Is there a role for Natural Desiccated Thyroid in the treatment of levothyroxine unresponsive hypothyroidism? Results from a Consecutive Case Series

Running Title: Natural Desiccated Thyroid: An evaluation of its effects

Adrian H Heald[1,2], Lakdasa Premawardhana[3], Peter Taylor[3], Onyebuchi Okosieme[3], Tasneem Bangi[2], Holly Devine[2], Mark Livingston[4], Ahmed Javed[2], Gabriela Y C Moreno[5], Torquil Watt[6] Mike Stedman[7], Colin Dayan,[3] Dyfrig A Hughes[8]

[1]The School of Medicine and Manchester Academic Health Sciences Centre; University of Manchester, Manchester, England
[2]Department of Endocrinology and Diabetes, Salford Royal Hospital, Salford, England
[3]Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, Wales
[4]Department of Clinical Biochemistry, Black Country Pathology Services, Walsall Manor Hospital, Walsall
[5] Coordinación Nacional de Investigación, Subdirección de Servicios de Salud. Petróleos Mexicanos; Ciudad de México; México.
[6]Department of Internal Medicine, Copenhagen University Hospital Herlev-Gentofte, Copenhagen, Denmark.
[7]Res Consortium, Andover, Hampshire, England
[8]Centre for Health Economics & Medicines Evaluation, Bangor University, Bangor, Wales

Key words: NDT, liothyronine, levothyroxine, free T3, free T4, quality of life

Word Count: 3403

Number of Figures: 3

Number of Tables: 1

Corresponding Author: Dr Adrian Heald, Department of Diabetes and Endocrinology, Salford Royal Hospital, Salford, UK

Telephone: +44 161 206 0108

Email: adrian.heald@manchester.ac.uk

Abstract

Introduction

Some levothyroxine unresponsive individuals with hypothyroidism are prescribed a Natural Desiccated Thyroid (NDT) preparation such as Armour Thyroid® or ERFA Thyroid®. These contain a mixture of levothyroxine and liothyronine in a fixed ratio. We evaluated the response to NDT in individuals at a single endocrine centre in terms of how the change from levothyroxine to NDT impacted on their lives in relation to quality of life (QOL) and thyroid symptoms.

Methods

The ThyPRO39 (thyroid symptomatology) and EQ-5D-5L-related QoL)/EQ5D5L (generic QOL) questionnaires were administered to 31 consecutive patients who had been initiated on NDT, before initiating treatment/6 months later.

Results

There were 28 women and 3 men. The dose range of NDT was 60mg-180mg daily. Age range was 26-77 years with length of time since diagnosis with hypothyroidism ranging from 2-40 years. One person discontinued the NDT because of lack of response; 2 because of cardiac symptoms.

EQ-5D-5L utility increased from a mean (SD) of 0.214 (0.338) at baseline, to 0.606 (0.248) after 6 months; corresponding to a difference of 0.392 (95% CI 0.241-0.542), t=6.82, p<0.001. EQ-VAS scores increased from 33.4 (17.2) to 71.1 (17.5), a difference of 37.7 (95%CI 25.2-50.2), t=-4.9, p<0.001.

ThyPRO scores showed consistent fall across all domains with the composite QoL-impact Score improving from 68.3 (95%CI 60.9-75.7) to 25.2 (95%CI 18.7-31.7), a difference of 43.1 (95%CI 33. -53.2) (t=5.6, p<0.001).

Conclusion

Significant symptomatic benefit and improvement in QOL was experienced by people with a history of levothyroxine unresponsive hypothyroidism, suggesting the need for further evaluation of NDT in this context.

What we knew

Around 5-10% of hypothyroid patients continue to experience profound and sometimes disabling symptoms, such as fatigue, depression and impaired cognition, in spite of being adequately replaced from a biochemical point of view.

It is now the right time to determine whether the alternatives to T4 alone such as natural desiccated thyroid (NDT) result in any benefit to the often very symptomatic patients with resistant hypothyroidism and to evaluate the intervention from a health economic point of view.

What we have learnt

We describe significant associated benefit, as measured by validated rating scales in quality of life, in people who by nature of their lack or response to levothyroxine have been given NDT.

