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# Cardiac and Metabolic Bone Changes in Adult Females with Subclinical Hypothyroidism

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**Abstract**

Subclinical Hypothyroidism (SCH) may affect several body systems. In the cardiovascular system it can affect systolic and diastolic function. Dyslipidemia is also a concern. The effect of SCH on BMD is still unclear. The aim of the study is to disclose the effect of SCH on cardiac function, bone density and lipid profile. This is a case control study included 45 participants classified into 2 groups: Group (1) 30 adult female patients newly diagnosed with subclinical hypothyroidism aged 18-40 years and Group (2) "Control group" 15 age matched female subjects with no history of thyroid or systemic disease. Patients with SCH shows a statistically significantly higher TSH level, TC level, LDL-C level, E/e' septum, GLS percentage, DBP than control group. Also Patients with SCH shows a statistically significantly lower FT4 level, BMD (spine and radius) and E/A ratio. Than control group. SCH is associated with adverse changes in cardiac systolic and diastolic function, moreover SCH is contributed to dyslipidemia, also negatively affects BMD.

**Keywords:** SCH, Speckle tracking Echo, DEXA scan, dyslipidemia

**Full-length article** *Corresponding Author, e-mail: Ibrahimahmad@mans.edu.eg

## 1. Introduction

A normal serum free thyroxine (T4) concentration combined with an elevated serum thyroid-stimulating hormone (TSH) concentration is known as subclinical hypothyroidism which defined on biochemical background [1] SCH is a prevalent condition, with an overall prevalence of 3.1% in Korea (males 2.26%, females 4.04%), 4.3% in the United States, and up to 20% in other studies. In fact, the prevalence may be substantially higher than previously thought because a significant proportion of the population may have undiagnosed SCH. *[2]*. However no available data about the prevalence of SCH in Egypt.

Clinical efforts to identify patients with SCH have been unsuccessful. Some cases with SCH may experience nebulous, nonspecific hypothyroid manifestations such as fatigue and constipation. Thus, this disorder can only be diagnosed on the basis of laboratory test results. [3,4] The majority of patients with subclinical hypothyroidism are caused by Hashimoto's thyroiditis, a chronic autoimmune thyroid condition. Antithyroid peroxidase (anti-TPO) antibodies, however, are not routinely measured in patients with subclinical hypothyroidism unless the decision to treat or monitor is unclear. Antibodies could be useful in this situation to help with management choices. (3) SCH carries the risk of progression to overt hypothyroidism especially in the presence of TPO ab. [5]. Subclinical thyroid dysfunction, hypothyroidism or hyperthyroidism, are potential contributors to developing cardiac complications. [6]

T3 is the biologically active form of the thyroid hormone. By lowering (PVR), free T3 and T4 lower (DBP) and lessen the afterload on the heart. The sensitivity to catecholamines in the blood is enhanced by thyroid hormones, which raises heart rate. T3 stimulates the sympathetic nervous system by increasing the myocardium's β-adrenergic receptor count. (TRs) regulate the expression of cardiac genes in the myocardium [7] According to earlier research, patients with subclinical hypothyroidism experienced diastolic dysfunction at rest and systolic dysfunction after exertion. These abnormalities were resolved when euthyroidism was restored. Normalization of cardiac function caused by hypothyroidism was accompanied by a decrease in isovolumic relaxation time, a decrease in pre-ejection period/ejection time, an increase in the left ventricular ejection fraction ratio, and an increase in the early diastolic/late diastolic mitral flow velocity ratio [8] A tissue doppler can be used to measure the E/A ratio, which is the ratio of peak blood flow, or the E wave, from left ventricular relaxation in early diastole to peak blood flow, or the A wave,

from atrial contraction in late diastole. This ratio is the most crucial factor in characterising the overall mitral flow velocity pattern and defining diastolic function; it has been demonstrated to be lower in SCH patients than in normal individuals.[9]

