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FUNCTIONAL 'UNRESPONSIVE' HYPOTHYROIDISM AND MANAGEMENT

THE FOLLOWING DISCUSSION MAY BE AT TIMES TECHNICAL, PURPOSELY, SO YOU CAN GIVE THE INFORMATION TO YOUR HEALTH PROVIDERS WHO MAY BE UNFAMILIAR WITH THE TERM 'FUNCTIONAL MEDICINE' AND ITS ROLE IN MEDICAL MANAGEMENT IN ENDOCRINE DISORDERS ESPECIALLY HYPOTHYROIDISM.

Up to 7% of general population worldwide has symptoms of hypothyroidism. The screening method is TSH (thyrotropin or thyroid stimulating hormone), and sometimes T4 (thyroxin) to confirm the diagnosis. TSH seems to have largely trumped clinical history and examination. If the TSH is 'normal range' it is very unlikely that the patient, even with very suggestive symptoms, will receive replacement thyroid hormones.
Many of these patients may not receive effective treatment or even a trial of treatment so often inappropriately treated with drugs such as antidepressants when they are not depressed other than from being tired and frustrated at getting incomplete relief from symptoms. The total reliance on TSH is being shown more and more by researchers and clinicians to be highly questionable. Endocrine systems (all hormones) in the human are incredibly complex and thyroid status can no longer be simply determined by a simple screening test like TSH in that subset group.

THIS DOCUMENT DISCUSSES THE OPTION OF NON-CONVENTIONAL THYROID TREATMENT – DESSICATED THYROID EXTRACT (DTE) AND OTHER NUTRITIONAL THERAPIES AS POTENTIALLY SUCCESSFUL MANAGEMENT FOR MANY CASES WHERE CONVENTIONAL STANDARD OF CARE (SOC) L-THYROXINE FAILS TO PROVIDE FULL RECOVERY OF HEALTH. ALSO KNOWN AS ARMOR, NATURAL THYROID, WHOLE THYROID EXTRACT (WTE), DESICCATED THYROID (DTE), COMPOUNDED T4+T3 AND T3 ALONE.

STANDARD OF CARE TREATMENT (SOC) WITH L-THYROXINE IS GENERALLY SUCCESSFUL, COST EFFECTIVE, ABSORBS WELL USUALLY, HAS LONG HALF-LIFE SO NO SUDDEN CHANGES WITH ALTERING OR MISSING DOSES.

INTRODUCTION

Functional Medicine doctors see many patients with symptomatic hypothyroidism, usually Hashimoto's autoimmune (AID) but not always, who are already on L-thyroxine but who are anything but well. A number have had total thyroidectomy and never regain their previous wellness on SOC treatment in spite of 'normal' TSH. What does that mean, when the patient indicates how terribly unwell they still feel, and worse, often made to feel that their symptoms are not real, even neurotic?

When the AACE (The American Association of Clinical Endocrinologists) established new TSH Guidelines (0.3 - 3.0 vs. 0.5 - 5.0) the number of people estimated to be affected by abnormal thyroid function almost doubled even by mainstream standards. (Now, the TSH lower range is considered by many as 2).

According to the AACE, the number of people affected by Thyroid Disease now surpasses the number of people diagnosed with Diabetes or Heart Disease.

- 27 Million: The number of Americans estimated to suffer from Thyroid Disease
- 13 Million: The number of Americans estimated to suffer from Thyroid Disease...but remain undiagnosed.
- 14 Million: Estimated number of Americans affected by Hashimoto's Thyroiditis (Autoimmune Thyroiditis / Hypothyroidism).
- Women are 5 to 8 times more likely to suffer from Hypothyroidism than men.
- 25%: Approximate number of women that will develop permanent hypothyroidism.

