Chapter 20
Non-thyroidal Hypothyroidism

James V. Hennessey

The Case: A 71-year-old Caucasian woman seeks consultation for a 3-month history of tiredness and feeling depressed. The first question to be answered is how likely is it that she is hypothyroid based on this clinical presentation? Over 20 years ago, a series of observations were made in regard to the association of symptoms of hypothyroidism and the presence of biochemically documentable disease. Canaris et al. reported in 1997 that when considering the frequency with which symptoms consistent with the presence of hypothyroidism were reported, the biochemical confirmation of a hypothyroid state was variable [1]. When considering subjects with no symptoms of hypothyroidism, about 40% of euthyroid subjects fit this profile as did just over 35% of those with documented subclinical hypothyroidism (SCHypo) and about 28% of patients with overt hypothyroidism (OHypo). Those complaining of one or two

J. V. Hennessey (✉)
Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA
e-mail: jhenness@bidmc.harvard.edu

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symptoms of hypothyroidism were nearly equally distributed across the spectrum of euthyroidism to overt hypothyroidism, but when four or more symptoms were present, overtly hypothyroid subjects were present in statistically significantly higher rates (about ¼) when compared to those with SCHypo (about 22%) and the euthyroid group where nearly 18% complained of symptoms consistent with the presence of hypothyroidism [1]. Clearly the ability of a clinician to accurately identify those with biochemical hypothyroidism based on the presence of symptoms is poor. In another report in 2000, the same authors examined the frequency with which specific symptoms were reported in subjects with OHypo and biochemically euthyroid controls without thyroid disease [2]. The most commonly reported symptom, dry skin, was noted by fewer than 30% of those with OHypo, while 25% of euthyroid controls had the same complaint. Because of the large number of subjects participating in this study, this difference was statistically significant, but again a seasoned clinician immediately recognizes that the specificity of this finding is lacking. These authors performed similar analysis of 14 symptoms consistent with hypothyroidism and found similar overlapping but statistically significant differences in 12 parameters. Although the authors concluded that the symptoms of hypothyroidism are noted more frequently in those with OHypo, the high prevalence of the same complaints among euthyroid individuals [2], who according to guidelines would not be candidates for thyroid hormone replacement [3], again provides a clear clinical caveat for the use of symptoms to make clinical decisions regarding thyroid hormone replacement. More recently, Carle et al. have looked at this issue using a different set of complaints that were found to be associated with hypothyroidism [4]. These authors analyzed the likelihood of finding biochemical hypothyroidism based on symptoms among subjects stratified by gender and age. The number of symptoms reported by patients with OHypo vs. euthyroid controls without thyroid disease was significantly

higher in younger subject, but the frequencies were far more similar in those over 60 and completely overlapping in those over 70 years of age [4]. Among the younger subjects (less than 50 years of age), those with three or fewer symptoms were unlikely to be hypothyroid, while in those over 60, the presence of one symptom predicted the absence of hypothyroidism [4]. While the likelihood of finding hypothyroidism did significantly increase as the number of symptoms rose above 4 in the younger group (<50 years), there was no significant predictive value of symptoms seen in the older subjects when 2–8+ symptoms were present [4]. Lastly, when stratified by age and gender, receiver operator curve analysis indicated that symptoms performed best for men under 50 and far worse for women over 60 years of age [4]. So to try to answer the first question posed, this patient is unlikely to be hypothyroid based on this clinical presentation.

But the patient is in her primary care MD's office expecting that her complaints will be addressed, so what does one do after a complete history and physical exam? Is there an indication for measuring thyroid function tests (TFTs) in a patient with this presentation? Of course, so who are the patients who are most frequently assessed with thyroid function testing in the primary care setting? Bould et al. systematically reviewed the thyroid function test ordering patterns of primary care practitioners in Bristol, England [5]. These authors reviewed the thyroid function test results associated with the indications for test ordering in 325 subjects who met all inclusion criteria of this prospective study. The thyroid function assessments had been ordered at the clinical discretion of the primary care physician. Those with tests ordered were invited to participate in this study which involved the completion of three questionnaires assessing psychiatric distress (GHQ-12), likelihood of depression (PHQ-9), and thyroid symptomatology (TSQ). The results of thyroid function testing on the 325 subjects, 78% of whom were women with a mean age of