The E/e' septal ratio is a useful index for assessing left ventricular filling pressure, and it is also measured by Tissue Doppler. It is used to identify diastolic heart failure. In spite of having a normal ejection fraction, it can predict heart failure [10]. E/e' septal ratio was found to be higher in patients with SCH compared to control. [11]. A straightforward metric called global longitudinal strain (GLS) provides a percentage expression for longitudinal shortening. Speckle Tracking Echo is the source of GLS, which measures tracking quality, integrates, and traces the myocardium. Waveforms can be utilised to demonstrate temporal dispersion and contraction delay in various myocardial segments; in adults, GLS values between 16 and 18 percent are borderline, GLS values less than 16 percent are abnormal, and GLS values greater than 18 percent are normal. The GLS is represented by a negative figure.[12] Studies have shown that patients with SCH have lower GLS than control which indicates the effect of SCH on left ventricular systolic function, Additionally, in patients with heart failure who had either HFpEF or HFrEF, SCH was linked to a lower GLS.[9,13]

The primary ways that thyroid hormone influences lipid levels are through increasing the number of LDL receptors in the liver and peripheral tissues, as well as through enhancing the activity of the transcription factor sterol regulatory element-binding protein 2 (SREBP-2), which positively modulates LDL receptor activity. T4 regulates the production of the SREBP-2 gene, which in turn regulates the action of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) enzyme and its fast beakdown.[14] Patients with subclinical hypothyroidism were shown to have increased serum levels of apolipoprotein B-48, which is thought to be a potential atherosclerosis predisposing factor and a component of chylomicron remnants. [15] Other mechanisms may also play a role. LDL oxidation is significantly increased in hypothyroid patients [16], reduced secretion of cholesterol into the bile has been observed in hypothyroid animals [17]

Reports of anomalies in hemostatic variables suggest that in subclinical hypothyroidism, hypercoagulable and hypofibrinolytic conditions may play a significant role in the development of atherosclerosis. The latter is mostly caused by factor VII and plasminogen activator inhibitor-1 being overactive. [18]. Triiodothyronine stimulates bone mass during bone growth, which is why it has anabolic effects. However, it also catabolic effects adult bone and stimulates bone turnover. Thyroid hormone deficiency in children causes delayed bone age, stops bone growth, causes epiphyseal dysgenesis, and retards skeletal development**.** [19] The key components needed for the development and upkeep of bone cells are osteoblasts, osteoclasts, osteocytes, and chondrocytes; among these, osteoblasts and chondrocytes are directly correlated with and responsive to thyroid hormones. Thyroid status changes can also affect osteoclast activity. [20] Subclinical thyroid dysfunction has a significant impact on bone status in older persons. Although prior research has focused on subclinical thyroid dysfunction and low bone mineral density (BMD) in older persons, few studies have focused on middle-aged adults. [21]

The aim of the study is to disclose the effect of SCH on cardiac function, bone density and lipid profile

## 2. Methods

This study is a case control study in which 30 adult female Patients were recruited from outpatient endocrinology clinic in specialized medical hospital, Mansoura University over a duration from June 2021 to May 2022 and 15 health control subjects. They were divided into the following groups:

1- **Group (1):** 30 adult female patients newly diagnosed with subclinical hypothyroidism aged 18-40 years.

2- **Group (2):** "Control group" 15 age matched female subjects with no history of thyroid or systemic disease

### *2.1. Exclusion criteria*

Any patient with past history of thyroid related illness or previous exposure to radiation and radioactive iodine or previous thyroid surgery, or patients with TSH >10 or are already on treatment for hypothyroidism, Also pregnant and lactating females, patients with bone diseases or cardiac disease or any chronic illness were excluded from the study. All patients and control subjects were subjected to History taking and physical examination, Laboratory investigation (TSH, Free T4, Fasting lipid profile, Anti-Tpo and Anti TG, Cardiac evaluation by conventional Echo, Tissue Doppler and speckle tracking Echo and DEXA scan.

### *2.2. Statistical analysis*

Data were analyzed using: IBM-SPSS software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

### *2.3. Data expression*

- Qualitative data were expressed as N (%).
- Quantitative data were tested for normality using Shapiro-Wilk's test with data being normally distributed if p>0.050. The presence of significant outliers (extreme values) was tested for by inspecting boxplots.
- Quantitative data were expressed as mean ± SD if normally distributed or median and interquartile range (Q1 or $25^{th}$ percentile – Q3 or $75^{th}$ percentile) if not

### *2.4. Data comparison*

- Qualitative data between groups:

For more than 2X2 cross tabulation, *Fisher-Freeman-Halton* test was used as the expected count in cells was < 5 in some of the cells.

