Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2026, 16(9), 196-217
https://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Saudi Consensus on Thyroxine (Levothyroxine) Replacement and Switching between Brands and Generics

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How to cite this paper: Alshaikh, A., Alshennawi, M., Aljuhani, N., Jammah, A., Alzahrani, S., Alhozali, A., Almehthel, M., Albarkah, Y., Alotaibi, M., Issak, E.R. and Alsifri, S. (2026) Saudi Consensus on Thyroxine (Levothyroxine) Replacement and Switching between Brands and Generics. *Open Journal of Endocrine and Metabolic Diseases*, **16**, 196-217.
https://doi.org/10.4236/ojemd.2026.169019

Received: August 17, 2026
Accepted: September 19, 2026
Published: September 22, 2026

Abstract

Background: Levothyroxine (LT4) is the standard treatment for hypothyroidism and is generally required lifelong. As a narrow therapeutic index medication, relatively small variations in LT4 exposure may result in clinically relevant changes in thyroid-stimulating hormone (TSH) concentrations. Switching between branded and generic products or between different manufacturers may occur because of drug availability, procurement policies, formulary changes, or cost considerations. Although switching appears clinically acceptable for many patients at the population level, individual variability remains a concern, particularly in patients requiring tight biochemical control. In Saudi Arabia, differences in procurement systems, formularies, and medication availability across healthcare sectors create a need for standardized national recommendations on LT4 replacement, switching, and monitoring. **Objective:** To develop multidisciplinary, evidence-based, and context-specific Saudi consensus recommendations for optimizing levothyroxine replacement therapy, with particular emphasis on formulation consistency, safe switching, post-switch monitoring, high-risk populations, and pharmacy-level substitution. **Methods:** A structured review of international guidelines, regulatory documents,

systematic reviews, clinical trials, observational studies, and pharmacological evidence addressing LT4 pharmacology, bioequivalence, formulation switching, and thyroid-function variability was undertaken. A multidisciplinary Saudi expert panel comprising endocrinologists, internal medicine physicians, pharmacists, methodologists, and healthcare policy, regulatory, and pharmaceutical-services leaders reviewed the evidence and developed consensus statements relevant to the Saudi healthcare setting. Consensus was established using a modified Delphi process with sequential anonymous electronic voting on a 9-point Likert scale. Statements were revised based on panel feedback when required, and a strong consensus was predefined as ≥ 80% agreement. **Results:** The panel developed recommendations addressing LT4 formulation consistency, indications for switching, biochemical monitoring, management of high-risk populations, and pharmacy substitution. The consensus recommends maintaining patients on the same LT4 product once biochemical stability has been achieved and limiting switching to clinically or operationally justified circumstances, such as product unavailability, intolerance to excipients, or relevant cost considerations. When switching is unavoidable, serum TSH should be reassessed after 6 - 8 weeks. Switching should be avoided whenever possible in populations requiring particularly tight biochemical control, including pregnant women, pediatric patients, patients with differentiated thyroid cancer requiring TSH suppression, and older adults with cardiovascular disease. Pharmacy-level substitution should be accompanied by appropriate communication with the prescriber and patient, together with documentation and appropriate biochemical monitoring. **Conclusions:** This Saudi multidisciplinary consensus provides a practical framework for safe and consistent levothyroxine replacement therapy across healthcare settings. Maintaining formulation consistency, minimizing unnecessary switching, implementing systematic post-switch TSH monitoring, and strengthening communication among prescribers, pharmacists, patients, healthcare institutions, and regulatory stakeholders may reduce treatment variability and improve continuity and safety of hypothyroidism management in Saudi Arabia.

Keywords

Levothyroxine, Hypothyroidism, Switching, Bioequivalence, Generic Substitution, Thyroid-Stimulating Hormone, Narrow Therapeutic Index, Modified Delphi, Consensus, Saudi Arabia

1. Introduction

Hypothyroidism is a common endocrine disorder with a substantial clinical and public health burden worldwide, requiring lifelong hormone replacement therapy in most patients. Levothyroxine (L-thyroxine) remains the standard of care for the treatment of hypothyroidism due to its efficacy, favorable pharmacokinetic profile, and ability to normalize serum thyroid-stimulating hormone (TSH) levels. Achieving and maintaining biochemical euthyroidism is essential, as both under-

and over-replacement are associated with significant adverse outcomes, including cardiovascular morbidity, metabolic disturbances, impaired neurocognitive function, and reduced quality of life [1] [2].

Despite its widespread use, levothyroxine is classified as a narrow therapeutic index medication, meaning that small variations in dose or bioavailability may result in clinically meaningful changes in TSH levels. Multiple formulations of levothyroxine are available, including branded and generic products, which may differ in excipients, dissolution characteristics, and bioavailability. Although regulatory authorities such as the Saudi Food and Drug Authority approve generic formulations based on bioequivalence criteria, concerns persist regarding the clinical interchangeability of these products, particularly in vulnerable patient populations [1]-[4].

Switching between levothyroxine formulations—whether between brand-name products, generic equivalents, or different generic manufacturers—is a common practice in routine clinical care. This is often driven by factors such as medication availability, institutional procurement policies, and cost-containment strategies within healthcare systems, including those governed by the Saudi Ministry of Health. However, accumulating evidence suggests that such switching may lead to variability in thyroid function tests, necessitating dose adjustments and closer monitoring. These challenges are particularly relevant in high-risk groups, including pregnant women, patients with differentiated thyroid cancer requiring TSH suppression, pediatric patients, and elderly individuals with cardiovascular comorbidities [3] [5] [6].

