ORIGINAL ARTICLE

Effects of subclinical hypothyroidism in type II diabetes mellitus patients on biochemical, coagulation, and fibrinolysis status

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ABSTRACT

The aim of the currnet study to examine the effect of subclinical hypothyroidism (SCH) in diabetic patients on coagulation parameters. This retrospective case–control study involves 130 patients diagnosed with type 2 diabetes mellitus (T2DM), divided into 65 T2DM with newly diagnosed SCH and 65 euthyroid (EUT) T2DM patients without SCH. Fibrinogen (FIB) was significantly higher in SCH (508.2 ± 63.0 mg/dL) than EUT (428.1 ± 44.8 mg/dL). In the SCH patients, FIB correlated with several parameters, such as age (β = 0.396), body mass index (β = 0.578), glycated hemoglobin (β = 0.281), and activated partial thromboplastin time (β = 0.276). In conclusion SCH in DM patients appears to increase the magnitude of coagulopathy.

Key words: Coagulation, diabetic, fibrinogen, glycated hemoglobin, subclinical hypothyroidism

INTRODUCTION

Thyroid diseases and diabetes (diabetes mellitus [DM]) commonly occur together as two types of endocrine disorders;[1] their relationship is characterized by a complicated and reciprocal interdependence: changes in glycemic status can cause considerable changes in the thyroid hormones, and thyroid hormones play a crucial role in controlling the metabolism of glucose.[2]

The etiology of heightened thrombosis susceptibility in diabetes is intricate and encompasses various pathways. Individuals diagnosed with diabetes experience early development of atherosclerosis and a greater extent of vascular disease, making them more susceptible to plaque rupture and the formation of blood clots.[3] Furthermore, these patients exhibit an elevated propensity for blood clot formation due to heightened platelet reactivity and enhanced activation of prothrombotic coagulation factors combined with reduced fibrinolysis.[3]

Subclinical hypothyroidism (SCH) manifests as an increased thyroid-stimulating hormone (TSH) level but within the normal range of free T4.[4] Recent meta-analyses have shown that there is a strong link between SCH and an increased prothrombotic state, in which the presence of SCH is associated with increased tissue plasminogen activator, plasminogen activator inhibitor type 1 (PAI-1), fibrinogen (FIB), and activated partial thromboplastin time (aPTT).[5]

No study has examined SCH's potential effect on the coagulation pathway in patients diagnosed with type 2

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DM (T2DM) since both conditions are associated with higher coagulation status. How much the coexistence of both conditions will influence the coagulation pathway and whether SCH will augment the effect of DM on coagulation remains to be seen. For this reason, we examined the association between SCH and coagulopathy in diabetic patients.

METHODS

Study design and settings

In a retrospective case–control study involving 130 patients diagnosed with T2DM, the patients were divided into two groups: the SCH group included 65 T2DM with newly diagnosed SCH and the other group (the control group) included 65 euthyroid (EUT) T2DM patients without SCH. All relevant data were collected retrospectively from the case files of patients who attended the Department of Endocrinology, Al-Kindy Teaching Hospital. The authors collected this data and entered it into an Excel sheet for later analysis. The data collected from August 5, 2023, to September 5, 2023.

Glycemic control was defined based on the American Diabetes Association (ADA) recommendations for nonpregnant adults using glycated hemoglobin (HbA1c) into good control (<7%), inadequate (between 7% and 8%), and poor control (more than 8%).[6]

Inclusion criteria

Adult patients diagnosed with previously diagnosed T2DM according to the ADA guidelines,[6] on maintenance antidiabetic medications, both sexes, duration of DM between 1 and 10 years, and age between 35 and 65 years. Regarding the SCH group comprised newly diagnosed SCH (TSH > 6.5 mIU/L; and normal free thyroxine [FT4]),[7] these patients were eligible to be included in the study.