The severity and chronicity of experienced symptoms and the fact that the majority of patients found these symptoms to be significantly alleviated, can be viewed as supportive evidence for the potential benefit of NDT when this is prescribed after careful consideration of other differential diagnoses and other treatment options.

Introduction

Primary hypothyroidism affects around 3% of people in Europe [1]. Although most people are treated satisfactorily with levothyroxine (L-thyroxine) up to 5% of treated, diagnosed hypothyroid individuals report impaired quality of life, despite laboratory thyroid function tests within the laboratory reference range [2]. A proportion of people with hypothyroidism who are seemingly treatment resistant, are prescribed liothyronine (L-tri-iodothyronine), usually in addition to levothyroxine and occasionally as monotherapy [3,4]. Some patients are prescribed Natural Desiccated Thyroid (NDT) [5].

NDT preparations such as Armour Thyroid® or ERFA Thyroid® [5], although not licensed in the UK for treatment of hypothyroidism, are prescribed for a small number of people as an imported pharmaceutical product. Similar preparations were in former times the usual treatment for hypothyroidism [5] and contain a mixture of levothyroxine and liothyronine in a fixed ratio (although this ratio can vary between batches and formulations). The body of opinion continues to be divided as to whether any other option than levothyroxine should be pursued in levothyroxine unresponsive individuals, with NDT among these other options available [6,7]

The National Institute for Health and Care Excellence (NICE), in its clinical guideline on thyroid disease [8], did not recommend prescription of NDT for people with hypothyroidism whose symptoms have not responded sufficiently to levothyroxine alone. However, clinicians have had to take a pragmatic approach in relation to the management of patients who report continuing symptoms, despite apparent adequate thyroid hormone replacement, with some prescribing NDT as a less costly alternative to liothyronine.

An important point of concern with NDT, particularly in older adults or in patients with pre-existing cardiovascular diseases, is the occurrence of transient elevations above the reference range in serum free T3 concentrations. However, studies of NDT that employed dose titration and sensitive methods to measure serum TSH, showed no differences versus levothyroxine in heart rate, blood pressure, serum lipids, or additional risk of atrial fibrillation, cardiovascular disease, or mortality [7, 9-11]. A recent qualitative study of patient experiences indicated a preference for NDT, attributable to a perception of better effectiveness and improved overall well-being [9,12].

Liothyronine/levothyroxine combination therapy was originally widely prescribed when synthetic thyroid hormones first replaced animal thyroid [4,5]. With its more favourable pharmacokinetics allowing for once daily dosing, and equivocal evidence for any additional benefit of liothyronine, levothyroxine monotherapy has prevailed as the treatment of choice for primary hypothyroidism. However, the early studies were small, used somewhat higher

doses of liothyronine than used in clinical practice, and resulted in adverse symptoms consistent with thyrotoxicosis [4]. NDT has continued to be prescribed for a small proportion of people [5] as an alternative to levothyroxine / liothyronine in combination

The aim of the present observational study was to evaluate the response to NDT in individuals with levothyroxine unresponsive hypothyroidism at a single endocrine centre in the UK where NDT is prescribed, in terms of how the change to NDT has impacted on the quality of their lives.

Methods

Patient recruitment

Between September 2018 and September 2020 at a single (UK) centre, consecutive clinic attendees with levothyroxine unresponsive hypothyroidism were prescribed NDT, either in the form of ERFA® thyroid or Armour Thyroid®. Referrals to the Endocrinology Clinic at the Salford Royal Foundation Trust were made by general practitioners or other endocrinologists from a wide catchment area spanning the Greater Manchester conurbation and beyond.

Patient selection was based on a clear temporal link between the onset of hypothyroid symptoms and biochemical diagnosis of hypothyroidism, with lack of improvement in symptoms on dose-adjusted levothyroxine in spite of achievement of biochemical euthyroidism and no evidence of non-adherence. Other physical diagnoses as a potential cause of the enduring symptoms were ruled out as was major psychiatric illness or personality factors.

Body mass index (BMI) was determined prior to initiation of NDT and at their last face-to-face follow-up appointment for those patients for whom a follow-up BMI was available (at the hospital or with their general practitioner). For a proportion of patients started on NDT from 1 March 2020, follow-up BMI measurements were unobtainable, owing to clinics being changed to telephone clinics as a consequence of COVID-19.

