*n* = 86(35%)] had low T3 syndrome (table 2). As shown in table 3, we discovered that the most prevalent thyroid dysfunction in different diseases (diabetes, hypertension, Coronary artery disease, renal impairment, and pulmonary affection) was low T3 syndrome in those elderly patients (56.4%, 50%, 37.7%, 51.7, and 50%; respectively). Clinical hypothyroidism came in the second place after low T3 syndrome as the more prevalent disorder associated with these different comorbidities. There was high significant difference between the patient with comorbidities and those without for the prevalence of all abnormal thyroid patterns ($p<0.001$).

Table 2: Prevalence of different abnormal thyroid patterns in studied patients.

Parameters (Number of cases in all studied patients and its percentage)	Total studied patients (N.=246)			
	Patients without comorbidity Number = 138 (56.1%)		Patients with comorbidity Number = 108 (43.9)	
	N	%	N	%
Euthyroidism 120 (48.8%)	86	62.3	34	31.5
Thyroid abnormal patterns 126 (51.2%)	52	37.7	74	68.5
Low T3 syndrome 86 (35%)	42	30.4	44	40.7
Clinical Hypothyroidism 20 (8%)	4	2.9	16	14.8
Subclinical hypothyroidism 12 (4.9%)	4	2.9	8	7.4
Clinical hyperthyroidism 8 (3.3%)	4	2.9	4	3.7
Subclinical hyperthyroidism 0 (0%)	0	0	0	0
Total Subjects With abnormal thyroid patterns = 126 from 246 studied subjects (51.2%)				

Table 3: Prevalence of different comorbidities with thyroid abnormalities

Comorbidities	**Thyroid abnormalities Total number of patients = 74**				**Euthyroid function N=34 (31%)**
	Hypothyroidism N = 16 (14.8%)	**Hyperthyroidism N = 6 (5.6%)**	**Subclinical hypothyroidism N = 8 (7.4%)**	**Low T3 syndrome N = 44 (40.7%)**	
Diabetes mellitus (n=39)	8 (20.5%)	0 (0%)	2 (5.1%)	22 (56.4%)	7 (18%)
Hypertension (n=36)	8 (22.2%)	0 (0%)	2 (5.6%)	18 (50%)	8 (22.2%)
Coronary artery disease (n=61)	12 (19.7%)	4 (6.6%)	2 (3.3%)	23 (37.7%)	20 (32.7%)
Renal impairment (n=58)	6 (10.4%)	0 (0%)	8 (13.8%)	30 (51.7%)	14 (24.1%)
Cerebrovascular diseases (n=6)	4 (66.7%)	0 (0%)	0 (0%)	0 (0%)	2 (33.3%)
Pulmonary diseases (n=4)	0 (0%)	0 (%)	0 (0%)	2 (50%)	2 (50%)

Multiple comorbidities can be present in the same patient.

n, number

Table 4: Comparison of Clinical, laboratory findings, and thyroid patterns between patients with and without comorbidities

Parameter	Patients without comorbidities (n=138) Mean ± STD	Patients with comorbidities (n=108) Mean ± STD	t	p
Sex (m/F)	72/66 (52.2% / 47.8%)	46/62 (42.6% /57.4 %)	X^2= 2.23	0.14
Age (in years)	69.74 ± 6.3	69.33 ± 6.24	0.5	0.62
Barthel's index	96.88 ± 3.93	82.13 ± 7.28	20.35	<0.001
Creatinine (mg/dl)	0.88 ± 0.56	1.8 ± 1.25	8.23	<0.001
Hemoglobin (gm/dl)	12.95 ± 0.95	12.13 ± 1.55	5.11	<0.001
White blood cells (x10^3/ml)	6.67 ± 2	7.13 ± 2.3	1.65	0.1
Platelets (x10^3/ml)	306.1 ± 86.1	312.7 ± 76.8	0.63	0.53
Bilirubin (mg/dl)	0.71 ± 0.15	0.71 ± 0.17	0.003	0.99
Albumin (gm/dl)	4.32 + 0.42	4.26 + 0.42	1.18	0.24
Cholrsterol (mg/dl)	201.83 ± 31.55	201.22 ± 37.59	0.14	0.89
Triglyceride (mg/dl)	138.59 ± 30.77	162.78 ± 41.86	5.22	<0.001
Low density lipoprotein (mg/dl)	113.26 ± 26.66	146 ± 41.17	7.54	<0.001
High density lipoprotein (mg/dl)	45.4 ± 7.9	38.57 ± 5.73	7.56	<0.001
Thyroid stimulating hormone (mU/L)	2.58 ± 2.53	5.51 ± 7.77	2.87	0.004
Free T4 (ng/dl)	1.57 ± 0.57	1.53 ± 0.77	0.34	0.73
Free T3 (ng/ml)	2.16 ± 1.51	1.6 ± 1.57	3.3	0.001
Normal thyroid pattern	n=86 (62.3%)	n=34 (31.5%)		
Low T3 syndrome	n= 40 (29%)	n= 46 (42.6%)		
Clinical hypothyroidism	n=4 (2.9%)	n=16 (14.8%)	X^2=30.95	<0.001
Subclinical hypothyroidism	n= 4 (2.9%)	n= 8 (7.4%)		
Clinical hyperthyroidism	n= 2 (1.4%)	n= 4 (3.7%)		

n, number

Table 5: Correlation between clinical and laboratory findings with thyroid hormones.