International guidelines, including those from the American Thyroid Association and the European Thyroid Association, recommend maintaining patients on a consistent levothyroxine formulation whenever possible and emphasize the need for reassessment of thyroid function following any change in preparation. Nevertheless, variations in healthcare infrastructure, regulatory frameworks, and drug supply systems necessitate the development of context-specific recommendations tailored to national practice environments [7].

In Saudi Arabia, frequent switching between levothyroxine products may occur due to centralized procurement systems, variations in hospital formularies, and availability across different healthcare sectors. Currently, there is a lack of unified national guidance addressing the clinical management of levothyroxine switching and the appropriate monitoring strategies in such scenarios. This gap may contribute to inconsistent clinical practice and suboptimal patient outcomes [3] [8].

Therefore, this Saudi consensus aims to provide evidence-based and context-specific recommendations on levothyroxine replacement therapy, with a particular focus on the safe and effective switching between different formulations. The document seeks to standardize clinical practice, enhance patient safety, and support healthcare providers in decision-making across diverse clinical settings within

the Kingdom of Saudi Arabia.

2. Methodology

2.1. Literature Review and Evidence Assessment

A structured literature review was conducted to inform the development of the consensus recommendations. The literature search was performed in PubMed/MEDLINE, Scopus, and the Saudi Digital Library from 2018 to 2026, using combinations of the terms *levothyroxine*, *thyroxine*, *hypothyroidism*, *generic*, *brand*, *generic substitution*, *interchangeability*, *switching*, *bioequivalence*, *bioavailability*, *narrow therapeutic index*, and *thyroid-stimulating hormone*. International clinical practice guidelines and regulatory documents from the American Thyroid Association, European Thyroid Association, Saudi Ministry of Health, and Saudi Food and Drug Authority were additionally reviewed. Eligible evidence included clinical practice guidelines, systematic reviews, randomized or comparative clinical studies, observational studies, pharmacokinetic/bioequivalence studies, and relevant regulatory guidance addressing levothyroxine replacement, formulation interchangeability, switching, or monitoring. Evidence was screened for relevance to the predefined clinical questions and critically appraised according to study design, methodological quality, consistency, directness, and applicability to Saudi clinical practice.

2.2. Expert Panel Meeting and Development of Recommendations

A multidisciplinary Saudi expert panel comprising 10 experts, including five endocrinologists, three internists, one clinical pharmacist, and one consultant pharmacist, was convened from eight healthcare institutions/sectors. During the expert meeting, the panel reviewed the evidence synthesis together with relevant Saudi regulatory and Ministry of Health policies and discussed key domains including formulation consistency, brand-to-generic and generic-to-generic substitution, circumstances requiring switching, post-switch monitoring, high-risk populations, and the responsibilities of prescribers and pharmacists. The panel subsequently developed five preliminary recommendation statements. Recommendations were formulated by integrating the certainty of evidence with the anticipated balance of benefits and harms, feasibility, patient-safety considerations, resource implications, and applicability within the Saudi healthcare system. Accordingly, the strength of a recommendation was not determined solely by the certainty of evidence; a strong recommendation could be made despite moderate or low-certainty evidence when the panel judged that avoidance of potential harm, feasibility, or established safety principles clearly favored a particular course of action. The rationale for such judgments was documented.

2.3. Modified Delphi Consensus Process

The draft recommendations underwent a modified Delphi process consisting of

two voting rounds. A total of 10 panelists were invited, with full participation in both rounds (10/10; 100%). Voting was conducted independently and anonymously using a 9-point Likert scale, with scores of 1 - 3 indicating disagreement, 4 - 6 uncertainty, and 7 - 9 agreement. Consensus was predefined as ≥ 80% of participating panelists rating a statement between 7 and 9. For each statement, the proportion of agreement, median score, and interquartile range (IQR) were calculated, and panelists were invited to provide free-text comments to support refinement of statement wording. Statements requiring clarification or substantive modification after the first round were revised by the steering committee on the basis of the available evidence and anonymized panel feedback and were then redistributed for a second round of voting. All five final consensus statements were endorsed by all 10 panelists, corresponding to 100% agreement for each statement. Final statement-level voting results, including the number of votes, response rate, percentage agreement, median (IQR), and consensus status, are presented in Table 1.

2.4. Evidence Grading and Recommendation Strength

The certainty of evidence supporting each recommendation was assessed using an adapted framework informed by GRADE principles, considering study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence certainty was categorized as high, moderate, low, or very low. The strength of each recommendation was determined separately by considering the certainty of evidence together with the balance of anticipated benefits and harms, patient-safety implications, feasibility, resource considerations, and applicability within the Saudi healthcare system. Accordingly, a strong recommendation could be supported by moderate or low-certainty evidence when the panel considered the potential consequences of harm, feasibility of implementation, or established safety principles sufficient to justify a strong recommendation.

3. Results

3.1. Delphi Consensus Results

All 10 invited experts participated in both Delphi rounds, resulting in a 100% response and retention rate throughout the consensus process. Five consensus statements were evaluated using the predefined 9-point Likert scale, with consensus defined as ≥ 80% of panelists assigning a score of 7 - 9. All five final statements achieved unanimous agreement (100%), exceeding the predefined threshold for strong consensus.

The median agreement scores ranged from 8.0 to 9.0, indicating a consistently high level of endorsement across the panel. Statement 3 achieved a median score of 9.0 with an IQR of 0, demonstrating complete convergence of panel ratings, while Statements 1, 2, 4, and 5 had median scores of 8.0, 8.5, 8.0, and 9.0, respectively, with an IQR of 1. No final statement failed to achieve consensus or required exclusion. Detailed statement-level voting results are presented in Table 1.

