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## New challenges for the multidisciplinary management of thyroid disease in menopause: a narrative review

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### ABSTRACT

**Objective.** Thyroid disorders pose a significant health concern in post-menopausal women, encompassing hypothyroidism, hyperthyroidism, and cancer. These conditions not only elevate cardiovascular risk but also contribute to increased general mortality. Despite the clinical importance, diagnosing thyroid dysfunction in this demographic remains challenging due to the prevalence of nonspecific symptoms and variations in thyroid function test interpretations.

**Materials and Methods.** We performed a narrative review using PRISMA methodology, in PubMed/Medline, SCOPUS, Scholar and Web of Science. Inclusion criteria were articles containing the keywords “menopause”, “thyroid”, and “disease” from the years 1990-2024 using MESH terminology in a broad-term search strategy.

**Results.** The search returned a total of 2,034 articles. After removing duplicates and unavailable abstracts, we screened 1,424 articles for abstracts. After excluding case reports, non-English articles, and articles without full text available, we used data from 57 articles. New evidences on the thyroid normal values in menopause are challenging the diagnosis of subclinical hypothyroidism and hyperthyroidism in the elderly. The challenges extend to thyroid cancer management in post-menopausal women, where outcomes and treatment efficacy may be inferior compared to younger cohorts. While overt thyroid dysfunction necessitates treatment, caution is advised for those concurrently using estrogen or SERMS.

**Conclusions.** In this paper, we assess a review of the current literature from a clinical point-of-view to give clinicians the “toolbox” to direct their diagnostics and treatment. A multidisciplinary team should be encouraged to manage thyroid disease in menopause while the gynaecologist could be the actual “case manager”, addressing the decisions to the patient’s needs and expectations.

## INTRODUCTION

The head and neck region represents a highly heterogeneous and anatomically complex topographic area, housing numerous vital structures and systems. This complexity poses significant challenges in clinical evaluation and diagnosis, particularly due to the close interplay of vascular, neural, muscular, and glandular components [1-5]. Histological analysis of the thyroid allows us to understand what changes affect thyroid function: signs of fibrosis similar to senescence, lymphocyte infiltration and degeneration of functional cells. In particular, the production of T3 and T4 decreases in elderly people, but their half-life increases as a compensatory mechanism [6]. The plasma concentration of TSH also varies with age through a significant increase in the mean and median concentration. Consequently, when evaluating thyroid function in older people, threshold values based on the patient’s age should be examined to prevent older patients from being erroneously classified as suffering from subclinical hypothyroidism [7, 8].

