

**BTF Q&As to accompany the  
2015 BTA Statement on the Management of Hypothyroidism**

The British Thyroid Association (BTA) statement on the Management of Hypothyroidism has been prepared by the British Thyroid Association. It summarises the key points in the American Thyroid Association (ATA) and the European Thyroid Association (ETA) guidelines and makes recommendations on the management of primary hypothyroidism based on the current literature, review of the published positions of the ETA and ATA, and in line with best principles of good medical practice. The statement is endorsed by the Association of Clinical Biochemistry, (ACB), British Thyroid Foundation, (BTF), Royal College of Physicians (RCP) and Society for Endocrinology (SfE).

<http://onlinelibrary.wiley.com/doi/10.1111/cen.12824/full>

In order to make the statement more accessible to patients, the BTF has prepared the following Q&As.

**Q1: How should hypothyroidism be treated?**

**Short answer:** Hypothyroidism or underactive thyroid needs to be treated with replacement doses of levothyroxine, the synthetic form of the natural thyroid hormone thyroxine.

**Longer answer:** The thyroid gland produces two types of thyroid hormone: thyroxine which has four iodine atoms and triiodothyronine (T3) which has three iodine atoms attached to it. Most (85%) of the hormone that is released into the bloodstream by the thyroid gland is T4, the rest being T3. Only T3 is active in stimulating cells. However, each organ in the body that requires thyroid hormones has the ability to generate its own T3 by converting T4 (by enzymes called deiodinases that take out one iodine atom from the molecule).

In hypothyroidism, where the thyroid gland is unable to produce thyroid hormones, the main deficiency is the supply of T4 and this is what is replaced in the form of levothyroxine. Our current understanding is that the 'missing' T3 which is normally made by the thyroid gland can be compensated for by increased conversion of T4 to T3 at the organ level. Levothyroxine is the synthetic form of thyroxine but works in exactly the same way and can also be measured in the blood by the same tests.

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## **Q2: The TSH reference ranges are very wide. Should they be narrowed?**

**Short answer:** There are arguments for and against, but what really matters for most people who are being investigated or treated for thyroid disease, is interpreting the results of the blood tests in the context of the individual and his / her symptoms, so that sensible decisions can be made.

**Longer answer:** Reference ranges (or intervals) are a guide to defining the limits of normality and helping doctors in making a diagnosis. Any blood test can sometimes be misleading unless its limitations are understood and tests should not be done unless there is a specific question that it is expected to address. Reference ranges are derived from testing for a particular chemical such as TSH in the healthy, normal population. To ensure that only the most representative values are included, reference ranges do not include the most extreme 5% of values. If the serum TSH is measured in randomly selected people without any known thyroid disease, then there will be a range of values, with roughly two-thirds being around 1-2 milliunits per litre (mU/L).

If we go through the same exercise of working out a TSH reference range, but now apply more strict criteria (for example excluding people with thyroid antibodies or with minor abnormalities in their thyroid ultrasound scan), the reference range is narrower, but this is complicated by the fact that if we do the same for older people, the upper limit of the reference range goes up, as it does for some ethnic groups (African Americans) and people with obesity. Conversely the reference range in pregnancy goes down and the TSH reference range in one geographical area may differ from another because of differences in iodine intake.

Although some might argue that by keeping the range wide, some patients with the earliest signs of thyroid damage are being missed, any narrowing of the reference range inevitably means that normal people are at risk of being over-diagnosed and over-treated. Since there is no known clinical benefit from treatment in people with a TSH at the upper end of the conventional reference range, the current consensus is not to narrow this range further.

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**Q3: My doctor only tests my TSH. Are there other tests I should have?**

A: **Short answer:** In the majority of people, a TSH test alone is sufficient. If the TSH level is not normal, then further tests including free T3 and/or free T4 may be useful and an antibody test may be required. In people recently treated with radioactive iodine for hyperthyroidism, or patients with known or suspected pituitary disease, free T4 should also routinely be checked.

**Longer answer:** In more than 99% of people with a normal TSH, who have no other reason to have a thyroid or pituitary problem, free T4 and free T3 will also be normal. If all three tests were performed routinely, then around £6m pounds a year would be spent unnecessarily. In someone without thyroid disease, if the TSH is raised then it should be repeated with a free T4 level. If persistently raised, then measuring an anti-TPO Ab tests (on one occasion – it is only useful to know whether it is positive or not, the actual level does not contribute much additional information) is useful. This is because if the anti-TPO test is positive, it is more likely that the thyroid level may deteriorate over the coming months or years. Anti-Tg antibody tests generally do not add much to anti-TPO results.

If the TSH is low, free T3 and free T4 measurement will diagnose hyperthyroidism, and if confirmed, a TSH receptor antibody test looking for Graves' disease is reasonable.

