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Assessment of Thyroid Hormonal Dysfunction and Related Oxidative Stress in Menopausal Women with Irritable Bowel Syndrome

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Abstract

***Background*:** The thyroid gland plays a vital role in regulating metabolism, development, and energy balance, and is particularly sensitive to hormonal fluctuations and the aging process. Menopause and irritable bowel syndrome (IBS) are two conditions that independently influence endocrine and gastrointestinal function, and their coexistence may further contribute to systemic physiological disturbances. As well as, the oxidative stress act as a potential mediator affecting both thyroid function and gastrointestinal symptoms. This study aimed to evaluates the relationship between thyroid function during menopausal lifestyle with IBS,

***Methodology*:** A total of 80 menopausal women were included: 50 patients with IBS (25 early menopause: 40–45 years and 25 late menopauses: 50–60 years) and 30 healthy women in same both menopause stages without IBS as controls (15 participants in each menopause stage). All participants provided informed consent. Serum levels of T3, T4, FT3, FT4, and TSH were measured using the automated Roche Cobas e411 immunoassay platform. Also, the human total oxidant status (TOS) and total antioxidant capacity (T-AOC) were determined (ELISA) method, according to the procedure provided by the manufacturer's instructions, Biont Co., Germany. A one-way ANOVA test was applied for data and used Least significant difference (LSD) to assess differences among groups. Pearson's correlation was used to evaluate the relationship between two numerical variables. A p-value of < 0.05 was considered statistically significant

***Results*:** Seum TSH and FT3 levels were significantly elevated and serum TT3, TT4 and FT4 were reduced in both early and late menopause in IBS women patients compared to both controls women with menopause stages without IBS respectively. Whereas, a high serum TSH concentration was observed in late menopause women with IBS compared to early menopause stage. Besides, a notable reduction ($P<0.0001$) of both serum TT4 and FT4 levels in late menopause compared to early menopause and control among IBS women patients. The oxidant-antioxidant status TOS showed a high significant in late menopause with IBS women compared the women without IBS in same stage. while, serum TOS levels not changeable significantly during early menopause among IBS patients than in control women. In conversely, serum TAC significantly reduced in both early and late menopause respectively among IBS women patients compared to the control women without IBS.

***Conclusion*:** This study reports that hormonal dysfunction status in thyroid gland during menopausal stage associated with IBS. This observed hormonal disturbances-particularly elevated TSH with lower both serum TT4 and FT4 levels upon HPT axis may be suggest an increased risk of hypothyroidism in late menopause than early menopause by the oxidative stress among IBS patient's women.

Keywords: *Hormone Thyroid Dysfunction, Menopause, IBS, Oxidative stress and Hypothyroidism.*

INTRODUCTION

Basically, the thyroid gland, which regulates metabolism, development, and energy balance, is particularly sensitive to hormonal changes and aging. During menopause, estrogen deficiency leads to a decline in thyroxine-binding globulin (TBG), subsequently reducing total T3 and T4 levels, though free hormone levels may remain within reference ranges (Gietka-Czernel, 2017a; Honour, 2018). Women are disproportionately affected, with symptoms often exacerbated during periods of hormonal fluctuation, such

as the menstrual cycle and menopause (Heitkemper & Chang, 2009). So, the menopause, well defined by the permanent cessation of menstruation for 12 consecutive months due to declining ovarian hormone production, is accompanied by systemic changes impacting multiple organ systems (Peacock et al., 2025). On the other hand, Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by recurrent abdominal pain and alterations in bowel habits, often linked to disruptions in the brain-gut axis (Lenhart et al. 2020).

Menopause and irritable bowel syndrome (IBS) frequently coexist in midlife women and share interrelated physiological mechanisms. Estrogen deficiency during menopause affects gastrointestinal motility, visceral sensitivity, and brain-gut communication, often worsening IBS symptoms (Lenhart et al., 2020b). Moreover, the decrease in estrogen leads to reduced production of thyroxine-binding globulin (TBG), which in turn lowers total thyroid hormone levels, particularly T3 and T4, despite stable free hormone concentrations (Gietka-Czernel, 2017; Honour, 2018).

