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Clinical Management, Lifestyle Factors, **1 and Quality of Life** in 1 Hypothyroidism: A Systematic Review 2 3 Abstract 4 This systematic review synthesizes contemporary evidence on the management 5 of hypothyroidism, with a focus on pharmacologic therapy, lifestyle factors, and 6 **quality of life (QoL)**. Eligible studies included adults with overt or subclinical 7 hypothyroidism and reported data on thyroid-specific or generic QoL, 8 biochemical outcomes, or cardiometabolic markers under pharmacologic and/or 9 lifestyle exposures. The literature comprised narrative reviews, randomized 10 controlled trials, observational studies, and instrument-validation papers. Across 11 studies, levothyroxine (LT4) monotherapy effectively normalized TSH in most 12 patients, yet a notable subset continued to experience fatigue, weight concerns, 13 and cognitive or mood symptoms despite biochemical euthyroidism. Emerging 14 approaches—such as LT4 plus liothyronine (LT3) and slow-release T3 15 formulations—showed more physiological T3 profiles and patient preference in 16 some trials, but consistent superiority over LT4 alone in QoL or symptom relief 17 has not been demonstrated, and long-term safety data remain limited. 18 Observational work linked lifestyle patterns (short or long sleep, low physical 19 activity, unhealthy diet, smoking, excess weight) with less favorable thyroid 20 indices and poorer QoL, while endurance-training interventions in subclinical 21 hypothyroidism improved fatigue and health-related QoL without major 22 changes in thyroid hormone levels. Nutritional reviews emphasized adequate— 23 but not excessive—intakes of iodine, selenium, iron, and other micronutrients, 24 and suggested that weight reduction may modestly improve thyroid function 25 and cardiometabolic risk in selected patients. Thyroid-specific patient-reported 26 outcome measures (ThyPRO and ThyPRO-39) demonstrated robust 27 psychometric properties and captured symptom burden not reflected by TSH 28 alone. Overall, current evidence supports LT4 as first-line therapy but highlights 29 unmet symptom needs, the potential adjunctive role of individualized 30 pharmacologic regimens and lifestyle interventions, and the importance of 31 routinely incorporating validated QoL instruments into the clinical and research 32 management of hypothyroidism. 33 34 35 36 37

Hypothyroidism: 41 A Systematic Review 42 1. Introduction 43 Hypothyroidism is a common endocrine disorder characterized by deficient 44 thyroid hormone production, leading to metabolic slowing, neurocognitive 45 symptoms, and increased cardiometabolic risk. Despite apparently adequate 46 levothyroxine (LT4) replacement, a substantial proportion of patients continue 47 to report fatigue, weight difficulties, and impaired quality of life. Growing 48 interest has therefore focused on alternative pharmacologic regimens (e.g., LT4 49 plus liothyronine [LT3], slow-release T3 formulations) and non-pharmacologic 50 strategies (diet, physical activity, and sleep optimization), as well as on 51 thyroid-specific patient-reported outcome measures. 52 The objective of this systematic review is to synthesize contemporary evidence 53 on (1) epidemiology and diagnosis of hypothyroidism, (2) pharmacologic 54 treatment including emerging formulations, (3) the role of lifestyle factors and 55 interventions, and (4) quality-of-life assessment and outcomes in adults with 56 overt or subclinical hypothyroidism. 57 58 2. Methods 59 2.1 Eligibility criteria (PICOS) 60 □ Population: Adults (≥18 years) with overt or subclinical hypothyroidism 61 of any etiology (autoimmune, post-surgical, radioiodine, drug-induced, or 62 idiopathic). 63 □ Interventions / Exposures: 64 o Pharmacologic: LT4 monotherapy, LT4+LT3, slow-release T3, 65 other novel thyroid hormone analogues. 66 o Lifestyle: structured exercise programs, dietary interventions, 67 weight-loss interventions, or observational assessments of lifestyle 68 (sleep, diet, physical activity, smoking). 69

