INPLASY PROTOCOL

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None declared.

Effect of hyperthyroidism treatments on heart rate variability: A systematic review and meta-analysis

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Review question / Objective: **The reversibility of HRV abnormalities in hyperthyroidism remains contradictory. The purpose of the study is to conduct a systematic review and meta-analysis on the effect of antithyroid treatments on HRV in hyperthyroidism. Population: Untreated hyperthyroid patients Intervention: Antithyroid treatment Control: Controls without hyperthyroidism Outcomes: Reversibility of heart rate variability abnormalities in hyperthyroidism Study design: Systematic review.**
Information sources: **All studies that addressed the effect of hyperthyroidism treatment on HRV were reviewed. Studies were searched electronically through the major article databases (PubMed, Cochrane Library, Embase, and Google Scholar) with the following keywords: ("hyperthyroidism" OR "hyperthyroid") AND ("heart rate variability" OR "HRV") until April 4, 2022.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 August 2022 and was last updated on 16 August 2022 (registration number INPLASY202280062).

INTRODUCTION

Review question / Objective: **The reversibility of HRV abnormalities in hyperthyroidism remains contradictory. The purpose of the study is to conduct a systematic review and meta-analysis on the effect of antithyroid treatments on HRV in hyperthyroidism. Population: Untreated hyperthyroid patients Intervention: Antithyroid treatment Control: Controls without hyperthyroidism Outcomes: Reversibility of heart rate variability abnormalities in hyperthyroidism Study design: Systematic review.**

Rationale: **The reversibility of HRV abnormalities after treatment of**

hyperthyroidism has been extensively studied in the literature. However, the results of the different studies are contradictory. We have therefore performed this meta-analysis on the effect of antithyroid treatments on HRV in hyperthyroidism. The results will allow us to conclude on various clinical situations. For example, we will be able to judge the necessity of treating subclinical hyperthyroidism in case of reversibility of HRV anomalies.

Condition being studied: Hyperthyroidism affects 0.6% people world wide with two biochemical entities, overt and subclinical hyperthyroidism. It results from excessive and inappropriate production of thyroid hormones and is characterised by a hyperkinetic state. One of the main complications of hyperthyroidism is cardiac arrhythmia, most often supraventricular. It remains accepted that overt hyperthyroidism must be treated, due to its many complications. The indication to treat subclinical hyperthyroidism remains controversial. Subclinical hyperthyroidism is a risk factor for atrial fibrillation in the elderly and is associated with excess cardiac mortality. Cardiovascular complications of hyperthyroidism may be linked with sympathovagal imbalance. Heart rate variability (HRV) – the change between two consecutive heartbeats – is a sensitive, quantitative and non-invasive tool for detecting cardiac sympathetic and parasympathetic activity. Hyperthyroidism has been associated to a reduced HRV, with increased sympathetic activity and decreased parasympathetic activity. Reduced HRV is most commonly associated with a risk of arrhythmic death and is an independent predictor of cardiac morbidity and mortality. Although the evaluation of antithyroid treatment on HRV parameters in hyperthyroidism has been assessed in several studies, results remain contradictory on the complete reversibility of sympathetic and parasympathetic disturbances, especially in subclinical hyperthyroidism. Synthetic antithyroid drugs are the first-line treatment for Graves' disease in Europe, while radioactive iodine and surgery are more popular in the US. For nodular disease, radioactive iodine and surgery remain the first-line treatments. Few studies have comprehensively evaluated the role of the most common variables, such as sociodemographic, clinical features or biochemical parameters of thyroid function on the effect of antithyroid treatment on HRV parameters. Therefore, we aimed to conduct a systematic review and meta-analysis of the impact of antithyroid treatment of overt or subclinical hyperthyroidism on HRV parameters. A secondary objective was to identify the most frequently reported explanatory variables.

METHODS

Search strategy: PubMed, Cochrane, Embase and Google Scholar were searched until April 4, 2022.

Participant or population: Untreated hyperthyroid patients.

Intervention: Antithyroid treatment.

Comparator: Controls without hyperthyroidism.

Study designs to be included: Any design of studies.

Eligibility criteria: The main exclusion criteria were pregnancy, severe graves' ophtalmopathy, chronic heart, liver or renal failure, use of any chronic treatment or influencing HRV parameters, hyperthyroid heart disease, thyroid cancer, diabetes mellitus, hypertension, cardiac arrhythmia and smokers.

Information sources: All studies that addressed the effect of hyperthyroidism treatment on HRV were reviewed. Studies were searched electronically through the major article databases (PubMed, Cochrane Library, Embase, and Google Scholar) with the following keywords: ("hyperthyroidism" OR "hyperthyroid") AND ("heart rate variability" OR "HRV") until April 4, 2022.

