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Review Article

Evaluation of Medicinal and Medical Effects on Quality of Life in Patients with Hyperthyroidism Due to Graves´ Disease

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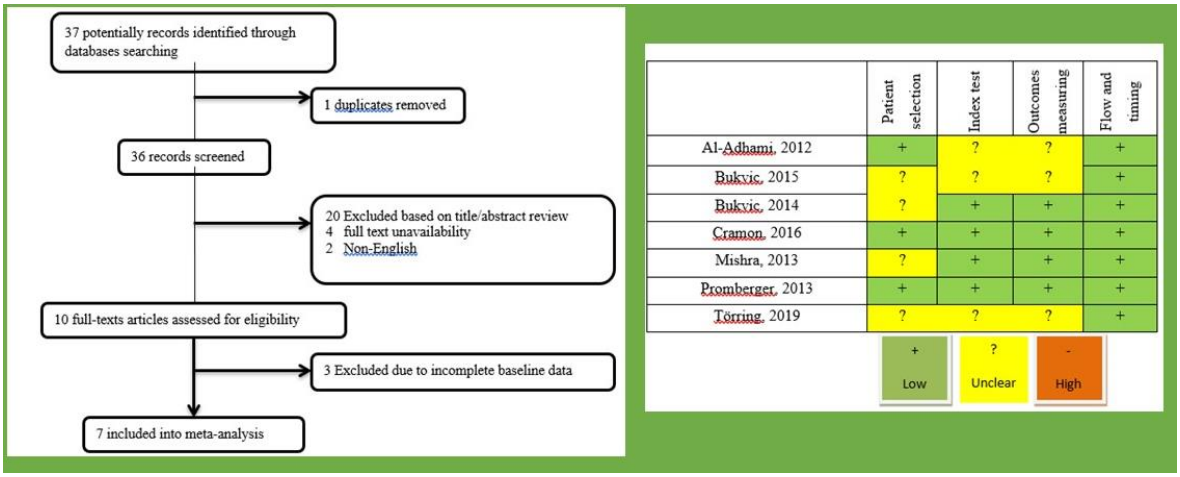
ABSTRACT

Different observational studies and randomized trials attempted to show advantages as well as limitations of surgical approaches for improvement in patients' quality of life (QOL) suffering hyperthyroidism caused by the Graves´ disease (GD). We aimed to systematically examine the impact of surgery (thyroidectomy) on different components of QOL in patients with GD. Two reviewers began to deeply search the various databases of article published including Medline, Web of knowledge, Google Scholar, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library for all eligible studies in accordance with the considered keywords. In final, seven articles were eligible for the final analysis that published between 2012 and 2019. The Comprehensive Meta-Analysis Software was employed for analysis. Assessing the level of quality of life using SF-36 tool showed significantly increase in both physical component score (weighted mean differences of 0.428, p <0.001) and psychological component score (weighted mean differences of 0.277, p <0.001) postoperatively compared with the baseline values. The assessment of QOL using the Thy PRO questionnaire also showed significantly improvement in total QOL score after surgery compared with before that (weighted mean differences of -1.466, p <0.001). We revealed considerably improving both physical and mental aspects of QOL following surgery in Graves' disease.