45.7 years, were then correlated with the symptom scores of the 3 assessment tools. Overall, only 6.2% of the population had a TSH greater than 4.0 which the authors designated as potential SCHypo [5]. Further breakdown of the thyroid function documented in this group of clinically eligible patients indicated that only 4% had a single TSH over 4.5 and no subjects with OHypo were reported. The mean TSQ score was 15.7 (1–32); when I took the TSQ, I scored a 6 and I learned that there are few if any standardized expected score ranges in euthyroid individuals. Overall psychiatric stress levels were high with 54.2% of the population indicating caseness on the GHQ-12 and 55.1% reflecting possible depression on the PHQ-9 scale [5]. None of these scales predicted the elevation of TSH which would have indicated a potential thyroid etiology of the symptoms [5]. Comparison of the TSQ-12 scores of the individuals in the Bould study to the control subjects, administered the same questionnaire by Saravanan et al., indicated that TSQ scores were worse in Bould's report (TSQ = 16) versus a TSQ of 12 in Saravanan's controls and 13 in those treated with LT4 for well-documented hypothyroidism [6]. Likewise the GHQ-12 rating of caseness (about 54%) was much higher [5] than the controls and LT4-treated subjects in the Saravanan report (25–35%), so the context of these ratings is limited. A TSH greater than 4.0 mIu/mL was not correlated with any of the quality of life (QOL) measures [5] further limiting the utility of factoring in patient-reported symptoms in clinical decision-making. Bould's report documents that those referred for thyroid function testing in the course of primary care practice (PCP) have high rates of psychological stress. There is a low correlation of symptoms and abnormal TFTs. Identification of mild TSH elevations often results in the initiation of LT4 Rx which assumes the symptoms are actually due to hypothyroidism. As a diagnostic label will be professionally affixed to the patient, the search for alternative explanations of symptoms usually ends. If LT4 is initiated in a patient without significant thyroid dysfunction, the therapy is likely to fail to cure what

should be considered *non*-thyroid symptoms [7] resulting in patient dissatisfaction and confusion. The authors of the Bould study specifically requested that PCPs keep psychological morbidity in mind and avoid prematurely labeling subjects as hypothyroid [5].

Who actually gets treated with LT4 in PCP offices? After appropriate exclusions, a study of 52,298 subjects receiving LT4 prescriptions over a 9-year period was assessed through the United Kingdom Clinical Practice Research Datalink [8]. The authors considered TSH and FT4 values obtained pre-LT4, and again after 5 years of LT4 therapy, correlations with demographic and concomitant diagnosis information were initiated and investigated. The TSH value available at the time of L-thyroxine initiation was less than 4.0 mIu/L (euthyroid) in about 6%; TSH was between 4.0 and 10.0 in 55.1% and greater than 10 in 38.8% [8]. The authors report a concerning trend of a decreasing TSH threshold for initiation of LT4 in successive years; this is mainly accounted for by an increase in the number of prescriptions written for TSH between 4.0 and 10.0 mIu/L, while prescriptions issued to subjects with TSH greater than 10.0 declined and LT4 offered to those with TSH less than 4.0 remained essentially unchanged over time [8]. This data is of concern as euthyroid subjects are apparently being offered a treatment that is unlikely to be of clinical benefit [7] and more patients are receiving treatment for degrees of hypothyroidism demonstrated to be unresponsive from a symptomatic perspective [9]. The sum of this data further documents the need to verify the presence of hypothyroidism prior to initiating or altering thyroid hormone replacement in patients with symptoms consistent with hypothyroidism.

