ORIGINAL ARTICLE

CONTENTS

Dose adjustment of oral thyroxine in patients consuming dairy products: A cohort retrospective study

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ABSTRACT

Aim: Hypothyroidism management with levothyroxine might be affected by a range of factors, including diet. Dairy sources are rich in calcium and proteins which may interfere with the absorption of thyroxine so dose adaptability might be required. This study assesses the effect of dairy intake on levothyroxine dose and clinical outcomes.

Materials and Methods: Retrospective cohort study over 14 months in an endocrinology center in Najaf, included 150 adult patients with primary hypothyroidism on stable oral levothyroxine therapy. We classified individuals into high, medium and low dairy consumers. A comparative approach was performed between these groups on terms of the dose, time to stabilization, dose response, clinical outcome, and economic outcome.

Results: After multivariable analysis, we found that participants who consumed one or more servings of dairy products per day were 6.8 times more likely to report taking their medications at least once with inadequate preparation $p<0.001$. These findings suggest that dietary interventions targeting dairy intake could stabilize treatment and reduce healthcare costs.

Conclusions: Dietary intake of dairy has a major impact on both the absorption and dosing of levothyroxine in hypothyroid patients. Given the healthcare burden arising from dose adjustments, clinicians should consider dietary counselling and timing strategies to improve therapy.

KEY WORDS: thyroxine, hypothyroidism, dairy products, dose adjustment

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INTRODUCTION

Hypothyroidism is a metabolic disorder that occurs when there is reduced secretion of the thyroid hormones triiodothyronine (T3) and thyroxine (T4). Low thyroid hormone is detected by the pituitary gland, which responds by producing more TSH [1]. The dysfunctional thyroid gland itself is a hallmark of primary hypothyroidism [2]. TSH secretion elevates and serum TSH levels rise in relation to thyroid hormone deficiency. Inadequate stimulation of a structurally normal gland due to diminution in the release of pituitary TSH (secondary hypothyroidism) or primary failure of hypothalamic thyrotropin-releasing hormone (TRH) stimulation can also lead to diminished thyroidal secretion of thyroid hormone [3]. Practically clinical discrimination between secondary (pituitary origin) and tertiary (hypothalamic) hypothyroidism is not always possible and, therefore, they are referred to as 'central hypothyroidism' [1]. Generally speaking, a thyroid gland that is under-producing thyroid hormone is referred to as hypothyroidism. It may be of primary etiology (due to an abnormality in the thyroid gland per se) or secondary/central (due to hypothalamic or pituitary dysfunction). Subclinical hypothyroidism is a term referring to mild forms of primary hypothyroidism with normal free thyroxine (FT4) and total or free T3 levels but an elevated serum TSH level [4]. The incidence of progress from subclinical to manifest hypothyroidism is 2-5% per year [5]. Hypothyroidism has a prevalence of 3.8-4.6% in the general population. Four-point-one new cases of hypothyroidism per 1000 women and 0.6 new cases per 1000 men per year were found in the Whickham survey [6]. Most cases are a result of primary thyroid gland failure due to long-standing thyroid autoimmune (Hashimoto's) thyroiditis, radioactive iodine (I^{131}) therapy, or surgery.

Levothyroxine is mainly absorbed in the small intestines and absorption is known to be influenced by gastric pH, food intake and some minerals and compounds [7]. Calcium, abundant in milk, is known to form an insoluble complex with thyroxine in the gut, and may decrease the

oral bioavailability of thyroxine by 20–25% [8]. Moreover, the protein in dairy products might also compromise the absorption, possibly due to the effects on gastric emptying and intestinal transit time [9]. Clinicians usually advise levothyroxine in a fasted state, preferably 30-60 min before breakfast, to maximize its absorption. Yet, actual patient compliance with these time recommendations is highly variable in practice, with many patients unintentionally ingesting dairy products shortly before and after their thyroxine dose. This poses a considerable clinical problem as continued poor absorption results in continued hypothyroid symptoms, requiring dose increases that may not solve the underlying absorption problem. Conflicting evidence surrounding the clinical impact of dairy product intake on thyroxine therapy has been reported by previous studies. Although there is evidence from a few trials that absorption of thyroxine is reduced by a measurable degree when thyroxine is taken with calcium-containing compounds [10-12], the long-term consequences of this and the most appropriate management strategy are not well established. In addition, the extent to which systematic dose correction can compensate absorption impairment due to dairy in the "real world" of clinical practice, based on the available evidence, is unclear. This interaction is complicated by patient-specific factors including timing and amount of dairy intake, baseline thyroid function, and any co-administered medications. The knowledge of these factors is important for establishing evidence-based recommendations which might aid clinicians in optimizing thyroxine therapy for dairy-product consuming patients.