In patients with known or suspect pituitary disease, the TSH level is misleading and free T4 should be measured. This is also true in other situations such as within three months of treatment of hyperthyroidism (when the TSH may stay lower than it should be) and with some genetic abnormalities of thyroid function. If a patient has a normal TSH but persistent symptoms suggestive of hyper- or hypothyroidism, measurement of free T4 and free T3 on one occasion is helpful to rule out a pituitary problem or these other rare conditions.

In monitoring patients already on thyroid hormone, TSH measurement alone is sufficient. If the TSH is not normal, free T4 (and possibly free T3) should also be measured. An exception is patients taking T3 alone or in mixed preparation when a free T3 measurement might be helpful. Follow-up measures of antibody tests are not normally required.

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**Q4: I have lots of symptoms of hypothyroidism but my doctor says I'm borderline (or subclinical) and therefore won't treat me. Why is this?**

**Short answer:** Because it is unlikely that your symptoms are due to the thyroid and unlikely that treatment with thyroid hormones will be beneficial.

**Longer answer:** “Subclinical hypothyroidism” (SCH) is defined on the basis of thyroid blood tests, when the level of thyroid stimulating hormone (TSH) is elevated, while the level of thyroid hormones (T3 and T4) is normal. It is also sometimes referred to as “mild” or “borderline” hypothyroidism. The commonest cause of SCH is “autoimmune thyroiditis”, when part of the thyroid gland has been destroyed by the body’s immune system. The level of the TSH reflects how extensive the destruction of the thyroid is. Most people with SCH have no symptoms, but over the following 10 years about 20-50% will progress to full-blown hypothyroidism. SCH can sometimes be transient and the thyroid blood tests can correct themselves without any intervention after a few months. The evidence points towards benefit in treating SCH with levothyroxine when the TSH is greater than 10 milliunits per litre (mu/L). For milder forms (TSH between the upper limit of normal and 10), the benefit is either marginal or none, except in pregnant women or women who are trying to conceive. For this reason current guidelines recommend treating SCH if the TSH is greater than 10 or in milder forms in women who are pregnant or plan a pregnancy. In the remainder of cases, a trial of levothyroxine may be justified if the patient has symptoms. Doctors frequently come across patients with severe symptoms such as fatigue who in the course of investigations for the cause of fatigue are found to have SCH. It is tempting to latch on to SCH as the explanation for the symptoms and expect a cure with thyroid hormone treatment. More often than not, treatment is disappointing, not because thyroid hormones are useless, but because the symptoms are not due to the thyroid.

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**Q5: I’ve heard that some people feel better with a combination of T3 and T4. Can I try this?**

A: **Short answer:** Although some people report feeling better on T3 and T4, in “blinded” clinical trials, patients have not been able to tell the difference except perhaps at high dose. It is harder to select, monitor and adjust the dose of T3 containing preparations than T4, and

it is likely therefore that using T3 and T4 will increase your risk of stroke and osteoporosis from slight over treatment over many years. Combination therapy is therefore not recommended.

**Longer answer.** Although the vast majority of patients on thyroid hormone (T4) feel well, a minority – around 6% more than expected - report that their symptoms have not improved. Symptoms such as weight gain, feeling cold, dry skin, hair loss, tiredness and poor concentration or “brain fog” may be due to reasons other than low thyroid hormone levels including recent illness, bereavement, stress, depression, anxiety, side-effects of other medication or other medical conditions. If the TSH level is in the reference range, such symptoms are not due to the thyroid hormone level. Repeated surveys show that up to 25% of the general population - people without a thyroid problem - have symptoms consistent with stress, depression, anxiety or other mental health disorder.

Patients with persistent symptoms despite a normal TSH sometimes ask whether a combination of T4 and T3, or an animal derived “natural thyroid extract” would be helpful. There have been over 20 clinical studies of comparing T4 to mixed T4+T3 preparations, and almost all of them have shown that if the study included a placebo that looks exactly the same as the thyroid hormone tablet, patients cannot tell which was which and the patients on the T4 alone improve as much as those on the combination. In three studies, patients seemed to prefer the combination, and this seems to have particularly been when higher dose were used. This raises the possibility that the combination is acting as a “drug” – since T3 is highly active – than as “hormone replacement”, similar to the case with over-replacement with testosterone in male athletes.

Two other factors add to the problem. First there is good evidence that levels of thyroid hormone at the top of the normal range as well as even slight levels of over- replacement increase the risk of a developing an irregular heart beat (atrial fibrillation) which carries a small but definite risk of sudden stroke, and bone thinning (osteoporosis) with a risk of bone fracture. Secondly, T3 has a shorter “half-life” in the body than T4, meaning that levels after a dose go up and come down over 4-6 hours. This makes it difficult to know whether to adjust the medication according to the higher level after the dose or the lower level before the next dose. So-called ‘natural’ thyroid extracts come from pigs and so are not natural in the sense of human hormones: pigs have 2-3 times more T3 (relative to T4) in their thyroid than humans.