GRAPHICAL ABSTRACT



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Introduction

Hyperthyroidism caused by the Graves´ disease (GD) is a common abnormality with an overall incidence range of 20 to 50 per 100.000 people whole of the world [1]. Interestingly, this phenomenon has been estimated to be higher even in developed countries [2]. Pathophysiologically, secretion of antibodies against the thyroid stimulating hormone (TSH) receptors can be trigger for thyroid hyper-activating and thus raising thyroid hormones [3]. In fact, hyperthyroidism has an autoimmune fundament. Graves' hyperthyroidism is frequently manifested by systemic symptoms such as dermopathy, ophthalmopathy, and acropathy with high affinity to recurrence even after different therapeutic options [4]. More importantly, the likelihood of cardiovascular morbidity and mortality can also rise due to hyperthyroidism flare [5,6]. Therefore, it is obvious that suffering hyperthyroidism is accompanied with the potential negative impact on the different physical and psychological aspects of quality of life (QOL) [7-9]. In this regard, it is suggested that employing various treatment protocols including medical and surgical approaches can improve patients' QOL, but with the different effectiveness [10-13]. Some researchers could indicate the similarity in efficacy of anti-thyroid drugs, radioiodine, and surgery [14], but some patients do not feel complete recovering in the long run following different treatments [15-17]. Overall, it is now evidenced that the patients with hyperthyroidism due to GD or toxic nodular goiter face with poor long-term quality of life unless they are treated with the highest efficacy; however, different treatments have been also different long-term efficacy. Recently, different observational and randomized trials attempted to show advantages as well as limitations of surgical approaches for treating hyperthyroidism caused by the GD; however, there is a significant divergent in the spectra of treatment outcomes especially on long-term QOL requiring systematically assessment of the results. In total, a pertinent question now rises that whether the results from different studies are reliable in terms of the efficacy of surgical approach for improving patients' QOL [18-20].

Material and methods

We performed the present systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyze (PRISMA) statement. Two reviewers began to deeply search the various databases of article published including Medline, Web of knowledge, Google Scholar, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library for all eligible studies in accordance with the considered keywords including: "thyroid", "hyperthyroidism", "quality of life", "Graves´ disease", and "surgery" based on the Mesh vocabulary [21-23].

Disagreements were resolved through discussion and decided by a third reviewer. No limitation was considered for the country or date of papers published. All English language-based studies were included for initial assessment. In this review, all cross-sectional, case-controls and clinical trials were included and thus the abstracts with unavailable full texts, case reports or case series as well as reviews were excluded in first step [24-26].

We also tried to contact authors by letters to obtain unpublished data or full texts. The inclusion criterion for retrieved the studies was to describe the quality of life of patients with hyperthyroidism caused by the GD treated with surgical approaches (thyroidectomy). However, those manuscripts focused on the surgical procedures on the effects on other organs except for thyroid were not included in the study [27-30].

Also, we considered the studies that assessed the change in QOL status after surgery by the two common and validated questionnaires including SF-36 and ThyPRO; therefore, the studies which used other national or population-specific tools were also not included in our final analysis. In addition to patients, demographics, type of procedure, tools for measuring QOL, time for following-up, the rate of improving different components of QOL, and procedure-related

complications were all considered for the end-points. The study quality was evaluated based on the following criteria:

1) the systematic review and meta-analysis based on the questions primarily described and formulated; [31].

2) inclusion and exclusion criteria predefined in the studies as eligibility criteria; [32].

3) searching the literature performed on a systematic and comprehensive approach; [33].

4) reviewing the full texts of the article to minimize the bias; [34].

5) rating the quality of included studies independently by the reviewers for appraising internal validity; [35].

6) listing studies' characteristics and findings comprehensively; [36].

7) listing the publication and risk of bias; [37]

8) assessing heterogeneity. The risk of bias for each study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and also according to QUADAS-2 tool [38-40].

For statistical analysis, the Comprehensive Meta-Analysis Software (CMA, version 3.0) was employed [41]. We presented dichotomous data related to pooled improvement of QOL score after treatment as prevalence rate and its 95% Confidence Interval (CI) [42]. Data were assessed by both fixed effects and random effect models; however, the random effect analyses were reported if the heterogeneity was significant evaluated by the I^2 statistic. Reported values were two-tailed, and hypothesis testing results were considered statistically significant at $p = 0.05$. The publication bias was assessed by drawing the funnel plot [43-45].

Result and Dissection

The flow diagram of the study selection process is presented in Figure 1. In this context, 37 articles were initially collected by database searching. After removing 1 article due to evidence of duplication, 36 records were primarily under-screened. Based on the titles and abstracts, 26 records were excluded and the remaining 10 citations were assessed for further eligibility [46-48].