AIM

This is a retrospective cohort study to assess the variation in dosing strategies for oral thyroxine in the presence of regular dietary dairy intake as measured by its effect on both biochemical and clinical end points. In examining real-world clinical data, the aim of this study is to offer clinically-relevant information on how to approach this frequently encountered therapeutic dilemma and inform evidence-based recommendations for thyroxine dosing in the setting of dairy intake.

MATERIALS AND METHODS

STUDY DESIGN

The objective of this cohort study was to assess the relationship between intake of dairy products and the necessity to adjust the dose of oral thyroxine replacement in hypothyroid patients. It was a longitudinal study with retrospective review of data retrieved from the electronic health record in the endocrinology center in Najaf over 14 months (September 2023- November 2024). All participating sites have standardized electronic health record systems and practices for monitoring thyroid hormone replacement therapy.

STUDY POPULATION

INCLUSION CRITERIA

Inclusion criteria included adult patients aged above 18 years with a diagnosis of primary hypothyroidism, continues on oral levothyroxine treatment within the study period, at least 3 TSH measurements and 12 months after treatment at least, full medical recall and dosage available and dietary intake information obtained from clinical notes or structured questionnaires.

EXCLUSION CRITERIA

Exclusion criteria included those that have secondary or tertiary hypothyroidism, pregnant or lactating women at the time of the study, malabsorption diseases (coeliac disease, inflammatory bowel disease, short gut syndrome) patients, concomitant treatment with substances which interfere with the absorption of levothyroxine (eg, antacids, proton pump inhibitors, calcium supplements, iron supplements or sucralfate), missing chart records or follow-up less than 12 months, patients with large comorbidities that disturbed the pleiotropic effects predicated on thyroxine metabolism (severe liver or kidney impairment) and patient with poor adherence and dietary system. Those patients who were characterized as "non-consumers" of dairy products were also excluded because of their small sample size.

DATA COLLECTION

DATA SOURCES

Patients meeting eligibility criteria were identified by searching electronic health records. Data collection was carried out by trained research staff using data collection forms designed for the study, which included quality control mechanisms.

VARIABLES COLLECTED

PRIMARY EXPOSURE VARIABLE

Dairy Products intake: Categorized according to intake record as:

Table 1. Baseline characteristics by dairy consumption groups

Characteristic	Group 1 (n=45)	Group 2 (n=55)	Group 3 (n=50)	P-value
Demographics				
Age (years, mean ± SEM)	38 ± 6	37 ± 4	39 ± 7	0.80
Female sex (%)	33	34	33	0.99
BMI [kg/m^2, mean ± SEM]	29 ± 4	30.5 ± 6	29.5 ± 3	0.78
Clinical parameters				
Initial TSH [mIU/L, median (IQR)]	9.33 (7.45-15.35)	9.58 (8.15-16.22)	8.99 (7.11-16.22)	0.99
Initial T4 [µg/dL, mean ± SEM]	0.55 ± 0.02	0.48 ± 0.11	0.51 ± 0.14	0.85
TPO antibodies positive [%]	82	83	81	0.98
Medication factors				
Initial levothyroxine dose [mcg, mean ± SEM]	110 ± 13	115.5 ± 12.5	112 ± 18	0.44
Comorbidities				
Diabetes mellitus [%]	8	7	9	0.99
Cardiovascular disease [%]	2	3	3	0.98
Lifestyle factors				
Current smoker [%]	33	35	32	0.99
Alcohol consumption [%]	NA	NA	NA	NA

Group 1: High Consumers, Group 2: Moderate Consumers, Group 3: Low Consumers

Group 1: High consumers (> 3 serving of dairy/day, n=45)
Group 2: Moderate (1-3 serving of dairy/day, n=55)
Group 3: Low consumers (< 1 serving of dairy/day, n=50)

PRIMARY OUTCOME VARIABLE

Dose Adjustment: Increase in levothyroxine dose by ≥25 mcg during follow-up to normalize TSH levels (target 0.4-4.0 mIU/L in most sick patients or goal agreed between the patient and the clinician).