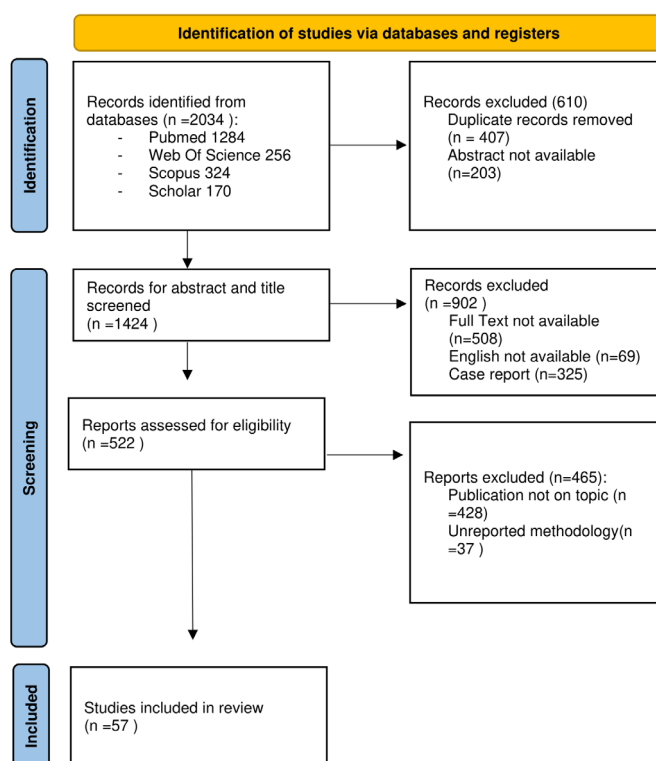
## MATERIALS AND METHODS

We evaluated, according to the Preferred Reporting-Items for Systematic-Reviews and Meta-Analysis (PRISMA) methodology, the electronic database of PubMed/Medline, SCOPUS, Scholar and Web of Science (WOS). Inclusion criteria were articles containing the keywords “menopause”, “thyroid”, and “disease” from the years 1990-2024 using MESH terminology in a broad-term search strategy. Exclusion criteria were duplicate records, unavailable abstract and full text, articles with unavailable English text, case reports, and articles with methodology not reported. The search returned a total of 2,034 articles. After removing duplicates and unavailable abstracts, we screened 1,424 articles for abstracts. After excluding case reports, non-English articles, and articles without full text available, we used data from 57 articles. Details are in **Figure 1**.

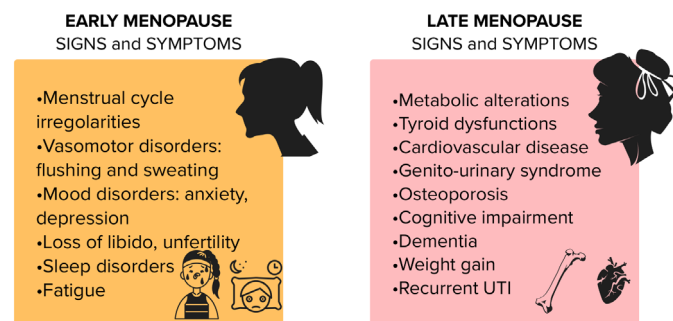
## RESULTS

According to international consensus, natural menopause (NM) is diagnosed after 12 consecutive

months of amenorrhea after the final menstrual period (FMP), excluding any evidence of other causes. MN occurs globally between the ages of 45 and 55, with a mean age of  $50 \pm 5$  years. In order to standardise the staging system of a woman’s reproductive life, in 2001, the 2001 Stages of Reproductive Aging (STRAW) workshop consensus proposed seven distinctive stages, updated in 2011 by the “STRAW + 10” criteria [9] (**Figure 2**).



**Figure 1.** Preferred-Reporting-Items for Systematic-Reviews and Meta-Analysis (PRISMA) methodology flow chart.



**Figure 2.** Stages of Reproductive Aging (STRAW), updated by the “STRAW+10” criteria.

The menopausal transition (MT), an intermediate phase characterised by hormone fluctuation and diminution of reproductive capacity, critically impacts women’s Health-Related Quality of Life (HRQoL). MT has been divided into “early” (STRAW -2) and “late” (STRAW-1), representing the increased variability in menstrual cycle length and FSH levels [26].

