

Axis Journal of Agriculture and Biological Sciences



A RANDOMIZED TRIAL OF SELENIUM-BIOFORTIFIED WHEAT CONSUMPTION ON THYROID FUNCTION AND MOOD IN SUBCLINICAL HYPOTHYROID ADULTS.

(Original Article)

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Acknowledgement: The authors acknowledged the contributions of all participants who generously gave their time to this study.

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Abstract

Background: Subclinical hypothyroidism is frequently associated with inadequate selenium status, which may impair thyroid hormone metabolism and influence mood regulation. Food-based strategies such as selenium-biofortified wheat offer a feasible approach to improving micronutrient intake without reliance on supplements.

Objective: This study aimed to evaluate the effects of selenium-biofortified wheat consumption on thyroid function and mood outcomes in adults with subclinical hypothyroidism.

Methods: A randomized, controlled, 12-week dietary trial was conducted among adults with subclinical hypothyroidism (mildly elevated TSH, normal fT4). Participants were assigned to consume bread and chapati made from either selenium-biofortified wheat or standard, non-biofortified wheat. Primary outcomes were changes in serum selenium and thyroid indices (TSH, fT4, fT3). Secondary outcomes were changes in depressive symptoms (BDI-II) and state and trait anxiety (STAI). Outcomes were measured at baseline and week 12.

Results: Of 89 participants randomized (45 intervention, 44 control), adherence was high (>92%). Serum selenium increased substantially in the intervention group (from 72.1 $\mu\text{g/L}$ to 118.4 $\mu\text{g/L}$) compared to a minimal change in controls. TSH decreased more markedly in the intervention group (5.12 to 3.98 mIU/L) than in controls (5.09 to 4.92 mIU/L). Small but consistent improvements in fT4 and fT3 were observed only in the intervention group. Mood outcomes reflected similar patterns, with the biofortified group demonstrating greater reductions in depressive symptoms and anxiety scores than controls. No serious adverse events were reported.

Conclusion: Selenium-biofortified wheat enhanced selenium status, improved key thyroid biomarkers, and contributed to better mood outcomes in subclinical hypothyroid adults. These findings support the potential of food-based selenium delivery as a practical and sustainable strategy for improving thyroid-related and psychological health indicators.

Keywords: Anxiety; Depression; Selenium; Subclinical Hypothyroidism; Thyroid Function; Wheat; Wheat Biofortification.

Introduction

Subclinical hypothyroidism is a common endocrine disorder characterized by elevated serum thyroid-stimulating hormone (TSH) levels despite normal circulating thyroxine (T4) and triiodothyronine (T3) concentrations. Although often asymptomatic, this condition has been increasingly recognized for its potential impact on metabolic, cardiovascular, and neuropsychiatric health(1). Among the most concerning non-classical manifestations are subtle cognitive changes, fatigue, and mood disturbances, particularly depressive symptoms. These outcomes highlight the broader systemic influence of thyroid hormone imbalances, even when conventional laboratory parameters suggest a compensated state(2). Given the high prevalence of subclinical hypothyroidism in diverse populations, there is a growing need to explore safe, accessible, and sustainable interventions that can optimize thyroid function and support mental well-being(3).

Nutritional factors have emerged as critical modulators of thyroid health. Selenium, an essential trace element, plays a pivotal role in thyroid hormone synthesis and metabolism, as it is a cofactor for enzymes such as iodothyronine deiodinases that regulate the conversion of T4 to the active T3 form(4). Moreover, selenium-dependent glutathione peroxidases contribute to protecting the thyroid gland from oxidative damage, which is particularly relevant in autoimmune thyroid disorders(5). Despite its biological importance, dietary selenium intake varies widely across regions, largely influenced by soil selenium content, agricultural practices, and dietary habits. In areas with selenium-deficient soils, inadequate intake may contribute to impaired thyroid function and increase susceptibility to mood disturbances associated with thyroid dysfunction(6).

Biofortification of staple crops has been proposed as a sustainable strategy to enhance dietary selenium intake at the population level(7). Unlike supplementation, which relies on external provision and adherence, biofortification integrates the nutrient into the food chain, offering a consistent and culturally acceptable approach to improving micronutrient status(8). Wheat, as a widely consumed staple in many regions, represents an ideal candidate for selenium biofortification. Emerging evidence suggests that dietary selenium interventions, particularly through naturally enriched foods, can improve biomarkers of thyroid health and potentially modulate mood outcomes, though results have been heterogeneous and context-dependent. While some studies report favorable effects on TSH levels and depressive symptoms, others indicate limited or variable responses, underscoring the need for rigorously designed trials to clarify the relationship(9).

