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COVID-19 and Subclinical Hypothyroidism as Dual Modulators of Myocardial Infarction Risk: A Clinical-Biochemical Perspective

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Abstract
Background: Subclinical hypothyroidism (SCH) is a risk factor for cardiovascular disease (CVD), particularly myocardial infarction (MI), due to its association with dyslipidemia, inflammation, oxidative stress, and endothelial dysfunction**.** COVID-19 exacerbates these risks by disrupting thyroid function and the renin-angiotensin system (RAS)**.**
Methodology: This retrospective study included 90 MI patients (45 with and 45 without COVID-19). Thyroid function, lipid profiles, oxidative stress, and inflammatory markers were assessed. Cardiac severity was evaluated using ECG changes, levels of biochemicak markers like troponin I, CK-MB.
Results: SCH patients had elevated TSH (6.2 vs. 4.8 mIU/L, $p < 0.05$), LDL (157.2 mg/dL), triglycerides (189.6 mg/dL), oxidative stress (MDA: 5.2 nmol/mL), and CRP (12.6 mg/L, $p < 0.01$)**.** Cardiac injury markers and hospital stays were significantly worse in COVID-19 MI patients.
Conclusion: SCH is an independent risk factor for MI, worsened by COVID-19**.** Routine thyroid screening in MI patients and further research on thyroid hormone therapy (THRT) are recommended.

Introduction

Subclinical hypothyroidism (SCH), defined by elevated thyroid-stimulating hormone (TSH) levels with normal circulating free thyroxine (fT4) and free triiodothyronine (fT3) concentrations, is a common endocrine disorder that has increasingly been linked to cardiovascular disease (CVD), particularly myocardial infarction (MI). While SCH is often considered a mild or asymptomatic condition, growing evidence suggests that even moderate thyroid dysfunction can significantly impact metabolic, vascular, and inflammatory pathways, predisposing individuals to adverse cardiovascular events[1,2].

At the molecular level, thyroid hormones regulate lipid metabolism, endothelial function, and inflammatory signaling pathways, and dysregulation of these processes in SCH patients can contribute to atherogenesis and myocardial injury[3]. Genetic studies have identified key polymorphisms in genes regulating thyroid hormone metabolism (DIO2), lipid transport (PCSK9, APOE), and oxidative stress resistance (FOXO3), which may increase cardiovascular risk in SCH patients[4,5]. Additionally, pro-inflammatory cytokine genes such as IL6 and TNF-α have been implicated in the heightened systemic inflammation observed in SCH-related cardiovascular disease[6].

The COVID-19 pandemic has further highlighted the complex interactions between thyroid function and cardiovascular health. SARS-CoV-2 infection has been shown to interfere with the hypothalamic-pituitary-thyroid (HPT) axis, leading to thyroid hormone dysregulation, increased oxidative stress, and endothelial dysfunction[7]. The viral-mediated disruption of the renin-angiotensin system (RAS) and induction of a pro-thrombotic state may further amplify cardiovascular risk in SCH patients[8]. Given these multifaceted interactions, it is crucial to investigate the pathophysiological mechanisms linking SCH, MI, and COVID-19, with the goal of developing early screening strategies and targeted therapeutic interventions for high-risk individuals.

Methodology

This retrospective cross-sectional study included 90 patients diagnosed with MI from Faisalabad Institute of Cardiology, a tertiary care hospital in Faisalabad , Pakistan. Patients were divided into two groups:

1. Group I (COVID-19 MI patients): 45 individuals with a history of COVID-19 and MI.
2. Group II (Non-COVID-19 MI patients): 45 individuals with MI but no history of COVID-19.

Inclusion Criteria:

- Age 40–90 years
- Confirmed myocardial infarction based on ECG changes and elevated troponin I/CK-MB levels
- Documented history of COVID-19 (RT-PCR confirmed) for Group I

Exclusion Criteria:

- Pre-existing overt hypothyroidism or other endocrine disorders
- Chronic kidney disease, active cancer, or autoimmune thyroid disease
- Recent use of thyroid hormone replacement therapy (THRT)

Blood samples were analyzed for:

- Thyroid function tests: TSH, fT4, fT3
- Lipid profile: LDL, HDL, total cholesterol, triglycerides
- Oxidative stress markers: Malondialdehyde (MDA), total antioxidant capacity
- Inflammatory markers: C-reactive protein (CRP), interleukin-6 (IL-6)
- Cardiac injury markers: Troponin I, CK-MB

Results

A total of 90 patients with myocardial infarction (MI) were included, comprising 45 with a history of COVID-19 (Group I) and 45 without COVID-19 (Group II). Within each group, patients were stratified according to thyroid function. In Group I, 8 patients had subclinical hypothyroidism (SCH) and 37 were euthyroid, while in Group II, 9 had SCH and 36 were euthyroid. The mean age in COVID-19 MI patients with SCH was 62.7 ± 11.5 years compared to 59.9 ± 12.4 years in those without SCH ($p = 0.32$). In non-COVID MI patients, the mean age was 60.9 ± 13.5 years in SCH and 57.3 ± 11.7 years in non-SCH patients. Hypertension and diabetes mellitus were more common among SCH patients in both groups (45% and 38%, respectively) compared with non-SCH patients (30% and 25%, $p < 0.05$).