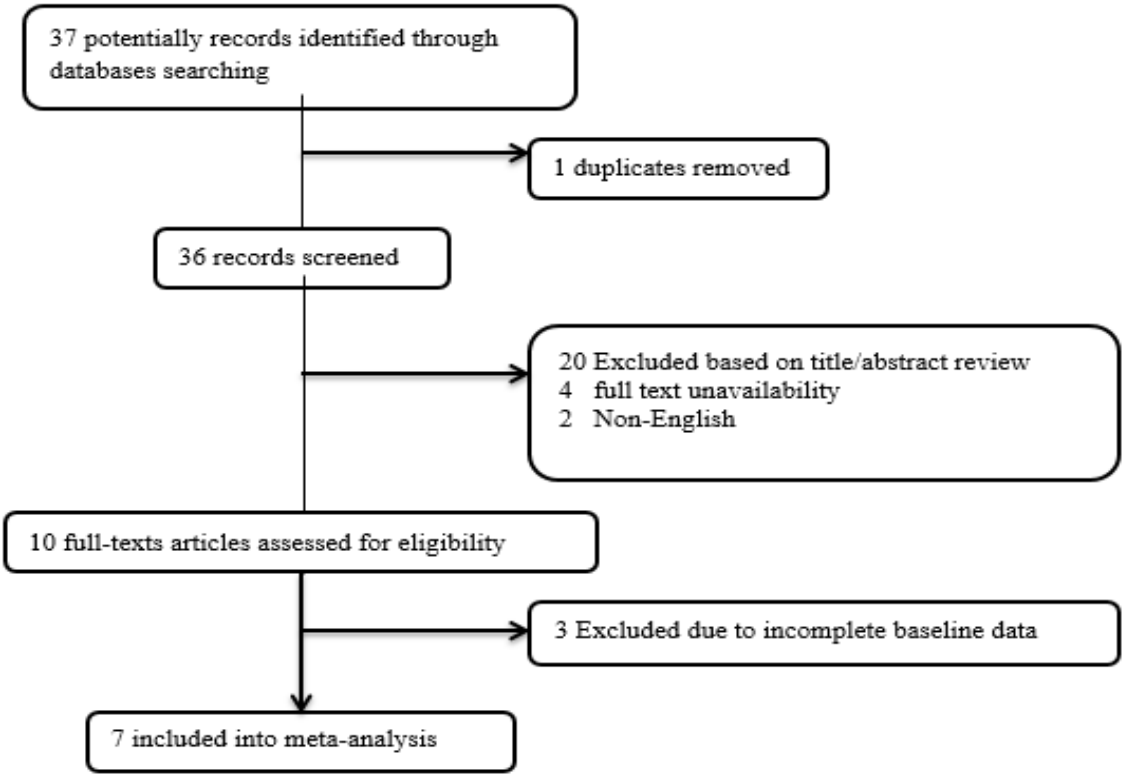


Figure 1: The flowchart of screening the eligible studies

Of those, 3 were also excluded due to incompleteness of the data and contents. Finally, 7 articles were eligible for the final analysis that published between 2012 and 2019 [49-51]. Assessment of publication and systematic bias showed that almost all studies were considered as low risk or with unclear biases and thus the obtained results could be considered valid and none of the citation was determined to have high risk of bias (Figure 2). Table 1 describes baseline characteristics of the studies included [52-55].

Table 1: Baseline characteristics in patients with Graves' disease undergoing thyroidectomy

Author, year	Type of study	No. patient	Male/female	Mean age	QOL questionnaire	Time to follow-up (month)
Al-Adhami, 2012 (11)	Cross-sectional	150	20/130	29.5	SF-36	>12
Bukvic, 2015 (12)	Case-control	31	2/29	42.9	ThyPRO	6
Bukvic, 2014 (13)	Case-control	132	20/112	52.7	ThyPRO	6
Cramon, 2016 (14)	Prospective Cohort	88	14/74	47.0	SF-36	6
Mishra, 2013 (15)	Prospective Cohort	100	19/81	40.5	ThyPRO	6
Promberger, 2013 (16)	Prospective Cohort	248	0/248	56.0	SF-36	>12
Törring, 2019 (10)	Prospective Cohort	233	34/199	35.0	ThyPRO, SF-36	>12

