Assessment of some inflammatory markers and lipid profile as risk factors for atherosclerosis in subclinical hypothyroid patients
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Background
Subclinical hypothyroidism (SCH) is associated with dyslipidemia and low grade inflammation leading to atherosclerosis. Atherosclerosis shows an association with inflammatory markers, which with dyslipidemia may accelerate the atherogenesis, in SCH.

Objective
The objective of this study was to investigate some inflammatory markers and lipid profile as risk factors for atherosclerosis in SCH.

Patients and methods
An overall 100 participants were included and classified into two groups: control group I included 20 healthy volunteer, patient group II included 80 SCH patients and was subdivided into group IIa (26 male patients) and group IIb (54 female patients). All patients were submitted to the following investigations: complete blood picture, liver function tests, renal function tests, Lipid profile, calculated risk ratio I and II and specific laboratory Investigations [thyroid-stimulating hormone (TSH), free thyroxine, free tri-iodothyronine, C-reactive protein (CRP), serum interleukin (IL)-6 and serum IL-10 assays].

Results
There were statistically high significant differences between the control group and the SCH group as regards serum triglycerides, cholesterol, low-density lipoprotein, risk ratio I and II, TSH, IL-6, IL-10 and CRP (P<0.001). Statistically significant higher levels of CRP, serum IL-6 and IL-10 were observed in SCH patients than in controls. TSH had a positive correlation in SCH patients with all studied parameters including all lipid parameters, CRP, IL-6 and IL-10 and was negative only to free tri-iodothyronine and free thyroxine, whereas IL-6 and IL-10 correlated also with all parameters except age.

Conclusion
SCH is associated with increased levels of inflammatory markers and dyslipidemia, which are indicators for atherosclerosis, and are good predictors of cardiovascular morbidity.

Keywords:
atherosclerosis, dyslipidemia, inflammatory markers, subclinical hypothyroidism

Introduction
Subclinical hypothyroidism (SCH) is characterized by elevated serum thyroid-stimulating hormone (TSH) levels despite normal free thyroid hormone [free tri-iodothyronine (FT3) and free thyroxin (FT4)] values [1]. Pathophysiology of atherosclerosis shows an association with inflammatory markers, which with dyslipidemia may accelerate the atherogenesis, in future in SCH [2]. Interleukin (IL)-6 and C-reactive protein (CRP) are inflammatory markers that are reliable and well-known predictors of cardiovascular risk [3]. CRP is a biochemical tool for diagnosis of coronary artery disease risk [4]. IL-6 is a cytokine and an established inflammatory marker that induces the activity of CRP [5]. Hyperlipidemia and dyslipidemia are the hallmark of hypothyroidism, with a tendency of raised serum cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides with decreased high-density lipoprotein (HDL) cholesterol, and it is associated with coronary atherosclerotic disease [6]. Few studies on inflammatory markers and lipid profile need a research on that issue to clarify and halt atherosclerosis in SCH patients. Thus, the present study aimed to analyze some inflammatory markers and blood lipid profile in SCH.

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Patients and methods
This was an observational descriptive cohort and analytic study and included 100 persons undergoing regular follow-up for SCH in the Endocrine Unit of the Internal Medicine Department and has been carried out in the Internal Medicine and Clinical Pathology Departments, Faculty of Medicine, Zagazig University, from June 2017 to March 2018.

Patients
They were enrolled in this study after they provided their written consent and were classified into two groups: (a) control group I included 20 healthy volunteers, nine male patients and 11 female patients with ages that ranged from 38 to 55 years and with mean±SD of 48.45±6.15 years. (b) Patient group II with ages that ranged from 38 to 55 years and with volunteer, nine male patients and 11 female patients groups: (a) control group I included 20 healthy persons and IIb including 54 female individuals with ages ranging from 38 to 55 years with mean±SD of 49.69±5.01 years, and (b) Patient group IIb including 26 male patients, with ages ranging from 40 to 55 years, with mean±SD of 49.69±5.01 years, and group IIB including 54 female individuals with ages ranging from 38 to 55 years with mean±SD age of 49.25±4.88 years. Exclusion criteria were as follows: persons with age over 60 years and less than 18 years, patients with thyroid diseases and or under any thyroidal treatment, pregnant and lactating female, all cases with fever, patients with renal, endocrinal, hepatic, malignant or rheumatic diseases, patients suffering from malignancy or under radiotherapy or chemotherapy, and patients with evidence of ischemic heart disease were also excluded.