Parameters	TSH		Free T4		Free T3	
	r	p	r	p	R	p
Age	0.016	0.797	0.032	0.616	0.041	0.527
Barthel's index	-0.089	0.162	-0.059	0.356	0.123	0.055
Hemoglobin	-0.062	0.333	0.004	0.944	0.12	0.059
White blood cells	0.033	0.611	-0.026	0.68	-0.143	**0.025***
Platelets	0.007	0.918	-0.028	0.661	0.047	0.465
Bilirubin	0.046	0.477	-0.118	0.065	0.001	0.993
Albumin	-0.017	**0.008****	0.12	0.06	0.128	**0.044***
Creatinine	0.185	**0.004****	0.025	0.694	-0.24	<**0.001****
Cholesterol	-0.098	0.124	0.235	<**0.001****	0.067	0.294
Triglyceride	0.028	0.663	-0.057	0.375	-0.031	0.632
Low density lipoprotein	-0.011	0.863	0.09*	0.159	-0.003	0.962
High density lipoprotein	0.018	0.778	-0.159	**0.013***	-0.082	0.199
Thyroid stimulating hormone			-0.661	<**0.001****	-0.396	<**0.001****
Free T4	-0.661	<**0.001****			0.316	<**0.001****
Free T3	-0.396	<**0.001****	0.316	<**0.001****		
Geriatric Index of Comorbidity	0.1	0.27	-0.2	**0.04***	-0.17	0.08
Disease Score	0.19	**0.003****	-0.05	0.41	-0.23	<**0.001****

*, Significant correlation. **, Highly significant correlation

There was no correlation between thyroid hormones levels and most studied clinical and laboratory parameters as age, hemoglobin, WBCs, platelets, bilirubin, triglycerides, and LDL. There was only direct correlation between TSH and creatinine and inverse one with albumin. Also, there was only direct correlation between FT4 and total cholesterol and inverse one with HDL. For fT3, there was only direct correlation with albumin only. There was highly significant inverse correlation between the disease score and free T3 and TSH. Also, there was significant inverse correlation between geriatric index of comorbidity and free T4.

DISCUSSION

Elderly individuals often have thyroid disorders which pass unnoticed [20], especially in associations with other diseases. In the elderly, thyroid disorders may manifest with different misleading clinical features. Symptoms as tiredness, memory loss/confusion, skin dryness, cold intolerance, constipation or cardiovascular complication as heart failure which attributed to ageing or comorbidities may be the only presentation in those patients. Therefore, a very low threshold of suspicion for screening for thyroid disorder in the elderly must be present [21-22]. This study explores the relationship between several comorbidity and thyroid hormones in older independently living patients. It is a trial to identify which of thyroid hormones patterns are more prevalent in those patients and it aids in comprehensive geriatric assessment for management decisions and appropriate treatment. In our present study, we studied an elderly population attending our outpatient clinics asking for control of their

chronic diseases or complaining of nonspecific complaints as chronic fatigue; otherwise, these patients were in relatively good health and living independently.

One of the common endocrine disorders of elderly is thyroid dysfunction with a 2 to 5% prevalence of clinically significant disease [23]. Subclinical hypothyroidism present in 15% of females over 60 years and subclinical thyrotoxicosis in 2% of people over 55 years [24]. TSH > 4.5 mU/L was found in 14% of people over 70 years [25]. 4 elderly patients without any comorbidity (2.9%) and 16 patients with comorbidity (14.8) have clinical hypothyroidism in our study. Low T3 syndrome was the most prevalent abnormality in both groups in our patients (30.4% and 40.7%; respectively) as founded by other studies in 32%-62% of older hospital patients [26-27]. Also, in a population of independently living elderly men, prevalence of low T3 syndrome founded to increase with age and the presence of disease **[28]**. The prevalence of clinical hypothyroidism and hyperthyroidism in all our studied elderly patients were 8.13% and 3.3%; respectively.

Low T3 syndrome (Sick euthyroid syndrome) is a relatively common finding following any acute or chronic illness, and is defined by the absence of an intrinsic abnormality of hypothalamic-pituitary and thyroid gland function. Whether it is a beneficial response or a maladaptive response has been much debated, but exciting evidence for the use of T3 or T4 therapy in patients with non-thyroidal illness is currently lacking [29]. The precise mechanism of low T3 syndrome is debated. Changes at thyroid hormone synthesis, secretion, transport, or cellular uptake are possible [30]. In elderly with aging, outer ring deiodination of T4 decreases [31]. This is responsible for the conversion of T4 to T3 and for the clearance of the inactive metabolite rT3 [32]. With advancing age, the net result is age dependent decline in total and free T3 and rT3 increment [33]. Also, age-related reduction in serum TSH occurs in healthy subjects due to an age-related decrease in TSH secretion by the pituitary [34]. The net results of all these changes are low TSH, near normal T4, low T3, and high rT3 in healthy elderly.

CONCLUSION

Care of elderly and especially those with comorbidity necessitate systemic recognition of the presence and severity of coexisting diseases and understanding their interaction and treatment. So, given the high prevalence of these thyroid hormones abnormal patterns in elderly and comorbid elderly and their atypical and often subtle presentations, it's critical for all clinicians to maintain high suspicion of their presence in elderly patients. Correction of these abnormal thyroid patterns in this unique group of patients especially those with comorbidity may improve their general health and improve their comorbid diseases. The controversy is about the treatment of subclinical conditions and low T3 syndrome. Many future studies are actually needed for declaration of the benefits of their correction on the physical fitness of the elderly patients and their comorbid diseases.

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