Back to the case, recall that this 71-year-old woman sought consultation for a 3-month history of tiredness and feeling depressed. Her past medical history is as follows: a gradual 60 lb. weight gain following birth of her third child at age 36 along with decreased physical activity and plantar fasciitis when her TSH was documented to be 1.4 mIu/L

and further a diagnosis of hypertension at age 45 (TSH 1.8) which had been treated with propranolol for the past 27 years. Next a diagnosis of hypercholesterolemia was made at age 49 when her TSH was documented to be 2.0. She reports being treated since then with simvastatin initially and now atorvastatin. At age 62 she was given a diagnosis of depression and had her TSH was documented to be 3.3 mIU/mL. She has been treated with SSRIs since that diagnosis. Relevant evaluation at age 70 includes thyroid function tests ordered by her PCP 12 months prior (age 70 years). TSH 4.6 mIU/mL (0.4–4.12 mIU/mL) at 16:30.

Again the question: is this patient hypothyroid and should she be treated now to relieve her symptoms? If we assume that SCHypo is potentially the basis of the patient's current symptoms and recognize that there was no indication that hypothyroidism played a role in the etiology of her other medical problems, a review of the incidence, the prediction of persistently elevated TSH, and if a single elevated TSH actually predicts progression to overt hypothyroidism are appropriate.

In a study of 3594 (non-LT4 using) subjects, ≥65 years of age, 85% (n = 3057) were euthyroid at baseline and 2.7% became SCHypo by a 2-year follow-up. A total of 12.8% (n = 459) met criteria for SCHypo at the baseline visit. Of the 369 completing a 2-year follow-up evaluation, 56% remained SCHypo, 35% reverted to euthyroidism, 2% progressed to overt hypothyroidism, and 7% had been started on LT4 [10]. At 4 years of follow-up among subjects with SCHypo at the 2-year follow-up, 58% remained SCHypo and 8% reverted to normal, 2% progressed to overt hypothyroidism, and 11% were on LT4. The bottom line here is that one set of TFTs with an elevated TSH consistent with SCHypo misclassifies more than 40% of the elderly. Clinical diagnosis requires more than one set of TFTs to establish SCHypo. In this observational study, TSH values greater than 10 increased the risk of persistent SCHypo and OHypo and the eventual clinical initiation of LT4 treatment [10].

Returning to the patient once again, relevant information at age 71 included thyroid function tests by her PCP 12 months prior (age 70) with a TSH 4.6 mIU/mL (0.4–4.12 mIU/mL) at 16:30 and a TSH of 5.3 mIU/mL 1 month later at 08:00. The FT4 1.5 ng/ml (0.8–1.7) and a TT3 81 ng/dL (80–200) were noted to be "low normal" in the PCP's note. Do these findings identify an individual with clinically relevant hypothyroidism that is likely to benefit from thyroid hormone replacement? To answer that question, we would need to consider what an upper normal cutoff for TSH is. Although in the past we have received recommendations suggesting a TSH >2.0 was too high, this was based on risk of developing overt hypothyroidism in the 20-year follow-up of a community-based thyroid health study [11]. Another recommendation was a statistically derived suggestion of 2.5 mU/L [12]. A more practical answer to this question may lie in analyzing TSH distribution patterns stratified by age in thyroid disease-free populations. One such study of the NHANES III population indicates that across all ages an upper limit cutoff of normal individuals falls at 4.12 mU/L [13]. When broken out by age groups however, a different pattern appears. For example, for those 20–29 years of age, the upper limit of normal (97.5%) appears to be 3.56 mIU/L, and only 2.4% of this normal population would be expected to have a TSH greater than 4.5 mIu/mL (the limit expected of the assay used in this analysis) [14]. Meanwhile, for those 70–79 years, the 97.5% was observed to be 5.9 mIU/L and fully 9.9% of this disease-free group would be expected to have a TSH greater than 4.5. Likely most telling is the observation that in those over 80 years, the upper normal cutoff would be 7.49 mIU/L and 12.0% of this presumably thyroid disease-free subpopulation would have a TSH over 4.5 [14]. Reproducible evidence of increasing TSH normal cutoffs with increasing age are found in several publications [15–17] with the 97.5%ile of TSH values being expected to be as high as 7.96 in those over 90 [18]. Other factors that may