- Quantitative data between more than two groups:

The one-way ANOVA test was used to compare normally distributed quantitative data between more than two groups. The Kruskal-Wallis H-test was used to compare non-normally distributed quantitative data between more than two groups.

### *2.5. Associations*

Point biserial correlation test was used to determine whether there is an association between a dichotomous variable (i.e., nominal variable with two categories) and a quantitative variable. The strength of association was considered low, medium, or high if the correlation coefficient ($r_{pb}$) was > 0.1 to <0.3, 0.3 to <0.5, or 0.5 or more, respectively. The Spearman's correlation test was used to determine whether there is a linear relationship association between two non normally distributed quantitative data. The strength of association was considered low, medium, or high if the correlation coefficient (r) was > 0.1 to <0.3, 0.3 to <0.5, or 0.5 or more, respectively.

Significance level for any of the used tests, results were considered as statistically significant if p value ≤ 0.050.

## 3. Results and Discussion

This study involved 45 participants divided into two groups:

- Group 1: 30 adult female patients newly diagnosed with subclinical hypothyroidism aged 18-40 years
- Group 2: "Control group" 15 age matched female subjects with no history of thyroid or systemic disease

Age and BMI of the 2 groups are shown in **(table 1)**. This table shows no statistically significant difference in age and BMI between the two groups. The diastolic blood pressure (DBP) was statistically significantly higher in patients with SCH than DBP in health control subjects. Both Systolic blood pressure (SBP) and Mean arterial pressure (MAP) were higher in patients with SCH than in health control subjects, however the difference wasn't statistically significant.

Group 1 showed a statistically significantly higher TSH level, It also shows a statistically significantly lower FT4 level than control group. Anti-TPO and anti-TG were positive in two-thirds and three-fifths of cases, respectively, and in none of the control subjects. As regard lipid profile group (1) showed a statistically significantly higher TC level and LDL-C than control group. Also they had higher TG level than control group but the difference wasn't statistically significant. Moreover they had lower HDL level than control group yet again the difference wasn't statistically significant.

While comparing BMD between the 2 groups. Group (1) showed a statistically significantly lower FT4 level, BMD (spine and radius). Patients with SCH had a non-significant lower EF than healthy individuals ($p$ = 0.123), however patients had statistically significant higher E/e' septum ratio ($p$ <0.001). Also patients had statistically significant lower E/A septum and GLS than control group ($p$ <0.001 both). SCH one of the commonest endocrinopathies, worldwide the prevalence of SCH ranges from 5% to 16% (22), SCH is more common in women than in men, and also in older people.(23). SCH is considered to be a potential contributor to cardiac complications (6). SCH both directly and indirectly influences the development of cardiovascular diseases. It contributes to a number of factors related with cardiovascular disease, all of which lead to reduced heart function (24).

Studies have shown an association between elevated TSH and total and low-density lipoprotein (LDL) cholesterol concentration (3). While few studies have considered the effect of SCH on bone density in middle aged and young adult, the effect of SCH on bone density is more prevalent in elderly (21).

In this study which included 45 participants classified into 2 groups: Group {1} 30 adult female patients newly diagnosed with subclinical hypothyroidism aged 18-40 years and Group {2} "Control group" 15 age matched female subjects with no history of thyroid or systemic disease, we compared cardiac function, lipid profile and BMD between the 2 groups. We didn't find any significant difference between patients with SCH and control group regarding BMI (*p = 0.559)*. Previous studies showed a discrepancy with regard to what kind of relationship exists between SCH and BMI. While this result was in agreement with Pan et al (33) who failed to find any significant relationship with BMI in either sex. Yan et al (34) has found that Obesity was associated with SCH in the presence of thyroid autoantibodies. The diastolic blood pressure (DBP) was statistically significantly higher in patients with SCH than DBP in health control subjects. Both SBP and MAP were higher in patients with SCH than in health control subjects, however the difference wasn't statistically significant. These results were similar to Zhang et al (25) results in a meta-analysis addressing the association between subclinical thyroid dysfunction and hypertension concluded that subclinical hyperthyroidism was associated with higher SBP and DBP.