DOCTORS MUST ADHERE TO BEST PRACTICE GUIDELINES

As doctors, we are required to follow 'best practice' guidelines. But what exactly are these? They may apply to the majority but not every single case. Human individuality, genetics, epigenetics and other factors come into play thus complicating interpretation and treatment strategies. Especially in the endocrine (hormone) systems.
So when the patient who is on L-thyroxine, with in-range TSH, says **'why do I still not feel well'** and after we exclude other differential diagnoses – what then, antidepressants? That seems to be the present pathway in many cases.

Or should we ask:

- Is the Thyroxine dose really the right dose for her, despite the 'TSH' saying it is?
- Is the TSH the only determinant for our judgement – does every patient respond the same to a given hormone dose and brand?
- Should we be more guided by our patients reporting of health – in other words what do we value most - the clinical presentation of the patient or one lab reference range result? Preferably we assess everything.
- Is the synthetic T4 – largely a pro-hormone, actually working? Is it being absorbed?
- Is it converting to T3? Is there selenium, iron, zinc or progesterone deficiency? Or other hormone dysfunctions including adrenal insufficiency. Drug interactions. Xeno-chemical receptor disruption (emerging to be a modern day environmental catastrophe).
- Increasing research shows our almost total fixation on TSH could be flawed – at least for some of our patients.
- Is low or suppressed TSH reason for concern when the patient finally feels normal? Only certain cases of suppressed TSH are associated with increased risks, such as true Graves thyrotoxicosis and toxic nodular goitre. Low or even suppressed TSH is not the same as thyrotoxicosis – which is a specific clinical diagnosis backed up with biochemical evidence. ***Low TSH in a healthy symptom-free patient is not thyrotoxicosis.*** Nevertheless, research is still mixed depending on other variables. Some say suppressed TSH itself may cause some increased bone loss, others say not. Whatever the case, it

would be extremely unlikely to be clinically relevant and certainly not a common finding.

- There is a wealth of literature condemning the blind adherence to TSH in the face of a clearly symptomatic thyroid patient – and even questioning the relevance of T4 and T3 'normal ranges' for that matter – in view of the high complexity of hormones in the human. It is understandable that mainstream clinicians refute the TSH concerns – it has been enshrined for many decades. Change is slow. Endocrine societies are conservative by nature – it protects from radical ideas but also dismisses the concept of personalised medicine. It awaits robust clinical studies to prove the claim. Laudable of course. But what of the suffering? Do they just have to wait? It is time that endocrinologists work WITH functional medical doctors and their patients rather than AGAINST them.
- Can patients on 'alternative options' become thyrotoxic? Of course, like many other guideline-based medical treatments, when instigating a new treatment to find optimum dosing, temporary overtreatment can happen. Patients can self-treat, alter their medications and forget to take them just like standard thyroid medications.

A TYPICAL SYMPTOM REVIEW:

Table 1. Percentage of 860 hypothyroid patients with various symptoms despite treatment

Symptom	Percentage still suffering from
• Fatigue	92%
• Inability to lose weight despite diet/exercise	65%
• Feel sluggish & lethargic	62%
• Trouble concentrating	60%
• No sex drive	58%
• Pains, aches, stiffness	51%
• Depression	45%
• Hair loss	43%
• Eyes dry & light sensitive	38%
• Strange feeling in neck or throat	38%

VERY BASIC BIOCHEMISTRY

In response to circulating T4, T3, T2 and maybe T1 – the hypothalamus control centre in the brain will instruct the pituitary to secrete TSH to stimulate the thyroid gland to produce more thyroid hormone.
Inactive T4 is produced and then in the liver and other tissues including the thyroid, it converts to the active hormone T3 – requiring enzyme de-iodination steps (to remove an iodine molecule) using co- factors selenium and zinc.
Our lab testing guidelines only allow for evaluating circulating TSH and unless it is abnormal will then test T4 but rarely allow T3. (the reason given is that the latter is too variable or the lab method inaccurate – that is strange as volumes of research papers involve measuring T3 levels?.