impact upon the upper limit of TSH may include gender with women demonstrating higher levels than men and variation by time of blood draw showing peak TSH values overnight and nadir results in the afternoon [15]. TSH varies by season in colder latitudes where not only is there an enhanced conversion of T4 to T3 in the winter months [19], but also higher TSH results are seen in the winter-spring season in both euthyroid and SCHypo subjects [20] and those treated with LT4 [21, 22]. Although the upper limit of TSH varies from study to study, a fairly clear increase in the expected upper normal TSH is observed in several studies, but at this time, it is unusual for clinical laboratories to stratify expected TSH results by age or by these other factors, and most clinical results are reported using a fixed upper normal of about 4–4.5 mIu/mL. Given this, it is likely safe to say that, as one set of TFTs with an elevated TSH consistent with SCHypo misclassifies more than 40% of the elderly, we should require at the very least that TSH elevations be persistent to establish the diagnosis of SCHypo. Finally as reproducible TSH values greater than 10 increase risk of persistent SCHypo and progression to OHypo, the initiation of LT4 therapy should be primarily focused on those meeting these criteria [3, 10].

Returning to the case, remember the evaluation at age 71 reviewed the thyroid function tests done by the primary care physician (PCP) 12 months prior to referral were a TSH of 4.6 mIU/mL (0.4–4.12 mIU/mL) at 16:30, and a repeat TSH of 5.6 mIU/mL was noted 1 month later when drawn at 08:00. Her FT4 was 1.5 ng/ml (0.8–1.7) and a TT3 of 81 ng/dL (80–200) which the PCP noted to be "low normal." Anti-thyroid antibodies were not done. The PCP started LT4 therapy for subclinical hypothyroidism at 50 mcg/day and this resulted in a follow-up TSH of 2.1 within 8 weeks. Based upon the discussion above, this patient does meet one of the recommended criteria for therapy [3], but more recent published data may require a reconsideration of this indication for a trial of LT4 in subjects

with TSH greater than the upper limit of local laboratory normal and less than 10 mIU/mL [3].

Does thyroid hormone therapy have an impact on symptoms in SCHypo? Does age impact LT4 response? In a study of 27 children with SCHypo, a questionnaire of 16 items typical of hypothyroidism was administered and showed significantly more symptoms in those with SCHypo in 3 of the 16 parameters versus controls [23]. Each of these subjects had been classified as SCHypo based on a TSH greater than 4.94 mIU/mL on two separate occasions, and all had FT4 within the normal range. Treatment with LT4 was titrated to a normal TSH. After 6 months of euthyroidism, the 16-item questionnaire was readministered, some improvement was noted in most symptoms, but this was statistically significant in only 2 of the 16 [23]. The results of a large study of LT4 impact on SCHypo on older adults with SCHypo were recently published [24]. The *T*hyroid Hormone *R*eplacement for *U*ntreated older adults with *S*ubclinical hypothyroidism – a randomized placebo controlled *T*rial (TRUST) study reported on 737 appropriately qualified adults ≥65 years (mean age, 74.4 years) with persistent (X 2) elevations in TSH > 4.6 ranging up to 19.99 mIU/L. The mean TSH at baseline was 6.40 indicating that few had TSH levels either greater than their age expected upper normal or 10 mIU/L. The follow-up TSH levels declined to 5.48 in the *placebo-treated* group by 1 year indicating a normalization of TSH in a substantial number of subjects without any treatment. TSH was significantly lower (3.63 mIu/L) in the *LT4*-treated group by the end of the first year of follow-up. At baseline and after LT4 therapy, the primary outcome measure was the *Thy*roid-Related Quality-of-Life *P*atient-*R*eported *O*utcome (ThyPRO) with focus on the hypothyroid symptoms score (four items) and the tiredness score (seven items). A planned secondary quality-of-life outcome was measured by generic health-related QOL assessments along with anthropometric parameters. Subjects were randomized 1:1 to either LT4 or