Quality of life measurement

Patients' health-related quality of life and health utility were measured using validated questionnaires. These included the EuroQol EQ-5D-5L questionnaire and accompanying EQ-VAS (visual analogue scale) (6). The EQ-5D-5L questionnaire asks about 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The questionnaire takes 5 minutes to complete. EQ-5D-5L profiles were converted to EQ-5D-3L index values (utilities, a preference-weighted measure of patients' health valuation) based on the cross walk value set for the UK (7). A self-rated score of 100 on the top of the EQVAS scale represents the "best imaginable health state" and 0 at the bottom representing the "worst imaginable health state."

The ThyPRO39 questionnaire (8) is self-administered and measures quality of life (QOL) with 14 scales, covering physical and mental symptoms, well-being and function as well as impact of thyroid disease on participation (i.e., social and daily life) and overall QOL. It consists of 39 items and, on average, takes 14 minutes to complete. ThyPRO scores were converted to domain scores and a composite score. Each score ranges between 0–100 with increasing scores indicating decreasing QOL (i.e. more symptoms or greater impact of disease).

Patients were asked to complete the questionnaires on two occasions, once prior to initiation of NDT and again 6 months after the start of NDT treatment. The questionnaires were completed using a paper format and either posted back to the Chief Investigator AHH or e-mailed back to a secure email address (nhs.net) as scanned documents.

After completing the questionnaires, patients were given the opportunity (if they wished) to describe their experience and feelings about NDT treatment.

Thyroid function tests

Assays for free T4, free T3 and TSH were performed on the Centaur immunoassay platform (Siemens, Camberley, UK). Subsequent blood samples were taken 2-4 hours after administration of NDT.

Statistical analyses

Comparisons were made between baseline and 6-month follow-up scores in EQ-5D-5L utility and ThyPRO scores. Shapiro-Wilks normality tests were applied to the summative scores for the EQ-5D-5L and ThyPRO questionnaires. Changes in EQ-5D utility were presented as the difference in means with associated 95% confidence interval, with statistical significance tested by a paired, 2-tailed t-test. Pre- and 6-months post NDT ThyPRO scores were similarly compared with reference to the 95% confidence interval for the difference. In exploratory analyses, the relations between changes in ThyPRO responses and median-split dose of NDT, baseline age and BMI were assessed as was the association of NDT treatment and BMI.

Patient experience

Patients were given an opportunity to report on their perspectives of having experienced NDT treatment. Responses were analysed thematically, according to broad domains covering impacts on: activities, energy /fatigue, sleep /psychological symptoms, and physical health.

Ethics approval

No formal ethics approval was sought, as this work was requested and approved by Greater Manchester Medicines Management Group (GMMMG) (UK) as the evaluation of NDT prescription in people with treatment unresponsive hypothyroidism. This was therefore a quality improvement project.

Results

Thirty-five patients were offered NDT treatment, of whom 4 declined and elected to continue with the liothyronine that they were purchasing on-line and taking with levothyroxine. The remaining 31 patients were included in the prospective evaluation with age range 26-77 years, with length of time since diagnosis with hypothyroidism ranging from 2-40 years (Table 1). There 28 women and 3 men. Aetiology of hypothyroidism was autoimmune thyroiditis in 28/31 individuals with 2 people having a history of total thyroidectomy for toxic

goitre and one person a history of radioactive iodine induced hypothyroidism. Comorbidities included Chronic Fatigue Syndrome in 6/31 patients and anxiety or depression (or mixed anxiety /depression) in 6 individuals. Other reported comorbidities were migraine (4 individuals), irritable bowel syndrome (4 people), vitamin D deficiency (2 people) and fibromyalgia (2 people).

At baseline, all had laboratory thyroid function tests within the reference range for free thyroxine (free T4) and thyroid stimulating hormone (TSH) but reported continuing significant symptoms of hypothyroidism following diagnosis. All the individuals had taken levothyroxine for at least 12 months before the initiation of NDT. In 3 cases they had intermittently taken liothyronine (although not in the 3 months before NDT was initiated for this study); and in one case had previously taken Armour Thyroid® (not in the 12 months before NDT was initiated for this study).