□ Comparators: Usual care, LT4 alone, placebo, or no lifestyle 70 intervention, as appropriate. 71 □ Outcomes: 72 o Primary: thyroid-specific quality of life (e.g., ThyPRO, 73 ThyPRO-39) or general health-related QoL (e.g., SF-36, EQ-5D). 74 o Secondary: TSH, free T4, free T3; cardiometabolic outcomes 75 (weight/BMI, lipids, blood pressure); symptom scores (fatigue, 76 mood, sleep). 77 □ Study designs: Randomized or quasi-randomized controlled trials, 78 prospective or retrospective cohorts, cross-sectional

studies 79 developing/validating QoL tools. Narrative reviews and editorials are 80 included only for contextual discussion, not as primary data sources. 81 2.2 Search strategy 82 You can describe a standard search, for example: 83 We searched MEDLINE, Embase, Web of Science, and the Cochrane Library 84 from inception to [month/year], using combinations of terms such as 85 —hypothyroidism,|| —subclinical hypothyroidism,|| —levothyroxine,|| 86 —liothyronine,|| —exercise,|| —diet,|| —quality of life,|| and —ThyPRO.|| Reference 87 lists of key reviews and included studies were hand-searched to identify 88 additional relevant articles. No language restrictions were applied initially; only 89 articles with an English abstract and sufficient extractable data were included. 90 In your actual manuscript you would insert the exact search strings and dates. 91 2.3 Study selection 92 Explain the PRISMA process: 93 Two reviewers independently screened titles and abstracts for relevance, 94 followed by full-text assessment against inclusion criteria. Disagreements were 95 resolved by discussion or third-reviewer adjudication. The selection process will 96 be documented in a PRISMA flow diagram. 97 You then state that 20 key articles met the criteria for qualitative synthesis (and 98 specify how many were trials vs observational vs instrument validation). 99 2.4 Data extraction 100 Describe that you extracted: 101

- Study characteristics: year, country, setting, design, sample size, 102 hypothyroidism type. 103
- Intervention or exposure details: drug regimen (dose, formulation), 104 lifestyle program (mode, intensity, duration). 105
- Outcomes: type of QoL instrument, timing of assessment, biochemical 106 and cardiometabolic outcomes. 107
- Effect estimates and measures of variability when available. 108

2.5 Risk of bias assessment 109

- RCTs: Cochrane risk-of-bias tool (randomization, blinding, incomplete 110 outcome data, selective reporting). 111
- Observational studies: Newcastle–Ottawa Scale (selection, comparability, 112 outcome assessment). 113
- Instrument studies: appropriate psychometric quality criteria (sample size, 114 factor structure, reliability, validity). 115

Because you are doing a systematic review (not necessarily a quantitative 116 meta-

analysis), you can limit yourself to qualitative judgments (low / moderate / 117 high risk).  
118 3. Results 119 3.1 Study selection and characteristics 120 Summarize what your 20  
articles represent. For example: 121 □ 6 broad reviews or overviews of hypothyroidism  
epidemiology, 122 diagnosis, and treatment. 123 □ 3 articles on emerging pharmacologic  
therapies and slow-release T3 124 preparations. 125 □ 4 studies focusing on lifestyle  
factors or interventions (exercise, diet, 126 weight loss). 127 □ 4 studies on quality-of-life  
measurement and ThyPRO / ThyPRO-39. 128 □ 3 patient-focused or survey studies  
exploring residual symptoms and 129 treatment satisfaction. 130 Give a short narrative  
describing the typical sample sizes and populations (e.g., 131 mostly middle-aged women  
with autoimmune hypothyroidism; some cohorts 132 with subclinical disease). 133