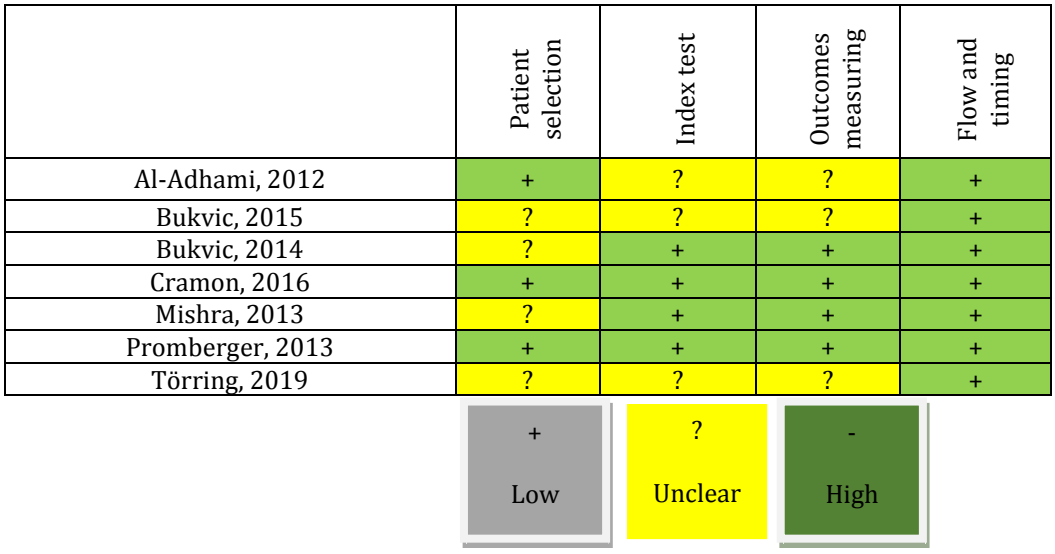


Figure 2: The Assessment of the risk of bias

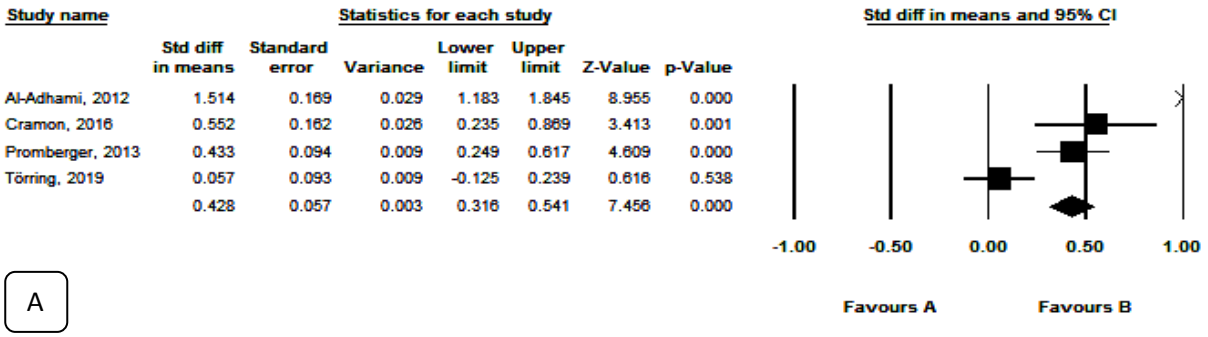
The systematic review and the meta-analysis included 7 studies (one cross-sectional, two case controls and four prospective cohort studies) with overall 982 patients with Graves' disease that candidate for subtotal and/or total thyroidectomy. In the studies assessed, two SF-36 and/or ThyPRO questionnaires were employed for assessment of quality of life preoperatively and postoperatively with a wide follow-up time 6 months to 14.3 years [56-59].