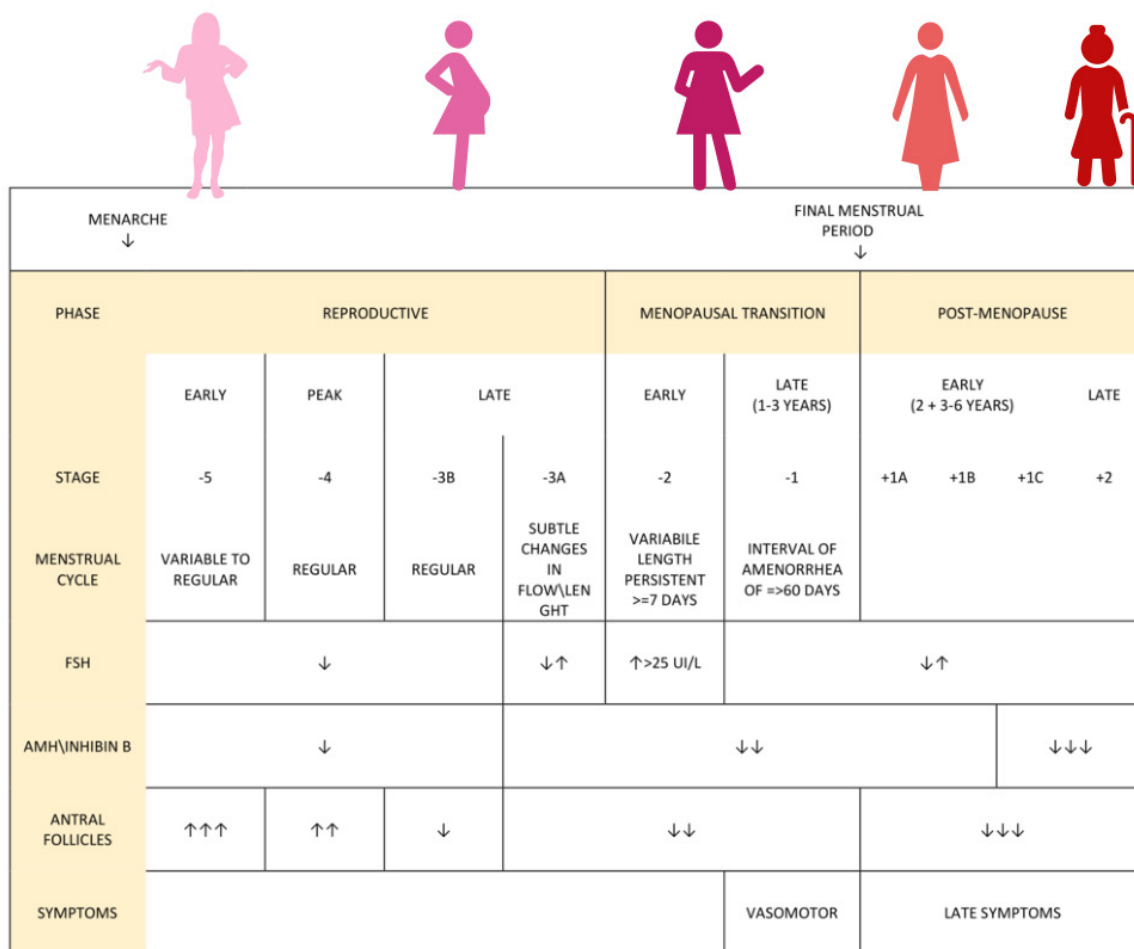


Figure 3. Menopausal Transition Related signs and symptoms.

This figure contrasts the clinical manifestations of early and late menopause: Early Menopause: Features include menstrual irregularities, vasomotor symptoms (e.g., flushing, sweating), mood disorders (e.g., anxiety, depression), reduced libido, infertility, sleep disturbances, and fatigue. Late Menopause: Associated with metabolic alterations, thyroid dysfunction, cardiovascular disease, genitourinary syndrome, osteoporosis, cognitive impairment, dementia, weight gain, and recurrent urinary tract infections.

**Causes of secondary Hypothyroidism**

- Hypothalamic disease e.g. tumours, trauma, infiltrative disorders, idiopathic
- Hypopituitarism e.g. trauma, tumours, surgery, irradiation, infiltrative, Sheehan syndrome
- Isolated TSH deficiency or inactivity

**Causes of primary Hypothyroidism**

- Autoimmune thyroiditis e.g. chronic phase of Hashimoto
- Iodine deficiency
- Iatrogenic e.g. I131, thyroidectomy, neck radiotherapy
- Medications e.g. iodine contrast media, amiodarone, lithium, antithyroid drugs, interferon α
- Congenital causes e.g. absent thyroid, dysmorphogenesis
- Infiltrative disorders e.g. amyloidosis, sarcoidosis, Riedel's thyroiditis

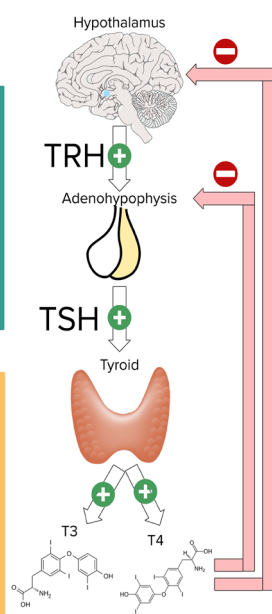


Figure 4. Causes of hypothyroidism.

Image showing the most common causes of hypothyroidism. This figure outlines the different causes of hypothyroidism based on pathophysiologic classification.

