SUMMARY

Context: In some patients symptoms of hypothyroidism persist despite therapy with T₄.

Objectives: The objective of the study was to compare the effectiveness of T₃-T₄ combination versus T₄ monotherapy for the treatment of clinical hypothyroidism in adults.

Data sources: Pubmed, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched in September 2005. References of all included trials were scanned for additional studies. There was no restriction on language, year of publication, or publication status.

Study selection: All randomized trials that compared the effectiveness of T₃-T₄ combination versus T₄ monotherapy for the treatment of clinical hypothyroidism in adults were included.

Data extraction: The data were extracted by two independent reviewers.

Data synthesis: The authors included 11 studies, in which a total of 1216 patients was included. No difference was found in the effectiveness of the combination treatment versus monotherapy in any of the following symptoms: bodily pain, depression, anxiety, fatigue, quality of life, body weight, total serum cholesterol, triglyceride levels, low-density lipoprotein, and high-density lipoprotein. Adverse events did not differ between regimens.

Conclusions: T₄ monotherapy should remain the treatment of choice for clinical hypothyroidism.

COMMENT

The routine use of computerized “search engines” and availability of computerized tools for comparing therapeutic trials constitutes one of the bases of evidence-based medicine and, in this approach, meta-analyses have become a mainstay in medical clinical research. At almost every international thyroid congress, we hear new data on hypothyroid patients who don’t feel well under “adequate” T₄ treatment and also new results on the potential advantage of combining T₃ with T₄ for this long term treatment.

Thyroxine is the logical treatment of hypothyroidism for the following main reasons: 1) physiologically, the thyroid gland produces essentially T₄ (and little T₃); 2) T₄ has a long half life (~1 week), hence providing stable quantities of T₃ by peripheral – intracellular – regulation of T₃
production through the progressive deiodination of T₄; 3) there is a log-
decimal inverse correlation between serum TSH and free T₄ levels (that does not exist
with free T₃); and finally 4) the administration of T₃ induces peaks of high
serum T₃ levels in the hours following its administration and, therefore, steady-state
levels cannot be achieved with this hormone when given once a day.

The authors undertook a systematic search of potentially relevant publications (N = 503). Of this large database, 490 publications were excluded because they were not randomized controlled trials (RCT). Of the 13 publications retrieved for further detailed evaluation, 2 others were excluded (1 because of insufficient data and 1 because of ‘double’ publication).

Finally, they were left with 11 RCT that met the eligibility criteria for meta-
analysis, corresponding to a total of over 1,000 patients. These studies are relatively recent, published from 1999 (Bunevicius) until 2005 (Appelhof; Escobar-Morreale; Rodriguez; Saravanan). The main result of the present analysis was that T₃-T₄ combination therapy used as replacement

therapy for patients treated for hypothyroidism provided no advantage when compared with the standard monotherapy using T₄. There was no benefit in terms of symptoms (fatigue, bodily pain, anxiety, depression) and no improvement in the quality of life. Moreover, the combination therapy led to no improvement in cognitive efficiency or the ability to undertake novel tasks, memory, attention, etc. Finally, lipid profile was not improved in patients prescribed the combination treatment. It

should also be mentioned that the trials varied in the doses of T₃ given as well as duration of treatment. However and despite these differences, the primary outcomes did not depend on T₃ dose or duration of prescription. My only personal addition to this excellent study is that with the only commercial T₃-T₄ combination therapy available in our country, we are often referred patients who present cardiac or arrhythmic detrimental side effects associated with high serum T₃ levels. Monotherapy with appropriate (and correctly monitored) doses of T₄ should remain the standard treatment for hypothyroidism.

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