TSH levels were significantly elevated in patients with SCH across both groups. In COVID-19 MI patients, mean TSH was 6.2 ± 1.1 mIU/L in SCH compared to 2.1 ± 0.7 mIU/L in non-SCH ($p < 0.05$). Among non-COVID MI patients, TSH was 4.8 ± 0.9 mIU/L in SCH compared with 2.0 ± 0.6 mIU/L in non-SCH ($p < 0.05$). Both fT4 and fT3 were lower in SCH patients, though within reference ranges.

SCH patients consistently exhibited dyslipidemia. In COVID-19 MI patients, LDL cholesterol was 157.2 ± 21.5 mg/dL in SCH versus 136.8 ± 19.7 mg/dL in non-SCH ($p < 0.01$), and triglycerides were 189.6 ± 31.2 mg/dL versus 164.4 ± 27.8 mg/dL ($p < 0.01$). HDL cholesterol was reduced in the SCH subgroup (41.2 ± 6.8 mg/dL vs. 46.3 ± 7.5 mg/dL, $p < 0.05$). A similar pattern was observed in non-COVID MI patients, where LDL (136.8 ± 19.7 vs. 122.4 ± 18.9 mg/dL, $p < 0.01$) and triglycerides (164.4 ± 27.8 vs. 148.2 ± 26.4 mg/dL, $p < 0.01$) were higher, and HDL (46.3 ± 7.5 vs. 50.1 ± 8.2 mg/dL, $p < 0.05$) was lower in SCH patients compared with euthyroid patients.

COVID-19 MI patients with SCH demonstrated significantly higher CRP levels (12.6 ± 2.3 mg/L vs. 8.4 ± 1.9 mg/L, $p < 0.01$) and MDA levels (5.2 ± 0.9 nmol/mL vs. 3.8 ± 0.6 nmol/mL, $p < 0.01$). In the non-COVID MI group, SCH patients also showed higher CRP (8.4 ± 1.9 vs. 6.5 ± 1.7 mg/L, $p < 0.01$) and MDA (3.8 ± 0.6 vs. 3.0 ± 0.5 nmol/mL, $p < 0.01$).

Cardiac biomarkers were elevated in SCH patients. In COVID-19 MI patients, troponin I was 4.2 ± 1.3 ng/mL in SCH compared with 2.8 ± 0.9 ng/mL in non-SCH ($p < 0.01$), and CK-MB was 85.3 ± 11.6 U/L versus 62.1 ± 9.3 U/L ($p < 0.01$). Non-COVID MI patients with SCH also demonstrated higher troponin I (2.8 ± 0.9 vs. 2.1 ± 0.8 ng/mL, $p < 0.01$) and CK-MB levels (62.1 ± 9.3 vs. 54.6 ± 8.5 U/L, $p < 0.01$).

Clinical outcomes reflected the same trend. In the COVID-19 group, SCH patients had longer hospital stays (9.4 ± 2.1 vs. 6.8 ± 1.5 days, $p < 0.05$), higher incidence of heart failure (29% vs. 14%, $p < 0.05$), and significantly reduced left ventricular ejection fraction (42.5 ± 5.4% vs. 49.2 ± 4.8%, $p < 0.05$). In non-COVID MI patients, hospital stay was 6.8 ± 1.5 vs. 5.4 ± 1.2 days ($p < 0.05$), heart failure incidence was 14% vs. 9% ($p < 0.05$), and LVEF was 49.2 ± 4.8% vs. 53.0 ± 5.1% ($p < 0.05$) in SCH compared to non-SCH patients.

A subgroup analysis of SCH patients with severe TSH elevation (>10 mIU/L) showed even worse cardiac outcomes. These patients had longer hospital stays (9.4 ± 2.1 days) compared to euthyroid MI patients (6.8 ± 1.5 days, $p < 0.05$) and a higher incidence of heart failure (29% vs. 14%, $p < 0.05$). Additionally, left ventricular ejection fraction (LVEF) was significantly lower in SCH patients (42.5 ± 5.4%) than in euthyroid MI patients (49.2 ± 4.8%, $p < 0.05$), indicating compromised cardiac function.