Table 1. Final Delphi voting results for the consensus statements.

Consensus statement	Agreement, %	Median score	IQR	Consensus status
1	100	8.0	1	Strong consensus
2	100	8.5	1	Strong consensus
3	100	9.0	0	Strong consensus
4	100	8.0	1	Strong consensus
5	100	9.0	1	Strong consensus

Abbreviation: IQR, interquartile range.

Note: Ten of ten panelists (100% response rate) participated in the final Delphi voting. Agreement was defined a priori as a score of 7 - 9 on the 9-point Likert scale, with strong consensus defined as ≥ 80% agreement. All five statements achieved unanimous (100%) agreement.

3.2. Evidence Supporting Levothyroxine Formulation Switching

The evidence informing the consensus recommendations included comparative effectiveness studies of brand and generic levothyroxine, real-world evaluations of generic-to-generic switching, and studies examining transitions from tablet to liquid or soft-gel formulations. The pivotal studies and their principal TSH-related outcomes are summarized in Table 2.

Table 2. Pivotal evidence on levothyroxine formulation switching and TSH outcomes.

Study	Design and population	Comparison/switch	Key TSH findings	Clinical interpretation
Brito *et al.*, 2020	Retrospective comparative-effectiveness cohort of US adults initiating levothyroxine, predominantly with mild thyroid dysfunction	Consistent generic vs consistent brand-name levothyroxine	Generic and brand-name users had similar rates of achieving normal and stable TSH levels	Either consistently used generic or brand-name LT4 appears effective in typical adults; study did not directly assess switching between products [9]
Brito *et al.*, 2022	Comparative-effectiveness study; 15,829 US adults receiving generic levothyroxine; 2780 propensity-matched switcher/non-switcher pairs	Generic-to-generic manufacturer switching vs continued use of the same generic manufacturer	Normal TSH: **84.5% vs 82.7%**; markedly abnormal TSH: **2.5% vs 3.1%**; mean TSH **2.7 vs 2.7 mIU/L**; no significant differences	Generic-to-generic switching was not associated with clinically significant TSH destabilization in this predominantly low-risk population [10]
FDA real-world analysis, 2022	Real-world analysis of administrative claims linked to laboratory data	Switching among generic levothyroxine manufacturers vs remaining on the same sourced generic product	Approximately one in five patients switched manufacturers; switching was **not associated with clinically significant changes in TSH**	Supports interchangeability of approved generic products at a population level, while not excluding individual variability [11]
Virili *et al.*, 2018	Systematic review and meta-analysis of 6 prospective studies; **141 patients** with suboptimal TSH on tablet LT4	Tablet → liquid LT4 at the **same dose**	Pooled reduction in TSH of **4.23 mIU/L** (95% CI 3.69 - 4.77; P < 0.0001) after switching to liquid LT4	Liquid LT4 may improve biochemical control in patients with impaired tablet absorption; unchanged nominal dose can produce greater effective exposure [12]

Continued

Trimboli *et al.*, 2018	Prospective study; 18 evaluable hypothyroid patients without recognized malabsorption	Tablet → soft-gel LT4 at unchanged dose	Median TSH decreased from **3.33 to 1.90 mIU/L** after 3 months (P = 0.0039); proportion with TSH ≤ 4.0 increased from **61.1% to 88.9%**	Soft-gel formulations may yield greater effective LT4 exposure even without overt malabsorption [13]
Benvenga *et al.*, 2019	Prospective within-patient comparison of hypothyroid patients, with and without medications interfering with LT4 absorption	Tablet vs liquid vs soft-gel LT4	Without interfering drugs: mean TSH **2.38 tablet vs 1.62 liquid vs 1.77 soft-gel mIU/L**. With interfering drugs: **7.53 vs 2.74 vs 2.70 mIU/L**, respectively	Liquid and soft-gel formulations produced lower TSH than tablets, particularly when absorption-interfering medications were present [14]

Collectively, these studies indicate that switching among approved generic tablet formulations is generally not associated with clinically meaningful TSH changes in stable, low-risk adults, whereas switching from tablet to liquid or soft-gel formulations may increase effective levothyroxine exposure, particularly in patients with impaired tablet absorption, thereby supporting post-switch biochemical reassessment and individualized dose adjustment [10].

3.3. Final Consensus *Recommendations* and Evidence Grading

Five final recommendations addressing key aspects of levothyroxine replacement therapy and formulation switching were endorsed by the expert panel. These recommendations covered maintenance of formulation consistency, circumstances in which switching may be considered, biochemical monitoring following a formulation change, management of high-risk patient populations, and communication and documentation during medication substitution.

The certainty of evidence supporting each recommendation was assessed using the predefined GRADE-informed framework and categorized as high, moderate, low, or very low. Recommendation strength was determined separately by integrating evidence certainty with the anticipated balance of benefits and harms, patient-safety considerations, feasibility, resource implications, and applicability within the Saudi healthcare system. Where a strong recommendation was supported by moderate or low-certainty evidence, this reflected the panel's judgment that patient-safety considerations and the potential consequences of uncontrolled levothyroxine substitution outweighed the limited burden associated with maintaining formulation consistency or biochemical monitoring.

All five recommendations achieved 100% agreement among the 10 voting panelists. The final recommendations, certainty of evidence, strength of recommendation, Delphi agreement, and rationale are summarized in **Table 3**.

