

Genetic variation in the enzyme that converts T4 to T3 may be responsible for why certain patients require L-T4/T3 combination therapy to achieve well-being

Most patients on thyroid hormone are treated with levothyroxine (T4) and do well on that. A patient with primary hypothyroidism can have the dose of levothyroxine titrated until the TSH is normalized, and most patients respond clinically with improvement in their symptoms. However, Dr. Friedman and other endocrinologists have become aware that many patients on proper levothyroxine replacement with normalized TSH levels do not feel well and do not return to their baseline health. These patients may be good candidates for T4/liothyronine (T3) combination therapy by either giving levothyroxine plus compounded slow-release T3, levothyroxine plus Cytomel, or Armour Thyroid, which has T4 and T3 in it. Dr. Friedman often adds an additional amount of levothyroxine as the Armour usually has too high of a ratio of T3 to T4 in it. Many but not all patients do better on this combination therapy than patients on levothyroxine alone who still have symptoms like fatigue and brain fog. However, until recently, we were unable to predict who would do well on this T4/T3 combination therapy.

A very important article was published in the May 2009 *Journal of Clinical Endocrinology and Metabolism* explaining this difference is probably due to a variation in what is called a polymorphism, which means a change in the DNA of patients so that the amino acid of an enzyme is modified. The enzyme we are talking about is called deiodinase D2, and this is the enzyme that converts T4 to T3 and is abundant in the brain. This article was published from a group of endocrinologists in Bristol in the United Kingdom, and the first author was Professor Panicker. There is an accompanying editorial by two endocrinologists in Miami, Drs. Kim and Bianco, in the same issue of *Journal of Clinical Endocrinology and Metabolism* explaining the role of the deiodinase enzyme. This polymorphism changes an amino acid from alanine to threonine of deiodinase D2, which does not necessarily affect the enzyme activity but was found in this paper to be correlated with a better clinical response to T4/T3 therapy. Specifically, the authors found that patients with this polymorphism of deiodinase D2 started off with worse general health questionnaire scores and then their general health questionnaire score improved more on the T4/T3 combination therapy than on T4 alone. Thus, it is suggested from this study that having this alteration in DNA giving this different polymorphism may predict people who do not do well on T4 replacement alone and would do better on T4/T3 combination or Armour/T4 combination therapy.

Most interesting, this polymorphism only occurs in 16% of the study population in this area of the United Kingdom. Thus, the majority of patients do not have this polymorphism, and as Dr. Friedman has experienced, do fine on T4 therapy alone. However, there is a percentage of patients, and those are usually the patients who are dissatisfied with the T4 therapy and maybe go see Dr. Friedman or are vocal on the internet, about the problems of T4 alone treatment. Most randomized clinical trials giving T4 versus T4/T3 treatment have not shown any difference in outcomes, but this is likely due to the low prevalence of this polymorphism.

This study, which took place in the Weston area of the United Kingdom, was called the "Westin area T4/T3 study (WATTS)" and is the largest study evaluating thyroid hormone replacement conducted with 697 participants. However, the combination therapy they used was to take the

patient's T4 dose and reduce it by 50 mcg and added 10 mcg of once-a-day T3, which is not physiological, as it should be given two or three times per day. It might have been better if they would have given either Armour Thyroid or the T3 in multiple doses. This study did not find any difference in serum levels of T4 or T3 between the group with the polymorphism and the other group, so we are probably referring to different T3 levels in the brain.

In conclusion, this study in *Journal of Clinical Endocrinology and Metabolism* does seem to point that different genetic factors may explain why certain patients respond better to T4/T3 replacement than with T4 alone. Dr. Friedman is working with the laboratory that he uses, Esoterix, to try to make detection of this polymorphism clinically available. For more information on Dr. Friedman's endocrinology practice, please go to goodhormonehealth.com.