Methods
All patients of the study were subjected to the following protocol: (a) full medical history taking and thorough clinical examination: according to checking patients’ records. (b) Laboratory investigations: all the investigations were carried out according to the methods applied in the Clinical Pathology Laboratories of Zagazig University Hospitals and included (a) routine laboratory investigations, which included complete blood picture (by Sysmex xs 1000), liver function tests by kinetic method, renal function tests by colorimetric method [8], lipid profile [total cholesterol (TC), serum triglycerides, LDL and HDL], calculated risk ratio I (ratio of TC to HDL with normal range 3.3–4.4), risk ratio II (ratio of LDL/HDL with normal range 1.5–3.2) and random blood glucose levels. (b) Specific laboratory investigations: C-Reactive protein (CRP) was measured by immunoturbidimetric technique on the Cobas Integra 400 analyzer Roche Diagnostics [9]. Thyroid-stimulating hormone (TSH), Free thyroxin (FT4) and Free triiodothyronine (FT3) were determined by cobas e immunoassay analyzers using the electrochemiluminescence immunoassay. Serum Interleukin 6 & 10 (IL6,IL10) were measured by sandwich ELISA kits supplied by AndyGene Biotechnology Co.LTD. [10,11]. (c) Other investigations: ECG and abdominal and thyroid ultrasound were also performed.

Statistical analyses
All data were collected, tabulated and statistically analyzed using SPSS 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and MedCalc 13 for Windows (MedCalc Software bvba, Ostend, Belgium). Quantitative data were expressed as the mean±SD (standard deviation), median and range, and qualitative data were expressed as absolute frequencies and ‘number’ and relative frequencies (percentage). Continuous data were checked for normality by using the Shapiro–Wilk test. Independent Student t-test was used to compare two groups of normally distributed data. Mann–Whitney U was used to compare two groups of non-normally distributed data. One-way analysis of variance test was used to compare more than two groups of normally distributed data. Kruskal–Wallis H-test was used to compare more than two groups of non-normally distributed data. Homogeneity of variance was tested by Levene’s test. Post-hoc test for multiple comparisons was performed by using least significant difference or Tamhane’s T2 method according to homogeneity of variance. Percent of categorical variables was compared using χ²-test or Fisher’s exact test when appropriate. Spearman’s coefficient was calculated to assess the relationship between TSH, IL-10, IL-6 and study parameters, positive sign indicates direct correlation and negative sign indicates inverse correlation; moreover, values near to 1 indicate strong correlation and values near 0 indicate weak correlation. To determine predictors for SCH, univariate logistic regression was performed. All tests were two-sided. P value less than 0.05 was considered statistically significant, P value less than 0.001 was considered highly statistically significant, and P value at least 0.05 was considered nonstatistically significant.

Results
There were statistically high significant differences between the control group and male and female SCH subgroups, as regards demographic and clinical data (P<0.001), except for age, which exhibited a nonsignificant difference (P>0.05; Table 1).
There were statistically high significant differences between the control group and the SCH subgroups, as regards routine laboratory findings ($P < 0.001$), except for HDL, which exhibited a significant difference ($P < 0.05$), and there were statistically high significant differences between the control group and male and female SCH subgroups, as regards specific laboratory findings ($P < 0.001$), except for FT3 and FT4, which exhibited a nonsignificant difference ($P > 0.05$; Table 2). All specific laboratory parameters were nonsignificantly different among the two SCH subgroups IIa and IIb (Table 3). Table 4 shows the correlation between TSH, IL-10, IL-6 and different study parameters, where an elevated level of TSH in SCH patients was positively correlated with all studied parameters including age, blood pressure, random blood glucose, all lipid parameters, CRP, IL-6 and IL-10 and negatively only with FT3 and FT4. IL-6 and IL-10 were positively correlated with all studied parameters except age (Table 4). None of the studied parameters was a predictor of SCH (Table 5).

**Discussion**

SCH refers to biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical features of hypothyroidism. Although SCH is often asymptomatic, nearly 30% of patients have symptoms that are suggestive of thyroid hormone deficiency [12]. SCH is characterized by elevated serum TSH levels despite normal free thyroid hormone (FT3 and FT4) values. SCH has been associated with increased cardiovascular risk factors like hypercholesterolemia, increased HDL and LDL cholesterol levels and increased CRP values, which increase the risk for atherosclerosis [13].

Thyroid hormone has a great impact on lipid metabolism, as it is needed for the synthesis and catabolism of lipids, and its deficiency may induce change in lipid metabolism, mostly degradation rather than synthesis. Previous studies have demonstrated that cardiovascular risk might be possible in SCH, but the effect of TSH range is not clearly stated [14].

The endothelium is a potential target of thyroid hormone and plays a major role in the maintenance of vascular function and integrity. Nitric oxide (NO) is the most important vasodilator substance produced by the endothelium, and, in endothelial dysfunction, there was decreased NO availability, which acts as a promoter of atherosclerosis and was associated with an increased cardiovascular risk [15].

