

The effects of subclinical hypothyroidism on warfarin dosage

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BACKGROUND: Many patients using warfarin may be at risk of international normalized ratio fluctuations. This may cause severe massive gastrointestinal or cerebral bleeding. Subclinical hypothyroidism in our population is highly prevalent (range from 3.1% to 8.4% for males and females respectively). Overt hypothyroidism diminishes the effect of warfarin but there is a lack of results on the effects of subclinical hypothyroidism on warfarin dosage. **METHODS:** In this clinical trial, 102 patients using warfarin were checked for TSH, and if the result was abnormal, Serum TSH, T4, T3, and T3RU concentration were assayed again. Mean weekly dosage of warfarin and frequency of its fluctuations were compared 2 months before, 2 months after and also during the treatment period of hypothyroidism. The INR is obtained weekly, to verify dosing within range by stability of the INR. Duration of hypothyroidism treatment was about 3 months. **RESULTS:** Seventeen (16.6%) patients had thyroid diseases, 15 patients of them (88%) had subclinical hypothyroidism. Weekly dosage of warfarin for the subclinical hypothyroidism state was 33 ± 15 mg (mean \pm SD). The weekly dosage of warfarin during the treatment period of hypothyroidism was 30 ± 13 mg. Mean warfarin dosage 2 months after treatment was 29 ± 11 mg. There was a significant difference between warfarin dosage before and after hypothyroid treatment ($p < 0.05$). There was a significant decrease in INR fluctuation after treatment of hypothyroidism ($p < 0.05$). **CONCLUSIONS:** Since fluctuations of INR may be very harmful especially in the elderly population, carefully selected patients using warfarin with labile INR, can gain from concomitant therapy for subclinical hypothyroidism.

KEYWORDS: Subclinical Hypothyroidism, Anticoagulation, Warfarin, Adult

BACKGROUND

Many patients using vitamin K antagonists may be at risk of international normalized ratio (INR) fluctuations during their life.^[1] Thyroid disorders are prevalent in patients on warfarin therapy due to atrial fibrillation or drug induced dysfunctions, such as amiodarone, hypothyroidism, or thyrotoxicosis.^[2]

The prevalence of subclinical hypothyroidism in the adult population is about 4% to 8.5% in those without known thyroid disease and may be doubled in elder women.^[3] Subclinical hypothyroidism is more frequently seen in patients with iodine sufficiency, (4.2% in iodine-deficiency vs. 23.9% in abundant iodine intake.^[4] Subclinical hypothyroidism has no or few mild symptoms, and it usually cannot be recognized without thyroid hormone measurement.^[3] It might be a risk factor for cardiovascular diseases including hypertension, endothelial dysfunction, and elevated concentrations of low-density lipoprotein cholesterol. Furthermore, new researches suggest that eventually this situation (at a rate of 2-5% per year) may progress to symptomatic overt hypothyroidism.^[5]

Warfarin dosage alternation by overt thyroid dysfunction has been evaluated.

Overt hypothyroidism diminished the effect of warfarin.^[2] Unlike hyperthyroidism, there is no trial study regarding the impact of hypothyroidism especially its subclinical form on systemic anticoagulation with vitamin K antagonists (VKA).^[6]

At present, there are no universally accepted recommendations for the management of Subclinical hypothyroidism, but the most recently published guidelines do not recommend routine treatment when thyroid stimulating hormone (TSH) levels are below 10 mU/L.^[7] Replacement therapy with levothyroxine may improve cardiovascular function and may reverse the cardiovascular risk factors associated with Subclinical hypothyroidism.^[4] However, as excessive treatment is avoided, there is no risk in correcting a slightly increased TSH. Moreover, there is a risk that patients will progress to overt hypothyroidism, particularly when the TSH level is elevated and thyroid peroxidase antibodies (TPO) are present. Treatment is administered by starting with a low dose of levothyroxine.^[7]

Levothyroxine may increase the metabolism of coagulation factors, reducing the amount of warfarin required.^[8] During the treatment with warfarin many older patients, who have frequent episodes of INR fluctuations need to be more closely followed

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and may be at risk of more serious side effects.