That's as far as our 'guidelines' allow us to be concerned as doctors. The multitude of books, websites, support groups detailing millions of people who are caught in this confusion and poor health gives some credence to the fact that our medical guidelines are in urgent need of overhaul if at the least to allow for more latitude with this non-responding patient group.

Look around at the health chaos at present. Fatigue, brain fog, depression, obesity, digestive disorders, inflammatory disorders, auto-immune epidemic – it's not only about poor lifestyle choices – we live in a time where biotoxins, enviro-toxins, hormone disruptors, infections, impaired immunity, stress - mess with our delicate genetic expression i.e. the blueprint we have inherited to make us who we are – or should be!

FOR TECHOS! – WHAT HAPPENS NEXT IS MORE CRUCIAL BUT TESTING IS NOT AVAILABLE

Iodine has to be oxidised and by *organification* converted to largely inactive thyroxin (T4). TSH is required. Active T3 then has to be transported across cell membranes (transporter proteins). T3 then has to locate intracellular receptors on mitochondria and genes – their numbers and availability are influenced by many factors. Genes can then turn off or on (express) so that RNA can produce proteins –which are the essence of life and energy. This delicate sequence can be affected in many ways that can result in hormone failure even when hormone levels are 'normal'. As all cells need energy and T3 is crucial for that – you can understand why optimum thyroid function critical and failure results in a wide array of symptoms.

Some reasons for failure of tissue T3 to do its job:

- Is there disruption of transport and Na/symporter mechanisms?
- Are there disruptive molecules already occupying receptors?
- What about *molecular mimicry*? Xeno-chemicals from environmental pollution, personal care products etc.?
  There is vast evidence of hormonal mimicry and other disruptor activity – well documented. Women appear to be most at risk for thyroid disruption. Why?
- Less common genetic disorders.
- Auto-antibodies may play a role in receptor dysfunction as well.
- Goitrogens can block iodine. *Peanuts, soy, brassica vegetables, halides incl. bromine and fluoride.*
- Mercury displaces iodine.
- Polyunsaturated fats (long chain seed oils) can be anti-thyroid and promote weight gain, which doesn't happen with stable sat fats like medium chain coconut oil! It now appears we *may* have been incorrect in over-promoting PUFA oils at the expense of saturated fats.

IS THERE A SOLUTION

Internationally, the problem is well recognised, but still not so much by mainstream where TSH is THE reference point. There has been some relaxation by reducing the lower limit for TSH to 3 (some groups even say it should be 2).

Depending on the presentation and possible factors selenium for T3 conversion etc. – a consistently good solution has been the prescribing of the combined gland extract which contains T4, T3, T2, and T1. This has been in existence for decades and now strictly

standardised like other pharmaceuticals. But why not just increase the dose of the standard L-Thyroxin medication? Yes, that is an option in some cases. Some patients just need levels up in the top reference range to feel well, finally.

WTE used to be THE treatment for hypothyroidism, but got superseded by synthetic patented T4 brands which were more consistent in quality though not always, especially as products are manufactured all over the world and standards are not guaranteed. Fortunately in NZ our Pharmac endevours to source quality product.

As high quality DTE 'desiccated extract' became available so did results become more consistent and far more effective in certain patient groups. Indeed, peer reviewed articles have demonstrated superior results from combined T4 - T3 therapy than T4 alone in some cases. (NEJM 1999 -340).

For the '***still symptomatically hypothyroid'*** patient who is on appropriate T4 dosing – and after considering T3 issues etc., the term *T3 tissue resistance* is useful to describe what may be taking place. Akin to metabolic syndrome, which was once highly controversial but now very mainstream. Resistance is well known but it's true genetic form is probably uncommon, so this term is used loosely to enable understanding. It may encompass many possible biochemical and epigenetic malfunctions.

TREATMENT

The patient is offered a trial on WTE (whole thyroid extract) in incremental dosing until they achieve clinically acceptable outcome. This requires proper supervision. The dosing depends on whether the person is already on thyroid medication.