matching placebo at a dose of 50 mcg daily to start, and blinded dose adjustments were made to normalize TSH [24]. ThyPRO outcomes indicated that very few symptoms were present at baseline with a score of 0 or *NO* symptoms on the hypothyroid scale found in (27%) of participants and (8.7%) scored 0 in the tiredness scale. After 1 year F/U, comparing the LT4-treated versus placebo groups, there was no significant difference in symptoms [24]. Among the multiple secondary outcome measures, most demonstrated no significant effect of LT4 therapy except for one: the EQ-5D descriptive rating was worse at 12 months in those treated with LT4 but paradoxically was rated as better than placebo during prolonged follow-up. Within the confines of this trial, the safety of LT4 therapy was reassuring, but the clinical impact of treating older individuals' symptoms with slight elevations of TSH was not evident.

So where does this leave our patient? At the first endocrine visit, we are faced with a 72-year-old woman with persistent tiredness and depression, sleeping poorly who cannot lose weight. She has discovered online that "LT4 does not work for most patients with hypothyroidism" and asked her PCP for additional laboratory testing and the addition of LT3, a switch to a natural thyroid hormone extract (THExtract), or to refer her to an "expert" who will accomplish these tasks for the patient. On physical exam you find that her pulse is 109 and seems irregularly irregular. Her BMI is 35.9 kg/m2 and the current LT4 dose is 175 mcg/day. The PCP's most recent laboratory assessment shows a TSH < 0.01, FT4 1.9, TT3 175, and rT3 28 (10–24 ng/dL). The patient suggests that she would like three grains of thyroid extract. You ask yourself, how can these symptoms persist with these circulating thyroid hormone levels?

Is there a correlation between circulating T3 and rT3 and are these symptoms consistent with hypothyroidism? Phrased in a different way, is the lack of endogenous T3 production and subsequent inadequate T3 levels the basis of

poor QOL? In a study of 143 patients (69.2% women, mean age 50.2 yrs.) who had undergone total thyroidectomy and 131-I ablation for differentiated thyroid cancer, at least 1 year prior to study inclusion, LT4 suppressive therapy as clinically appropriate was administered to avoid frank thyrotoxicosis [25]. The investigators assessed QOL with the RAND-36, thyroid-specific QOL with the ThyPRO instrument, and fatigue with a Multidimensional Fatigue Inventory (MFI). The results of these QOL measures were correlated with circulating TFTs. Unique to this study population but similar to our patient, median TSH was 0.042 mU/L (ref 0.4–4.3), median FT4 25.6 pmol/l (ref 11–25), and median TT3 1.93 nmol/l (ref 1.4–2.5), while the median rT3 was 0.53 nmol/l (ref 0.22–0.54). Based upon these assessments, athyreotic subjects with thyroid cancer on LT4 scored lower than Dutch reference for QOL, but none of the TFTs were associated with their QOL. Determinates of QOL showed a negative association with the total number of drugs used and a positive association time since diagnosis, but there was no association with either RAND-36 or ThyPRO and curation, BMI, or the presence of hypoparathyroidism [25]. Associations with general fatigue, physical fatigue, reduced motivation, and reduced physical activity as measured by the MFI were positive only for the number of drugs used. The authors concluded that higher than normal but not thyrotoxic circulating FT4 and TT3 (remained within the normal range) were not associated with QOL and those with the lowest TT3 levels did not differ when compared to the higher levels. There was no relationship between TFTs and complaints of fatigue or impaired QOL [25]. A study gleaned from the Swedish Cancer Registry study involved 279 (79% response rate) subjects with DTC (diagnosed 1995–1998), who completed a SF-36 14–17 years after their initial diagnosis. Although only 19 (7%) reported a recurrence of their DTC, 239/279 (85%) reported at least 1 thyroid-related symptom such as fatigue (77%), sleep disorder (59%), irritability(57%), and lower stress resistance (56%),