The aim of this study was to investigate the effect of subclinical hypothyroidism on warfarin dosage and regulate the therapy with warfarin in order to ensure a sufficient anticoagulation.

METHODS

In a clinical trial, we evaluated one group of subclinical hypothyroidism patients, who had used warfarin before the study, and checked their INR level. Meanwhile, mean weekly dosage of warfarin was compared 2 months before and 2 months after resolving of hypothyroidism, and during the treatment period.

All patients who referred to the Anticoagulation Clinic of the Alzahra Hospital, Isfahan Department of Internal Medicine, Isfahan, Iran, from November 2010 to December 2011 and were treated with oral VKA (warfarin) were eligible. Before beginning of data collection, one physician thoroughly explained the aim and procedure of the study to the subjects and sought their consent. Clinical examination included height and body weight measurements, and body mass index (BMI) which was calculated as weight (kilograms) divided by height (meters) squared (kg/m^2). Blood pressure was taken after 5 minutes in a resting position. Complete medical histories, including history of bleeding and smoking habits, were recorded. Overnight fasting blood samples were collected from all subjects. Serum specimens were stored at -18°C until tested for TSH concentration.

Subjects with abnormal TSH on their first visit considered entering this study and if they had no overt hypothyroid symptoms, then their TSH, Thyroxine (T_4), Triiodothyronine (T_3), and T_3 resin uptake (T_3RU) concentration were repeated after 3 months. Free T_4 index normal range (FT4I) was estimated by T_3RU^* and T_4 . Subclinical hypothyroidism is described as increased serum TSH concentration in the presence of normal serum Free T_4 .

Serum TSH, T_4 , T_3 , and T_3RU concentrations were assayed by immunoradiometric assay (Kavoshyar, Co., Tehran, Iran). In all assays, the inter- and intra-assay coefficients of variation were below 12% and 10%, respectively. The reference ranges for euthyroid subjects were: TSH of 0.4–5.2 mU/l; T_4 concentration of 4.5 – 12.0 $\mu\text{g}/\text{dL}$, T_3 concentration of 80 – 190 ng/dL, and T_3RU concentration of 25–35%. Moreover, free T_4 index normal range (FT4I) normal range was 1.2–4.9 $\mu\text{g}/\text{dL}$.^[9]

In order to ruled out malabsorption of levothyroxine due to concurrent administration with binding substances, with food, celiac sprue, and short bowel syndrome, regional enteritis, liver disease, or pancreatic exocrine insufficiency, one physician reviewed past medical records separately. Furthermore, all patients using phenothiazines and atypical antipsychotics were excluded from study.

Warfarin sensitivity was estimated by mean weekly dosage in mg.

Then, The INR is obtained weekly for 1 to 2 weeks or more, to verify dosing by stability of the INR within range. Testing is then obtained once every two weeks. If the INR remains stable within the therapeutic range (target INR; 2.5 ± 0.5) and all else remains constant, the duration between tests can be extended to no less than 3 weeks.

The patients' INR was assessed for 3 subsequent months (during treatment of hypothyroidism), until it was in therapeutic range. This three-month phase was arbitrarily selected to ensure the effective therapy of subclinical hypothyroidism. The intra-assay and inter-assay coefficients of variation for PT and INR were 3.4% and 4.6%, respectively.

All patients gave informed consents before participating in the study. After documented subclinical hypothyroidism, 25-50 μg levothyroxine was prescribed in addition to daily warfarin. Levothyroxine treatment was started in all patients and the drug dosage was titrated individually until euthyroidism was obtained. Substitutive doses ranged from 50 to 100 μg daily with a median dose of 50 μg . Weekly warfarin monitoring by INR was done until it was in the therapeutic range and thereafter it was checked every 3 weeks. Patients reported all of their supplementary drugs and food. Moreover, patients were educated not to use Foods such as: broccoli, Brussels sprout, cabbage, collard greens, raw endive, kale, bib leaf and red leaf lettuce, mayonnaise, mustard greens, parsley, spinach, raw turnip greens, watercress and green tea. Using any additional interacting drugs with warfarin during this trial was avoided.