In one study, the patients were assessed by the two questionnaires. The SF-36 questionnaire assesses the quality of life in eight components of physical functioning, physical role, pain, general health, vitality, social function, emotional role, and mental health and two mental and physical total quality of life scores, while ThyPRO questionnaire evaluate eight domains with the different approaches including cognition impairment, anxiety, depressivity, emotion suscept, social impact, daily impact, sex life, and

cosmetic complaints leading a total QOL score. Assessing the level of quality of life using SF-36 tool (Table 2) showed significantly increase in all QOL components scores and ultimately in both physical component score (weighted mean differences of 0.428, 95%CI: 0.316 to 0.541, p <0.001) (Figure 3) and psychological component score (weighted mean differences of 0.277, 95%CI: 0.166 to 0.369, p <0.001) postoperatively as compared with the baseline values [60-63].

Table 2: The change in quality-of-life components following surgery according to SF-36 questionnaire

Author, year	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
Al-Adhami, 2012 (11)	83.1±21.7 90.0±22.2	81.2±26.6 93.8±25.4	68.2±26.2 73.0±27.1	60.9@25.4 62.0±26.4	48.8±24.5 56.3±25.5	74.4±26.4 87.5±27.4	78.2±24.8 91.7±25.6	65.5±20.8 75.0±22.8	46.6±21.1 79.7±22.6	43.7±19.8 77.6±21.3
Cramon, 2016 (14)	43.0±11.0 50.0±9.0	40.0±12.0 47.0±10.0	50.0±13.0 54.0±9.0	45.0±10.0 48.0±9.0	38.0±10.0 49.0±13.0	44.0±13.0 50.0±10.0	42.0±13.0 46.0±13.0	40.0±12.0 49.0±11.0	46.0±10.0 51.0±8.0	40.0±12.0 48.0±13.0
Promberger, 2013 (16)	62.0±15.0 72.0±15.0	85.0±22.0 90.0±23.0	75.0±18.0 75.0±17.0	80.0±22.0 100	55.0±15.0 57.5±15.0	87.5±23.0 87.5±23.0	100 100	68.0±17.0 68.0±18.0	75.5±20.4 84.5±21.2	77.6±21.5 78.2±23.4
Törring, 2019 (10)	85.0±17.0 87.0±19.0	79.0±28.0 82.0±26.0	74.0±22.0 81.0±18.0	68.0±18.0 69.0±14.0	57.0±15.0 57.0±14.0	83.0±19.0 90.0±14.0	76.0±31.0 76.0±29.0	67.0±13.0 70.0±19.0	50.0±18.0 51.0±17.0	47.0±18.0 48.0±18.0



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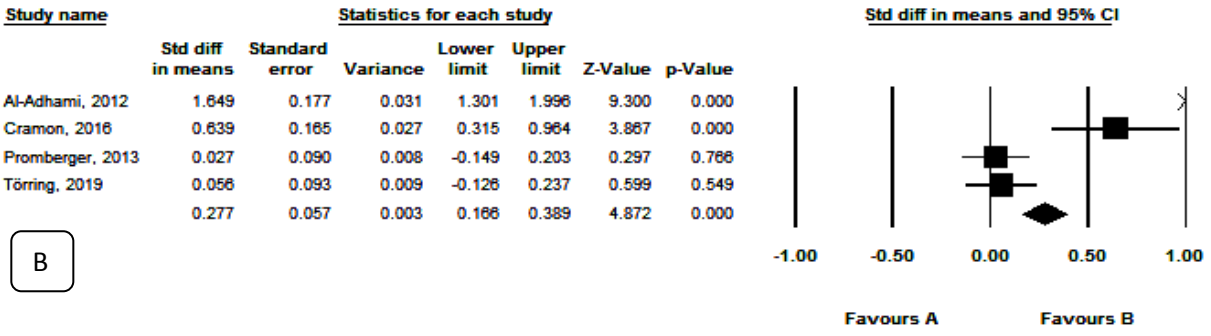