TSH will reduce and even suppress as return to normal health is achieved. T3 usually increases even to high normal range and sometimes above, though keeping within the reference range is preferred. If symptoms of over-treatment occur (thyrotoxicosis) then dosing is adjusted same as conventional L Thyroxine – BUT based on clinical judgment, T4, T3 and not JUST the TSH.

T4 may increase but more likely reduce as feedback suppresses endogenous T4. **That's not such an issue as T3 is the more tissue active hormone – it will increase.**

RESULTS

Most patients have good to excellent response and THEY report results and THEY know which treatment gets their life back to some normality again.

Patients have thyroid questionnaires, databases, clinical exam, lab workup and temperature charting to strengthen the diagnosis.

THE FINAL CONFIRMATORY 'TEST' IS THE 'TOT' - TRIAL OF TREATMENT

SO WHAT ABOUT THE SUPPRESSED TSH?

Research papers as well as well as experience from experts shows that suppressed TSH below the 'normal' range is NOT an issue unless a high risk cardiac patient when closer monitoring and small dose increases required. But these patients are also required to have optimal thyroid function too because suboptimal thyroid is a heart risk itself! If the patient with low or suppressed TSH is symptomatically hyperthyroid on treatment then that is overdosing.

When the TSH is suppressed, many doctors call this *thyrotoxicosis* irrespective of the patient's absence of thyrotoxic symptoms. Commonly, treatment-suppressed TSH occurs WITHOUT thyrotoxicosis symptoms *AND the patient feels well* – for the first time in a long time.

The risks of cardiac events and osteoporosis is extremely rare. Of course, we are assuming the patient is not already exhibiting significant CHD (heart disease) or OP (osteoporosis) risk already. Post-menopausal women are at risk of bone density loss if they do not take estrogen BHRT.
So TSH suppression remains controversial. The evidence is strong that it is not of significant concern with the above caveats. The alternative is an unwell patient who is at very real health risk!

THE RISKS ARE SMALL CONSIDERING THE SIGNIFICANT POOR HEALTH ALREADY SUFFERED BY THESE PATIENTS.

Yes, those risks do occur in the disease thyrotoxicosis – which is different from exogenous thyroid replacement in the subset who appear to have cellular T3 'resistance'.
Thyroid cancer patients are treated with high dose thyroid medication to purposely suppress the TSH – osteoporosis does not occur.

MONITORING

As WTE is increased to get tissue responsivity and resolution of fatigue, myalgia and other symptoms, we monitor for hyper-stimulation - it is extremely rare even on some necessarily high T4/T3 doses. Tissue response is not uniform. In other words, before we get to a dose to reduce fatigued mitochondria*, cardiac sensitivity with increased basal pulse rate may preclude any further increase in dose or reduction. Very uncommon but it's an example of bio-individual or personalised treatment.

- Regular 3-6 monthly T4, T3 and TSH (rT3 option) testing.
- Bone markers, Bone Scan if appropriate.
- ECG to monitor early electrical heart changes when indicated.
- **Symptom review**
- Clinical exam as appropriate
- Standard Adult Health Checks

T3 ALONE TREATMENT

Rare cases still may not respond and are quite difficult. There may be many reasons but once filtered, there are cases which may respond to T3 only. This may require single or divided dosing options. It's a more complex subject and beyond this discussion document.

Suppressing endogenous T4 to low levels (to reduce rT3) and using only T3 seems to be a solution here. It may be linked to reverse T3 (rT3) occupying receptor sites or epigenetic methylation marks hence the strategy of suppressing the rT3 source i.e. T4, for a time.

I HOPE THIS WILL IN SOME WAY PROVIDE A BRIEF EXPLANATION OF A VERY INTRIGUING, COMMON, COMPLEX AND CONTROVERSIAL SITUATION IN THIS EPIDEMIC OF CLINICAL AND SUBCLINICAL HYPOTHYROIDISM PARTICULARLY IN WOMEN, POORLY RESPONSIVE TO USUAL GUIDELINE-BASED TREATMENT.

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