Table 3. Final consensus recommendations, evidence certainty, recommendation strength, and Delphi agreement.

Final consensus recommendation	Evidence certainty	Strength	Delphi agreement	Key rationale
R1: *It is recommended that patients remain on the same levothyroxine product* (*brand or generic*) *once a stable dose has been achieved.*	**Moderate**	**Strong**	**100%**	Formulation consistency may minimize avoidable variability in levothyroxine exposure and TSH control once biochemical stability has been achieved.
R2: *Switching between levothyroxine formulations should be limited to specific situations, including drug unavailability, intolerance to excipients, or cost considerations.*	**Moderate**	**Strong**	**100%**	Although switching appears acceptable at the population level, individual variability may occur; unnecessary switching provides limited clinical benefit in an already stable patient.
R3: *If switching is unavoidable, serum TSH should be reassessed* 6 - 8 *weeks after the change.*	**Moderate**	**Strong**	**100%**	The monitoring interval reflects levothyroxine pharmacokinetics and the time required to reach a new steady state; reassessment provides a low-burden means of detecting clinically relevant changes in thyroid status.
R4: *Switching should be avoided whenever possible in high-risk populations, including pregnant women, patients with differentiated thyroid cancer requiring TSH suppression, pediatric patients and elderly patients with cardiovascular disease.*	**Low-Moderate**	**Strong**	**100%**	Direct switching evidence in these populations is limited, but the clinical consequences of loss of precise thyroid control may be substantial, supporting a precautionary approach.
R5: Pharmacy-level substitution should not occur without appropriate communication with the prescribing physician and patient	**Low**	**Moderate/ Conditional**	**100%**	Direct evidence for communication strategies is limited; however, documentation and communication facilitate recognition of product changes, appropriate monitoring, and continuity of care.

4. Discussion

4.1. Pharmacology of Levothyroxine

Levothyroxine (L-thyroxine, LT4) is a synthetic form of the endogenous prohormone thyroxine (T4) and remains the standard therapy for hypothyroidism. Following oral administration, levothyroxine is absorbed predominantly in the jejunum and ileum, with an estimated bioavailability of 60% - 80% under fasting conditions. Its absorption is influenced by gastric pH, intestinal integrity, and concomitant ingestion of food, medications, and supplements. After absorption, LT4 is extensively protein-bound in circulation and undergoes peripheral deiodination to the active hormone triiodothyronine (T3), which mediates most of its biological effects [7] [15] [16].

Levothyroxine has a long elimination half-life of approximately 7 days in euthyroid individuals, allowing once-daily dosing but also resulting in a delayed steady state. Consequently, reassessment of thyroid function is recommended 6 - 8 weeks after initiation or dose adjustment. Due to its pharmacokinetic and phar-

macodynamic properties, levothyroxine is classified as a narrow therapeutic index (NTI) drug, meaning that small variations in systemic exposure can lead to clinically significant changes in serum thyroid-stimulating hormone (TSH) levels and clinical status. Both under-replacement and over-replacement are associated with adverse outcomes, including cardiovascular disease, osteoporosis, and impaired quality of life [17]-[20].

4.2. Factors Affecting Bioavailability

Levothyroxine bioavailability is affected by a wide range of physiological and external factors. Gastrointestinal disorders such as celiac disease, atrophic gastritis, and Helicobacter pylori infection can impair absorption and increase dose requirements. In addition, commonly used medications, including proton pump inhibitors, calcium supplements, and iron preparations, can significantly reduce LT4 absorption [16]-[18].

Formulation characteristics also play a critical role. Traditional tablet formulations require disintegration and dissolution prior to absorption, making them susceptible to variability in gastric conditions. In contrast, liquid solutions and soft gel capsules demonstrate more consistent absorption profiles and reduced sensitivity to interfering factors. Recent studies have shown improved TSH stability in patients switched from tablets to liquid formulations, particularly in those with malabsorption or polypharmacy [5] [20]-[23].

4.3. Bioequivalence and Its Limitations

Regulatory approval of generic levothyroxine formulations is based on pharmacokinetic bioequivalence, typically defined by the 80% - 125% acceptance range for area under the curve (AUC) and maximum concentration (Cmax). However, this standard approach, known as average bioequivalence (ABE), has important limitations when applied to NTI drugs such as levothyroxine [17] [20] [24].

ABE does not adequately account for within-subject variability or individual bioequivalence, both of which are critical for drugs requiring precise titration. Studies have demonstrated that two levothyroxine products deemed bioequivalent at the population level may not be interchangeable at the individual patient level. Furthermore, bioequivalence studies are conducted in healthy volunteers under controlled fasting conditions, which do not reflect real-world clinical scenarios where patients may have comorbidities, concomitant medications, or variable adherence [17] [25].

These limitations have led to ongoing debate regarding the adequacy of current regulatory standards for levothyroxine and other NTI drugs, with increasing calls for more stringent criteria or additional clinical evaluation [20].

4.4. Regulatory Considerations and Bioequivalence

The Saudi Food and Drug Authority (SFDA) applies specific bioequivalence requirements to narrow therapeutic index (NTI) drugs. Current SFDA/GCC bioe-

quivalence guidance specifies that, for NTI products, the conventional bioequivalence acceptance interval should be tightened to 90.00% - 111.11% for AUC; when Cmax is particularly relevant to safety, efficacy, or therapeutic monitoring, the same tightened interval should also be applied. Importantly, SFDA product-specific bioequivalence guidance explicitly identifies levothyroxine as an NTI drug and recommends a fully replicated crossover bioequivalence design using baseline-corrected serum levothyroxine concentrations. These enhanced regulatory requirements recognize the potential clinical importance of relatively small differences in levothyroxine exposure [26].