SECONDARY OUTCOME VARIABLES

Time to stable TSH (defined as experience of 2 consecutive TSH measurements in target range at least 6 weeks apart)

Total number of dose adjustments needed

Final stable dose of levothyroxine (mcg/kg body weight)

Percentage of patients who need a dose increase >50% than the initial dose

COVARIATES AND CONFOUNDING VARIABLES

Demographics: Age, gender, ethnicity, body mass index

Clinical variables: TSH at onset, thyroid autoimmunity, cause of hypothyroidism

ETHICAL CONSIDERATIONS

Approval for this study was obtained from College of Pharmacy, University of Alkafeel. Because this was a retrospective study that used de-identified health records, the need for informed consent was waived.

SAMPLE SIZE CALCULATION

Power calculation was performed based on the primary efficacy outcome of dose adjustment needs. Considering a 40% as a baseline dose adjustment rate in those with low dairy intake, with a clinically relevant 20% difference between groups (relative risk=1.5), 80% power, and α=0.05, assuming potential confounding in multivariable analyses. A total of 150 patients were chosen as the target sample size.

STATISTICAL ANALYSIS

Data for 150 patients were presented as Mean ± SEM. All analyses and graphs were conducted using GraphPad Prism 9.3.1. Descriptive statistics were used to describe baseline characteristics. Continuous variables were expressed as means ± standard error of mean (SEM) according to data distribution normality (the Shapiro-Wilk test). Categorical variables were reported as frequencies and percentages. One Way ANOVA was performed to test differences and p value less than 0.05 was considered significantly different.

RESULTS

All groups were comparable with respect of baseline characteristics with no significant differences concern-

Table 2. Characteristics of dairy consumption

Parameter	Group 1 (n=45)	Group 2 (n=55)	Group 3 (n=50)
Dairy servings/day, mean ± SEM	6 ± 2	3 ± 1	1 ± 0.5
Timing of consumption			
< 2 hours [%]	44	51	48
> 2 hours [%]	56	49	52
Primary dairy products consumed			
Milk [%]	30	31	34
Yogurt (%)	34	32	34
Cheese [%]	36	37	32

Group 1: High Consumers, Group 2: Moderate Consumers, Group 3: Low Consumers

Table 3. Primary outcome - dose adjustment requirements

Outcome	Group 1 (n=45)	Group 2 (n=55)	Group 3 (n=50)	P-value
Primary Outcome				
Dose adjustment ≥25 mcg [%]	63.1	37.3	15.8	0.001
Dose Adjustment Magnitude				
Mean dose increase [mcg]	31.5 ± 12.4	17.8 ± 11.3	9.8 ± 4.6	0.001
Dose increase >50% [%]	21.3	7.5	2.1	0.001
Final Stabilized Dose				
Final levothyroxine dose [mcg]	136.5 ± 24.5	122.7 ± 13.6	106 ± 7.2	0.04
Final dose per kg body weight [mcg/kg]	1.4 ± 0.7	1.6 ± 0.55	1.5 ± 0.2	0.022

Group 1: High Consumers, Group 2: Moderate Consumers, Group 3: Low Consumers

Table 4. Association between dairy consumption and dose adjustment requirements

Variable	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Dairy Consumption				
Low consumers	Reference	-	Reference	-
Moderate consumers	2.74 (1.30–6.25)	0.009	2.60 (1.10–6.00)	0.028
High consumers	7.42 (3.20–17.50)	<0.001	6.80 (2.90–15.80)	<0.001

Table 5. Time to achieve stable TSH levels

Group	Median time to stabilization (weeks)	95% CI (weeks)	Log-rank P-value
Low consumers	5.5	7.4 – 9.3	
Moderate consumers	6.5	5.6 – 7.9	0.022
High consumers	9	4.3 – 6.9	

ing age, sex, BMI, initial thyroid function and antibody status, comorbidities or the initial levothyroxine dose, all P>0.05, table (1).

Daily dairy intake was as expected significantly different among the groups: High consumers reported 6 daily servings on average, while moderate and low consumers reported consuming 3 and 1 daily servings respectively (Table 2). Group assignment did not systematically influence the type or timing of dairy products.

