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Effect of levothyroxine plus liothyronine combination therapy on hypothyroid patients quality of life: A review

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REVIEW

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ABSTRACT

Background
Liothyronine combination with Levothyroxine(T4-T3) has been tried to improve the quality of life among hypothyroid patients on levothyroxine immunotherapy and normal thyroxine stimulating hormone levels. However, the efficacy of such a combination is unknown. The current review aimed to assess the effects of T4-T3 combination therapy on quality of life.

Aims
The current review aimed to compare levothyroxine mono-therapy versus T4-T3 combination therapy on quality of life among hypothyroid patients.

Methods
The Pub Med and Google Scholar databases were systematically searched for relevant articles. Articles published in the English language from the first available article up to March 2020 were approached. The terms hypothyroidism, levothyroxine, and liothyronine were used. Out of hundred and eight articles retrieved, only six fulfilled the inclusion and exclusion criteria.

Results
In majority of randomized control trials (4 out of 6 RCTs), T4/T3combination therapy fail to show superiority over the standard levothyroxine mono-therapy.

Conclusion
Levothyroxine remain the standard of care in hypothyroid patient.

Key Words
Levothyroxine, quality of life, liothyronine, hypothyroidism

What this study adds:

1. What is known about this subject?
Levothyroxine is the cornerstone management of hypothyroidism. However, up to ten percent remain symptomatic with impaired quality of life.

2. What new information is offered in this study?
Combination therapy effective in optimising hypothyroid patient's quality of life. In fact, no added value of combination T4-T3 over levothyroxine mono-therapy.

3. What are the implications for research, policy, or practice?
Levothyroxin recommended as the mainstay treatment of hypothyroidism by achieving clinical and biochemical eu-thyroid state.

Background

Hypothyroidism is a relatively common condition. The prevalence of overt hypothyroidism and subclinical hypothyroidism In community surveys, range from 0.1–2 percent and from 4–10 percent respectively.[1-3] In the US National Health and Nutrition Examination Survey (NHANES) III, a prevalence of 4.6 per cent was noted in participants ≥12 years of age (0.3 percent overt and 4.3 percent subclinical).[4]

levothyroxine (L-T4) substitution is the treatment of choice for treating hypothyroidism.[5] However, Studies conducted to assess quality of life (QOL)in hypothyroid patients treated with levothyroxine(L-T4) failed to optimise the quality of life (QOL), despite serum thyroid hormone (TSH) levels within the reference range.[6-7] several attempts to improve hypothyroid symptoms and quality of life in hypothyroid patients by administrating higher levothyroxine dose,[8] aiming for lower TSH target[9] and combining T4-T3.[10]

We performed a systematic comparing the effectiveness of T4-T3 combination therapy versus T4 mono-therapy on quality of life.

Method

Eligibility criteria according to population intervention comparison outcome study design (PICOS):

Randomized controlled trials (RCTs) investigating the T4-T3 combination therapy effect on quality of life were included.

Type of participants:

Studies among adults treated by levothyroxine for hypothyroids of any aetiology with TSH within the reference range. Studies conducted on newly diagnosed or TSH above the reference range.

Outcomes measures: Quality of life.

Information source and search methods:

A systematic electronic search was conducted in Pub Med and Google scholar. Articles published in the English language from the first published up to March 2020 were approached. The terms hypothyroidism, levothyroxine, liothyronine and T3 combination were used in different combinations.

Studies selection and data extraction:

The retrieved articles were manually searched for relevant articles, two authors (H.M. I.A.) screened the titles and abstracts to exclude irrelevant articles and any discrepancy was resolved by consensus. Out of hundred-eight articles retrieved, only six fulfilled the inclusion and exclusion criteria. The author's name, county, year of publication, type of study, number of patients included, the duration of follow-up if applicable, and the results were reported. The different stages of the review process were shown in the PRISMA chart[11] Figure 1.

Results

There were hundred and eight articles, eighty - six manuscripts remain after the removal of duplication and irrelevant articles, and only six articles fulfilled the inclusion and exclusion criteria all of them randomized controlled trials. Three studies were from Europe, one was published in the USA, one was published in South America and one from Australia. The retrieved RCTs include 419 patients, 56 per cent were from Europe, while 25 per cent were published in Australia, around 10 percent were published in USA and South America each, the duration of the studies ranged from 10–24 weeks with average mean of 16.5 weeks. Table: 1 depicted the effect of T4-T3 combination therapy on the quality of life. Two out of six randomized trials conclude that a T4-T3 combination therapy was superior to mono-therapy by improving quality of life. first randomized control trial conducted in the year (1999) in Lihuania, Europe described an improvement in quality of life over (QoL) in hypothyroid patients with substitution of 50µg LT4 by 12.5µg LT3 daily when comparing combination therapy with T4 and T3 to mono-therapy with T4.[12]

The second RCT was designed to evaluate the benefits of treating primary hypothyroidism with T4-T3 combination therapy versus levothyroxine mono-therapy and found combination therapy was superior to mono-therapy by evaluating several QOL.[13] The remaining four randomized trials show that there is no evidence supporting the superiority of T4-T3 combination therapy regarding improving quality of life over levothyroxine mono-therapy. The largest study by Appelhof et al. Included 141 chronic autoimmune thyroiditis patients in a non-cross-over, double-blind study with three treatment arms (LT4 mono-therapy, combination therapy with T3:T4 ratio of 10:1 and combination therapy with T3:T4 ratio of 5:1). T4 mono-therapy was comparable to a combination therapy with either a T4:T3 ratio.[14]