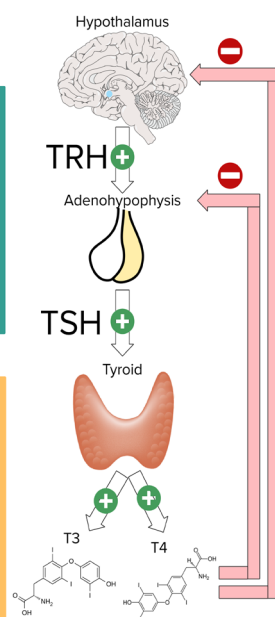
An image synopsis of signs and symptoms typical of the menopausal transition is in Figure 3. Elevated serum TSH characterises hypothyroidism as the hallmark; in the general population, it is most commonly caused by iodine deficiency along with chronic autoimmune thyroiditis [10]. Despite that, hypothyroidism represents the most common disorder of thyroid function in populations living in areas with sufficient iodine supply. The causes of primary hypothyroidism are summarised in Figure 4. Subclinical hypothyroidism (ScH) is a thyroid insufficiency from mild to moderate, characterised by normal serum levels of thyroid hormones (FT3 and FT4) with mildly elevated serum TSH. It represents the most common thyroid dysfunction in post-menopausal women [11]. In ScH, TSH values ≥ 10 mIU / per age < 65 years seem to be related to cardiovascular disease, heart failure and cardiovascular mortality risk. No cognitive benefit has been shown in women affected by ScH in the elderly over 65 treated with L-Tyroxine, considering the two largest RCTs

### Causes of secondary Hyperthyroidism

- TSH-secreting pituitary adenoma
- Thyroid hormone resistance syndrome
- Gestational thyrotoxicosis
- Tumours secreting gonadotropins

### Causes of primary Hyperthyroidism

- Graves' disease
- Autoimmune thyroiditis e.g. acute phase of Hashimoto
- Toxic multinodular goiter and adenoma
- Thyroid carcinoma functioning metastases
- Struma ovarii
- Jod - Basedow phenomenon (iodine excess)
- McCune-Albright syndrome: TSH receptor or G protein activating mutations



**Figure 5.** Pathophysiology and causes of primary and secondary hyperthyroidism.

Secondary Hyperthyroidism: Attributed to abnormalities in the hypothalamic-pituitary axis, including TSH-secreting pituitary adenomas, thyroid hormone resistance syndrome, gestational thyrotoxicosis, and gonadotropin-secreting tumours. Primary Hyperthyroidism: Originates from intrinsic thyroid dysfunction, with causes such as Graves' disease, autoimmune thyroiditis, toxic multinodular goiter/adenoma, thyroid carcinoma with functioning metastases, struma ovarii, iodine excess (Jod-Basedow phenomenon), and McCune-Albright syndrome: TSH receptor or G protein activating mutations. The diagram integrates hormonal regulation, indicating suppressed feedback to the hypothalamus and pituitary, leading to excessive thyroid hormone production.

with longer follow-ups [12]. Hyperthyroidism is characterised by undetectable serum TSH values associated with elevated FT3 and FT4 concentrations. Instead, low or undetectable serum TSH values associated with normal FT3 and FT4 concentrations define subclinical hyperthyroidism.

The causes of hyperthyroidism are summarised in **Figure 5**.

The prevalence of hyperthyroidism increased progressively from 0.7% in children to 15.4% in subjects over 75 years of age and was more frequent in subjects with nodular goitre [13]. Another study shows that patients with thyroid adenoma have a risk of developing overt hyperthyroidism of 4% per year; the risk amounts to 9-30% over the next 1-7 years in patients with nodular goitre [14].

Subclinical hyperthyroidism is associated with an increased average heart rate and a higher prevalence of atrial arrhythmia. Instead, the state of thyrotoxicosis can lead to possible bone fractures in post-menopausal women as it increases the activity of osteoblasts and osteoclasts resulting in increased bone resorption and formation. However, bone resorption is not compensated by bone formation, so

progressive bone demineralisation is observed. The cortical part of the bone is more affected than the trabecular part [15]. TSH serum concentration below 2.5 percentile indicates significantly low bone mineral density (BMD). It is sufficient to restore the euthyroid state to increase BMD.

