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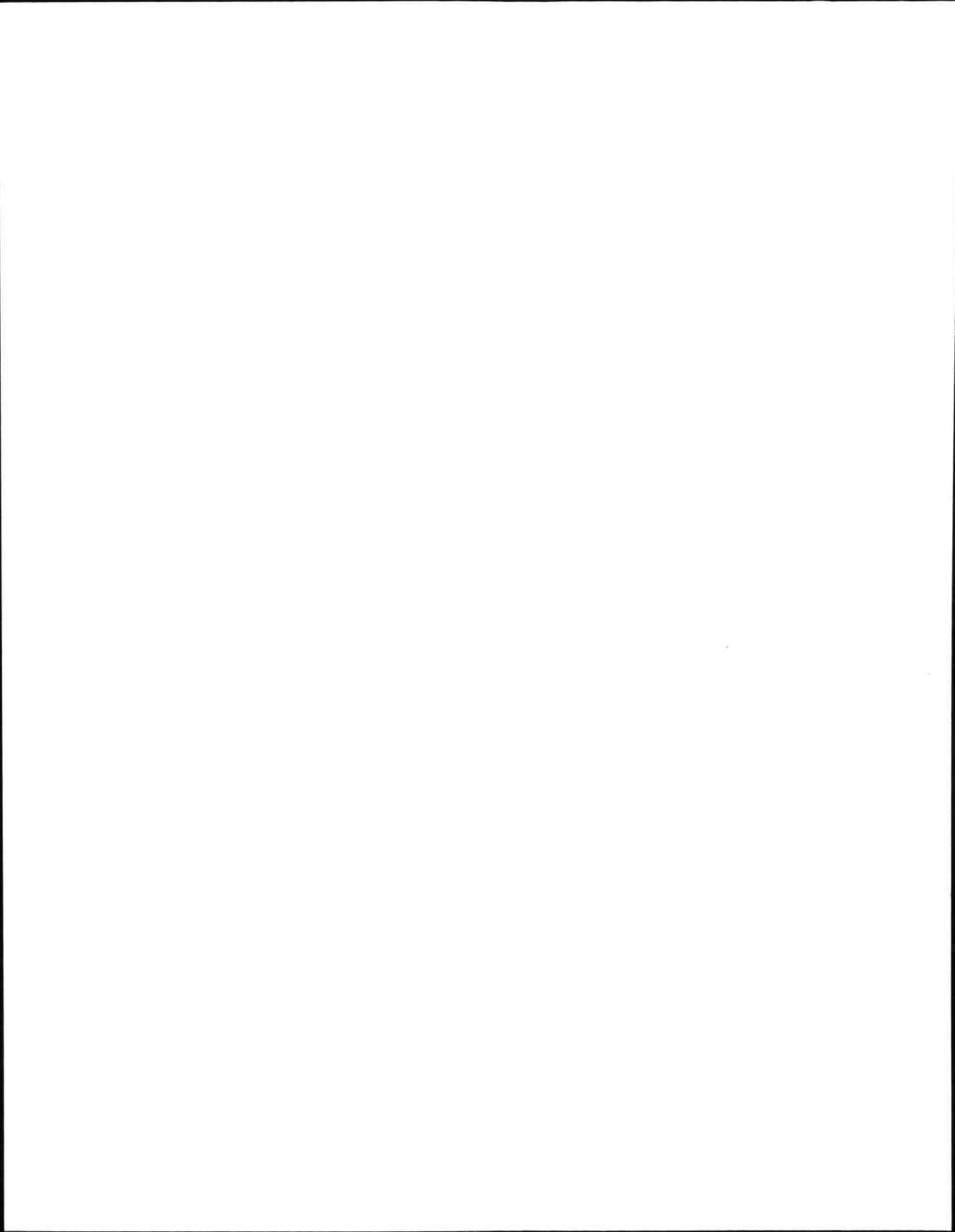
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Summary



T3, OR NO T3 ? A SYNOPSIS

The main aim of this thesis was to investigate whether or not the thyroid hormone triiodothyronine (T3) is beneficial as an addition in the medical treatment of two disorders, primary hypothyroidism and major depression. To this end, two randomized clinical trials were carried out. The data of these randomized clinical trials provided the opportunity to investigate several other important issues.

STUDIES IN HYPOTHYROIDISM

The results of neurocognitive tests of our study population of 141 patients with primary autoimmune hypothyroidism on levothyroxine (T4) replacement therapy were compared with the reference values for these tests. We found that patients had poor performance on various domains of neurocognitive functioning compared with the mean standard reference values for the general Dutch population, especially on a complex attention task and on verbal memory tests (*Chapter 2*). This suggests that neurocognitive functioning, which is impaired during hypothyroidism, may not be completely restored notwithstanding long-term adequate T4 treatment. In addition, we found patients to have a higher mean SCL-90 total score than the general population, as well as lower mean Rand-36 'vitality' and 'mental health' scores, all indicating lower levels of psychological well-being.