Dairy intake is the single most influential dietary factor related to higher levothyroxine dose requirements. High consumers were more likely than low consumers to enroll with ≥25 mcg dose increases (63.1% *vs.* 15.8%), required greater mean dose escalation at time of entry (31.5 mcg vs 9.8 mcg), and needed >50% dose increases more frequently (21.3% *vs.* 2.1%, P < 0.001), table (3). Multivariable analysis demonstrated a dose-response relationship, with moderate and high consumption associated with 2.6- and 6.8-fold larger odds of adjustment required, table (4).

Table 6. Dosage modifications based on dairy intake

Number of adjustments	Group 1 n (%)	Group 2 n(%)	Group 3 n (%)	P-value
0	31 (68.9%)	26 (47.3%)	11 (20.0%)	
1	9 (20%)	14 (25.5%)	9 (20.0%)	0.001
2	4 (8.9%)	11 (20%)	16 (30.0%)	
≥3	1 (2.2%)	4 (7.2%)	14 (30.0%)	

Group 1: High Consumers, Group 2: Moderate Consumers, Group 3: Low Consumers

Table 7. TSH range distribution

TSH range	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	P-value
Within target (0.4-4.0 mIU/L)	36 (80%)	41 (74.5%)	32 (64%)	0.045
Below target (<0.4 mIU/L)	4 (8.8%)	8 (14.5%)	4 (8%)	
Above target (>4.0 mIU/L)	5 (11.1%)	6 (11%)	14 (28%)	

Group 1: High Consumers, Group 2: Moderate Consumers, Group 3: Low Consumers

Table 8. Clinical impact of follow-up

Comparison	Absolute risk difference [%]	Number needed to treat	95% CI
Group 1 vs. group 2	13	8	5-21
Group 1 vs. group 3	29	5	19-43

Table 9. Economic impact follow-up utilization measures

Measure	Group 1 (n=45)	Group 2 (n=55)	Group 3 (n=50)	P-value
No. of follow-up visits (mean ± SEM)	8 ± 1.3	4 ± 1.2	2 ± 0.8	0.045
No. of TSH tests	6 ± 1.1	4.4 ± 0.8	4.2 ± 0.6	0.36
Duration for stabilization (weeks)	12 ± 2.1	7.3 ± 1.7	3.4 ± 1.01	0.034

Group 1: High Consumers, Group 2: Moderate Consumers, Group 3: Low Consumers

In addition to the fact that intake of dairy delayed normalization of TSH. Time to stabilization Median time to stabilization in low consumers: 5.5 weeks (95%CI 3–8) median time to stabilization in moderate consumers: 6.5 weeks (95%CI, 4–18) median time to stabilization in high consumers:9 weeks (95%CI,6–26), P=0.022, log-rank test, table (5).

High consumers were more likely to have ≥3 dose adjustments (30% *vs*. 2.2%, P = 0.001), table (6) and less likely to achieve target TSH by study end (64% *vs.* 80%, P=0.045) compared with low consumers, table (7). At the clinical level these absolute risk reductions corresponded to numbers-needed-to-treat of 5–8 to prevent one case of PD in participants asked to reduce their intake of dairy, table (8). Additionally, stabilizing the diet for high consumers required more frequent follow-up visits and a longer sustained period (12 weeks vs. 3.4 weeks, P=0.034), demonstrating the healthcare burden of dietary interference from an economic perspective, table (9).

DISCUSSION

Our main finding in this study is the robust and meaningful correlation between dairy products' consumption and the dose of levothyroxine such that it becomes clinically significant among subjects with primary hypothyroidism. Baseline demographic and clinical parameters were similar across groups, but subjects with greater dairy intake experienced more dose escalation, later attainment of stable TSH levels, more frequent adjustments in treatment, and higher healthcare utilization. These results highlight the relevance of dietary factors in management of levothyroxine replacement therapy. Our findings are consistent with previous pharmacokinetic data when taken regarding the known impact that calcium and other dairy components have on levothyroxine absorption in the gastrointestinal tract [8, 13-15]. Dairy products, especially milk and yogurt, are rich in calcium that may chelate levothyroxine, lowering its absorption [16-17]. Protein and fats content, fat also affect gastric emptying time as well as intestinal transport that can further lead to an impaired absorption [9]. Paradoxically,