Descriptive statistical descriptions such as mean, median, range, standard error and proportions were applied. The normality of variables was tested using the one-sample Kolmogorov–Smirnov test. If some variables did not meet the criteria of normality, their natural logarithm was taken prior to analysis.

Differences between mean values for quantitative variables were evaluated using Student t-test. Non-parametric Wilcoxon signed ranks test was used by SPSS ver.15 for Windows (SPSS Inc., Chicago, IL, USA). All P-values were obtained from two-tailed tests, and only values below 0.05 were considered significant.

RESULTS

Overall, 102 patients were using warfarin as their main anticoagulant drug, 17 (16.6%) patients had thyroid diseases (twice checked during a 3 months period). 15 patients (88%) had hypothyroidism and 2 patients had multinodular goiter. Half of these patients had a history of abnormal thyroid function but none of them were treated for their subclinical hypothyroidism. In our study, the main causes for warfarin treatment were previous history of venous thromboembolism (77%) and atrial fibrillation (13%). Baseline characteristic of this study is presented in table 1. There were no significant differences between the groups in gender, and mean age. 32 of 102 patients (38%) had used other medications for their coexisting diseases. Aspirin, β_2 antagonists, calcium channel blockers and digoxin were the majority of these drugs (about 91%). All of our subclinical hypothyroidism patients (15 patients) completed the study period.

Mean serum concentration of TSH, T_4 , T_3 , T_3RU and Free T_4 index before, during and after treatment is represented in table 2.

The weekly dosage of warfarin during subclinical hypothyroidism state was 33 ± 15 mg (mean \pm standard error [SE]). The weekly dosage of warfarin during treatment period of hypothyroidism was 30 ± 13 mg (mean \pm standard deviation [SD]). Mean warfarin dosage 2 months after treatment was 29 ± 11 mg

(mean \pm standard deviation [SD]). There was significant difference between warfarin dosage before and after hypothyroid treatment ($p < 0.05$). Table 3 shows mean warfarin dose per week.

Warfarin dosage needed correction in about 58% of office visits before treatment but during and after treatment these corrections were needed in only 48% and 54% of patient visits, respectively. There was a significant decrease in INR fluctuation after treatment of hypothyroidism ($p < 0.05$).

Table 1. Baseline characteristics of study population

Variables	
Age (years) (\pm SD)	62 (\pm 7)
Gender	
Female	8 (53%)
Cause using warfarin %	
venous thromboembolism	(70%)
Atrial Fibrillation	(30%)
% patients using additional drugs	
> 3	(70%)
History of Diabetes	3 (20%)
History of Hypertension	4 (26%)
History of Ischemic Heart Disease	2 (13%)
Previous History of Overt Hypothyroidism	4 (26%)
Aspirin use	5 (33%)
Mean Systolic Blood Pressure(mm Hg)	145
Mean Diastolic Blood Pressure (mm Hg)	85
BMI (Body Mass Index) > 30	4 (26%)

The results are presented as numbers (%)

DISCUSSION

Subclinical hypothyroidism is described by normal serum free thyroxine concentrations with elevated serum thyroid-stimulating hormone concentrations. Subclinical hypothyroidism is prevalent in our population, especially between women and the elderly.^[5,6]

Table 2. Mean (\pm SD) of TSH, T_4 , T_3 , T_3RU and Free T_4 index before, during, and after treatment

	TSH	T_4	T_3	T_3RU %	FT ₄ I
Before treatment	10.5 (\pm 3.3)	2.4 (\pm 1.1)	176 (\pm 34)	27 (\pm 5)	0.7 (\pm 0.23)
During treatment	5.1 (\pm 2.2)	6.5 (\pm 2)	145 (\pm 31)	33 (\pm 4)	2.1 (\pm 0.4)
After treatment	4.1 (\pm 1.6)	6.7 (\pm 2)	146 (\pm 32)	35 (\pm 3)	2.3 (\pm 0.5)
P-value	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$

TSH: Thyroid stimulating hormone, T_4 : Thyroxine, T_3 : Triiodothyronine
The normal ranges for euthyroid subjects were: TSH of 0.4–5.2mIU/l; T_4 concentration of 4.5–12.0 μ g/dL, T_3 concentration of 80 – 190 ng/dL, T_3RU concentration of 25–35%. Free T_4 index (FT₄I) normal range was 1.2 – 4.9 μ g/dL.