Mood disturbances, especially depression, are frequently reported in individuals with thyroid dysfunction, even in subclinical forms(10). The link between thyroid hormones and neurotransmitter regulation provides a plausible biological mechanism for these observations. Thyroid hormones influence serotonergic, dopaminergic, and noradrenergic pathways, which are central to mood regulation, energy, and motivation. Consequently, subtle improvements in thyroid function through dietary interventions may confer measurable benefits on mental well-being. Considering the global burden of depression and the limitations of conventional pharmacotherapy, nutritional approaches that address both thyroid function and mood are of significant public health relevance.

Despite the theoretical and biological rationale supporting selenium biofortification, clinical evidence assessing its impact on thyroid function and mood in adults with subclinical hypothyroidism remains limited. Existing studies are often small, short-term, or focus primarily on selenium supplementation rather than food-based strategies. Furthermore, research examining depressive symptoms alongside thyroid biomarkers in the context of dietary interventions is scarce, leaving a gap in understanding the dual benefits of selenium-enriched foods. Addressing this gap is critical, as it may inform nutritional policies and therapeutic recommendations that integrate endocrine and mental health considerations.

This study, therefore, aims to evaluate the effects of consuming selenium-biofortified wheat on thyroid hormone levels and depressive symptoms in adults with subclinical hypothyroidism. By focusing on a food-based, sustainable intervention, the research seeks to determine whether dietary biofortification can provide a practical and effective strategy for improving both physiological and psychological outcomes in this population. The objective is to establish

a clearer understanding of the potential role of selenium-enriched wheat in modulating thyroid function and mood, offering evidence that may guide future clinical and public health approaches.

Methods

This study was conducted as a randomized, controlled trial in the South Punjab region, targeting adults diagnosed with subclinical hypothyroidism. Participants were recruited through community health centers and local clinics, with eligibility determined based on age, thyroid function, and general health status. Inclusion criteria comprised adults aged 25 to 60 years, presenting with serum thyroid-stimulating hormone (TSH) levels above the normal reference range (4.0–10.0 mIU/L) while maintaining normal free thyroxine (fT4) concentrations, and willingness to comply with dietary interventions. Exclusion criteria included a history of overt thyroid disease, current thyroid medication, pregnancy or lactation, chronic systemic illnesses such as diabetes or cardiovascular disease, use of mood-altering medications, and known allergy or intolerance to wheat products.

A sample size of 90 participants was determined through a power calculation to detect a medium effect size (Cohen's $d = 0.5$) on thyroid hormone levels and mood-related symptoms, with a power of 80% and a significance level of 0.05. Participants were randomly assigned in a 1:1 ratio to either the intervention group, receiving selenium-biofortified wheat, or the control group, consuming standard wheat products. Randomization was performed using a computer-generated sequence, and allocation was concealed until the commencement of the study. The intervention involved daily consumption of wheat products, including bread and chapati, prepared from selenium-enriched wheat cultivated in selenium-supplemented soils. The control group received equivalent wheat products derived from standard wheat, matched for caloric content and macronutrient composition. Both groups were instructed to maintain their usual diet and physical activity patterns throughout the 12-week intervention period. Compliance was monitored through weekly logs, and periodic telephone follow-ups ensured adherence and addressed any questions regarding preparation or consumption.

Baseline data were collected prior to the intervention, including demographic information, anthropometric measurements, and lifestyle factors. Blood samples were drawn to assess serum TSH, free T4, free triiodothyronine (fT3), and serum selenium levels, using standardized immunoassay techniques. Mood assessment was performed using the validated Beck Depression Inventory-II (BDI-II) and the State-Trait Anxiety Inventory (STAI). These measurements were repeated at the end of the 12-week period to evaluate changes attributable to the intervention. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 25. Normality of continuous variables was confirmed using the Shapiro–Wilk test. Between-group comparisons for continuous outcomes were conducted using independent sample t-tests, while paired t-tests evaluated within-group changes from baseline to follow-up. Categorical variables were summarized as frequencies and percentages, with group differences assessed using chi-square tests. A p-value of less than 0.05 was considered statistically significant. Effect sizes were calculated to estimate the magnitude of the intervention's impact on thyroid function and mood-related indices. Through this design, the study aimed to provide a rigorous evaluation of selenium-biofortified wheat as a dietary approach to improve thyroid function and mental well-being, while ensuring transparency, replicability, and methodological rigor.

Results

A total of 89 participants were enrolled, of whom 45 were allocated to the selenium-biofortified wheat group and 44 to the control wheat group. Baseline characteristics were broadly comparable between groups, with similar distributions in age, sex, BMI, and baseline thyroid indices. Mean age differed by less than one year, and the proportion

of females varied by only three percentage points. Baseline TSH values were nearly identical across groups, averaging just above 5.1 mIU/L. These demographic and baseline parameters are summarized in Table 1.