The results of a randomized clinical trial among the same population of 141 patients with primary autoimmune hypothyroidism show that patients preferred combined treatment with T4 and T3 over T4 monotherapy (*Chapter 3*). Study medication was preferred to usual treatment by 41% and 52% in the 10:1 ratio and 5:1 ratio groups, respectively, compared with 29% in the group that remained on T4 (Chi square test for trend, $p=0.02$). This subjective preference for combined therapy was not objectified by results of any of the secondary outcome measures: scores on questionnaires and neurocognitive tests consistently ameliorated, but the amelioration was not different among the treatment groups. Decrease in body weight was associated with the proportion of T3 in the substitution treatment, as well as with the level of satisfaction with the study medication, which might explain the preference for T4/T3 combination therapy. Overtreatment may have played a role in this outcome, as a substantial portion of participants in the combined treatment groups had

suppressed serum TSH values after 15 weeks. This is a cause for concern, since overtreatment with exogenous thyroid hormone is a risk factor for atrial fibrillation and may possibly lead to osteoporosis. If only those patients with endpoint TSH serum values within the reference range were included in the analysis, results for the primary outcome measure were similar, but failed to reach significance due to a loss of statistical power. The results of this study do not currently support combined T4/T3 therapy as a standard treatment of patients with hypothyroidism, but encourage further research in this field.

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The outcome of the abovementioned trial does not preclude the possibility that a certain subgroup of patients may benefit from combined T4/T3 therapy. Levothyroxine-treated patients derive T3 from deiodination of T4 which, in the central nervous system, is regulated by type II deiodinase (DII). We investigated whether two recently identified polymorphisms in the DII gene (DII-ORFa-Gly3Asp and DII-Thr92Ala) are determinants of well-being and neurocognitive functioning, as subtle changes in enzyme activity that may be linked to these DII polymorphisms may have important consequences for T3 availability in the central nervous system. In addition we examined their association with a preference for replacement therapy with a combination of T3 and T4.

In *Chapter 4*, it was shown that polymorphisms in the deiodinase type II gene do not explain differences in well-being, neurocognitive functioning or appreciation of T4/T3 combination therapy in patients treated for hypothyroidism.

STUDIES IN MAJOR DEPRESSION

In a controlled study among a population of 113 outpatients with major depression (*Chapter 5*), free from antidepressant therapy, a slightly higher serum TSH was the only endocrine alteration we found compared with 113 age and sex matched controls. No alterations in serum or urinary cortisol levels were observed. In a subgroup of patients with atypical features, serum cortisol levels were lower than in depressed patients without these features. These results are in contrast with the existing literature, in which major depression is often described as associated with lower serum TSH and higher T4 and FT4 levels, and with hyperactivity of the HPA axis as evidenced by increased cortisol levels. On closer inspection of the literature however, it seems that these endocrine alterations occurred only in inpatients, not in outpatients.

In two meta-analyses, the addition of T3 to a tricyclic antidepressant (TCA) was described to be effective in accelerating treatment response, and in turning TCA non-responders into responders.

In *Chapter 6*, we describe the results of a randomized clinical trial among 113 outpatients with major depression, the first trial to investigate whether T3 addition is beneficial in combination with a SSRI, paroxetine. We found that addition of the thyroid hormone triiodothyronine (T3) to paroxetine had no advantage over addition of placebo in the treatment of non-refractory major depressive disorder. Treatment with T3 did not accelerate the response to treatment; neither did T3 addition influence response or remission rates. In fact, the main difference between treatments appears to be that patients in the T3-addition groups experienced more adverse effects compared to those on paroxetine alone, especially those who received the higher dose of 50 µg T3 daily. The results of the clinical trial in this thesis do not support a role for T3-addition to SSRIs in the treatment of non-refractory major depressive disorder. On the contrary, more adverse reactions occurred in T3 treated patients.

In *chapter 7*, we investigated whether response to antidepressant treatment in outpatients treated for major depression is predicted by Hypothalamus-Pituitary-Thyroid (HPT) axis parameters, or by a recently discovered polymorphism in type II deiodinase (DII). Higher serum TSH was found to be associated with response to paroxetine treatment in patients with major depression. The DII polymorphism (Thr92Ala) was not related to treatment response.

In *chapter 8*, we established in our outpatient population whether treatment response in major depression is predicted by Hypothalamus-Pituitary-Adrenal (HPA) axis parameters, or by genetic polymorphisms in the glucocorticoid receptor (GR). Higher ACTH response in the DEX/CRH test was found to be associated with non-response to antidepressant treatment with paroxetine. Carriers of the BclII glucocorticoid receptor polymorphism had higher ACTH levels than non-carriers.

Finally, we investigated whether post-treatment DEX/CRH test parameters were related to the occurrence of relapse in a population of 45 outpatients with clinically remitted major depression (*chapter 9*). We found that higher post-treatment maximal ACTH and cortisol levels, as well as delta ACTH and cortisol levels were associated with relapse of major depression.

T3, or no T3?

In the general discussion (*chapter 10*), an overview of the abovementioned studies is presented, and their scientific and clinical implications are discussed. In analogy with Hamlet's famous soliloquy, to which the title of this thesis unmistakably refers, the key question of this thesis is not followed by a clear-cut and definitive answer, but rather by more questions as put forward in the preceding sections.

In short, the results of our clinical trials give reason to think that there might be a role for T3 in the treatment of (subgroups of) patients with primary hypothyroidism, but, conversely, question the role of T3 in the treatment of major depression.