being the most frequently reported. The presence of any thyroid-related symptoms or surgery/131-I symptoms resulted in lower health-related QOL [26]. Further insights into the relationship of fatigue and physical activity in hypothyroid subjects treated with thyroid hormone are evident in a similar survey of 205 (63.1% response rate) DTC survivors, ¾ of whom were women, with a mean age of 52.5 years, 6.8 years out from their initial diagnosis. These individuals were surveyed and their outpatient records were reviewed [27]. The subjects completed a Brief Fatigue Inventory (BFI) as well as an International Physical Activity Questionnaire (IPAQ-7). Based on these responses, moderate-to-severe fatigue was reported by 41.4%. Women did not report worse fatigue than in men, but individuals who were unemployed or unable to work had higher levels of fatigue ($p < 0.001$). Increased physical activity was associated with lower levels of fatigue ($p = 0.002$) [27], and as seen in the Massolt study, biochemical variables and ATA risk staging were *not* associated with complaints of fatigue [27]. Indeed it has been noted that simply the awareness of having a chronic disease results in diminished QOL in patients with hypothyroidism treated with LT4 [28].

Complaints of fatigue and lower QOL in those with various forms of hypothyroidism on LT4 have been documented for some time. In 2002 Saravanan reported on 597 LT4-treated hypothyroid patients (T4-P), 397 of whom were said to have a "normal" TSH (0.1–6.0 mU/L) in the previous 12 months, and compared their QOL to 551 non-hypothyroid controls [6]. Both groups were subjected to the *G*eneral *H*ealth *Q*uestionnaire-12 (GHQ-12) and the *T*hyroid *S*ymptom *Q*uestionnaire-12 (TSQ-12). A GHQ-12 score greater than 3 (maximum score 36) was considered caseness, and 25.6% of the normal euthyroid controls (mean score 11.39) were designated as cases. This control frequency was compared to the 34.4% of those with a normal TSH on LT4 (mean score 12.11) designated as cases; of course this resulted in a statistically significant difference

($p < 0.05$). TSQ scores were also slightly but significantly higher in the LT4-treated subjects [6]. Side-by-side comparisons in bar graph data show substantial overlap in the mean scores and designated caseness rates of both the GHQ-12 and TSQ-12 results making an objective clinical identification of those suffering from truly inadequate LT4 treatment problematic as there was obviously no way to blind results to the LT4 treatment and the inherent bias of known chronic disease. A subsequent publication from the same group on an expanded cohort of 697 LT4-treated hypothyroid patients with TSH values in a more narrow "normal" range (0.3–4.0 mIu/mL) showed a correlation with the GHQ-12 score with FT4 and the log TSH but not FT3, rT3, rT3/FT4, rT3/FT3, nor TPO antibody positivity. TSQ-12 was found to correlate with FT4, log TSH, FT3/FT4, rT3/FT4, but not FT3, rT3, FT3/rT3, nor TPO. An additional assessment of depression with the Hospital Anxiety and Depression Scale (HADS) found no correlation with any thyroid function parameter [29]. Treatment with LT4 for hypothyroidism does demonstrate a significant positive impact on QOL as documented in 10 of the 11 parameters evaluated by Nygaard et al. [30]. These investigators also found no correlation between individual TFTs and QOL measures [30] further bringing into question our patient's request for additional thyroid function testing.

Does baseline T3 predict LT4/LT3 (combination therapy as requested by the patient) success rates? In a study of 37 subjects on LT4 with persistent hypothyroid symptoms, all with normal TFTs and no comorbidities who were treated openly with LT4/LT3 (in a 17/1 ratio as per ETA [31] recommendations), each subject had TSH, FT4, TT3, and FT3I measured at baseline, 3 months, 6 months, and 12 months [32]. After adding in the LT3, the subjects were to self-classify as a responder or nonresponder. By 3 months, 70% reported feeling better and 30% reported no improvement in their symptoms, by 12 months 65% reported being bet-

ter, and by now 35% did not feel improved compared to LT4 alone. Obviously this result does not objectively tell us much other than how patients will feel when trying something new that they believe in, but the fact that the thyroid function results were unknown at the time LT4/LT3 was initiated is of interest in determining the utility of checking TFTs to predict this subjective response. Neither age, BMI, baseline TSH, TT3, nor FT3 index predicted the patient-reported response to the addition of the LT3 [32]. So it would appear that our patient's request for more thyroid function testing would be unlikely to provide any useful information which would help her clinician to manage her symptoms.