On studying the effect of SCH on lipid metabolism, we observed that the level of TC, LDL-C and TG was higher in patients with SCH than the control group but the difference was statistically significant regarding TC level and LDL-C level only, Also lower level of HDL was observed in the case group comparing to control group but the difference failed to show a statistical significance. Those results were in accordance with the results of a study by Ejaz et al (26) that compared lipid profile in individuals with and without SCH in which TC and LDL was significantly higher in participants with SCH compared to participants without SCH. Hypercholesterolemia in SCH is mainly due to a reversible reduction in the low-density lipoprotein (LDL) receptor number and activity *(27)* In the current study Mean Z scores of spine and radius were lower in SCH group than control group and the difference were statistically significant. However there was no statistically significant difference of BMD of femur between the two groups. Studies on the effect of SCH on BMD are scanty and controversial, while the negative impact of SCH on BMD has been shown by Lee et al (28**),** no association was found between subclinical hypothyroidism and hip fracture risk or BMD by other studies.(21, 29, 30). Patients with SCH had a non-significant lower EF than healthy individuals, however patients had statistically significant higher E/e' septum ratio. Also patients had statistically significant lower E/A septum and GLS than control group reflecting the negative impact of SCH on systolic and diastolic cardiac function moreover enhancing the role of tissue Doppler and speckle tracking Echo in diagnosis. Those results were in agreement with Navoka et al (31) who observed lower GLS in SCH patients (-19.55 ± 2.3) compared to healthy control group (-20.9 ± 1.7) which indicates the effect of SCH on left ventricular systolic function also Patients with SCH had a lower E/A ratio than control (1.03 ± 0.29 vs. 1.26 ± 0.36, p < 0.01) and higher E/e' septum ratio than control (7.62 ± 2.29 vs. 6.04 ± 1.64, p < 0.01).

**Table 1.** Age and BMI in the study groups

| Parameter | Group 1<br>N=30 | Group 2<br>N=15 | p-value |
|---|---|---|---|
| Age (years) | 31(28.5 -33.3) | 27 (22.3 - 31.5) | .110 |
| BMI (kg/m$^2$) | 27 (22- 32) | 29.5 (23.5 - 32.5) | .379 |

Notes: Categorical data is N (%), and the test of significance is Fisher's exact test, while numerical data is median (Q1 – Q3), and the test of significance is Mann-Whitney U-test

| Parameter | Group 1<br>N=30 | Group 2<br>N=15 | p-value |
|---|---|---|---|
| HR (BpM) | 78 (66.75 - 82.5) | 75 (67.5 - 88.5) | .818 |
| SBP (mmHg) | 120 (110 - 130) | 115 (107 - 122) | .272 |
| DBP (mmHg) | 75 (70 - 86) | 65 (60 - 70) | **.020** |
| MAP (mmHg) | 87.5 (83.3 - 100.8) | 85 (76.7 - 87.6) | .054 |

(SBP: systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure)

**Table 3.** Comparisons of laboratory data in cases vs. control

| Parameter | Group 1<br>N=30 | Group 2<br>N=15 | p-value |
|---|---|---|---|
| TSH (µIU/l) | 7.4 (6.18 -8.92) | 2.35 ( 1.13- 3.35 ) | **<.001** |
| Free T4 (ng/ dL) | 1.15 (1 - 1.3) | 1.55 (1.08 - 1.63) | **.036** |
| Positive anti-TPO | 20 (66.7%) | 0 (0%) | **<.001** |
| Positive anti-TG | 18 (60%) | 0 (0%) | **<.001** |

**Table 4.** Comparisons of lipid profile in cases vs. control

| Parameter | Group 1<br>N=30 | Group 2<br>N=15 | p-value |
|---|---|---|---|
| TC (mg/ dL) | 194 (183- 214) | 176 (167- 184) | **.001** |
| TG (mg/ dL) | 147 (131 - 167) | 134 (128 -141) | .054 |
| LDL-C (mg/ dL) | 110 (96 - 122) | 96 (92 - 106) | **.024** |
| HDL-C (mg/ dL) | 46.5 ( 42.8 - 52.8) | 52 (49.5- 55.3) | .058 |