Main outcome(s): An initial search produced 638 possible articles. The number of articles reporting the effect of antithyroid therapy on HRV in untreated hyperthyroidism was reduced to 11 articles after using the selection criteria and removing duplicates. In comparison to untreated patients, we noted strong evidence (p <0.01) that treated patients had significantly higher RR intervals (ES = 4.04, 95% CI 2.06 to 6.02), SDNN (3.72, 1.45 to 5.98), RMSSD (1.06, 0.38 to 1.74), pNN50 (1.66, 0.55 to 2.76), TP (2.41, 1.32 to 3.5), LF power (1.93, 0.92 to 2.94), HF power (2.41, 1.5 to 3.32), HFnu (4.55, 2.26 to 6.83) and VLF power (4.00, 1.52 to 6.48) and lower LFnu (-3.11, -4.98 to -1.25) and LF/HF ratio (-3.44, -5.28 to -1.60). Some HRV abnormalities persist in treated hyperthyroid patients (p <0.05) with lower SDNN (-1.39, -2.13 to -0.64), LFnu (-0.91, -1.8 to -0.01) and higher HFnu (0.95, 0.04 to 1.87), without significant difference in other parameters (RR intervals, RMSSD, pNN50, TP, LF, HF, VLF and LF/HF).

Additional outcome(s): In comparison to untreated patients, the following HRV parameters were increased in both overt treated hyperthyroidism and subclinical treated hyperthyroidism, respectively: RR intervals (ES = 4.95, 95% CI 2.61 to 7.29 and 0.62, 0.17 to 1.07) and pNN50 (1.22, 0.19 to 2.24 and 3.07, 2.29 to 3.85) (p <0.05). Some HRV parameters were only modified in treated overt hyperthyroidism: higher SDNN (5.37, 2.44 to 8.31) and RMSSD (1.46, 0.37 to 2.54) than untreated patients (p 90%), except for parameters explored by few studies in subclinical hyperthyroidism (RR intervals, pNN50). None of the clinical parameters (age, BMI, blood pressure, statue of hyperthyroidism, duration of treatment) and biological parameters (TSH, fT4, fT3) were associated with a significant increase or decrease in time- or frequency-domain HRV parameters. The most severe patients tended to have lower RR-intervals improvement following treatment than subclinical patients (p=0.10).

Quality assessment / Risk of bias analysis: We used the Scottish Intercollegiate Guidelines Network (SIGN) criteria to check the quality of included articles with the dedicated evaluation grids. For cohort and cross-sectional studies, checklists are composed in two sections: design of the study (14 items), and overall evaluation (3 items). For clinical trials, checklists consist of 10 items if randomized and 7 items if non-randomized, based on the main causes of bias. There were 4 possibilities of answers (yes, no, can't say or not applicable) (Figure S2 and S3). We also used the "STrengthening the Reporting of OBservational studies in Epidemiology" (STROBE – 32 items/subitems) for cohort and cross-sectional studies and the Consolidated Standards of Reporting Trials (CONSORT – 37 items/subitems) for randomized trials. One point was assigned to each item or subitem, to achieve a maximal score of 32 or 37, respectively, then converted into percentage.

Strategy of data synthesis: We used Stata software (v16, StataCorp, College Station, US) for the statistical analysis. Main characteristics were synthetized for each study population and reported as mean ± standard deviation (SD) for continuous variables and number (%) for categorical variables. When data could be pooled, we conducted random effects meta-analyses (DerSimonian and Laird approach) for each HRV parameter comparing treated with untreated hyperthyroid patients. A positive effect size (ES, standardised mean differences - SMD) denoted higher HRV in treated patients than in untreated. An ES is a unitless measure, centered at zero if the HRV parameter did not differ between untreated and treated patients. An ES of 0.8 reflects a large effect i.e. a large HRV increase in treated compared to untreated patients, 0.5 a moderate effect, and 0.2 a small effect.

Subgroup analysis: We conducted meta-analyses stratified on biochemical status of hyperthyroidism, i.e. subclinical or overt.

Sensitivity analysis: We evaluated heterogeneity in the study results by examining forest plots, confidence intervals (CI) and I-squared (I2). I2 is the most common metric to measure

heterogeneity between studies, ranging from 0 to 100%. Heterogeneity is considered low for I2<25%, modest for 25<I250%. We also searched for potential publication bias by examining funnel plots of these meta-analyses. We verified the strength of our results by conducting further meta-analyses after exclusion of studies that were not evenly distributed around the base of the funnel.

Language restriction: English.

Country(ies) involved: France, Iran, UK.

Keywords: thyroid; biomarker; autonomic nervous activity; prevention; public health; antithyroid treatment.

Contributions of each author:

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