At 6-months' follow-up, the dose range of NDT was 60mg to 180mg daily with the mean dose 123.5mg (Table 1). All but 2 patients took all the NDT at a single time, the other 2 patients taking it in 2 split doses. Thyroid stimulating hormone (TSH) concentrations varied from <0.01-8.5 mIU/L (reference range 0.35-5.50 mIU/L). Free T3 level varied from 4.0-11.9 pmol/L (reference range 3.5-6.5pmol/L). Free T4 ranged from 8.3-30.0 pmol/L (reference range 10-25pmol/L)

Discontinuation rate

Of the individuals who started on NDT, 28/31 remained on this medication at the censor date (March 2021) with a follow-up ranging from 6 months to 2.2 years.

Two people discontinued the NDT at 2 and 4 months because of experiencing palpitations on the NDT. These 2 individuals had pre-existing intermittent symptoms of palpations but no diagnosed tachydysrhythmia. 12-lead electrocardiogram (ECG) and 24-hour ambulatory ECG recording did not indicate evidence of NDT tachydysrhythmia in either case. Both were assessed

by a consultant cardiologist. The palpitations resolved after discontinuation of the NDT in both cases.

In the other case, the person did not feel that the NDT made any difference and discontinued after 2.5 months.

Quality of Life (QoL) measures

The EQ-5D-5L and ThyPRO questionnaires were completed by 31 and 29 individuals, respectively. At baseline, 30 (97%) of respondents reported an EQ-5D-5L domain score of greater than 2; 23 (74%) a score of >3; and 15 (48%) a score >4 (Figure 1a). The most common impairment (score >2) was in patients' abilities to perform usual activities, and reporting of being anxious or depressed = 0.214 (0.338, -0.353, 0.735) (Mean (SD, min, max)) with EQ-VAS scores = 33.4 (17.2, 0, 65.0) (Mean (SD, min, max)).

There was improvement between baseline and 6-months across all domains of the EQ-5D-5L (Figure 1b), with only 10 (32%) reporting a domain score of >2; 5 (16%) a score >3; and none reporting a score of >4 in any domain. At 6-months post initiation of NDT EQ-VAS scores = 71.1 (17.5, 20.0, 100.0) (Mean (SD, min, max)), ($t=-4.9$, $p<0.001$).

The majority of patients showed an improvement in EQ-5D-5L Utility score with only 2 showing a decrease between baseline and 6-month follow-up (Figure 2). Specifically EQ-5D-5L utility increased from a mean (SD) of 0.214 (0.338) at baseline, to 0.606 (0.248) after 6 months; (a lower score equates to poorer perceived health) corresponding to a difference of 0.392 (95% CI 0.241-0.542), (t for change=6.82, $p<0.001$).

ThyPRO scores (Figure 3) indicated an overall reduction in symptoms and QoL-impairment on NDT. ThyPRO scores showed a consistent improvement across all domains including Depression (reduction of 39.2; 95% CI 26.5-51.9), Anxiety (reduction of 33.5; 95% CI 19.7-47.4), tiredness (53.5; 95% CI 43.5-63.4), Cognitive Problems (43.0; 95% CI 32.0-54.1) and Impaired Social Life (33.8; 95% CI 19.9-47.6), with the Composite Score improving from 68.3 (95% CI

60.9-75.7) to 25.2 (95% CI 18.7-31.7), a difference of 43.1 (95% CI 33.0-53.2) (t=5.6, p<0.001).

Association between changes in ThyPRO score, age and NDT dose

When split by median age of the group (49.2 years) ThyPRO Composite Score improved more in younger people (≤49.2 years) between baseline and 6 month follow-up at -51.8, than for older people (>49.2 years) at -41.5. When split by median dose of NDT (120mg/day) those on >120mg daily showed a greater improvement in ThyPRO Composite Score at -55.1 than did those on ≤120mg of NDT daily at -43.8.

Association between Body Mass Index (BMI) and NDT treatment and change in ThyPRO Composite Score

Overall mean BMI did not change significantly with NDT treatment between baseline (30.6; 95% CI 29.1-32.1 kg/m^2) and the most recent follow-up post NDT (30.0; 95% CI 28.4-31.6 kg/m^2) (n=17). There was no relation between change in BMI and change in ThyPRO Composite Score.

