Background: Venous thromboembolism (VTE) that have significant morbidity and mortality for patients in the community and hospital. A recent meta-analysis found a significantly increased risk of incidence VTE among patients with hyperthyroidism compared to patients without hyperthyroidism. To our knowledge, no study has attempted to explore whether screening for TSH levels in VTE patients leads to a diagnosis of undiagnosed thyroid dysfunction as VTE could be the first presenting symptom. **Method:** We conducted a retrospective cohort study and analyzed data of all patients treated at University Medical Center, Lubbock, Texas in 18-85 years of age with a diagnosis of DVT and/or PE in 2019. Qualitative chart review to identify cases of clinically significant TSH screening in VTE patients that leads to thyroid dysfunction diagnosis. Associations between variables tested using Student's t-test, chi-square, and Fisher's exact test. **Results:** Of total of 533 participants with diagnosis of VTE in 2019, 85 participants were included in the study. Seven participants (8.24%) were found to have high TSH level (>4.2 mIU/mL). None of them was found to have low level of TSH. Participants in high TSH group were more likely to be female (71.43%) and Caucasian (71.43%). In high TSH group patients tended to have both PE and DVT diagnosis at the same admission (71.43%). Weight and BMI were significance higher than those with normal TSH level. Segna et al conducted a prospective multicenter cohort study on association between thyroid dysfunction and venous thromboembolism. The study measure thyroid hormones and thrombophilic biomarkers at 1 year after the acute VTE and follow for the recurrent VTE (rVTE). They found that after 20.8 months of follow-up, 9% developed rVTE. However, none of them was found in subclinical hyperthyroidism group. Furthermore, in their multi-variate analyses, the hazard ratio for rVTE was 0.80 (95%CI 0.23-2.81) subclinical hyperthyroidism compared with euthyroid participants. They concluded that subclinical hyperthyroidism may be associated with lower rVTE risks. Similarly, with Liviu study found hyperthyroidism was not associated with an increased risk of VTE. Qualitative chart review in our patients with high TSH resulted that none of them had history of tobacco use. One participant was on birth control pills with the history of cervical carcinoma. **Conclusion:**The association of thyroid dysfunction and the development of VTE is debated on the literature review. In our study we found multiple patients with high TSH level (8.24%) in VTE patients with no prior history of thyroid dysfunction. TSH could play an important role in hypercoagulable state. Subclinical hypothyroidism and/or hypothyroidism may induce a prothrombotic event. However, larger cohort studies with higher prevalence of high TSH participants are needed to prove a relationship between TSH level and VTE events.

Thyroid

FROM HYPO- TO HYPERTHYROIDISM

Daily Versus Weekly Levothyroxine Tablet Replacement in Adults With Hypothyroidism: A Meta-Analysis

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Background and Objectives: Hypothyroidism is a common hormone deficiency with a prevalence ranging from 4-5% worldwide. It is a very treatable condition with treatment in the form of thyroid hormone replacement, with an overall excellent prognosis if patients are compliant to regular treatment. Daily levothyroxine (LT4) is the treatment of choice and standard of care, sufficient to restore the thyroid stimulating hormone (TSH) to the normal range. For many patients, daily and lifelong therapy is required, and compliance/adherence then becomes a major issue. In such cases, weekly replacement may be a suitable alternative in terms of improving patient compliance. In this study, we aimed to determine the efficacy and safety of weekly versus daily levothyroxine replacement in patients with hypothyroidism.

Methods: Electronic databases were searched, supplemented with manual searches. Two reviewers independently screened the abstracts, reviewed full-text papers, independently critically appraised the quality of included studies and abstracted the data. A meta-analysis was performed using the random-effects model on randomized controlled trials (RCTs) that reported standard doses of daily versus weekly levothyroxine administration in the treatment of hypothyroidism. The primary outcome is the difference in serum TSH levels between daily versus weekly levothyroxine administration, while secondary outcomes included clinical symptoms and adverse events using the hypothyroidism symptom scale.

Results: The study included two randomized trials (N = 109) in the primary analysis. The difference in TSH levels was 1.78 mIU/mL higher (95% CI: 1.28, 2.28; $P < 0.00001$) at 6 weeks and 1.22 mIU/mL higher (95% CI: 0.76,1.67; $P < 0.00001$) at 12 weeks for the weekly replacement regimen, respectively. There was no significant heterogeneity noted between the two groups. There was no significant difference in terms hyperthyroid symptoms and adverse events measured by the hypothyroid symptom scales and echocardiographic parameters, respectively, before and after LT4 within each group.

Conclusions: Our results showed that weekly LT4 administration has less suppression of TSH levels, while still remaining within the reference range of normal. It may be an alternative for patients especially in setting of noncompliance. However, more randomized trials with larger sample sizes and a longer duration of follow-up are needed to firmly establish the definite role of weekly LT4.