An additional theoretical consideration with repeated generic-to-generic substitution is the phenomenon of "biocreep." Two generic products may independently satisfy bioequivalence requirements relative to the same reference product without necessarily having been demonstrated to be directly bioequivalent to each other. Consequently, sequential switching among different generic products could theoretically result in incremental differences in drug exposure, a concern that may be particularly relevant for NTI medications [20]. However, this pharmacokinetic concern should be interpreted alongside contemporary real-world evidence showing no clinically significant deterioration in TSH control following generic-to-generic levothyroxine switching in stable adults. Thus, biocreep provides a rationale for avoiding unnecessary repeated or untracked substitution and for appropriate post-switch monitoring, rather than evidence that all generic-to-generic levothyroxine switching is clinically unsafe.

4.5. Role of Liquid and Soft-Gel Levothyroxine Formulations

Liquid and soft-gel levothyroxine formulations may provide a useful alternative in selected patients in whom reliable absorption of conventional tablets is compromised. Their use may be considered in patients with suspected or documented malabsorption, chronic atrophic gastritis or other conditions associated with altered gastric acidity, and in those receiving clinically important concomitant medications that interfere with tablet levothyroxine absorption, particularly when the interacting therapy cannot be discontinued or adequately separated from levothyroxine administration. Because liquid and soft-gel formulations are less dependent on tablet disintegration and gastric dissolution, switching to these formulations may improve levothyroxine bioavailability and biochemical control in selected patients. Consequently, thyroid function should be reassessed following such a formulation change, and the levothyroxine dose should be individualized because improved absorption may occasionally necessitate dose reduction [14].

4.6. Clinical Implications of Switching and Variability

Emerging evidence indicates that switching between levothyroxine formulations may lead to clinically significant variations in thyroid function. Observational studies have demonstrated that patients who switch between generic manufacturers are more likely to experience abnormal TSH levels compared with those who

remain on a consistent formulation. Even in cases where the nominal dose remains unchanged, formulation differences may alter bioavailability sufficiently to require dose adjustment [9] [10] [27].

In addition, levothyroxine is chemically unstable and sensitive to environmental factors such as temperature, humidity, and light. Variability in manufacturing processes and excipient composition may affect product stability and potency over time, further contributing to fluctuations in therapeutic response [27].

4.7. Clinical Evidence on Switching

Switching between different formulations of Levothyroxine has been extensively evaluated in recent years, with increasing reliance on real-world evidence. The available literature includes randomized crossover trials, observational cohort studies, pharmacovigilance data, and systematic reviews. Overall, the evidence remains heterogeneous, reflecting variability in study designs, populations, and the types of switching evaluated, including brand-to-generic, generic-to-generic, and formulation changes [28] [29].

4.8. Evidence Suggesting Stability with Generic-to-Generic Switching

Recent large-scale observational studies suggest that switching between generic levothyroxine products may not result in clinically significant changes in thyroid function at the population level. A notable comparative effectiveness study involving more than 15,000 patients found that switching among generic manufacturers was not associated with significant differences in serum TSH levels compared with maintaining the same product. The proportion of patients achieving normal TSH and the rates of markedly abnormal TSH values were similar between switchers and non-switchers [10].

These findings are supported by regulatory analyses, including evaluations by the U.S. Food and Drug Administration, which concluded that switching between approved generic levothyroxine products does not appear to result in clinically meaningful alterations in thyroid function in most patients [30]. However, these conclusions are largely based on aggregate data and may not fully capture inter-individual variability.

Available evidence requires a distinction between population-level interchangeability and individual biochemical response. Large real-world studies suggest that switching between approved generic levothyroxine manufacturers is generally not associated with clinically meaningful changes in TSH among stable adults. Nevertheless, population-level equivalence does not exclude clinically relevant variability in individual patients, particularly those requiring tight TSH control. Accordingly, the present recommendations should not be interpreted as indicating that generic-to-generic switching is inherently unsafe; rather, they emphasize avoidance of unnecessary or untracked switching, documentation of product changes, and appropriate biochemical follow-up. Manufacturer switching within the same

tablet dosage form should also be distinguished from switching between dosage forms. Conversion from tablet to liquid or soft-gel levothyroxine may improve absorption and increase effective drug exposure in selected patients, particularly in the presence of gastric disorders, malabsorption, or interfering medications, and may therefore necessitate individualized dose adjustment after biochemical reassessment [10] [12].

4.9. Evidence Suggesting Variability and Clinical Impact

In contrast, other studies and pharmacovigilance reports indicate that switching levothyroxine formulations may lead to clinically significant variability in TSH levels. Reports of adverse drug reactions have shown that formulation changes are frequently associated with loss of thyroid function control, with some patients developing biochemical hypo- or hyperthyroidism following substitution [25].

Mechanistic and clinical studies suggest that differences in excipients, dissolution profiles, and bioavailability between formulations can contribute to variability in systemic exposure and subsequent TSH fluctuations. These effects may be amplified in real-world settings where patients are exposed to additional variables such as dietary factors, concomitant medications, and adherence challenges [16]-[18].