It remains possible that a small group of patients might feel better on T3+T4. At present we have no way of predicting who that will be. And it seems likely that because we cannot adjust the dose so easily, most people taking T3+T4 are being slightly overdosed. Although they may feel better now, these levels may not be good for their bodies in the longer term. So taking all the factors together, T4 alone remains the recommended treatment for thyroid hormone replacement. For the group of people who want to try alternative treatment, this may be possible under the supervision of an interested endocrinologist. If patients do not derive benefit from combination therapy (T3+T4), it should certainly be stopped. And if it is continued, patients need to be fully informed about the potential risks they run.

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**Q6: I don't feel well taking levothyroxine (T4) but my doctor says my blood tests are normal. What can I do?**

**Short answer:** You need to ask your doctor to investigate for other causes of your symptoms as the symptoms of an underactive thyroid are non-specific and may be due to other reasons.

**Longer answer:** The main symptoms of an underactive thyroid are tiredness, weight gain, dry skin, lethargy and feeling low. Although any single or combination of these symptoms should alert a clinician to the possibility of an underactive thyroid this needs to be confirmed by a detailed history, clinical exam and blood tests. The pituitary hormone TSH is the best marker of body thyroid hormone status in the vast majority of people. So, for someone on T4 who doesn't feel well and may still have symptoms of an underactive thyroid, the blood TSH level is a good marker of whether adequate thyroxine is being replaced or not. Some people may improve with a slightly higher dose of T4 as long as it is not excessive (as evidenced by low TSH levels).

The symptoms of an underactive thyroid are not specific to the thyroid and may be due to many other conditions. If the TSH is within the reference range and dose adjustment has not helped, then the doctor should look for other causes of these symptoms. The list of possible alternative conditions is long but includes pernicious anaemia, coeliac disease, vitamin D deficiency, sleep apnoea, poor lifestyle and lack of sleep, depression, fibromyalgia, chronic fatigue syndrome and side-effects of medications.

## References:

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### **Q7: Does it matter which brand of levothyroxine I take?**

**Short Answer:** No, the amount of levothyroxine in all brands of tablets available in the UK is carefully controlled.

**Longer answer:** The amount of levothyroxine in all brands of tablets available in the UK is carefully controlled by the Medicines and Healthcare products Regulatory Agency (MHRA), so for almost everybody, there is no difference between brands. However, as well as levothyroxine, the tablets contain 'fillers', which are also known as excipients or bulking agents. Very rarely people may be sensitive or allergic to these fillers and in that case, you should find a brand that you don't have a problem with and stick to that one brand. For most other people, the differences between different formulations are likely to be comparable to the everyday small fluctuations that affect levothyroxine absorption. These fluctuations include things such as the time after taking your tablet that you next eat or drink, and what you eat and drink; with coffee, high fibre and soy containing foods, and several medications impairing absorption. The recent MHRA report on levothyroxine recommends:  
*"Levothyroxine should be prescribed and dispensed in quantities covering three months supply, where appropriate, in order to address issues of continuity of supply and also to improve convenience to patients."*

## References:

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### **Q8: I have been diagnosed with hypothyroidism and am trying for a baby. What should I do?**

**Short Answer:** Take your levothyroxine as prescribed and have your blood tests monitored, aiming for a serum TSH of 0.4-2.5 prior to pregnancy. Have your blood tests monitored regularly throughout the pregnancy.

**Longer answer:** During pregnancy the thyroid will normally make extra thyroid hormones. We know that having poorly controlled hypothyroidism during pregnancy is a risk factor for miscarriage, as well as for poorer brain development in the baby and pregnancy complications for the mother. For this reason, you should plan to go into pregnancy with excellent control of your hypothyroidism, aiming for a blood TSH of 0.4-2.5mU/l. As soon as

you find out that you are pregnant, you should immediately increase your levothyroxine dose by 25mcg daily, and seek another blood test to monitor the thyroid function. You should then have your thyroid tests rechecked every 4 to 8 weeks during pregnancy. Don't wait to see your doctor or midwife before increasing the dose, as this leaves you and your baby potentially vulnerable in early pregnancy, which is the most critical time. If your doctor and midwife aren't aware of the need to change your dose, please refer them to the recent guidelines (references 5 and 6 below). During the first 3 months of pregnancy the target for treatment of hypothyroidism is different, aiming for a TSH of 0.4 to 2.5mU/l. After that, the target TSH range is 0.4 to 3.0mU/l for 'singleton' pregnancies. People carrying twins have slightly lower target TSH values. You should go back to your pre-pregnancy dose of levothyroxine when the baby is born, and have your TSH rechecked at the '6-week' mother and baby check.