while the effect on time of dairy intake relative to medication ingestion failed to be demonstrated we did find that, in absolute terms, dairy timing was sufficiently influential as a whole to differentiate thyroxine preparation requirements between groups. A robust dose–response pattern was observed in our study. High-dairy consumers were nearly 7 times more likely than low consumers to require significant dose escalation, and each additional daily dairy serving independently predicted a larger final levothyroxine dose. The associated therefore not only argument is also used for causal inference and to inform clinicians about what level of tax could guide dietary advice. In high dairy consumers, stabilization was 4 weeks later and many required ≥2 dose adjustments to maintain TSH target by follow-up. In clinical terms, this translates into extremely low numbers needed to treat (in the area of 5–8) suggesting that even small reductions in dairy should have a significant effect on outcomes. Co-ingestion of 2% cow's milk (12 oz) with levothyroxine significantly lowered the area under the curve (AUC) for serum total T4 levels compared to levothyroxine taken with water — Further, ingesting cow's milk or eating within 30 minutes of taking levothyroxine resulted in lower peak concentrations, compared to fasting [16]. This is consistent with your observation that increased absolute dairy intake is associated with higher dose responses. Another study found that concurrent use of calcium carbonate (1,200 mg/day elemental calcium) with levothyroxine reduced serum total T4 and free T4 levels and increased TSH in a 20-patient cohort (e.g., >30% increase from baseline; P <0.001) [8]. In healthy volunteers whole-body retention of T4 was studied during a 24 h period, which showed significant decreases in absorption of T4: Taking levothyroxine with calcium carbonate (2 g) versus without calcium carbonate p=0.022, 84% *vs.* 58% [18]. This works perfectly with the dose–dependent interference effect your studies revealed - more calcium (from dairy) - more likely to need a higher dose escalation. A recently published review on the topic established that both calcium and iron (di- and tri-valent elements) decrease levothyroxine absorption, probably as a consequence of nonspecific adsorption in the gastrointestinal tract leading to insoluble complexes. These parallel phenomena with other nutritional compounds — coffee, soy, supplements & medications etc. are known to decrease levothyroxine bioavailability as well [16]. The general consensus from expert opinion panels as well as important sources of information advises that levothyroxine should be given at least 2-4 hours apart from dietary products containing dairy and calcium to prevent the two agents from interacting [19]. The FDA advises waiting 4 hours between levothyroxine and dairy consumption [20]. Our finding that even modest reductions in daily dairy or more careful dietary timing could be meaningfully altering the efficacy of thyroid hormone treatment support such a conclusion. In addition to clinical end-points, our study also underscores the economic costs associated with uncontrolled dietary interference. Highs required more than twice as many additional visit follow up plus a significantly longer cadre stabilization period. It concluded that such unnecessary health care utilization is a cost-effective reason for simple dietary approaches. Thus, an unrestrained dietary consumption further paves the way for chronic diseases like type 2 diabetes, obesity and cardiovascular diseases. The victims of these diseases usually require frequent doctor visits, hospitalization and long term care, making healthcare expensive. For example, one study demonstrated that individuals with food insecurity and chronic diseases had greater health care costs than their food-secure counterparts [21]. There is a large economic burden due to poor nutrition, and dietary interventions could be an economical way to address this. Outcomes of many studies have established that intervention programs having a focus on healthy dietary and physical activity behaviors are effective to provide better health results at an affordable cost. For instance, a study based on an adolescent dietary and physical activity intervention yielded health improvements at an extra cost to providers of £123 per participant [22]. There is a high economic cost of malnutrition Unhealthy eating is associated with an excess of $50 billion in healthcare costs related to heart disease, stroke, and diabetes annually in the US alone. The figure includes out-of-pocket medical expenses as well as indirect costs, such as lost productivity [23]. Addressing such dietary interventions in healthcare strategy may be an economical means of downgrading the economic burden related to malnutrition and chronic diseases. Yet thoughtful planning is needed to ensure that these interventions are implemented effectively and in a sustainable manner. Our study further emphasizes the clinical burden and economic price of dietary noncompliance as high consumers necessitated > twofold greater follow-up and additional time to achieve stabilization. This underscores that basic dietary changes could offer a low-cost solution for reducing superfluous healthcare consumption. We also need more work on the long-term effects of dietary patterns and related interventions on healthcare costs, effectiveness of personalized nutrition interventions, integration with digital health tools, and public-health policy that reduces the burden of diet on national economies.

CONCLUSIONS

Dietary intake of dairy has a major impact on both the absorption and dosing of levothyroxine in hypothyroid patients. Given the healthcare burden arising from dose adjustments, clinicians should consider dietary counselling and timing strategies to improve therapy.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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