Circulating inflammatory markers are strongly associated with cardiovascular events, even in individuals with normal lipoprotein profiles, but little is known with regard to the impact of SCH [16].

Thus, the aim of our study was to measure and investigate some inflammatory markers and lipid profile as risk factors for atherosclerosis in subclinical hypothyroidism. Our study included 100 patients, divided into two groups; the case group included 80 patients with SCH and the control group included 20 healthy patients. There are 35 male individuals and 65 female individuals. Their age range was 38–59 years with mean±SD of 49.21±5.15 years. All patients in this study were age-matched and sex-matched with the control group.

Our SCH group of patients showed significantly higher values of both systolic and diastolic blood pressure and also random blood glucose levels versus the control group, which is in agreement with Nagasaki et al. [17].

Considering random blood glucose level, although it was within the normal range, yet it was significantly higher in SCH thyroid patients than in the control.

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**Table 1** Comparison between the control group and subclinical hypothyroidism subgroups as regards demographic and clinical data

| Demographic and clinical data | Total | Group I (N=20) | Group IIa (N=26) | Group IIb (N=54) | Test | $P$-value |
|------------------------------|-------|---------------|------------------|------------------|------|-----------|
| Age (years) | | | | | | |
| Mean±SD | 48.45±6.15 | 49.69±5.01 | 49.25±4.88 | $0.402\text{b}$ | 0.818 |
| Median (range) | 50 (38–55) | 51 (40–55) | 50 (38–55) | | |
| SBP (mmHg) | | | | | | |
| Mean±SD | 120±0 | 149.23±9.34 | 148.03±13.33 | $49.233\text{b}$ | <0.001 |
| Median (range) | 120 | 150 (130–160) | 150 (130–180) | | |
| DBP (mmHg) | | | | | | |
| Mean±SD | 80±0 | 90.38±3.72 | 92.77±3.96 | $56.017\text{b}$ | <0.001 |
| Median (range) | 80 | 90 (80–95) | 90 (90–100) | | |

Group I: control group, group IIa: male SCH group, group IIb: female SCH group. Categorical variables was expressed as n (%). $P<0.05$, significant. SCH, subclinical hypothyroidism. $\text{bKruskal–Wallis } H$-test.
This denoted early changes towards diabetes mellitus, which constitute, with insulin resistance, a spectrum of proatherogenic changes [18].

As regards the lipid profile in our SCH thyroid patients, serum triglycerides, TC and LDL-cholesterol levels, and TC/HDL and LDL/HDL ratios were all significantly higher than in the control group, with the observation of a significantly lower level of HDL. This refers to the association between atherosclerosis lipid risk factors (state of endothelial dysfunction) and SCH; this finding is in agreement with Rossi et al. [19]. However, Cabral et al. [20] reported that endothelial dysfunction may represent the early development of cardiovascular damage in SCH patients. Our results are in agreement with Celik et al. [21] who observed that SCH women are characterized by dyslipidemia. Gao et al. [14] also supported the findings of our study, and they have also concluded that dyslipidemia and hypertension have been associated with SCH in middle-aged women.

Considering risk ratios, TC/HDL and LDL/HDL ratio (risk ratio I and II), which are better predictors of
cardiovascular morbidity, were both significantly higher in our SCH than in the control group; this refers to the future development of cardiovascular disease. This is in agreement with Marwaha et al. [22], who reported that SCH had also been associated with a high prevalence of dyslipidemia, and a high prevalence of coronary heart disease in elderly men and women.

Chronic inflammation may initiate and promote atherosclerosis or its complications by adverse effects on the vascular endothelium, and it may be one of the contributing factors that lead to the increased endothelial dysfunction and atherosclerosis in patients with SCH. Türemen et al. [23] observed not only an elevation of several inflammation indicators, including IL-6, tumor necrosis factor-α (TNF-α) and CRP, in patients with SCH, but also a positive correlation of flow-mediated dilation between these inflammation factors, indicating that low-grade chronic inflammation may be one of the factors that can promote atherosclerosis in SCH.

As regards CRP, it was significantly higher in the patients than in the participants in the control group. This is in agreement with Cabral et al. [20], who revealed higher CRP and IL-6 values and reduced vasodilatation to acetylcholine in the SCH patient, compared with the controls. CRP, one of the ‘acute phase proteins’ generated by the liver under inflammatory challenge, a traditionally used inflammatory marker, later discovered to be indicative of cardiovascular events, was observed to be increased in patients with SCH [24]. CRP can interfere with endothelial function directly by downregulation of endothelial NO synthase and upregulation of endothelin-1, which is a potent
The assessment of risk factors of atherosclerosis holds a great deal of promise as an assessment tool for the preclinical stage. The predisposition of patients with SCH to atherosclerosis has been observed and may be partially explained by the factors also found in patients with SCH, including dyslipidemia, low-grade chronic inflammation, oxidative stress, and insulin resistance [16].