Patient reports

Individual descriptions of the response to NDT in relation to improvement in quality of life and reduction in symptoms are presented in Appendix 1. Recurring themes include patients reporting improvement in energy, resolution of 'brain fog', stabilisation of sleep pattern, feeling more alert and stronger, lifting of depression, reduction in anxiety and tension and improved vigour / strength.

Discussion

Here we have described significant associated benefit, as measured both by EQ-5D-5L utility scores and ThyPRO scores, in people who by nature of their lack or response to levothyroxine have been given NDT, as measured both by the EQ-5D-5L and ThyPRO ratings (Figures 1, 2 and 3). The improvements in ThyPRO scores were large – up to several multiples of the Minimal Important Change for all scales [18]. For the 17 patients for whom we had a follow-up

BMI, there was no change in BMI. We accept the caveat that this is an open study with no control group. However this paper looks at one option for managing people with treatment unresponsive hypothyroidism.

There was improvement in ThyPRO scores regarding fatigue, as expected, but also scales measuring more complex (often referred to as “distal”) concepts such as Impaired Daily Life, in relation to classical physical symptoms. The greater improvement in thyroid-related QoL in young people (median age or less) suggests that the benefit of NDT may be greater in younger individuals. The greater fall in ThyPRO scores with a higher dose of NDT indicates the importance of titration of NDT dose, while monitoring thyroid function tests and potential cardiac symptoms closely. It might also indicate a greater effect in patients with less intrinsic production of thyroid hormones.

While this is a highly selected group of people in terms of the fact that they were all referred up to a single specialist clinic, the severity and chronicity of their symptoms and the fact that the majority of patients found these symptoms to be alleviated, could be viewed as supportive evidence for the potential benefit of NDT when given after careful consideration of other differential diagnoses and other treatment options. This of course contrasts with the results of the randomised, double-blind, crossover study of Hoang et al [9] who did not find any differences in symptoms or neurocognitive measurements between NDT and levothyroxine. However, their group of patients were not exclusively those whose symptoms endure in spite of levothyroxine treatment, in contrast to the cohort described here. Furthermore in the Hoang study 48.6% of the participants expressed a preference for NDT over levothyroxine.

As a result of NDT being around for so long (first utilised in the 1880s) it did not ever need to go through the licensing process in North America – it was classed as a “grandfathered drug”. It has always been approved by the Food and Drug Administration (FDA) but not licensed in the same way that many other drugs have been [5]. Nonetheless, today’s manufacturing of NDT must comply with Good Manufacturing Practice as enforced by the FDA, and follow the procedures and standards described in the United States Pharmacopeia.

Variable quality, which impacted on earlier clinical evaluations of NDT, and which may have contributed to safety concerns, might be less of a concern with current branded products; although some maintain that due to the 'lack of standardization' in the liothyronine content, the use of Armour Thyroid® should be avoided [19].

There is emerging evidence that may account for the efficacy of liothyronine (NDT contains a mixture of levothyroxine and liothyronine) in people who are symptomatically unresponsive to levothyroxine [20]. Free T3 is the endogenous thyroid hormone, converted from Free T4 predominantly by local de-iodination in tissues. Increased free T4 levels, as seen with levothyroxine therapy alone, appear to inhibit local deiodination except in the pituitary, so that levothyroxine monotherapy may result in TSH inhibition while reducing active thyroid hormone bioavailability in other tissues. Polymorphisms in the genetic coding of the deiodinase-2 (DiO2) enzyme, present in 13% of the population, have the potential to reduce T3 levels in many tissues, including the brain, without affecting serum levels [21]. This may represent a pharmacogenetic component in those who are non-responsive to levothyroxine.

The body of opinion continues to be divided as to whether any other option than levothyroxine should be pursued in levothyroxine unresponsive individuals, with NDT among these other options available. While there are some studies that have found that some patients do better on NDT, there are many doctors who oppose the idea of prescribing NDT. Unfortunately, there have been no randomised, double-blind controlled trials comparing NDT and levothyroxine in relevant patient populations. Nevertheless, the American Thyroid Association concluded in 2014 that there is a role for long-term outcome clinical trials testing combination therapy or thyroid extracts [22].

