

# Biliary Lithiasis and Subclinical Hypothyroidism: Myth or Truth?

**Salem Bouomrani<sup>1,2\*</sup>**

<sup>1</sup>Department of Internal medicine, Military Hospital of Gabes, Tunisia

<sup>2</sup>Sfax Faculty of Medicine, University of Sfax, Tunisia

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**\*Corresponding author:** Salem Bouomrani, Department of Internal medicine, Military Hospital of Gabes, Gabes 6000, Tunisia

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## Abstract

With an average prevalence in the general population at 4-15% and more than 20% in the elderly, Subclinical Hypothyroidism (SCH) is the most common thyroid dysfunction. The clinical and biological impact of SCH is sometimes atypical, unusual, and very challenging in current medical practice. Among these atypical manifestations of SCH, some publications have suspected a particularly promoting role in the genesis of biliary lithiasis. The purpose of this review is to clarify the relationship between this thyroid dysfunction and gallstones. The systematic review of the literature allows us to conclude that the association between biliary lithiasis and SCH is far from mere chance. Diminished bile secretion, decreased liver cholesterol metabolism, and reduced sphincter of Oddi relaxation are the mechanisms involved in the formation and accumulation of biliary stones in subjects with SCH. Thus systematic screening for SCH is highly recommended in any patient diagnosed with biliary lithiasis.

**Keywords:** Biliary lithiasis; Subclinical hypothyroidism; Common bile duct stone; Gallstone; Hypothyroidism

## Introduction

Subclinical Hypothyroidism (SCH) is the most common thyroid dysfunction [1-3]. Its prevalence in the general population is estimated on average at 4-15% [3] but can reach more than 20% in the elderly [3]. It is far more common than overt hypothyroidism, but often remains underdiagnosed and unrecognized [1-3]. In fact, the American national survey estimated the frequency of subclinical hypothyroidism at 4.3% of the general population against only 0.3% for overt hypothyroidism [4]. Subclinical hypothyroidism is defined as the elevation of the thyroid-stimulating hormone (TSH) in plasma with normal levels of thyroid hormones (triiodothyronine (T3) and free total thyroxine (fT4)). Clinical manifestations related to the deficit of thyroid hormones are, by definition, absent during this dysthyroidism [1-3]. However, there are some controversies regarding the clinical presentations of subclinical hypothyroidism [3]. Indeed, it was noted that by applying the Billewicz-Zulewski scale which groups together the specific clinical signs of hypothyroidism (the total score goes from 0: no clinical sign is present, to 12: all clinical signs are present), a positive score between 3 and 5 was noted in all patients diagnosed with SCH [5]. This variability in the possible clinical presentations of subclinical hypothyroidism can be explained by the existence of an individual "set-point" of TSH; the interindividual variability of which would explain the great clinical polymorphism in patients with the same TSH value [3,6]. The clinical and biological impact of SCH is sometimes atypical, unusual, and very challenging in current medical practice [7-9]. Some publications have suspected a promoting role of SCH in the genesis of biliary lithiasis [10-13]. The purpose of this review is to clarify the relationship between this thyroid dysfunction and gallstones.

## Biliary stones in SCH

Hypothyroidism is currently recognized as a risk factor for biliary lithiasis, whether gallstone's or of the common bile duct (CBD) [10-12]. Indeed, in Ahmad MM [13] series, hypothyroidism was noted in 16% of patients with choledocholithiasis and in 8% of patients with cholelithiasis [13]. Similarly, Laukkarinen et al, in their large study found a prevalence of hypothyroidism (both overt and subclinical) of 10.2% in patients with common bile duct stone [11]. Inkinen et al. [10] demonstrated this association between hypothyroidism and biliary lithiasis by revealing a statistically higher prevalence of primary hypothyroidism in patient with choledocholithiasis compared to healthy control group: 8% Vs 1%,  $p < 0.01$  [10].

## Mechanisms of hypothyroidism-associated biliary stones

The biliary lithogenesis during primary hypothyroidism goes through several pathogenic mechanisms, namely the decrease in the hepatic metabolism of cholesterol which will accumulate in the bile making it saturated and thick [14], the decrease in the hepatic clearance of bile [15] and the reduced sphincter of Oddi relaxation [16,17]. Taken together, these factors make biliary lithiasis significantly frequent in hypothyroid patients compared to the general population: 11% versus 2% according to Laukkarinen J [18] study. All these mechanisms promoting biliary lithogenesis during overt hypothyroidism have also been validated in subjects with SCH, justifying that 75% of patients with hypothyroidism-associated biliary lithiasis was diagnosed as having subclinical forms of this endocrinopathy in Ahmed MM et al series [13].

## Biliary stones in subclinical hypothyroidism

Association between biliary lithiasis and subclinical hypothyroidism was noted in several studies and in several populations [10-18]. Laukkarinen J et al. [12], in their Finnish prospective study, objectified a statistically significant prevalence of common bile duct stone in patients with SCH compared to the general euthyroid population: 5.3% Vs 1.4%. This difference was much more marked in women older than 60 year: 11.4% Vs 1.8% [11]. Rassam Ghadhban B & Najim Abid F [19] cross-sectional study regrouping 103 Iraqi patients with gallstones, objectified eight with SCH (7.8%) [19]. Moreover, 75% of patients with biliary stone and SCH had positive family history of cholelithiasis [19]. Ajdarkosh H [20] study evaluating thyroid function pattern in 151 patients with common bile duct stones, objectified SCH in 30.6% of them contrary to only 22.5% of cases in the healthy individuals control group [20]. They also noted a mean serum TSH levels statistically higher among patients with CBD stone than controls ( $2.79 \pm 4.86$  Vs  $2.03 \pm 4.13$ ;  $p = 0.01$ ), with a statistically significant difference between the two groups to be at risk for SCH; thus they concluded that SCH could be a risk factor for the development of CBD stones [20]. The association between SCH and biliary stone seems to be statistically increasing among females over 40 years, patients with positive family history of cholelithiasis, and patients with single gall stone on abdominal ultrasound [11,17,19,20]. Similarly, choledocholithiasis is more

prevalent in females with SCH [13,19,20]. Thus, some authors recommend systemic screening of thyroid function in any patient with gallstones' or common bile duct stone, even in the absence of any symptom or sign of hypothyroidism. This screening is all the more recommended whether it is female or elderly [11,17,18].

## Conclusion

The association between biliary lithiasis and subclinical hypothyroidism seems to be far from mere chance. Subjects with this thyroid dysfunction appear to have a significantly increased risk of developing gallbladder stones and common bile duct lithiasis. This risk is particularly increased in women and the elderly. Thus systematic screening for SCH is highly recommended in any patient diagnosed with biliary lithiasis.

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