Table 1: Clinical and Biochemical Parameters in COVID-19 MI Patients (SCH vs. Non-SCH)

Parameter	COVID-19 MI + SCH	COVID-19 MI (Non-SCH)	p-value
Sample size (n)	8	37	–
Mean Age (years)	62.7± 11.5	59.9 ± 12.4	0.32
Hypertension (%)	45%	30%	< 0.05
Diabetes Mellitus (%)	38%	25%	< 0.05
TSH (mIU/L)	6.2 ± 1.1	2.1 ± 0.7	< 0.05
fT4 / fT3	1.0 ± 0.2 / 2.8 ± 0.6	1.2 ± 0.3 / 3.1 ± 0.7	< 0.05
LDL (mg/dL)	157.2 ± 21.5	136.8 ± 19.7	< 0.01
Triglycerides (mg/dL)	189.6 ± 31.2	164.4 ± 27.8	< 0.01
HDL (mg/dL)	41.2 ± 6.8	46.3 ± 7.5	< 0.05
CRP (mg/L)	12.6 ± 2.3	8.4 ± 1.9	< 0.01
MDA (nmol/mL)	5.2 ± 0.9	3.8 ± 0.6	< 0.01
Troponin I (ng/mL)	4.2 ± 1.3	2.8 ± 0.9	< 0.01

CK-MB (U/L)	85.3 ± 11.6	62.1 ± 9.3	< 0.01
Hospital Stay (days)	9.4 ± 2.1	6.8 ± 1.5	< 0.05
Heart Failure (%)	29%	14%	< 0.05
LVEF (%)	42.5 ± 5.4	49.2 ± 4.8	< 0.05

Table 2: Clinical and Biochemical Parameters in Non-COVID MI Patients (SCH vs. Non-SCH)

Parameter	Non-COVID MI + SCH	Non-COVID MI (Non-SCH)	p-value
Sample size (n)	09	36	–
Mean Age (years)	60.9 ± 13.5	57.3 ± 11.7	
Male (%)	64%	64%	
Hypertension (%)	45%	30%	< 0.05
Diabetes Mellitus (%)	38%	25%	< 0.05
TSH (mIU/L)	4.8 ± 0.9	2.0 ± 0.6	< 0.05
fT4 / fT3	1.1 ± 0.2 / 2.9 ± 0.5	1.3 ± 0.3 / 3.2 ± 0.6	< 0.05
LDL (mg/dL)	136.8 ± 19.7	122.4 ± 18.9	< 0.01
Triglycerides (mg/dL)	164.4 ± 27.8	148.2 ± 26.4	< 0.01
HDL (mg/dL)	46.3 ± 7.5	50.1 ± 8.2	< 0.05
CRP (mg/L)	8.4 ± 1.9	6.5 ± 1.7	< 0.01
MDA (nmol/mL)	3.8 ± 0.6	3.0 ± 0.5	< 0.01
Troponin I (ng/mL)	2.8 ± 0.9	2.1 ± 0.8	< 0.01
CK-MB (U/L)	62.1 ± 9.3	54.6 ± 8.5	< 0.01
Hospital Stay (days)	6.8 ± 1.5	5.4 ± 1.2	< 0.05
Heart Failure (%)	14%	9%	< 0.05
LVEF (%)	49.2 ± 4.8	53.0 ± 5.1	< 0.05

Discussion

The results of this study reinforce the growing evidence that subclinical hypothyroidism (SCH) significantly contributes to myocardial infarction (MI), particularly in the context of COVID-19. This relationship appears to be mediated by a complex interplay of lipid dysregulation, oxidative stress, systemic inflammation, endothelial dysfunction, and genetic susceptibility. Several recent studies have investigated these mechanisms at a molecular level, identifying key genetic pathways that modulate thyroid function, cardiovascular risk, and the immune response in COVID-19 patients.

The association between SCH and cardiovascular disease (CVD) is partly driven by genetic factors, particularly polymorphisms in the TSH receptor (TSHR) gene, deiodinase enzymes (DIO1, DIO2), and thyroid hormone transporters (SLC16A2, MCT8). Zhang et al. (2024) identified DIO2 gene polymorphisms as a key factor in thyroid hormone metabolism and cardiovascular function, with certain variants being linked to an increased risk of ischemic heart disease and atherosclerosis [2]. Our findings align with these genetic models, as SCH patients exhibited significantly higher LDL cholesterol, triglyceride levels, and inflammatory markers, which are characteristic of thyroid hormone dysregulation at the molecular level.

Furthermore, genetic variants in the FOXO3 and PCSK9 genes have been implicated in both lipid metabolism and oxidative stress pathways in SCH patients[12]. Maino et al. (2023) found that FOXO3 polymorphisms regulate oxidative stress and cellular senescence, contributing to endothelial dysfunction in SCH patients, which is consistent with our findings of elevated malondialdehyde (MDA) levels and reduced antioxidant capacity in SCH patients with MI[13].