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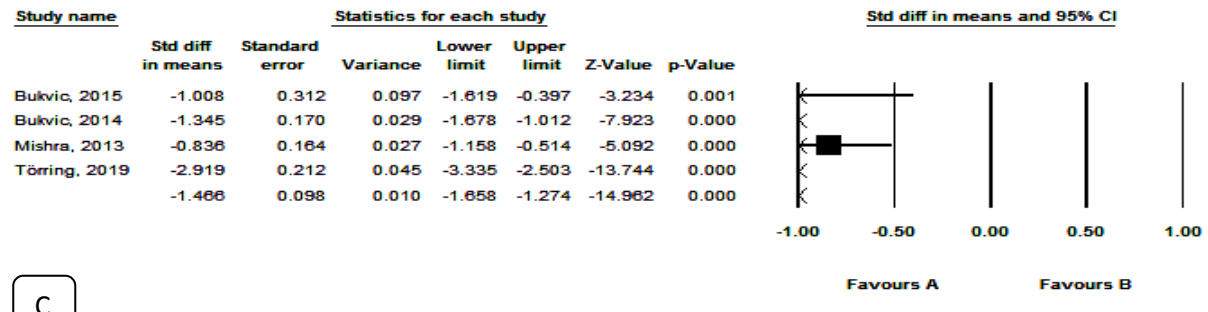

C

Figure 3: The pooled effects of surgery on different QOL components assessed by SF-36 (A and B) or ThyPRO (C) questionnaires

The assessment of QOL using the ThyPRO questionnaire (Table 3) also showed significantly improvement in total QOL score after surgery as compared with before that (weighted mean differences of -1.466, 95%CI: -1.658 to -1.274, p <0.001) [64-67].

Table 3: The change in quality-of-life components following surgery according to ThyPRO questionnaire

Author, year	CI	Anxiety	Depression	Emotional	Social	Daily life	Sexual	Cosmetic	Total
Bukvic, 2015 (12)	13.2±18.1 9.4±14.3	38.4±24.4 16.8±12.2	35.1±25.9 19.1±12.7	34.7±22.5 16.2±12.4	14.3±25.0 7.5±15.0	25.9±26.9 6.0±10.5	31.0±31.8 9.7±12.8	26.1±24.6 5.2±12.0	43.5±35.3 14.5±20.2
Bukvic, 2014 (13)	14.3±17.8 10.3±13.8	24.9±20.9 10.9±16.5	26.7±19.4 15.4±12.2	23.6±19.2 10.1±9.5	8.8±13.8 4.0±7.6	16.6±19.2 7.3±11.7	16.2±29.2 5.3±16.2	11.1±14.3 1.5±4.1	35.2±30.4 4.0±12.3
Mishra, 2013 (15)	25.7±26.7 1.5 ± 3.5	29.6 ± 28.6 1.8 ± 4.6	33.9 ± 21.2 1.3 ± 2.7	34.9 ± 21.2 0.8 ± 1.9	15.4 ± 19.5 1.4 ± 36	18.7 ± 22.5 1.3 ± 3.6	20.9 ± 27.6 1.7 ± 5.8	14.7 ± 15.1 1.0 ± 2.9	27.0 ± 32.6 5.5 ± 16.1
Törring, 2019 (10)	19.0±1.6 17.0±3.6	24.0±1.6 21.0±3.5	18.0±1.7 16.0±3.7	25.0±1.6 20.0±3.6	9.0±1.3 4.0±2.7	9.0±1.4 5.0±3.2	19.0±2.4 16.0±5.2	19.0±2.4 13.0±3.1	19.0±2.2 13.0±1.9

The heterogeneity across the studies in all measurements was significantly relevant with the I^2 values ranging 94.815 to 96.162 with the p values of less than 0.001 for all. The Egger test also detected a significant publication bias for all assessments (Figure 4) [68-71].