Our study provides the first evaluation of NDT using validated measures of quality of life and health utility. While observational in design, and in size, the results lend support to the need for further clinical assessment using rigorous research methods. The observed associations between reductions in symptoms and improvements in quality of life with the administration of NDT,

as described in our study by the change in scores on the ThyPRO and EQ-5D-5L scales, provide some evidence of potential benefit. Exploratory analyses suggested greater change (fall) in the ThyPRO composite score in younger people than in older in terms of numbers of prescriptions and this was dose-dependent, supporting the importance of titration of NDT dose while monitoring thyroid function tests and potential cardiac symptoms closely. It also suggest that the benefits seen with NDT are pharmacological in origin not purely idiosyncratic.

Patient experience can provide powerful testimony as qualitative descriptors of treatment effect [12]. Individual descriptions of the response to NDT in relation to improvement in quality of life and reduction in symptoms were very telling in our study, and moving in terms of how people perceived their situation change. Some clinicians regard NDT as an agent that could benefit people with ongoing symptoms of hypothyroidism despite levothyroxine treatment, and as a 'lifeline' to people who may for many years have experienced debilitating symptoms. While 436 people in England were prescribed NDT by their general practitioners in 2018-19, at a total cost of £1,013,356 [23,24], the need for a definitive clinical trial is essential to support the licensing and use of NDT in the UK.

Strengths and limitations

The people who came to our specialist endocrinology clinic are, by their nature, self-selecting. However, the fact that 28/31 of these individuals have felt much better on NDT is suggestive of some benefit of NDT in people with levothyroxine unresponsive hypothyroidism - that is enduring. A limitation is that we were not able to access thyroid hormone profile on all the individuals from the point of initial diagnosis. However, all had a historical coded diagnosis of hypothyroidism confirmed by previous elevation of serum TSH. Bone mineral density was not assessed, as the duration of treatment was less than 3 years for all individuals at the time of writing.

This is a single centre, real world, observational study with no comparator group nor blinding. As such it is prone to bias and should not serve to change clinical

practice. Account must be taken of an undoubted placebo-effect observed here, in an unblinded study. We accept this as a major limitation

The study benefited from utilising validated questionnaires that were administered to all attendees at our clinic and completed by all. Importantly all the individuals were screened for other physical disorders as a cause of their symptoms and for major psychiatric disorders.

Conclusion

Significant benefit was experienced by people who by nature of their lack or response to levothyroxine therapy have been treated with NDT. The severity and chronicity of their symptoms and the fact that the majority of patients found these symptoms to be significantly alleviated, can be viewed as supportive evidence for the potential benefit of NDT when this is prescribed after careful consideration of other differential diagnoses and other treatment options.

While this paper is an evaluation of an intervention with no control group, given the considerable debate currently about the role of none levothyroxine alternatives in the treatment of hypothyroidism, we feel that these findings are of relevance to all clinicians who see patients with this condition.

References

1. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, Okosieme OE. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol. 2018;14:301-316.

2. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf). 2002;57:577-85.

3. McAninch EA, Bianco AC. The History and Future of Treatment of Hypothyroidism. Ann Intern Med. 2016; 164: 50-6.

4. Smith RN, Taylor SA, Massey JC. Controlled clinical trial of combined triiodothyronine and thyroxine in the treatment of hypothyroidism. Br Med J 1970: 17;4:145-8.

5. Gaby AR. Sub-laboratory hypothyroidism and the empirical use of Armour thyroid. Altern Med Rev. 2004;9:157-79.

6. Hennessey JV. The emergence of levothyroxine as a treatment for hypothyroidism. Endocrine. 2017; 55: 6-18.

7. Idrees T, Palmer S, Maciel RMB, Bianco AC. Liothyronine and Desiccated Thyroid Extract in the Treatment of Hypothyroidism. Thyroid. 2020; 3: 1399-1413.