Table 5: Univariate logistic regression for possible predictors for subclinical hypothyroidism at the study (N = 100) by univariate analysis

| Variables | β  | SE  | OR (95% CI) | P-value |
|-----------|----|-----|-------------|---------|
| Age (years) | +0.035 | 0.048 | 1.036 | 0.944–1.137 | 0.460 |
| Female | +0.530 | 0.509 | 1.669 | 0.627–4.607 | 0.298 |
| CRP (mg/ml) | +15.343 | 969.448 | 460.392 | 0 | 0.987 |
| IL-10 | +0.422 | 45.499 | 1.525 | 0 | 0.993 |
| IL-6 | +37.349 | 675.878 | 1.662 | 0 | 0.956 |

P < 0.05, significant. β, regression coefficient; CI, confidence interval; CRP, C-reactive protein; IL, interleukin; OR, odds ratio; SE, standard error.

Conclusion

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Whether SCH leads to endothelial dysfunction, which is an early stage of atherosclerosis, or whether it is just associated with endothelial dysfunction needs to be clarified. Alibaz Oner et al. [13] mentioned that hypothyroidism accelerates atherogenesis through the modification of atherosclerotic risk factors, and direct effects on the blood vessels and endothelial functions improved after l-thyroxine therapy in SCH patients. La-Vignera et al. [30] mentioned that SCH accelerates atherosclerosis through traditional effects on risk factors that promote atherosclerosis and nontraditional effects on vasculature. In particular, SCH is associated with an increase of LDL-cholesterol, diastolic blood pressure, and markers of chronic inflammation (CRP) and simultaneously reduces the bioavailability of NO to blood vessels and increases the expression of angiotensin receptor. Furthermore, replacement therapy seems to improve all these aspects.

Considering thyroid hormone values, the TSH level in male and female SCH patients was higher than in control patients, but it did not differ when comparing male to female sex. This is supported by Shekhar et al. [6] who stated that the prevalence of SCH increases with age and is higher in women after the sixth decade of life. In fact, the median age of our patients was 50 years, and 97% of them were 40–59 years old. In addition, 2/3 of our SCH patients were of female sex. One explanation to the relation of SCH to endothelial dysfunction and atherosclerosis is that TSH is able to bind hepatocyte thyroid-stimulating hormone receptors (TSHRs) to induce IL-6 synthesis, bind adipocyte TSHR to promote cholesterol synthesis and bind bone marrow cell TSHR to increase TNF-α secretion [29]. In our study, the elevated level of TSH in SCH patients correlated with all studied parameters including age, blood pressure, random blood glucose, all lipid parameters, CRP, IL-6 and IL-10 and negatively only with FT3 and FT4. Notably, the TC/HDL and LDL/HDL ratios, which are valuable predictors of cardiovascular morbidity, were also found to be significantly associated with SCH and positively correlated with TSH values, pointing towards the higher risk for atherogenicity. IL-6 and IL-10 correlated with all studied parameters except age; this emphasizes the parallel association of increased levels of both cytokines with SCH state and also with markers of endothelial dysfunction and atherosclerosis. None of the studied parameters was found predictor of the state of SCH, and this points to the value of measuring TSH specifically in patients suspected to have the state of SCH.

As regards IL-6 as a proinflammatory marker and IL-10 as an anti-inflammatory marker in our SCH patients, both were significantly higher in the patient group than in controls. IL-6, a proinflammatory cytokine, indirectly promotes atherogenesis by increasing the hepatic production of CRP [25]. Taddei et al. [26] concluded that SCH patients were characterized by higher CRP and IL-6. CRP, indirectly promoted by IL-6, plays an important role in the progression of atherosclerosis. Türemen et al. [23] reported a significantly higher concentration of IL-6 in SCH patients.

We found a significantly higher level of serum IL-10 in our SCH patients than in the control group. This is explained by the fact that IL-10 is a major anti-inflammatory cytokine that has been associated with insulin resistance [27]. Moreover, IL-10 is required for regulating immune functions and is effective at decreasing the levels of proinflammatory cytokines including IL-6, and thus minimizes inflammation [23]; it proved to have a protective effect against atherosclerosis and endothelial dysfunction. Furthermore, our finding is supported by the finding of Nielsen et al. [28] who mentioned a significant correlation between IL-10 and IL-6, CRP, and TNF-α levels.

Vasoconstrictor that can antagonize NO action [5]. Shekhar et al. [6] suggested that SCH has been strongly associated with dyslipidemia and cardiovascular risk along with abnormal CRP level.

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Conflicts of interest

There are no conflicts of interest.

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