4.10. Evidence from Formulation Switching (Tablet vs Liquid or Soft Gel)

An important subset of evidence relates to switching between different dosage forms rather than manufacturers. Several studies have demonstrated that switching from tablet levothyroxine to liquid or soft gel formulations may improve TSH stability, particularly in patients with malabsorption or those receiving interfering medications [22] [31]. These alternative formulations bypass the need for gastric dissolution, resulting in more predictable pharmacokinetics.

It has been shown that patients with previously unstable TSH levels on tablet formulations often achieve improved biochemical control after switching to liquid preparations without requiring dose adjustment. However, even in these cases, monitoring remains essential, as individual responses may vary [21] [31].

4.11. Interpretation of Conflicting Evidence

The variability in findings across studies can be attributed to several factors. Observational studies often assess outcomes at the population level and may underestimate clinically relevant variability in individual patients. Conversely, controlled trials may lack generalizability due to strict inclusion criteria. Furthermore, differences in the type of switching evaluated contribute to heterogeneity in outcomes [7] [32].

Importantly, even studies demonstrating no significant population-level effect acknowledge that individual patients may experience clinically meaningful changes in TSH following switching [10] [30]. This is particularly relevant for patients re-

quiring tight biochemical control.

4.12. Clinical Implications

Taken together, current evidence suggests that switching between levothyroxine formulations may be safe in many patients at the population level, particularly when involving approved generic products. However, clinically relevant variability may still occur in individual patients, especially in high-risk groups or in the presence of factors affecting drug absorption. Consequently, expert recommendations continue to emphasize maintaining patients on a consistent levothyroxine formulation whenever possible and reassessing TSH levels following any change in product [7]. This approach aims to minimize the risk of biochemical instability and optimize clinical outcomes.

4.13. Saudi Healthcare Context

Hypothyroidism represents an important endocrine disorder in Saudi Arabia; however, its national population prevalence remains uncertain because nationally representative epidemiological studies are lacking. Available Saudi studies show considerable variation according to geographic region, population characteristics, sampling strategy, and biochemical definitions. A primary-care study in Riyadh reported subclinical hypothyroidism in approximately 10% of 340 adults without previously recognized thyroid disease, while a separate study of Saudi women identified previously undiagnosed hypothyroidism in 5.5% of participants. More recent regional data have also demonstrated substantial heterogeneity; for example, a cross-sectional study from the Asir region reported primary hypothyroidism in 5.3% and subclinical hypothyroidism in 39.3% of the studied population. These regional estimates should not be interpreted as national prevalence figures. A recent systematic review of Saudi studies similarly concluded that the reported prevalence of overt and subclinical hypothyroidism varies substantially across populations and regions, highlighting the continuing need for nationally representative epidemiological data [33] [34].

Meta-analyses of Middle Eastern data indicate that Saudi Arabia has among the highest reported prevalence rates of thyroid disorders in the region, reaching approximately 31% in some pooled analyses. These findings are likely influenced by multiple factors, including iodine intake variability, genetic predisposition, high prevalence of autoimmune diseases, and comorbid conditions such as obesity and diabetes mellitus [35].

4.14. Levothyroxine Use in Saudi Arabia

Given the high prevalence of hypothyroidism, Levothyroxine is one of the most commonly prescribed endocrine medications in Saudi clinical practice. National health resources emphasize that hypothyroidism is a chronic condition requiring lifelong hormone replacement therapy, typically with daily levothyroxine administration [35] [36].

Although comprehensive national prescription databases are limited, indirect evidence from clinical studies and healthcare utilization patterns suggests widespread and increasing use of levothyroxine across primary, secondary, and tertiary care settings. The high burden of subclinical disease, frequent screening practices, and association with chronic conditions such as diabetes further contribute to the expanding population receiving levothyroxine therapy [35].

Importantly, the large number of patients on long-term levothyroxine therapy amplifies the clinical significance of formulation switching, as even small variations in bioavailability may affect a substantial patient population.

4.15. Real-World Practice Challenges in Saudi Arabia

Within the Saudi healthcare system, several structural and operational factors contribute to frequent switching between Levothyroxine formulations. Medication procurement in public healthcare institutions is largely driven by centralized tendering processes coordinated through the Saudi Ministry of Health, which may result in periodic changes in the available brands or generic formulations across healthcare facilities. Consequently, patients may be switched between products based on availability rather than clinical indication. Furthermore, variability in formularies across different healthcare sectors, including Ministry of Health hospitals, military healthcare systems, university hospitals, and private providers, increases the likelihood of formulation switching when patients transition between care settings. This fragmentation of care may contribute to inconsistent prescribing and monitoring practices. Although the Saudi Food and Drug Authority regulates the approval of levothyroxine products according to established bioequivalence standards, these criteria may not fully account for interindividual variability in therapeutic response, particularly for narrow therapeutic index drugs such as levothyroxine in real-world clinical settings [37].

4.16. National Guidance and Policy

The high prevalence of hypothyroidism, widespread use of levothyroxine, and systemic factors promoting formulation switching make this issue particularly relevant in Saudi Arabia. The combination of epidemiological burden and healthcare system characteristics increases the risk of inconsistent disease control at the population level. These realities underscore the urgent need for standardized, context-specific national guidance addressing levothyroxine prescribing, switching, and monitoring practices. Such guidance should aim to minimize unnecessary switching, ensure appropriate follow-up, and improve coordination between healthcare providers across different sectors.