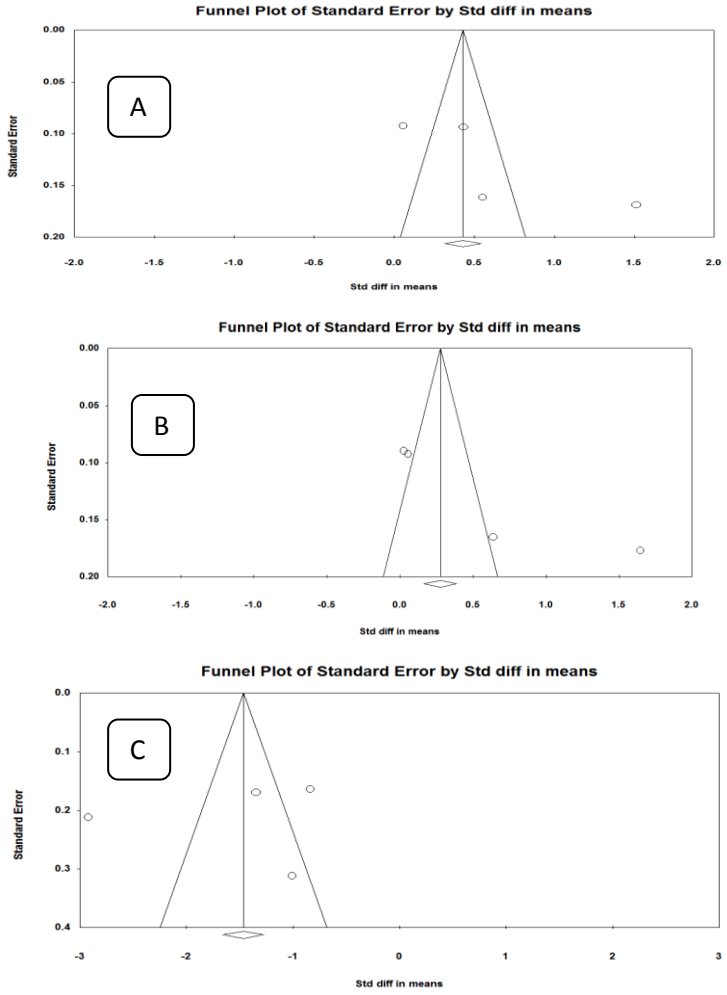

Figure 4: The publication bias across the studies assessed by SF-36 (A and B) or Thy PRO (C) questionnaires

Conclusion

Graves' disease is the main etiology for hyperthyroidism and thyrotoxicosis with a prominent superiority in women than in men and with the age peak of 40 to 60 years. This phenomenon is mainly characterized by goiter, hyperthyroidism and some non-thyroidal manifestations and sequels such as dermopathy, ophthalmopathy, and even gradually disfiguring. Along with its systemic and metabolic related disturbances, the affects patients may face with psychological impairments such as depression, anxiety, hostility, unhappiness, panic episodes, isolations, and social disturbances. Thus, impairment of different components of QOL in patients without appropriate treatment approach can be highly disturbed even for a long time. As another important point, there are some strong pieces of evidence on the effectiveness of different therapeutic options (as medical or surgical) on improvement of both physical and psychological disabilities in such patients; however, it seems that surgical approaches may have higher efficacy in improving patients' disabilities. In some studies, it has been found that surgical approaches in patients suffering Graves' disease can lead to general improvement in about 69% to 75%. However, due to the differences in studies design, divergent samples sizes, different tools employed, and in inclusion criteria, different results on the improvement of QOL domains following surgery is expected. Surprisingly, systematically reviewing the literature could effectively show significant improvement in all components of QOL following thyroidectomy measuring either by SF-36 or Thy PRO questionnaires. However, despite powerful significant difference in QOL after surgery as compared with before that, the results were accompanied by a significant heterogeneity due to different suggested reasons. First, the details of surgical techniques (total or subtotal thyroidectomy concomitant with other interventions) have not been described and their effects on the study outcomes have not been detailed as main confounders. Second, the different designing the studies as cross-sectional, prospective or retrospective could powerfully affect QOL measurements. Moreover, the difference in study sample sizes (ranged from 31 to 248) along with the different follow-up time (widely ranged from 6 months to higher than 14 years) could also affect the scores of QOL assessed. However, besides the pointed heterogeneity, we revealed considerably improving both physical and mental aspects of QOL following surgery in Graves' disease regardless of the baseline characteristics.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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