3.2 Epidemiology and diagnosis 134 Use the general reviews and epidemiology paper to  
state: 135 □ Hypothyroidism is highly prevalent, with higher rates in women and 136 older  
adults. 137 □ Diagnostic practice relies on TSH, supported by free T4 (and sometimes 138  
TPO antibodies) to distinguish overt from subclinical disease. 139 □ The recent editorials  
highlight ongoing debate about TSH cut-off values, 140 individualized reference ranges,  
and the clinical significance of 141 subclinical hypothyroidism. 142 3.3 Pharmacologic  
management and emerging therapies 143 From the treatment-oriented papers, you can  
synthesize: 144 □ Levothyroxine monotherapy remains the standard of care and 145  
effectively normalizes TSH in most patients, but 10–15% report 146 persistent symptoms  
despite biochemical euthyroidism. 147 □ Combination LT4+LT3 therapy: Trials and  
position papers indicate 148 that, on average, combination therapy does not consistently  
outperform 149 LT4 alone in QoL or cognitive outcomes, but subsets of patients may 150  
prefer it, and genetic variation in deiodinase enzymes has been proposed 151 as a  
modifier. 152 □ Slow-release T3 formulations: Pilot studies show more physiologic T3 153  
profiles (less peak-trough variability), with preliminary evidence of 154 improved symptom  
control in some patients, but long-term safety and 155 definitive benefit remain unclear.  
156 □ Guideline perspective: Recent consensus pieces emphasize that LT4 157

monotherapy should remain first-line, with combination therapy 158 considered only in selected patients after careful discussion, and 159 preferably within research protocols. 160 3.4 Lifestyle factors and interventions 161 Using the lifestyle and QoL papers: 162 □ Cross-sectional lifestyle associations: 163 o Studies in subclinical hypothyroidism report that short or long 164 sleep, low physical activity, smoking, and poorer diet quality are 165 associated with higher TSH or adverse thyroid homeostasis indices. 166

o Women with hypothyroidism often display clustering of unhealthy 167 behaviors (sedentary time, suboptimal diet), which correlates with 168 worse self-reported QoL and fatigue. 169 □ Exercise interventions: 170 o A randomized trial of endurance training in women with 171 subclinical hypothyroidism found significant improvements in 172 health-related QoL (particularly vitality/fatigue domains) and 173 exercise capacity, with only modest or no change in thyroid 174 hormone levels. 175 o These data suggest that physical activity primarily improves 176 symptoms and cardiometabolic fitness rather than —curingll 177 hypothyroidism biochemically. 178 □ Diet and weight-loss interventions: 179 o Systematic and narrative reviews indicate that correcting overt 180 iodine deficiency and ensuring adequate selenium and iron intake 181 are important for thyroid health, but routine high-dose 182 supplementation is not supported for all patients. 183 o Weight-loss programs and bariatric surgery can reduce TSH and 184 may allow modest dose reductions of LT4 in obesity-related 185 hypothyroidism, although normalization of thyroid function 186 depends mostly on underlying etiology. 187 o Specific restrictive patterns (e.g., gluten-free in non-celiac patients) 188 lack robust evidence and should be individualized. 189 Overall, the lifestyle literature supports holistic cardiovascular risk reduction 190 and symptom management, rather than lifestyle alone as a primary therapy for 191 established hypothyroidism. 192 3.5 **1 Quality of life and** patient-reported outcomes 193 From the ThyPRO and patient survey papers: 194 □ Instrument development and validation: 195 o ThyPRO and its short form ThyPRO-39 are reliable, multi-domain 196 instruments that capture thyroid-specific physical, cognitive, and 197

emotional impacts. 198 o Factor analyses confirm stable domain structures and good internal 199 consistency across languages and cultures. 200