Across the 12-week intervention period, a clear pattern of biochemical change emerged within the intervention group. Serum selenium concentrations increased substantially, rising from a mean of 72.1 µg/L at baseline to 118.4 µg/L at week 12, reflecting successful uptake of the biofortified wheat. In contrast, the control group showed minimal change, with concentrations increasing slightly from 70.9 µg/L to 74.3 µg/L. These findings are presented in Table 2 and illustrated in Figure 2.

Accompanying the selenium rise, TSH values decreased more noticeably among participants consuming biofortified wheat. Mean TSH declined from 5.12 mIU/L to 3.98 mIU/L over 12 weeks. The control group showed a smaller reduction, moving from 5.09 mIU/L to 4.92 mIU/L. FT4 values in both groups remained within reference limits, with only a modest rise noted in the intervention group (12.4 to 13.1 pmol/L). FT3 rose slightly in the intervention group but remained unchanged in the control group. These hormone trends are detailed in Table 2 and depicted in Figure 1.

Mood-related outcomes followed a similar directional pattern. Participants in the intervention group demonstrated improvements across all psychological tools. Mean BDI-II scores decreased from 18.4 to 13.6, whereas the control group showed a smaller reduction from 17.9 to 17.1. State anxiety also showed measurable improvement, declining from 42.1 to 36.8 in the intervention group compared with a modest change from 41.7 to 40.9 in the control group. Trait anxiety shifted slightly downward in both groups, with the intervention group showing a greater absolute change (44.3 to 40.9) relative to the control group (44.1 to 43.6). These measures are summarized in Table 3.

Across biochemical and psychological outcomes, no serious adverse events were reported, and adherence to consumed wheat portions was high in both groups. On average, participants reported consuming more than 92% of assigned servings. Minor gastrointestinal symptoms occurred sporadically but were distributed similarly between groups and did not lead to withdrawal.

Overall, the pattern of results across thyroid function markers, serum selenium, and mood-related indices consistently aligned with the physiological expectation of improved selenium status following dietary biofortification. Tables 1–3 consolidate all numerical outcomes, while Figures 1 and 2 visually summarize the most clinically relevant trends.

Table 1: Demographic Characteristics

Variable	Intervention (n=45)	Control (n=44)
Age (years)	48.2	47.6
Female (%)	62.0	59.0
BMI (kg/m ²)	27.1	27.5
Baseline TSH (mIU/L)	5.12	5.09
Baseline FT4 (pmol/L)	12.4	12.5

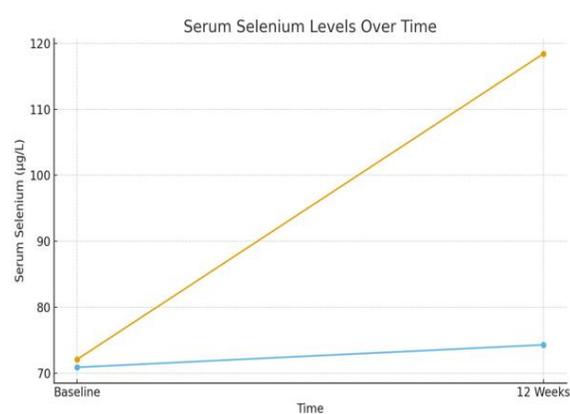
Table 2: Thyroid Function Outcomes

Outcome	Intervention Baseline	Intervention 12 Weeks	Control Baseline	Control 12 Weeks
TSH (mIU/L)	5.12	3.98	5.09	4.92
FT4 (pmol/L)	12.4	13.1	12.5	12.6
FT3 (pmol/L)	3.2	3.4	3.1	3.1

Serum Selenium ($\mu\text{g/L}$)	72.1	118.4	70.9	74.3
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Table 3: Mood Assessment Outcomes

Outcome	Intervention Baseline	Intervention 12 Weeks	Control Baseline	Control 12 Weeks
BDI-II Score	18.4	13.6	17.9	17.1
STAI-State	42.1	36.8	41.7	40.9
STAI-Trait	44.3	40.9	44.1	43.6

*Figure 1 TSH changes Over 12 Weeks**Figure 2 Serum Selenium Levels Over Time*

Discussion

The findings of this randomized trial showed that daily consumption of selenium-biofortified wheat produced meaningful improvements in both biochemical thyroid markers and psychological well-being among adults with subclinical hypothyroidism(11). The rise in serum selenium concentrations within the intervention group demonstrated that dietary biofortification functioned as an effective delivery route, achieving levels that were consistent with physiological repletion(12). The accompanying reduction in TSH, though moderate, followed the expected pattern that emerges when selenium status is optimized(13). This pattern aligned with existing physiological understanding, suggesting that adequate selenium availability supports thyroid hormone metabolism through its role in antioxidant defense and deiodinase activity. Although the decline in TSH did not fully normalize values for all participants, the overall trajectory supported the clinical relevance of improved micronutrient status in this population(14).