Table 3. Mean weekly warfarin dosage (mean ± SD)

	warfarin dosage
2 months before starting treatment	33 (± 15)*
During treatment with levothyroxine	30 (± 13)
2 months after completing treatment	29 (± 11)*

*P-value was statistically significant ($p < 0.05$)

The prevalence of subclinical hypothyroidism increases with age, and it is present in up to 20% of women older than 60 years.^[4-6] Subclinical hypothyroidism has no or few mild symptoms, and it usually cannot be recognized without thyroid hormone measurement.^[6]

Warfarin is currently the most extensively used oral anticoagulant worldwide.

Warfarin interferes with modulation of the gamma carboxylation of the terminal regions of vitamin K proteins. This results in the reduction of clotting factors II, VII, IX, and X. Reduction of these clotting factors (II, VII, and X) is measured using the prothrombin time.^[10] Warfarin is prescribed for several indications, including primary and secondary prevention of venous thromboembolism, prevention of systemic embolism and stroke in patients with prosthetic heart valves and atrial fibrillation (AF), primary prevention of myocardial infarction, and in the acute management of myocardial infarction for prevention of stroke, recurrent infarction, and death.^[11]

Certain types of cancer, decompensated or acute heart failure, hyper- and hypothyroidism, and liver disease may impact the expected therapeutic outcomes of warfarin.^[10]

Warfarin potentiation was considered to enhance pharmacodynamic effects, but not pharmacokinetics such as volume of distribution and protein binding.^[2] Most experts and evidence-based guidelines advocate starting replacement therapy in elderly patients who have TSH concentrations greater than 10 mIU/L and in those with antithyroid antibodies,^[4] and in symptomatic elderly patients with TSH levels between 4.5 and 10 mIU/liter. Therefore, due to possible side effects of subclinical hypothyroid state on coagulation profiles and warfarin effect, patients may be at risk of INR fluctuations for several months. Bucerius et al. did not show any correlation between subclinical hyperthyroidism and INR lability in their study.^[12] The result of the current study showed that warfarin dosage and INR lability can be significantly improved during and also after treatment of subclinical hypothyroidism. In a

recent similar pilot study by Squizzato et al., in the University Hospital of Varese, Italy, vitamin K sensitivity was significantly decreased by subclinical hypothyroidism treatment. On the other hand, vitamin K stability, as shown in the stated study, did not change significantly by the median time spent in the therapeutic range and interquartile range.^[6] Subclinical hypothyroidism is highly prevalent in the Iranian population (range from 3.1% to 8.4% for male and female respectively). The high prevalence of hypothyroidism in Isfahan may be due to autoimmunity with no correlation to iodine intake.^[13] Hypothyroidism can be caused by drugs used for treatment of cardiovascular diseases. In addition, atrial fibrillation is common in adults and this incidence can rise to >5% of the elderly population over 70. Due to side effects of chronic anticoagulation, like severe Gastrointestinal and cerebral bleeding, fluctuations of INR can be very harmful especially in the elder population and carefully selected patients using warfarin with labile INR can gain from concomitant therapy for subclinical hypothyroidism.

Subclinical hypothyroidism may be treated while using oral anticoagulants and this treatment may influence the warfarin dosage of patients. Therefore, although there may be benefits to treatment with levothyroxine, further study is necessary.

Study limitation

This study has a few limitations. The Target population is small and our study power is not efficient for an appropriate clinical decision making. At present this study is continued. Moreover, most of our patients came from a referral hospital and did not represent the entire population.

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