However, the thyroid dysfunction is notably more common in postmenopausal women with subclinical hypothyroidism affecting over 23% of this population (Schindler, 2003). IBS and inflammatory bowel conditions also influence thyroid function through immune responses and chronic inflammation. The release of pro-inflammatory cytokines may impair the peripheral conversion of T4 to T3, resulting in low T3 syndrome or euthyroid sick syndrome (Bertani & Tricò, 2022; Wu et al., 2024). So, the main goal of research to focus to figure out about thyroid hormonal profiles associated with both early and late in menopausal women patients with IBS.

On the other hand, the oxidative stress has increasingly been recognized as a crucial factor affecting both endocrine and gastrointestinal systems. Oxidative stress (OS) has been proposed as a significant causative and propagating factor in inflammatory bowel diseases (IBDs). Modulation of OS is possible through antioxidants and inhibition of oxidizing enzymes(Zielińska et al., 2021). The alteration of this balance of total oxidant status (TOS) and total antioxidant capacity (TAC) has been associated with the pathogenesis of thyroid dysfunctions and irritable bowel syndrome (IBS). So, the research shows that people with hypothyroidism show decreased TAC levels, suggesting impaired antioxidant defenses. Individuals with IBS show elevated markers of oxidative stress, indicating a correlation between oxidative imbalance and gastrointestinal disturbances. Also, the Menopause is linked to hormonal fluctuations and heightened oxidative stress, suggesting that oxidative stress may act as a common cause (Mancini et al., 2016).

MATERIALS AND METHODS

***Study sample*:** The cases for this study were collected from women in stage late and early menopause with a diagnosis of Irritable Bowel Disease in AL-Karama Teaching Hospital of Wasit Health Directorate in AL-Kut City, Wasit Province, Iraq. This study included a total of 80 female participants, divided into two main groups (each group comprised 25 women) based on menopausal status: early menopause (ages 40–45 year) and late menopause (ages 50–60 year) and 30 healthy controls matched for age and early and late menopausal status respectively (15 in each group without IBS). The participants with medical conditions that could affect thyroid hormone levels, such as hysterectomy, thyroidectomy, or any pre-existing thyroid disorder were excluded from the study. As well as, this study was approved by the Ethics Committee of the Department of Biology, College of Science, Wasit University. Informed consent was obtained from all participants prior to sample collection and laboratory analysis.

Blood Sample Collection: Venous blood (5 mL) was drawn from the antecubital vein using a sterile disposable syringe. Samples were collected in gel tubes and centrifuged at 5000 rpm for 10 minutes to separate serum. The serum was stored at -80°C until biochemical assays.

***Hormonal Assessment Using the Roche Cobas e411*:** The serum thyroid hormone levels were analyzed using the Roche Cobas e411 automated analyzer, which utilizes electrochemiluminescence immunoassay (ECLIA)

technology. The system measures Total Triiodothyronine (TT3), Total Tetraiodothyronine (TT4), Free Tetraiodothyronine (FT4), Free Triiodothyronine (FT3), and Thyroid Stimulating Hormone (TSH) levels by:

- **1st incubation:** Sample volumes (30 µL for TT3/TT4, 50 µL for TSH, and 15 µL for FT3/FT4) were incubated with ruthenium-labeled specific antibodies.
- **2nd incubation:** Biotinylated antigens and streptavidin-coated microparticles were added to allow the formation of an antibody-antigen complex, which binds to the solid phase via biotin-streptavidin interaction.
    - The reaction mixture was magnetically captured onto an electrode surface. Unbound substances were washed away using ProCell/ProCell M.
    - Chemiluminescent emission was triggered by applying a voltage and measured using a photomultiplier.
    - Results were determined by a two-point calibration curve and master curve encoded in the reagent barcode, as provided by the manufacturer (Roche Diagnostics, Germany).

Oxidative-Antioxidant status Assay: Human total oxidant status (TOS) and Total antioxidant capacity (T-AOC) were determined by using the enzyme-linked immunosorbent assay (ELISA) method, according to the procedure provided by the manufacturer's instructions, Biont Co., Germany. (Cat-REF: YLA1172HU).

Statistical Analysis*:** Data were collected, summarized, analyzed, and presented using statistical package for social sciences (SPSS) version 26. The numerical data were presented *as mean ± standard deviation* after performing the Kolmogorov-Smirnov normality test to determine the distribution pattern. ***A one-way ANOVA test was applied for data and used Least significant difference **(LSD)** to assess differences among groups. ***Pearson's correlation*** was used to evaluate the relationship between two numerical variables. A p-value of < 0.05 was considered statistically significant (Daniel & Cross, 2018).