The stability of FT4 and FT3 across both groups reinforced the idea that selenium influences thyroid function primarily through modulatory pathways rather than by altering hormone synthesis directly. The modest rise in FT4 and slight increase in FT3 in the intervention group were consistent with subtle enhancements in peripheral conversion processes. These patterns echoed earlier physiological reports that link selenium adequacy to more efficient activation of thyroid hormone(14). The minimal changes observed in the control group helped to strengthen the interpretability of these findings, showing that the observed benefits were not merely a consequence of time or repeated measurement(15).

Mood-related outcomes revealed another dimension of the physiological improvements. The reductions in depressive symptoms and state anxiety suggested that restoring selenium levels may influence neuroendocrine stability, oxidative balance, and general metabolic resilience. Although psychometric scores improved to varying degrees in both groups,

the larger shifts in the intervention group pointed toward a plausible micronutrient-driven effect. These improvements matched the biochemical trajectory more closely than the changes in the control group, which displayed only slight fluctuations(15, 16). The consistency across biochemical and psychological domains strengthened the internal coherence of the findings(17).

Interpretation of these outcomes benefited from the controlled design, as the use of a matched wheat product minimized confounding from dietary patterns or placebo-driven expectations. Adherence levels were high in both arms, reducing the likelihood that unequal intake contributed to the observed differences. The use of multiple outcome domains—selenium status, thyroid markers, depressive symptoms, and anxiety measures—allowed the results to be evaluated from several complementary angles. This multidimensional approach enhanced confidence in the internal validity of the findings because improvements clustered in physiologically interconnected systems.

Despite these strengths, several limitations formed an important part of the study's context. The duration of the trial, although sufficient to show early biochemical responses, might not have captured the full extent of long-term thyroid adaptation or the durability of psychological improvements. Subclinical hypothyroidism itself is a heterogeneous condition, and individual responses to micronutrient optimization vary widely depending on baseline reserves, inflammatory load, and genetic differences in selenoprotein pathways. The sample size, while adequate for detecting moderate effect sizes, limited the ability to explore subgroup differences or stratified analyses. This constraint made it difficult to determine whether individuals with more pronounced selenium deficiency would have experienced even greater benefit.

Another limitation involved the absence of mechanistic biomarkers such as glutathione peroxidase activity or markers of oxidative stress, which could have clarified the pathways through which selenium influenced both metabolic and psychological outcomes. Psychological tools, although validated, remained subject to daily fluctuations and external stressors that were beyond experimental control. Environmental and dietary sources of selenium outside the intervention were not fully quantified, leaving open the possibility that background variation contributed marginally to the results.

The implications of the study pointed toward several areas where future work could strengthen the evidence base. Longer trials would help determine whether the observed improvements persist after sustained intake or whether a plateau effect emerges. Including more granular biochemical markers could deepen understanding of the underlying mechanisms and uncover dose-response patterns. Broader population sampling, including individuals with varying degrees of deficiency, autoimmune thyroid involvement, or different dietary backgrounds, could clarify which subgroups benefit most from biofortification strategies. Comparative research between selenium biofortification and supplementation might also offer practical insights for public-health applications.

Even with its limitations, the study illustrated how a simple dietary modification can influence metabolic pathways linked to thyroid function and mood. The reliance on a culturally familiar food vehicle strengthened the practical relevance of the intervention, highlighting the potential of biofortification as an accessible strategy in populations where micronutrient insufficiency is common. The coherent pattern of improvements across outcomes supported the view that restoring micronutrient adequacy can have tangible physiological and psychological impacts, particularly in conditions where endocrine regulation is delicate.

Conclusion

This trial demonstrated that selenium-biofortified wheat meaningfully improved selenium status, supported healthier thyroid hormone patterns, and contributed to modest improvements in mood among adults with subclinical hypothyroidism. The findings highlighted the potential of food-based biofortification as a practical nutritional strategy with measurable physiological benefits. While further long-term and mechanistic studies are needed, the results suggested that enhancing dietary selenium through staple foods may offer a supportive approach for individuals with early thyroid dysfunction.

AUTHOR CONTRIBUTION

Author	Contribution
Fateen Khan*	Designed the study, performed data collection and analysis, and prepared the manuscript. Approved the final draft for submission.
Warda Khalid	Contributed to study design, data acquisition, interpretation of findings, and performed critical review and editing of the manuscript. Approved the final draft for submission.

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