## DISCUSSION

There is no consensus among international societies about universal screening for thyroid dysfunction in post-menopausal and older women [16]. The American Thyroid Association 2021 guidelines recommend adult screening for thyroid dysfunction by measuring serum TSH concentration every five years starting from age 35 [17]. The American College of Physicians recommends screening with serum TSH test to women over 50 with clinical symptoms that could be linked to thyroid disease, followed by measurement of FT4 if the TSH level is not detectable or greater than 10 mIU/L [15]. However, the evidence is not sufficient to recommend screening in large populations, excluding pregnant women or women with a family history of thyroid disease [18]. However, the evidence is not sufficient to recommend screening in large populations, excluding pregnant women or women with a family history of thyroid disease [16]. It is crucial to establish the appropriate reference range for serum TSH concentration. In the III National-Health-and-Nutrition Examination Survey (NHANES III), the evaluation of a population without thyroid disease from 1988 to 1994 showed a significant mean and median serum TSH concentration increase with age. The analysis also showed an increase in the lower and upper limits of serum TSH concentration in relation to age, as shown in **Table 1** [19].

**Table 1.** Serum TSH concentration (median, 2.5 and 97.5 centiles) of thyroid disease-free population in all ethnic groups included in the NHANES III.

Age (Years)	<2.5 Centile	Median	>97.5 Centile
12-19	0.40	1.25	3.65
20-29	0.38	1.26	3.88
30-39	0.33	1.41	4.71
40-49	0.60	1.59	5.77
50-59	0.52	1.70	10.74
60-69	0.45	1.99	11.64
70-79	0.46	2.00	12.97
>80	0.30	2.10	10.79

The values are in mIU/L.

The Italian Society of Endocrinology published a national guidelines (2024) in which they stated that in post-menopausal women with age < 70-75 years it is not advisable to have a TSH at the low end of the normal range, given the demonstrated moderate elevation of its value in the general population [15]. The reference values commonly used to analyse serum TSH concentration do not take into account the age and sex of the patient, although some studies point out that normal serum TSH values may depend on age [7, 20]. There is no agreement about objective clinical data to be considered to start therapy in cases of sub-clinical thyroid dysfunction, hypothyroidism and hyperthyroidism. Almost all scientific papers focusing on these clinical conditions refer to standard ranges for serum value of TSH and are independent of the sex and age of patients for the diagnosis of subclinical thyroid dysfunction. This condition leads to an increased risk of misdiagnosis and excessive treatment in cases of subclinical thyroid dysfunction [21, 22]. Based on the use of hormone replacement therapy (HRT) in post-menopausal women, which includes estrogen therapy (ET) and estrogen-progestogen therapy (EPT), and the prevalence of hypothyroidism in this population, it is estimated that approximately 5% of all post-menopausal women receive treatment with both HRT and thyroid hormone replacement (L-T4) [23]. The risks related to HRT depend on dose, pharmacology, time of use and route of administration, yet it remains the most effective way to manage vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM). Moreover, benefits have been shown in preventing bone loss and fracture. Estrogen hormones have a dual function with both direct and indirect effects on the thyroid parenchyma. The latter implicates an increase in thyroxine-binding globulin concentration (TBG), together with sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG), which are glycoproteins produced by the liver. Indirect effects do not cause free-thyroxine (FT4) and free-triiodothyronine (FT3) variations. The direct effects involve modulation of proliferation and function of thyroid cells mediated by estrogen-receptors. The ERT administration route plays a central role in terms of potential side effects. Both systemic estrogens and progestogens can be administered as oral drugs. While non-oral routes of administration include transdermal, vaginal, and intrauterine systems. Significantly, equivalent doses of oral or transdermal estrogen replacement