Exclusion criteria

Age under 18 years old, <1 year and more than 10 years' duration of T2DM, the presence of any serious medical conditions that may affect the blood coagulation system, such as inflammatory disease, renal disease, liver disease, hematopoietic disorders, cardiovascular risk factors (e.g., hypertension and dyslipidemia) or medication use (e.g., statins, anticoagulants), immunopathies, pregnancy, a history of taking estrogen replacement therapy or anticoagulants before the enrolment in the study, history of substance abuse, history of taking alcohol, and severe increase in TSH (≥10.0 mU/L). The control patients with T2DM were recruited among patients attending for asymptomatic benign nodules.

Sample size

The prevalence of SCH in a previous study was 4.3%,[8] the estimated sample size was 63 for each group, and 65 was chosen as the final sample size to account for possible drop cases.

$$minimum\ sample\ size(n) = p\frac{(1-p)Z^2_{0.95}}{d^2}$$

Laboratory assessment

Thyroid function

All analyses were carried out using COBAS e411 (Roche® analytical platform) analyzer automated chemiluminescent immunoassays (Roche Diagnostics, Mannheim, Germany) (Roche cobas e 411 analyzer [RRID: SCR_018369]). Based on a previous study by Alibrahim *et al*. in 2021, the normal range of TSH was (0.2–6.5 µIU/mL), and free T4 (0.8–1.70 ng/dL), these parameters defined EUT.

The definition of subclinical hyperthyroidism is based exclusively on laboratory findings, not clinical criteria. SCH is defined biochemically by a subnormal serum TSH level, with normal FT4,TT3 and/or free FT3 according 2015 European Thyroid Association Guidelines. We adapted recent study on TSH levels to be above 6.5 mIU/L as diagnostic criteria for SCH in Iraqi patients.[7]

Coagulation parameters

Serum aPTT high (20.6–27.0 s), prothrombin time (PT) (9.6–12.0 s), FIB (196–428 mg/dL), and D-dimer (DD) (<0.5 µg FEU/mL] were performed with a computerized blood coagulation analyzer (cobas t 411 coagulation analyzers, Roche Diagnostics).

Ethical approval

The study received approval from the relevant authorities of the Scientific Unit and Medical Ethics Committee of Al-Kindy College of Medicine (ethical approval number: 19, date: August 1, 2023). Written and informed consent was obtained from all the participants.

Statistical analysis

All analyses used (GraphPad Prism version 10.0.0 for Windows, GraphPad Software, Boston, Massachusetts USA). All variables followed a normal distribution (assessed using the Darling test). An independent *t*-test was used to assess the difference between EUT and SCH, whereas linear regression analysis was used to assess the relationship. The level of significance was <0.05 (two tailed).

RESULTS

The study included 130 DM patients divided into two groups; there was no significant difference in age, body mass index (BMI), sex, smoking, mode of therapy of T2DM, duration of DM, or family history of T2DM. Regarding the serum levels of the thyroid hormone panel, there was no significant difference in free T4, whereas TSH was significantly higher in SCH compared to the EUT group. Regarding the coagulation parameters, no difference in levels of aPTT, DD, and PT, whereas FIB was significantly higher in SCH compared to EUT, as illustrated in Table 1.

Levels of HbA1c were significantly higher in SCH compared to EUT (9.23 ± 8.2 vs. 7.76 ± 0.44%, $P \leq 0.001$), and the percentage of patients with poor glycemic control was significantly higher in SCH compared to EUT (92.3% vs. 29.2%, $P < 0.001$), binary logistic regression was performed and reveal significant association between poor glycemic control and SCH compared inadequate glycemic control (odd ratio; 95% confidence interval: 29.05; 10.09–83.64, $P < 0.001$, as illustrated in Figure 1.

In the EUT group, there was an inverse correlation between TSH with sex (in which females had higher levels of TSH compared to males) and an inverse correlation with duration of DM; meanwhile, in the SCH group, there was no significant correlation between TSH and sex. The other parameters in both EUT and SCH groups were not correlated with TSH, as illustrated in Table 2.