**Table 5.** Comparisons of BMD in cases vs. control

| Parameter | Group 1<br>N=30 | Group 2<br>N=15 | p-value |
|---|---|---|---|
| BMD Spine ( Z score) | -0.25 (-0.63 to 0.30) | 0.3 (-0.18 to 0.65) | **.033** |
| BMD Femur ( Z score) | 0.3 ( -0.3 to 0.5) | -0.1 (-0.43 to 0.35) | .116 |
| BMD Radius ( Z score) | -0.8 (-1.05 to -0.40) | 0.1 (- 0.28 to 0.33) | **<.001** |

**Table 6**. Comparisons of cardiac parameters in cases vs. control

| Parameter | Group 1<br>N=30 | Group 2<br>N=15 | p-value |
|---|---|---|---|
| EF (%) | 64 ( 62 - 66 ) | 66 (64.75 - 67) | .123 |
| E/e' septum (Cm/s) | 7.2 (6.70 - 8.8) | 5.95 ( 5.73- 6.73) | **<.001** |
| E/A | 1.10 (1.02 - 1.20) | 1.35 ( 1.28 -1.40) | **<.001** |
| GLS percentage (%) | -17.25 ( -16 to -18.83) | -20.6 ( -21 to -19.68) | **<.001** |

(GLS: Global longitudinal strain, EF: Ejection fraction)