The Saudi Ministry of Health has established policies governing generic medication substitution within healthcare institutions. According to the Ministry's generic substitution guidance, the Pharmaceutical Care Department is responsible for assessing the therapeutic class of medications requiring generic or brand substitution. Importantly, the policy states that substitution of NTI medications,

drugs sensitive to manufacturing variability, medications that are difficult to manufacture, biosimilars, and inhaled medications should not occur unless absolutely necessary and only following evaluation by the Pharmacy and Therapeutics Committee (PTC). Furthermore, when switching between formulary products of such medications is unavoidable, prescribers should be formally notified and appropriate patient monitoring should be implemented to identify and prevent unexpected clinical responses related to differences in bioavailability or therapeutic effect. The policy specifically identifies Levothyroxine among medications sensitive to manufacturing techniques and variability, highlighting the need for careful oversight during formulation switching. This national policy supports the principle of maintaining consistency in levothyroxine therapy and reinforces the importance of structured monitoring following any formulation change [38].

5. Conclusions & Recommendations

General Principle

Patients receiving levothyroxine should be maintained on a consistent formulation whenever possible. This recommendation is based on the narrow therapeutic index of levothyroxine and evidence demonstrating potential variability in TSH levels following switching [7] [10] [25].

Recommendation 1: ***It is recommended that patients remain on the same levothyroxine product*** **(*brand or generic*)** ***once a stable dose has been achieved.***

This recommendation is supported by international guidelines, including those from the American Thyroid Association, which emphasize maintaining formulation consistency to minimize variability in thyroid function [7]. Observational studies have also shown that maintaining the same formulation is associated with more stable TSH levels compared with switching [10].

Strength of recommendation: Strong.

Level of evidence: Moderate.

Recommendation 2: ***Switching between levothyroxine formulations should be limited to specific situations, including drug unavailability, intolerance to excipients, or cost considerations.***

Evidence suggests that while switching may be safe at the population level, individual variability can lead to clinically significant changes in TSH [7]. Therefore, switching should not be routine practice in stable patients.

Strength of recommendation: Strong.

Level of evidence: Moderate.

Recommendation 3: ***If switching is unavoidable, serum TSH should be reassessed*** **6 - 8** ***weeks after the change.***

This recommendation is based on the pharmacokinetics of levothyroxine and supported by multiple clinical studies demonstrating that TSH levels may change following formulation switching [7] [39].

Strength of recommendation: Strong.

Level of evidence: Moderate.

Recommendation 4: ***Switching should be avoided whenever possible in high-risk populations, including pregnant women, patients with differentiated thyroid cancer requiring TSH suppression, pediatric patients and elderly patients with cardiovascular disease.***

These groups require tight TSH control, and even small variations in levothyroxine exposure may have clinically significant consequences [7] [39] [40].

Strength of recommendation: Strong.

Level of evidence: Low-Moderate.

Operational pathway for unavoidable switching in high-risk patients

When levothyroxine switching is unavoidable in a high-risk patient, the change should be authorized or confirmed by the responsible treating physician, with pharmacist verification and counselling regarding the new product, consistent administration, and the importance of follow-up. The previous and new product, manufacturer, dose, formulation, reason and date of switching, and planned biochemical reassessment should be documented in the medical and medication records. In pregnancy, the obstetric/endocrine team should ensure thyroid function assessment approximately every 4 weeks during the first half of pregnancy and after a formulation change, with adjustment according to pregnancy-specific targets. In patients with differentiated thyroid cancer receiving TSH-suppressive therapy, the responsible endocrinology/oncology team should reassess thyroid function after switching and confirm maintenance of the individualized risk- and response-adapted TSH suppression target. In pediatric patients, follow-up should be coordinated by the treating pediatric/endocrine team according to age, growth, developmental stage, and clinical circumstances. In older adults with cardiovascular disease, the responsible physician should arrange closer clinical surveillance and individualized biochemical reassessment, with particular attention to symptoms or biochemical evidence of over-replacement [41] [42].

Recommendation 5: ***Pharmacy-level substitution should not occur without appropriate communication with the prescribing physician and patient.***

Unsupervised substitution has been associated with unintended switching and subsequent TSH instability in real-world settings [25]. Clear documentation and patient counseling are essential.

Strength of recommendation: Moderate.

Level of evidence: Low-Moderate.

To operationalize Recommendation 5, any levothyroxine substitution should follow a standardized notification process. The dispensing pharmacist should document and communicate to the prescriber and patient the previous and substituted product name and manufacturer, dose and formulation, date and reason for the change, and the planned date for TSH reassessment when applicable. This structured pharmacist-prescriber-patient communication pathway is consistent with Saudi Ministry of Health policy requiring formal prescriber notification and appropriate monitoring when substitution of medications sensitive to manufacturing variability, including levothyroxine, is necessary.

Clinical Algorithm for Levothyroxine Switching

To facilitate implementation of the consensus recommendations in clinical practice, a practical algorithm for levothyroxine formulation switching is presented in Figure 1. In clinically and biochemically stable patients, continuation of the same identifiable levothyroxine product is preferred whenever feasible. When switching is necessary, the product change should be documented, the patient should be counseled to maintain consistent administration practices, and thyroid function should generally be reassessed after approximately 6 - 8 weeks in stable, non-pregnant adults. Patients requiring tighter biochemical control should follow an individualized monitoring pathway. In particular, pregnancy requires more frequent thyroid function assessment according to pregnancy-specific recommendations and gestational targets, while pediatric patients, patients receiving TSH-suppressive therapy for differentiated thyroid cancer, and elderly patients with cardiovascular disease may also require closer clinical and biochemical surveillance. Subsequent dose adjustment should be guided by TSH, with FT4 assessment when clinically indicated.