Thyroid

FROM HYPO- TO HYPERTHYROIDISM

Desiccated Thyroid Extract Versus Synthetic LT4/T3 Combination Versus LT4 Monotherapy in the Treatment of Primary Hypothyroidism With Special Attention to the Thr92AlaD2 Polymorphism. With Special Attention to the Gene Polymorphism

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Introduction: Before the availability of levothyroxine (LT4), patients were treated with desiccated thyroid extract (DTE). When switching from DTE to LT4, despite adequate dosing based on serum TSH levels, some patients still feel unwell with fatigue, mental fogginess, weight gain etc. A recent randomized, crossed over study between DTE vs. LT4 conducted in our department showed that once-daily DTE caused modest weight loss and possible improvement in mental health scores without appreciable adverse effects; also, nearly half of the study patients preferred DTE over LT4. A few studies have shown that LT4/T3 combination had beneficial effects in improving quality of life relative to LT4 alone. Furthermore, it has been reported that patients with CC genotype in the deiodinase type 2 polymorphism responded more favorably with LT4/T3 combination than T4 monotherapy. **Hypothesis**: This study investigated the efficacy and effectiveness of DTE vs. LT4/T3 combination vs. LT4 monotherapy in hypothyroid patients based on genotypic differences of deiodinase type 2.
Methodology: This was a prospective, randomized, double-blind, crossover study. 75 subjects completed the study. There were 3 arms: DTE, LT4+T3 combination, and LT4 alone. Each subject was randomly allocated to one of these 3 arms for 12 weeks randomly. The study was powered to detect the primary outcome. The primary endpoint was post-treatment score on the 36-point thyroid symptom questionnaire. Secondary endpoints were weight, general health questionnaire, the Beck depression inventory, Wechsler Memory testing, lipid panels and thyroid function tests. Analysis was performed with a linear mixed model using subject as a random factor and group as a fixed effect.
Results: There was no significant difference between the 3 arms on the thyroid symptom questionnaire (p=.32), and the secondary outcomes showed no between group differences. Auditory memory index (p=.008), and visual working memory index (p=.02) were higher in the Hashimoto's than non-Hashimoto's group. There was no significant primary or secondary outcome difference among various genotypes of deiodinase 2. There was no relationship between Hashimoto's vs. non-Hashimoto's based on genotypes or likelihood of carrying Thr92AlaD2 polymorphism. Though there was no statistically significant preference for any treatment, numerically more patients with Hashimoto's preferred DTE and LT4/T3 combination than LT4-monotherapy.
Conclusions: There was no significant difference between hypothyroid patients taking DTE vs. LT4/T3 combination vs. LT4 monotherapy. Numerically, Hashimoto's patients tended to prefer DTE and LT4/T3 combination. Also, there was no observed relationship between Hashimoto's and polymorphism. Further studies with more patients may be needed.

Thyroid
FROM HYPO- TO HYPERTHYROIDISM

Development of High-Throughput Measurement of Free Thyroxine in Serum Using Equilibrium Dialysis in Couple With Liquid Chromatography-Tandem Mass Spectrometry

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Free thyroxine (FT4) measurements are critical in the diagnosis, classification, and treatment of thyroid diseases. It is estimated that about 18 million FT4 tests are requested in the USA per year annually. In clinical laboratories, most of FT4 assays are performed by using immunoassays (I As). However, the significant bias of IAs and large variation between laboratories have been reported. The reference measurement procedures (RMPs) of FT4based on equilibrium dialysis (ED) - liquid chromatography-tandem mass spectrometry (LC-MS/MS) have been established and recognized by the clinical chemistry community. However, the FT4 RMP is relatively low throughput and labor-intensive. Also, an aliquot of 1 mL sample is required for an RMP. A routine FT4 assay high-throughput procedure that is based on ED LC-MS/MS and utilized less sample volume will allow to conduct large biomonitoring studies and establish FT4 levels in US population. In the described method, FT4 in 150 uL of serum was separated from protein-bound T4 at 37.0 ºC in 96-well Micro-ED Teflon devices from HTDialysis. The ED conditions suggested by CLSI C45-A guideline were followed. A volume of 150 uL dialysate samples with FT4 was obtained after the ED step. FT4 in the dialysate was purified by extractions before LC-MS/MS analysis. Chromatographic separation of T4 from the sample matrix is achieved on a C18 UPLC column with a gradient of methanol and water with 0.1% formic acid. Quantification of FT4 was performed by using selective reaction monitoring in positive electrospray ionization mode. The IRMM-468 certified primary reference material (JRC, Belgium) of T4 is used for the calibration curves. FT4 concentrations reached equilibrium after 4 hours under current dialysis conditions, which was also observed in the RMP setting. The developed routine FT4 assay 96-well ED system is within 5% bias from the FT4 RMP based on preliminary method comparison study using human serum. The studies to further characterize the FT4 routine method performance are ongoing. In summary, we are developing an analytical method based on a 96-well ED-LC-MS/MS system for the measurements of FT4 in serum. By comparison with RMP, the described method significantly improve throughput and reduce sample volume, which will fulfill the requirement of FT4 routine assay in clinical laboratories and allow for its use in the large biomonitoring studies and other activities in the research and public health settings.

Thyroid
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