8. NICE. https://www.nice.org.uk/guidance/indevelopment/gid-ng10074: accessed 2 November 2020.

9. Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. J Clin Endocrinol Metab 2013; 98:1982-90

10. Tariq A, Wert Y, Cheriyath P, Joshi R. Effects of Long-Term Combination LT4 and LT3 Therapy for Improving Hypothyroidism and Overall Quality of Life. South Med J. 2018;111: 363-369

11. Kuye R, Riggs C, King J, Heilmann R, Kurz D, Milchak J. Thyroid Stimulating Hormone Stability in Patients Prescribed Synthetic or Desiccated Thyroid Products: A Retrospective Study. Ann Fam Med 2020 ;18: 452-454

12. Toloza FJK, Espinoza Suarez NR, El Kawkgi O, Golembiewski EH, Ponce OJ, Yao L, Maraka S, Singh Ospina NM, Brito JP. Patient

Experiences and Perceptions Associated with the Use of Desiccated Thyroid Extract. Medicina (Kaunas) 2020; 56: 161

13. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001; 33: 337-43

14. Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012; 15: 708-15

15. Balestroni G, Bertolotti G. L'EuroQol-5D (EQ-5D): uno strumento per la misura della qualità della vita [EuroQol-5D (EQ-5D): an instrument for measuring quality of life]. Monaldi Arch Chest Dis 2012; 78:155-9.

16. Watt T, Cramon P, Hegedüs L, Bjorner JB, Bonnema SJ, Rasmussen ÅK, Feldt-Rasmussen U, Groenvold M. The thyroid-related quality of life measure ThyPRO has good responsiveness and ability to detect relevant treatment effects. J Clin Endocrinol Metab 2014;99:3708-17.

17. Watt T, Bjorner JB, Groenvold M, Rasmussen AK, Bonnema SJ, Hege düs L, Feldt-Rasmussen U. Establishing construct validity for the thyroid-specific patient reported outcome measure (ThyPRO): an initial examination. *Quality of Life Research* 2009;18:483–496.

18. Nordqvist SF, Boesen VB, Rasmussen ÅK, Feldt-Rasmussen U, Hegedüs L, Bonnema SJ, Cramon PK, Watt T, Groenvold M, Bjorner JB. Determining minimal important change for the thyroid-related quality of life questionnaire ThyPRO. Endocr Connect. 2021; 10: 316-324

19. Coutinho J, Field JB, Sule AA. Armour® Thyroid Rage - A Dangerous Mixture. Cureus. 2018;10:e2523

20. Castagna MG, Dentice M, Cantara S, Ambrosio R, Maino F, Porcelli T, Marzocchi C, Garbi C, Pacini F, Salvatore D. DIO2 Thr92Ala Reduces Deiodinase-2 Activity and Serum-T3 Levels in Thyroid-Deficient Patients. J Clin Endocrinol Metab 2017;102:1623-1630.

21. Panicker V, Saravanan P, Vaidya B, Evans J, Hattersley AT, Frayling TM, Dayan CM. Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. J Clin Endocrinol Metab 2009;94:1623-9

22. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, Sawka AM; American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid. 2014 ;24: 1670-751.

23. https://digital.nhs.uk/data-and-information/publications/statistical/practice-level-prescribing-data: accessed 31 December 2020.

24. Stedman M, Taylor P, Premawardhana L, Okosieme O, Dayan C, Heald AH. Trends in Costs and Prescribing for Liothyronine and Levothyroxine in England and Wales 2011-2020. Clin Endocrinol (Oxf). 2021 Jan 7. doi: 10.1111/cen.14414. Epub ahead of print. PMID: 33411974.

Figure Legends

Figure 1a. Distribution of responses to each dimension of the EQ-5D-5L before receiving NDT. Levels 1-5 correspond to increasing severity in each of the domains from a rater point of view, 5 being most severely affected

Figure 1b. Distribution of responses to each dimension of the EQ-5D-5L ≥6 months after receiving NDT. Levels 1-5 correspond to increasing severity in each of the domains from a rater point of view, 5 being most severely affected

Figure 2. EQ-5D utility scores before, and ≥6 months after administration of NDT. Data are presented as means (standard deviation) and significance based on a 2-sided, paired t-test

Figure 3. Change in ThyPRO ratings over time from baseline pre- NDT initiation to 6 months post NDT initiation.

Supplementary appendix

Appendix 1: Patient reports of their experience on NDT

Acknowledgments

To Yvonne Birkett at Salford Royal Hospital, the PA of first author AHH, for sending out all the questionnaires to our patients.

Conflict of Interest

None of the co-authors has any conflict of interest.

Funding

No external funding was received for this study

Data sources

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.