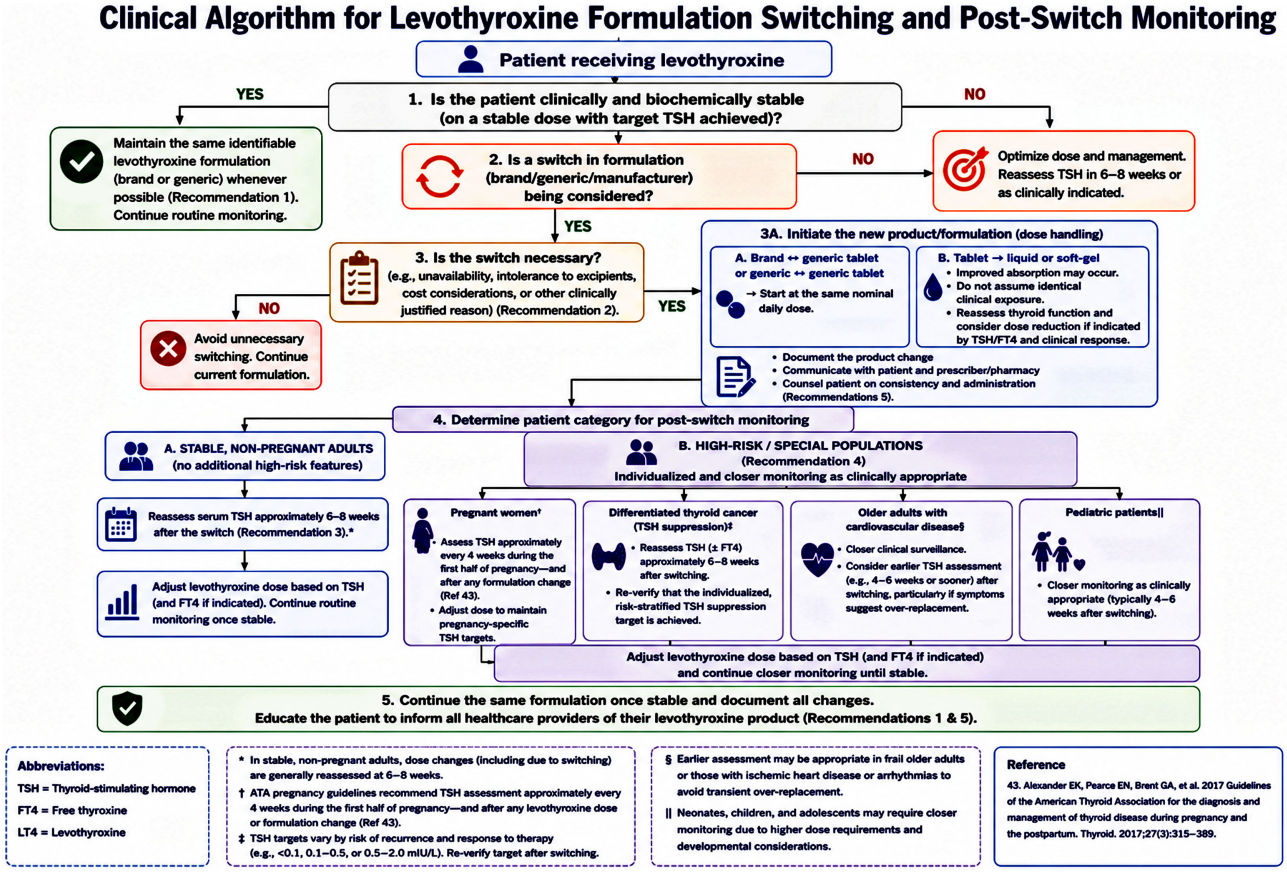

Figure 1. Clinical algorithm for levothyroxine formulation switching and post-switch monitoring.

The algorithm summarizes the recommended approach to patients receiving levothyroxine when a change in brand, generic manufacturer, or formulation is considered. Stable patients should preferably continue the same identifiable prod-

uct. When switching is necessary, the change should be documented and communicated to the patient and relevant healthcare professionals, followed by biochemical reassessment. In stable, non-pregnant adults, TSH should generally be reassessed approximately 6 - 8 weeks after switching. High-risk populations require individualized and potentially more intensive surveillance; in particular, pregnant women should undergo thyroid function monitoring according to pregnancy-specific intervals and therapeutic targets rather than the routine 6 - 8-week schedule. Abbreviations: FT4, free thyroxine; TSH, thyroid-stimulating hormone.

Funding

This consensus project received no external funding.

Expert Panel Membership

All members of the expert panel who participated in the consensus and Delphi voting are included as authors of this manuscript. Their institutional affiliations and professional disciplines are provided in the author information. Emad R. Issak contributed to the manuscript but was not a voting member of the expert panel and did not participate in the Delphi voting.

Patient and Public Involvement

Patients and members of the public were not involved in the development, deliberation, or Delphi voting of the consensus recommendations.

Author Contributions

Abdulrahman Alshaikh, Mohammed Alshennawi, Nasser Aljuhani, Anwar Jammah, Saad Alzahrani, Amani Alhozali, Mohammed Almehthel, Yasser Albarkah, Metib Alotaibi, and Saud Alsifri contributed to the expert-panel discussions, development and refinement of the consensus statements, and Delphi voting. Emad R. Issak contributed to the methodology, literature review and evidence synthesis, data curation and analysis of the consensus results, and preparation of the original manuscript draft. All authors contributed to the critical review and editing of the manuscript, approved the final version, and agreed to be accountable for the work.

Conflicts of Interest

The authors declare no conflicts of interest.

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