Walsh et al. conducted a double-blind, randomized, controlled trial with a crossover design included 101 patients with primary hypothyroidism in which liothyronine (10µg) was substituted for 50µg (ratio 5:1). Study show that no significant differences of QOL scores between patient

treated with T4 mono-therapy compared to a combination therapy.[15]

Clyde et al. Published a randomized controlled trial including 44 patients with four months' follow-up showed Compared with levothyroxine alone, treatment of primary hypothyroidism with combination levothyroxine plus liothyronine demonstrated a non-significant difference in QOL.[16]

This non-superiority of combination therapy over LT4 mono-therapy also concluded in a recent RCT, conducted in Brazil by Kaminski et al. included thirty two patients diagnosed with primary hypothyroidism on standard LT4 in a randomized, double blind cross over (8 weeks) study in which levothyroxine dose range between (125mcg to 150 mcg), combined T4-T3 (75mcg/15mcg).[17]

Discussion

This systematic review has provided insight into the clinical trials of T4-T3 combination therapy on quality of life among hypothyroid patients. T4-T3 combination therapy used as replacement therapy for patients treated for hypothyroidism provided no advantage when compared with standard T4 monotherapy in the majority of randomized, controlled trials included in the present review.[14-17]

The improvement in QoL was observed in two trials only.[12,13] On further analysis of Bunevicius et al.[12] study, the significant benefit of the T4-T3 combination was limited to athyreotic thyroid cancer patients. This finding suggests that the effect of the T4-T3 combination may be influenced by primary thyroid disease.

These contradicting rather than complimenting finding may be contributed to the heterogeneity in the primary disease (autoimmune thyroiditis versus thyroid cancer), different T4:T3 ratio, and T3 frequency (once versus twice daily). Further studies are needed to clarify the real effect of combination therapy on hypothyroid patients Qol.

Conclusion

In conclusion, till development of high quality evidence on the role of adding liothyronine, levothyroxine remain the standard of care in hypothyroid patient.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Table 1: Levothyroxine\ Liothyronine combination therapy effect on quality of life (Randomized control trial)

Author	Year	Country	Methods	Follow-up	Results
Bunevicius et al.	1999	Lihuania	Thirty – three patients of chronic autoimmune thyroiditis or thyroid cancer on T4 replacement treated by near total thyroidectomy. Randomized into standard LT4 dose group or combination group LT4 with replacement of 50µg by 12.5µg LT3 aiming for LT4: LT3 ratio 5:1 or 10:1 Qol assessment tool : Short Form Health Survey (SF-36)	10 weeks (5 cross-over weeks)	Improvement in cognitive and mood as evident by several scales favouring of combination therapy
Nygaard et al.	2009	Denmark	Fifty – nine patients diagnosed with Autoimmune primary hypothyroidism on T4 replacement for ≥6 months with TSH 0.1-5.0mIU/L. Randomized into standard LT4 dose group or LT4 with replacement of 50µg by 20µg LT3 Qol assessment tool : SF-36	24 weeks (12 cross-over weeks)	Combination therapy show superiority as evident by 7 out of 11 quality of life, depression and anxiety rating scales
Appelhof et al.	2005	Netherlands	RCT included 141 patients diagnosed with autoimmune primary hypothyroidism who is on LT4 treatment for 6 months or more, a stable dose for 6 wk or more, and serum TSH levels between 0.11 and 4.0 microU/ml (mU/liter). Randomized into usual LT4 dose group or combination group aiming for LT4: LT3 ratio 5:1 or 10:1 Qol assessment tool : SF-36	15 weeks	No significant differences quality of life or cognitive tests
Walsh et al.	2003	Australia	hundred and ten Patients with primary hypothyroidism diagnosis of ≥6 mo, stable LT4 dose of ≥ 100µg in previous 2 mo, and serum TSH between 0.1 and 4.0mIU/L Randomized into standard LT4 dose group or combination group LT4 with replacement of 50µg by 10µg LT3 Qol assessment tool : SF-36	20 weeks (6 cross-over weeks)	Combined treatment does not improve cognitive function, or quality of life compared with T(4) alone.
Clyde et al.	2003	United States	Forty four Patients with primary hypothyroidism receiving stable doses of LT4 for ≥3 mo Randomized into standard LT4 dose group or combination group LT4 with replacement of 50µg by twice daily 7.5µg LT3 Qol assessment tool : hypothyroid HRQL questionnaire	4 months	No added value of combination therapy on quality of life.
Kaminski et al.	2016	Brazil	Thirty two patients diagnosed with primary hypothyroidism on standard LT4. Randomized into standard LT4 dose group or combination group 75µg of LT4 with plus 15µgof LT3 Qol assessment tool : Health Related Quality of Life (HRQOL) questionnaire	16 weeks (8 cross-over weeks)	No added value of combination therapy on quality of life.

Figure 1: Flow diagram through the different phases of the systematic review (PRISMA flowchart)