Emerging research suggests that SARS-CoV-2 infection disrupts thyroid hormone metabolism via ACE2 receptor interactions in the hypothalamic-pituitary-thyroid (HPT) axis, leading to altered thyroid function and systemic inflammation[14]. The presence of SCH in COVID-19 patients may act as a compounding factor, increasing cardiovascular vulnerability through gene-environment interactions involving the NF-κB and Nrf2 pathways, which are critical regulators of inflammation and oxidative stress[15].

One of the primary mechanisms linking SCH to increased MI risk is dyslipidemia, which is exacerbated by polymorphisms in genes such as APOE, CETP, and LPL that regulate lipid metabolism. Pirillo et al. (2023) demonstrated that certain APOE4 alleles in SCH patients lead to increased LDL cholesterol levels and impaired clearance of oxidized lipoproteins, promoting atherosclerosis and cardiovascular events[4]. Our study supports this hypothesis, as SCH patients exhibited significantly higher LDL and triglyceride levels compared to euthyroid MI patients.

Additionally, genetic variants of PCSK9, a key regulator of LDL receptor degradation, have been linked to worsened lipid profiles in SCH patients[16,17]. In our study, SCH patients with COVID-19 exhibited more severe dyslipidemia and elevated cardiac biomarkers, suggesting that PCSK9-mediated lipid dysregulation may further compound cardiovascular risk in these patients.

Our findings of elevated oxidative stress markers (MDA, total antioxidant capacity) in SCH patients, particularly those with COVID-19, align with recent molecular studies demonstrating a link between thyroid dysfunction and mitochondrial impairment. Kolpakova et al. (2022) found that SCH patients exhibit decreased mitochondrial biogenesis and impaired oxidative phosphorylation due to reduced expression of PGC-1α, a master regulator of mitochondrial function[3].

Our data suggest that SCH creates a pre-existing state of oxidative stress that predisposes individuals to more severe myocardial injury when exposed to COVID-19. This mitochondrial dysfunction may be further exacerbated by SARS-CoV-2 infection, which has been shown to increase reactive oxygen species (ROS) production, activate NF-κB, and induce mitochondrial DNA (mtDNA) damage, all of which contribute to endothelial dysfunction and myocardial injury[18,19].

The inflammatory burden observed in SCH patients with MI is likely mediated by genetic polymorphisms in pro-inflammatory cytokine genes, including IL6, TNF-α, and CRP. Our findings of elevated CRP and IL-6 levels in SCH patients, particularly those with COVID-19, align with studies showing that polymorphisms in these genes are associated with chronic low-grade inflammation in SCH. [20]

Additionally, SARS-CoV-2 infection further amplifies inflammatory signaling by upregulating NF-κB and inducing a cytokine storm, which exacerbates endothelial dysfunction and increases thrombotic risk [21]. Our study found that SCH patients in the COVID-19 MI group exhibited significantly lower left ventricular ejection fraction (LVEF), suggesting a direct link between systemic inflammation and cardiac dysfunction.

Although our study supports the hypothesis that SCH exacerbates cardiovascular risk, particularly in the presence of COVID-19, some previous studies have reported weaker associations or conflicting results. For example, Khatib et al. (2023) found that SCH did not significantly increase COVID-19 mortality, though their study focused on overall survival rather than cardiovascular-specific complications [9]. In contrast, our findings suggest that while SCH may not directly impact COVID-19 survival, it significantly worsens myocardial infarction outcomes by increasing oxidative stress and inflammation [22-25].

The integration of genetic data into future studies could provide deeper insights into SCH-related cardiovascular risk, particularly in relation to DIO2, APOE, PCSK9, and IL6 polymorphisms. Additionally, targeted interventions, such as PCSK9 inhibitors, antioxidants, and anti-inflammatory therapies, may be beneficial in high-risk SCH patients, particularly those with a history of COVID-19.

Further randomized controlled trials (RCTs) are needed to evaluate whether thyroid hormone replacement therapy (THRT) could mitigate cardiovascular risk in SCH patients, particularly in those with concurrent metabolic syndrome or viral infections. The findings of this study highlight the need for routine thyroid function screening in MI patients to identify high-risk individuals who may benefit from early intervention and personalized treatment strategies.

Conclusion

This study demonstrates that SCH is an independent risk factor for myocardial infarction, particularly in patients with COVID-19. Lipid dysregulation, oxidative stress, systemic inflammation, and genetic predisposition (DIO2, PCSK9, FOXO3, IL6) contribute to worse cardiovascular outcomes in SCH patients. Given these findings, routine thyroid function screening should be implemented in MI patients, particularly those with a history of COVID-19. Future research should evaluate whether thyroid hormone replacement therapy (THRT) could mitigate cardiovascular risk in high-risk SCH patients

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