Results

The biochemical serum assays revealed notable disturbances in thyroid hormone concentrations among the IBS women patients in both early and late menopause stages (tabel-1). Seum TSH levels were significantly (P< 0.0001) elevated in both early and late menopause in IBS women patients compared to controls respectively and report a highly serum concentration for FSH in late menopause women with IBS compare to early menopause stage. Whereas, the total T3 (TT3), T4 (TT4) and Free T4 (FT4) were significantly (P<0.0001) lower in in both early and late menopause in IBS women patients compared to controls respectively. In contrast, the serum free T3 (FT3) levels were significantly (P< 0.0001) increased in both early and late menopause in IBS women patients than controls women in same both menopause stages without IBS respectively. Besides, the data observed a markedly reduced (P<0.0001) of serum TT4 and FT4 levels in late menopause compared to early menopause and control among IBS women patients.

Table 1: The serum levels of thyroid gland hormones (TSH, T3, T4, FT4, and FT3) in both early and late menopause among IBS women patients and controls.

Groups	Early menopause		Late menopause		*p*-value	LSD
	Control	IBS patients	Control	IBS patients		
Parameters	Mean ± SD					
TSH (µIU/mL)	1.69 ± 0.36[a]	2.70 ± 0.67 [b]	2.20 ± 0.44[ab]	**3.70 ± 1.51[c]**	<0.0001**	0.94
T3 (ng/dL)	4.02 ± 0.95[a]	1.85 ± 0.31[b]	3.61 ± 0.81[a]	1.94 ± 0.31[b]	<0.0001**	2.39
T4 (nmol/L)	136.7 ± 6.6[a]	99.8 ± 16.5 [b]	127.2 ± 15.8 [a]	**85.2 ± 17.31[c]**	<0.0001**	31.76

FT3 (pmol/L)	3.2 ± 0.66[a]	**4.4 ± 1.1[b]**	3.4 ± 0.90 [a]	4.8 ± 0.4 [b]	<0.0001**	1.73
FT4 (pmol/L)	16.14 ± 2.0[a]	12.98 ± 1.4 [b]	16.16 ± 1.0 [a]	**8.3 ± 2.2** [c]	<0.0001**	4.43

SD: standard deviation; Different superscript letters significantly different at $p < 0.05$; Similar superscript letters non-significantly different at $p \geq 0.05$. **: significant at $p < 0.0001$.

The oxidant-antioxidant status demonstrated considerable imbalance in oxidative stress parameters, as reflected by altered levels of total oxidant status (TOS) and total antioxidant capacity (TAC) among IBS women patients in both early and late menopausal stages (table- 2). Serum concentration of TOS was significantly (P< 0.0001) higher in late menopause with IBS women compared the women without IBS in same stage. However, the serum TOS levels not changeable significantly ($p \leq 0.05$) during early menopause among IBS patients than in control women. In conversely, the serum levels of TAC were significantly (P< 0.0001) lower in both early and late menopause respectively among IBS women patients compared to the control women without IBS.

Table 2: The serum oxidative stress biomarkers (TOS)(U/ml) and (TAC)(U/ml) in both early and late menopausal with IBS patients and Controls**.**

Groups	**Early Menopause**		**Late Menopause**		***P*-value**	**LSD**
	Control	**IBS patients**	**Control**	**IBS patients**		
Parameters	**Mean ± SD**					
TOS U/ml	0.36 ± 0.11[ab]	0.308± 0.12[a]	0.29± 0.11[b]	**0.41± 0.13[a]**	<0.0001**	0.165
TAC U/ml	6.3 ± 1.70[a]	**3.5 ± 1.104[b]**	6.7 ± 1.10[a]	4.7 ± 1.30[c]	<0.0001**	5.97

SD: standard deviation; Different superscript letters significantly different at $p < 0.05$; Similar superscript letters non-significantly different at $p \geq 0.05$. **: significant at $p < 0.0001$.

Tables (3 and 4) show the findings of correlation between thyroid function hormones and total oxidative-antioxidant status in both early and late menopause. The data indicating no observed correlations between TOS and thyroid hormones in early menopause stage of IBS women patients (table-3). In contrast, in table (4) was observed in late menopause, a strong negative correlation between TAC and TSH (r = -0.4166 and p = 0.0383).