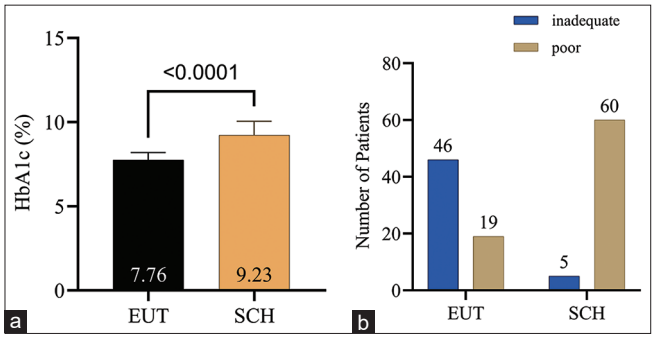

Figure 1: Assessment of (a) glycated hemoglobin (%) levels and (b) glycemic control according to the study groups. HbA1c: Glycated hemoglobin, EUT: Euthyroid, SCH: Subclinical hypothyroidism

In the SCH group, there was a direct correlation between FIB with BMI, HbA1c [Figure 2], and aPTT. The rest of the parameters did not correlate significantly with FIB, as illustrated in Table 3.

Thyroid markers (fT4 and TSF) and coagulation markers (aPTT, PT, DD, and FIB) did not show significant differences among various treatment modes of T2DM, as illustrated in Table 4.

DISCUSSION

In the present study, serum FIB was significantly higher in patients with SCH compared to those with EUT; in addition,

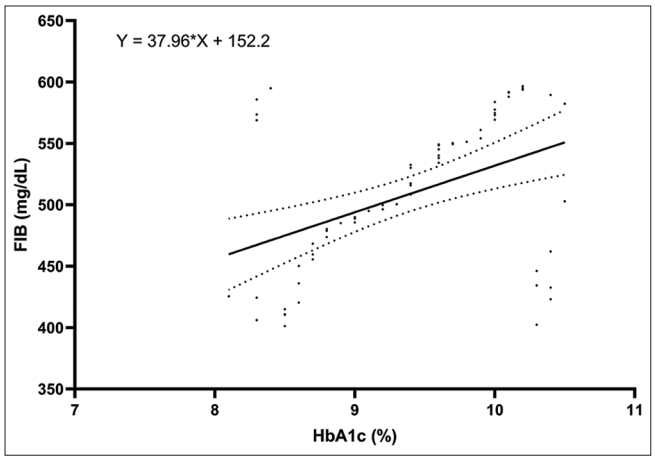

Figure 2: Scatterplot of the relationship between fibrinogen and glycated hemoglobin. FIB: Fibrinogen, HbA1c: Glycated hemoglobin

Table 1: Assessment of demographic and laboratory variables

Parameters	EUT diabetic	SCH with diabetes	*P*
Number	65	65	-
Age (years)	50.3±9.7	47.8±8.2	0.124
BMI (kg/m^2)	25.6±2.1	25.2±1.9	0.302
Sex, *n* (%)			0.840
Female	49 (75.4)	48 (73.8)	
Male	16 (24.6)	17 (26.2)	
Smoker, *n* (%)	11 (16.9)	13 (20.0)	0.651
Duration of T2DM (years)	5.37±2.19	5.75±2.13	0.313
Family history of T2DM, *n* (%)	8 (12.3)	16 (24.6)	0.071
Mode of treatment, *n* (%)			0.711
Oral hypoglycemic drugs	37 (56.9)	33 (50.8)	
Insulin	9 (13.8)	12 (18.5)	
Both	19 (29.2)	20 (30.8)	
DD (μg FEU/mL)	9.59±5.25	10.86±5.61	0.186
TSH (μIU/mL)	3.6±0.6	8.7±1.0	<0.001 significant
FT_4 (ng/dL)	1.26±0.24	1.22±0.24	0.317
FIB (mg/dL)	428.1±44.8	508.2±63.0	<0.001 significant
FIB >428, *n* (%)	34 (52.3)	54 (83.1)	<0.001 significant
aPTT (s)	24.78±2.73	25.03±2.71	0.605
PT (s)	11.21±1.21	11.56±1.10	0.092