□ Use in treatment studies: 201 o QoL scores improve after initiation or optimization of LT4 in 202 newly diagnosed hypothyroidism, but many patients remain more 203 symptomatic than healthy controls. 204 o Exercise interventions show clinically meaningful reductions in 205 fatigue and improvements in vitality domains of generic QoL 206 measures. 207 □ Patient perspectives: 208 o International surveys highlight frequent dissatisfaction with care, 209 perceived under-recognition of residual symptoms, and interest in 210 individualized treatment approaches (including combination 211 therapy and lifestyle guidance). 212 3.6 Risk of bias 213 Provide a brief narrative: 214 □ Many lifestyle studies are cross-sectional and therefore susceptible to 215 confounding and reverse causality. 216 □ Exercise and pharmacologic trials often have small sample sizes and short 217 follow-up, limiting power to detect long-term effects on hard endpoints. 218 □ Blinding is challenging in lifestyle trials; subjective QoL outcomes are 219 particularly prone to expectation bias. 220 □ QoL instrument validation studies generally meet modern psychometric 221 standards but are not designed to assess treatment efficacy. 222 223 4. Discussion 224 4.1 Main findings 225 Summarize the synthesis: 226 □ Standard LT4 replacement remains effective for biochemical correction, 227 but a non-trivial subgroup experiences persistent symptoms. 228 □ Emerging therapies (LT4+LT3, slow-release T3) offer theoretical 229 advantages and may help selected patients, yet robust evidence for broad 230 adoption is lacking. 231

□ Lifestyle factors—especially physical activity, sleep patterns, and overall 232 dietary quality—are consistently associated with thyroid function and 233 **1 quality of life, and** structured exercise interventions appear beneficial for 234 symptoms and general health even when hormone levels change little. 235 □ Thyroid-specific QoL tools such as ThyPRO/ThyPRO-39 are valuable for 236 capturing the patient experience and should be

incorporated into both 237 research and routine care. 238 4.2 Clinical implications 239 □ Clinicians should go beyond TSH normalization, systematically assessing 240 fatigue, mood, sleep, and daily functioning using validated 241 questionnaires. 242 □ Exercise and general lifestyle counselling should be considered integral 243 components of hypothyroidism management, particularly in subclinical 244 disease and in patients with cardiometabolic risk factors. 245 □ Combination or novel hormone therapies might be considered on an 246 individual basis after ruling out other contributors to symptoms (e.g., 247 depression, sleep apnea, anemia), ideally within research frameworks or 248 with careful monitoring. 249 250 4.3 Research gaps 251 From this set of articles, you can highlight: 252 □ Need for large, long-duration RCTs of LT4+LT3 and slow-release T3, 253 with standardized QoL endpoints and stratification by genetic markers 254 (e.g., deiodinase polymorphisms). 255 □ Well-designed trials of combined lifestyle interventions (exercise, diet, 256 sleep hygiene) in overt and subclinical hypothyroidism, including 257 mechanistic biomarkers (inflammation, metabolic parameters). 258 □ Greater representation of low- and middle-income countries and diverse 259 populations, especially given differences in iodine nutrition and 260 healthcare access. 261 □ Continued development and cross-cultural validation of thyroid-specific 262 PROMs and exploration of minimally important differences for clinical 263 decision-making. 264 4.4 Strengths and limitations of this review 265

□ Strengths: Integrates recent high-quality reviews, trials, observational 266 studies, and QoL instrument work; emphasizes both biomedical and 267 lifestyle dimensions of hypothyroidism. 268 □ Limitations: Heterogeneity of study designs and outcomes precludes 269 formal pooled meta-analysis; many included lifestyle studies are 270 observational; some emerging therapies have very small early-phase 271 trials. 272 273 5. Conclusion 274 Recent literature underscores that hypothyroidism is not solely a biochemical 275 disorder corrected by TSH normalization. While LT4 monotherapy remains the 276 therapeutic mainstay, persistent symptoms in a subset of patients,

together with 277 evidence for lifestyle influences and validated QoL measures, argue for a more 278 holistic, patient-centered approach. Future research should prioritize rigorous 279 trials of individualized pharmacologic regimens and multifaceted lifestyle 280 interventions, using thyroid-specific patient-reported outcomes to evaluate 281 real-world benefit. 282 283

## Sources

1 <https://pmc.ncbi.nlm.nih.gov/articles/PMC7232900/>  
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