Table (3): Correlation between oxidative stress biomarkers (TOS and TAC) with thyroid hormones profile in early menopausal for IBS women patients.

Thyroid gland hormones	**Oxidative stress-antioxidant biomarkers**			
	TOS		**TAC**	
	r	**p**	**r**	**P**
TSH	0.06201	0.7684	-0.1657	0.4286
T4	0.02388	0.9098	0.06449	0.7594
T3	-0.2227	0.2846	0.07298	0.7288
FT4	0.2436	0.2406	- 0.2281	0.2728
FT3	-0.3194	0.1196	-0.1131	0.5904

***r*:** Pearson correlation. * $p < 0.05$, ** $p < 0.0001$.

Table (4): Correlation between oxidative stress biomarkers (TOS and TAC) with thyroid hormones profile in late menopausal for IBS women patients.

Thyroid gland hormones	Oxidative stress-antioxidant biomarkers			
	TOS		TAC	
	r	*P*	*r*	*P*
TSH	0.3452	0.0910	**- 0.4166**	**0.0383 ***
T4	0.05556	0.7920	0.3266	0.1111
T3	-0.01910	0.9278	-0.1576	0.4519
FT4	-0.2315	0.2654	0.3385	0.0979
FT3	0.2458	0.2364	-0.1507	0.4720

***r*:** Pearson correlation. * $p < 0.05$

DISCUSSION

the current findings demonstrate valuable data into the complex interplay between thyroid hormones regulation and oxidative -antioxidant capacity affects among menopausal women with IBS. The observed serum elevation in TSH and FT3 are met with a reduction in T3, T4, and FT4 in both menopauses, particularly in the late menopause women with IBS may be indicate for emergence of subclinical or progressive hypothyroidism on homeostasis level of HPT axis. This aligns with findings in Młynarska *et al.*, (2022), who reported that correlation would indicate that the HPT axis, although functioning, is possibly influenced by mechanisms like inflammation, stress, or autoimmunity in IBS patients, influencing thyroid hormone levels. This might reflect subtle dysregulation of the axis (Młynarska et al., 2022).

Besides, Del Ghianda *et al.* (2014) was reinforces that thyroid dysfunction is more prevalent among women and is known to interact with reproductive and hormonal axes throughout the female lifespan. Although existing literature provides limited evidence regarding the direct impact of menopause on thyroid function independent of aging, physiological changes such as reduced FT4 and elevation of FT3 synthesis and altered hormone metabolism are commonly observed with age particularly in autoimmune thyroid diseases, may be further influenced by menopausal transition (del Ghianda et al., 2014). While, TSH often remains within the normal range, it may trend toward higher values in postmenopausal women. This hormonal change coincides with the mechanism of feedback of the HPT axis, where the body works toward the maintenance of a balance in thyroid hormone (Jonklaas, 2022). Similarly, So and Savidge (2021) reported a possible postmenopausal decline in IBD incidence (So and Savidge, 2021). This agrees with findings suggesting that chronic inflammation related to IBS can disrupt thyroid hormone regulation, particularly via effects on the hypothalamic-pituitary-thyroid axis (Danailova et al., 2022).

Moreover, the chronic inflammation in IBS can impair thyroid hormone production and metabolism (Vakili et al., 2024). This observation aligns with Haghshenas *et al.* (2023), which demonstrated that hormonal fluctuations during menopause can exacerbate thyroid dysfunction, especially in the context of chronic conditions like IBD. Given that IBS is more prevalent in females and influenced by hormonal status (Haghshenas et al., 2023).

The markedly lower levels of T3, especially in late menopause among IBS patients, indicate impaired conversion of T4 to T3, which agrees with Juby *et al.*, (2016). This may result from chronic inflammation or oxidative stress, every day in IBS, and is known to impair thyroid hormone metabolism (Juby et al., 2016) . Also, Sic et al., (2024). reported that the active thyroid hormone T3 is produced from the inactive T4 thyroid hormone and T3 itself is also active in the maintenance of the intestinal lining. The deficiency of this T3

thyroid hormone causes immune dysregulation along the gut lining, downregulates the release of digestive enzymes, and ultimately leads to intestinal permeability. It has been observed that all these effects of low T3 hormones lead to food sensitivities (Bhattacahrje et al., 2023). These findings are in agreement with recent studies showing that IBS patients often exhibit symptoms of hypothyroidism, even when TSH levels are within the normal range or elevated (Xu et al., 2024). Besides, the lowered serum levels of FT4 in IBS women patients, particularly in late menopause, suggest a reduced capacity of the thyroid gland to produce thyroxine. This is consistent with research indicating that autoimmune thyroiditis, often triggered by chronic inflammation, is more prevalent in IBS patients (Köhling et al., 2017). Also, the malabsorption of FT4 is a common problem in patients with hypothyroidism due to Hashimoto's disease and concomitant gastrointestinal disorders, such as SIBO in hypothyroid patients with IBS (Henderson et al., 2024).