Data presented as, mean±SD. SD: Standard deviation, BMI: Body mass index, DM: Diabetes mellitus, T2DM: Type 2 DM, TSH: Thyroid-stimulating hormone, FIB: Fibrinogen, aPTT: Activated partial thromboplastin time, SCH: Subclinical hypothyroidism, EUT: Euthyroid, PT: Prothrombin time, FT_4: Free thyroxine

67.7% of the patients had serum FIB levels above the upper normal limit (UNL), with 52.3% in the EUT group had levels above UNL. In comparison, 83.1% of the SCH had a level above UNL; the higher levels of FIB in SCH could be attributed to coexisting diabetes since DM is associated with increased FIB levels, as reported by previous studies.[9-11] In addition, in the present study, FIB correlated with several parameters such as age (β = 0.396), BMI (β = 0.578), HBA1c (β = 0.281), and aPTT (β = 0.276). Other reported similar relationships between FIB with HbA1c,[9,10] BMI,[9,10] and age.[9]

Table 2: Association between thyroid-stimulating hormone with various parameters in diabetes mellitus patients

Parameters	EUT diabetic		SCH with diabetes	
	β	*P*	β	*P*
Age	−0.052	0.679	0.129	0.305
BMI	−0.048	0.702	0.165	0.189
Sex	−0.277	0.026 significant	0.037	0.768
Smoking	−0.001	0.995	0.000	1.000
Family history of DM	−0.151	0.229	−0.101	0.423
HbA1c	0.092	0.468	0.043	0.735
DD	−0.130	0.302	−0.008	0.947
aPTT	0.167	0.185	−0.136	0.280
PT	−0.076	0.545	−0.222	0.076
FIB	0.034	0.790	0.064	0.611
DM duration	−0.287	0.021 significant	−0.017	0.893

β: Correlation coefficient. BMI: Body mass index, FIB: Fibrinogen, aPTT: Activated partial thromboplastin time, DM: Diabetes mellitus, DD: D-Dimer, SCH: Subclinical hypothyroidism, EUT: Euthyroid, PT: Prothrombin time, HbA1c: Glycated hemoglobin

Table 3: Association between fibrinogen with various parameters in diabetes mellitus patients

Parameters	EUT diabetic		SCH with diabetes	
	β	*P*	β	*P*
Age	−0.016	0.901	0.396	0.001 significant
BMI	−0.064	0.613	0.578	<0.001 significant
Sex	0.013	0.918	0.263	0.034
Smoking	0.147	0.244	−0.071	0.572
Family history of DM	−0.117	0.353	−0.022	0.862
HbA1c	−0.021	0.869	0.281	0.023 significant
DD	−0.073	0.562	0.043	0.732
aPTT	−0.192	0.126	0.276	0.026 significant
PT	−0.142	0.259	0.217	0.082
DM duration	−0.242	0.052	−0.168	0.182

β: Correlation coefficient. HbA1c: Glycated hemoglobin, BMI: Body mass index, aPTT: Activated partial thromboplastin time, DM: Diabetes mellitus, DD: D-Dimer, SCH: Subclinical hypothyroidism, EUT: Euthyroid, PT: Prothrombin time

Several studies examined the effect of FIB in nondiabetic patients; serum FIB was found to be slightly higher in SCH compared to EUT, but it did not reach statistical significance.[12,13] In these studies, the values of FIB were within the normal reference range, except for only one study that reported otherwise, and no significant difference was observed.[14] A recent meta-analysis examining SCH's effects on FIB reported that FIB was significantly higher in SCH than in EUT; however, the results showed moderate heterogenicity. In addition, higher FIB was associated with higher TSH levels.[5] In the present study, about half of the EUT patients had elevated levels of FIB; this indicates that diabetic increased hypercoagulable status caused by SCH.