A summary of the above information should in a narrow sense have us thinking that patient selection and expectations for the utility of thyroid hormone intervention go a long way in providing symptomatic relief of hypothyroid symptoms to those with actual hypothyroidism. A series of assumptions have been made in this case which have "thyroidised" this patient's symptoms and associated these symptoms with thyroid function test results that likely do not provide conclusive evidence of a thyroid etiology of her clinical presentation. A decision to initiate LT4 therapy has been made which advances us along the road to thyroid predation, creating a vision seen through a thyroid tunnel and cementing this diagnosis in the patient's mind. These circumstances are far more acceptable to the patient and apparently more easily treatable than other, more likely explanations of her complaints. She is losing her faith in the primary diagnoser and prescriber of her LT4 and has driven this otherwise objective practitioner to advance the dose of the thyroid hormone replacement to toxic levels associated with not only cardiac [8, 33–36] but also skeletal [33, 37, 38] risk for the patient. Her frustration in seeking relief from her symptoms has driven her to the Internet where she has "discovered" that she is not being managed as the experts on several non-endocrine-based websites suggest, and she

pressures her PCP to request more extensive testing, which we have learned is unlikely to provide any helpful information for management of her "thyroid condition." It would appear that her PCP has succumbed to her pressure for further testing but has thankfully drawn the line and will not add LT3 or thyroid hormone extract to an already iatrogenically thyrotoxic patient.

Back to the patient one more time, at the initial visit, the endocrinologist assembles all of the relevant data and recognizes that the TSH elevations that triggered the assumption that this patient's symptoms were thyroid related are essentially within the expected range for a woman of this age. That in fact she might not be hypothyroid at all and therefore would not be expected to respond to thyroid hormone intervention [7] is perhaps not the primary message to convey to this Internet-inspired patient at the first encounter. The fact however must not be lost as it must be recognized that we are most likely involved with a case of non-thyroid-related "hypothyroidism," and the optimal end goal would be to effectively remedy this situation. At the first visit, the fact that the patient was already thyrotoxic on the LT4 is excuse enough to avoid adding LT3 or substituting extract at this visit, and a plan to decrease the current LT4 dosage to "safe" levels to avoid potential cardiac and skeletal issues was the first step. Plans for follow-up after sufficient time to allow equilibrium on the lower dose, to obtain further TFTs at that time, and to include anti-thyroid antibodies to assess the risk of potentially "real" thyroid disease underlying the initial findings are put in motion. Three months later the TSH is still suppressed, anti-thyroid antibodies are negative, and further dose reductions are planned as the patient is sleeping better now although several of her symptoms persist. The PCP is alerted to the fact that the symptoms may be *non*-thyroidal. A differential diagnosis of non-thyroidal considerations for her symptoms is offered (Table 20.1). And the endocrinologist lives happily ever after.

Table 20.1 Alternative physical etiologies for the nonspecific symptoms considered consistent with hypothyroidism

Endocrine/ autoimmune	**Nutritional**	**Lifestyle**
Diabetes mellitus	Vitamin B12 deficient	Stressful life events
Adrenal insufficiency	Folate deficiency	Poor sleep pattern
Hypopituitarism	Vitamin D deficiency	Work exhaustion
Celiac disease	Iron deficiency	Alcohol excess
Pernicious anemia	*Metabolic*	*Others*
Hematologic	Obesity	Obstructive sleep apnea
Anemia	Hypercalcemia	Viral syndromes
Multiple myeloma	Electrolyte abnormality	Post-viral syndromes
End-organ damage	*Drugs*	Chronic fatigue syndrome
Chronic kidney disease	Beta-blockers	Carbon monoxide poisoning
Chronic liver disease	Statins	Depression/anxiety
Congestive heart failure	Opiates	Polymyalgia rheumatic
		Fibromyalgia

Modified from Okosieme et al. [39]

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