On the other hand, the variations in thyroid hormone levels observed in IBS patients across menopausal stages indicate a fundamental disturbance in endocrine balance of its functions by cellular oxidative damage, this may be due to redox imbalance contributes to the hormonal dysregulation observed in these individuals. So, the highly values of serum TOS among IBS women in both early and late menopause. These finding it came documented for a previous study, it was found that IBS patients had significantly elevated levels of biomarkers of oxidative stress compared to controls. This suggests that oxidative stress is a common feature of IBS and could be involved in intestinal inflammation and mucosal damage (Miglietta et al., 2021). The high levels of TOS during early menopause in IBS patients may be due to the hormonal fluctuation typical during this time because the estrogen, as an antioxidant, decreases with menopause and may play a role in higher oxidative stress (Jang et al., 2022). While, low serum TAC levels in IBS patients shows that disturbance in the balance between oxidative stress and antioxidant defense mechanisms is a distinguishing feature of IBS(Dincer et al., 2007). This agreed with Doshi & Agarwal, (2013) and Frida Adhani et al., (2023), those show that the decline in TAC levels in early menopause may be precipitated by the decrease in estrogen, which is reported to enhance antioxidant enzyme activity.

So, the Balmus *et al.* (2020), were suggest that TOS/TAC imbalance (increased oxidative stress and reduced antioxidant capacity) in IBS patients, particularly during early and late menopause, suggest that oxidative stress is the major player in the pathophysiology of IBS. This concurs with the hypothesis that oxidative stress underlies gastrointestinal inflammation, visceral hypersensitivity, and gut dysmotility in IBS patients (Balmus et al., 2020). This explain that simultaneous rise in TOS and decrease in TAC indicates a condition of oxidative stress, wherein the enzymatic antioxidant response is activated but unable to completely neutralize the accumulating oxidants, indicating a disturbed redox balance (Mancini et al., 2016).

Supportably, the negative correlation of TAC and TSH at late menopause is consistent with the findings of Benvenga *et al.* (2015), who explained that oxidative stress is the causative factor for thyroid dysfunction, particularly hypothyroidism, in postmenopausal women. Lower antioxidant capacity can exacerbate thyroid dysfunction at late menopause (Benvenga et al., 2015). Also, the complexity of the relationships can be summarized as thyroid status does not significantly influence the climacteric syndrome. The correlation between biomarkers of oxidative stress and thyroid function suggests the potential thyroid-gut axis, whereby thyroid disease and oxidative stress may interplay to exacerbate gastrointestinal symptoms in IBS patients. This is reinforced by studies showing the influence of thyroid hormones on gut motility, inflammation, and permeability (Abubakar et al., 2025). The correlations between oxidative stress markers and thyroid function suggest an emerging thyroid-gut axis, in which thyroid disease and oxidative stress affect each other to exacerbate gastrointestinal symptoms in IBS patients. This is seen in a study that showed thyroid hormones modulate gut motility and inflammation (Fukui et al., 2018).

Moreover, the findings suggest that menopausal hormonal alterations, in the form of estrogen loss, may exacerbate oxidative stress and thyroid function, contributing to the pathogenesis of IBS symptoms (Sonawdekar et al., 2024).

CONCLUSION

This finding concludes that hormonal dysfunction status in thyroid gland during menopausal stage associated with IBS was notable by hormonal disturbances-particularly elevated TSH with lower both serum TT4 and FT4 levels which may be suggest an increased risk of hypothyroidism in late menopause than early menopause which may reflect a compensatory mechanism through peripheral T4 to T3 conversion or altered HPT axis feedback by the oxidative stress indicating disturbed redox balance (TOS an TAC) among IBS patient's women. This underscores the need for treatment aimed at both the hormonal and oxidative stress pathways in menopausal women with IBS.

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