FIB is associated with an increased risk of cardiovascular risk factors;[15] the current study showed that the presence of both SCH and DM had substantial effects on FIB levels, among other markers of coagulation pathways. This finding suggests that SCH in DM patients will have a pronounced effect on cardiovascular risk; thus, it is appropriate to consider screening for SCH in diabetic patients to treat and detect SCH early.

Several potential mechanisms could contribute to hyperfibrinogenemia in SCH. One possibility is that a procoagulant condition is frequently present in individuals with T2DM, and the coexistence of SCH may further exacerbate this state. The serum level of various coagulation factors, including PAI-1, von Willebrand factor, FIB, factor VII, and thrombin antithrombin complexes, has been observed to rise in correlation with both macrovascular and microvascular illness and poor glycemic control.[9] The relationship between FBS control and FIB may be attributed to two factors. First, glycosylated FIB may exhibit reduced susceptibility to plasmin degradation. Second, individuals

Table 4: Effect of mode of therapy of type 2 diabetes mellitus on thyroid and coagulation markers in subclinical hypothyroidism patients

Parameters	Oral	Insulin	Both	*P*
TSH (μIU/mL)	8.50±1.22	8.88±0.72	8.79±0.69	0.430
FT_4 (ng/dL)	1.27±0.23	1.10±0.20	1.21±0.24	0.075
FIB (mg/dL)	508.35±68.49	489.95±53.02	518.84±59.21	0.461
aPTT (s)	26.79±2.43	26.66±2.13	26.64±2.32	0.971
PT (s)	13.02±1.21	12.83±1.14	12.83±1.06	0.791
DD (μg FEU/mL)	11.12±6.00	9.38±5.85	11.30±4.90	0.603

Data presented as mean±SD. TSH: Thyroid-stimulating hormone, SD: Standard deviation, aPTT: Activated partial thromboplastin time, DD: D-dimer, FIB: Fibrino, PT: Prothrombin time, FT_4: Free thyroxine

with diabetes who experience relative insulin deficiency may undergo abnormal protein production, characterized by a 29% reduction in albumin production and a 50% increment in FIB production.[16] In a biokinetics study that assessed the relationship between FIB and DM, using radioactive leucine isotope, the authors found that plasma FIB concentrations increased by 50% compared to healthy control; also, FIB fractional synthesis/secretion rate was about 35% greater in the DM compared to healthy control, and FIB absolute secretion rate was increased by two-fold higher in the diabetic patients. There was a direct significant correlation between FIB and plasma glucagon but no relationship between FIB synthesis/secretion and plasma glucose.[17] These findings give us an idea about the strong relationship between FIB and DM, which is related to increased synthesis and poor FIB catabolism in these patients.

In the present study, both aPTT and PT were slightly higher in SCH compared to EUT, but it did not achieve a statistical difference; this was in line with others that found aPTT and PT were slightly elevated in SCH compared to EUT;[13,14] meanwhile, one study found no significant differences in aPTT between SCH and EUT.[12] A recent meta-analysis by Xu *et al*. reported no significant difference in aPTT levels between SCH and EUT and no significant association between aPTT levels with TSH levels, which agrees with the current study.[5]

In the current study, DD levels were slightly elevated in SCH compared to EUT, but it did not reach statistical significance; this was in agreement with other research;[13,14] in addition, Xu *et al*. meta-analysis showed no significant differences in DD between SCH and EUT.[5]

Limitations of the study

The study's observational design provides only a temporal relationship between coagulation parameters and SCH; cohort studies are necessary to examine this relationship extensively. We did not include other diseases that could affect or potentiate the effects on coagulation pathways; further studies are needed to examine the effects of other conditions.

CONCLUSION

Diabetic mellitus appears to increase the magnitudes of coagulopathy in subclinical hypothyroidism. Based on the current study findings, it is appropriate to consider screening for SCH in diabetic patients to treat and detect SCH early since both conditions are associated with an increased risk of cardiovascular diseases.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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