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## **Q9: What about alternative remedies like natural desiccated thyroid (NDT) or dietary supplements, for example iodine?**

**Short answer:** Although 'natural' sounds attractive, there's no evidence to suggest it's better than pure levothyroxine and iodine supplements can aggravate existing thyroid disease.

**Longer answer:** There is no substantial evidence that NDT preparations are superior to levothyroxine, and they contain several things that aren't needed to treat your thyroid problem. Also, the makeup of thyroid hormones in an animal thyroid gland is different from that in a human, so we wouldn't expect NDT to provide perfect replacement for a human. For instance, Armour thyroid is mashed up and dried pig thyroid and contains one part of tri-iodothyronine (T3) to four-five parts of levothyroxine (T4); this compares to a T3/T4 ratio of about 1:14 in human thyroid. This gives a risk of problems from overtreatment from excessive T3. In addition, compared to levothyroxine these compounds are expensive for



the NHS (a month of levothyroxine 100mcg costs less than £2.00, compared to around £40.00 for a month of NDT 120mg), with no obvious benefit. Unless clear evidence of the benefit from NDT preparations becomes available, they should be avoided.

Iodine, kelp and similar dietary supplements do not work for treatment of hypothyroidism. In addition, they may overload the body with iodine and result in worse hypothyroidism or even hyperthyroidism. There is no benefit to taking such preparations in addition to levothyroxine.

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**Q10: I want to try alternative treatments because I feel so unwell and I am prepared to accept the potentially harmful effects later on in my life, why are doctors reluctant to prescribe them?**

The objective of medical treatments is to improve the patient's condition. All medical treatments are potentially harmful. A doctor has to make a judgment on whether a treatment is more likely to be beneficial than harmful. If that judgment is against treatment, it is unethical for the doctor to prescribe it. Ethics is a vitally important set of principles that governs the behaviour of doctors and its aim is to protect patients. Our society rightly demands that health care in the UK is of the highest standard, and that requires among other things, that doctors should apply the principles of ethics in their practice. Sometimes conflicts arise where the patient's wish for a treatment is against a doctor's recommendation. In these circumstances it would be wrong for the doctor to collude with the patient's wishes against the doctor's professional judgment, a view that is supported by the General Medical Council (the regulatory body for doctors). However, in most cases where such a conflict arises, it is possible for patient and doctor to resolve it by careful consideration and sharing of the medical evidence, searching for alternative causes of symptoms, shared decision making, negotiation, formulation of a short- and long-term strategy that includes limitation of potential harm, an overall holistic approach, and where appropriate seeking another expert opinion. Central to this process is for doctors to inspire trust, and for doctors and patients to have mutual respect about their views and opinions.

## **ABBREVIATIONS AND GLOSSARY**

**Anti-TPO:** antibodies to thyroid peroxidase. These are antibodies found in more than 90% of people with autoimmune hypothyroidism and about 10% of normal people and are "markers" of autoimmunity

**Free T3:** free tri-iodothyronine. Thyroid hormones circulate in the bloodstream tightly bound to proteins. A very small fraction of the total amount of circulating thyroid hormones are unbound or "free" and it is this fraction that tissues and cells respond to. Modern blood tests can estimate the "free" thyroid hormones, which is a more accurate measure than the total amount of thyroid hormones.

**Free T4:** free thyroxine. Thyroid hormones circulate in the bloodstream tightly bound to proteins. A very small fraction of the total amount of circulating thyroid hormones are

unbound or “free” and it is this fraction that tissues and cells respond to. Modern blood tests can estimate the “free” thyroid hormones, which is a more accurate measure than the total amount of thyroid hormones.

**Levothyroxine:** same as T4, but usually referring to it as a treatment

**Liothyronine:** same as T3, but usually referring to it as a treatment

**MHRA:** Medicines and Healthcare products Regulatory Agency

**NDT:** Natural desiccated thyroid. These are animal products that contain both T3 and T4.

**SCH:** subclinical hypothyroidism. A “grey zone” between normal thyroid function and hypothyroidism. It is defined by blood tests for free T4 (which in SCH is normal) and TSH (which in SCH it is elevated).

**T3:** tri-iodothyronine. This is the active thyroid hormone, which tissues and cells sense and respond to.

**T4:** thyroxine. Thyroxine has little activity by itself and tissues and cells do not respond to it. It acts as a store for thyroid hormones in the body. It is converted in the body to the active hormone T3.

**TSH:** thyroid stimulating hormone. A hormone produced by the pituitary gland, which controls the production of thyroid hormones (T3 and T4) from the thyroid gland.

**British Thyroid Foundation 2016**