therapy (ERT) affect TBG production differently. Because of its hepatic first-pass effect, oral estrogen therapy causes an increase in circulating levels of TBG, thus decreasing the free (bioactive) fraction of circulating thyroxine (FT4). As a consequence, oral ERT may increase the L-T4 dosage requirements of women being treated for primary hypothyroidism. For this reason, the initiation of oral estrogen replacement therapy in these patients requires frequent monitoring of thyroid function parameters (TSH, FT4) and may require multiple dose adjustments of L-T4 to maintain a euthyroid state. On the contrary, transdermal estrogens do not affect TBG levels and do not alter thyroid function. Hence, it may be a preferable modality of administration for post-menopausal women who require concomitant treatment with HRT and T4 [12]. Another population worth mentioning is the one of women undergoing Selective Estrogen Receptor Modulators (SERM) therapy for breast cancer. Breast cancer is considered as one of the “big killers” in post-menopausal women and often requires SERM treatment. While this therapy’s most common side effects noted, less is known about the side and collateral effects on the thyroid gland. Tamoxifen, the most commonly used molecule, have shown estrogenic effects on the liver, with reported increased serum TBG levels through reduced clearance. The clinical relevance of tamoxifen is controversial and characterised by a slight serum decrease in FT3 and FT4 and an increase in TSH, usually within the normal range [24]. Regarding the new SERM (Bazedoxifene, Ospemifene), there is no evidence yet on the possible effect on thyroid function and TBG and TSH levels. Yamada *et al.* evaluated TSH, FT4, and FT3 levels in healthy individuals and proposed new reference values concerning different ages and genders. Hence, the prevalence of subclinical thyroid dysfunction was assessed using the obtained gender- and age-specific reference values [25]. A gradual but statistically significant age-dependent increase in serum TSH levels was observed. In women, it was highlighted that a substantial proportion of individuals were overdiagnosed. Among patients aged 30-39 years, more than 50% of those who were classified as having subclinical hypothyroidism using the standard reference range were overdiagnosed [26, 27]. The percentage of over-diagnosed patients increased with age: 78% of women aged 60-69 years were reassessed as euthyroid when the age- and sex-specific reference range was applied. This study emphasises the need for age- and sex-specific

reference values regarding TSH, fT4 and fT3 levels [28, 29]. These should be considered to accurately assess thyroid function in clinical practice, particularly in diagnosing subclinical hypothyroidism and hyperthyroidism, to avoid over- and under-diagnosis and apply appropriate therapies [30, 31].

#### **Limitations of the study and future prospective**

This narrative review highlights significant challenges in diagnosing and managing thyroid dysfunction in post-menopausal women but also underscores limitations that warrant further investigation. First, the reliance on retrospective data and variability in study designs across the reviewed articles may limit the generalizability of findings. Additionally, the heterogeneity in thyroid function reference values for this demographic complicates standardization, impeding uniform diagnostic criteria. The study's exclusion of non-English articles and case reports may have overlooked potentially valuable data. Future research should focus on prospective, longitudinal studies to better delineate thyroid function norms in post-menopausal women and their correlation with clinical outcomes. Investigating the interplay of estrogen, selective estrogen receptor modulators (SERMs), and thyroid function could provide deeper insights into personalized therapeutic strategies. Moreover, addressing disparities in thyroid cancer management outcomes through targeted clinical trials and exploring advanced diagnostic tools like molecular markers or imaging techniques could further enhance care in this population.

## **CONCLUSIONS**

Menopause, senescence, and thyroid dysfunction represent independent conditions in women that can often overlap. It is up to the physician to recognise them in their different phenotypes to personalise and optimise the clinical management of each patient. There is no clear benefit in treating elevated TSH values in post-menopausal individuals, but there is a possibility that treatment of subclinical hypothyroidism in the elderly may lead to adverse outcomes. Further large-scale intervention studies are needed to confirm these findings definitively. However, a single abnormal TSH result must be monitored over time since a considerable number of people with subclinical thyroid disease will normalise spontaneously. In asymptomatic

post-menopausal women, universal screening for thyroid dysfunction is controversial but should be considered in cases of overt symptomatology or reported familial dysthyroidism.

## **COMPLIANCE WITH ETHICAL STANDARDS**

#### **Authors' contribution**

M.C., A.G., M.E.G., M.D.: Research protocol, writing – original draft, writing – review & editing. M.B., S.D.N., R.P., A.G.: Writing – review & editing. G.T., G.R.D.: Writing – review & editing, project administration. R.A., I.R., A.V., E.C., M.D.: Supervision.

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#### **Study registration**

N/A.

#### **Disclosure of interests**

The authors declare that they have no conflict of interests.

#### **Ethical approval**

This is a narrative review. No Ethics Committee approval is required.

#### **Informed consent**

N/A.

#### **Data sharing**

Data are available along with the article.

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