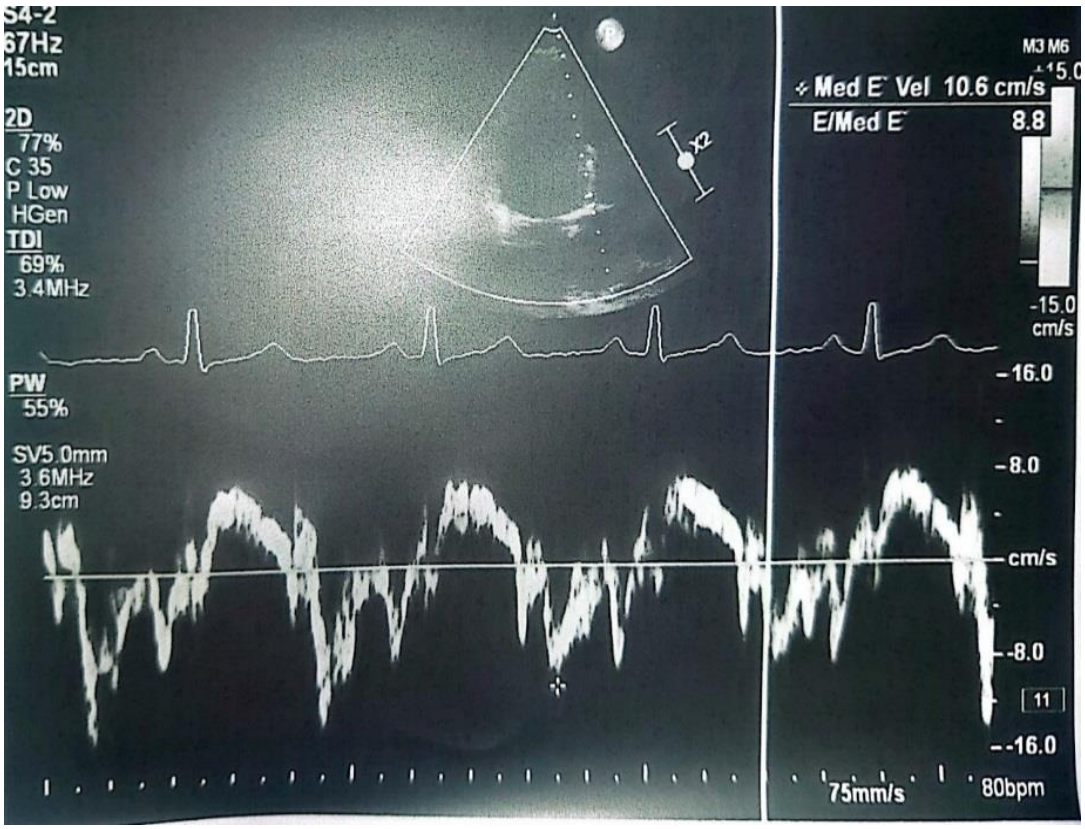


**Figure 1**. E/e' septum in SCH patient

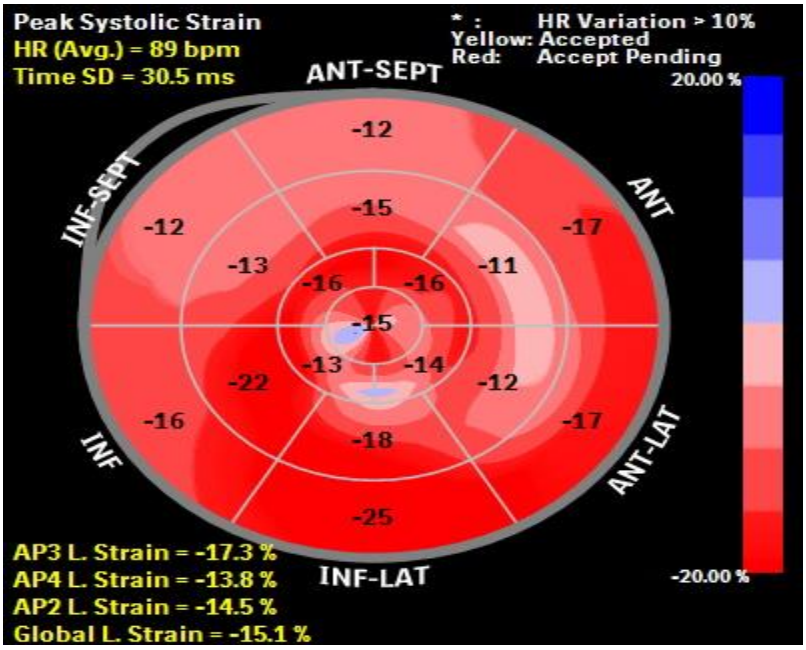


**Figure 2.** GLS in SCH patient

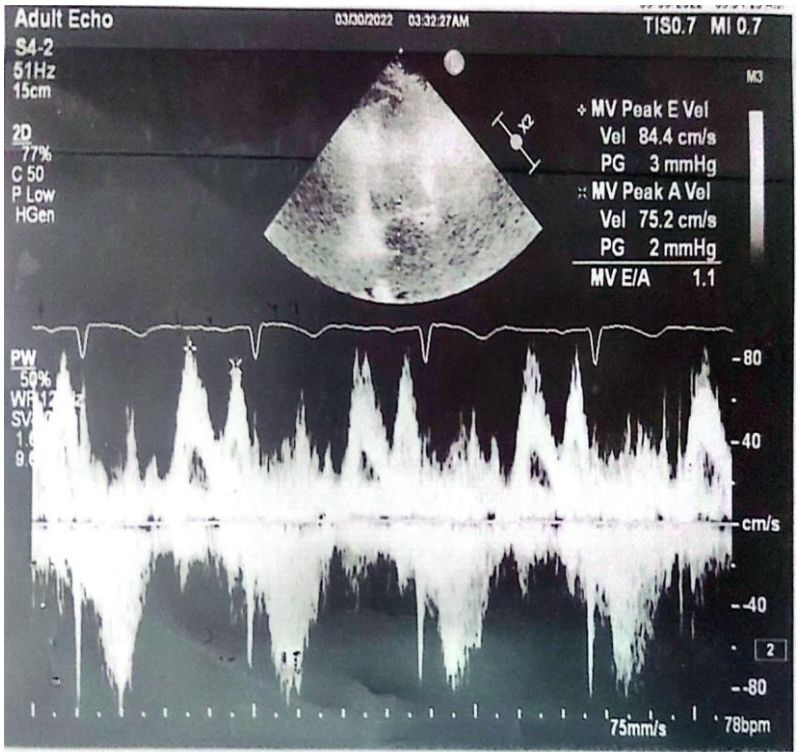


**Figure 3.** E/A ratio in SCH patient

These results are comparable with Huang et al (32) who observed that Subjects with SCH had significantly more prolonged deceleration time and isovolumic relaxation time, higher E/A, and worse GLS (−19.0% versus −20.2%) than those in the eu-thyroid group (all $P$<0.05).

## 4. Conclusion

From our study we concluded that, SCH has negative impact on lipid profile specially increasing serum cholesterol level and LDL level, also has harmful effect on cardiac systolic and diastolic function, moreover SCH may affect BMD.

## 5. Limitations

Multicenter study with larger number of cases and control are needed to validate the studies, also following up of those patients is necessary to disclose the effect of replacement therapy on the showed effects of SCH.

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